UiT The Arctic University of Norway

Faculty of Health Science, Institute of Community Medicine, Norway's National Research Center in Complementary and Alternative Medicine | NAFKAM

Complementary and alternative medicine use for supportive care in childhood cancer

Prevalence of use, effectiveness, safety, and clinical practice

Dana Catalina Mora

A dissertation for the degree of doctor philosophiae

June 2023

Complementary and alternative medicine use for supportive care in childhood cancer

Prevalence of use, effectiveness, safety, and clinical practice

By

Dana Catalina Mora

Norway's National Research Center in Complementary and Alternative Medicine | NAFKAM

Institute of Community Medicine

Faculty of Health Science

UiT The Arctic University of Norway

Tromsø, Norway

June 2023

To la abuela Rebeca, el abuelo Juan, Jorge, and Trooper, nothing is ever possible without unconditional love and care.

Acknowledgments

"It is in collectivities that we find reservoirs of hope and optimism." — Angela Y. Davis

This doctoral research project was conducted at Norway's National Research Center in Complementary and Alternative Medicine, Institute of Community Medicine, Faculty of Health Science, UiT, The Arctic University of Norway. Funding was provided by The Children's Cancer Society of Troms and Finnmark and the Ekhaga Foundation.

First, I want to thank my supervisors, Trine Stub and Agnete E. Kristoffersen. Trine, I wish to express my most profound appreciation. It was thanks to you that I even considered pursuing a doctoral degree. Thanks for planting the seed in my head and lending me the opportunity to see it flourish. Thank you for always being available when I needed your help, knowledge, and support and for the countless hours of mentoring. Thank you for sharing your invaluable knowledge of the CAM field and for challenging me to submerse myself in it and think critically about it. Most of all, thank you for your unconditional support (inside and outside of academia) and for believing in my skills and abilities even when I doubted them. Thank you for guiding me in this incredible journey of pursuing a doctoral degree and moving to a new country to do so, it has not always been easy, but it has certainly never felt lonely, thanks to your care. Agnete, thank you for your profound knowledge of surveys and your patience and willingness to always help with statistical and software inquiries. I especially appreciate the conversations in the breakroom and your willingness to sit and listen. Thank you both for your graciousness and availability despite being incredibly busy. You complement each other's skills and knowledge as supervisors, making you a great mentoring duo and one I feel privileged to have.

I would also like to thank Miek Jong. Miek, thank you for your leadership and unconditional support. I greatly appreciate your constructive criticism and insightful suggestions throughout this research process. Thank you for always having your door open and being available despite your busy schedule. Most of all, thank you for the care, great talks, encouragement, and mentoring.

I would be remiss not to thank all the co-author of my publications who graciously offered their time and knowledge to this research project. Thank you for your help and support.

Thank you also to everyone who helped me with the recruitment process and, most importantly, to all the people that participated in the qualitative and quantitative components. I hope you find the information here reported beneficial.

I also wish to thank all the NAFKAM colleagues. It has been a privilege to work alongside you. I appreciate your support and the equalitarian job environment. Special thanks to Tine Lillegård Bergli and Vegard Sørnes for your technical support with the flowcharts.

To my fellow Ph.D. student Kiwumunlo Nakandi, thank you for lending your ear when the frustration and tiredness set in. I admire your sharpness and the clarity with which you can express your beliefs and ideas. Thank you for the raw conversations and the support.

To my far away friends, thank you for caring so much, for the support, and for the great messages and talks. Ailin, thank you for encouraging me to take this opportunity when I was scared out of my mind, mi hermana te adoro! Margaret, thank you for all the help and support; your encouragement and advice have made this journey more manageable and pleasurable to navigate.

To the friends I made in Tromsø, thank you so much for offering me your friendship and kindness. Raquel, thank you for being so supportive and for the countless hours of listening to my ordeals. I wouldn't have made it without your emotional support, humor, and honesty.

Finally, the most heartfelt thank you to my family; without your unconditional love and support, none of this would have been possible. To my mom and my dad, I love you immensely; thank you for always supporting and encouraging me to pursue my goals. To my uncle, thank you for always having kind words of encouragement. To my grandma, thank you for leading by example and being a courageous woman, te amo con todo mi corazon.

Your endless love and care have gotten me to this point.

Thank you, gracias, takk,

Dana

Table of Contents

1 List of Tables

2 List of Figures

3 Abstract

Childhood cancer treatment protocols have been successful due to the prompt and accurate diagnosis, availability of care, and access to high-quality medical resources. As the survival rates increase in high-income countries (HIC), the emphasis has shifted from survival to survival, emphasizing quality of life. The health complaints and adverse effects of cancer treatment are burdensome for children, yet many of the most burdensome ones lack adequate conventional medical treatment. To help cope with and alleviate these health challenges, parents seek ways to improve their children's quality of life and use supportive care modalities, including complementary and alternative medicine (CAM).

The global aim of this doctoral thesis was to delineate the use, effectiveness, safety, and practice of supportive care in childhood cancer. The project was conducted in different stages to achieve the aims, and mixed methods were used. A cross-sectional survey was implemented to assess the prevalence and associations of supportive care use in Norway among children with cancer. Two systematic literature reviews were conducted to evaluate the effect, safety, and types of modalities used to help patients cope with the adverse effects and health complaints of cancer treatment. Semi-structured interviews were used to assess the clinical experiences and perceptions healthcare providers working with pediatric oncology patients have regarding supportive care. Finally, interviews were also used to evaluate how providers perceive and evaluate risk when patients use conventional and supportive care.

Over half of the parents who participated in the survey used supportive care, and 47% used CAM to help their children cope with the adverse effects of cancer treatment. Less than 10% reported adverse effects from supportive care modalities. Results from the meta-analysis demonstrated that CAM (including acupuncture and hypnosis) has a significant effect ($p<.00001$) on the intensity and/or episodes of chemotherapy-induced nausea and vomiting (CINV). Furthermore, over 60% of the included studies lacked reporting the absence or presence of adverse effects. This result makes it difficult to evaluate the safety associated with these modalities.

The semi-structured interviews showed that healthcare providers' main aim is to identify the parent's treatment goals and help the children with their most immediate complaints. Among providers, safety was the most important criterion considered when recommending a supportive care modality. This criterion was based on a risk versus benefit evaluation.

Providers emphasized the importance of open and respectful communication with parents about supportive care modalities, as these modalities empower parents through the care of their children.

Parents in Norway widely use supportive care modalities; therefore, they need information on the effectiveness and safety of these modalities. Healthcare providers such as doctors, nurses, and rehabilitation personnel should have access to reliable information on these modalities to communicate with patients properly. As survival rates increase and late and long-term effects become more prevalent, it is essential to investigate safe and non-invasive treatments to alleviate this burden in children with cancer and survivors. Further methodologically rigorous research should be conducted to investigate the effectiveness and safety of supportive care modalities. In conclusion, if appropriately used by professional healthcare providers, supportive care modalities may decrease health complications from cancer treatment and contribute to a better quality of life for children with cancer and their families.

4 Sammendrag (Summary in Norwegian)

Behandlingsprotokoller for barn med kreft har vært vellykket på grunn av hurtige og tydelige diagnoser, tilgjengelig behandling og tilgang til medisinsk personell med høy faglig kompetanse. Tidligere ble det fokusert bare på overlevelse. Nå blir det lagt mer vekt på livskvalitet fordi overlevelsesraten har økt i høyinntekstland. Helseutfordringer og bivirkninger som følge av kreftbehandling er svært belastende for barn. Likevel får disse barna ikke tilstrekkelig medisinsk behandling for mange av disse plagene. Foreldre søker derfor alternativer som kan hjelpe barna med å håndtere og lindre disse helseutfordringene. Slike alternativer er bruk av støttende behandlingsformer som inkluderer alternativ behandling.

Målet med denne doktorgradsavhandlingen var å kartlegge hvordan barn med kreft bruker støttende behandlingsformer, hvor effektiv og trygg disse behandlingene er og hvordan behandlingsformene blir praktisert.

Forskningsprosjektet ble utført i flere trinn og det ble benyttet en mixed methods tilnærming. Vi gjennomførte en spørreundersøkelse for å evaluere forekomsten og assosiasjonene knyttet til støttende behandlingsformer av barn med kreft i Norge. Vi gjennomførte to systematiske litteraturgjennomganger for å evaluere effekt, trygghet og hvilke behandlingsformer som ble brukt for å hjelpe pasienter med å håndtere bivirkninger og helseplager knyttet til kreftbehandling. Vi benyttet semistrukturerte intervjuer for å evaluere hvilke kliniske erfaringer og holdninger pediatrisk helsepersonell har med å gi støttende behandling til barn med kreft. Til slutt brukte vi data fra disse intervjuene til å kartlegge hvordan helsepersonell oppfatter og vurderer risiko når pasienter bruker konvensjonell og støttende behandlingsformer som del av sin kreftomsorg.

Mer enn halvparten av foreldrene som deltok i spørreundersøkelsen brukte støttende behandlingsformer, og 47% brukte alternativ behandling for å hjelpe barna sine med å håndtere bivirkninger av kreftbehandling. Færre enn 10% rapporterte om bivirkninger ved bruk av disse behandlingsformene. Resultatene fra meta-analysen viste at alternativ behandling (inkludert akupunktur og hypnose) har en signifikant effekt ($p<.00001$) på intensitet og/eller tilfeller av kvalme og oppkast etter cellegiftbehahandling. Mer enn 60% av de inkluderte studiene i oppsummeringene manglet informasjon om bivirkninger. Dette gjør det vanskelig å evaluere sikkerheten knyttet til disse behandlingsformene.

De semistrukturerte intervjuene viste at hovedmålet til behandlerne var å kartlegge foreldrenes mål for behandlingen og hjelpe barna med de verste plagene. Når behandlerne anbefalte pasientene å bruke støttende behandlingsformer, var det viktigste kriteriet at behandlingen skulle være trygt. Dette kriteriet var basert på en risiko -nytte evaluering. I tillegg understreket behandlerne hvor viktig det var å snakke åpent og respektfullt med foreldrene om disse behandlingsformene. En slik samtale er viktig fordi ved bruk av disse behandlingsformene blir foreldrene involvert i kreftomsorgen av sine barn. Dette styrker foreldrene.

Foreldre til barn som har kreft, benytter ofte støttende behandlingsformer. Helsepersonell som leger, sykepleiere og rehabiliteringspersonell bør derfor ha tilgang til pålitelig informasjon om disse behandlingsformene for å kunne kommunisere med pasientene på en god og informativ måte. Overlevelsesraten øker, og seneffekter blir mer utbredt blant kreftoverlevere. Derfor er det viktig å undersøke hvilke behandlinger some er trygge og mindre belastende for barnekreft-overlevere. Det er nødvendig å gjennomføre mer (grundig) forskning for å kartlegge hvor effektive og trygge disse behandlingsformene er.

Konklusjon: Støttende behandlingsformer kan redusere helseplager etter kreftbehandling hos barn hvis de brukes på en riktig måte, utført av kompetente behandlere. Dette kan bidra til bedre livskvalitet for barn med kreft og familiene deres.

5 List of papers

Paper I

Mora DC, Kristoffersen AE, Arcury TA, Quandt SA, Jong MC, Stub T. Prevalence of supportive care among children diagnosed with cancer in Norway: A cross-sectional study. Eur. J. Pediatr. 2023. Under Review.

Paper II

Mora DC, Overvåg G, Jong MC, Kristoffersen AE, Stavleu DC, Liu J, Stub T. Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young adults: a systematic review and meta-analysis of randomized controlled trials. BMC Complement Med Ther. 2022 Apr 2;22(1):97.

Paper III

Mora DC, Kristoffersen AE, Overvåg G, Jong MC, Mentink M, Liu J, Stub T. Safety of Complementary and Alternative Medicine (CAM) treatment among children and young adults who suffer from adverse effects of conventional cancer treatment: A systematic review. Integr Cancer Ther. 2022 Jun;21

Paper IV

Mora DC, Jong MC, Quandt SA, Arcury TA, Kristoffersen AE, Stub T. Supportive care for cancer-related symptoms in pediatric oncology: a qualitative study among healthcare providers. BMC Complement Med Ther. 2023 Dec;23(1):1-3.

Paper V

Mora DC, Kristoffersen AE, Jong MC, Hervik JB, Stub T. A qualitative study among healthcare providers on risks associated with the use of supportive care for cancer treatment-related symptoms in children, adolescents, and young adults. Integr Cancer Ther. 2023: Under Review.

6 Definition of Terminology

Alternative modalities: refer to modalities that are used instead of conventional medicine (1).

Adverse effects: an undesired reaction to a drug or other type of treatment (2).

Complementary and alternative medicine: a group of diverse medical health care systems, practices, and products that are not presently considered part of conventional medicine (3).

Childhood cancer: a group of cancers that arise between birth and 19 years of age (4). The definition of childhood cancer, specifically with the age group, differs between countries. In Norway, it is defined as 0-18 years of age (5).

Complementary therapies: is nonmainstream practices applied alongside conventional medicine (1)**.**

Integrative medicine: merges evidence-based conventional and complementary modalities in a coordinated way (1).

Risk: The chance of something happening that will have a negative impact. It is measured in terms of consequences and likelihood(6).

Direct risk: is related to the intervention, e.g., harm caused by pharmacological products, medical treatment, and procedures (7).

Indirect risk: is related to adverse effects of the treatment context, for example, the CAM provider rather than the medicine. A patient can be harmed by a care context, possibly preventing the patient from receiving the best possible treatment relevant to her or his health needs related to the setting effects, such as the providers rather than the medicine (8).

Integrative health care: a caring approach that involves combining complementary and conventional treatment approaches in a coordinated manner to address an individual's health needs (9).

Late and long effects: long-lasting health problems following cancer treatment (10).

Rare cancer: a disease with an incidence of fewer than six cases for every 100 000 people (11).

Supportive care: the provision of the necessary services for those living with or affected by cancer to meet their physical, emotional, social, psychological, informational, spiritual, and practical needs during the diagnostic, treatment, and follow-up phases, encompassing issues of survivorship, palliative care and bereavement (12).

Safety: Freedom from hazard (6).

7 List of Abbreviations

ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
AST	Anthroposophic supportive treatment
CAM	Complementary and alternative medicine
CINV	Chemotherapy-induced nausea and vomiting
CNS	Central nervous system
COREQ	Consolidated criteria for reporting qualitative research
EEA	European economic area
EU	European union
HIC	High-income countries
MESH	Medical subject heading
NCR	Norwegian Cancer Registry
NAFKAM	Norway's National Research Center in Complementary and Alternative Medicine
NOK	Norwegian krone
NOPHO	Nordic Association for Pediatric Hematology and Oncology
PICO	Population, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	The International Prospective Register of Systematic Reviews
SCP	Subcutaneous port
SMD	Standardized mean difference
SIOP	International Society of Paediatric Oncology
SUMARI	System for Unified Management
RCT	Randomized controlled trial

SDR	Socially desirable responding
SR	Systematic review
T&CM	Traditional and complementary medicine
US	United States
VAT	Value-added tax
VR	Virtual reality
WBC	White blood cell
WHO	The World Health Organization

8 Introduction

8.1 History of childhood cancer globally and in Norway

The earliest descriptions of cancer appeared in papyri dating as far back as 2500 B.C. (13). Various strides were made through the centuries. In the 19th century, due to the invention of better microscopes, it was discovered that cancer cells are different from normal cells. Early in the 20th century, oncology was developed to understand living organisms' structures, functions, and chemistry (13).

During the first half of the 20th century, it was believed that little could be done to help children with cancer besides providing palliative care as the disease progressed (14). Dr. Joseph Burchenal pioneered the cooperative group approach to childhood cancer (15). Dr. Farber was the first to achieve partial remission of leukemia in children in 1947 with folic acid antagonists (14, 15). Systematic treatment for cancer became available in the 1950s (11). In Europe, the International Society of Paediatric Oncology (SIOP) was founded in 1969, and they initially undertook formal collaborative clinical research for childhood cancers (11).

During the 1980s and 1990s, collaborative patient-centered research prevailed across national borders, leading to multidisciplinary teamwork that helped raise the standard of care. Based on this collaboration, the hub-and-spoke model has been implemented in some countries to improve the standard of care. The hub-and-spoke model is one in which specialized centers are responsible for accurate diagnoses, risk stratification, and complex treatments. At the same time, the centers cooperate with local hospitals to provide less intricate components of supportive care, monitoring, and simple chemotherapy closer to patients' homes (11).

In Norway, the first systematic studies of cancer incidence were reported as early as 1870 by Frans Casper Klær and later followed by Georg Fredik Gade in 1929. However, it was not until 1948 that the Norwegian Cancer Registry (NCR) was established following an agreement to a proposal by the World Health Organization (WHO) to investigate the frequency of cancer in the population of five countries, including Norway. That same year the National Association Against Cancer proposed the establishment of a nationwide cancer registry. In 1951, the Ministry of Social Affairs mandated doctors to report all cancer cases to the registry starting January 1952 (16).

Although all cancers were reported to the NCR, the coding system was unsuitable for registering childhood cancers, especially solid tumors, as they are classified by morphology

and tissue type. Therefore, it was decided in 1984 by the Nordic children's cancer organizations that all cancers of children under 15 should be anonymously registered in the Nordic Association for Pediatric Hematology and Oncology (NOPHO) (17).

The Nordic Association in Pediatric Oncology and the Nordic Club of pediatric hematology joined forces and founded NOPHO in 1984 due to a long line of collaborations between the Nordic countries that started as early as 1916 (18). After World War II, young doctors were interested in traveling to the United States (US) and working there. Many of those doctors acquired knowledge in pediatric subspecialties, including hematology. Dr. Martin Seip was the first Norwegian pediatrician to specialize in hematology. He introduced systematic treatment of childhood leukemia with cytostatic in 1954 (19), and in 1959 the Department of Pediatric Research at the National Hospital in Oslo was established (19).

As it was challenging to build up scientific environments in pediatric hematology that provided sufficient scientific power, treatment evolved in the 1960s, and more collaborations emerged (18, 20). Pediatrician Peter Johan Moe began registering all new leukemia and malignant lymphoma cases in Norwegian children.

The Norwegian Ministry of Social Affairs and Health established the Competence Center for Solid Tumors in 1999. Still, it was not until 2002 that solid tumor registration for childhood cancer was included in the NCR. In 2006 leukemia data obtained from the NCR was incorporated into the clinical register for solid tumors, and the Norwegian Children's Cancer Registered emerged (17).

8.2 Epidemiology

It is estimated that 400,000 children between 0-19 years develop cancer worldwide each year (4, 21), suggesting that cancer is the leading cause of death among children and adolescents worldwide (21). Although it is the leading cause of death among children, childhood cancer is a rare disease that accounts for 1-4% of all cancers (11). The disease differs from adult cancers in that it emerges in developing organs and tissues, generally growing rapidly and with different spread patterns.

Childhood cancers are classified according to morphology and tissue type in which it occurs (4, 22). Leukemias, brain cancers, lymphomas, and solid tumors are the most common cancers among children (21). Most childhood cancers do not have a known cause, and few are

preventable (4, 21). It is believed that many cancers originate during embryonic development (4, 21). The rapid growth and spread of many childhood cancers make them more responsive and sensitive to chemotherapy. Most childhood cancers are treated more aggressively with chemotherapy than adult cancers, as the tumors respond faster, and most children tolerate chemotherapy better than adults (4). Due to the success of chemotherapy treatments and the quality of care, the overall survival rate of childhood cancer in high-income countries (HIC) is over 80% (23).

In Norway, 6,781 children were diagnosed with cancer between 1985-2021. Childhood cancer is the leading cause of death among children one year and older. However, the five-year survival rate is 87.6%, and less than 1% of all cancers are diagnosed among children and adolescents (14). The cancers most often diagnosed are leukemias (26.3%) and central nervous system tumors (CNS) (27.7%) (5). Leukemias and lymphomas are generally treated with chemotherapy only. CNS tumors are typically operated on if possible, and chemotherapy, radiotherapy, or both are used post-treatment, depending on the type of tumor. Solid tumors are usually treated with multimodal treatment (24). The Norwegian Directorate of Health has established treatment guidelines for childhood cancer (24), and Norway follows the hub-and-spoke model of care. The treatment takes place at the four leading hospitals across the country (Oslo University Hospital, Haukeland University Hospital in Bergen, St. Olav's Hospital in Trondheim, and the University Hospital of Northern Norway (UNN) in Tromsø).

8.3 Supportive care, including CAM

As a result of the high survival rates effects in high-income countries (HIC), the treatment focus was shifted from survival as a primary goal to survival with minimal late effects (5). Late effects are defined as effects that develop several years after treatment (24). In addition to conventional care, parents often seek supportive care to help their children mitigate symptoms, enhance coping skills and improve well-being derived from the long burdensome treatments (25). Supportive care is defined as the provision of the necessary services for those living with or affected by cancer to meet their physical, emotional, social, psychological, informational, spiritual, and practical needs during the diagnostic, treatment, and follow-up phases, encompassing issues of survivorship, palliative care and bereavement (12). CAM modalities, such as healing and natural remedies, are often considered by parents of children with cancer and consequently included as a part of supportive care in this research project.

CAM definitions vary extensively between countries. This thesis used the definitions provided by the US National Center for Complementary and Integrative Health (see definition section) and the definition provided by Norwegian law. The definition used in the Norwegian law about alternative treatment - Lov om Alternativ behandling mv (2003-06-27-64) (26) states :

"Med alternativ behandling menes helserelatert behandling som utøves utenfor helse- og omsorgstjenesten, og som ikke utøves av autorisert helsepersonell. Behandling som utøves i helse- og omsorgstjenesten eller av autorisert helsepersonell, omfattes likevel av begrepet alternativ behandling når det brukes metoder som i all vesentlighet anvendes utenfor helse- og omsorgstjenesten."

"Alternative treatment means health-related treatment that is carried out outside the health and care service and which is not carried out by authorized health personnel. Treatment carried out in the established health service or by authorized health personnel is nevertheless covered by the term alternative treatment when methods are used that are essentially used outside the established health service."

In Norway, conventional providers are authorized, meaning they have responsibilities and obligations regulated by law (27). The government does not regulate CAM providers; they can belong to professional organizations in their fields that require specific standards for practice, and they can register themselves in a voluntary registry for CAM providers in Norway (28). In mental health, for example, healthcare providers are either considered conventional healthcare providers or CAM providers, depending on their qualifications (29). Psychiatrists and psychologists are authorized healthcare providers. Psychotherapists are not subject to formal qualification requirements and therefore are considered CAM providers (29).

8.4 Literature review

This literature review will present studies published in the last five years (from 2018 to April 2023). Systematic reviews on the effect and safety of CAM modalities up to 2020 were conducted and are presented in papers 1 and 2 of this thesis. The latest systematic review on the prevalence of CAM use was conducted in 2017 (30); studies between 2017 and April 2023 will be presented below.

8.4.1 Prevalence of CAM among children with cancer

Bishop et. al., published a systematic review on the prevalence of CAM use in pediatric cancer from 1950-2007. The review showed that the prevalence of CAM ranged from 6% to 91%, and the most used modalities were herbal remedies, diets/nutrition, and faith healing. CAM was used to help cure or fight cancer, alleviate symptoms, and support the ongoing use of conventional therapy (3). Furthermore, in 2017 Diorio et. al., conducted a systematic review on the global use of Traditional and Complementary Medicine (T&CM) in childhood cancer from 1977-2015 (30). The use of T&CM was wide, ranging from 6% to 100%. The study showed that the use of these modalities varied according to country income. Low, lower-income, and upper-middle countries reported a prevalence use of 60% or above. HIC reported a prevalence use of 47%. The most reported modalities were oral supplements, dietary changes, alternative medical systems, and spiritual treatments. The respondents reported using these modalities because they wanted to do everything possible for the child by boosting the immune system, improving general well-being, and treating the adverse effects of conventional therapy (30).

A systematic search was conducted to identify studies on the prevalence and associations for the use of CAM between 2018 and April 2023. Five electronic databases were searched (AMED, CINAHL, EMBASE, MEDLINE/PubMed, and PsycINFO). Six studies from six countries were identified (Cameroon, France, India, Netherlands, Switzerland, and the US).

A survey was administered in Cameroon among 80 parents of children with cancer to determine the prevalence and types of T&CM used at three hospitals. The findings demonstrated that 68% of participants used at least one form of T&CM before diagnosis, and 26% reported using such modalities after diagnosis. Among the modalities commonly used were herbs and other remedies taken by mouth, praying, and skin cutting. The factors associated with T&CM use among this population were living more than 5 hours away from the treatment center, costs, and the habit of consulting a traditional healer when sick (31).

A survey conducted in France found that among 202 patients, 49% reported CAM use. Eighty-five percent of those who used CAM said it was used to manage the adverse effects of conventional treatment (32). The most common modalities used were homeopathy, chiropractor, and faith healing (43%).

A South Indian hospital survey reported 8% of the 277 pediatric oncology patients interviewed used CAM. Ayurveda was the modality most often used. CAM was used because children were not improving with conventional treatment, or a complete cure was expected (33).

A survey to assess the needs of children with cancer regarding CAM was conducted in the Netherlands. Seventy parents participated. Over half (56%) of the parents reported using CAM for their child. The modalities more often used were food supplements and vitamins (32%), massage (22%), and homeopathy (22%) (34).

A total of 44% reported the use of CAM in a Swiss study conducted among 140 pediatric oncology patients. Among them, 54% used CAM before diagnosis, and 69% used CAM after diagnosis. The modalities most often used were homeopathy, supplements, osteopathy, hypnosis, and Bach flowers medicine. Osteopathy and homeopathy were more likely to be used before diagnosis, and hypnosis was most likely used during oncology treatment (35).

Lastly, a retrospective study administered at Memorial Sloan Kettering Cancer Center in the US found that 1,877 pediatric oncology patients (0-39 years of age) had received integrated medicine services in eight years. Among those patients, dance therapy (45%) was the most frequently used service, followed by massage (26%), music therapy (23%), mind-body therapies (4%), and acupuncture (1%). Infants and toddlers were more likely to use music and dance therapy, whereas mind-body therapies, massage, and acupuncture were more likely to be used by older children and young adults (36).

Based on this systematic search, the overall use of CAM ranged from 8% to 56%. The participants reported using various CAM modalities such as faith healing, herbs, supplements, dance and art therapies, osteopathy, homeopathy, acupuncture, and massage. The reported reasons for use were to help children cope with the disease and treat the consequences of conventional cancer treatment. In low-income countries, the reasons for use were the long distance to hospitals and a belief in CAM as a curative option.

8.4.2 Effectiveness and safety of CAM modalities

The candidate conducted systematic reviews of RCTs (37) and non-RCT (38) studies in 2020. A literature review was performed to cover the time gap between 2020 and the development of this thesis in April 2023.

8.4.2.1 Randomized controlled trials (RCTs)

The literature review was conducted by searching six electronic databases (AMED, CINAHL, Cochrane Central Register for Controlled Trials, EMBASE, MEDLINE/PubMed, and PsycINFO). The search returned six RCTs that investigated the effects of CAM on childhood cancer.

An RCT from Iran evaluated the efficacy of the herb chamomile on chemotherapy-induced neutropenia in children with acute lymphoblastic leukemia (ALL) (39). The trial was conducted among forty children between 2 and 18 years of age. The design consisted of a treatment and a placebo group. The treatment group was given 2.5 ml of chamomile syrup with orange flavor for 30 days. The placebo group was assigned an orange-flavored placebo syrup. The primary outcomes measured during and after the intervention were white blood cell (WBC) and absolute neutrophil count (ANC). The results showed a significant increase ($p = 0.02$) in ANC among the participants in the treatment group. There was an increase in WBC among the treatment group, but the differences were not significant. The study reported that chamomile did not interact with chemotherapy. Nothing was reported regarding adverse effects derived from the intervention.

A single-blinded RCT was conducted to assess the effect of Manuka honey and olive oil on oral mucositis and pain derived from oral mucositis (40). Forty-six children between 5-17 years diagnosed with ALL who received high-dose chemotherapy were included in the trial. The participants were allocated randomly to three different groups. Group 1 was given 2.5 cm^3 of honey, group 2 was given 2.5 cm^3 of olive oil, and group 3 was assigned 5 cm^3 of standard-care medication. The substances were administered three times daily for seven days. The groups receiving honey or olive oil) had significantly less severe oral mucositis ($p = 0.00$) and less pain ($p = 0.00$) than the control group. Participants in group 1 reported no complaints, but children in group 2 did not like the taste of the substance. None of the children reported adverse effects derived from either of the two interventions.

An RCT that assessed the effect of Glutamine for vincristine (a chemotherapy drug)-induced neuropathy in children and adolescents was conducted in the US (41). Fifty-six participants diagnosed with leukemia, lymphoma, extracranial solid tumor, or medulloblastoma between 5 and 21 years of age were included in the study. All participants expected to receive a minimum cumulative dose of 6 mg/m^2 of vincristine. Participants were randomized into two groups; one group received Glutamine, and the placebo group received (L-glycine). The

substances were administered two times per day for three weeks. The RCT found that Glutamine may provide a significant protective effect ($p = 0.02$) on the sensory but not motor neurons. The investigators concluded that Glutamine is well tolerated and associated with improved sensory function. Only mild adverse effects were reported, and there was no significant difference in adverse effects observed between the glutamine and placebo groups.

An RCT was conducted in Germany to evaluate the effects of Anthroposophic supportive treatment (AST) on chemotherapy-induced toxicity (42). A sum score for hematology, mucositis, general condition, and infection measured the primary outcome (toxicity). The study included children between 1-18 years of age undergoing intensive-phase chemotherapy treatment for various malignancies and tumor types. Participants were randomly allocated to an intervention or a control group. The intervention group was given AST regimen as a supplementary therapy (Mistletoe injections and different homeopathic remedies) as an add-on to standard chemotherapy treatment. The control group received the standard chemotherapy treatment only. The AST was tailored according to diagnosis. Two-hundred and eighty-eight participants were included in the intention-to-treat analysis. The results showed no significant differences between the treatment and control groups. Minor adverse effects were recorded among 123 participants, and three serious ones were recorded. Later, the investigators concluded that the serious adverse effects resulted from the chemotherapy, not the intervention.

The effect of a home-based multimodal symptom-management program for alleviating symptoms such as chemotherapy-induced nausea and vomiting (CINV), fatigue, pain, mucositis, and anxiety were examined in this trial (43). Fifty children and adolescents (10-18 years of age) undergoing chemotherapy for hematological malignancies or solid tumors were included. Participants were assigned to an intervention group (home-based multimodal symptom management program plus standard care) or a control group (standard care only). The intervention consisted of multiple nonpharmacological interventional components (progressive muscle relaxation, distraction strategies, guided imagery, energy conservation, meal preparation advice, oral care, and warm and cold pads). The targeted symptoms were measured at baseline, at the first two weeks of each cycle of chemotherapy, and at six months after baseline. The results show that the home-based symptom-management program may be beneficial for reducing fatigue. However, no differences were found between groups for the other symptoms. Nothing was reported regarding adverse effects derived from the

intervention. This study was a mix-methods study where a qualitative study was conducted simultaneously with an RCT; see results from the qualitative study in section 6.4.2.2.

Hundert et al. (44) explored the feasibility and effectiveness of using virtual reality (VR) as a distraction technique for children (8-18 yrs.) with cancer undergoing painful needle procedures (implementing a needle into a subcutaneous port (SCP)). Forty participants were randomly allocated to get the VR intervention (underwater environment) or active distraction control with an iPad. The study took place over eight weeks. The study found that VR was feasible and acceptable to patients, families, and clinicians. Although no significant differences were reported between the two groups, the trial suggested that VR may effectively reduce procedural pain and distress in this population. Minor adverse effects (motion sickness and dizziness) were reported among 10% of the participants without significant differences between the control and intervention groups.

In conclusion, the six articles evaluated the effectiveness of CAM, categorized as biological-based modalities, alternative medical systems, and mind and body modalities, for adverse effects of cancer treatment among children and adolescents. Four out of six trials reported adverse effects from the modalities; the adverse effects reported were all minor. The results of the studies demonstrated that biological treatments such as Chamomile, Honey, Olive oil, and Glutamine could positively impact adverse effects such as ANC, oral mucositis and pain from oral mucositis, or sensory neuropathy. Alternative medical systems, such as anthroposophic medicine, did not reduce chemotherapy-induced toxicity. The multimodality intervention, which mainly consisted of mind and body modalities, significantly affected fatigue. Lastly, VR proved to be a feasible modality to implement; it may reduce procedural pain and distress in children with cancer.

8.4.2.2 Observational, quasi-experimental, and qualitative studies

The literature review was conducted by searching five electronic databases (AMED, CINAHL, EMBASE, MEDLINE/PubMed, and PsycINFO). The search returned three non-RCTs that investigated CAM's effects, effectiveness, and safety among children with cancer.

A quasi-experimental evaluated the use of yoga to reduce stress and pain in children with cancer or hematologic diseases and reduce stress among caregivers (45). Fifteen children between 7-17 yrs. were included in this study, and 18 parents (20-49 yrs.). The researchers considered pain and extended anxiety as tools to measure the effects of yoga. The yoga

intervention consisted of a single session that lasted 20-60 mins administered in the participant's room by a yoga teacher. The study found a significant decrease in pain but not anxiety post-yoga. The study found a significant ($p<.001$) decrease in anxiety among parents and adolescents. Nothing was reported regarding adverse effects derived from the use of yoga.

The second study was an observational cohort study aimed to assess the feasibility, effectiveness, safety, and satisfaction of an osteopathic intervention in children, adolescents, and young adults affected by hematological malignancies undergoing intensive phases of cancer treatment (46). The intervention consisted of an 11-week training program three times per week and/or 4-10 osteopathic treatments (depending on the participant's clinical history and intensity of chemotherapy protocol). A hundred and twenty-six participants were included; one hundred and four received the training program and osteopathic treatments, and 22 received only osteopathic treatment. Although no significant tests were conducted, results demonstrated improved range of motion of the spinal column and/or limbs, chest and abdomen mobility, and cranial-sacral rhythmic impulse. Only minor adverse effects were reported.

The third study was a qualitative study nested within an RCT(43). The qualitative study aimed to understand the patients' and parents' experiences with the symptom management program. The findings suggested that children and parents received the symptom-management program positively. The program helped improve children's and parents' knowledge, coping skills, and psychological preparation for chemotherapy-related symptoms (43).

To conclude, one quasi-experimental, one observational, and a qualitative study were identified. The observational and quasi-experimental studies measured the effectiveness of mind-body CAM modalities on stress, pain, and mobility of children and adolescents with cancer. The studies found positive outcomes on mobility, pain, and stress (among adolescents and caregivers). The qualitative study concluded that the multimodal intervention helped to improve knowledge and coping skills for adverse effects derived from chemotherapy. Only a third of the quasi-experimental and qualitative studies reported adverse effects from CAM interventions.

8.5 Patient Safety

Norway's National Research Center in Complementary and Alternative Medicine (NAFKAM) has established patient safety as one of its core values (47) . Its mission is to increase patient safety awareness by facilitating informed and knowledge-based health choices for patients who want to use CAM (48). Consequently, safety is emphasized throughout this thesis. According to the WHO, safety aims to prevent and reduce risks, errors, and harm that occur to patients during the provision of health care (49). Safety has been a central pillar of healthcare since ancient times. The Hippocratic Oath has emphasized for millennia the principle of considering the patient's benefit and refraining from causing harm (50). One of the leading causes of death and disability in the world is the occurrence of adverse events due to unsafe care (49).

The discussions about safety and risk in CAM focus on issues of direct risk, usually related to adverse effects of products and negative interactions with conventional treatment interactions (51). The emphasis on the risks of the modalities is a consequence of the lack of regulation of CAM modalities and products before they are marketed (regarding efficacy, effectiveness, quality, and safety) (52). In addition to the assumption by the patient that natural products equate safe products (53).

Conventional drugs must undergo several testing phases (Figure 1). First in laboratories and on animals and then on different groups of healthy and sick people to assure the efficacy and safety of the drug (Phase I, II, III, and IV studies). After the drug is approved for distribution, tests are conducted to investigate possible long-term adverse effects. Long-term effects are a problem that is caused a disease or treatment of a disease and may continue for months or years (54).

In Norway, *CAM medicinal products* are subject to the same market authorization procedures as other medicinal products, with the possible exception of documentation of efficacy in the EU (55)

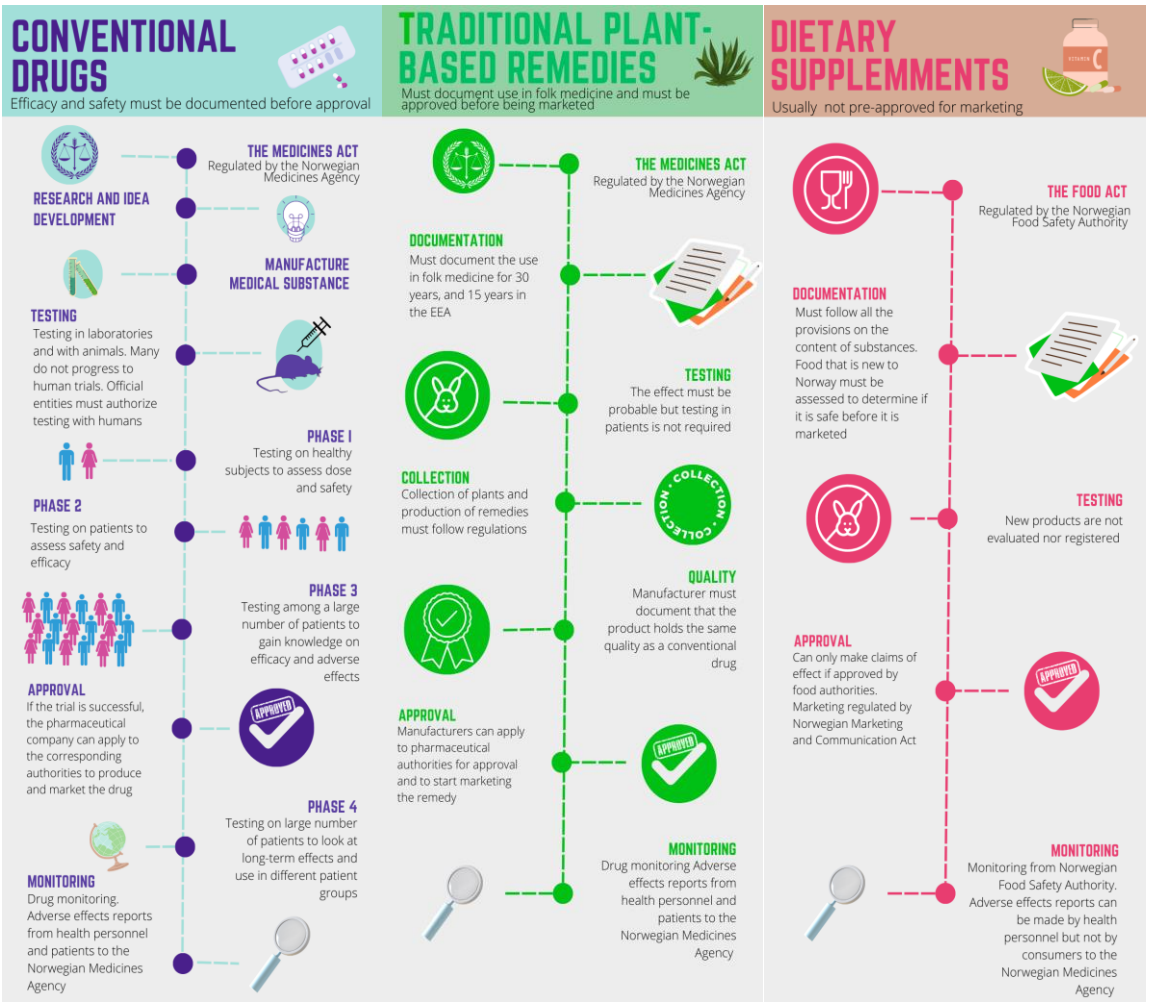

Figure 1. Regulation of conventional drugs, plant-based remedies, and dietary supplements in Norway. Figure adapted from Borud H. Alvorlig å love helbredelse. English: It is serious to promise to heal. Aftenposten.2014; 11 March. https://www.aftenposten.no/norge/i/3j74v/al
vorlig-aa-love-helbredelse.

Traditional plant-based remedies are regulated differently than conventional drugs; no testing for efficacy is required. Remedies can be approved for marketing if it can be documented by the manufacturer that it has been used for the past 30 years and 15 of those years in the European Economic Area. The effect of traditional plant-based medicines must be probable but is not required before marketing. Lastly, the manufacturer must document that the product has the same quality as a conventional drug. After they are approved for distribution, reports of adverse effects on conventional and traditional plant-based remedies can be made to the Norwegian Medicines Agency by health personnel and consumers.

Dietary supplements are regulated under the Food Act, not the Norwegian Medicines Act. The manufacturer must follow a provision on the content of substances to determine if they are safe. The producer of the supplements can only make claims on effect approved by the

food authorities, and the Marketing and Communication Act of Norway regulates the marketing. After they are approved for distribution, health personnel or users can report adverse effects to the Norwegian Medicines Agency. Healthcare providers, but not consumers, can report adverse effects of dietary supplements to the Norwegian Medicines Agency (Figure 1) (56).

Based on European and national regulations and the above information, CAM medicinal products, traditional plant-based remedies, and supplements are marketed without evidence for efficacy and safety; it is important to conduct research on safety to protect the population from harm caused by these products. This is the rational for NAFKAM's strategic plan, which emphasizes conducting research on safety before researching efficacy (52).

To evaluate the safety and efficacy of supportive care, including CAM modalities used in oncology, guidelines recommend that when a patient enquires about CAM, conventional healthcare providers should first determine the level of risk of the modality and then determine efficacy (57).

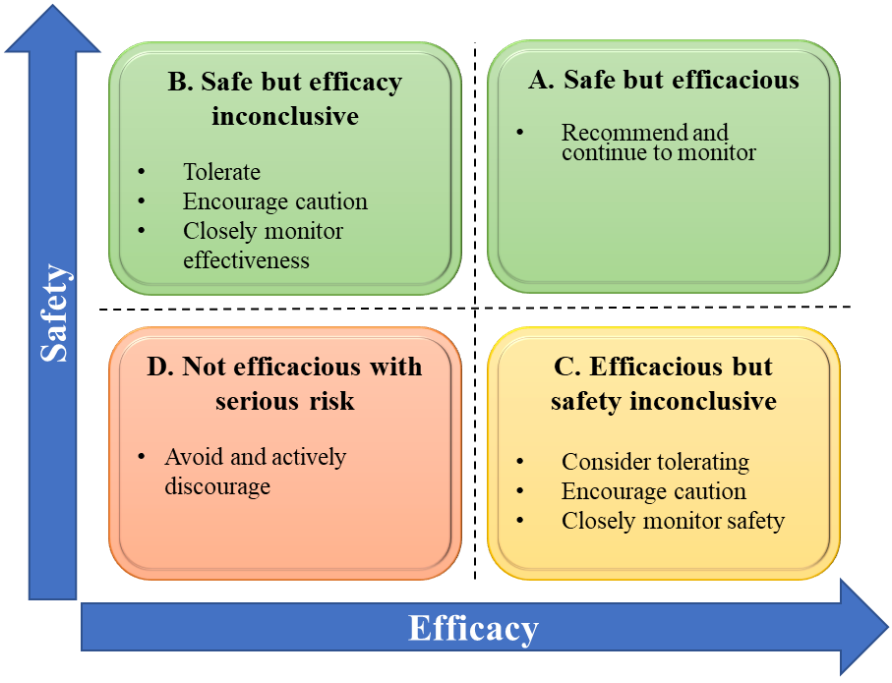

Figure 2. Clinical decision-making based on risk versus efficacy. Figure reprinted from *Deng* GE, Frenkel M, Cohen L, Cassileth BR, Abrams DI, Capodice JL, et al. Evidence-based clinical practice guidelines for integrative oncology: complementary therapies and botanicals. J Soc Integr Oncol. 2009; 7(3).

Providers are encouraged to evaluate the modalities according to the safety/efficacy grid (Figure 2). The purpose of the grid is to serve as a guide when assessing the available

evidence to recommend modalities. The grid is established in a safety/efficacy continuum. If the modality is safe and effective, it is recommended. If it is safe, but the evidence on effectiveness is inconclusive, then it is recommended with caution. If the modality is effective, but the safety factor is inconclusive, it can be tolerated but with caution. Lastly, if the modality is unsafe and ineffective, providers are advised to avoid it and inform patients not to use it (57).

In medical science, risk is defined as a measure of the probability and severity of adverse effects (58). Risk can be divided into direct and indirect risks. Direct risks are adverse effects or reactions relating to injuries caused by medical intervention or related to error (51). Indirect risks are risks not caused by medical intervention or errors and are connected to setting effects such as medical error rather than the medication (59). For example, a provider with insufficient medical experience and skills may overlook serious symptoms and thereby cause a delay in necessary conventional treatment.

The study of risk, including direct and indirect risks, has been widely explored in adult cancer research (51), but the research is limited among children with cancer (60). In this research project, the findings showed that the safety of CAM modalities is underreported, as only 34% reported adverse effects.

Furthermore, out of the risks reported, only direct risks were reported. For parents of children with cancer, knowledge on the safety of supportive care modalities is important because they do not want to afflict their children who already experience burdensome symptoms from cancer treatment, such as nausea, vomiting, and fatigue. Hence it is important to research direct risks to increase safety in this patient group.

Indirect risks such as lack of healthcare providers with pediatric oncology skills, a lack of knowledge about supportive care, including CAM modalities among conventional healthcare providers, patients who withhold information about their use of modalities that may negatively interact with conventional treatment, and poor provider-patient relationship were poorly reported in the review included in this thesis. These indirect risks may impose additional harm to children with cancer and are therefore important to include when reporting risks in research.

8.6 Aim of the research project

The global aim of this doctoral thesis was to delineate the use, effectiveness, safety, and practice of supportive care, including CAM, in childhood cancer. To fulfill the aim, the prevalence and association of the use of supportive care in Norway were examined in a cross-sectional survey. Systematic literature reviews assessed supportive care modalities' effectiveness and safety. Lastly, healthcare providers' experiences and perceptions about these practices were investigated. The following table presents this project's main aims, research questions, and methodology for this research project.

Table 1. The aims, research questions, and methodology applied in the research project

Aims	Research Questions	Methodology	Publication
To investigate the current prevalence of supportive care use (including CAM) among children diagnosed with cancer in Norway	To investigate I) what supportive care and CAM modalities are being used and II) what are the associations of use	A cross-sectional survey among members of the Norwegian Children's Cancer Society (Barnekreftforeningen)	1
To estimate whether CAM is effective in reducing the adverse effects of conventional cancer treatments in children and young adults with cancer	To review the research literature to identify any CAM modalities used to treat adverse effects of conventional cancer treatment among children and young adults and, if data allows it, perform a meta-analysis to assess the beneficial effect of these modalities	Perform a systematic review and meta-analysis	2
To investigate if supportive care and CAM modalities used to treat adverse effects from conventional cancer treatment in childhood cancer are associated with risks	To identify observational, quasi-experimental, and qualitative studies that investigate CAM modalities used for treating adverse effects of conventional cancer treatment and 2. investigate the safety of the included modalities, and 3. investigate the methodological quality of the included studies	Perform a systematic review	3

To gather nuanced information, through qualitative research, about experiences that healthcare providers have about the use of CAM and other supportive care modalities in children and adolescents with cancer and adolescents with cancer	To investigate the clinical experiences and perceptions that pediatric oncology experts, conventional healthcare providers, and CAM providers have with the use of supportive care, including CAM	Semi-structured interviews with 22 different healthcare providers, including oncology experts (doctors and nurses), conventional healthcare providers (physiotherapist, nutritionists), and CAM providers (acupuncturists, healers)	4
To investigate, through qualitative research, how healthcare providers handle risks and patient safety associated with the use of supportive care modalities in childhood cancer	To explore how healthcare providers handle risks and how they evaluate patient safety when patients combine CAM and other supportive care modalities with conventional medicine in clinical practice, and how they communicate and inform parents about the use of these modalities in childhood cancer	Semi-structured interviews with 22 different healthcare providers, including oncology experts (doctors and nurses), conventional healthcare providers (physiotherapist, nutritionists), and CAM providers (acupuncturists, healers)	5

9 Methods and Results for this research project

Each study will be presented separately in this section, with the following paragraphs:

- Specific aim of the study
- Methodology applied in the study
- Abstract as presented in the published or submitted articles

The reason for this approach was that each study has different but interdependent methodologies.

9.1 General methodology applied (summary- mixed methods)

Mixed method design is a research approach where quantitative and qualitative research methods, approaches, concepts, and techniques are mixed or combined in one research project (61, 62). It allows the investigator to select components that offer the best research method for the research question. In this research project, qualitative methods were used to explore the study participants' experiences and perceptions of using supportive care modalities, and quantitative research was used to investigate the effectiveness, safety, and prevalence of use of these modalities.

9.2 Paper 1

9.2.1 Aim

The global aim was to investigate the current prevalence of supportive care use, including CAM, among children diagnosed with cancer in Norway.

The specific aims were:

I) to investigate what modalities are being used.
II) to investigate the associations of use.

9.2.2 Method

In this study I used a cross-sectional study design to estimate the prevalence of a condition or health care modalities. All information in a cross-sectional study is collected at a point in time, therefore it provides a snapshot of the current situation. This is often called point

prevalence, which allows the investigator to obtain developmental data in a relatively short period of time (63) .

9.2.3 Abstract paper 1

Purpose: Survival rates among children with cancer have increased in high-income European countries in the last 30 years. The scientific literature on the prevalence of CAM use among children with cancer is scarce. Hence, this study aims to determine the prevalence and associations of supportive care use, including CAM, among children with cancer in Norway.

Methods: A cross-sectional survey was conducted in Norway among parents (n=117) of children with cancer. Respondents were recruited through the Norwegian Children's Cancer Society and its local chapters.

Results: Over two-thirds (67%) of the respondents reported their children used at least one supportive care modality to cope with the adverse effects of cancer treatment. Among those who reported supportive care use, 47 % used CAM. Thirty-seven percent visited a health care/CAM provider, 43% attended a leisure activity, and 37 % used natural remedies. For more than half of the children who used supportive care, parents reported that the modalities helped reduce the adverse effects of cancer treatment. Moreover, 7% reported that their children experienced adverse effects from the supportive care modalities.

Conclusions: In Norway, children with cancer widely use supportive care to cope with the adverse effects of cancer treatment. As the survival rates increase and pharmacological treatments are unavailable or have a poor impact on common adverse effects of cancer treatment, providers may consider engaging in conversations with families regarding treatment options and quality of care that include supportive care modalities.

9.3 Paper 2

9.3.1 Aim

The specific aims were:

I) to review the research literature to identify any CAM modalities used to treat adverse effects of conventional cancer treatment among children and young adults.
II) to perform a meta-analysis to assess the beneficial effect of possible CAM modalities (if data allows it).

9.3.2 Method

The purpose of performing systematic reviews is to provide clinicians, policymakers, healthcare managers, and other stakeholders with quality information on the effect, safety, feasibility, and appropriateness of different healthcare interventions (64). A meta-analysis is a statistical combination of results from two or more studies.

9.3.3 Abstract paper 2

Background: Dealing with the symptom burden of cancer diagnosis and treatment has led parents to seek different self-management strategies, including Alternative and Complementary Medicine (CAM). The aim of this study was to perform a systematic review and meta-analysis about the use and effect of CAM modalities to treat adverse effects of conventional cancer treatment among children and young adults.

Methods: Six scientific research databases were used to identify randomized controlled trials (RCTs) from 1990 to September 2020. Included studies investigated the use of CAM to treat cancer treatment related adverse effects in children and young adults compared to controls.

Results: Twenty RCTs comprising 1,069 participants were included in this review. The included studies investigated acupuncture, mind–body therapies, supplements, and vitamins for CINV, oral mucositis, and anxiety among children and young adults who underwent conventional cancer treatment. Seven studies (315 participants) were included in the meta-analysis. The overall effect of CAM (including acupuncture and hypnosis only) on chemotherapy-induced nausea and/or vomiting and controls was statistically significant with a standard mean difference of -0.54, 95% CI [-0.77, -0.31] $I^2 = 0\%$ ($p < 0.00001$). There was a significant difference between acupuncture and controls ($n = 5$) for intensity and/or episodes

of CINV with an SMD -0.59, 95% CI [-0.85, -0.33] ($p < 0.00001$). No significant difference was found between hypnosis and controls (n = 2) for severity or episodes of CINV with an SMD -0.41, 95% CI [-1.09, 0.27] $I^2 = 41\%$ ($p = 0.19$).

Conclusion: Current evidence from this meta-analysis of randomized controlled trials shows that CAM, including acupuncture and hypnosis only, is effective in reducing chemotherapy-induced nausea and vomiting in children and young adults. More rigorous trials and long-term effects should be investigated if acupuncture and hypnosis are to be recommended for clinical use.

9.4 Paper 3

9.4.1 Aim

The specific aims were:

I) to identify observational, quasi-experimental, and qualitative studies that investigate CAM modalities used for treating adverse effects of conventional cancer treatment.

II) to investigate the safety of the included CAM modalities.

III) to investigate the quality of the included studies.

9.4.2 Method

When performing systematic reviews, the investigators have the potential to collect all empirical evidence included in the eligibility criteria to answer a specific research question. This approach was used to investigate safety issues related to the use of CAM modalities in childhood cancer care.

9.4.3 Abstract paper 3

Background: Complementary and Alternative Medicine (CAM) is widely used around the world to treat adverse effects derived from cancer treatment among children and young adults. Parents often seek CAM to restore and maintain the child's physical and emotional condition during and after cancer treatment.

Objectives: The objectives of this review were (i) to identify literature that investigates CAM use for treating adverse effects of conventional cancer treatment, (ii) to investigate the safety of the included CAM modalities, and (iii) to evaluate the quality of included studies.

Methods: Five scientific research databases were used to identify observational, quasi-experimental, and qualitative studies from January 1990 to May 2021. Included studies investigated the use of CAM to treat adverse effects of cancer treatment in childhood cancer. Results: Fifteen studies were included in this review. Ten quasi-experimental, three observational studies (longitudinal/prospective), two qualitative studies, and one study with a quasi-experimental and qualitative arm were identified. Less than half (n = 6; 40%) of the studies included reported adverse effects for the CAM modality being studied. Among the studies that reported adverse effects, they were mostly considered as direct risks, as 13% reported mainly bleeding and bruising upon acupuncture treatment and dizziness with yoga treatment. All adverse effects were assessed as minor and transient. CAM modalities

identified for treating adverse effects of cancer treatment were alternative medical systems, manipulative and body-based therapies, biologically based therapies, and mind-body therapies. CAM modalities were used to alleviate anxiety, pain, toxicity, prevent trauma, and improve health-related quality of life, functional mobility, and physical activity levels. All studies assessed scored 70% or above according to the Joanna Briggs Institute critical appraisal for study quality checklists.

Conclusion: Most of the studies (58.3%) included in this review did not report adverse effects from CAM modalities used to treat adverse effects of cancer treatment in children and young adults. This lack of safety information is of concern because parents need to know whether the modality represents an extra burden or harm to the child. To improve awareness about safety in the field, a universal and uniform reporting system for adverse effects in CAM research is needed.

9.5 Paper 4

9.5.1 Aim

The specific aim was:

I) To gain insight into the clinical experiences and perceptions that pediatric oncology experts, conventional healthcare providers and CAM providers in Norway, the United States, the Netherlands, Germany, and Canada have with the use of supportive care, including CAM, among children (0–9) and adolescents (10–19) with cancer.

9.5.2 Method

Semi-structured interviews were employed in this study. The interviews focused on capturing lived experiences which involved an informal, interactive process aimed at invoking a comprehensive account of the participants experience of the phenomenon (65).

9.5.3 Abstract paper 4

Background: The aim of this study is to gain insight into the clinical experiences and perceptions that pediatric oncology experts, conventional healthcare providers, and complementary and alternative medicine (CAM) providers in Norway, Canada, Germany, the Netherlands, and the United States have with the use of supportive care, including CAM among children and adolescents with cancer.

Methods: A qualitative study was conducted using semi-structured in-depth interviews (n = 22) with healthcare providers with clinical experience working with CAM and/or other supportive care among children and adolescents with cancer from five different countries. Participants were recruited through professional associations and personal networks. Systematic content analysis was used to delineate the main themes. The analysis resulted in three themes and six subthemes.

Results: Most participants had over ten years of professional practice. They mostly treated children and adolescents with leukemia who suffered from adverse effects of cancer treatment, such as nausea and poor appetite. Their priorities were to identify the parents' treatment goals and help the children with their daily complaints. Some modalities frequently used were acupuncture, massage, music, and play therapy. Parents received information about

supplements and diets in line with their treatment philosophies. They received education from the providers to mitigate symptoms and improve the well-being of the child.

Conclusions: Clinical experiences of pediatric oncology experts, conventional health care providers, and CAM providers give an understanding of how supportive care modalities, including CAM, are perceived in the field and how they can be implemented as adaptational tools to manage adverse effects and to improve the quality of life of children diagnosed with cancer and the families.

9.6 Paper 5

9.6.1 Aim

The specific aims were:

I) to explore healthcare providers' perceptions of risk and how they evaluate patient safety when patients combine CAM and other supportive care modalities with conventional medicine in clinical practice.
II) how they communicate and inform parents about the use of these modalities in childhood and adolescent cancer care.

9.6.2 Method

This study draws on qualitative data obtained through individual semi-structured interviews among pediatric oncology experts and CAM providers in Norway and internationally. This type of design is appropriate when existing theories and research literature is limited (66). For the analysis of text data, a qualitative content analysis was employed.

9.6.3 Abstract paper 5

Introduction: Although more than 300,000 children and adolescents worldwide are diagnosed with cancer yearly, little research has been conducted investigating how healthcare providers consider risk and patient safety connected with supportive care (including complementary and alternative medicine (CAM)) in this age group. This study aimed to explore how different healthcare providers perceive and evaluate risk when patients combine supportive care and conventional medicine in clinical practice and how they communicate and inform parents about the use of these modalities.

Materials and Methods: In-depth semi-structured interviews were conducted with 22 healthcare providers with expertise in treating pediatric oncology patients from five countries. Systematic content analysis was conducted using Nvivo 1.61. The analysis resulted in three themes and eight subthemes.

Results: Generally, participants were cautious about implementing unproven new procedures or tests when recommending supporting care modalities to parents of children and adolescents with cancer. The most important criterion when recommending a modality was evidence for safety based on a risk/benefit evaluation. Negative interactions with conventional medicine

were avoided by using the half-life of a drug approach (the time it takes for the amount of a drug's active substance in the body to reduce by half). Depending on the patient's severity of symptoms, less invasive modalities were used. To enhance safety, participants practiced open and egalitarian communication with parents.

Conclusion: Healthcare providers reported using a variety of approaches to achieve a safe practice when parents wanted to combine supportive care and conventional cancer treatment. They emphasized that these modalities should be foremost safe and not become an extra burden for the patients. Providers highlighted patient-centered care to meet the individual's specific health needs and desired health outcomes. A lack of national and regional standardized training programs for supportive care in pediatric oncology was considered a hazard to patient safety.

10 Discussion

The findings of this research project contribute to the pediatric oncology field in different aspects. First, parents of children with cancer in Norway often use supportive care modalities to alleviate health complaints derived from cancer diagnosis and treatment. Second, the meta-analysis found that CAM, including acupuncture and hypnosis, reduces chemotherapy-induced nausea and vomiting. Third, safety is healthcare providers' primary criterion when recommending CAM modalities; however, research lacks reporting direct and indirect risks. Forth, healthcare providers use tools such as the half-life method to accommodate the use of CAM modalities and ensure the child's safety. Fifth, providers use different supportive care modalities (such as using ginger and peppermint teas) to help children with health complaints derived from chemotherapy such as nausea. Lastly, the interviews with the providers highlight the need for adequately trained CAM providers who can manage the burdens these children and their families experience.

10.1 Concepts used in this research

The research presented in this project shows that parents of children with cancer seek different ways to help their child manage burdensome symptoms and improve their quality of life. Below, the three concepts presented in this research will be discussed in more detail.

10.1.1 Supportive care

Supportive care is the provision of the necessary services for those living with or affected by cancer to meet their physical, emotional, social, psychological, informational, spiritual, and practical needs during the cancer continuum, encompassing issues of survivorship, palliative care, and bereavement (12). The supportive care framework was first conceptualized as a tool to aid cancer professionals in understanding the kind of help cancer patients and their families have and how it can be delivered to them. The concept of supportive care is broad, and in this research project, supportive care is defined as a concept encompassing both conventional modalities and CAM. According to its definition, the supportive care framework does not include the child’s primary cancer treatment (such as chemotherapy, radiation, and surgery) (67). See Figure 3.

When parents use a supportive care modality for their child, they are not always interested in how it is defined. Whether it is defined as supportive care, CAM, integrative medicine, or any other definition established by researchers is of less concern for the parents. They merely look

for modalities that may lessen the burdens derived from cancer diagnosis and treatment (68). Although definitions might not be relevant in everyday life, for research, implementation, enforcement of laws, and funding purposes, those definitions gain relevance. For parents, how the modality is regulated impacts their finances. A service not included in the official healthcare system must be paid out of pocket.

10.1.2 Complementary and alternative medicine (CAM)

The definition of what is considered and regulated as CAM fluctuates by country. What is understood as CAM has become more complex as societies evolve and new trends, health paradigms, and medical treatments emerge. The status of CAM in Europe is characterized by heterogeneity in all aspects, including the terminology used, the methods provided, the prevalence, and the national legal status and regulation. The diversity and plurality of opinions and attitudes towards CAM, even within a relatively small academic CAM community, renders a coordinated European approach to CAM research difficult (69).

In Norway, the definition of CAM derives from the Norwegian Act on Alternative Treatment of Disease (26), which aims to address patient safety and regulation of CAM practice (70). NAFKAM has the mission to develop knowledge about how CAM (alternative treatment) may possibly support users with health complaints and illnesses (71). The Norwegian health authorities have expressed to NAFKAM that it is difficult to make general statements on what is understood as an alternative treatment. Currently, it is assessed on a case-by-case basis. Therefore, an article was published on the topic in 2023 by Norheim et al. (70). The article aimed to explain the current spectrum of what could be considered alternative medicine in Norway (and the gray areas in the field). They found that alternative treatment has five gray areas, which intercept with several services and offerings. These five areas are *adjunctive medical treatment*, *folk medicine*, *integrative treatment*, *self-treatment and self-health*, and *other services* (Figure 3).

Following Norheim et al. (70), ad*junctive medical treatment* (such as dietary supplements and vitamins) is used together with the primary conventional treatment to assist the primary treatment. This is considered CAM when used in excess of the recommended dosage, outside of what is medically instructed by healthcare personnel, or used outside the conventional health service to support health problems or reduce symptoms thereof.

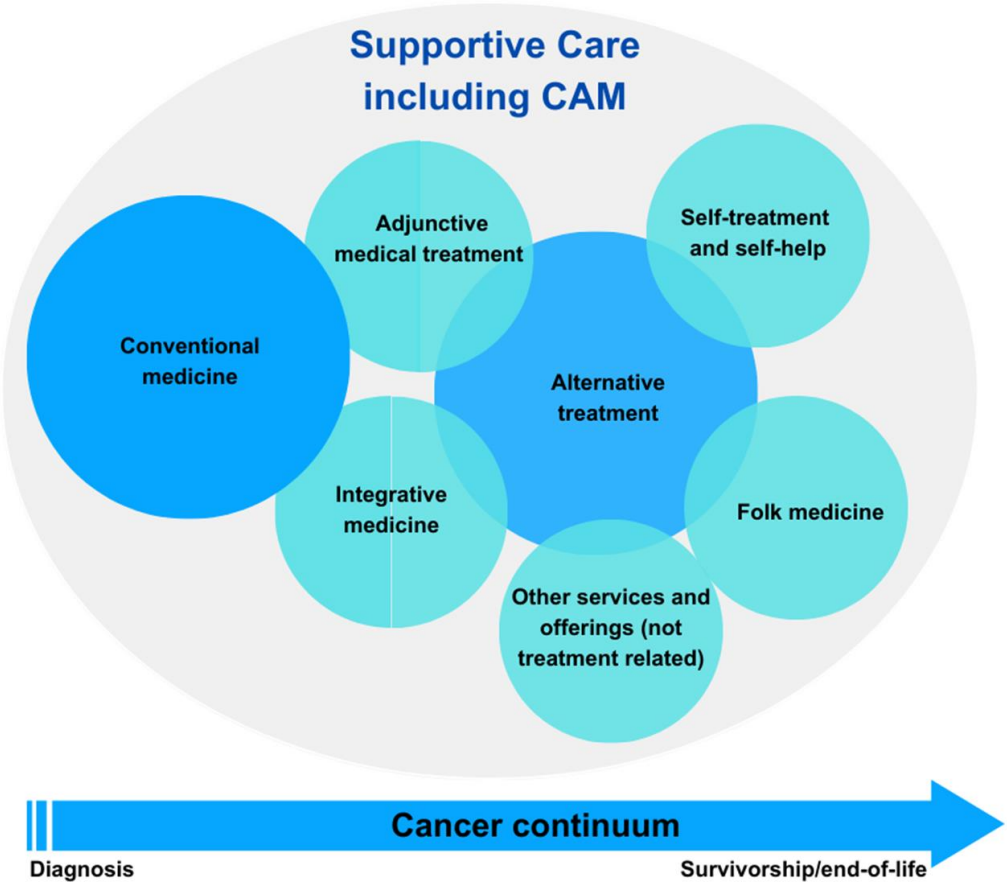

Figure 3. The concepts of supportive care and CAM in this research project. Supportive care among children with cancer includes conventional medicine (apart from primary cancer treatment), CAM modalities, and modalities considered gray areas. Among children with cancer, these modalities can be interpreted as modalities chosen by their parents. Supportive modalities are offered throughout the cancer continuum from diagnosis through survivorship and/or to the end of life. Figure derived from Norheim AJ, Kristoffersen AE, Jong M. Alternative treatment and gray areas. Tidsskrift for Den Norske Legeforening. 2023

Self-treatment and *self-help* techniques are modalities people use independently for health purposes and without professional supervision (such as yoga or meditation) (70). Among children, these can be interpreted as modalities chosen by their parents. If these modalities are offered for health-related purposes in a patient-provider relationship outside the conventional health service, they are considered CAM. This area contains some gray areas as it is hard to establish when these modalities become treatment with health-promoting purposes.

Folk medicine (such as herbs) comprises health aspects of traditional knowledge that are developed within the folk beliefs of various societies and are founded in beliefs and experiences (70, 72). This area is considered CAM if it is offered within a patient-provider relationship. Rituals and other religious practices are not covered by the Norwegian Act on Alternative Treatment of Disease unless they occur in a commercial setting.

Non-related services, such as beauty care, well-being treatments, and personal development present a legal gray area, especially when dealing with non-licensed healthcare professionals (70).

Research shows that patients who use CAM do so in combination with conventional medicine and spend significantly more money on conventional health care services than non-CAM users (73). Further, CAM use by cancer survivors is associated with more visits to conventional health care services compared to individuals who do not use CAM (74). However, sometimes it may be unclear which form of healthcare patients use (70). Norway has a voluntary registration scheme; approximately 80% of alternative provider associations participate in this register (the Norwegian Register of Complementary Providers) (28). Until recently, an advantage of being listed in the register was an exemption from value-added tax (VAT) on services offered. Since the exemption from VAT ended in 2021, the number of registered CAM providers has decreased substantially (34 % in one year). The decrease in registrations has made the register less useful in defining alternative treatment in Norway (70).

10.1.3 Integrative oncology

Integrative oncology uses both conventional and complementary medicine to meet the needs of each individual patient. The concept focuses on the whole person and includes principles of individualization, dynamism, synergism, holism, and collaboration (75). Integrative oncology is "a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments" (76). Its focus is to support patients and their families through the cancer continuum (from prevention through survival or end-of-life), and it aims to uphold the inherent ability of each person to heal (75). Different integrative pediatric oncology programs exist in HIC outside of Norway, such as in the US and Germany (77, 78). In Norway, integrative medicine would be subject to the Norwegian Health Care Professional Act regardless of where it is offered (27).

A majority of Norwegian hospitals offer some sort of CAM (79). A study from 2013 found that CAM was offered in 64.4% of Norwegian hospitals. No major differences were found between public and private or between somatic and psychiatric hospitals. Acupuncture was the most frequent modality, followed by art, expression therapy, and massage (79). Moreover, Vardesentrene (a free meeting place for everyone affected by cancer, located at seven

hospitals in the country operated as a collaboration between the Norwegian Cancer Society and the four health trusts in Norway) offers activities such as medicinal yoga and massage (80). Although some CAM modalities, such as for example acupuncture and music therapy, are offered at different hospitals in the country, integrative medicine or integrative oncology are not known as such in Norway(81, 82, 83, 84).

As illustrated in Figure 3, supportive care is sought by children and their families from diagnosis through survival or end of life. Survival is defined as the balance of life of an individual from the time of cancer diagnosis (85). A study conducted in Norway shows that among childhood cancer survivors, 62% reported having at least one late effect of cancer treatment. Of those, 69% reported not receiving follow-up care for late effects (86). Since many childhood cancer survivors carry the burden of managing late effects in everyday life, it is imperative that different CAM modalities are explored. Integrated with conventional treatment, CAM modalities can support the patients in their healing as they evolve over time and in accordance with their own and their family's needs and values.

10.2 Methodological aspects

10.2.1 Cross-sectional study

Cross-sectional studies are a type of observational study in which a "snapshot" is taken of the proportion of individuals in the population that are, for example, diseased and non-diseased at one point in time (63). Cross-sectional studies can be divided into descriptive and analytical studies. Descriptive cross-sectional studies aim to characterize the prevalence of one or multiple health outcomes within a particular population (87). Hence they are considered good tools for measuring prevalence (88). An advantage of conducting cross-sectional surveys is that they are inexpensive and straightforward to implement. The disadvantage is that they are not best suitable for hypothesis testing.

Data for this project were collected using a cross-sectional survey to assess the prevalence of supportive care use to manage health complaints derived from cancer treatment among children with cancer in Norway. The I-CAM-Q questionnaire designed to collect information on the use of CAM among different populations was adapted to collect data for this project (89). The I-CAM-Q was modified based on previous knowledge from the existing literature and interviews conducted with parents of children with cancer in Norway (68). The survey was implemented from January to December 2021. The chief adviser of scientific

development at The Norwegian Children's Cancer Society reviewed the questionnaire before distributing it to their members. One hundred and seventeen parents responded to the survey. The average response time was 20 minutes. After implementation, a respondent contacted the candidate asking if a question could be added. The respondent's child had died from cancer, and the person in question wanted to be able to have this option in the questionnaire. The question was not previously added because the research team agreed it might be sensitive. After contacting the parent and further inquiring about the input, a question was added at the beginning of the survey asking if the child had died.

Dillman's tailored design methods were used to develop and implement the survey to ensure a high quantity and quality of responses (90). The Dillman method emphasizes the importance of sending information to the participants that explains the study's rationale. The method also addresses the significance of explaining to the participants that this research would be impossible without their participation and help. The method also includes sending reminders and thanking respondents who completed the questionnaire.

Parents were recruited through the Norwegian Children's Cancer Society and its regional chapters. Reminders were posted three times in the Children's Cancer Society newsletter and its local chapters' Facebook pages. To incentivize parents to participate, they were given the opportunity to sign up to win one of ten gift cards worth 1,000 NOK each. Furthermore, the survey was distributed through an organization highly trusted by parents of children with cancer in Norway (following the Dillman method).

10.2.1.1 Validity

In quantitative research, validity is the accuracy of a measuring instrument. A cross-sectional study is an appropriate method when the main research question is to investigate the prevalence of supportive modalities used in a population (91). *Face validity* is ensured if the respondent in a survey responds meaningfully, as in our survey. *Content validity* is the extent to which the questions used in a survey cover the research area of interest. The questionnaire used in this research project was based on information from relevant scientific literature and the research's team knowledge of the field (92). Additionally, this concept agrees with tests in the field. There is a lack of available, validated instruments assessing the use of supportive care modalities in childhood cancer. The results of this study regarding supportive care use align with what has been reported in other HIC (32, 34, 35, 93, 94, 95), ensuring criterion validity.

Bias refers to any consistent deviation in an epidemiological study, leading to an inaccurate estimation of the connection between exposure and the health outcome (96). Bias can affect the validity of a study (91). Bias can occur during any stage of the research process, and many sources of bias exist (96).

Selection bias occurs when bias is introduced, affecting the study population (96). For this research project, convenience sampling was used (97), a non-probability method that introduces sampling bias to the study because those who responded were not chosen randomly. Although the latter source of error can reduce the study's external validity, it is important to highlight that according to information published by the Norwegian Childhood Cancer Registry (98) and the Norwegian Directorate of Health (24), our sample is comparable to the Norwegian pediatric population in terms of age, cancer diagnosis, and symptom diagnosis.

Non-response bias happens when those unwilling or unable to participate in a survey differ from those who participate (96). It is also possible the survey results were affected by non-response bias as participation in the survey was voluntary. Confidentiality was ensured, and reminders to participate in the survey were sent on three different occasions to mitigate that source of bias. Moreover, the survey was distributed through the Norwegian Children's Cancer Society, an organization whose members are primarily parents of children with cancer.

Response bias is participants' tendency to respond inadequately to a question (99). Response bias can include socially desirable responding (SDR), acquiescence, and extremity bias. SDR refers to "participants presenting a favorable image of themselves" (100). Acquiescence is "the tendency to agree rather than disagree with propositions in general" (99). Lastly, extremity is "the tendency to use extreme choices in a rating scale" (99). Response bias presents itself more often in surveys. Response bias may be present in the survey we implemented. There were questions related to non-conventional medicine and children with cancer; some of those questions could be considered socially sensitive by parents. The researchers attempted to limit the previously mentioned bias by using neutral language and ensuring different question formats were used.

Recall bias occurs when there are differences in the recall of memories of significant situations (101). It is possible recall bias happened among the respondents in the survey.

Parents were asked to participate if their children had ever been diagnosed with cancer. Suppose the child received a cancer diagnosis many years ago. Parents may not recall all the supportive care modalities used to help their child cope with cancer diagnosis and treatment. The latter might lead to inaccurate responses.

10.2.1.2 Reliability

Reliability refers to the degree to which the results are replicable (102). Although the survey used for this research project is not validated, the measurements were asked consistently for all modalities. Standardized instruments were used when possible, such as the self-rated health question used in many health questionnaires (103). The survey was self-administered; therefore, the instructions and wording were the same for all parents. All of the latter provide consistency in the measurements used.

10.2.1.3 Generalizability

The sample size of a survey is important because it can influence the research findings. The research team attempted to increase the sample size by advertising the survey at different times through the main newsletter distributed by the Children's Cancer Society and by distributing the survey link to the Facebook groups of the local chapters of the cancer society in 13 regions throughout Norway. The research group also attempted unsuccessfully to recruit parents through the pediatric oncology units of the four leading hospitals in Norway. Although several attempts were made to increase the sample size, it is important to acknowledge that the sample size of the survey (n=117) did not reach the size dictated by the power calculation. The sample size is small, so checking the tests' assumptions is difficult, and it is hard to extrapolate the results to the entire population. Despite a small sample size, the sample resembles the Norwegian pediatric population when considering age (24), cancer diagnosis (104), and symptom diagnosis (86, 105, 106, 107). Furthermore, the study is important because it is the first to measure supportive care use among pediatric oncology patients in Norway (108, 109).

10.2.2 Semi-structured interviews

A qualitative research approach by means of interviews is presented in this research project. . Semi-structured interviews were used to collect the experiences and perceptions of healthcare providers working with children with cancer who use CAM. Qualitative interviews are attempts to understand the world from the subjects' point of view and to unfold the meaning

of peoples' experiences (66). A semi-structured interview is neither a highly structured questionnaire nor an open conversation. It follows an interview guide that includes suggested questions (66). The guide consists of open-ended, planned, and unplanned follow-up questions that enable the participant to provide nuanced answers (110).

The interview guide used in this research included questions like: *What modalities have you used/recommended to your pediatric cancer patients? When do you recommend the modality? Did your patient have any adverse effects from the modality?* It was developed based on a review of the literature and the investigators' knowledge of the field. Although the questions were organized under different topics, they served just as a guide, and the order in which they were asked varied by interview. All the interviews started by asking participants about their professional background and the group of children, and the diagnosis they most often treated. Then participants were asked about their experiences with CAM modalities. Depending on the responses to the previous questions, the interviewer would ask questions on different topics, such as the safety or effectiveness of the modalities. The interviews lasted, on average, sixty minutes and were conducted face-to-face or through a cloud-based video conferencing tool (Teams).

A conventional content analysis was considered a suitable analysis for this research project as to answer the research questions in the qualitative studies. Content analysis is a method used to subjectively interpret qualitative data through a systematic classification process of coding and identifying themes or patterns (111). Following the immersion of the data, codes were developed inductively. Inductive category development means that" researchers immerse themselves in the data to allow new insights to emerge" (111). Some of the codes that emerged were interactions, safety, efficacy, CAM treatment, empowerment, etc. The codes were then categorized into subthemes based on how they related. The subthemes were then developed into the themes presented in the papers.

In qualitative research, objectivity is irrelevant as the interviewer can be considered the "instrument," and the participants can contribute to the data analysis and interpretation. Hence validity, reliability, and generalizability become essential in evaluating the quality of qualitative research (66).

10.2.2.1 Validity

Validity pertains to whether the ultimate result, typically referred to as a "model," faithfully represents the content it intends to convey (102). Internal validity can be assessed through transparency. Transparency is crucial because it enables the readers not only to learn about the trustworthiness of a study but also to replicate it or adopt the study's methods and strategies in their own future studies. A basic definition of transparency holds that researchers must disclose all relevant research processes honestly, detailing aspects of the data collection process and the rules used to analyze data (112). Tuval-Mashiach 2017, suggests the following steps to improve transparency in research where the researcher must ask themself three questions: *what I did* (methodology), *how I did it* (Strategy), and why I did it (reflexivity). These reflexive questions pertain to all stages of the research, including planning, data collection, analysis, and writing the final papers. In this research project, the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used to ensure the study's quality and contribute to the study's transparency (113). The method section described the following: guiding paradigm and qualitative approach used, in addition to the name of the method used for analysis. Further, the following strategies were described: What is the approach, unit of analysis, and analysis mechanism? Lastly, we explained why a specific method was used, how the researcher's interest impacted the analysis, how context impacted the interaction with the research and analysis, and the type of reflexivity used. In the present research, the researchers' social backgrounds, assumptions, positioning, and behavior may have impacted the research process. To mitigate the impact, techniques such as note-taking during the interview, discussion about how the interviews were conducted, and interactions with the participants were discussed among researchers through the interviewing process. During the writing process, the context of the manuscripts was discussed among the researcher group to ensure one researcher's assumptions minimally impacted the research.

Internal validity can further be evaluated using quotations from the data to illustrate and confirm the interpretation of the data. Direct quotes were widely used in the qualitative paper presented in this project. Two co-authors with experience in qualitative research contributed to the reflection of the codes and the analyzing process, with input from the research team.

10.2.2.2 Reliability

Reliability can be assessed through dependability (114). The interviews used for this research project were conducted by researchers with previous experience conducting interviews. They

were aware of not formulating leading questions that could influence the participants' answers. All the research team members have experience with qualitative research and have contributed to reflections on the themes and codes and the analytical process. The latter is understood as triangulation in qualitative research and is an analytical approach that enhances the reliability of the studies (115).

10.2.2.3 Generalizability

Transferability refers to the degree to which the results of qualitative research can be generalized or transferred to other contexts or settings. Transferability is established by providing readers with evidence that the research findings could apply to different contexts, situations, times, and populations (66). According to the qualitative methodology, the research findings are less transferable to other populations. However, this research aims to explain how the findings are applicable. A study is considered to meet the criterion of transferability when "its findings can fit into contexts outside the study situation and when clinicians and researchers view the findings as meaningful and applicable in their own experiences" (116). This research project's findings apply to parents of children with cancer and healthcare providers who work with this patient group.

10.2.3 Systematic reviews

A systematic review aims to minimize bias by using reproducible methods to find, critically appraise, and synthesize pertinent available evidence (101). Meta-analysis is used to obtain the best-estimated effect of an intervention (96). Although not always appropriate to use, meta-analysis quantitatively synthesizes the data collected in systematic reviews (117). The research project included two systematic reviews. One systematic review included RCTs, and the other included observational and quasi-experimental studies. The protocols for both reviews were submitted and registered at The International Prospective Register of Systematic Reviews (PROSPERO). They were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (118).

The focus question for the systematic review of RCT was "Which CAM modalities are used to treat adverse effects of conventional anti-cancer treatment among children and young adults?" The question for the second review was, "Are CAM modalities used in childhood cancer (to treat adverse effects of conventional cancer treatment) associated with adverse effects?". The PICOS (Population, Intervention, Comparison(s), Outcome, and Study type)

construct was used while searching for the articles in the review and during the synthesis of the included studies.

Although standard procedures were followed to ensure the validity, reliability, and generalizability of the reviews, the findings ought to be understood considering their inherent limitations. Although the help of a librarian was enlisted, different databases were searched, and different languages were included, some studies might have been overlooked. Feasibility and pilot studies were included due to the limited body of work in the field. Some of the studies included investigated children but also included young adults. The limited research on supportive care modalities creates another limitation, as not all the supportive care modalities used to manage adverse effects were included in these reviews. Lastly, for the observational and quasi-experimental studies, the articles included were heterogenous; therefore, the research team could not conduct a meta-analysis.

10.2.3.1 Validity

In a systematic review, it is essential to conduct searches to identify all relevant studies for a review (117). Therefore, the literature searches were conducted with the help of a librarian (with professional competence in performing systematic searches), thereby ensuring the study's validity. Medical subject headings (MESH) and text words were included. Articles were searched in six databases for the RCTs and five for the observational studies. Studies were searched in seven different languages. Furthermore, the references list of the included articles was searched, and gray literature was searched in google scholar and books. The meta-analysis conducted among the RCTs used the Cochrane Collaboration software Review Manager v.5.4.

10.2.3.2 Reliability

To ensure reliability, two authors worked on selecting, extracting, and assessing the quality of the articles. The Joanna Briggs Institute quality assessment of studies tool SUMARI (System for Unified Management) software was used to evaluate the quality of the included studies (119). All disagreements were discussed among the researchers until a consensus was reached. All the procedures and methods used to conduct the reviews are clearly stated to ensure the reproducibility of the reviews.

10.2.3.3 Generalizability

Applicability and clinical relevance are important factors in a systematic review (120). For the reviews presented in this research project, the patients are described in detail to help clinicians decide if they are comparable to their patients. The interventions were described in the review tables. The reviews recorded all the clinically relevant outcomes, and the effect size was reported for the RCTs. Due to the lack of reporting of adverse effects (meaning that the articles did not report absence or presence), it was not possible to report with certainty if the modalities outweighed their potential adverse effects.

10.2.4 Ethics

Vulnerable populations are defined as a disadvantaged subset of the population that requires the highest care, specific additional considerations, and augmented protections in research (121). Children are among the groups that are considered vulnerable populations as they lack the developmental maturity to make autonomous decisions (122). Although the research conducted for this thesis is about children, the research was conducted among their parents as they are the ones that, as legal guardians, make the decisions on the child's health treatments. Compliant with the Norwegian research ethics regulations for research, authorization was obtained from the Norwegian Center for Research Data.

The survey among parents of children with cancer was authorized on the 4th of December 2020, Ref# 493228. Authorization to interview healthcare providers was obtained on the 17th of September of 2021, Ref# 978969. Among parents completing the survey, informed consent was provided before the beginning; parents taking the survey could only complete it once they agreed to participate by ticking a box on the website. Healthcare providers were informed of what the interview would be about when they were first contacted; if they were interested in participating, they were sent a consent form before the interview, which they were asked to sign before beginning the interview. Healthcare providers were also informed their interview would be audio recorded and were verbally asked to confirm their consent before the interview started.

10.3 Implications for research and practice

In its last annual report, the Norwegian childhood cancer registry stated that the emphasis on pediatric cancer has transitioned from mere survival to achieving survival while minimizing long-term effects (5). This research project has the potential to contribute towards achieving

the latter objective by identifying and presenting potential implications for both practice and further research that can be drawn from these findings.

10.3.1 Implications for practice

Although guidelines exist for treating health complaints from cancer diagnosis and treatment among children with cancer, they are not always implemented. The results of this research can provide helpful information on how the findings can be translated into practice.

Previous research (68) conducted in Norway regarding parents' communication needs and CAM has shown that parents want information about CAM. In addition, this research demonstrates that Norwegian parents are using supportive care to help their children. Many people turn to the internet as their first source of information. Health information seeking through the internet can be useful for patients to gain a better understanding of specific modalities to discuss with their healthcare team, but only if the information is comprehensive, high quality, and reliable (123). Consequently, based on this research, NAFKAM aims to develop an evidence-based website or decision aid tool that supports parents and healthcare providers in their decision-making on supportive care modalities to manage health complaints from cancer diagnosis and treatment. Such a website or tool will follow the format of high-quality CAM related to cancer resources (123), such as CAM Cancer (124), and will be developed with input from parents and oncology experts to ensure the information is readily accessible and understandable to the target audience.

It is known from the literature that parents do not always communicate the use of CAM to conventional care providers and that most providers do not have basic knowledge about CAM modalities (68, 125). The results of this thesis can be incorporated into existing information about the use of supportive care, including CAM, to create introductory courses for pediatric oncology providers that can be easily accessed online as continuing education courses. Such courses can also be offered through existing international networks such as the International Society of Pediatric Oncology and the Children’s Oncology Group

The risk and patient safety of supportive care services concerned the healthcare providers interviewed for this project. Furthermore, there is a lack of reporting of direct and indirect risks in the included systematic review studies. Currently, direct risks can be reported by health personnel or patients through a system accessed by the Norwegian Medicines Agency (126). To encourage further voluntary reporting, systems can be implemented specifically for

CAM providers to report adverse effects. Reporting indirect risks is more complex; however, some measures can be taken to diminish them. Assuring standardized training for CAM providers who treat children with cancer can reduce indirect risks; this can be set as a requirement to practice guided by benchmarks established by the WHO for different (CAM) modalities (127).

In countries where integrated medicine is offered as a healthcare service, the healthcare centers where it is offered control the quality of supportive care, including CAM, that the children receive. Among the quality control exercised is hiring well-trained personnel, decreasing the probability of indirect risks. In countries where CAM is not integrated, incorporating evidence-based modalities in healthcare could diminish the likelihood of indirect risks. Another way to decrease indirect risks is to establish a list of well-trained CAM providers through professional societies and distribute those names through different pediatric networks such as the Norwegian Children's Society or NOPHO.

Lastly, practical guidelines can be created in different health professions, such as nursing. To develop and implement clinical guidelines, health personnel, and rehabilitation services providers should be informed and trained on the different supportive care modalities that are safe and effective to improve the child's quality of life.

10.3.2 Implications for research

Research in pediatric oncology and the use of supportive care is limited. Conducting high-quality research in this area can lead to more evidence-based results on the effectiveness and safety of these modalities. Since childhood cancer is a rare disease, it is hard to set up RCTs with large sample sizes to assess the effectiveness and safety of any supportive care modality. However, the field of pediatric oncology owes its success of high survival rates to the multidisciplinary and multi-center consortia that have led to successful RCT studies (11). The already established collaboration within nations and across borders can also be used to investigate different kinds of supportive care, including CAM, that can help manage the late effects of cancer treatment.

Added to the complexity of conducting research with a rare disease is the complexity of conducting CAM research. Although RCTs are considered the gold standard method in research, they cannot assess long-term outcomes and how each patient’s sole physical, social, and cultural context may affect the treatment outcomes. Hence it is important to give other

study types (such as crossover trials, observational studies, or qualitative studies) similar relevance to achieve conclusive evidence on different modalities, just like it is attempting to be done with conventional treatments (128). For example, prospective and retrospective observational studies can be used to identify the late and long-term effects of cancer, and qualitative studies can further help to identify possible indirect risks and to map experiences in clinical practice systematically.

Apart from mapping experiences in clinical practice from qualitative interviews, a system should be implemented for both conventional and non-conventional providers to be able to record and communicate their experiences from clinical practice. Such system should be methodologically robust such that the information there can be analyzed to provide possible areas where research should be conducted.

Aside from the different research methods, the quality must be optimal. The research of this project found that studies neglect to report whether adverse effects emerged or not from the modalities they studied. It would be wise to include, for example, such points among methodological quality checklists for CAM research. Furthermore, the measuring tools researchers use to access similar outcomes and modalities should be informed on previous research and, if possible, standardized. Using different measuring tools hinders a field such as supportive care in pediatric oncology as small-size studies are common, and it is difficult to combine research, for example, in meta-analysis, to reach conclusive results.

The limited research in pediatric oncology and supportive care modalities indicates that future studies are needed. Future studies should be conducted on safety, effectiveness, and other aspects such as dosage (i.e., amount or/and intensity of massage treatments). Also, further research should be conducted in modalities such as acupuncture to assess the effectiveness of less invasive methods such as acupressure vs. needles. Moreover, research is also needed on tools and techniques to increase communication about these modalities among parents, conventional, and CAM providers in different variations.

A theme in this research was the empowerment of parents provided by supportive care through the cancer continuum. It is, therefore, essential to research the mechanisms that provide empowerment and resilience among childhood patients and their families, as well as the decision process they experience to use supportive care and CAM.

11 References

1. National Center for Complementary and Integrative Health. Complementary, alternative, or integrative health: What's in a name? Bethesda, Maryland 2018 [cited 2019 04. January]. Available from: https://nccih.nih.gov/health/integrative-health#hed1.
2. National Cancer Institute. NCI Dictionaty of Cancer terms: National Cancer Institute [cited 2023 22 May]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adverse-effect.
3. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT. Prevalence of Complementary Medicine Use in Pediatric Cancer: A Systematic Review. Pediatrics. 2010;125(4):768-76.
4. CureAll framework: WHO Global Initiative for Childhood Cancer. Increasing access, advancing quality, saving lives. Geneva; 2021.
5. Nasjonalt kvalitetsregister for barnekreft [National quality register for childhood cancer]. Årsrapport 2021 [Annual Report 2021]: Kreftregisteret [Cancer Registry]; 2022 [cited 2022 22 May]. Available from: https://www.kvalitetsregistre.no/sites/default/files/2022-06/%C3%85rsrapport%202021%20Nasjonalt%20kvalitetsregister%20for%20barnekreft.pdf.
6. Runciman WB. Shared meanings: Preferred terms and definitions for safety and quality concepts. Med J Aust. 2006;184(10):41-3.
7. Stub T, Musial F, Quandt SA, Arcury TA, Salamonsen A, Kristoffersen A, et al. Mapping the risk perception and communication gap between different professions of healthcare providers in cancer care: a cross-sectional protocol. BMJ open. 2015;5(9).
8. Wardle JL, Adams J. Indirect risks of complementary and alternative medicine. In: Adams J, Andrews GJ, Broom A, Magin P, editors. Traditional, complementary and integrative medicine. Hampshire: Palgrave Macmillian; 2012. p. 212-9.
9. Kania-Richmond A, Metcalfe A. Integrative health care - What are the relevant health outcomes from a practice perspective? A survey. BMC Complement Altern Med. 2017;17(1):548-.
10. The Norwegian Cancer Society. Senskader (English: Late effects) The Norwegian Cancer Society; 2018 [cited 2021 September 07]. Available from: https://kreftforeningen.no/om-kreft/senskader/.
11. Pritchard-Jones K, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G, et al. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. Lancet Oncol. 2013;14(3):e95-e103.
12. Fitch M. Supportive care framework. Canadian Oncology Nursing Journal/Revue canadienne de soins infirmiers en oncologie. 2008;18(1):6-14.
13. SEER Training Modules CRSMCaaD-AHPUSNIoH, National Cancer Institute. 10 April 2023 https://training.seer.cancer.gov/. [
14. Wilkinson E. How has childhood cancer research changed since the 1800s? : Children's cancer and leukemia group; 2022 [Available from: https://www.cclg.org.uk/our-research/research-blog/how-has-childhood-cancer-changed-since-the-1800s.
15. O'Leary M, Krailo M, Anderson JR, Reaman GH. Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. Semin Oncol. 2008;35(5):484-93.
16. Norwegian Cancer Registry. Cancer registry 60 years - The background 2012 [cited 2023 19 April]. Available from: https://www.kreftregisteret.no/Generelt/Nyheter/Kreftregisteret-60-ar---Kartlegging-av-forekomst-av-kreft-1870-1951/.

17. Norwegian Childhood Cancer Registry. Annual Report Oslo: National Competence Service for Solid Tumors in Children and the Cancer Registry; 2009 [Available from: https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/aarsrapport_barnekreftregisteret_2009.pdf.
18. Hellebostad M. Paediatric Oncology in Europe: from national activities to pan-European research approaches: The case of NOPHO: European Society for Paediatric Oncology (SIOP) 2014 [cited 2023 19 April]. Available from: https://www.nopho.org/organization/history/NOPHO%20history%20SIOPE%20news%202014-02.pdf.
19. Seip M. Pediatric hematology and oncology in Norway: a brief historical review. Pediatr Hematol Oncol. 1991;8(4):313-21.
20. Seip M, Åhstrøm L. Frugtbart nordisk samarbeid i pediatrisk hematologi og onkologi English: Fruitful Nordic collaboration in paediatric hematology and oncology: Nordic Society of Paediatric Hematology and Oncology; 2000 [cited 2023 19 April]. Available from: https://www.nopho.org/welcome/frame.htm.
21. World Health Organization Childhood cancer World Health Organization 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/cancer-in-children.
22. Norwegian Childhood Cancer Registry. Annual Report 2019. Results and improvement measures from the national quality register for childhood cancer. Oslo2020 [Available from: https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2020/arsrapport-2019-nasjonalt-kvalitetsregister-for-barnekreft.pdf.
23. Bhakta N, Force LM, Allemani C, Atun R, Bray F, Coleman MP, et al. Childhood cancer burden: a review of global estimates. Lancet Oncol. 2019;20(1):e42-e53.
24. Norwegian Directorate of Health. National action program with guidelines for diagnosis, treatment and follow-up of cancer in children Oslo: Norwegian Directorate of Health 2017 [cited 2023 14 March]. Available from: https://www.helsedirektoratet.no/retningslinjer/kreft-hos-barn-handlingsprogram
25. Evans S, Cousins L, Zeltzer L. Complementary and alternative medicine use in children with cancer2012. 135-42 p.
26. LOV-2003-06-27-64 Lov om alternativ behandling av sykdom mv. Act No. 64 2003 English: Act relating to the alternative treatment of disease, illness, etc,, Helse og omsorgsdepartementet (Ministry of Health and Care Services)(2003).
27. LOV-1999-07-02-64 Lov om helsepersonell m.v. (helsepersonelloven- hlspl) English: Act 1999-07-02-64. Act relating to Healthcare personnel etc, Helse og omsorgsdepartementet (Ministry of Health and Care Services), (1999).
28. Brønnøysundregistrene. Registrere alternativ behandler. In English: Register Complementary and Alternative Provider Brønnøysund: Brønnøysundregistrene; ; 2011 [Available from: https://www.brreg.no/person/registrering-av-utovere-av-alternativ-behandling/.
29. The Norwegian Directorate of Health. Psychologist in Norway Helse Norge [updated December 5, 2022; cited 2023 7 May]. Available from: https://www.helsenorge.no/en/psykisk-helse/psychologist-in-norway/.
30. Diorio C, Lam CG, Ladas EJ, Njuguna F, Afungchwi GM, Taromina K, et al. Global Use of Traditional and Complementary Medicine in Childhood Cancer: A Systematic Review. J Glob Oncol. 2017;3(6):791-800.
31. Afungchwi GM, Kruger M, Hesseling P, van Elsland S, Ladas EJ, Marjerrison S. Survey of the use of traditional and complementary medicine among children with cancer at three hospitals in Cameroon. Pediatr Blood Cancer. 2022;69(8):e29675.

32. Menut V, Seigneur E, Gras Leguen C, Orbach D, Thebaud E. [Complementary and alternative medicine use in two French pediatric oncology centers: A common practice]. Bull Cancer. 2019;106(3):189-200.
33. Rajanandh MG, Scott JX, Reddy JS, Raju JM, Kaniarivi M, Raj KR. Pattern of complementary and alternative medicine use in pediatric oncology patients in a South Indian hospital. Journal of Cancer Research and Practice. 2018;5(1):20-3.
34. Jong MC, Boers I, van Wietmarschen H, Busch M, Naafs MC, Kaspers GJL, et al. Development of an evidence-based decision aid on complementary and alternative medicine (CAM) and pain for parents of children with cancer. Support Care Cancer. 2020;28(5):2415-29.
35. Lüthi E, Diezi M, Danon N, Dubois J, Pasquier J, Burnand B, et al. Complementary and alternative medicine use by pediatric oncology patients before, during, and after treatment. BMC Complement Med Ther. 2021;21(1):96-.
36. Yun H, Romero SAD, Record B, Kearney J, Raghunathan NJ, Sands S, et al. Utilization of integrative medicine differs by age among pediatric oncology patients. Pediatr Blood Cancer. 2019;66(6):e27639.
37. Mora DC, Overvåg G, Jong MC, Kristoffersen AE, Stavleu DC, Liu J, et al. Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young adults: a systematic review and meta-analysis of randomized controlled trials. BMC Complementary Medicine and Therapies. 2022;22(1):1-21.
38. Mora DC, Kristoffersen AE, Overvåg G, Jong MC, Mentink M, Liu J, et al. Safety of Complementary and Alternative Medicine (CAM) treatment among children and young adults who suffer from adverse effects of conventional cancer treatment: A systematic review. Integr Cancer Ther. 2022;21:15347354221105563.
39. Daneshfard B, Shahriari M, Heiran A, Nimrouzi M, Yarmohammadi H. Effect of chamomile on chemotherapy-induced neutropenia in pediatric leukemia patients: A randomized triple-blind placebo-controlled clinical trial. Avicenna J Phytomed. 2020;10(1):58-69.
40. Badr LK, El Asmar R, Hakim S, Saad R, Merhi R, Zahreddine A, et al. The efficacy of honey or olive oil on the severity of oral mucositis and pain compared to placebo (standard care) in children with leukemia receiving intensive chemotherapy: A randomized controlled trial (RCT). J Pediatr Nurs. 2023.
41. Sands S, Ladas EJ, Kelly KM, Weiner M, Lin M, Ndao DH, et al. Glutamine for the treatment of vincristine-induced neuropathy in children and adolescents with cancer. Support Care Cancer. 2017;25(3):701-8.
42. Seifert G, Blakeslee SB, Calaminus G, Kandil FI, Barth A, Bernig T, et al. Integrative medicine during the intensive phase of chemotherapy in pediatric oncology in Germany: a randomized controlled trial with 5-year follow up. BMC Cancer. 2022;22(1):652.
43. Cheng KK, Tan LML. A pilot study of the effect of a home-based multimodal symptom-management program in children and adolescents undergoing chemotherapy. Cancer Rep (Hoboken). 2021;4(3):e1336.
44. Hundert AS, Birnie KA, Abla O, Positano K, Cassiani C, Lloyd S, et al. A Pilot Randomized Controlled Trial of Virtual Reality Distraction to Reduce Procedural Pain During Subcutaneous Port Access in Children and Adolescents With Cancer. Clin J Pain. 2021;38(3):189-96.
45. Fukuhara JS, O'Haver J, Proudfoot JA, Spies JM, Kuo DJ. Yoga as a Complementary and Alternative Therapy in Children with Hematologic and Oncologic Disease. J Pediatr Oncol Nurs. 2020;37(4):278-83.

46. Barbieri M, Zardo W, Frittoli C, Rivolta C, Valdata V, Bouquin F, et al. Osteopathic Treatment and Evaluation in the Clinical Setting of Childhood Hematological Malignancies. Cancers (Basel). 2021;13(24).
47. Norway's National Research Center in Complementary and Alternative Medicine. Strategic plan 2021-2025. Tromsø: NAFKAM; 2021 [cited 2023 11 May]. Available from: https://nafkam.no/sites/default/files/2021-03/Final_210329_%20English_NAFKAM%20strategic%20plan%202021_2025%20%28003%29_0.pdf.
48. Lillegård Bergli T. About us: Norway's National Research Center for Complementary and Alternative Medicine; 2018 [cited 2022 19 May]. Available from: https://nafkam.no/en/about-us.
49. World Health Organization. Patient Safety 2019 [Available from: https://www.who.int/news-room/fact-sheets/detail/patient-safety.
50. National Institute of Health. History of Medicine: Greek Medicine: National Library of Medicine; 2002 [updated 07 February 2012. Available from: https://www.nlm.nih.gov/hmd/greek/greek_about.html.
51. Wardle JJL, Adams J. Indirect and non-health risks associated with complementary and alternative medicine use: an integrative review. European Journal of Integrative Medicine. 2014;6(4):409-22.
52. Fonnebo V, Grimsgaard S, Walach H, Ritenbaugh C, Norheim AJ, MacPherson H, et al. Researching complementary and alternative treatments - the gatekeepers are not at home. BMC Med Res Methodol. 2007;7(1):7-.
53. Myers SP, Cheras PA. The other side of the coin: safety of complementary and alternative medicine. Med J Aust. 2004;181(4):222-5.
54. NCI Dictionary of Cancer Terms. Long-term side effect: National Cancer Institute,; [cited 2023 05 June]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/long-term-side-effect.
55. Fønnebø VM, Kristiansen TT, Falkenberg T, Hegyi G, Hök J, di Sarsina PR, et al. Legal status and regulation of CAM in Europe Gernany: Techn. Univ. Munich; 2012 [cited 2023 14 May]. Available from: www. cam-europe. eu/dms/files/CAMbrella_Reports/CAMbrella-WP2-part_1final. pdf.
56. Borud H. Alvorlig å love helbredelse. Aftenposten. 2014 11 March 2014 https://www.aftenposten.no/norge/i/3j74v/alvorlig-aa-love-helbredelse.
57. Deng GE, Frenkel M, Cohen L, Cassileth BR, Abrams DI, Capodice JL, et al. Evidence-based clinical practice guidelines for integrative oncology: complementary therapies and botanicals. J Soc Integr Oncol. 2009;7(3).
58. Lowrance WW. Of acceptable risk: Science and the determination of safety. 1976.
59. Stub T. Safety of treatment provided by homeopaths homeopathic aggravations, adverse effects and risk assessment. Tromsø UiT The Artict University of Norway; 2014.
60. Chotsampancharoen T, Sripornsawan P, Duangchu S, Wongchanchailert M, McNeil E. Survival Outcome of Alternative Medicine Treatment for Newly Diagnosed Acute Leukemia in Children. Acta Haematol. 2018;140(4):203-8.
61. Burke Johnson R, Onwuegbuzie AJ. Mixed Method Reasearch: A Research Paradigm Whose Time Has Come. Educational Researcher. 2004;33(7):14-26.
62. O'Cathain A, Murphy E, Nicholl J. Why, and how, mixed methods research is undertaken in health services research in England: a mixed methods study. BMC Health Services Research. 2007;7(85).
63. Kesmodel US. Cross-sectional studies – what are they good for? Acta Obstet Gynecol Scand. 2018;97(4):388-93.

64. Lefebvre C, Manheimer E, Glanville J, On behaf of the Cochrane Information Retrieval Methods Group. Searching for studies. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Sussex, England: John Wiley & Sons Ltd; 2012.
65. Quinn Patton M. Qualitative research & evaluation methods. Integrating theory and practice. California: SAGE publications, Inc; 2015.
66. Kvale S. Interviews. An introduction to qualitative research interviewing. Thousand Oaks California: Sage; 1996.
67. Loeffen EAH, Kremer LCM, Mulder RL, Font-Gonzalez A, Dupuis LL, Sung L, et al. The importance of evidence-based supportive care practice guidelines in childhood cancer-a plea for their development and implementation. Support Care Cancer. 2017;25(4):1121-5.
68. Stub T, Quandt SA, Kristoffersen AE, Jong MC, Arcury TA. Communication and information needs about complementary and alternative medicine: a qualitative study of parents of children with cancer. BMC Complement Med Ther. 2021;21(1):85.
69. Community Research and Development Information Service (CORDIS). Final Report Summary - CAMBRELLA (A pan-European research network for complementary and alternative medicine (CAM)). 2013.
70. Norheim AJ, Kristoffersen AE, Jong M. Alternative treatment and gray areas. Tidsskrift for Den norske legeforening. 2023;143(7).
71. Nasjonalt forskningssenter innen komplementær og alternativ medisin (NAFKAM). Strategiplan 2021-2025. https://nafkamno/sites/default/files/2021-04/Final%20text_210406%20Norwegian%20Strategic%20Plan%202021_2025%20pdf. 2021.
72. World Health Organization (WHO). Traditional, complementary and integrative medicine World Health Organization; 2023 [cited 2023 29 May]. Available from: https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine#tab=tab_1.
73. The National Research Center in Complementary and Alternative Medicine (NAFKAM). NAFKAM-undersøkelsen 2022, Bruk av alternativ behandling i Norge. English: The NAFKAM population survey 2022. Use of complementary and alternative medicine in Norway Tromsø2022 [cited 2017 15.08]. Available from: http://nifab.no/hva_er_alternativ_behandling/tall_og_fakta/tidligere_undersoekelser/nafkam_undersoekelsen_2012.
74. Nakandi K, Mora D, Stub T, Kristoffersen AE. Conventional health care service utilization among cancer survivors that visit traditional and complementary providers in the Tromsø study: a cross-sectional study. BMC Health Serv Res. 2022;22(1):53.
75. Leis AM, Weeks LC, Verhoef MJ. Principles to guide integrative oncology and the development of an evidence base. Current Oncology. 2008;15(s2):83-7.
76. Witt CM, Balneaves LG, Cardoso MJ, Cohen L, Greenlee H, Johnstone P, et al. A Comprehensive Definition for Integrative Oncology. J Natl Cancer Inst Monogr. 2017;2017(52).
77. Columbia University Department of Pediatrics. Integrative Therapies 2022 [cited 2022 15 July]. Available from: https://www.pediatrics.columbia.edu/about-us/divisions/hematology-oncology-and-stem-cell-transplantation/center-comprehensive-wellness/patient-care/integrative-therapies.
78. Gemeinschaftskrankenhaus Herdecke Witten/Herdecke University. Department of Pediatric Oncology and Pediatric Hematology 2022 [cited 2022 15 July]. Available from: https://www.gemeinschaftskrankenhaus.de/medizin-therapie-pflege/fachabteilungen/kinder-/jugendmedizin/kinderonkologie/uebersicht/.

79. Jacobsen R, Fønnebø MV, Foss N, Kristoffersen AE. Use of complementary and alternative medicine within Norwegian hospitals. BMC Complement Altern Med. 2015;15:275.
80. Vardesenteret. Tilbud og aktiviteter. English: Offerings and activities . Tromsø: Vaardesenteret Troms og Finnmark; 2023 [cited 2023 2 June]. Available from: https://kreftforeningen.no/vardesenteret/tilbud/?county=troms-og-finnmark.
81. Oslo University Hospital R. Children's Department for Cancer and Blood Diseases 2022 [cited 2022 15 July]. Available from: https://oslo-universitetssykehus.no/behandlinger/barnekreft?sted=barneavdeling-for-kreft-og-blodsykdommer#barne--og-ungdomsaktiviteter.
82. St. Olavs Hospital. Will invest in music therapy 2022 [cited 2022 15 July]. Available from: https://stolav.no/korus/vil-satse-pa-musikkterapi.
83. University Hospital of Northern Norway (UNN). Barnekreft (Childhood cancer) Tromsø: University Hospital of Northern Norway (UNN); 2022 [cited 2022 15 July]. Available from: https://unn.no/behandlinger/barnekreft#vardesenteret.
84. Haukeland University Hospital. Children and young people in the hospital 2022 [cited 2022 15 July]. Available from: https://helse-bergen.no/avdelinger/barne-og-ungdomsklinikken/barn-og-unge-pa-sjukehus#aktivitetar-for-barn-og-unge.
85. National Cancer Institute D. Dictionary of Cancer Terms, Survivor United States: National Cancer Institute; [cited 2023 29 May]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/survivor.
86. Mellblom AV, Kiserud CE, Rueegg CS, Ruud E, Loge JH, Fosså SD, et al. Self-reported late effects and long-term follow-up care among 1889 long-term Norwegian Childhood, Adolescent, and Young Adult Cancer Survivors (the NOR-CAYACS study). Support Care Cancer. 2021;29(6):2947-57.
87. Wang X, Cheng Z. Cross-Sectional Studies: Strengths, Weaknesses, and Recommendations. Chest. 2020;158(1, Supplement):S65-S71.
88. Aggarwal R, Ranganathan P. Study designs: Part 2 - Descriptive studies. Perspect Clin Res. 2019;10(1):34-6.
89. Quandt SA, Verhoef MJ, Arcury TA, Lewith GT, Steinsbekk A, Kristoffersen AE, et al. Development of an International Questionnaire to Measure Use of Complementary and Alternative Medicine (I-CAM-Q). The Journal of Alternative and Complementary Medicine. 2009;15(4):331-9.
90. Dillman DA, Smyth JD, Christian LM. Internet, phone, mail, and mixed-mode surveys: The tailored design method: John Wiley & Sons; 2014.
91. Bordens KS, Abbott BB. Research design and methods: A process approach: McGraw-Hill; 2002.
92. Stub T, Kristoffersen AE, Overvåg G, Jong MC. An integrative review on the information and communication needs of parents of children with cancer regarding the use of complementary and alternative medicine. BMC Complement Med Ther. 2020;20(1):90.
93. Magi T, Kuehni CE, Torchetti L, Wengenroth L, Lüer S, Frei-Erb M. Use of complementary and alternative medicine in children with cancer: a study at a Swiss University Hospital. PLoS One. 2015;10(12):e0145787.
94. Laengler A, Spix C, Seifert G, Gottschling S, Graf N, Kaatsch P. Complementary and alternative treatment methods in children with cancer: A population-based retrospective survey on the prevalence of use in Germany. Eur J Cancer. 2008;44(15):2233-40.
95. Sanchez HC, Karlson CW, Hsu JH, Ostrenga A, Gordon C. Complementary and Alternative Medicine Use in Pediatric Hematology/Oncology Patients at the University

of Mississippi Medical Center. The Journal of Alternative and Complementary Medicine. 2015;21(11):660-6.
96. Jekel JF. Epidemiology, biostatistics, and preventive medicine: Elsevier Health Sciences; 2007.
97. Taherdoost H. Sampling methods in research methodology; how to choose a sampling technique for research. International Journal of Academic Research in Management. 2016;5(2):18-27.
98. Dahlen AH , Gunnes MW, Due-Tønnessen BJ, Lund B, Kranz S, Bjørnland K. National Quality Register for Childhood Cancer, Annual Report 2021. Oslo: National Quality Register for Childhood Cancer; 2022.
99. Paulhus DL. Measurement and control of response bias. Measures of personality and social psychological attitudes. Measures of social psychological attitudes, Vol. 1. San Diego, CA, US: Academic Press; 1991. p. 17-59.
100. van de Mortel TF. Faking It: Social Desirability Response Bias in Self-report Research. The Australian Journal of Advanced Nursing. 2008;25(4):40-8.
101. Peat J. Health science research: A handbook of quantitative methods: Sage; 2013.
102. Grossoehme DH. Overview of Qualitative Research. J Health Care Chaplain. 2014;20(3):109-22.
103. Baćak V, Ólafsdóttir S. Gender and validity of self-rated health in nineteen European countries. Scand J Public Health. 2017;45(6):647-53.
104. Dahlen AH, Zeller B, Due-Tønnessen BJ, Ruud E, Bjørnland K, Lund B. National Quality Register for Childhood Cancer -Annual Report 2020. Oslo: National Quality Register for Childhood Cancer; 2021.
105. Linder LA, Hooke MC. Symptoms in children receiving treatment for cancer—Part II: pain, sadness, and symptom clusters. J Pediatr Oncol Nurs. 2019;36(4):262-79.
106. Hooke MC, Linder LA. Symptoms in children receiving treatment for cancer—part I: fatigue, sleep disturbance, and nausea/vomiting. J Pediatr Oncol Nurs. 2019;36(4):244-61.
107. Hedén L, Pöder U, von Essen L, Ljungman G. Parents' Perceptions of Their Child's Symptom Burden During and After Cancer Treatment. J Pain Symptom Manage. 2013;46(3):366-75.
108. Ramholdt B. Alternativ behandling hos kreftsyke barn. English: Alternative and complementary treatment for children with cancer Omsorg. 1992;2:21-6.
109. Krogstad T, Nguyen M, Widing E, Toverud EL. Bruk av naturpreparater og kosttilskudd hos kreftsyke barn i Norge. English: Children with cancer and their use of natural products. Tidsskr Nor Laegeforen. 2007;127(19):2524-6.
110. DeJonckheere M, Vaughn LM. Semistructured interviewing in primary care research: a balance of relationship and rigour. Family Medicine and Community Health. 2019;7(2):e000057.
111. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15(9):1277-88.
112. Tuval-Mashiach R. Raising the curtain: The importance of transparency in qualitative research. Qualitative Psychology. 2017;4(2):126.
113. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349-57.
114. Fossey E, Harvey C, McDermott F, Davidson L. Understanding and evaluating qualitative research. Aust N Z J Psychiatry. 2002;36(6):717-32.
115. Patton MQ. Qualitative research & evaluation methods: Integrating theory and practice. California: Sage publications; 2014.

116. Hammarberg K, Kirkman M, de Lacey S. Qualitative research methods: when to use them and how to judge them. Hum Reprod. 2016;31(3):498-501.
117. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of interventions version 6.3: Cochrane; 2022 [cited 2023 21 May]. Available from: www.training.cochrane.org/handbook.
118. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
119. Pearson A, White H, Bath-Hextall F, Apostolo J, Salmond S, Kirkpatrick P. Methodology for JBI mixed methods systematic reviews. The Joanna Briggs Institute Reviewers Manual. 2014;1:5-34.
120. Malmivaara A, Koes BW, Bouter LM, van Tulder MW. Applicability and Clinical Relevance of Results in Randomized Controlled Trials: The Cochrane Review on Exercise Therapy for Low Back Pain as an Example. Spine. 2006;31(13).
121. Shivayogi P. Vulnerable population and methods for their safeguard. Perspect Clin Res. 2013;4(1):53.
122. Gordon BG. Vulnerability in Research: Basic Ethical Concepts and General Approach to Review. Ochsner J. 2020;20(1):34-8.
123. Sansevere ME, White JD. Quality Assessment of Online Complementary and Alternative Medicine Information Resources Relevant to Cancer. Integr Cancer Ther. 2021;20.
124. Norway's National Research Centre for Complementary and Alternative Medicine. CAM Cancer: UiT The Arctic University of Norway; 2023 [cited 2023 30 May]. Available from: https://cam-cancer.org/en.
125. Wode K, Sharp L, Fransson P, Nordberg JH. Communication About Complementary and Alternative Medicine When Patients Decline Conventional Cancer Treatment: Patients' and Physicians' Experiences. Oncologist. 2023.
126. Statens legemiddelverk (Norwegian Medicines Agency). Melding om mistenkt bivirkning ved bruk av legemidler (ink. naturlegemidler) Oslo: Folkehelseinstituttet; 2009 [Available from: www.legemiddelverket.no.
127. World Health Organization (WHO). The Traditional, Complementary, Integrative Medicine Americas VHL. Benchmarks OMS Brazil: Virtual Health Library Traditional, Complementary, and Integrative Medicine; 2023 [cited 2023 02. June]. Available from: https://mtci.bvsalud.org/en/benchmarks-oms-2/.
128. Kyr M, Svobodnik A, Stepanova R, Hejnova R. N-of-1 Trials in Pediatric Oncology: From a Population-Based Approach to Personalized Medicine-A Review. Cancers (Basel). 2021;13(21).

Paper I

Prevalence of supportive care among children diagnosed with cancer in Norway: A cross-sectional study

Prevalence of supportive care among children diagnosed with cancer in Norway: A cross-sectional study.

Submitted to: **The European Journal of Pediatrics**

Dana C. Mora, MPH[1]
dana.c.mora@uit.no
ORCID 0000-0003-1209-3526
Agnete E Kristoffersen PhD[1]
agnete.kristoffersen@uit.no
ORCID 0000-0003-4642-0310
Thomas A. Arcury, PhD[2]
tarcury@wakehealth.edu
ORCID 0000-0001-9523-9492
Sara A. Quandt, PhD[3]
squandt@wakehealth.edu
ORCID 0000-0002-2968-5459
Miek C. Jong, PhD[1]
miek.jong@uit.no
ORCID 0000-0001-8523-9632
Trine Stub, PhD[1]
trine.stub@uit.no
0000-0002-7053-509X

[1]National Research Center in Complementary and Alternative Medicine, NAFKAM, Department of Community Medicine, Faculty of Health Science, UiT The Arctic University of Norway, 9037 Tromsø, Norway
[2] Department of Family and Community Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA
[3]Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA

Corresponding author:
Dana C. Mora, MPH
National Research Center in Complementary and Alternative Medicine, NAFKAM
Faculty of Health Science,
Department of Community Medicine,
UiT The Arctic University of Norway
9037 Tromsø, Norway
Phone: +4777645660
E-mail: dana.c.mora@uit.no

Funding
This study was funded by Barnekreftforeningen (The Children's Cancer Society) in Troms og Finnmark, Norway; Ekhagastiftelsen (2020-76), Stockholm, Sweden.

Abstract

Purpose

Survival rates among children with cancer have increased in high-income European countries in the last 30 years. The scientific literature on the prevalence of CAM use among children with cancer is scarce. Hence, this study aims to determine the prevalence and associations of supportive care use, including CAM, among children with cancer in Norway.

Methods

A cross-sectional survey was conducted in Norway among parents (n=117) of children with cancer. Respondents were recruited through the Norwegian Children's Cancer Society and its local chapters.

Results

Over two-thirds (67%) of the respondents reported their children used at least one supportive care modality to cope with the adverse effects of cancer treatment. Among those who reported supportive care use, 47 % used CAM. Thirty-seven percent visited a health care/CAM provider, 43% attended a leisure activity, and 37 % used natural remedies. For more than half of the children who used supportive care, parents reported that the modalities helped reduce the adverse effects of cancer treatment. Moreover, 7% reported that their children experienced adverse effects from the supportive care modalities.

Conclusions

In Norway, children with cancer widely use supportive care to cope with the adverse effects of cancer treatment. As the survival rates increase and pharmacological treatments are unavailable or have a poor impact on common adverse effects of cancer treatment, providers may consider engaging in conversations with families regarding treatment options and quality of care that include supportive care modalities.

What is known:

- Research on the use of supportive care, including CAM, among children with cancer is limited.
- Parents of children with cancer seek supportive care to help their children face the burdensome health complaints derived from cancer treatment.

What is new:

- In Norway, 67% of children with cancer use non-pharmacological supportive care.
- Forty-seven percent use complementary and alternative medicine to cope with symptoms of cancer treatment.

Keywords: Complementary and Alternative Medicine (CAM), integrative medicine, childhood cancer, prevalence, supportive care

Abbreviations

CAM	Complementary and alternative medicine
NAFKAM	Norway's National Research Center for Complementary and Alternative Medicine
NSD	Norwegian Center for Research Data
UNN	University Hospital of Northern Norway
I-CAM-Q	International Questionnaire to Measure Use of Complementary and Alternative Medicine

Introduction

Childhood cancer is a rare disease; globally it accounts for 1-4% of all cancers [1]. Childhood cancer is the leading cause of death among children above one year of age in Norway [2]. According to the Norwegian childhood cancer registry, 6,781 children and adolescents in Norway have been diagnosed with cancer since 1985 [3, 4]. Norway's five-year total survival for children and young people with cancer is 86.7% [3, 5], similar to other high-income countries.

The most common adverse effects of cancer treatment in children are anemia, fatigue, infection, and mucositis due to immunosuppression. Malnutrition, nausea and vomiting, pain, and psychosocial complaints are also common[6, 7]. Given the high survival rates, the adverse effects, and the length of the treatment, cancer can become burdensome for both parents and patients [7, 8]. High survival rates come at a cost. Childhood cancer survivors experience long-lasting health problems as sequelae from treatment [1]. To offset the burden derived from the cancer diagnoses and adverse effects of cancer treatment, parents have looked for other ways to help their children cope [9, 10].

Supportive care is the arrangement of services needed by those affected with or living with cancer to meet their overall needs (physical, emotional, social, psychological, informational, spiritual, and practical) during the diagnostic, treatment, and follow-up phases [11]. Supportive care is comprehensive, and it can include treatments ranging from drugs to reduce chemotherapy-induced nausea and vomiting [12] to non-pharmacological treatments such as music therapy to reduce anxiety, stress, or pain [13]. Complementary and alternative medicine (CAM) is a form of supportive care.

CAM is a group of diverse medical and health systems, practices, and products not generally considered part of conventional medicine [14]. For the research presented in this paper, supportive care is defined as a concept encompassing both conventional modalities (excluding primary cancer treatment such as chemotherapy, radiation, and surgery) and CAM.

In Norway, conventional health care follows the Nordic welfare model. This model strongly subsidizes treatment offered within the official healthcare system, offering it free of charge or with a small co-paid fee. It is free for children up to 16 years of age [15]. Some supportive modalities are offered inside the conventional healthcare system (nutrition counseling, play, and music therapy). In contrast, most CAM modalities are offered outside this system (acupuncture, reflexology, and healing). Some modalities are offered outside and inside the conventional healthcare system (physiotherapy and psychotherapy). Supportive care offered outside this system is fully paid out of pocket by parents or patients.

The prevalence of CAM use among children with cancer is variable worldwide [10]. In Europe, the use of CAM among children with cancer is estimated to be 52%, but this number ranges between 5% to 90% among European countries [16-18]. The knowledge of CAM use among children with cancer in is limited. Since 2018, three articles from European countries have been published on prevalence use of CAM among children with cancer [18-20]. In Norway, two studies have been conducted to assess the use of CAM among children with cancer. A 1992 study of 31 children estimated that the use of CAM varied between 30-60% [21]. In this study, herbal medicines, religious practices, and diets were more often used. The second was a qualitative study that reported the use of herbs and supplements among twenty-one families of children with cancer. The study found that parents were cautious when giving herbs and supplements to their children due to fear of interaction with conventional medicines [22].

Our research team at Norway's National Research Center for Complementary and Alternative Medicine (NAFKAM) is developing an evidence-based decision-aid tool on CAM use for supportive care for parents of children with cancer. Given the age and small samples in the existing Norwegian studies, our research team aimed to conduct a study to investigate the current prevalence of non-

pharmacological supportive care use, including CAM, among children diagnosed with cancer in Norway. We aim to investigate I) what modalities are being used and II) the associations of use.

Design and Methods

Cancer diagnoses and treatment protocols for childhood cancer are difficult and strict; hence families find it hard to take the time to participate in research. To reach parents, the research team worked with the Norwegian Children's Cancer Society (Barnekreftforeningen) to distribute a cross-sectional survey among its members between January - December 2021. The society is a nationwide organization run by families who have or have had children with cancer. The Norwegian Center for Research Data (NSD) reviewed and approved the study protocol in November 2020 [NSD/ 493228].

Recruitment and respondent inclusion criteria

Convenience sampling was used to recruit the sample [23]. This sampling method is a non-probability method where respondents are selected because they are readily available [23]. The investigators partnered with the Norwegian Children's Cancer Society in the recruitment process; according to their research leader, the society has close to 700 active members (patients, parents, family members), but the exact number of active members is unknown. They sent an invitation letter, including an online link to the survey, to all members, distributed through their quarterly newsletter in 3 editions. In addition, the survey link was distributed to 13 regional associations through Facebook on three different occasions throughout 2021. The investigators also collaborated with the childhood oncology unit at the University Hospital of Northern Norway (UNN) to distribute informational pamphlets to their hospitalized patients about the survey, including the survey link. The link was also shared through the social media pages of NAFKAM. To be eligible, participants had to be older than 18 years of age and parents of a child who had ever been diagnosed with cancer as a child before the age of 18 since 1990. Completion of the survey was contingent on the participant's ability to access it digitally.

Data collection

The online data collection was designed and managed with nettskjema.no - a survey solution developed and hosted by the University of Oslo [24]. The data collection was based on the Dillman survey procedure [25]. Participation in the survey was voluntary and anonymous. Before completing

the survey, respondents had to read the consent form and agree to participate by clicking on the webpage. As an incentive to participate, respondents had the opportunity to sign-up after completing the survey for a lottery where twelve gift cards for 1,000 NOK were randomly distributed.

Questionnaire content

The survey was adapted from the International Questionnaire to Measure Use of Complementary and Alternative Medicine (I-CAM-Q) [26]. The questions in I-CAM-Q were further developed based on information from previous knowledge acquired from qualitative interviews conducted among parents of children diagnosed with cancer in Norway [27]. The chief adviser for scientific development at Norwegian Children's Cancer Society reviewed the questionnaire before data collection started.

Measures

Personal Characteristics

The gender of the parents and the children was assessed by asking if they were a woman/man or a girl/boy. The parent's age at the time of the survey was obtained as a continuous variable. In the analysis, the parents' age was categorized into three levels (26-40 years, 41-50 years, and 51-62 years). Level of parental education was recorded using six levels: primary education (up to 10 years), upper secondary education (from 11-13 years), lower levels at university/college (up to 4 years), higher levels at university/college (more than 4 years), don't know, and refuse to answer. These were merged into a measure with four categories (less than 13 years of education, college/university less than 4 years, college/university 4 years or more, don't know, and refuse to answer). Household income was collected using the following categories: NOK <150,000, 150,000-250,000; 251,000-350,000; 351,000-450,000; 451,000-550,000; 551,000-750,000; 751,000-1,000,000; and more than NOK 1,000,000, don't know, and refuse to answer). These were then categorized into low (< NOK 550,000/USD 55,000), middle (NOK 550,000 – 1,000,000/USD 55,100-100,000), high household income (>NOK 1,000,000), and refuse to answer. None of the respondents answered "don't know" so it was not included in the categories. Other personal characteristics included location (city -more than 50,000 inhabitants, town- between 10,000 and 50,000, village-less than 10,000, rural area, don't know, and refuse to answer).

Supportive care, including CAM

The questionnaire measured various supportive care modalities used to help children cope with the cancer diagnosis and/or treatment. For comparison between studies, the modalities were grouped following the format used by Kristoffersen et al. 2008 [28]. Supportive care was grouped as *visits to providers*, such as acupuncturists, psychotherapists, physiotherapists, and healers; *natural remedies*, such as turmeric, aloe vera, mistletoe, and shark cartilage; *dietary supplements* such as multivitamins, vitamin B, vitamin C, and vitamin D; *special diets* such as low carb diet, vegetarian, and homemade food only; *spiritual practices* such as meditation, going to church and yoga; and *leisure activities* such as horseback riding and going to the cabin [28]. Going to the cabin refers to a custom among many Norwegian families to go to the cabin during weekends and holidays to relax and be in contact with nature. For each modality, respondents were asked if they had used it to reduce specific symptoms (i.e., pain, fatigue, nausea/vomiting).

Two outcome measures were created: CAM as supportive care (including acupuncture, healing, homeopathy, massage/aromatherapy, psychology, reflexology, vitamins B, C, D, and E, turmeric garlic, blueberry extract, ginger, fasting, music -both listening/playing and therapy, art -both therapy and other manual arts, and yoga), and overall supportive care (including CAM [see above], conventional modalities like physiotherapy, and leisure activities). Psychology can be categorized as both CAM and non-CAM in Norway, depending on the therapist's education and qualifications [29]. It was categorized as CAM and included in the CAM supportive care outcomes. For each of the provider and natural remedies/supplements modalities, respondents were asked if the strategy had any effect (yes/no), what kind of effect (cured symptoms, reduced symptoms, no change, don't know), and if there were any adverse effects (yes/no) from the modality. For the diet modalities, respondents were asked the same follow-up questions except if there were any adverse effects. For leisure/emotional/spiritual activities, parents were asked if they were used for a specific reason (yes/no) and what reason (keep a normal routine, help the family to think about something else, take a break from the illness/hospital, beneficial for the child, I don't know). Parents were also asked if

supportive care was used during active cancer treatment, after cancer treatment, or/and during palliative care.

Cancer diagnosis and treatment

Respondents were asked about the child's cancer diagnoses (leukemia, lymphoma, neuroblastoma, bone cancer, Wilms tumor of the kidney, soft-tissue sarcoma, retinoblastoma, germ cell tumor, don't know, other). They were asked about their child's cancer treatment and to check all that applied (chemotherapy, surgery, radiotherapy, stem cell/bone marrow transplantation, antibody treatment, cancer treatment with hormones, and other). Parents were asked to mark adverse effects experienced by the child as a consequence of cancer treatment (i.e., weakened immune system, lack of appetite). The recurrence of cancer was assessed by asking if the child had cancer again after the first time (yes/no). The child's age at cancer diagnosis was asked as a continuous variable and then grouped into three categories (0-5 years, 6-10 years, and 11-16 years representing the age range of the children in the study). The child's age at the time of the survey was asked as a continuous variable. The child's age when the child went into remission if the child was no longer undergoing treatment was asked. Parents were also asked if the child was alive (yes/no) and the age of death if the child had died.

Overall health of the child

A categorical scale was used to ask parents about the child's overall health (very good, good, neither good nor bad, bad, very bad), their overall health compared to other children their age (better health, similar health, poorer health, don't know), and to rate how the effects of cancer treatment affected their child's cognitive development (minimally, to some extent, very much, don't know). For analysis, three categories were created to analyze the variables "overall health" (very good/good, neither good nor bad, bad/very bad) and "health compared to other children their age" (better/similar health, poorer health, don't know).

Parents were also asked about sources of support from official institutions (i.e., the government, schools, homeschool, equipment, no support, other) and support from friends and family (i.e., babysitting, financial, fundraising, practical help, no support, other). In the support from friends and

family category, emotional support was created as a category after analyzing the responses given in the "other" category.

Statistical methods

With a margin of error of 5%, a confidence level of 95%, and a heterogeneity of 50%, we needed a minimum sample of n=362 to represent the 6,781 Norwegian children with a current or previous cancer diagnosis for adequate study power [23, 30]. The number used to calculate the power was the number of children diagnosed with cancer regardless of survival status. Although children have died, the questionnaire was administered among parents. Descriptive statistics (frequencies and percentages) were used to describe the sample characteristics and the prevalence of supportive care modalities used among the sample respondents. Significance tests were conducted to look for trends in the data. The prevalence among those who used CAM and overall supportive care was compared using the Pearson chi-square test, Fisher's exact test, and the independent t-test. The mean number of modalities used was calculated and compared within each group using the Mann-Whitney and the Kruskal-Walls H tests. These tests were applied as the distribution of the number of modalities used had a non-normal distribution. Analysis was performed using SPSS v.28.0.1.0. A p-value less than .05 was considered statistically significant.

Results

Participant characteristics

We obtained 117 responses from the survey. The majority of respondents were women (81%, n=95), and the mean age was 43 years of age [Table 1]. Most parents attended university/college (71%, n=83), and 43% (n=50) reported completing four or more years of university training. Accordingly, 43% (n=50) of the respondents had a household income higher than NOK 1,000,000 (USD 100,000) [Table 1]. Most respondents (58%, n=68) lived in towns, cities, and villages. Fifty-two percent (n=61) of the children diagnosed with cancer were girls, and over half (61%, n=71) of the children were diagnosed between 0 and 5 years of age [Table 1]. The ages of diagnoses ranged from 0-16 years of age [Table 2]. The most reported cancer diagnoses were leukemia (53%, n=62) and brain cancer (15%, n=18) [Table 2]. Most of the children received chemotherapy (94%, n=110), surgery (37%, n=42), and

radiotherapy (27%, n=32). Adverse effects derived from conventional cancer treatment were reported for 100% (n=117) of the children. The most common adverse effects reported were a weakened immune system (73%, n=85), lack of appetite (70%, n=82), nausea and vomiting (70%, n=82), pain (68%, n=78), and fatigue (61%, n=71). Seventeen percent (n=20) reported cancer reoccurrence [Table 2].

Most parents received financial help from the government (96%, n=112). Sixty-seven percent (n=78) received support from family and friends through babysitting, as well as practical help (44%, n=53), financial (10%, n=12), and emotional support (8%, n=9). Parents also received support from other organizations, such as schools (38%, n=44), as well as help with equipment such as wheelchairs (40%, n=47) [data not shown in tables].

Supportive care use

Overall supportive care use

Among the respondents, 67% (n=78) reported that their children used supportive care to cope with the adverse effects of cancer diagnoses and treatment [Table 3]. Forty-four percent (n=52) attended a supportive care provider. The most attended were physiotherapists (37.6%, n=44), psychotherapists (8.5%, n=10), and massage/aromatherapists (7.7%, n=9). Thirty-seven percent (n=43) reported that their children used natural remedies/supplements such as multivitamins (27%, n=31) and vitamin D (19%, n=22). A small number of respondents (n=8) reported using diet to help their children with symptoms from cancer treatment. Lastly, 43% (n=50) used leisure/emotional/spiritual activities such as walking (31%, n=36), playing (29%, n=34), doing exercise (23%, n=27), or going to the cabin (20%, n=23) mostly to keep normality and because parents perceived it was good for the child.

Among those who reported supportive care use, 86% (n=67) stated that the modality they used influenced the symptoms, with 60% (n=40) reporting that the symptoms were reduced. Most children used the modalities during (85%, n=66) or after cancer treatment (81%, n=63). Less than 8% (n=6) reported adverse effects from the modalities used. The modalities used ranged from 1 to 14, with a mean of 4.65 (SD=2.89) different modalities. Although not significant ($p>0.05$), a trend exists among

parents with higher education to use supportive care to help their children cope with cancer more frequently than those with lower education.

Children with brain cancer were more likely to use supportive care (89%, $p<0.05$) compared to those who did not have brain cancer diagnoses [Table 2]. Supportive care was more often used among those having difficulty with memory and concentration (82.6%, n=38 $p<0.05$), feeling worried (76.4, n=42, $p<0.05$), and with nausea and vomiting (61.0%, n=50 $p<0.05$).

CAM supportive care use

Forty-seven percent (n=55) of the parents reported that their child used at least one CAM modality [Table 3]. The number of CAM modalities used ranged from 1 to 5, with a mean of 2.15 (SD =1.11). The most often used CAM modalities were Vitamin D (19%, n=22), music (18%, n=21), art (16%, n=19), psychotherapy (9%, n=10), and massage/aromatherapy (8%, n=9) [Table 3]. Twenty-seven percent (n=31) of the parents reported their child took a CAM supplement. Twenty-one percent (n=24) used a CAM provider and/or a CAM leisure /emotional /spiritual activity. Among those who used CAM, 53% (n=24) stated that the CAM modality helped reduce their symptoms. Seven percent (n=51) reported adverse effects from CAM modalities. Most of the CAM modalities were used after (80.0%, n=44) or during (70%, n=40) cancer treatment [Table 3]. Children with shortness of breath (71% n=15 $p<0.05$), feeling worried (62% n=34 $p<0.05$), fatigued (58% n=41 $p<0.05$), and who had difficulty with memory and concentration (67% n=31 $p<0.05$), were significantly more likely to use CAM than those who did not report the latter symptoms [Table 2].

Discussion

Parents in Norway seek practices outside conventional cancer treatment protocols to help their children cope with the adverse effects of cancer treatment. The results from our survey show that 67% of the parents who participated reported that their child used supportive care. Most users used supportive care, including CAM, during and after cancer treatment. The prevalence of CAM use in our survey was 47%; furthermore, children used, on average, at least two different modalities. Over half of the parents reported that the modalities used reduced their child's symptoms. Additionally, 8% of the parents reported that the modalities used caused an adverse effect.

The results of our study regarding CAM use are similar to what has been reported in other high-income countries [16, 17, 19, 31, 32]. Studies conducted in Switzerland [18, 31], Germany [16], the Netherlands [19], and the United States [32] have found childhood cancer CAM use ranges from 35% to 70%. The CAM modalities most often used in this study were vitamins, music, and psychotherapy. The use of vitamins as one of the modalities more often used is in line with the results of previous studies [16, 19, 31, 32]. For example, Sanchez et al., reported that 15% of the respondents used vitamins. The finding that one of the most often used modalities was psychotherapy could be unique to Norway [10, 16, 19, 31, 32]. In Norway, depending on the qualifications and training of the provider, they can be considered either CAM or conventional care providers [29]. Among those who reported visiting a psychotherapist, the main reasons were feeling worried, psychological reactions, and sadness. The results are in line with the literature that shows that children with long-term physical conditions such as cancer are at a higher risk for psychological conditions such as anxiety and depression [33]. Our study also shows that 18% of children use music to cope with symptoms from cancer treatment. Regarding the use of music as supportive care, studies have demonstrated that music therapy is used to help reduce distress, anxiety, and pain and increases well-being among children with cancer [13]. To our knowledge, no previous studies have reported on the prevalence use of music among pediatric oncology patients. Still, there is a consensus that music therapy is widely used in pediatric oncology around the world [34, 35].

Similar to previous studies [16, 31, 32], over half of the parents (53%) in our study reported that CAM therapies had a positive effect on their children's health. In our study, 82% of the parents reported an effect from CAM, and 53% of the latter reported a reduction in symptoms from cancer treatment. Comparably a study from Switzerland [31] reported 87% of the parents perceived the effects of CAM. Among those, 76% reported improvement in the general condition of their child, and 54% reported fewer adverse effects from cancer chemotherapy/radiotherapy. Similar to a study by Laengler et al. [16], our findings show less than 8% of the parents reported adverse effects from CAM modalities. Lüthi et al. [18] found that over half of the children who used CAM used it after diagnosis. Likewise,

our study found that the majority of parents reported their children used supportive care, including CAM, during and after cancer treatment.

This study also revealed that those with brain cancer were more likely to use non-pharmacological supportive care. Although no information is available on the use of complementary medicine among children with brain cancer, a study by Armstrong et al. reported that among adults with brain tumors, 34% reported using CAM [36]. Our study shows that 89% of children with brain cancer used supportive care. The latter result could be a consequence of the significant morbidity children with brain cancer endure because of having to undergo multiple cancer treatments such as surgery, radiation, and chemotherapy [37].

Parents may be more inclined to use supportive care modalities for their children due to factors such as the prevalence of burdensome symptoms and the limited availability of pharmacological treatment options. Children with symptoms such as fatigue, nausea/vomiting, a weak immune system, feeling worried, and difficulty with concentration were more likely to use supportive care, including CAM. Fatigue, for example, is a prevalent symptom that affects the quality of life during and after cancer treatment and a symptom for which it is not recommended to use pharmacological approaches routinely (39). Chemotherapy-induced nausea and vomiting is a common symptom treated with antiemetic drugs but is still only partially controlled [38]. In previous studies, one of the most often reported reasons supportive care is used among children with cancer is to strengthen the immune system [16, 31]. The risk of late infections and the potential need for reimmunization among children with cancer are insufficiently described [39]. Furthermore, children undergoing cancer treatment experience severe anxiety [40], and feeling worried is reported as a very distressing symptom [8]. Despite the severity and prevalence of the symptom, clinicians rarely assess or manage anxiety [40]. Lastly, difficulty with concentration is another symptom prevalent among this patient group and one for which treatments are limited [41]. Consequently, CAM modalities such as music therapy [42, 43] and acupuncture [44] can be good treatment options in such cases.

Strengths and limitations

It is important to consider the limitations of this study when interpreting the findings. Although we attempted to reach respondents through different avenues, the number of respondents who answered the survey was small. The low response can be due to various factors, among them the fatigue parents experience taking care of a child with cancer while they must continue their normal routine, including taking care of other children. Furthermore, it was not possible to determine the exact number of active members at the Children's cancer society, keeping us from calculating a response rate. Because the sample was small, the power sample size was not reached, and it was obtained through convenience sampling, it is not possible to assess the generalizability of this study, and it affects the power to detect group differences. Furthermore, the questionnaire was not validated; however, the findings regarding supportive care use align with what has been reported in other high-income European countries [16, 18-20, 31, 32], ensuring criterion validity.

Due to the latter limitations, it is important to interpret the statistical analysis with caution. Future studies with larger sample sizes should confirm these results. Although small, our sample is comparable to what is found among children diagnosed with cancer in Norway. Like in our sample, in the Norwegian children's cancer population, leukemias and central nervous system tumors make up the largest diagnoses groups [3]. The majority of our sample was five years of age or younger when diagnosed with cancer, which is also comparable to the total population of children with cancer in Norway, in which cancer is more often diagnosed among children between 0-6 years of age [45]. The symptoms more often reported (weakened immune system, lack of appetite, nausea/vomiting, pain, and fatigue) correlate with what is reported in the literature [8, 38, 46]. The findings of this study regarding Despite its limitations, this study offers valuable information because it is the first nationwide study about supportive care modalities including CAM use among children with cancer in Norway [21, 22].

Practice Implications

As the survival rates of childhood cancer increase, it is important to be aware of the supportive care modalities parents of children use to alleviate the adverse effects of cancer treatment. Most of those who use supportive care use it during cancer treatment; therefore, it is important to support parents

during this process. One way parents can be supported is by providing information and reliable contacts to qualified supportive care providers. Furthermore, through the knowledge of the supportive care modalities used with children, conventional healthcare providers such as nurses and rehabilitation service personnel can be better informed and trained on different modalities to further aid children with cancer as they move through treatment and survival.

Different guidelines exist to help children and their families cope with burdensome adverse effects (such as anxiety, pain, and fatigue) [40, 45, 47]. Although guidelines exist, it might be difficult to implement them depending on different aspects, such as the size of the facility offering treatment, the availability of sufficient care personnel, and the availability of qualified providers [48]. Hence it is important to address the latter barriers but also to enhance the skills and knowledge of providers to be concurrent with the existing and updated guidelines.

Given that several of the most burdensome and prevalent symptoms reported are not adequately treated by pharmacological supportive care, it is important to explore non-pharmacological supportive care modalities, including CAM. To do this, conventional healthcare professionals (doctors, nurses, rehabilitation personnel) may establish networks to collaborate with qualified, supportive care and CAM provider organizations to integrate and implement existing non-pharmaceutical supportive care modalities but also to conduct research to assess the safety and effect of some of the less researched modalities. More quality research will lead to more evidence-based results and the implementation of better guidelines as children move into rehabilitation services with sequelae from cancer treatment.

Conclusion

Childhood cancer diagnosis and treatment can become burdensome for children and their families. The results of this study show the wide use of supportive care modalities in Norway. The high survival rates show the success that collaboration among different working groups and disciplines has had in improving treatment protocols. As survival rates will likely continue to increase, it is important to assess and support new ways in which childhood cancer patients and survivors can manage adverse

effects, especially when there is a deficiency of adequate pharmacological treatments to treat some of the most burdensome adverse effects such as anxiety, fatigue, and nausea/vomiting.

Statements and Declarations

Ethics approval

This study was conducted according to guidelines laid down in the Declaration of Helsinki, and written informed consent was obtained from the participants all participants. Furthermore, the Norwegian Center for Research Data (NSD) reviewed and approved the study protocol in November 2020 [NSD/ 493228].

Competing Interest

The authors have no relevant financial or non-financial interest to disclose

Author contributions

Dana C. Mora: Data curation, Formal analysis, Investigation; Methodology; Project administration, Resources**,** Roles/Writing - original draft, Software, Visualization. *Agnete E Kristoffersen* - Data curation, Formal analysis, Methodology, Supervision, Software, Validation, Visualization, Writing - review & editing. *Thomas A. Arcury***:** Visualization, Writing - review & editing *Sara A. Quandt:* Visualization, Writing - review & editing *Miek C Jong:* Conceptualization, Methodology, Writing - review & editing *Trine Stub:* Conceptualization, Funding acquisition Investigation, Methodology, Supervision Visualization.

References

1. Pritchard-Jones, K., R. Pieters, G.H. Reaman, L. Hjorth, P. Downie, G. Calaminus, M.C. Naafs-Wilstra, and E. Steliarova-Foucher 2013, *Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries.* Lancet oncology. **14**(3): p. e95-e103.
2. Barnekreft Kreftregisteret [Norwegian Childhood Cancer Registry]. *Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2019 [Annual Report 2019. Results and improvement measures from the national quality register for childhood cancer]*. 2020 [cited 2023 February 2]; Available from: https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2020/arsrapport-2019-nasjonalt-kvalitetsregister-for-barnekreft.pdf.
3. Dahlen, A.H., B. Zeller, B.J. Due-Tønnessen, E. Ruud, K. Bjørnland, and B. Lund. *National Quality Register for Childhood Cancer, Annual Report 2020. The Cancer Registry*. 2021;

Available from: https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2021/arsrapport-nasjonalt-kvalitetsregister-for-barnekreft-2020.pdf.
4. Cancer Registry of Norway. *Cancer in Norway 2020. Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway.* 2021 [cited 2021 29 September]; Available from: https://healthtalkweb.s3.amazonaws.com/documents/Cancer_in_Norway_2020.pdf.
5. Ward, Z.J., J.M. Yeh, N. Bhakta, A.L. Frazier, F. Girardi, and R. Atun 2019, *Global childhood cancer survival estimates and priority-setting: a simulation-based analysis.* The Lancet Oncology. **20**(7): p. 972-983 DOI: https://doi.org/10.1016/S1470-2045(19)30273-6.
6. Bryant, R. 2003, *Managing side effects of childhood cancer treatment.* Journal of Pediatric Nursing. **18**(2): p. 113-125 DOI: https://doi.org/10.1053/jpdn.2003.11.
7. Salvador, Á., C. Crespo, A.R. Martins, S. Santos, and M.C. Canavarro 2015, *Parents' Perceptions About Their Child's Illness in Pediatric Cancer: Links with Caregiving Burden and Quality of Life.* Journal of Child and Family Studies. **24**(4): p. 1129-1140 DOI: 10.1007/s10826-014-9921-8.
8. Hedén, L., U. Pöder, L. von Essen, and G. Ljungman 2013, *Parents' Perceptions of Their Child's Symptom Burden During and After Cancer Treatment.* Journal of Pain and Symptom Management. **46**(3): p. 366-375 DOI: https://doi.org/10.1016/j.jpainsymman.2012.09.012.
9. Fisher, R.S., et al. 2021, *Childhood cancer physical symptom burden and parent distress: The role of parent rumination.* Clinical Practice in Pediatric Psychology. **9**(3): p. 251.
10. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, and L. GT 2010, *Prevalence of Complementary Medicine Use in Pediatric Cancer: A Systematic Review.* Pediatrics. **125**(4): p. 768-776 DOI: 10.1542/peds.2009-1775.
11. Fitch, M. 2008, *Supportive care framework.* Canadian Oncology Nursing Journal/Revue canadienne de soins infirmiers en oncologie. **18**(1): p. 6-14.
12. Loeffen, E.A.H., L.C.M. Kremer, R.L. Mulder, A. Font-Gonzalez, L.L. Dupuis, L. Sung, P.D. Robinson, M.D. van de Wetering, and W.J.E. Tissing 2017, *The importance of evidence-based supportive care practice guidelines in childhood cancer—a plea for their development and implementation.* Supportive Care in Cancer. **25**(4): p. 1121-1125 DOI: 10.1007/s00520-016-3501-y.
13. Facchini, M. and C. Ruini 2021, *The role of music therapy in the treatment of children with cancer: A systematic review of literature.* Complementary Therapies in Clinical Practice. **42**: p. 101289 DOI: https://doi.org/10.1016/j.ctcp.2020.101289.
14. National Center for Complementary Integrative Health. *Complementary, alternative, or integrative health: what's in a name?* 2018 22 October 2022]; Available from: https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name.
15. Kuhnle, S., A.H. Bay, B. Hvinden, and C. Koren, *Article in Does the Welfare State Work? [in Norwegian: Virker Velferdsstaten?]*. null. Vol. null. 2001. 87.
16. Laengler, A., C. Spix, G. Seifert, S. Gottschling, N. Graf, and P. Kaatsch 2008, *Complementary and alternative treatment methods in children with cancer: A population-based retrospective survey on the prevalence of use in Germany.* European Journal of Cancer. **44**(15): p. 2233-2240.
17. Zuzak, T.J., et al. 2012, *Use of complementary and alternative medicine by children in Europe: Published data and expert perspectives.* Complement Ther Med. **21**: p. S34-S47 DOI: 10.1016/j.ctim.2012.01.001.
18. Lüthi, E., M. Diezi, N. Danon, J. Dubois, J. Pasquier, B. Burnand, and P.-Y. Rodondi 2021, *Complementary and alternative medicine use by pediatric oncology patients before, during, and after treatment.* BMC Complement Med Ther. **21**(1): p. 96-96 DOI: 10.1186/s12906-021-03271-9.
19. Jong, M.C., I. Boers, H. van Wietmarschen, M. Busch, M.C. Naafs, G.J.L. Kaspers, and W.J.E. Tissing 2020, *Development of an evidence-based decision aid on complementary and alternative medicine (CAM) and pain for parents of children with cancer.* Supportive Care in Cancer. **28**(5): p. 2415-2429 DOI: 10.1007/s00520-019-05058-8.

20. Menut, V., E. Seigneur, C. Gras Leguen, D. Orbach, and E. Thebaud 2019, *[Complementary and alternative medicine use in two French pediatric oncology centers: A common practice]*. Bull Cancer. **106**(3): p. 189-200 DOI: 10.1016/j.bulcan.2018.11.017.
21. Ramholdt, B. 1992, *Alternativ behandling hos kreftsyke barn.* English: Alternative and complementary treatment for children with cancer. Omsorg. **2**: p. 21-6.
22. Krogstad, T., M. Nguyen, E. Widing, and E.L. Toverud 2007, *[Children with cancer and their use of natural products]*. Tidsskrift for Den Norske Laegeforening. **127**(19): p. 2524-6.
23. Taherdoost, H. 2016, *Sampling methods in research methodology; how to choose a sampling technique for research.* International Journal of Academic Research in Management. **5**(2): p. 18-27.
24. *University of Oslo Nettskjema*. [cited 2021; Available from: https://www.uio.no/english/services/it/adm-services/nettskjema/.
25. Dillman, D.A., J.D. Smyth, and L.M. Christian, *Internet, phone, mail, and mixed-mode surveys: The tailored design method*. 2014: John Wiley & Sons.
26. Quandt, S.A., M.J. Verhoef, T.A. Arcury, G.T. Lewith, A. Steinsbekk, A.E. Kristoffersen, D.L. Wahner-Roedler, and V. Fønnebø 2009, *Development of an international questionnaire to measure use of complementary and alternative medicine (I-CAM-Q).* The Journal of Alternative and Complementary Medicine. **15**(4): p. 331-339.
27. Stub, T., S.A. Quandt, A.E. Kristoffersen, M.C. Jong, and T.A. Arcury 2021, *Communication and information needs about complementary and alternative medicine: a qualitative study of parents of children with cancer.* BMC Complement Med Ther. **21**(1): p. 85 DOI: 10.1186/s12906-021-03253-x.
28. Kristoffersen, A.E., V. Fønnebø, and A.J. Norheim 2008, *Use of complementary and alternative medicine among patients: classification criteria determine level of use.* The Journal of Alternative and Complementary Medicine. **14**(8): p. 911-919.
29. Lov om helsepersonell m.v. , *LOV-1999-07-02-64 Lov om helsepersonell m.v. (helsepersonelloven- hlspl) English: Act 1999-07-02-64. Act relating to Healthcare personnel etc, Helse og omsorgsdepartementet (Ministry of Health and Care Services)*. 1999.
30. Aina H. Dahlen, M.W.G., Bernt J. Due-Tønnessen, Bendik Lund, Simon Kranz, Be M. Wormda, Kristin Bjørnland, , *National Quality Register for Childhood Cancer, Annual Report 2021*. 2022, Cancer Register 2022.
31. Magi, T., C.E. Kuehni, L. Torchetti, L. Wengenroth, S. Lüer, and M. Frei-Erb 2015, *Use of complementary and alternative medicine in children with cancer: a study at a Swiss University Hospital.* PloS one. **10**(12): p. e0145787.
32. Sanchez, H.C., C.W. Karlson, J.H. Hsu, A. Ostrenga, and C. Gordon 2015, *Complementary and Alternative Medicine Use in Pediatric Hematology/Oncology Patients at the University of Mississippi Medical Center.* The Journal of Alternative and Complementary Medicine. **21**(11): p. 660-666 DOI: 10.1089/acm.2014.0371.
33. Thabrew, H., K. Stasiak, S.E. Hetrick, L. Donkin, J.H. Huss, A. Highlander, S. Wong, and S.N. Merry 2018, *Psychological therapies for anxiety and depression in children and adolescents with long-term physical conditions.* Cochrane Database of Systematic Reviews,(12) DOI: 10.1002/14651858.CD012488.pub2.
34. Giordano, F., et al. 2023, *Use of music therapy in pediatric oncology: an Italian AIEOP multicentric survey study in the era of COVID-19.* Eur J Pediatr. **182**(2): p. 689-696 DOI: 10.1007/s00431-022-04720-4.
35. Knott, D., M. Biard, K.E. Nelson, S. Epstein, S.L. Robb, and C.M. Ghetti 2020, *A Survey of Music Therapists Working in Pediatric Medical Settings in the United States.* J Music Ther. **57**(1): p. 34-65 DOI: 10.1093/jmt/thz019.
36. Armstrong, T., et al. 2006, *Complementary and Alternative Medicine Use and Quality of Life in Patients with Primary Brain Tumors.* Journal of Pain and Symptom Management. **32**(2): p. 148-154 DOI: https://doi.org/10.1016/j.jpainsymman.2006.02.015.
37. Madden, J.R., P. Mowry, D. Gao, P.M. Cullen, and N.K. Foreman 2010, *Creative arts therapy improves quality of life for pediatric brain tumor patients receiving outpatient chemotherapy.* Journal of Pediatric Oncology Nursing. **27**(3): p. 133-45 DOI: https://dx.doi.org/10.1177/1043454209355452.

38. Hooke, M.C. and L.A. Linder 2019, *Symptoms in children receiving treatment for cancer—part I: fatigue, sleep disturbance, and nausea/vomiting.* Journal of Pediatric Oncology Nursing. **36**(4): p. 244-261.
39. Perkins, J.L., A. Harris, and T.C. Pozos 2017, *Immune dysfunction after completion of childhood leukemia therapy.* Journal of pediatric hematology/oncology. **39**(1): p. 1-5.
40. Lazor, T., C. De Souza, R. Urquhart, E. Serhal, and A.R. Gagliardi 2021, *Few guidelines offer recommendations on how to assess and manage anxiety and distress in children with cancer: a content analysis.* Supportive Care in Cancer. **29**(5): p. 2279-2288 DOI: 10.1007/s00520-020-05845-8.
41. Phillips, N.S., E.S. Duke, H.T. Schofield, and N.J. Ullrich 2021, *Neurotoxic Effects of Childhood Cancer Therapy and Its Potential Neurocognitive Impact.* J Clin Oncol. **39**(16): p. 1752-1765 DOI: 10.1200/jco.20.02533.
42. Mellingen, M., *Music therapy as procedural and treatment support in paediatric healthcare: a review of the literature from a Nordic perspective*. 2020, Norges musikkhøgskole.
43. Giordano, F., B. Zanchi, F. De Leonardis, C. Rutigliano, F. Esposito, N. Brienza, and N. Santoro 2020, *The influence of music therapy on preoperative anxiety in pediatric oncology patients undergoing invasive procedures.* The Arts in Psychotherapy. **68**: p. 101649 DOI: https://doi.org/10.1016/j.aip.2020.101649.
44. Mora, D.C., G. Overvåg, M.C. Jong, A.E. Kristoffersen, D.C. Stavleu, J. Liu, and T. Stub 2022, *Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young adults: a systematic review and meta-analysis of randomized controlled trials.* BMC Complementary Medicine and Therapies. **22**(1): p. 1-21.
45. Norwegian Directorate of Health. *National action program with guidelines for diagnosis, treatment and follow-up of cancer in children [online document]. Oslo: Norwegian Directorate of Health (last professionally updated 26 May 2020, read 14 March 2023). Available from https://www.helsedirektoratet.no/retningslinjer/kreft-hos-barn-handlingsprogram* 2017.
46. Linder, L.A. and M.C. Hooke 2019, *Symptoms in children receiving treatment for cancer—Part II: pain, sadness, and symptom clusters.* Journal of Pediatric Oncology Nursing. **36**(4): p. 262-279.
47. Robinson, P.D., et al. 2018, *Management of fatigue in children and adolescents with cancer and in paediatric recipients of haemopoietic stem-cell transplants: a clinical practice guideline.* The Lancet Child & Adolescent Health. **2**(5): p. 371-378 DOI: https://doi.org/10.1016/S2352-4642(18)30059-2.
48. Scialla, M.A., K.S. Canter, F.F. Chen, E.A. Kolb, E. Sandler, L. Wiener, and A.E. Kazak 2017, *Implementing the psychosocial standards in pediatric cancer: Current staffing and services available.* Pediatr Blood Cancer. **64**(11) DOI: 10.1002/pbc.26634.

Paper II

Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young adults: a systematic review and meta-analysis of randomized controlled trials.

BMC Complementary Medicine and Therapies

RESEARCH

Open Access

Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young adults: a systematic review and meta-analysis of randomized controlled trials

Dana C. Mora[1*], Grete Overvåg[2], Miek C. Jong[1], Agnete E. Kristoffersen[1], Debbie C. Stavleu[3], Jianping Liu[4] and Trine Stub[1]

Abstract

Background: Dealing with the symptom burden of cancer diagnosis and treatment has led parents to seek different self-management strategies including Alternative and Complementary Medicine (CAM). The aim of this study was to perform a systematic review and meta-analysis about the use and effect of CAM modalities to treat adverse effects of conventional cancer treatment among children and young adults.

Methods: Six scientific research databases were used to identify randomized controlled trials (RCTs) from 1990 to September 2020. Included studies investigated the use of CAM to treat cancer treatment related adverse effects in children and young adults compared to controls.

Results: Twenty RCTs comprising 1,069 participants were included in this review. The included studies investigated acupuncture, mind–body therapies, supplements, and vitamins for chemotherapy-induced nausea and vomiting (CINV), oral mucositis, and anxiety among children and young adults who underwent conventional cancer treatment. Seven studies (315 participants) were included in the meta-analysis. The overall effect of CAM (including acupuncture and hypnosis only) on chemotherapy-induced nausea and/or vomiting and controls was statistically significant with a standard mean difference of -0.54, 95% CI [-0.77, -0.31] $I^2 = 0\%$ ($p < 0.00001$). There was a significant difference between acupuncture and controls ($n = 5$) for intensity and/or episodes of CINV with an SMD -0.59, 95% CI [-0.85, -0.33] ($p < 0.00001$). No significant difference was found between hypnosis and controls ($n = 2$) for severity or episodes of CINV with an SMD -0.41, 95% CI [-1.09, 0.27] $I^2 = 41\%$ ($p = 0.19$).

Conclusion: Current evidence from this meta-analysis of randomized controlled trials shows that CAM, including acupuncture and hypnosis only, is effective in reducing chemotherapy-induced nausea and vomiting in children and

*Correspondence: dana.c.mora@uit.no
[1] Department of Community Medicine, Faculty of Health Science, National Research Center in Complementary and Alternative Medicine, NAFKAM, UiT The Arctic University of Norway, 9037 Tromsø, Norway
Full list of author information is available at the end of the article

young adults. More rigorous trials and long-term effects should be investigated if acupuncture and hypnosis are to be recommended for clinical use.

Keywords: Complementary and alternative medicine (CAM), Pediatric oncology, Adverse effects, Chemotherapy-induced nausea and vomiting (CINV)

Background

Worldwide, approximately 400,000 children and adolescents up to 19 years old are diagnosed with cancer each year. In Norway, approximately 350 children and young adults (0–19 years) receive a cancer diagnosis yearly [1]. Cancer is among the top causes of death in children and adolescents worldwide, especially in high-income countries (HICs). The most common cancers in children are acute leukemia, brain tumors, lymphomas, bone and soft tissue sarcomas, and germ cell tumors [2]. As a result of medical advancements, survival rates for children with cancer have risen in most HICs. The increase in survival rates means that survivors have to deal with a symptom burden during and after cancer treatment [3]. Parents of children with cancer have described some of the symptoms derived from cancer treatment as pain, fatigue, emotional distress, and loss of appetite [4]. The burden brought about by conventional cancer treatments has led parents to seek different self-management strategies.

One group of self-management strategies is Complementary and Alternative Medicine (CAM). CAM is defined as a group of diverse medical health care system practices and products that are not considered part of conventional medicine [5]. If a CAM modality is used together with conventional medicine, it is considered complementary medicine. If the modality is used in place of conventional medicine, it is considered alternative medicine [6]. Although these modalities alone are not effective for anti-cancer treatment, using them complementary to conventional medicine has shown to improve the health of cancer patients [7]. Studies have reported that massage therapy [5] and acupuncture [8, 9] among others, provide benefits to patients during cancer treatment. The complementary modalities more often used among children with cancer are herbal remedies, diet and nutrition, and faith healing [10].

Although CAM use among parents of children with cancer is prevalent, studies have shown that the most common source of information on possible CAM use is friends and family [4]. In a study by Krogstad et al. [11], parents found the information from friends and family burdensome because they were unable to follow up their advice. Parents of children with cancer want accurate and reliable information on formal strategies from the healthcare providers treating their children, and from authorized sources such as the Norwegian Children's Cancer Society [4].There is sparse research on how to cope with the adverse effects of conventional cancer treatment in children and young adults with cancer. The existing literature mostly reflects on the prevalence of the use of CAM, but it is limited to investigate the effectiveness of CAM modalities used to alleviate the symptom burden during and after conventional cancer treatment. To the best of our knowledge, this is the first systematic review of RCTs that aims to investigate CAM modalities used to cope with adverse effects of conventional cancer treatment among children and young adults. The aim of this systematic review is to review the research literature to identify any CAM modalities used to treat adverse effects of conventional cancer treatment among children and young adults and if data allows it, perform a meta-analysis to assess the beneficial effect of possible CAM modalities.

Methods

Results were reported according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) checklist (see Supplementary file) [12].

The focus question was:

Which CAM modalities are used to treat adverse effects of conventional anti-cancer treatment among children and young adults?

The PICOS (Population, Intervention, Comparison, Outcome and Study type) format was used when searching for relevant articles, which included the following four parts:

Population: Children and young adults that were ever diagnosed with cancer or undergoing cancer treatment.
Intervention: Any CAM modalities.
Comparison: Conventional medicine, usual care, waiting list, other CAM modalities, and placebo.
Outcome: Reduction/Improvement of adverse effects (such as nausea, vomiting, toxicity, and mucositis) of conventional anti-cancer treatment.
Study types: Single RCTs; double-blinded RCTs; cross-over RCTs, pilot RCTs and feasibility RCTs.

A protocol for the systematic review was created, submitted, and registered with PROSPERO

(CRD42021216505). The protocol was registered on October 26, 2020. Six electronic databases were searched for eligible studies: AMED (EBSCO), Cinahl (EBSCO), Cochrane Central Register for Controlled Trials (Central) in the Cochrane Library (Wiley Interscience), Embase (Elsevier), PsycINFO (APA), and Medline (NLM). References of all included studies were hand-searched for additional eligible studies according to the search methodology. A manual search for gray literature was also performed using Google Scholar and books.

Search Methods: Various combinations of controlled vocabulary/thesaurus terms (eg. Mesh) and text words, adjusted for each database, were used. The following Mesh terms were used: Exp Neoplasms, exp Complementary Therapies, exp Integrative medicine, Alternative Therapies, exp Child, exp Adolescent, exp Young Adult, exp Infant, Adverse effects. sf (subheading, fs), adverse event, side effects and adverse reactions, Drug Related Side Effects and Adverse Reactions, exp Adverse drug reaction reporting systems, exp Randomized controlled trials.

These text words were used: neoplasm, leukemia, lymphoma/soft tissue sarcoma, pediatric cancer, pediatric oncology, integrative oncology, cancer treatment, childhood cancer, pediatric, palliative care, CAM modalities, CAM treatment, CAM, integrative medicine, complementary medicine, alternative medicine, unconventional medicine, spiritual healing/faith healing, children, child*,[1] infant, adolescent, juvenile, pediatric, puberty, young adults, young person, teen*[1], childhood, toddler, side effects, safety, risks factors, harm, adverse reactions, indirect/direct risks, adverse drug reaction, symptom management, hopelessness, suffering. The search string with the search terminology is attached as supplementary material.

Inclusion and exclusion criteria

The filters were human, Danish, Dutch, English, German, Norwegian, Spanish, and Swedish. The searches were limited to the period from January 1990 to April 2021. The inclusion comprised RCTs that reported CAM modalities to treat adverse effects of conventional cancer treatment among children and young adults. All adverse effects and CAM modalities were considered. Studies were excluded based on the following criteria: (i) studies did not report adverse effects of cancer treatment; (ii) studies unrelated to cancer or CAM; (iii) studies that were not RCTs, pilot RCTs, or feasibility RCTs; (iv) studies that were conducted among adults with cancer; (v) studies that were in languages other than the ones previously stated.

Study selection and data management

Search results were uploaded in the reference manager program Endnote to facilitate study selection, and a single data management file was produced identifying all references in the search process. Duplicates were removed and two authors (DCM and TS) screened the remaining references independently. Reasons for excluding articles were documented. Neither of the review authors was blind to the journal titles, study authors, or institutions. A flowchart of the study selection and identification according to the PRISMA guidelines [12] was generated.

Three authors (DCM, TS, and GO) developed the search strategy and performed the searches. The first and last authors screened the abstracts and searched for articles that met the inclusion criteria. DM and TS read the articles, extracted the data, and conducted the quality appraisal of the included articles independently. They also screened the abstracts and searched for articles that met the inclusion criteria using Rayyan web app [13].

Placebo

The placebo methods used consisted of sham acupuncture, sham herbs and supplements (i.e., shampoo syrup and placebo capsules), and sham products.

Data extraction

Data from the RCTs were extracted according to the Cochrane Handbook for Systematic Reviews of Interventions [14]. A table to extract data was created and included fifteen fields: study ID, objectives, method, design, setting, aim(s), sample size, dropout, participants (intervention/control groups), intention to treat & power calculation, inclusion/exclusion criteria, intervention (treatment vs. control), results, adverse effects due to the use of CAM, and funding.

Joanna Briggs Institute (JBI) quality assessment of the studies

The included trials were imported into the System for the Unified Management, Assessment and Review of Information (SUMARI—software program JBI) for methodological assessment and critical appraisal of study quality utilizing the checklist for RCTs [15]. Two authors (DM and TS) independently rated the methodological quality of the included articles using the critical appraisal checklists in SUMARI. Discrepancies between the reviewer's quality assessments were discussed among the reviewers and resolved. Articles were scored by assigning 1 point for each yes answer and zero points for no or unclear answers. To obtain the score, the points were added, and

[1] *= truncation—the search is done for the beginning of the word and all possible endings.

a percentage was calculated. For this systematic review, articles with > 75% yes scores on the critical appraisal items were classified as high quality, from 50 to 74% as medium quality, and < 50% as low quality [16]. Low quality studies were excluded from further analysis.

Description of meta-analysis

Meta-analysis was conducted using Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020 [17]. The study population was divided into those who received CAM modalities (acupuncture, acupressure, or hypnosis) and those who did not receive CAM for nausea and vomiting induced by conventional cancer treatment. The studies were combined into the meta-analysis if they were homogenous regarding study design, participants, intervention, control, and outcome measures. Studies that did not meet these criteria were excluded from the meta-analysis. For continuous outcomes, a random effect model was used, and standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated as the difference in means between groups divided by the pooled standard deviation using Hedges's correction for small study samples [14]. When missing standard deviations, they were calculated from standard errors, or by using the sample data provided in the article [14].

Results

Outcome of literature searches

The search produced a total of 273 hits. Seven hits were identified in Cinahl, 19 in Cochrane Central Register for Controlled Trials, 81 in Embase, 165 in Medline/Pubmed, and one in Psychoinfo. After the identification process, 36 studies were identified as duplicates and therefore excluded. Studies were evaluated based on titles and abstracts. During the screening process, 215 studies were excluded for the following reasons: 2 were abstract/posters; 8 duplicates; 17 were irrelevant; 29 were not about cancer; 19 were not about CAM; 70 were about adults with cancer, and 6 were in languages other than Danish, Dutch, English, German, Norwegian, Spanish, and Swedish, 64 were other study types. In a second round, 3 trials were excluded, 2 were not about CAM, and 1 did not include adverse effects. After reviewing the references of the 19 eligible articles, the authors included 2 more RCTs that met the eligibility criteria [18, 19]. A total Twenty-one [8, 9, 18–36] RCTs comprising 1,149 participants were eligible for inclusion in this review. Among them were six [22, 23, 32, 33, 35, 37] RCTs that had included participants up to the age of 21 years. Since all these studies focused on the effectiveness of CAM in the pediatric population, the review team decided, following a discussion, to include them in the review. Upon completion of the data extraction, assessment, and critical appraisal of study quality, one [18] study was excluded because it was determined to be of low quality. Although the excluded study was included in the data extraction table, no further results were reported. Consequently, a total of 20 studies ($n = 1{,}069$) were included in this review (Fig. 1).

Methodological quality of studies

Detailed characteristics of the included studies are presented in Table 1. Sample size refers to the total number of participants in the study. In the participant group, n refers to the number of participants who received the treatment or who were in the control group respectively. Dropout refers to the number of participants who left the study before completion.

Seven [18–23] of the 21 studies did not report sources of funding, and two studies [24, 25] stated that they received no financial support. Eight [18–21, 24, 26–28] studies did not report power calculations.

Fifteen studies ($n = 15$) [8, 9, 19–21, 24, 26, 27, 29–35] were assessed as high quality because they had scores of 75% or higher (Table 2). Two studies ($n = 2$) [29, 30] met the criteria for 13 out of 13 items (see Table 2). Seven studies ($n = 7$) [20, 25, 26, 31–33, 35] addressed 12 items, and six studies ($n = 6$) [8, 9, 19, 21, 24, 27] addressed ten items. Five studies ($n = 5$) [22, 23, 28, 36, 37] were assessed as medium quality because they obtained scores between 50 and 74%. Two studies ($n = 2$) [22, 36] addressed nine items, and three studies ($n = 3$) [23, 28, 37] addressed eight items. One ($n = 3$) [18] paper was assessed as low-quality (< 50%) as it addressed only 5 out of 13 items, and was excluded from further analysis.

CAM modalities

The results of the literature search indicate that the existing RCTs about the use of CAM modalities to alleviate the adverse effects of conventional cancer treatment in children and young adults can be divided into three main areas: Alternative medical systems, biological-based therapies, and mind–body therapies. The search returned seven [8, 9, 19, 24, 31, 35, 37] RCTs that have been conducted using acupuncture as a treatment for chemotherapy-induced nausea and vomiting. Ten [18, 20–22, 26, 29, 30, 33, 36, 38] studies emerged where supplements such as zinc, vitamin E, aromatherapy, pycnogenol, milk thistle, ginger powder, bovine colostrum, propolis, glutamine, and probiotics were examined in the treatment of adverse effects such as oral mucositis, nausea, vomiting, hepatotoxicity, fever, and the prevention of infection. Lastly, four [23, 25, 27, 28] studies emerged where mind–body therapies were used to treat stress, anxiety, nausea, vomiting, and to improve the quality of life among children and young adults with cancer undergoing treatment.

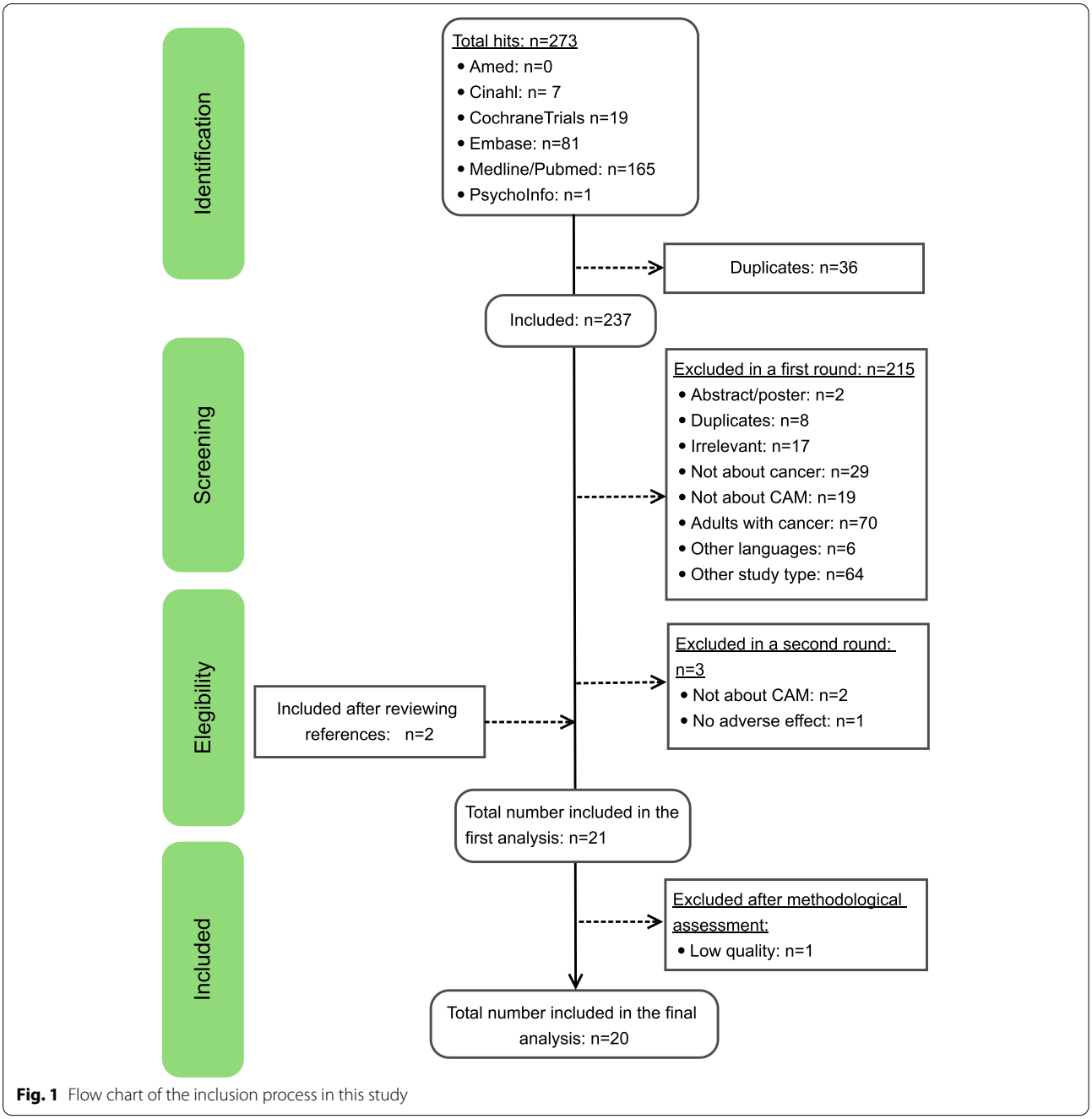

Fig. 1 Flow chart of the inclusion process in this study

Alternative medical systems

All of the studies related to alternative medical systems investigated if different acupuncture treatments could alleviate chemotherapy-induced nausea and vomiting among children and young adults undergoing conventional cancer treatment. Acupressure was used in four of the studies, two [19, 31] used wristbands, one [37] used auricular seeds, and one [24] used fingers. Two studies [8, 9] used needle acupuncture and one [35] used laser acupuncture. Neither of the studies accessing treatment with wristbands [19, 31] showed any significant difference in nausea and vomiting between the intervention and control groups (sham acupuncture, standard care). Although insignificant, Yeh et al. [37] found that patients receiving seed auricular acupuncture had lower occurrence of acute and delayed nausea and shorter vomiting duration than patients receiving sham acupuncture and standard care. Ghezelbash et al. [24] found a significant

Table 1 Characteristics of included studies

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Alternative medical systems														
Dupuis, L 2018 [25]	Acupressure bands for chemotherapy-induced nausea	RCT	Single-blind RCT	Medical centers in Canada	Compare CIN control in the acute phase provided by standard antiemetic agents combined with acupressure bands versus sham bands in children 4–18 yrs. of age receiving HEC***. Compare CIN^{+} control in the delayed phase compared to CIV§ control in the acute and delayed phases	187	22	Children 4—18 yrs. old. $n=83$ (acupressure bands) vs 82 (sham bands). Total: ($n=165$)	Power calculation reported	**Inclusion**: English speaking patients aged 4–18 yrs. with non relapsed cancer and with and English speaking guardian **Exclusion:** Patients with prior history of acupressure use or who planned to received antiemetic agents other than ondansetron, granisetrin, dexamethasone, or aprepitant on a scheduled basis	Acupressure bands 30 min before chemo vs. Sham band	Bands did not improve CIN or CIV control in children	Six adverse events (four in the intervention group and 2 in the sham group). Bands being too tight. No serious adverse effects reported	National cancer institute
Ghezelbash, S 2017 [30]	Acupressure for nausea-vomiting and fatigue management in acute lymphoblastic leukemia in children	RCT	Single-blind RCT	Two pediatric hospitals in Iran	Examine the effectiveness of acupressure for controlling CINV^ and CRF (cancer related fatigue)	120	0	Children ages 8–12 yrs. old. Finger acupressure $n=60$ vs. Sham acupressure $n=60$. Total:($n=120$)	NR	**Exclusion:** Patients with low platelet count (<50,000), a bleeding disorder, hemoglobin levels < 9 g/dl and hematocrit < 30, or were on active treatment for anemia	Finger acupressure (p6, st36) vs. sham acupressure (SI3,LI12)	Significant differences were observed between the two groups based on the fatigue and nausea intensity immediately and one hour post intervention ($P \leq 0.001$)	NR	NR
Gottschling S, 2008 [7]	Acupuncture to alleviate chemotherapy-induced nausea and vomiting	RCT	Single-blind RCT crossover trial	5 pediatric oncology centers in Germany	Evaluate the efficacy and acceptance of acupuncture as an additive antiemetic treatment during highly emetogenic chemotherapy in pediatric cancer patients	23	0	Children 4- 18 yrs. old. $n=23$ (intervention) vs 23 (standard care only). (Participants were their own controls). Total: ($n=23$)	Power calculation reported	**Exclusion:** Patients with full control of CINV without need of antiemetic rescue mediation during 1st chemo course. Children under 6 or over 18, previous experience with acupuncture within the last 6 months	Acupuncture vs chemotherapy/ antiemetic regime	Use of rescue antiemetic medication was lower among those using acupuncture ($p=0.001$). Episodes of vomiting among those receiving acupuncture were lower ($p=0.01$) in pediatric oncology patients	Four cases of pain from needling. Adverse effects were minor and transient	NR

Table 1 (continued)

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Jones, PA 2008 [32]	Acupressure for CIVN in children with cancer	Pilot study	Prospective randomized crossover clinical trial (RCT)	Children's hospital USA	Assess feasibility, safety, and effectiveness of acupressure therapy for preventing or reducing CIVN in children receiving chemotherapy	21	3	Children ages 2–20 yrs. old. $n=18$ (acupressure band) vs 18 (placebo band). Total: ($n=18$) (Participants were their own controls)	NR	**Exclusion:** If patients were not expected to received at least 3 courses of chemotherapy, parents did not consent, were over 7 yrs. old and did not assent to participate, no English speaking	Acupressure wrist bands vs. sham wrist bands (wrist bands placed on wrist prior to starting chemo)	Acupressure bands did not offer significant benefits	NR	NR
Reindl, TK 2006 [8]	Acupuncture for CIVN in children with cancer	RCT, multicenter crossover trial	Randomized multicenter, prospective crossover trial	4 German pediatric oncology centers	Evaluate the efficacy and acceptance of acupuncture as a supportive antiemetic approached during highly emetogenic chemotherapy	11	0	Children 6–18 yrs. old ($n=11$). $n=11$ (needle acupuncture) vs 11 (standard care only). Total: ($n=11$). Participants were their own controls	Did not reach power	**Inclusion:** Children who received several courses of highly melogenic chemotherapy as part of therapy protocols for Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma, including 5-HT3 antagonists as basic antiemetic medication	Antiemetic medication vs. Antiemetic medication plus acupuncture. Acupuncture was applied on day 1 and throughout the chemotherapy course	Acupuncture enable patients to experience higher levels of alertness during chemo and reduced nausea and vomiting	One case of needle pain	CD Foundation and Friedrich-Sicker Foundation
Varejão, C 2019 [29]	Laser acupuncture for relieving nausea and vomiting in pediatric patients undergoing chemotherapy	Single-blinded RCT	Single-blind randomized clinical trial	Oncology Hospital in Rio de Janeiro, Brazil	1.Apply laser acupuncture in children and adolescents undergoing chemo 2. Analyze the effects of laser acupuncture in terms of preventing and/or relieving nausea and vomiting 3. Propose a nursing care protocol using laser acupuncture to prevent and/or relieve nausea and vomiting	18	1	Children between 6–17 yrs. old. $n=7$ (intervention) vs 10 (sham acupuncture). Total:($n=17$)	Power calculation reported and reached	**Inclusion:** Children 6–17 yrs. with solid tumors. Patients going chemo with cisplatin, methotrexate, doxorubicin, etoposide, infosfamide, and/or cyclophosphamide. Use of medium and/or highly emetogenic drugs **Exclusion:** previous history of gastrointestinal diseases or antiulcer treatment. Prior history of acupuncture treatment. Use of aprepitant	Laser acupuncture vs sham laser acupuncture. A total of 26 treatments in each group (1 day of chemo)	Significant relief from nausea in the intervention group ($p<.0005$). Decrease in the number of vomiting episodes on the 2nd and 3rd day of chemotherapy ($p=.0001$)	NR	Provided by researchers. No funding from companies or public agencies

Table 1 (continued)

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Yeh, CH 2012 [18]	Auricular acupuncture for nausea and vomiting	Pilot study crossover trial	Randomized single blinded crossover trial	Hospital in Taiwan	Determine if auricular acupressure point is more effective than sham acupressure point and standard care for chemotherapy induced nausea and vomiting	17	7	Children ages 5–18 yrs. old $n=10$ auricular acupressure, $n=10$ Sham acupressure intervention. Total: ($n=10$). Participants were their own controls	Power calculation reported	**Inclusion:** Children diagnosed with cancer and that had at least one round of chemotherapy treatment who were prescribed chemotherapy drugs with high or moderate level of emetogenic agents; were prescribed standard antiemetics with their chemotherapy drugs and had not previously received any acupuncture or acupressure treatments in the previous 3 months	Auricular acupressure (AAP) vs. Sham acupressure intervention (SAP)	Patients in the auricular acupuncture point group had lower occurrence and severity of acute and delayed nausea ($p=0.0289$) and shorter vomiting ($p=.0024$) duration than patients receiving sham acupuncture and standard care	NR	NR
Biological-based therapies														
Consolo, Lzz 2013 [24]	Zinc supplement for weight gain and infectious episodes in children with acute leukemia	Double blinded RCT	Double blind placebo controlled study	Regional Hospital in Brazil	Evaluate the effects of oral zinc supplementation on weight gain and infectious episodes in children and adolescents with acute leukemia	38	0	Children 1–18 yrs. old, $n=20$ (intervention, syrup with zinc) vs $n=18$ (placebo, only syrup). Total ($n=38$)	NR	**Inclusion:** Children with previously established clinical and laboratorial diagnoses either for lymphocytic or myeloid leukemia. **Exclusion:** acute infectious disease, renal failure, post surgery status or usage of zinc containing drug	Group A: Oral placebo syrup containing no zinc. Group B syrup containing zinc	Significant difference was found in favor of the intervention group regarding weight gain ($p=0.032$) and the number of infections episodes ($P=0.02$). No significant differences in xerostomy, taste dysfunction nausea and vomiting between the two groups ($P=0.812$)	NR	Brazilian agencies CNPq and FUNDECT-MS
El-Housseiny, AA 2007* [19]	Effectiveness of vitamin E to treat mucositis	RCT	Randomized controlled trial	Oncology department Alexandria University and El-Talaba hospital of Alexandria	To compare the effect of vitamin E topically and systematically in the treatment of chemotherapy induced oral mucositis	80	17	Children under 12 yrs. old $n=30$ (Vitamin E topical), $n=33$ (Vitamin E systemic). Total: ($n=63$)	NR	**Inclusion**: Children with chemotherapy induced oral mucositis	Topical Vitamin E application vs. Systemic Vitamin E intake	Topical application of Vitamin E twice daily was significant more effective than systemic Vitamin E for chemotherapy-induced mucosis ($P>0.001$)	NR	NR

Table 1 (continued)

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Evans, A 2018 [26]	The use of aromatherapy to reduce CIN in children with cancer	Double-blinded RCT, with three arms	double blind placebo controlled study	Infusion center for emetogenic chemo in So. California	To investigate the utility of ginger aromatherapy in relieving chemotherapy-induced nausea in children with cancer	49	0	Children 8 to 21 yrs. old, $n=10$ (water gr), $n=19$ (shampoo gr), $n=20$ (ginger gr). Total: ($n=49$)	Power calculation / Intent to treat reported	**Inclusion:** Diagnoses of cancer with any type and amount of prior therapy. Thirty minute infusion of moderately emetogenic chemotherapy. **Exclusion:** Patients with asthma on daily medication. Patients unable to complete the four point face scale	Aromatherapy (inhalation of ginger aroma oil) vs. no treatment (inhalation of water) vs. placebo (shampoo)	Ginger aromatherapy did not significantly decrease nausea. Fifty-nine percent ($n=29$) reported no change while 29% ($n=14$) reported improvement	NR	J. Patrick Barnes Grant from the DAISY foundation
Khurana, H 2013 [27]	An evaluation of Vitamin E and Pycnogenol (P) in children suffering from oral mucositis during cancer chemotherapy treatment	Single blinded RCT	Single-blind randomized controlled clinical trial	CSM Medical University, Lucknow. India	Evaluate P for its beneficial effects on oral mucositis in children and to compare with E	72	0	Children 16–15 yrs. old $n=24$ (Pycnogenol); $n=24$ (Vitamin E); $n=24$ (Placebo (glycerine)). Total: ($n=72$)	NR	**Inclusion**: Children receiving chemotherapeutic regime with signs of chemotherapy-induced mucositis and patients whose parent /guardian provided consent. **Exclusion:** Children who received chemotherapy in the head and neck region, on anti-platelet or anticoagulant therapy, having pre-existing oral disease	Preparations of Vitamin E vs Pycnogenol vs Glycerine	Both drugs Vitamin E and Pycnogenol were effective for treatment of oral mucositis compared to placebo ($P<0.001$)	NR	NR
Ladas, EJ 2010 [22]	Milk thistle (Silybum marianum) for the treatment of hepatotoxicity in childhood ALL^^	A double-blind RCT	Randomized, controlled, double-blind study	Columbia University Medical Center	To evaluate the safety and feasibility of Milk thistle for the treatment of hepatotoxicity in children with ALL who are receiving maintenance-phase chemotherapy	50	1	Children between 1 -21 yrs. old, $n=23$ (Milk Thistle), $n=26$ (placebo). Total: ($n=49$)	Power calculation reported	**Inclusion:** Children with ALL. Maintenance phase of therapy Hepatic toxicity of grade 2 or greater on ALT, AST, total bilirubin. **Exclusion**: Patients with extra hepatic biliary obstruction, or malabsorption syndromes	Milk thistle vs placebo for 28 days	Milk Thistle was associated with trend toward significant reductions in liver toxicity (AST* $P=.05$; ALT** $P=.07$)	Seven cases of adverse effects in the intervention group: Diarrhea ($n=2$), flatulence ($n=1$),irritability ($n=2$) and stomach ache ($n=2$). Six cases in the placebo group: Decreased appetite ($n=1$), Diarrhea ($n=2$), Stomach ache ($n=2$), soft stools ($n=1$). No significant differences in patient reported adverse effects	American Institute for Cancer Research. The Tamarind Foundation. Part of NCI grant

Table 1 (continued)

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Pillai AK, 2011 [33]	Ginger powder vs. Placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy	Double-blind RCT	Prospective double-blind, randomized single institutional study	All India Institute of medical sciences,New Delhi, India	To evaluate the efficacy of ginger powder in reducing CINV	60	3	Children and young adults 8–21 yrs. old, $n=30$ (Ginger gr), $n=27$ (Placebo gr),Total: ($n=57$)	NR	**Inclusion:** Children newly diagnosed bone sarcomas undergoing therapies with high emetogenic chemo. **Exclusion:** Children with weight < 20 kg or > 60 kg, those receiving radiotherapy and patients additionally receiving aprepitnat with the standard antiemetics were excluded	Ginger root powder capsules vs placebo	Ginger root powder significantly reduced the severity of both acute and delayed CINV ($p=0.003$); Acute vomiting ($p=0.002$); Delayed nausea ($p=<0.001$); Delayed vomiting ($p=0.022$)	NR	NR
Rathe, M 2019 [21]	Bovine colostrum against chemotherapy-induced gastrointestinal toxicity in children with ALL	Double-blinded RCT	Double blind placebo controlled clinical trial	Hans Christian Andersen Children's Hospital, Odense University Hospital and Rigshopitalet. University Hospital of Copenhagen, Denmark	To investigate nutrition supplementation with bovine colostrum effect on fever, infectious morbidity, and mucosal toxicity during induction treatment for childhood ALL	62	0	Children 1–18 yrs. old, $n=30$ (treatment), $n=32$ (placebo), Total: ($n=62$)	Power calculation and intention to treat analysis performed	**Inclusion:** Newly diagnosed with ALL. **Exclusion**: Children with known lactose intolerance or allergy to cow's milk protein	Received daily dietary supplement with either bovine colostrum or a placebo supplement from the first day of chemotherapy until day 29 or end of induction therapy	Peak severity of oral mucositis was significantly reduced by colostrum compared with placebo ($p=0.02$). No difference was observed for days of fever, neutropenic fever, intravenous antibiotics, or incidence of bacteremia	No adverse effects of the supplement were reported	Danish Childhood Cancer Foundation, Odense University Hospital research fund, common research fund b/w Odense University Hospital and Rigshospitalet and University of Southern Denmark
Tomaževič T, 2013 [23]	Propolis (bee glue) for effectiveness in the treatment of severe oral mucositis in chemotherapy treated children	Single blinded RCT	Single-blind randomized controlled clinical trial	Slovenia University children's hospital	Assess the efficacy of propolis versus placebo for the treatment of chemotherapy induced oral mucositis	50	10	Children 1–19 yrs. old ($n=19$ propolis) vs ($n=21$, placebo). Total:($n=40$)	Power calculation reported	**Inclusion:** Pediatric patients who had been diagnosed with cancer and had started chemotherapy. **Exclusion**: Allergy to propopolis and pre-diagnosed oral disease or therapy for oral disease	Propolis vs placebo	No significant difference were found between the groups.Propolis cannot be recommended for severe oral mucositis	No adverse effects of the supplement were reported	Colgate Palmolive Adria

Table 1 (continued)

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Wada M, 2010 [34]	Effects of the administration of Bifidobacterium breve (probiotic) on patients undergoing chemotherapy for pediatric malignancies	Single-blinded RCT	Single-blinded, placebo controlled trial	Juntendo University Hospital, Tokyo Japan	To evaluate the effects of probiotic, Bifidobacterium breve, and its ability to prevent infection, fecal micro flora, and intestinal environments in cancer patients on chemotherapy	40	2	Children ages 1–13 yrs. old, $n=17$ (probiotic), $n=21$ (placebo), total: ($n=38$)	Power calculation reported	**Exclusion**: Presence of congenital immune deficiency and oral intake of the probiotic during 2 weeks prior to the trial	Probiotic vs. placebo	Frequency of fever ($p=0.02$) and use of IV antibiotics were lower in the probiotic group ($p=0.04$), suggesting that probiotic could be beneficial for immunocompromised hosts by improving intestinal environment	NR	NR
Ward E, 2009 [35]	The effect of high-dose enteral glutamine on the incidence and severity of mucositis in pediatric oncology patients	RCT cross-over trial	Randomized controlled	St. James's University Hospital, Leeks, UK Yorkshire Regional Center for Pediatric oncology	To determine if enteral glutamine daily for 7 days was effective in reducing the incidence an severity of mucositis in pediatric oncology patients	76	26	Children between 1–21 yrs., total: ($n=50$). Patients were their own control	Power calculation reported	**Inclusion**: Patients who had two identical courses of chemo and were receiving chemotherapy likely to cause mucositis	Glutamine vs. placebo administered daily for 7 days	The study showed that high-dose enteral glutamine did not reduced the incidence and severity of oral mucositis as determined by subjective toxicity measurements, but did show a significant reduction in parenteral nutrition usage ($p=.049$)	NR	SHS International (provided glutamine)

Table 1 (continued)

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Mind–body therapies														
Abdulah, DM 2018 [31]	Investigated group art therapy on quality of life in pediatric patients with cancer	RCT	Randomized controlled trial	Heevi Pediatric Hospital in Duhok, Iraq	To evaluate the effectiveness of art therapy on the health related quality of life for children undergoing chemotherapy	61	1	Children ages 7–16 yrs. old, $n=30$ (treatment), $n=30$ (control). Total: ($n=60$)	Power calculation reported	**Inclusion:** Children previously diagnosed with cancer and had received chemotherapy for at least the last 6 months. **Exclusion:** Patients who attended fewer than six two hours painting and drawing sessions	Art therapy (painting) vs control (not explained)	Patients in the experimental group were more physically active and energetic ($p<0.001$), were less depressed and had fewer stressful feelings ($P=0.004$). They also had more opportunities to structure and enjoyed their social and leisure time and participation in social activities ($P=0.003$), creates more social relationships ($P=0.043$) and had better overall health ($P<0.001$)	NR	NR
Jacknow, DS 1994 [20]	Hypnosis in the prevention of CINV in children	Single-blinded RCT	Randomized and controlled single-blind trial	Lucille Salter Packard Children's Hospital (Stanford Univ.) and Moffitt/ Long Hospitals (Univ. Of California- San Francisco)	To study the effectiveness of hypnosis for decreasing antiemetic medication usage and treatment of CINV	20	1 loss to follow-up, data was used in the analysis	Children ages 6–18 yrs. old, $n=10$ (treatment), $n=10$ (control), Total: ($n=20$)	NR	**Inclusion**: Newly diagnosed patients with no previous experience with chemotherapy. **Exclusion:** Evidence of central nervous system disease	Hypnosis and antiemetics vs standard antiemetic regimen/ conversation with therapist	The hypnosis group experienced less anticipatory nausea than the control group ($p<.02$) and used less antiemetic medication ($p<.04$)	NR	DHHS Maternal and child health bureau
Nguyen, TN 2010 [28]	Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture (LP)	Single-blinded RCT	Single blinded randomized clinical trial	National Hospital of pediatrics. Hanoi. Vietnam	To evaluate if music therapy influences pain and anxiety in children with cancer	40	0	Children 7–12 yrs. old, $n=20$ (treatment), $n=20$ (control). Total: ($n=40$)	Power calculation reported	**Inclusion:** Patients that were due to undergo LP and had previously undergone LP at least once previously **Exclusion:** Children had any significant hearing or visual impairments or cognitive disorder	Music vs control (no music)	Lower pain ($p<.003$), respiratory rate ($p<.003$) and anxiety scores ($p<.001$) were significant lower in music group after the LP compared with the control group	NR	There was no financial support

Table 1 (continued)

Study ID	Objectives	Method	Design	Setting	Aim (s)	Sample size	Drop-out	Participant(s) intervention/ control	Intention to treat & power calculation	Inclusion/exclusion criteria	Intervention treatment vs control	Results	Adverse effects due to the use of CAM	Funding
Zeltzer, LK 1991 [36]	Behavioral intervention (hypnosis) for chemotherapy distress in children	RCT	Randomized controlled trial	Two pediatric oncology centers University of Texas Health Science Center in San Antonio and Children's Hospital of Los Angeles	To determine the relative efficacy of the two forms of behavioral intervention for reducing chemotherapy related distress	54	0	Children 5–17 yrs. old, $n=21$ (hypnosis), $n=16$ (support), $n=17$ (control), Total: ($n=54$)	Not reported	**Inclusion:** Children with cancer, reliable reporting of significant chemotherapy related nausea and / or vomiting during baseline assessment and were able to consistent independent self reports of their chemotherapy related distress. **Exclusion:** Patients that could not provide reliable consistent reporting	Hypnosis vs support (relaxation) vs control (causal conversation)	Children in hypnosis group reported the greatest reduction of both vomiting ($p=<.005$) and shorter duration of nausea ($p=<.001$)	NR	Grant from the National Cancer Institute

^^ ALL: Acute lymphoblastic leukemia *AST: Aspartate amino transferase**ALT: Amino alanine transferase***HEC: Highly melogenic chemotherapy: §CIV:chemotherapy induced vomiting: + CIN:chemotherapy induced nausea:CINV^: chemotherapy induced nausea-vomiting: NR: Not reported in publication *excluded from further analysis due to low quality

Table 2 Studies quality assessment

Citation	**Q1.** Was true randomization used for assignment of participants to treatment groups?	**Q2.** Was allocation to treatment groups concealed?	**Q3.** Were treatment groups similar at baseline?	**Q4.** Were participants blind to treatment assignment?	**Q5.** Were those delivering treatment blind to treatment assignment?		**Q7.** Were treatments groups treated identically other than the intervention of interest?	**Q8.** Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	**Q9.** Were participants analyzed in the groups to which they were randomized?	**Q10.** Were outcomes measured in the same way for treatment groups?	**Q11.** Were outcomes measured in a reliable way?	**Q12.** Was appropriate statistical analysis used?		**Quality %**
Abdulah, DM 2018 [31]	Y	Y	Y	N	N	U	U	Y	Y	Y	Y	Y	U	61.54%
Consolo, Lzz 2013 [24]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	92.31%
Dupuis, L 2018 [25]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	92.31%
El-Housseiny, AA 2007 [19]	U	U	U	N	N	U	Y	Y	N	Y	Y	Y	U	38.46%
Evans, A 2018 [26]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	92.31%
Ghezelbash, S 2017 [30]	Y	Y	Y	Y	U	U	Y	Y	Y	Y	U	Y	Y	76.92%
Gottschling S, 2008 [7]	Y	Y	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	76.92%
Jacknow, DS 1994 [20]	Y	U	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	76.92%
Jones, PA 2008 [32]	Y	Y	Y	Y	N	U	Y	Y	Y	Y	Y	U	Y	76.92%
Khurana, H 2013 [27]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	92.31%
Ladas, EJ 2010 [22]	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	92.31%
Nguyen, TN 2010 [28]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	92.31%
Pillai AK, 2011 [33]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	76.92%
Rathe, M 2019 [21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.00%
Reindl, TK 2006 [8]	Y	Y	Y	Y	N	U	Y	Y	Y	Y	Y	Y	U	76.92%
Tomaževič T, 2013 [23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.00%
Varejão, C 2019 [29]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	92.31%
Wada M, 2010 [34]	U	U	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	69.23%
Ward E, 2009 [35]	Y	N/A	Y	N/A	N/A	U	Y	Y	Y	Y	Y	Y	Y	69.23%
Yeh, CH 2012 [18]	U	U	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	61.54%
Zeltzer LK, 1991 [36]	Y	U	Y	N	N	U	Y	Y	Y	Y	Y	Y	U	61.54%

Y = Yes N = No U = Unclear N/A = Not applicable

< 50% = Low-quality 50% -75% = Medium-quality > 75% = High-quality

difference in lower nausea intensity in the intervention and placebo groups immediately ($p = 0.02$) after and one hour ($p \leq 0.001$) after intervention. The fatigue intensity was also considerably reduced in both groups one-hour post-intervention ($p \leq 0.01$). Gottschling, et al. [8] found that the need for rescue antiemetic medication

was significantly ($p<0.001$) lower during acupuncture courses compared to control courses, and episodes of vomiting per course were significantly lower in courses with acupuncture ($p=0.01$). Reindl et al. [9] found that antiemetic medication used was reduced in courses with acupuncture ($p=0.024$) compared to the courses where acupuncture was not used. Vereajão et al. [35] found that laser acupuncture relieved nausea during chemotherapy ($p<0.0001$) and relieved vomiting on the second and third day after chemotherapy ($p=0.0001$) compared to those receiving sham laser acupuncture.

In conclusion, two [8, 9] studies found that acupuncture treatment lowered the use of antiemetic medication. Also, two [8, 35] studies found that acupuncture relieved vomiting during treatment, and one [35] study found that it relieved nausea post-chemotherapy treatment, however, at an insignificant level (for further information see the meta-analysis section).

Biological-based therapies

Ten studies [18, 20–22, 26, 29, 30, 33, 36, 38] identified in the literature search evaluated the effectiveness of supplements, such as vitamin E, zinc, ginger, bovine colostrum, propolis, probiotics, and glutamine, on alleviating chemotherapy-induced adverse effects such as oral mucositis, nausea, vomiting, hepatotoxicity, weight loss, and infection. The use of ginger aromatherapy to treat nausea and propolis to treat oral mucositis showed insignificant difference between the intervention and control groups [30, 38]. Consolo et al. [26] found that children taking zinc had significant ($p=0.03$) weight gain and fewer infections ($p=0.02$) compared to those in the control group. Three studies showed a significant effect of CAM modalities on oral mucositis. Khurana et al. [20] evaluated the effects of vitamin E and pycnogenol among children suffering from oral mucositis during cancer chemotherapy. Results showed significant improvements in mucositis among those who received vitamin E and pycnogenol treatment ($p<0.001$) compared to those in the control group. Ward et al. [36] investigated the effect of enteral glutamine on the incidence and severity of mucositis among children and young adult oncology patients. Glutamine did not reduce the severity or incidence of mucositis, but the use of parenteral nutrition was significantly reduced ($p=0.049$). Rathe et al. [29] evaluated the efficacy of bovine colostrum to treat chemotherapy-induced gastrointestinal toxicity, the incidence of fever, and infectious complications among children with cancer. The results showed no difference between the experimental and control groups among gastrointestinal toxicity and incidence of fever but there was a significant ($p=0.02$) reduction in the severity of oral mucositis among participants who received bovine colostrum when compared to those in the control group [29].

Ladas et al. [33] looked at the effectiveness of using milk thistle for the treatment of hepatotoxicity. Milk thistle did not show any significant difference in frequency of adverse effects, incidence or severity of toxicity, or infections. Participants receiving milk thistle treatment did, however have significantly ($p=0.05$) lower aspartate aminotransferase (AST) measurements on day 28 and 56. Pillai et al. [21] investigated the effectiveness of ginger powder in chemotherapy-induced nausea and vomiting. The findings showed that acute moderate to severe nausea ($p=0.003$) and vomiting ($p=0.002$), and delayed moderate to severe nausea ($p<0.001$) and vomiting ($p=0.02$) were significantly more common among the control group participants compared to those in the experimental group. Lastly, Wada et al. [22] evaluated the effects of probiotic *bifidobacterium breve* among children undergoing chemotherapy. Results showed that the frequency of fever ($p=0.02$) and the use of intravenous antibiotics ($p=0.04$) were significantly lower in the participants receiving probiotics than those in the placebo group.

In summary, several biological-based therapies have been shown to have positive effects on children and young adults undergoing anti-cancer treatment. Zinc helped children gain weight and had fewer infections [26]. The severity of mucositis was reduced among those who took vitamin E, pycnogenol, and bovine colostrum [20, 29]. Glutamine decreased the use of parenteral nutrition [36]. Milk thistle lowered the AST measurements [33]. Probiotic *bifidobacterium breve* lowered the frequency of fever and the use of intravenous antibiotics [22]. Lastly, ginger powder reduced acute and delayed nausea/vomiting [21].

Mind–body therapies

Four studies ($n=4$) [23, 25, 27, 28] assessed the use of mind–body therapies such as hypnosis, music and art therapy to treat chemotherapy-induced adverse effects (i.e., nausea, vomiting, stress, anxiety, and pain). Two of the studies ($n=2$) [27, 28] evaluated the use of hypnotherapy to treat chemotherapy-induced nausea and vomiting. Jacknow et al. [27] found that patients receiving hypnosis treatment used less supplemental antiemetic medication compared to those in the control group during the first ($p<0.04$) and second ($p<0.02$) course of chemotherapy. The research group also found that participants receiving hypnosis treatment experienced less anticipatory nausea ($p<0.02$) than those in the control group [27]. In a different study, Zeltzer et al. [28] examined the effects of hypnosis and support groups on reducing chemotherapy-related distress. They found that the duration of

nausea was significantly shorter for those in the hypnosis ($p<0.001$) and support ($p<0.01$) groups compared to those in the control group. Shorter duration of vomiting was also significant among the patients in the hypnosis group compared to those in the control group ($p<0.005$) [28]. Music therapy was used as a treatment to reduce pain and anxiety in children with cancer undergoing lumbar puncture. Nguyen et al. [25] found that those receiving music therapy during and after lumbar puncture had significantly lower pain scores during ($p<0.001$) and after ($p<0.003$) the procedure. Anxiety scores were also lower among those receiving music therapy ($p<0.001$). There was a significant reduction in respiratory rate ($p=0.009$) and heart rate ($p=0.009$) in children receiving music therapy during the procedure. There were also significant differences in respiratory rate ($p=0.003$) for the children in the music group after the procedure [25]. Abdulah et al. [23] measured the effectiveness of group art therapy on the quality of life in pediatric patients. They found that those in the art therapy group were significantly more physically active ($p<0.001$), less depressed, less emotional, and less stressed ($p=0.004$). The results also showed that they enjoyed their leisure time more and participated in more social activities ($p=0.003$). They also showed improvement in their relationships with other children ($p=0.043$) and had better overall health status ($p<0.001$) [23].

In conclusion, mind–body therapies have shown to have positive outcomes on the adverse effects experienced by children with cancer undergoing treatment. Hypnosis decreased the need for supplemental antiemetic medication and reduced anticipatory nausea [27] and the duration of nausea/vomiting [28]. Music therapy decreased anxiety and pain as well as respiratory and heart rate during treatment procedures, and also decreased the respiratory rate after treatment [34]. Finally, art therapy had a positive impact on the quality of life of the children undergoing cancer treatment [23].

Safety of CAM interventions

Six studies ($n=6$) [8, 9, 29–31, 33] reported adverse effects from the interventions. Among the acupuncture studies, three ($n=3$) [8, 9, 31] reported adverse effects. Dupuis et al. [31] reported six ($n=6$) adverse effects of bands being too tight. Gottschling et al. [8] reported four ($n=4$) cases of pain from needling, and Reindl et al. [9] reported one case of needle pain. Among the biological-based therapies, Ladas et al. [33] reported seven cases of adverse effects as follows: diarrhea ($n=2$), flatulence ($n=1$), irritability ($n=2$), and stomachache ($n=2$). Rathe et al. [29] and Tomaževič et al. [30] noted no adverse effects reported by the participants in their RCTs.

In conclusion, only twenty-nine percent ($n=6$) of the RCTs collected data on safety. Adverse effects were reported as mild and transient, suggesting that the therapies presented in this review have minor risks. No cases of serious adverse effects were reported.

Meta-analysis on nausea and vomiting

Seven randomized control trials ($n=7$) [8, 9, 19, 24, 27, 28, 35] with 315 participants were included in the statistical analysis. Studies in the meta-analysis consisted of two group interventions ($n=166$) (acupuncture and hypnosis) versus control ($n=149$) (standard medical care and placebo) (Fig. 2). Conventional standard care consisted of standard antiemetic medicines.

Overall effect of CAM for CINV

An overall comparison was made between CAM modalities (included acupuncture and hypnosis only) for chemotherapy-induced nausea and/or vomiting and controls. The difference between participants treated with CAM those in the control group was statistically significant with a standard mean difference of -0.54, 95% CI [-0.77, -0.31] $I^2=0\%$ ($p<0.00001$). The participants that received CAM treatment reported less episodes and intensity of nausea and/or vomiting.

Different sensitivity analyses were performed according to the categories of CAM treatment and are presented below. All studies eligible for the meta-analysis, with the exception of one [19], were performed among children aged 18 years or younger.

Acupuncture for nausea and/or vomiting

A comparison was made between acupuncture treatments for chemotherapy-induced nausea and/or vomiting and controls. Five studies ($n=5$) [8, 9, 19, 24, 35] with 241 participants (intervention $n=119$, control $n=122$) were included in this comparison. A statistically significant difference was found between those who received acupuncture and those who did not -0.59, 95% CI [-0.85, -0.33] $I^2=0\%$ ($p<0.00001$) (Fig. 2). The participants that received acupuncture treatment reported less episodes and/or intensity of nausea and/or vomiting during or at the end of chemotherapy treatment.

Hypnosis for nausea and/or vomiting

A comparison was made between hypnosis treatments for chemotherapy-induced nausea and/or vomiting and controls. Two studies ($n=2$) [27, 28] with 74 participants were included in this comparison (intervention $n=47$, control $n=27$). No statistically significant difference was found between those who received hypnosis and those who did not -0.41, 95% CI [-1.09, 0.27] $I^2=41\%$ ($p=0.19$) (Fig. 2).

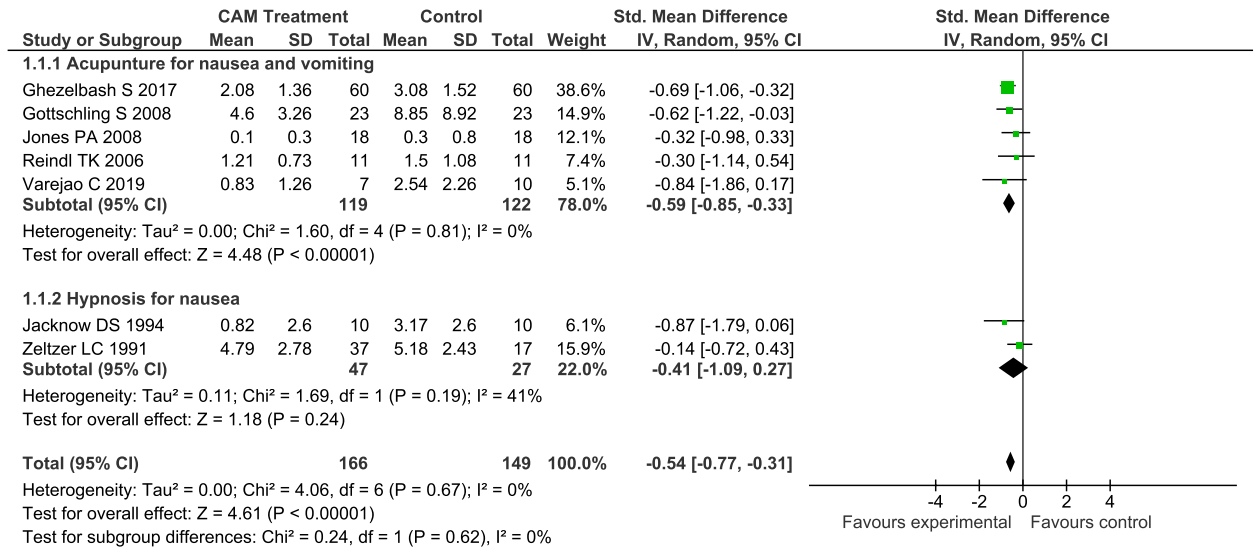

Fig. 2 Forest Plot CAM Treatment vs. Control for CINV

We excluded 13 studies from the meta-analysis due to the following reasons:

(1) The studies ($n=13$) [20–23, 25, 26, 29–33, 36, 37] presented incomparable outcomes and CAM treatments
(2) The reported data was inadequate to conduct a meta-analysis in four studies ($n=4$) [20, 21, 29, 38]

Discussion

This systematic review and meta-analysis demonstrate that CAM may be beneficial in relieving adverse effects of cancer treatment among children and young adults. Twenty RCTs comprising 1069 participants were included in this review. The majority (62%) of the included studies were assessed to have high methodological quality according to the JBI SUMARI tool. CAM modalities used for treating adverse effects of cancer treatment were: aleternative medical systems, biological-based therapies, and mind–body therapies. According to this review, CAM modalities helped relieve nausea, vomiting, mucositis, weight loss, anxiety, pain, and improve the overall quality of life measures. The meta-analysis demonstrated that acupuncture was effective in relieving chemotherapy-induced nausea and vomiting compared to controls.

Alternative medical systems

Acupuncture is a promising modality for treating chemotherapy-induced nausea and vomiting in children and young adults with cancer. The results of this review are in line with other studies showing that acupuncture is beneficial. It is also included in the guidelines to treat nausea and vomiting in cancer care among both adults [39, 40] and children [41]. Acupuncture is considered to be a modality that is less invasive, more natural, and less liable to adverse effects than many conventional forms of treatment, [42] and potentially cost-effective [43]. Studies conducted among adults have demonstrated that acupuncture is effective for the management of nausea and vomiting. However, studies conducted among children are few and tend to have small sample sizes [8, 9, 19, 35, 44]. The results of this review are important because all studies included in the meta-analysis were assessed as high-quality RCTs and demonstrated a statistically significant effect towards acupuncture to treat chemotherapy-induced nausea and vomiting. The results from the meta-analysis show that overall CAM (-0.54, 95% CI [-0.77, -0.31]) (included acupuncture and hypnosis only) and acupuncture (-0.59, 95% CI [-0.85, -0.33]) have a medium effect size as defined by Cohen, J (1988) [45]. There are no existing comparison studies to establish the clinical significance of the results. However, when compared to the effect sizes of conventional emetic treatments, most of them have small or medium effect sizes [46–50]. Although emetic treatments and acupuncture are not comparable, the results from this review suggest that the use of acupuncture as a complement to conventional emetic treatment might be beneficial for the patients to control CINV.

Biological-based therapies

Biological-based therapies including herbs and vitamins are among the most frequently used CAM modalities by children with cancer [10]. Similar to previous studies reviewing CAM use among pediatric oncology patients [5], we found that biological-based therapies were the most commonly researched modalities used for chemotherapy-induced symptoms among children and young adult oncology patients. Ten of the twenty-one studies included in this review were related to biologically based products such as vitamin E, zinc, ginger, and bovine colostrum. This is in line with Bishop et al. [51] who reported in a systematic review that the most commonly used modalities were herbal remedies, diets, and nutrition. Seven studies were classified as high quality [20, 21, 26, 29, 30, 32, 33], two as medium quality [22, 36], and one as poor quality [18]. Given the different outcomes and treatment modalities investigated, it was not possible to perform a meta-analysis with these studies. The high prevalence in the use of biological-based therapies among children and young adults with cancer indicates that further research should be conducted to further assess the existing modalities being used and others that have not yet been properly researched [52]. Some supplements have known interactions with chemotherapy [53, 54]. In the studies included in this review, there were no major drug interactions or adverse effects reported. One study [33] reported some minor adverse effects with the use of milk thistle, and two [29] reported no adverse effects.

Mind–body therapies

Psychosocial factors play a significant role in disease onset and progression, and people's quality of life. Hence, mind–body therapies play an important role in mitigating and controlling symptoms derived from cancer treatment [55]. Several studies have investigated the effectiveness of mind–body therapies on the treatment of anti-cancer treatment-induced symptoms and quality of life [56]. Four of the studies included in this review were related to mind–body therapies and classified as medium ($n=3$) or high-quality ($n=1$) studies. Two of the studies related to hypnosis were included in the meta-analysis and the overall effect on nausea and pain was insignificant. However, previous research [57] reported that hypnotherapy significantly reduced cancer-related procedural pain combined with standard care ($p<0.00001$). Despite insignificant effect, it should be noted that the current meta-analysis was conducted with only two studies. Therefore, more randomized controlled trials should be conducted to have a larger sample size and improve the estimated effect of hypnosis on CINV. Studies excluded from the meta-analysis showed a significant effect of music and art therapy on the quality of life, and relief of symptoms such as pain and anxiety among children undergoing cancer treatment. These results are in line with other studies [58] which confirm that music and art therapy have positive effects on symptoms of anxiety and pain among children.

After reviewing the literature, it is noticeable that there is a great mismatch between the vast number of papers describing the prevalence of CAM use among children with cancer and the studies researching the effect of those treatments. The lack of RCTs in this field might be because it is more challenging (parents do not want to add extra burden to the child, risk of liability, etc.) to conduct trials in children than in adults, especially concerning cancer. Therefore, the number of studies as well as the number of pediatric patients in studies are still limited [59, 60]. The lack of studies can also be due to lack of funding to conduct CAM research [61].

This systematic review must be interpreted in light of its limitations. We may have overlooked some studies even though we carefully searched the literature in several databases and the gray literature. Also, limiting the studies to English, German, Dutch, Spanish, and the Scandinavian languages might have led us to miss relevant papers. Including pilot and feasibility studies might also be considered a limitation. However, it was important to include these studies due to limited body of work to investigate the effects of CAM modalities to treat the adverse effects of cancer treatment among children and young adults. Another limitation is that it included six articles where the age of included participants was higher than 18 years [19, 21, 30, 33, 36, 38]. The results reported in this review, therefore, do not solely represent the pediatric cancer population, but also to some extent young adults with cancer. Even though this review has limitations, they have been counteracted by the search methods being carefully implemented by a research librarian and with the use of critical appraisal tools to assess the methodological quality of the articles. The methodological quality of the studies varied between medium and high. One study was classified as low quality and was excluded from further analysis.

Implication for practice and further research

The review and meta-analysis indicate that CAM and more specifically acupuncture treatments have a positive effect in the treatment of vomiting and nausea associated with cancer treatment in children and young adults. Acupuncture is considered less invasive, and less liable to adverse effects [42].

Implication for research

Even though the meta-analyses show a positive effect of acupuncture on chemotherapy-induced nausea and vomiting in children and young adults, it is important to conduct further research to establish if some forms of acupuncture (acupressure, needle acupuncture, or laser acupuncture) are more effective than others. While hypnosis did not show a significant effect in the meta-analysis, it is important to conduct more RCTs with large sample sizes to further determine the effect of hypnosis on CINV. It is also important to expand the research on different CAM modalities that are being used to treat cancer treatment-induced symptoms in children. Future research should focus on conducting RCTs with larger samples size to further establish the effect of (the) CAM therapies. Also, RCTs should more diligently report whether there were any adverse effects from the therapies studied. Although some studies in this review reported adverse effects, the majority did not. Adverse effects are underreported in CAM research, the majority of the studies in this review ($n=15$, 71%) did not collect any safety data (see Table 1). The report of adverse effects is important to establish the safety of the CAM therapies especially related to interactions with conventional chemotherapy treatment. It is also important for the researchers to carefully design the studies to use standard measurements of the outcomes to enable comparison to other studies in the area.

Conclusion

This systematic review and meta-analysis suggest a significant overall effect of CAM (including acupuncture and hypnosis only) on CINV among children and young adults compared to the control interventions. The use of acupuncture might be considered as a complementary measure to help children cope with nausea and vomiting. CAM modalities such as acupuncture or hypnosis can easily be implemented in healthcare settings, however more rigorous trials are needed, and long-term effects should be investigated before it is recommended for clinical practice. To further establish the safety of CAM modalities and the findings of this review, it is imperative to conduct more research on different CAM modalities.

Abbreviations

ALL: Acute lymphoblastic leukemia; AST: Aspartate amino transferase; ALT: Amino alanine transferase; HEC: Highly melogenic chemotherapy; CAM: Complementary and alternative medicine; CIV: Chemotherapy-induced vomiting; CIN: Chemotherapy-induced nausea; CINV: Chemotherapy-induced nausea-vomiting:; HICs: High-income countries; NR: Not reported in the publication; JBI: Joanna Briggs Institute; PRISMA: Preferred Reporting Items for Systematic review and Meta-Analyses; RCTs: Randomized controlled trials; SMD: Standardized mean difference; SUMARI: System for the Unified Management, Assessment, and Review of Information.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12906-022-03537-w.

Additional file 1. Literature review search strategy.

Additional file 2. PRISMA 2020 checklist CAM children.

Acknowledgements

Not applicable (NA).

Authors' contributions

TS conception; DCM & TS design of the work; DCM, TS, and GO acquisition of data; DCM, TS, and JL analysis; DCM, TS interpretation of data; DCM & TS have drafted the work; DM, GO, MJ, AK, DS, JL, and TS substantively revised it. All authors have read and approved the manuscript.

Authors information

The first author (DM) holds a master's in public health in and has considerable expertise performing health research and is a doctoral student researching childhood cancer and CAM. The second author GO is a senior librarian and responsible for the training of students and researchers in literature search and Endnote at the Institute of Health Science at UIT, The Arctic University of Norway. The third author MJ holds a Ph.D. in medicine and has considerable expertise in performing many different types of systematic reviews. The fourth author (AEK) holds a Ph.D. in medical science. The fifth author (DS) is a medical doctor and Ph.D. student researching childhood cancer. The sixth author (JL) is a professor and director of the center for Evidence-Based Chinese Medicine in China. The last author (TS) holds a Ph.D. in medical science and has considerable expertise in performing many types of systematic reviews.

Funding

This research was funded by Ekhaga Stiftelsen (2020–76), Sweden, and the Childrens' Cancer Society in Troms and Finnmark, Norway. Open Access funding provided by UiT The Arctic University of Norway.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

Not applicable (NA).

Consent for publication

Not applicable (NA).

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Community Medicine, Faculty of Health Science, National Research Center in Complementary and Alternative Medicine, NAFKAM, UiT The Arctic University of Norway, 9037 Tromsø, Norway. [2]Science and Health Library, UiT, The Arctic University of Norway, Hansine Hansens veg 19, 9019 Tromsø, Norway. [3]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands. [4]Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine and Pharmacology, Beijing, China.

Received: 16 June 2021 Accepted: 21 February 2022
Published online: 02 April 2022

References

1. Cancer Registry of Norway. Cancer in Norway 2020. Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of

Norway. https://healthtalkweb.s3.amazonaws.com/documents/Cancer_in_Norway_2020.pdf; 2020.
2. Lam CG, Howard SC, Bouffet E, Pritchard-Jones K. Science and health for all children with cancer. Science. 2019;363(6432):1182–6.
3. Hedén L, Pöder U, von Essen L, Ljungman G. Parents' Perceptions of Their Child's Symptom Burden During and After Cancer Treatment. J Pain Symptom Manage. 2013;46(3):366–75.
4. Stub T, Kristoffersen AE, Overvåg G, Jong MC. An integrative review on the information and communication needs of parents of children with cancer regarding the use of complementary and alternative medicine. BMC Complement Med Ther. 2020;20(1):90.
5. Radossi AL, Taromina K, Marjerrison S, Diorio CJ, Similio R, Njuguna F, et al. A systematic review of integrative clinical trials for supportive care in pediatric oncology: a report from the International Society of Pediatric Oncology. T&CM collaborative Support Care Cancer. 2018;26(2):375–91.
6. Complementary, Alternative, or Integrative Health: What's In a Name? National Center for Complementary and Integrative Health2018 [updated 2018. Available from: https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name.
7. Hawkins J, Hires CY, Dunne EW, Keenan LA. Aromatherapy reduces fatigue among women with hypothyroidism: A randomized placebo-controlled clinical trial. Journal of Complementary & Integrative Medicine. 2020;17(1):1–9.
8. Gottschling S, Reindl TK, Meyer S, Berrang J, Henze G, Graeber S, et al. Acupuncture to alleviate chemotherapy-induced nausea and vomiting in pediatric oncology - A randomized multicenter crossover pilot trial. Klin Padiatr. 2008;220(6):365–70.
9. Reindl TK, Geilen W, Hartmann R, Wiebelitz KR, Kan G, Wilhelm I, et al. Acupuncture against chemotherapy-induced nausea and vomiting in pediatric oncology. Interim results of a multicenter crossover study. Sup Care Cancer. 2006;14(2):172–6.
10. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT. Prevalence of complementary medicine use in pediatric cancer: a systematic review. Pediatrics. 2010;125(4):768–76.
11. Krogstad T, Nguyen M, Widing E, Toverud EL. Children with cancer and their use of natural products. Tidsskr Nor Laegeforen. 2007;127(19):2524–6.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372.
13. Ouzzani M, Hammady H, Fedorowicz Z, A E. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
14. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. London: Willey-Blackwell; 2008.
15. Peters M, Godfrey C, McInerney P, Soares C, Khalil H, Parker D. The Joanna Briggs Institute reviewers' manual 2015: methodology for JBI scoping reviews. 2015.
16. Stub T, Kristoffersen AE, Overvåg G, Jong MC, Musial F, Liu J. Adverse effects in homeopathy. Explore (NY): A systematic review and meta-analysis of observational studies; 2020.
17. Review Manager (RevMan) [Computer program] Version 5.4. The Cochrane Collaboration, 2020 2020.
18. El-Housseiny AA, Saleh SM, El-Masry AA, Allam AA. The effectiveness of vitamin "E" in the treatment of oral mucositis in children receiving chemotherapy. J Clin Pediatr Dent. 2007;31(3):167–70.
19. Jones E, Isom S, Kemper KJ, McLean TW. Acupressure for chemotherapy-associated nausea and vomiting in children. J Soc Integr Oncol. 2008;6(4):141–5.
20. Khurana H, Pandey RK, Saksena AK, Kumar A. An evaluation of Vitamin E and Pycnogenol in children suffering from oral mucositis during cancer chemotherapy. Oral Dis. 2013;19(5):456–64.
21. Pillai AK, Sharma KK, Gupta YK, Bakhshi S. Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy. Pediatr Blood Cancer. 2011;56(2):234–8.
22. Wada M, Nagata S, Saito M, Shimizu T, Yamashiro Y, Matsuki T, et al. Effects of the enteral administration of Bifidobacterium breve on patients undergoing chemotherapy for pediatric malignancies. Support Care Cancer. 2010;18(6):751–9.
23. Abdulah DM, Abdulla BMO. Effectiveness of group art therapy on quality of life in paediatric patients with cancer: A randomized controlled trial. Complement Ther Med. 2018;41:180–5.
24. Ghezelbash S, Khosravi M. Acupressure for nausea-vomiting and fatigue management in acute lymphoblastic leukemia children. Journal of Nursing & Midwifery Sciences. 2017;4(3):75–81.
25. Nguyen TN, Nilsson S, Hellstrom AL, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. J Pediatr Oncol Nurs. 2010;27(3):146–55.
26. Consolo LZZ, Melnikov P, Consolo FZ, Nascimento VA, Pontes JCDV. Zinc supplementation in children and adolescents with acute leukemia. Eur J Clin Nutr. 2013;67(10):1056–9.
27. Jacknow DS, Tschann JM, Link MP, Boyce WT. Hypnosis in the prevention of chemotherapy-related nausea and vomiting in children: a prospective study. J Dev Behav Pediatr. 1994;15(4):258–64.
28. Zeltzer LK, Dolgin MJ, LeBaron S, LeBaron C. A randomized, controlled study of behavioral intervention for chemotherapy distress in children with cancer. Pediatrics. 1991;88(1):34–42.
29. Rathe M, De Pietri S, Sangild PT, Husby S, Frandsen TL, Wehner SW, et al. The use of bovine colostrum against chemotherapy-induced gastrointestinal toxicity in children with acute lymphoblastic leukemia: A double-blind placebo-controlled randomized trial. Pediatr Blood Cancer. 2018;65(Supplement 2):S109.
30. Tomazevic T, Jazbec J. A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. Complement Ther Med. 2013;21(4):306–12.
31. Dupuis LL, Kelly KM, Krischer JP, Langevin AM, Tamura RN, Xu P, et al. Acupressure bands do not improve chemotherapy-induced nausea control in pediatric patients receiving highly emetogenic chemotherapy: A single-blinded, randomized controlled trial. Cancer. 2018;124(6):1188–96.
32. Evans A, Garretson C, Pedroja E, Malvar J, Margol A, Sposto R, et al. The use of aromatherapy to reduce chemotherapy-induced nausea in children with cancer; A randomized, double blind, placebo controlled trial. Neuro-Oncol. 2016;18(Supplement 3):iii137.
33. Ladas EJ, Kroll DJ, Oberlies NH, Cheng B, Ndao DH, Rheingold SR, et al. A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). Cancer. 2010;116(2):506–13.
34. Nguyen TN, Nilsson S, Hellström A, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. J Pediatr Oncol Nurs. 2010;27(3):146–55.
35. Varejao CDS, Santo F. Laser Acupuncture for Relieving Nausea and Vomiting in Pediatric Patients Undergoing Chemotherapy: A Single-Blind Randomized Clinical Trial. J Pediatr Oncol Nurs. 2019;36(1):44–54.
36. Ward E, Smith M, Henderson M, Reid U, Lewis I, Kinsey S, et al. The effect of high-dose enteral glutamine on the incidence and severity of mucositis in paediatric oncology patients. Eur J Clin Nutr. 2009;63(1):134–40.
37. Yeh CH, Chien LC, Chiang YC, Lin SW, Huang CK, Ren D. Reduction in nausea and vomiting in children undergoing cancer chemotherapy by either appropriate or sham auricular acupuncture points with standard care. J Altern Complement Med. 2012;18(4):334–40.
38. Evans A, Malvar J, Garretson C, Pedroja Kolovos E, Baron NM. The Use of Aromatherapy to Reduce Chemotherapy-Induced Nausea in Children With Cancer: A Randomized, Double-Blind. Placebo-Controlled Trial J Pediatr Oncol Nurs. 2018;35(6):392–8.
39. Tsukinoki R, Murakami Y. Non-communicable disease epidemic: epidemiology in action (EuroEpi 2013 and NordicEpi 2013): Aarhus, Denmark from 11 August to 14 August 2013. Eur J Epidemiol. 2013;28(1):1–270.
40. O'Regan D, Filshie J. Acupuncture and cancer. Auton Neurosci. 2010;157(1):96–100.
41. Flank J, Robinson PD, Holdsworth M, Phillips R, Portwine C, Gibson P, et al. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer. 2016;63(7):1144–51.
42. Vincent C. The safety of acupuncture. BMJ (Clinical research ed). 2001;323(7311):467–8.
43. Chokshi SK, Ladas EJ, Taromina K, McDaniel D, Rooney D, Jin Z, et al. Predictors of acupuncture use among children and adolescents with cancer. Pediatr Blood Cancer. 2017;64(7):e26424.

44. Yeh CH, Zhao TY, Zhao MD, Wu Y, Guo YM, Pan ZY, et al. Comparison of effectiveness between warm acupuncture with local-distal points combination and local distribution points combination in breast cancer-related lymphedema patients: a study protocol for a multicenter, randomized, controlled clinical trial. Trials. 2019;20(1):403.
45. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, N. J: Laurence Erlbaum; 1988.
46. Qiu T, Men P, Xu X, Zhai S, Cui X. Antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting: An updated systematic review and meta-analysis. Medicine (Baltimore). 2020;99(33).
47. Yuan D-M, Li Q, Zhang Q, Xiao X-W, Yao Y-W, Zhang Y, et al. Efficacy and safety of neurokinin-1 receptor antagonists for prevention of chemotherapy-induced nausea and vomiting: systematic review and meta-analysis of randomized controlled trials. Asian Pac J Cancer Prev. 2016;17(4):1661–75.
48. Fugetto F, Filice E, Biagi C, Pierantoni L, Gori D, Lanari M. Single-dose of ondansetron for vomiting in children and adolescents with acute gastroenteritis—an updated systematic review and meta-analysis. Eur J Pediatr. 2020;179(7):1007–16.
49. Tricco AC, Blondal E, Veroniki AA, Soobiah C, Vafaei A, Ivory J, et al. Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis. BMC Med. 2016;14(1):216.
50. Lau Moon Lin M, Robinson PD, Flank J, Sung L, Dupuis LL. The Safety of Metoclopramide in Children: A Systematic Review and Meta-Analysis. Drug Safety. 2016;39(7):675–87.
51. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT. Prevalence of Complementary Medicine Use in Pediatric Cancer: A Systematic Review. Pediatrics. 2010;125(4):768–76.
52. Diorio C, Kelly KM, Afungchwi GM, Ladas EJ, Marjerrison S. Nutritional traditional and complementary medicine strategies in pediatric cancer: A narrative review. Pediatr Blood Cancer. 2020;67.
53. Kelly KM. Complementary and alternative medical therapies for children with cancer. Eur J Cancer. 2004;40(14):2041–6.
54. Cheng C-W, Fan W, Ko S-G, Song L, Bian Z-X. Evidence-Based Management of Herb-Drug Interaction in Cancer Chemotherapy. EXPLORE. 2010;6(5):324–9.
55. Sagar SM. Evidence-based clinical practice guidelines for integrative oncology: complementary therapies and botanicals (2009). J Soc Integr Oncol. 2009;7(3):83–4.
56. Kanitz JL, Camus MEM, Seifert G. Keeping the balance – an overview of mind–body therapies in pediatric oncology. Complement Ther Med. 2013;21:S20–5.
57. Jong MC, Boers I, van Wietmarschen H, Busch M, Naafs MC, Kaspers GJL, et al. Development of an evidence-based decision aid on complementary and alternative medicine (CAM) and pain for parents of children with cancer. Support Care Cancer. 2020;28(5):2415–29.
58. Facchini M, Ruini C. The role of music therapy in the treatment of children with cancer: A systematic review of literature. Complement Ther Clin Pract. 2021;42.
59. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357–69.
60. Bond MC, Pritchard S. Understanding clinical trials in childhood cancer. Paediatr Child Health. 2006;11(3):148–50.
61. Pirotta M. Towards the application of RCTs for CAM. Researching Complementary and Alternative Medicine London: Routlledge; 2007. p. 52–71.

Publisher's Note

Paper III

Safety of Complementary and Alternative Medicine (CAM) treatment among children and young adults who suffer from adverse effects of conventional cancer treatment: A systematic review

Review Article

Integrative Cancer Therapies
Volume 21: 1–22

DOI: 10.1177/15347354221105563
journals.sagepub.com/home/ict
SAGE

Safety of Complementary and Alternative Medicine (CAM) treatment among children and young adults who suffer from adverse effects of conventional cancer treatment: A systematic review

Dana C. Mora, MPH[1], Agnete E. Kristoffersen, PhD[1], Grete Overvåg[1], Miek C. Jong, PhD[1], Marit Mentink, MSc[2], Jianping Liu, PhD[3], and Trine Stub, PhD[1]

Abstract

Background: Complementary and Alternative Medicine (CAM) is widely used around the world to treat adverse effects derived from cancer treatment among children and young adults. Parents often seek CAM to restore and maintain the child's physical and emotional condition during and after cancer treatment. **Objectives:** The objectives of this review were (i) to identify literature that investigates CAM use for treating adverse effects of conventional cancer treatment, (ii) to investigate the safety of the included CAM modalities, and (iii) to evaluate the quality of included studies. **Methods:** Five scientific research databases were used to identify observational, quasi-experimental, and qualitative studies from January 1990 to May 2021. Included studies investigated the use of CAM to treat adverse effects of cancer treatment in childhood cancer. **Results:** Fifteen studies were included in this review. Ten quasi-experimental, 3 observational studies (longitudinal/prospective), 2 qualitative studies, and 1 study with a quasi-experimental and qualitative arm were identified. Less than half (n = 6; 40%) of the studies included reported adverse effects for the CAM modality being studied. Among the studies that reported adverse effects, they were mostly considered as direct risk, as 13% reported mainly bleeding and bruising upon acupuncture treatment, and dizziness with yoga treatment. All adverse effects were assessed as minor and transient. CAM modalities identified for treating adverse effects of cancer treatment were alternative medical systems, manipulative and body-based therapies, biologically-based therapies, and mind-body therapies. CAM modalities were used to alleviate anxiety, pain, toxicity, prevent trauma, and improve health-related quality of life, functional mobility, and physical activity levels. All studies assessed scored 70% or above according to the Joanna Briggs Institute critical appraisal for study quality checklists. **Conclusion:** Most of the studies (58.3%) included in this review did not report adverse effects from CAM modalities used to treat adverse effects of cancer treatment in children and young adults. This lack of safety information is of concern because parents need to know whether the modality represents an extra burden or harm to the child. To improve awareness about safety in the field, a universal and uniform reporting system for adverse effects in CAM research is needed.

Keywords

systematic review, observational studies, qualitative studies, complementary and alternative medicine, risk, patient safety

Submitted March 1, 2022; revised May 4, 2022; accepted May 21, 2022

[1]UiT The Arctic University of Norway, Tromsø, Norway
[2]Netherlands Institute for Health Services Research, Utrecht, The Netherlands
[3]Beijing University of Chinese Medicine and Pharmacology, Beijing, China

Corresponding Author:
Dana C. Mora, National Research Center in Complementary and Alternative Medicine, NAFKAM, Department of Community Medicine, Faculty of Health Science, UiT The Arctic University of Norway, PO Box 6050 Langnes, Tromsø 9037, Norway.
Email: dana.c.mora@uit.no

Background

Cancer is the leading cause of death among children and adolescents in many countries.[1] The causes of childhood cancer are often unknown.[1] However, available data suggest that 10% of all children with cancer have genetic factors that predispose them to the disease.[2] The survival rate of childhood cancer has increased especially in the western world, where more than 80% of the children with cancer are cured.[1] The increase in survival rate is due to the accessibility of conventional care services and an improvement in therapy, including risk-adapted stratification.[1] In low-and middle-income countries (LMIC), the organization and delivery of health are poor due to the lack of resources, the cost of treatment, limited accessibility, and cultural health beliefs. All of the latter lead people to seek Complementary and Alternative Medicine (CAM) treatments.[3] Nevertheless, according to research, these modalities are not as effective as curative cancer treatments. It has previously been demonstrated that the overall 5-year survival rate with only CAM treatment of acute leukemia in children was 0%.[4] The most common types of childhood cancer are leukemias, brain cancers, lymphomas, and solid tumors. The delivery of health services depends on the understanding of what types of cancers and long-term effects of cancer treatment can be expected (ie, fatigue, cognitive difficulties, etc.).[5] Even though the survival rates from childhood cancer are increasing it is important to understand how to effectively decrease the burden of morbidities and incorporate supportive rehabilitation treatments that will increase and improve the well-being of children with cancer.

The combined use of CAM and conventional medicine in children undergoing cancer treatment is high in several countries.[6-8] In Switzerland, Lüthi et al[7] reported that 69.3% of patients after diagnosis used CAM. CAM is defined as "a group of diverse medical health care systems, practices, and products that are not presently considered to be part of conventional medicine."[9] If a non-mainstream approach is used together with conventional medicine, it is considered complementary. If a non-mainstream approach is used in place of conventional medicine it is considered alternative.[3] Integrated health brings conventional and complementary approaches together in a coordinated way. Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments and aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum.[10] CAM among pediatric patients is often used as part of supportive care as a way for parents to do everything possible for the child, to boost their immune system, improve their general well-being, and/or treat adverse effects of conventional therapy.[11,12] CAM modalities most often used in pediatric oncology patients are herbal remedies,[9] homeopathy,[7,8] diet, and nutrition.[9]

CAM modalities are often considered to be natural and therefore safe, but patients may react unexpectedly to treatment that may cause harm.[13] It is therefore of significant importance to investigate the safety of these modalities when used to complement conventional medicine. Risk in medical science is defined as a measure of the probability and severity of adverse effects.[14] Risk in CAM can be divided into direct (related to interventions) and indirect (related to the setting effect) risk.[15,16] Direct risk is related to the intervention, for example, harm caused by pharmacological products, medical treatments, and procedures. Direct risk is often described as adverse effects, adverse reactions, and adverse drug reactions. Adverse effects is a more suitable term to describe risk for most CAM modalities as they encompass physical and psychological complaints and are defined as all the unwanted or harmful reactions that result from medication or intervention regardless of their relation to the actual treatment.[15,16] Indirect risk is related to the setting effects, such as the practitioner, rather than to the medicine. An example of indirect risk is a provider who overlooks serious symptoms and thereby causes a delay in necessary conventional treatment.[16]

The adverse effects of cancer therapies can be burdensome to children undergoing cancer treatment as well as their parents, because apart from dealing with symptoms at the time of treatment, they have to endure the consequences of treatment for the rest of their lives.[17] Late and long-term effects are understood as long-lasting health problems following cancer treatment.[18] Some may develop during treatment and persist (*long-term effects*) such as fatigue, whereas others may develop many years later (*late effects*) such as secondary cancer and cardiovascular diseases.[19] Children have a developing body, and cancer treatments may have more or less strong adverse effects.[20] During growth children's cells are dividing faster than adult cells. Cancer treatment such as chemotherapy and radiotherapy damages cancer cells as well as normal cells and this leads to adverse effects. For example, radiation treatment can slow the growth of bone and muscle in children causing serious effects.[21] Some of the adverse effects often reported are cough, drowsiness, fatigue, cognitive problems, and lack of energy. The most distressing symptoms reported by parents are lack of appetite, nausea, and pain, as well as psychological symptoms, such as feeling irritable and sad.[22]

Although CAM modalities are widely used among pediatric cancer patients, CAM modalities are still underinvestigated.[23,24] Our research teams conducted a systematic review of RCTs in 2021.[25] The systematic review aimed to review the research literature to identify any CAM modalities used to treat adverse effects of conventional cancer treatment among children and young adults. The meta-analysis showed that CAM (including acupuncture and hypnosis) was effective in reducing chemotherapy induced nausea and vomiting (CINV) in children and young adults.

The analysis demonstrated that only 29% of the studies included reported data on safety.[25] Many studies about CAM modalities (ie, acupressure, healing touch, massage, music therapy, reiki) investigate effectiveness, but they do not address or report safety events among the reviewed studies.[26-28] In this review we want to investigate the safety of CAM modalities used to treat adverse effects of conventional cancer treatment in children and young adults. As observational and quasi-experimental studies are suitable to investigate adverse effects of an intervention,[29] we will investigate this using this methodology. Since many of these studies have a qualitative arm nested within the design, we decided to include qualitative studies as well. Therefore, the overall aim of this study is to gain more insight about CAM modalities used to treat adverse effects of conventional cancer treatment and their safety in real-life settings.

Aims

The aims of this systematic review were to evaluate the research literature to (i) to identify observational, quasi-experimental, and qualitative studies that investigate CAM modalities used for treating adverse effects of conventional cancer treatment, (ii) to investigate the safety of the included CAM modalities, and (iii) to investigate the quality of the included studies.

Methods

Results are reported according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) checklist (see Supplemental File).[30]

The focus question was:

> Are CAM modalities used in childhood cancer (to treat adverse effects of conventional cancer treatment) associated with adverse effects?

The PICOS format was used when searching for relevant articles, which included the following 4 parts:

> **P**opulation: Children and young adults who were ever diagnosed with cancer and who used CAM to treat adverse effects of conventional cancer treatment (the pediatric population is considered 0-21 years old).
>
> **I**ntervention: Any CAM modality/All CAM modalities.
>
> **C**omparison: Conventional medicine, usual care, waiting list, and other CAM modalities.
>
> **O**utcome: Reduction/improvement of adverse effects of conventional cancer treatment, adverse events, adverse reactions, adverse drug reaction, harm, indirect/direct risks, risks factors, side effects, safety.
>
> Types of **S**tudy: Prospective and retrospective studies, cohort studies, non-experimental studies, clinical studies, quasi-experimental studies, and qualitative studies.

A protocol for the systematic review was created, submitted, and registered by PROSPERO (CRD42022302788). Three authors (DCM, TS, GO) developed the search strategy and performed the searches. Eligible studies were searched in 5 electronic databases, central webpages, and journals were searched for eligible studies: AMED, CINAHL, EMBASE, PsycINFO, and MEDLINE/PubMed. According to the search methodology references of all included studies were hand-searched for additional eligible studies. A manual search was also performed in the gray literature.

Search Methods: Various combinations of controlled vocabulary/thesaurus terms (eg, MESH) and text words, adjusted for each database were used. The following controlled vocabulary/thesaurus terms were used: *Exp neoplasms, exp complementary therapies, exp integrative medicine, alternative therapies, exp child, exp adolescent, exp young adult, exp infant, adverse effects. sf (subheading, fs), adverse event, side effects and adverse reactions, drug related side effects and adverse reactions, exp adverse drug reaction, reporting systems, exp cohort studies, exp qualitative studies, qualitative research, exp interview, exp observational study, exp nonexperimental studies.*

These text words were used: *Neoplasm, leukemia, lymphoma/soft tissue sarcoma, pediatric cancer, pediatric oncology, integrative oncology, cancer treatment, childhood cancer, pediatric, palliative care, CAM modalities, CAM treatment, CAM, integrative medicine, complementary medicine, alternative medicine, unconventional medicine, spiritual healing/faith healing, children, child*, infant, adolescent, juvenile, pediatric, puberty, young adults, young person, teen*, childhood, toddler, side effects, safety, risks factors, harm, adverse reactions, indirect/direct risks, adverse drug reaction, symptom management, hopelessness, suffering* (the search string from MEDLINE is attached as Supplemental Material).

Inclusion and Exclusion Criteria

The filters used were human, Danish, Dutch, English, German, Norwegian, Spanish, and Swedish. The searches had a limited period from January 1990 to May 2021. The inclusion comprised observational and qualitative studies that reported CAM modalities to treat adverse effects of cancer treatment among children and young adults. The search considered any adverse effects and CAM modalities. Studies including data on parents/caregivers of children

with cancer and their health care providers were also included. Studies with children and young adults up to 21 years of age were included when this age group was described as part of the pediatric cancer population in the publication.

The studies excluded did not provide adverse effects from conventional cancer treatment, were not related to cancer or CAM, were not observational, quasi-experimental, and qualitative studies, were conducted among adults with cancer, or were in languages other than the ones previously stated.

Study Selection and Data Management

Endnote was used as the reference manager to upload the results and facilitate study selection, and a single data management file was produced of all references identified through the search process. Duplicates were removed and 2 authors screened the remaining references independently for inclusion using Rayyan web app[31] (DCM and TS). Reasons for excluding articles were documented. Neither of the review authors was blind to the journal titles, study authors, or institutions. A flowchart of the study selection and identification according to the (PRISMA-P) guidelines[32] was generated.

Control Interventions

The control interventions consisted of usual care, and other CAM modalities such as yoga, acupuncture, and art and music therapy.

Methodological Assessment of the Studies

Data from observational and quasi-experimental studies were validated and extracted according to 10 technical items[33]: *Indication, sample size, baseline comparability, inclusion/exclusion criteria, intervention (treatment vs control), dropout, objectives, duration of treatment, main results*, and *funding* (Table 1). The first and last authors (DCM and TS) extracted the data. Checklists used to critically appraise observational and quasi-experimental studies tend to concentrate on issues of external and internal validity, including items like comparability of subjects, details of intervention and outcome measures, statistical analysis, and funding.[34-36] Thus, these recommended items are in line with those applied in this systematic review. Data from qualitative studies were validated and extracted according to the following 10 criteria: *Population, method, design/analysis, setting, aim(s), participants, sample size, inclusion/exclusion criteria, duration of treatment, results*, and *funding*.[37]

For methodological assessment, the included studies were exported to the System for the Unified Management, Assessment and Review of Information (SUMARI software program, Joanna Briggs Institute (JBI))[38] for critical appraisal of study quality. Two reviewers (DCM, TS) independently assessed the methodological quality of included articles using the critical appraisal checklists in SUMARI (checklist for quasi-experimental studies and qualitative research).

A meta-analysis could not be performed because the safety data in the studies was not reported consistently. As it was not possible to conduct a meta-analysis, the research group conducted a descriptive synthesis of the studies.

Results

A total of 448 hits were identified. Twenty hits were identified in AMED, 32 in CINAHL, 117 in EMBASE, 238 in MEDLINE/PubMed, and 31 in PsycINFO. A total of 5 studies were identified after searches in reference lists. A total of 57 were excluded from further examination because they were duplicates and a total of 386 studies were included for further screening. Ten studies were identified from citation searching. Three hundred and seventy-six studies were excluded for the following reasons: 4 were duplicates, 93 were irrelevant (according to the criteria), 55 were not about cancer, 63 were not about CAM, 92 were about adults with cancer, 4 were written in languages other than the ones stated above, 42 were other study types, 22 were not about adverse effects of cancer treatment (Figure 1). A total of 15[39-53] studies were included in this review, 10 quasi-experimental[39,41,42,46-48,50-53] (Table 1), 3 observational studies[40,44,45] (Table 2), and 2 qualitative studies[43,49] (Table 3).

All of the included studies were written in English except one written in Spanish.[45] Detailed characteristics of the included studies are presented in Tables 1 to 3. Sample size refers to the total number of participants in the study. In the participant group, n refers to the number of participants who received the treatment or control intervention, respectively. Dropout refers to the number of participants who left the study before completion. Six studies[39,42,44,47,48,53] did not report exclusion criteria. Three studies[40,42,51] did not report a dropout. In addition, Favera-Scacco et al[42] did not report the duration of intervention. Nine (n = 9, 60%) of the 15 studies stated that they received financial support[39,42-44,46,48,50,52,53] 3 studies (n = 3) reported that they did not receive financial support.[41,47,49] Three (n = 3, 20%)[40,45,51] of the 15 studies did not report sources of funding (Table 1).

Safety of CAM Modalities for Interventions

Adverse effects were recorded as reported in the included studies. This means that 1 study participant could experience and report several adverse effects. Six studies (n = 6, 40%),[40,41,44,47,48,51] reported data on adverse effects (Table 4). Across yoga studies,[41,47,48,49-53] only 1 case of dizziness[47] was reported among 49 participants (2%). The other 4

Table 1. Methodological Assessment of Quasi-Experimental Studies.

Quasi-experimental studies (n = 10)

		Participants		Criteria		Intervention	Dropout				
Study ID	Indication	Sample size	Baseline comparability	Inclusion	Exclusion	Treatment vs control (n)	Treatment vs control (n)	Objectives	Duration of treatment (follow-up)	Main results	Funding
Barrera et al[40]	Music therapy for anxiety	Hospitalized children with cancer (n = 70)	The participants differ regarding age and stages of cancer and treatment. These differences were accounted for in the statistical analysis.	Hospitalized children with cancer 0 to 17 y of age	NR	A music therapist was with the child for more than 15 min, engaging in calming interactive music experiences leading the child to other activities. About 1 to 3 sessions for each child ranging from 15 to 45 min.	n = 5	Examine the general benefits of music therapy for hospitalized pediatric cancer patients	Depended on the length of time the child stayed at the hospital. Participants received no more than 3 music sessions.	Significant improvement in children's rating of their feelings from pre to post music therapy ($P < .01$). However, the results varied with the age of the children.	Association of families of children with cancer, Toronto, Ontario; Hematology/ Oncology Program, Hospital for Sick Children
Diorio et al[42]	The feasibility of a 3-wk yoga program for fatigue	Children receiving chemotherapy or HSCT (n = 22)	NA (a single group)	Inpatient children with AML, relapsed ALL, stages 3 and 4 Burkitt's lymphoma; about to receive HSCT, 7 to 18 y old at enrollment, expected to be an inpatient for at least 3 wk after initiation of chemotherapy or conditioning	Unable to perform yoga; motor disability; cardiopulmonary symptoms; fractures; parents who do not understand English	Yoga, 3 times weekly (n = 11)	n = 11	Determine the feasibility of individualized yoga for hospitalized children receiving chemotherapy	3 wk	The yoga program was feasible. Qualitative feedback from both children and parents indicated the physical and psychological benefits of yoga.	No grant funding for this study
Favera-Scacco et al[43]	Art therapy for painful procedures during cancer treatment	Children with leukemia who underwent lumbar puncture or bone marrow aspiration (n = 49)	The children in the intervention group were younger than those in the control group	Children with leukemia who were candidates for lumbar puncture and bone marrow aspiration	NR	Art therapy (n = 32) vs usual care (n = 17). Art therapy consisted of: Introduction of a toy: a safe person; visual imagination; medical play; drawing; reading; dramatization	NR	Investigate art therapy as support (reduce stress and anxiety) for children with leukemia during painful procedures	NR	Art therapy can be a useful intervention that can prevent trauma and support children and parents during intrusive interventions	Supported by a grant from Regione Sicilia and MURST (40% grant)
Geyer et al[51]	Yoga to improve quality of life	Children and adolescents with oncological diagnoses (Edwin sarcoma, All, AML, Fanconi's anemia [n = 6] parents/ caregivers [n = 4])	NA (a single group)	Children and adolescents with oncological diagnoses. Platelet counts more than 5000, absolute neutrophil count more than 200, and hemoglobin 8 to 10 g/dL	Comorbid diseases, or developmental disorders, in the induction phase of treatment	Therapeutic yoga (1 h) 5 consecutive weekly section	No dropout	To describe the effect of therapeutic yoga on child and parental reports of quality of life in children hospitalized with oncological diagnoses	5 wk	Therapeutic yoga positively affected child's perception of gross motor function ($P = .016$)	Lance Armstrong Foundation

(continued)

Table 1. (continued)

Quasi-experimental studies (n = 10)

		Participants		Criteria		Intervention	Dropout				
Study ID	Indication	Sample size	Baseline comparability	Inclusion	Exclusion	Treatment vs control (n)	Treatment vs control (n)	Objectives	Duration of treatment (follow-up)	Main results	Funding
Govardhan et al[52]	To establish the feasibility and therapeutic effect of yoga on pediatric brain tumor and to provide a foundation for the development of an RCT	Children and adolescents between 6 and 18 planned for either radiation or chemotherapy for brain tumors (n = 18)	NA (a single group)	Children and adolescents between 6 and 18 planned for either radiation or chemotherapy for brain tumors	Children with metastasis, developmental or intellectual disorders, and prior exposure to yoga	Individualized yoga for an hour at least 3 times a week over a 4-wk timeframe after conventional cancer treatment (n = 13)	NR	To establish the feasibility and therapeutic effect of yoga to address the effects of radiotherapy and chemotherapy in pediatric brain tumor	4 wk	The yoga intervention was feasible. A significant difference was reported in respect to pain ($P = .0001$), relief in headache ($P = .0005$), increase in appetite ($P = .0005$), better sleep ($P = .0003$), and reduced fatigue ($P = .007$), and overall daily activity ($P = .0018$)	NR in publication
Hooke et al[53]	Yoga to improve fatigue, anxiety, balance, and sleep	Children and adolescents between 10 and 18 who completed therapy in the past 2 to 24 mo (n = 18)	NA (a single group)	Children and adolescents (10-18 y) who completed therapy in the past 2 to 24 mo for pediatric cancer, received chemo, radiotherapy, or if CNS tumor was treated with surgery, had not participated in a yoga class the previous 3 mo	Had an antecedent neurological, developmental, or genetic disorder before their cancer diagnoses	45-min yoga classes, for 6 wk (n = 13)	n = 2 due to relapse n = 3 dropped out	Determine if children and adolescents who were cancer survivors had less fatigue, better balance, and sleep quality, and less psychological distress compared with baseline measurements	6 wk	The anxiety score decreased significantly among children ($P = .04$) but not for adolescents. The scores for fatigue, sleep, and balance showed no significant changes	Alex's Lemonade Stand Foundation
Nilsson et al[47]	Non-immersive virtual reality (VR) for painful procedures	Children and adolescents with cancer (n = 42)	The groups did not differ at baseline	Children and adolescents 5 to 18 y old, who have undergone painful procedures at least once before	Children with cognitive impairment; children of parents who did not understand Swedish	Children played the virtual world game that started 1 to 5 min before the procedure and continued until the procedure was completed (n = 21) vs no game application (usual care) (n = 21)	n = 5	Examine the effect of using non-immersive VR a 3 D display during a needle procedure on reported pain or distress of children/adolescents with cancer	For how long the needle procedure lasted	No statistical difference was found between the intervention group and the control group	Children's Cancer Foundation at the Queen Silvia Children's Hospital, the Sigurd and Elsa Goljes Foundation, the Federation of Swedish County Councils (VG-region), the Ebba Danelius Foundation, and the Wilhelm and Martina Lundgrens Foundation

(continued)

Table 1. (continued)

Quasi-experimental studies (n = 10)

Study ID	Indication	Participants		Criteria		Intervention	Dropout	Objectives	Duration of treatment (follow-up)	Main results	Funding
		Sample size	Baseline comparability	Inclusion	Exclusion	Treatment vs control (n)	Treatment vs control (n)				
Orsey et al[54]	This study had 2 objectives: (1) To assess the feasibility of the study and (2) To assess the efficacy of yoga intervention for pain management, fatigue, stress, anxiety, and overall QoL for pediatric cancer patients and their families	(1) Children undergoing cancer treatment (n = 20) parents (n = 20) and (2) Dyads (n = 22)	NA (a single group)	Children 8 to 18, with cognitive ability at least at 8-y old level undergoing cancer treatment, parents older than 18, parents and children physically able to do yoga. English speakers. (2) ability to attend at least 8 yoga sessions over 8 wk	NR	A weekly yoga intervention. Patients could pick from (a) bedside yoga (b) classroom yoga (c) chair yoga (n = 10)	12 dyads withdrew (study 2)	(1) To study the feasibility of a yoga intervention (2) To test the efficacy of yoga intervention on the well-being of pediatric patients during active cancer treatment	8-wk	Study (1) Demonstrated high levels of interest from patients and family members Study (2) Results trend toward improvement of QoL for patients and their parents	In CHIP Seed Grant Funding in Cancer Control
Thygeson et al[48]	Yoga for anxiety and distress	Children with cancer (n = 20); adolescents with cancer (n = 12); parents of children with cancer (n = 45)	NA	Children/adolescents 7 to 18 y old, who were hospitalized with cancer or blood disorders; spoke English; activity level appropriate for yoga; no previous yoga experience. Parents: Had a child with cancer, who spoke English, no previous experience with yoga.	NR	A total of (n = 49) participants: (n = 11) children; (n = 5) adolescents and (n = 33) parents received one yoga session	n = 28	Explore the feasibility of a single yoga session for children/ adolescents (and parents) hospitalized with cancer or other blood disorders	45 min	Adolescents ($P = .04$) and parents ($P < .01$) experienced a significant decrease in anxiety scores. Children's anxiety scores did not change from pre-class ($P = .21$).	No grant funding for this study
Wurz et al[49]	Yoga for physical benefits (health-related quality of life [HRQL]; physical fitness outcomes and physical activity levels [PAL])	Children with cancer (n = 11)	NA (1 group only)	Children 5 y and older (5-17 y old); outpatient; limited previous yoga experience; not meeting the Canadian society for exercise physiology guidelines	NR	A total of (n = 8) received yoga 2 times weekly for 12 wk	n = 3	Explore the feasibility and benefits of yoga for pediatric cancer patients	12-wk Yoga intervention 2 times/ weekly/60-min sessions	This 12-wk yoga program was feasible and provided preliminary evidence for the benefits of yoga ($P = .02$); Parent-reported HRQL ($P = .03$), functional mobility ($P = .01$), and total PAL ($P = .02$)	Grant from Canadian Institutes of Health Research; Alberta Children's Hospital Research Institute; Psychosocial Oncology Research Training Program, University of Calgary

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; NR, not reported; NA, not applicable.

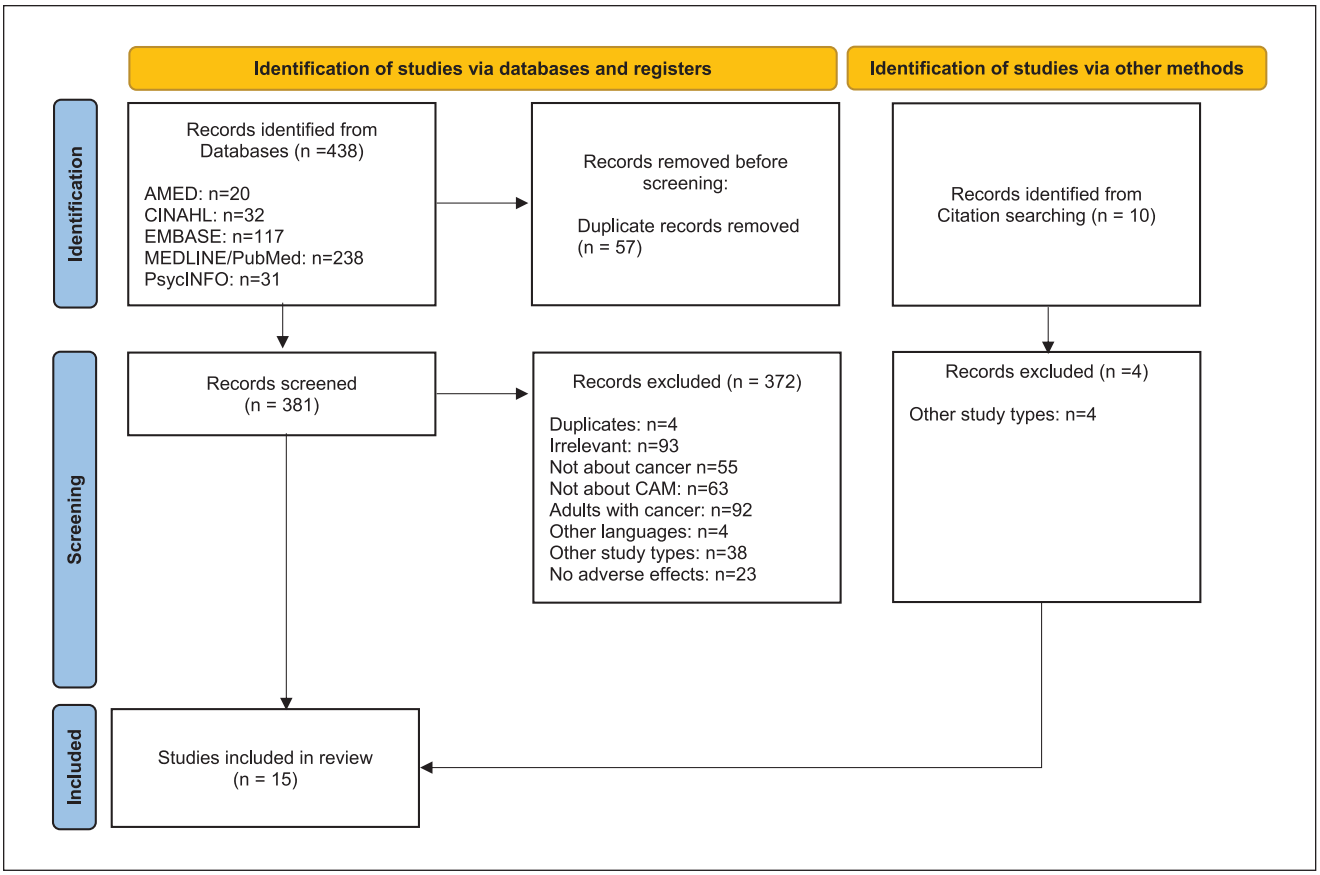

Figure 1. Flow chart of the selection process of included studies.

studies[41,44,48,51] that reported safety data, reported that the participants did not experience any adverse effects of the yoga programs. Choksi et al[40] reported 15 cases of bleeding with acupuncture treatment (out of 252 sessions, 6%) and 5 cases of bruising (2%). They reported no increase in acute or delayed adverse effects in patients with and without thrombocytopenia ($P = .189$) or neutropenia ($P = .497$). Kennedy et al[44] reported no adverse effects of antioxidant supplementation. Among the studies that reported safety data, events were reported as adverse effects,[40,47] which are considered direct risks. None of the studies reported events considered as indirect risks.

In summary: Safety data is underreported as 60% of the studies did not collect data on safety. All the adverse effects reported were associated to direct risks. The events were assessed by the researchers as minor and transient. No serious adverse effects were noted for acupuncture, yoga, and antioxidant supplements.

CAM Modalities

The results of the literature search indicated that the existing observational and qualitative studies about the use of CAM modalities to alleviate the adverse effects of cancer treatment in children and young adults can be divided into 4 main areas: *Alternative medical systems*; manipulative and body-based therapies, mind-*body therapies*, and *biologically-based therapies.* These areas are in line with the National Institute of Health's National Center for Complementary and Integrative Health, which organizes CAM into the following categories: biologically-based therapies, mind-body therapies, manipulative and body-based therapies, energy therapies, alternative medical systems, and lifestyle therapies.[54]

Alternative medical systems (acupuncture). Two studies investigated acupuncture. One study investigated the use and safety of acupuncture among children receiving cancer treatment at Columbia Medical Center, USA,[40] and another delineated the use of acupuncture for symptom management and general well-being[43] among hospitalized children. The latter was a qualitative study nested within a clinical acupuncture trial. Chokshi et al[40] looked at individualized needle acupuncture and reported that 54% of the children preferred acupuncture for symptom management compared to other complementary therapies such as massage, yoga, meditation, or nutrition counseling. They received a median of 4 treatment sessions/acupuncture was more likely to be used for gastrointestinal and constitutional symptoms

Table 2. Methodological Assessment of Observational Studies.

Observational studies (n = 3)

		Participants		Criteria		Intervention	Dropout				
Study ID	Indication	Sample size	Baseline comparability	Inclusion	Exclusion	Treatment vs control (n)	Treatment vs control (n)	Objectives	Duration of treatment (follow-up)	Main results	Funding
Chokshi et al[40]	Acupuncture for symptom management	Children receiving cancer treatment (n = 90)	Differences in age of participants accepting acupuncture compared to those who did not. The ethnicity of patients/ parents was significantly associated with acceptance of acupuncture.	Acupuncture naive children/ adolescents undergoing treatment for cancer at Columbia University Medical Center	Children who had previous experience with acupuncture and children with planned treatment protocols less than 6 mo	Individualized acupuncture (n = 49) vs CAM modalities (massage, yoga, meditation, nutrition counseling) (n = 41)	NR	Evaluate the use of acupuncture as a component of existing supportive care regimens among children and adolescents undergoing treatment for cancer	6 mo	Acupuncture was more likely than other CAM modalities to be used for gastrointestinal/ constitutional symptoms ($P > .0001$), lack of energy ($P = .0001$), and pain ($P = .001$)	NR in publication
Kennedy et al[44]	Antioxidants supplements (vitamin E; carotenoid; betacaroten; vitamin A) for inadequate plasma antioxidant concentrations	Children and adolescents with ALL (n = 103)	NA (1 single group)	Children and adolescents 1 to 21 y old with newly diagnosed ALL	NR	Received vitamin E; carotenoid; betacaroten; vitamin A (n = 100)	Timepoint 1: n = 3; timepoint 2: n = 16, timepoint 3: n = 16	Investigate whether patients with sufficient antioxidant intakes while undergoing chemotherapy will have better tolerance to the treatment and experience fewer treatment-related adverse effects than those with insufficient antioxidant intakes	6 mo	Greater vitamin C intake was associated with fewer therapy delays, less toxicity, and fewer days in hospital. Greater vitamin E intake was associated with a lower incidence of infection. Greater betacaroten intake was associated with a decrease in toxicity. Lower intakes of antioxidants were associated with increase in adverse side effects of chemotherapy.	Supported by a grant from the American Institute for Cancer Research, The Lener and Schwartz Family, and the American Cancer Society
Medina Córdoba and Pérez Villa[45]	Non-pharmacological measures (touch, play, music) for pain	Children with ALL (n = 35)	NA (1 group only)	Children $<$18 y old diagnosed with ALL	Children without clinical information on variables of interest; parents who show lack of interest	Touch; encourage children; explaining the procedures; music; play; video games; movies; thought replacement; images; drawing; comparing pain; breathing; massage; muscle contraction; relaxation images; TV; hot and cold applications (n = 35)	No dropout	Evaluate non-pharmacological measures to treat pain for children with ALL	As long as the patient was in the hospital, the average stay was 7 d	Music was the one factor that significantly improved pain ($P = .01$)	NR in publication

Abbreviations: ALL, acute lymphoblastic leukemia; NR, not reported; NA, not applicable.

Table 3. Methodological Assessment of Qualitative Studies.

Qualitative interview studies (n = 3)

Study ID	Population	Method	Design/analysis	Setting	Aim(s)	Participant(s)	Sample size	Inclusion/exclusion criteria	Duration of treatment (follow-up)	Results	Funding
Clerici et al[49]	Magic tricks as support to psychological approaches for children with cancer	Psychological interviews with pediatric patients	Qualitative design. Descriptive study of consultations with patients.	Hospital setting	Describe illusionist techniques (magic), suggest utility, and arouse interest	Children who underwent cancer treatment younger than 10 y of age	n = 30	Children's difficulty adapting to disease and treatment; relational problems with the hospital team; stressful treatments; problems with compliance to treatment, emotional distress; adaptation problems in survivors; terminal disease; relational problems in the family; psychological problems; psychopathologic conditions	NR	The use of magic in the context of pediatric oncology can represent a useful resource as a complement to traditional psychological support approaches	This study did not receive any funding
Hu et al[43]	Childhood cancer and acupressure for well-being and positive emotions	Semi-structured interviews lasting 60 to 90 min, and participant observation of the acupuncture sessions	Qualitative design. Interviews were transcribed verbatim. Data were analyzed using grounded theory symbolic (interactionism and phenomenology).	This study was nested within a clinical trial testing the effect of acupressure on children being treated for cancer	Explore whether and how acupressure, when provided by a professional or trained caregiver, was perceived as eliciting a sense of well-being	Acupressure providers (n = 3); primary caregivers of children with cancer (n = 13)	Total sample (n = 16)	Caregivers of children 5 to 21 y of age receiving hospital-based cancer treatment, who have demonstrated engagement in the acupuncture intervention were asked to participate. Caregivers who had a minimal interest were not asked.	NR	Acupressure brought symptom relief, physical relaxation, and comfort to the child and caregiver	Patient-centered outcomes research institute: Pierre's birthday fund; the National cancer institute: the National center for complementary and alternative medicine
Nilsson et al[46]* (qualitative arm)	Non-immersive virtual reality (VR) for painful procedures	Semi-structured interviews with 21 children and adolescents following the completion of the intervention. Median time for the interviews was 8.5 min	Qualitative design. Interviews were transcribed verbatim and analyzed using a qualitative content analysis.	This was a qualitative arm nested within a clinical trial testing VR for painful procedures	Examine the participants' response to the use of VP equipment during painful procedures	Children and adolescents with cancer (n = 21)	Total sample (n = 21)	Children and adolescents 5 to 18 y old, who have undergone painful procedures at least once before	During needle procedures	These interviews showed that non-immersive VR was a positive experience for children undergoing painful procedures	Children's Cancer Foundation at the Queen Silvia Children's Hospital, the Sigurd and Elsa Goljes Foundation, the Federation of Swedish County Councils (VG-region), the Ebba Danelius Foundation, and the Wilhelm and Martina Lundgrens Foundation

Abbreviation: NR: not reported.

Table 4. Safety Assessment of the Included Studies (n = 15).

Study ID	Objectives	Reported adverse effects (yes/no)	Types of adverse effects	Direct risk	Indirect risk
Quasi-experimental studies (n = 10)					
Barrera et al[39]	Examine the general benefits of music therapy for hospitalized pediatric cancer patients	No	NR	NR	NR
Diorio et al[41]	Determine the feasibility of individualized yoga for hospitalized children receiving chemotherapy	Yes	No adverse effects were experienced by the participants	NR	NR
Favera-Scacco et al[42]	Investigate art therapy as support (reduce stress and anxiety) for children with leukemia during painful procedures	No	NR	NR	NR
Geyer et al[50]	To describe the effect of therapeutic yoga on child and parental reports of quality of life in children hospitalized with oncological diagnoses	No	NR	NR	NR
Govardhan et al[51]	To establish the feasibility and therapeutic effect of yoga to address the effects of radiotherapy and chemotherapy in pediatric brain tumor	Yes	No adverse effects were experienced by the participants	NR	NR
Hooke et al[52]	Determine if children and adolescents who were cancer survivors and participated in the intervention had less fatigue. Improve balance, improve sleep quality, and less psychological distress compared with baseline measurements.	No	NR	NR	NR
Nilsson et al[46]	Examine the effect of using non-immersive VR a 3 D display during a needle procedure on reported pain or distress of children/adolescents with cancer	No	NR	NR	NR
Orsey et al[53]	To study the feasibility of a yoga intervention. To test the efficacy of yoga intervention on the well-being of pediatric patients during active cancer treatment.	No	NR	NR	NR
Thygeson et al[47]	Explore the feasibility of a single yoga session for children/adolescents (and parents) hospitalized with cancer or other blood disorders	Yes	One case of dizziness (child)	Yes	NR
Wurz et al[48]	Explore the feasibility and benefits of yoga for pediatric cancer patients	Yes	No participants experienced adverse effects from the yoga program	NR	NR
Longitudinal/prospective observational studies (n = 3)					
Chokshi et al[40]	Evaluate the use of acupuncture as a component of existing supportive care regimens among children and adolescents undergoing treatment for cancer	Yes	15 cases of bleeding (out of 252 sessions); 5 cases of Grade I bruising; No increase in acute or delayed adverse effects in patients with and without thrombocytopenia ($P = .189$) or neutropenia ($P = .497$). No serious events were reported.	Yes	NR

(continued)

Table 4. (continued)

Longitudinal/prospective observational studies (n = 3)					
Kennedy et al[44]	Investigate whether patients with sufficient antioxidant intakes while undergoing chemotherapy will have better tolerance to the treatment and experience fewer treatment-related adverse effects than those with insufficient antioxidant intakes	Yes	Supplementation was not associated with adverse effects at any of the time points	NR	NR
Medina Córdoba and Pérez Villa[45]	Evaluate non-pharmacological measures to treat pain for children with ALL	No	NR	NR	NR
Qualitative interview studies (n = 3)					
Study ID	Population	Reported adverse effects (yes/no)	Types of adverse effects		
Clerici et al[49]	To describe illusionist techniques (magic), suggest utility, and arouse interest	NR	NR	NR	NR
Hu et al[43]	Explore whether and how acupressure, when provided by a professional or trained caregiver, was perceived as eliciting a sense of well-being	NR	NR	NR	NR
Nilsson et al[46] (qualitative arm)	Examine participants' response to the use of VR equipment during painful procedures	NR	NR	NR	NR

Abbreviations: ALL, acute lymphoblastic leukemia; VR, virtual reality; NR, not recorded in manuscript.

including drowsiness ($P < .0001$), lack of energy ($P = .0001$), and pain ($P = .001$). Hu et al[43] investigated acupressure together with therapeutic touch, and qualitative data were obtained through semi-structured interviews with caregivers and acupuncturists. According to these participants, acupressure brought symptom relief (ie, pain, nausea, etc.), physical relaxation, and comforting touch to the child as well as to the parents.

In summary: Acupuncture studies report through statistical and/or analytical data beneficial outcomes for children with cancer for symptom management. A meta-analysis was not conducted because the studies presented incomparable outcomes and the reported data was inadequate to conduct a meta-analysis.

Mind-body therapies (art, music, and imagination therapy). Five studies (n = 5)[39,42,45,46,49] investigated different CAM modalities for supportive care in pediatric cancer patients. Three of these studies investigated CAM modalities for pain and painful procedures during cancer treatment.[42,45,46] One study[39] investigated music therapy to decrease anxiety and increase support and finally, one study[49] used magic techniques (illusionism) as a support resource for children with cancer. Nilsson et al[46] used a virtual reality device for needle-related pain and reported no statistically significant difference between the intervention and control group regarding pain and distress during and after the procedures. No statistical difference was found in heart rate during the procedure between the groups. In a qualitative arm, nested within this study, the participants reported that the virtual device was a positive experience. Medina Córdoba and Perez Villa[47] investigated non-pharmacological measures such as therapeutic touch, play, and music for painful procedures in children with acute lymphoblastic leukemia (ALL). They found that music therapy was the only modality that significantly improved pain ($P = .01$) for painful procedures. Favara-Scacco et al[42] investigated art therapy (visual imagination, play, drawing, and dramatization) for children with ALL who underwent lumbar puncture and bone marrow transplantation. Compared to the control group, children who used art therapy exhibited collaborative behavior before the procedure. The modality was shown to be a useful intervention, and parents declared that they were better able to manage the painful procedures when art therapy was offered to the child. Barrera et al[39] investigated music therapy for children hospitalized with cancer. In a pre-and post-design, they reported a significant improvement in children's feelings from pre to post music therapy ($P < .01$). There was also a significant main effect of engagement, indicating that actively engaged children had higher scores than the passive children ($P < .01$). However, the results varied with the age of the child. In a qualitative design, Clerici et al[49] explored the use of magic tricks as support to psychological approaches in consultations with hospitalized children. Based on these data, they suggested the use of magic tricks to be helpful in providing support for communication and relations, as well as for compliance and rehabilitation for children with cancer.

In summary: Art, music, and imaginary modalities studies report beneficial support for children with cancer through statistical and narrative results.

Mind-body therapies (yoga). Seven studies (n = 7) investigated the benefits of yoga[41,47,48,50-53] for children with cancer. Diorio et al[41] investigated the feasibility of a 3-week yoga program for children who were receiving intensive chemotherapy. In addition, they investigated whether yoga could be a useful intervention for cancer-related fatigue. They found that yoga was feasible, as 10/11 participants met the threshold for feasibility. Feedback from parents and children indicated the physical and psychological benefits of yoga. Thygeson et al[47] looked at yoga for distress and anxiety and investigated whether 1 yoga session could offer benefits to children and their parents in an outpatient oncology unit. Children with a normal anxiety score pre-class did not change ($P = .21$). Parents ($P < .01$) and adolescents ($P = .04$) experienced a significant decrease in anxiety scores after the yoga session. Wurz et al[48] investigated the feasibility and benefits of a 12-week yoga program. The program was feasible and indicated significant improvement for patients ($P = .02$), and parents reported improved health according to the health-related quality of life (HRQL) scale ($P = .03$), functional mobility ($P = .01$), total physical fitness outcomes and physical activity (PAL) ($P = .02$) pre- to post-intervention. Geyer et al[50] described the effect of therapeutic yoga on child and parents. The study reported quality of life in children hospitalized with oncological diagnoses. Therapeutic yoga had a positive effect on a child's perception of gross motor functioning ($P = .016$). Govardhan et al[51] wanted to establish the feasibility and therapeutic effect of yoga to address the effects of radiotherapy and chemotherapy in pediatric brain tumors. The feasibility of the yoga intervention was established. The median sessions attended were 16 of 20. Significant difference was reported in respect to pain ($P = .0001$), relief in headache ($P = .0005$), increase in appetite ($P = .0005$), better sleep ($P = .0003$), reduced fatigue ($P = .007$), and overall daily activity ($P = .0018$). Hooke et al[52] sought to explore the feasibility and benefits of a 6-session weekly yoga intervention for pediatric cancer survivors who completed therapy in the past 2 to 24 months. About 72% of the participants enrolled completed the study, establishing the feasibility of the study. After the 6-week yoga intervention, most of the symptoms measured (balance, fatigue, and sleep) remained unchanged. Anxiety scores had a significant ($P = .04$) decrease after the yoga intervention. Orsey et al[53] determined the feasibility and preliminary efficacy of a yoga intervention for pediatric cancer patients in active treatment

and their families. The study reported significant improvement in measures of emotional ($P = .03$) and social function ($P = .03$) and the total score ($P = .006$). Furthermore, among parents, the mental health composite score significantly ($P < .05$) increased post-intervention.

In summary: The studies report that yoga programs were feasible through both narrative and statistical results, and both parents and children indicated physical and psychological benefits of yoga.

Biologically-based therapies. One study investigated biological therapies. Kennedy et al[44] investigated whether patients with sufficient antioxidant intakes while undergoing chemotherapy would have better tolerance to the treatment and experienced fewer treatment-related adverse effects than those with insufficient antioxidant intakes. The researchers found that lower intakes of antioxidants were associated with increases in adverse effects of chemotherapy. Participants were classified as having adequate or inadequate nutrient plasma concentrations as compared with clinical chemistry standards for vitamins A, C, and E.

Methodological Quality of Studies

The Joanna Briggs Institute's quasi-experimental study appraisal checklist was used to assess the quality of the quasi-experimental studies, the cohort studies checklist was used for the observational studies (longitudinal and prospective), and the checklist for qualitative research was used for the interview studies. All studies scored above 70% (Tables 5-7). One study (n = 1)[46] met the criteria for checking every item (9 out of 9 items for quasi-experimental studies and 10 out of 10 items for qualitative studies). Eight studies (n = 8)[39,41,47,48,50-53] addressed 8 out of 9 items (Table 5). For the observational studies, 1 study addressed 9,[44] another 8,[45] and another 7[40] of the 11 items for cohort studies (Table 6). Two qualitative studies[43,49] addressed 8 and 9 out of 10 items respectively and finally, 1 study[42] addressed 7 out of 9 items (Table 7).

In summary: According to the SUMMARI software program from Joanna Briggs Institute, the score for the methodological quality of most (n = 15) of the included studies was 70% and above. One study (n = 1)[46] obtained a total score of 100% and 13 studies (n = 13)[39,41-45,47-53] obtained scores between 75% and 90%. One study[40] obtain a score of 70%.

Discussion

As cancer survival among children increases, it is important to assess different methods to alleviate the adverse effects derived from cancer treatment and thereby lessen the burden on children, young adults, and their families. Hence, we performed this present review and found that no serious adverse effects from the CAM treatments were reported among the studies included in this review, but less than half of the studies reported adverse effects, which is a threat to patient safety. However, all included studies had critical appraisal scores above 70% according to the JBI SUMMARI tool criteria. CAM modalities were used with the purpose to alleviate anxiety, pain, toxicity, prevent trauma, and improving HRQL, functional mobility and physical activity levels. Both children and parents reported physical and physiological benefits such as a decrease in anxiety from acupuncture and yoga.

Safety

In the hierarchy of study designs, observational studies are categorized methodologically at an intermediate level, and randomized controlled trials (RCTs) as the studies with the gold standard methodology.[55] Although RCTs are leading in evidence-building, it is important to acknowledge the contributions that results from observational studies can provide to the healthcare field.[55] Unlike RCTs, observational studies are less restrictive of the sample of patients selected, the intervention delivered, or the outcome(s) measured; hence contributing to the generalizability of the study.[55] Observational studies also identify serious uncommon harms and longtime effects of medical interventions[56] as they are often conducted for longer periods and are in real-life settings.[57] In contrast to conventional medicine, CAM therapies have no regulatory gatekeeper controlling their therapeutic quality, safety, efficacy, and effectiveness before they are marketed. Thus, many CAM modalities were traditionally and widespread in use before they were investigated or regulated. In addition, CAM modalities are often provided as an integrated "whole system" of care (ie, Ayurveda), without careful consideration of safety issues.[58] Even though the results of this review show minor adverse effects to CAM treatments, the results are in line with literature that shows that adverse effects are seldom reported in studies with CAM.[59,60] Natural remedies are often perceived as safe; however, that is not always the case because they might interact negatively with conventional cancer treatment.[61] In an evaluation of the safety of CAM trials, Tuner et al[59] reported that more than half of the trials in their review had inadequate reporting of safety data. According to the literature,[62] parents do not want to use modalities that add further suffering to their child. Safety information is therefore of high importance for parents as they want to avoid CAM modalities that have known adverse effects.[12]

In contrast, other studies have reported that adverse effects in acupuncture[63] and homeopathy[64] are commonly reported. The report of adverse effects among these modalities could be attributed to well-established reporting guidelines such as the Standard for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) guidelines[65]

Table 5. Quasi-Experimental Studies Appraisal.

Citation	Q1. Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Q2. Were the participants included in any comparisons similar?	Q3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Q4. Was there a control group?	Q5. Were there multiple measurements of the outcome both pre and post the intervention/ exposure?	Q6. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Q7. Were the outcomes of participants included in any comparisons measured in the same way?	Q8. Were outcomes measured in a reliable way?	Q9. Was appropriate statistical analysis used?	%
Barrera et al[39]	Y	Y	Y	N	Y	Y	Y	Y	Y	89
Diorio et al[41]	Y	Y	Y	N	Y	Y	Y	Y	Y	89
Favara-Scacco et al[42]	Y	Y	Y	Y	Y	Y	Y	U	U	78
Nilsson et al[46]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Geyer et al[50]	Y	Y	Y	N	Y	Y	Y	Y	Y	89
Govardhan et al[51]	Y	Y	Y	N	Y	Y	Y	Y	Y	89
Hooke et al[52]	Y	Y	Y	N	Y	Y	Y	Y	Y	89
Orsey et al[53]	Y	Y	Y	N	Y	Y	Y	Y	Y	89
Thygeson et al[47]	Y	Y	Y	N	Y	Y	Y	Y	N	89
Wurz et al[48]	Y	Y	Y	N	Y	Y	Y	Y	Y	89

Abbreviations: Y, Yes; N, No; U, unclear.

Table 6. Longitudinal/Prospective Observational Studies Appraisal.

Citation	Q1. Were the 2 groups similar and recruited from the same population?	Q2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Q3. Was the exposure measured in a valid and reliable way?	Q4. Were confounding factors identified?	Q5. Were strategies to deal with confounding factors stated?	Q6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Q7. Were the outcomes measured in a valid and reliable way?	Q8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Q9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Q10. Were strategies to address incomplete follow up utilized?	Q11. Was appropriate statistical analysis used?	%
Chokshi et al[40]	U	Y	Y	N	N	Y	Y	Y	Y	NA	Y	70
Kennedy et al[44]	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	81
Medina Córdoba and Pérez Villa[45]	Y	Y	Y	N	N	Y	Y	Y	Y	NA	Y	80

Abbreviations: Y, yes; N, no; NA, not applicable; U, unclear.

Table 7. Qualitative Studies Appraisal.

Citation	Q1. Is there congruity between the stated philosophical perspective and the research methodology?	Q2. Is there congruity between the research methodology and the research question or objectives?	Q3. Is there congruity between the research methodology and the methods used to collect data?	Q4. Is there congruity between the research methodology and the representation and analysis of data?	Q5. Is there congruity between the research methodology and the interpretation of results?	Q6. Is there a statement locating the researcher culturally or theoretically?	Q7. Is the influence of the researcher on the research, and vice-versa, addressed?	Q8. Are participants, and their voices, adequately represented?	Q9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Q10. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	%
Clerici et al[49]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	90
Hu et al[43]	Y	Y	Y	Y	Y	U	Y	Y	U	Y	80

Abbreviations: Y, Yes; N, No; U, unclear.

and Consolidated Standards of Reporting Trials (CONSORT) for herbal medicine.[66]

The lack of regulation for CAM modalities and products as well as the lack of a standardized reporting system for the field as a whole, make it difficult to compare studies on safety. Given the substantial use of CAM worldwide, it is important to have accurate information on the safety of such treatments and modalities. Fønnebø et al[58] proposed a research strategy for CAM that accounts for the lack of regulation of CAM in western countries. The strategy proposes to (1) look at the context, paradigms, philosophical understanding; (2) assess the safety status; (3) examine the effectiveness of the treatment; (4) assess the efficacy; and (5) understand the biological mechanism of the treatment.[58] According to this strategy, it is important to investigate safety before the effect of a modality. Deng et al[67] also highlight the importance of examining the safety and efficacy of different CAM modalities. In this clinical practice guidelines for integrative oncology, the researchers make recommendations based on a risk versus efficacy evaluation. If a CAM modality is considered safe and efficacious the modality should be recommended. If the modality is considered safe but the evidence for efficacy is inconclusive, the modality should be recommended, however, effectiveness should be closely monitored. If the modality is efficacious, but the evidence for safety is inconclusive, the modality should be recommended, but the safety should be closely monitored. Lastly, if the modality is not efficacious and is connected with serious risks, the modality should be avoided. Research strategies and recommendations guidelines such as the ones provided by Fønnebø et al and Deng et al should be adopted and implemented throughout the different CAM modalities for research and clinical practice.

It is essential to extend the existing guidelines in journals and study appraisal checklists to encourage appropriate standardized reporting of adverse effects of CAM studies. STRICTA guidelines, for example, include in their checklist the reporting of harms.[65] Such reporting will improve the quality of the research and provide a greater understanding of the safety of CAM treatments and products.

CAM Modalities

Twelve[39,41,42,45-53] out of the 12 studies reviewed in this article were related to mind and body practices. All of the studies reported beneficial results from CAM treatments for physical and emotional symptoms derived from cancer treatment. Existing literature is consistent with the results of this review.[68-77] Several studies have reported promising results of yoga among pediatric patients[69-71,73] as well adult cancer patients.[72,74,75] For example, Mandanmohan et al[76] reported that yoga training among children produced significant gains in muscle strength. Five [39,42,45,46,49] of the studies reported in this review examined the effects of art and music therapy among pediatric patients undergoing cancer treatment. Most of the studies demonstrated that art-music therapy and magic tricks had a positive effect on symptoms such as pain, anxiety, engagement, support, and communication. This is in line with other studies that found art and music therapy beneficial for children with cancer.[26-28,78-83] Acupuncture was used in 2 studies[40,43] included in this review. Existing acupuncture literature among children[84] and adults[85,86] with cancer is consistent with the findings of this review. In a systematic review, Jindal et al[87] reported that acupuncture was used to treat gastrointestinal disorders and pain in children.[87] One study[44] included in this review accessed the association of antioxidant intake and increases in the adverse effects of chemotherapy in children. Different vitamins were attributed different benefits. The use of different vitamins such as vitamin D deficiency has shown an association with oral mucositis in pediatric patients but the effects of vitamins to treat adverse events of cancer in children are still inconclusive.[44,88,89] More research with a rigorous design (RCTs), is needed to confirm these results before recommendations for clinical practice.

Limitations

This review should be understood considering its limitations. Among the limitations of this review are that the studies included were not homogenous regarding study design, participants, intervention, control, and outcome measures therefore making it impossible for meta-analysis to access the safety of the modalities used to treat adverse effects caused by cancer treatment in children. Another limitation is the size of the studies; most of the studies presented had small samples affecting the generalizability of the results. CAM is a field that encapsulates many modalities and not all of them are presented in this review. Generally, many CAM modalities are under-researched, especially among this population. Efforts have been made to retrieve all observational, quasi-experimental, and qualitative studies of interest, but it is impossible to be entirely certain that all potentially eligible studies have been found. The literature was searched in several databases, but it is possible studies were overlooked. Limiting the studies to the languages stated in the methods could also have led us to miss some relevant papers. Another limitation is that there are 2 articles[43,44] where participants older than 18 years were included. The results reported in this review therefore to some extent also represent young adults with cancer. Although this review has limitations, those are counteracted by carefully implementing the search methods by a research librarian and by assessing the methodological quality of the articles with the use of critical appraisal tools. Although we used well-known critical appraisal tools it is possible that

other tools can provide different results from the ones presented in this review.

Implication for Practice

The review indicates that CAM modalities such as mind and body treatments are being used in the management of symptoms from cancer treatment such as anxiety, yet they lack appropriate reporting for adverse effects. The latter finding should be used to promote further research and pilot tests related not only to safety but also to other aspects such as dosage for different CAM modalities used among children and young adults with cancer.

Implication for Research

Unlike conventional medicine, CAM is evaluated holistically. Hence, research should focus on the different aspects of treatment and implementation.[58] Symptoms of distress among children and young adults undergoing cancer treatment are high.[90] Symptoms do not often present themselves individually but as clusters. A symptom cluster is defined as 2 or more symptoms that occur together and are related to each other.[91] CAM modalities (ie, massage and reiki) have shown possible effectiveness on cluster symptom management[27] and could be considered more often to treat symptom clusters that conventional medicine has difficulty treating such as feeling nervous, sad, and lacking energy.[27] Furthermore, quality assessment and peer review tools should be modified to encourage adequate reporting of harmful events for CAM studies. Also, due to their comprehensive nature, more RCTs, as well as observational, quasi-experimental, and qualitative studies, should be implemented to enhance our understanding of the effect, effectiveness, and safety of CAM treatments.

Conclusion

This review demonstrates that the majority of the studies of CAM use in pediatric cancer lack proper reporting of safety. It is therefore important to encourage CAM researchers to record and report adverse effects of interventions. This is particularly important in pediatric oncology where parents do not want to add any unnecessary burden to the child and need adequate safety information on CAM.

Author Contributions

TS: Conceived the study. Together with DCM, they performed the searches, selected studies for inclusion and collected study data, assessed the studies for risk of bias (methodological assessment) and performed the methodological assessment of the studies according to the JBI methodology, and drafted the manuscript. GO: Developed the search strategy and performed the searches together with TS and DCM. AEK, GO, MJ, MM, JPL: Contributed with intellectual content and reviewed subsequent versions of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Ekhagastiftelsen (2020-76) and NAFKAM. The publication charges for this article have been funded by UIT The Arctic University of Norway.

ORCID iD

Dana C. Mora https://orcid.org/0000-0003-1209-3526

Supplemental Material

Supplemental material for this article is available online.

References

1. WHO. World Health Organization childhood cancer. Accessed September 7, 2021. https://www.who.int/news-room/fact-sheets/detail/cancer-in-children
2. Zhang J, Nichols KE, Downing JR. Germline mutations in predisposition genes in pediatric cancer. *N Engl J Med*. 2016;374:2336-2346.
3. National Center for Complementary and Integrative Health. Complementary, alternative, or integrative health: what's in a name? May 10, 2021. Updated 2018. Accessed May 10, 2021. https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name
4. Chotsampancharoen T, Sripornsawan P, Duangchu S, Wongchanchailert M, McNeil E. Survival outcome of alternative medicine treatment for newly diagnosed acute leukemia in children. *Acta Haematol*. 2018;140:203-208.
5. Bhakta N, Force LM, Allemani C, et al. Childhood cancer burden: a review of global estimates. *Lancet Oncol*. 2019;20:e42-e53.
6. Ladas EJ. Integrative medicine in childhood cancer. *J Altern Complement Med*. 2018;24:910-915.
7. Lüthi E, Diezi M, Danon N, et al. Complementary and alternative medicine use by pediatric oncology patients before, during, and after treatment. *BMC Complement Med Ther*. 2021;21:96.
8. Zuzak TJ, Boňková J, Careddu D, et al. Use of complementary and alternative medicine by children in Europe: published data and expert perspectives. *Complement Ther Med*. 2013;21(Suppl 1):S34-S47.
9. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT. Prevalence of complementary medicine use in pediatric cancer: a systematic review. *Pediatrics*. 2010;125:768-776.
10. Witt CM, Balneaves LG, Cardoso MJ, et al. A comprehensive definition for integrative oncology. *J Natl Canc Inst Monogr*. 2017; 57:3-8. doi:10.1093/jncimonographs/lgx012
11. Diorio C, Lam CG, Ladas EJ, et al. Global use of traditional and complementary medicine in childhood cancer: a systematic review. *J Glob Oncol*. 2017;3:791-800.

12. Stub T, Kristoffersen AE, Overvåg G, Jong MC. An integrative review on the information and communication needs of parents of children with cancer regarding the use of complementary and alternative medicine. *BMC Complement Med Ther*. 2020;20:90.
13. MacLennan AH, Myers SP, Taylor AW. The continuing use of complementary and alternative medicine in South Australia: costs and beliefs in 2004. *Med J Aust*. 2006;184:27-31.
14. Lowrance WW. Of acceptable risk: science and the determination of safety. William Kaufmann; 1976.
15. Stub T. Safety of treatment provided by homeopaths homeopathic aggravations, adverse effects and risk assessment. [PhD thesis]. UiT The Arctic University of Norway; 2013.
16. Stub T, Salamonsen A, Kristoffersen A, Musial F. How to handle worsening of condition during treatment – risk assessment in homeopathic practice. *Forsch Komplementmed*. 2015;22:30-35.
17. Barnekreftforeningen. English: children's cancer society. Childhood Cancer. July 23, 2021. Accessed July 22, 2021. https://www.barnekreftforeningen.no/barnekreft
18. The Norwegian Cancer Society. Senskader (English: late effects) the Norwegian Cancer Society. September 7, 2021. Accessed September 7, 2021. https://kreftforeningen.no/om-kreft/senskader/
19. Helsedirektoratet. The Norwegian Directorate of Health. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft hos barn. September 7, 2021. Accessed September 7, 2021. https://www.helsedirektoratet.no/retningslinjer/kreft-hos-barn-handlingsprogram/Nasjonalt%20handlingsprogram%20med%20retningslinjer%20for%20diagnostikk,%20behandling%20og%20oppf%C3%B8lging%20av%20kreft%20hos%20barn.pdf/_/attachment/inline/bb5802ba-8f82-494f-aeb8-0abf0e59382d:51e8734fdfed4f99153c96b98fb775d6f2d59341/Nasjonalt%20handlingsprogram%20med%20retningslinjer%20for%20diagnostikk,%20behandling%20og%20oppf%C3%B8lging%20av%20kreft%20hos%20barn.pdf
20. Lissauer TCGP. *English: Pedriatrics*. FADL's Forlag; 2016.
21. Bottomley SJ, Kassner E. Late effects of childhood cancer therapy. *J Pediatr Nurs*. 2003;18:126-133.
22. Hedén L, Pöder U, von Essen L, Ljungman G. Parents' perceptions of their child's symptom burden during and after cancer treatment. *J Pain Symptom Manag*. 2013;46:366-375.
23. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. *Br J Clin Pharmacol*. 2015;79:357-369.
24. Bond MC, Pritchard S. Understanding clinical trials in childhood cancer. *Paediatr Child Health*. 2006;11:148-150.
25. Mora DC, Overvåg G, Jong MC, et al. Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young adults: a systematic review and meta-analysis of randomized controlled trials. *BMC Complement Med Ther*. 2022;22:1-21.
26. Nunes MDR, Bomfim E, Olson K, et al. Interventions minimizing fatigue in children/adolescents with cancer: an integrative review. *J Child Health Care*. 2018;22:186-204.
27. Lopes-Júnior LC, Urbano IR, Schuab SIPDC, Pessanha RM, Rosa GS, Lima RAGD. Effectiveness of complementary therapies for the management of symptom clusters in palliative care in pediatric oncology: a systematic review. *Rev Esc Enferm USP*. 2021;55:1-14
28. Lopes-Júnior LC, Bomfim EO, Nascimento LC, Nunes MD, Pereira-da-Silva G, Lima RA. Non-pharmacological interventions to manage fatigue and psychological stress in children and adolescents with cancer: an integrative review. *Eur J Cancer Care*. 2016;25:921-935.
29. Vandenbroucke JP. When are observational studies as credible as randomised trials?. *Lancet*. 2004;363:1728-1731.
30. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.
31. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. A E. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210.
32. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;74:790-799.
33. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-349.
34. Mallen C, Peat G, Croft P. Quality assessment of observational studies is not commonplace in systematic reviews. *J Clin Epidemiol*. 2006;59:765-769.
35. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. *J Clin Epidemiol*. 2010;63:1061-1070.
36. Waddington H, Aloe AM, Becker BJ, et al. Quasi-experimental study designs series-paper 6: risk of bias assessment. *J Clin Epidemiol*. 2017;89:43-52.
37. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons; 2008.
38. Piper C. System for the unified management, assessment, and review of information (SUMARI). *J Med Libr Assoc*. 2019;107:634-636.
39. Barrera ME, Rykov MH, Doyle SL. The effects of interactive music therapy on hospitalized children with cancer: a pilot study. *Psychooncology*. 2002;11:379-388.
40. Chokshi SK, Ladas EJ, Taromina K, et al. Predictors of acupuncture use among children and adolescents with cancer. *Pediatr Blood Cancer*. 2017;64:e26424. doi:10.1002/pbc.26424
41. Diorio C, Schechter T, Lee M, et al. A pilot study to evaluate the feasibility of individualized yoga for inpatient children receiving intensive chemotherapy. *BMC Complement Altern Med*. 2015;15:2.
42. Favara-Scacco C, Smirne G, Schilirò G, Di Cataldo A. Art therapy as support for children with leukemia during painful procedures. *Med Pediatr Oncol*. 2001;36:474-480.
43. Hu H, Shear D, Thakkar R, et al. Acupressure and therapeutic touch in childhood cancer to promote subjective and intersubjective experiences of well-being during curative treatment. *Glob Adv Health Med*. 2019;8:2164956119880143.
44. Kennedy DD, Tucker KL, Ladas ED, Rheingold SR, Blumberg J, Kelly KM. Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. *Am J Clin Nutr*. 2004;79:1029-1036.
45. Medina Córdoba CA, Pérez Villa M. Medidas no farmacológicas implementadas por las enfermeras para el dolor de

niños con Leucemia Linfocítica Aguda. *Index de Enfermería*. 2019;28:46-50.
46. Nilsson S, Finnström B, Kokinsky E, Enskär K. The use of virtual reality for needle-related procedural pain and distress in children and adolescents in a paediatric oncology unit. *Eur J Oncol Nurs*. 2009;13:102-109.
47. Thygeson MV, Hooke MC, Clapsaddle J, Robbins A, Moquist K. Peaceful play yoga: serenity and balance for children with cancer and their parents. *J Pediatr Oncol Nurs*. 2010;27: 276-284.
48. Wurz A, Chamorro-Vina C, Guilcher GM, Schulte F, Culos-Reed SN. The feasibility and benefits of a 12-week yoga intervention for pediatric cancer out-patients. *Pediatr Blood Cancer*. 2014;61:1828-1834.
49. Clerici CA, Pagani Bagliacca E, Silva M, et al. Illusionist techniques as a complement to psychological support for children with cancer. *Tumori J*. 2021;107:171-174.
50. Geyer R, Lyons A, Amazeen L, Alishio L, Cooks L. Feasibility study: the effect of therapeutic yoga on quality of life in children hospitalized with cancer. *Pediatr Phys Ther*. 2011;23:375-379.
51. Govardhan H, Nelson N, Khaleel I, et al. Effect of yoga on the symptoms response in pediatric brain tumor in-patients undergoing chemo and radiotherapy. *Oncol Radiother*. 2019;1: 34-38.
52. Hooke MC, Gilchrist L, Foster L, Langevin M, Lee J. Yoga for children and adolescents after completing cancer treatment. *J Pediatr Oncol Nurs*. 2016;33:64-73.
53. Orsey AD, Park CL, Pulaski R, Shankar NL, Popp JM, Wakefield D. Results of a pilot yoga intervention to improve pediatric cancer patients' quality of life and physical activity and parents' well-being. *Rehabil Oncol*. 2017;35:15-23.
54. Bondurant S, Anastasi J, Berman B, et al. *Complementary and Alternative Medicine in the United States*. Institute of Medicine, National Academies Press; 2005.
55. Concato J. Observational versus experimental studies: what's the evidence for a hierarchy? *NeuroRx*. 2004;1:341-347.
56. Papanikolaou PN, Christidi GD, Ioannidis JP. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. *CMAJ*. 2006;174:635-641.
57. Stub T, Kristoffersen AE, Overvåg G, Jong MC, Musial F, Liu J. Adverse effects in homeopathy: a systematic review and meta-analysis of observational studies. *Explore*. 2022;18: 114-128.
58. Fønnebø V, Grimsgaard S, Walach H, et al. Researching complementary and alternative treatments – the gatekeepers are not at home. *BMC Med Res Methodol*. 2007;7:7-6.
59. Turner L-A, Singh K, Garritty C, et al. An evaluation of the completeness of safety reporting in reports of complementary and alternative medicine trials. *BMC Complement Altern Med*. 2011;11:67.
60. Karkhaneh M, Zorzela L, Jou H, Funabashi M, Dryden T, Vohra S. Adverse events associated with paediatric massage therapy: a systematic review. *BMJ Paediatr Open*. 2020;4:e000584.
61. Myers SP, Cheras PA. The other side of the coin: safety of complementary and alternative medicine. *Med J Aust*. 2004;181:222-225.
62. Stub T, Quandt SA, Kristoffersen AE, Jong MC, Arcury TA. Communication and information needs about complementary and alternative medicine: a qualitative study of parents of children with cancer. *BMC Complement Med Ther*. 2021;21:85.
63. Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: a systematic review. *Pediatrics*. 2011;128:e1575-e1587.
64. Stub T, Musial F, Kristoffersen AA, Alræk T, Liu J. Adverse effects of homeopathy, what do we know? A systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2016;26:146-163.
65. MacPherson H, Altman DG, Hammerschlag R, et al. Revised STandards for reporting interventions in clinical trials of acupuncture (Stricta): extending the CONSORT statement. *PLoS Med*. 2010;7:e1000261.
66. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. *Ann Intern Med*. 2006;144:364-367.
67. Deng GE, Frenkel M, Cohen L, et al. Evidence-based clinical practice guidelines for integrative oncology: complementary therapies and botanicals. *J Soc Integr Oncol*. 2009;7:85-120.
68. Kanitz JL, Camus ME, Seifert G. Keeping the balance—an overview of mind-body therapies in pediatric oncology. *Complement Ther Med*. 2013;21(Suppl 1):S20-S25.
69. Birdee GS, Yeh GY, Wayne PM, Phillips RS, Davis RB, Gardiner P. Clinical applications of yoga for the pediatric population: a systematic review. *Acad Pediatr*. 2009;9: 212-220.e1.
70. Galantino ML, Galbavy R, Quinn L. Therapeutic effects of yoga for children: a systematic review of the literature. *Pediatr Phys Ther*. 2008;20:66-80.
71. Kuttner L, Chambers CT, Hardial J, Israel DM, Jacobson K, Evans K. A randomized trial of yoga for adolescents with irritable bowel syndrome. *Pain Res Manag*. 2006;11:217-223.
72. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer*. 2004;100:2253-2260.
73. Rheingans JI. A systematic review of nonpharmacologic adjunctive therapies for symptom management in children with cancer: review systematic review. *J Pediatr Oncol Nurs*. 2007;24:81-94.
74. Michalsen A, Grossman P, Acil A, et al. Rapid stress reduction and anxiolysis among distressed women as a consequence of a three-month intensive yoga program. *Med Sci Monit*. 2005;11:CR555-CR561.
75. Mustian KM, Palesh O, Sprod L, et al. Effect of YOCAS yoga on sleep, fatigue, and quality of life: a URCC CCOP randomized, controlled clinical trial among 410 cancer survivors. *J Clin Oncol*. 2010;28:9013-9013.
76. Mandanmohan M, Jatiya L, Udupa K, Bhavanani AB. Effect of yoga training on handgrip, respiratory pressures and pulmonary function. *Indian J Physiol Pharmacol*. 2003;47:387-392.
77. Juangpanich U, Onbunreang J, Khansorn T, Lunlud J, Vatanasapt P. Effect of music therapy on anxiety and pain in cancer patients. *J Nurses' Assoc Thailand, North-Eastern Div*. 2012;30:46-52.
78. Nguyen TN, Nilsson S, Hellstrom AL, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial:

randomized controlled trial. *J Pediatr Oncol Nurs*. 2010;27:146-155.
79. Velez-Florez G, Velez-Florez MC, Mantilla-Rivas JO, Patarroyo-Rodríguez L, Borrero-León R, Rodríguez-León S. Mind-body therapies in childhood cancer. *Curr Psychiatry Rep*. 2018;20:58.
80. Facchini M, Ruini C. The role of music therapy in the treatment of children with cancer: a systematic review of literature. *Complement Ther Clin Pract*. 2021;42:101289.
81. Abdulah DM, Abdulla BMO. Effectiveness of group art therapy on quality of life in paediatric patients with cancer: a randomized controlled trial. *Complement Ther Med*. 2018;41:180-185.
82. Aguilar BA. The efficacy of art therapy in pediatric oncology patients: an integrative literature review. *J Pediatr Nurs*. 2017;36:173-178.
83. Lopes-Junior LC, Silveira DSC, Olson K, et al. Clown intervention on psychological stress and fatigue in pediatric patients with cancer undergoing chemotherapy. *Cancer Nurs*. 2020;43:290-299.
84. Flank J, Robinson PD, Holdsworth M, et al. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. *Pediatr Blood Cancer*. 2016;63:1144-1151.
85. Tsukinoki R, Murakami Y. Non-communicable disease epidemic: epidemiology in action (EuroEpi 2013 and NordicEpi 2013): Aarhus, Denmark from 11 August to 14 August 2013. *Eur J Epidemiol*. 2013;28:1-270.
86. O'Regan D, Filshie J. Acupuncture and cancer. *Auton Neurosci*. 2010;157:96-100.
87. Jindal V, Ge A, Mansky PJ. Safety and efficacy of acupuncture in children: a review of the evidence. *J Pediatr Hematol Oncol*. 2008;30:431-442.
88. Diorio C, Kelly KM, Afungchwi GM, Ladas EJ, Marjerrison S. Nutritional traditional and complementary medicine strategies in pediatric cancer: a narrative review. *Pediatr Blood Cancer*. 2020;67(Suppl 3):e28324.
89. Ladas EJ, Jacobson JS, Kennedy DD, Teel K, Fleischauer A, Kelly KM. Antioxidants and cancer therapy: a systematic review. *J Clin Oncol*. 2004;22:517-528.
90. Williamson Lewis R, Effinger KE, Wasilewski-Masker K, Mertens A, Xiao C. Self-reported late effect symptom clusters among young pediatric cancer survivors. *Support Care Cancer*. 2021;29:8077-8087.
91. Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer Nurs*. 2005;28:270-282; quiz 283-284.

Paper IV

Supportive care for cancer-related symptoms in pediatric oncology: a qualitative study among healthcare providers

Mora *et al.*
BMC Complementary Medicine and Therapies (2023) 23:104
https://doi.org/10.1186/s12906-023-03924-x

BMC Complementary Medicine and Therapies

RESEARCH

Open Access

Supportive care for cancer-related symptoms in pediatric oncology: a qualitative study among healthcare providers

Dana C. Mora[1*], Miek C. Jong[1], Sara A. Quandt[2], Thomas A. Arcury[3], Agnete E. Kristoffersen[1] and Trine Stub[1]

Abstract

Background The aim of this study is to gain insight into the clinical experiences and perceptions that pediatric oncology experts, conventional healthcare providers, and complementary and alternative medicine (CAM) providers in Norway, Canada, Germany, the Netherlands, and the United States have with the use of supportive care, including CAM among children and adolescents with cancer.

Methods A qualitative study was conducted using semi-structured in-depth interviews ($n = 22$) with healthcare providers with clinical experience working with CAM and/or other supportive care among children and adolescents with cancer from five different countries. Participants were recruited through professional associations and personal networks. Systematic content analysis was used to delineate the main themes. The analysis resulted in three themes and six subthemes.

Results Most participants had over 10 years of professional practice. They mostly treated children and adolescents with leukemia who suffered from adverse effects of cancer treatment, such as nausea and poor appetite. Their priorities were to identify the parents' treatment goals and help the children with their daily complaints. Some modalities frequently used were acupuncture, massage, music, and play therapy. Parents received information about supplements and diets in line with their treatment philosophies. They received education from the providers to mitigate symptoms and improve the well-being of the child.

Conclusions Clinical experiences of pediatric oncology experts, conventional health care providers, and CAM providers give an understanding of how supportive care modalities, including CAM, are perceived in the field and how they can be implemented as adaptational tools to manage adverse effects and to improve the quality of life of children diagnosed with cancer and the families.

Keywords CAM, Integrative medicine, Pediatric oncology, Qualitative, Resilience, Supportive care modalities

*Correspondence:
Dana C. Mora
dana.c.mora@uit.no
Full list of author information is available at the end of the article

Background

Cancer is the leading cause of death for children and adolescents around the world [1, 2]. Overall, estimated annual incidence rates vary between 50 and 200 per million in children under 15 years of age, and between 90–300 per million individuals who are in the age group of 15 to 19 years old [1]. The overall incidence of cancer among children (0–17) in Norway is 170 per million [3], which is similar to the rest of Europe [4]. The types of cancers that occur in children mainly comprise neoplasms of the blood and lymphatic system (leukemia or lymphoma), embryonal tumors (e.g., retinoblastoma, neuroblastoma, nephroblastoma), and tumors of the brain, bones, and connective tissues [5]. In high-income countries, including Norway, 80% of children survive their cancers, but there are significant variations depending on the tumor type [6]. In low- and middle-income countries, only about 20% survive [7].

Most children survive cancer with conventional medicines, and the treatment protocols vary according to diagnosis. For leukemia and lymphomas, the treatment is chemotherapy [6, 8]. Brain tumors are treated with surgery, chemotherapy, or radiotherapy. Other tumors are most often treated with surgery in addition to chemotherapy [8]. Children have a developing body, and cancer treatment may cause strong adverse effects. Radiotherapy, especially, can damage the healthy tissue of the brain, skeleton, and metabolic system, as well as other organs that are not fully developed [8]. When children receive treatment, it is common for the immune system to weaken. This means that the child is susceptible to infections, which, for a period of time, means that the child cannot participate in normal activities such as school, daycare, and group leisure activities. Moreover, children receiving treatment must live with any consequences of treatment for the rest of their lives [9].

The burden brought about by conventional medicine treatments has led parents to seek different complementary and alternative medicine (CAM) modalities within supportive care [10]. Supportive care is defined by the United States National Cancer Institute as care given to improve the quality of life of people who have an illness or disease by preventing or treating, as early as possible, the symptoms of the disease and the side effects caused by treatment of the disease. Supportive care includes physical, psychological, social, and spiritual support for patients and their families [11]. CAM is defined as a group of diverse medical healthcare system practices and products that are not considered part of conventional medicine [12]. Different countries have different definitions and regulations for CAM [13]. What is considered CAM in one country might not be considered CAM in another country. Hence the umbrella term of supportive care describes well the different modalities used in integrative care. Integrative health care is a caring approach that involves bringing together complementary and conventional treatment approaches in a coordinated manner to address an individual's health needs [14]. Although CAM modalities alone have not proven to be effective for cancer treatment, using them as complements to conventional medicine has been shown to improve the health of cancer patients [12]. Studies have reported that massage therapy [12] and acupuncture [15, 16] among others provide benefits to children during cancer treatment. A systematic review of randomized controlled trials (RCT) from 2022 [17] showed that CAM, including acupuncture and hypnosis, reduces chemotherapy-induced nausea and vomiting.

This research team carried out a focused ethnographic study through semi-structured interviews of families of children with cancer in Norway [18]. Results showed that parents are interested in discussions about CAM and other supportive care modalities that help them to care for themselves, their children, and their families (i.e., reduce anxiety, make healthy food, and keep a normal daily routine). Parents reported they prefer to obtain CAM information from reliable sources such as conventional healthcare providers (doctors or nurses).

Although oncologists generally discuss treatment options with patients, they largely ignore CAM [19]. A 2016 national survey among oncology experts and CAM providers in Norway found that the majority of medical doctors and nurses believed that it is risky to combine CAM and conventional cancer treatment (78% and 93%, respectively). Eighty-nine percent believed that CAM modalities should be subjected to more scientific testing before being accepted by conventional healthcare providers. This contrasts with 57% of the CAM providers [20]. Thus, the philosophical divergence of conventional and CAM approaches to health has often resulted in professional tension between conventional and CAM providers, resulting in opposition to CAM use and integration in parts of the medical community [21, 22]. This situation puts patients who use CAM at risk because they are resistant to disclosing their CAM use to their health care team.

Therefore, to gather more nuanced information about the use of CAM and other supportive care modalities in childhood cancer, we aimed to collect information from different healthcare providers with clinical experience in the area. We hoped that their experiences with supportive care modalities can provide another perspective and contribute to new insight in a field that is under-researched.

The aim of this study is to gain insight into the clinical experiences and perceptions that pediatric oncology

experts, conventional healthcare providers and CAM providers in Norway, the United States, the Netherlands, Germany, and Canada have with the use of supportive care, including CAM, among children (0–9) and adolescents (10–19) [23] with cancer. To reach our aim we interviewed pediatric oncology experts (pediatric oncologist and nurses), other conventional healthcare providers (physiotherapists, nutritionists, and play therapists), and CAM providers (acupuncturists, healers, and massage therapists).

Methods

This is a qualitative study [24], consisting of 22 semi-structured individual interviews. Qualitative design is useful when examining a phenomenon of previously limited knowledge [25]. It is important to understand the philosophical and medical context of supportive care modalities including CAM. A qualitative design is suitable for generating such information [26, 27].

Study area and setting

This study was conducted in Norway, but healthcare providers from different countries (Canada, the Netherland, Norway, Germany, and the United States) were interviewed. Norway follows the Nordic health model of universal health care [28]. Canada [29], Germany [30], and the Netherlands [31] also have universal health care systems. The United States has multiple health systems that operate independently. The private sector plays a stronger role where private third-party payer sources (i.e., insurance companies) cover more than half of Americans' health expenses [32]. In all the countries, regardless of the healthcare system, supportive care modalities such as CAM are mostly offered outside the conventional healthcare system.

Inclusion criteria

Inclusion criteria for healthcare providers were: (1) trained as pediatric oncology expert (doctor, nurses); conventional healthcare providers other than doctors and nurses; or CAM provider (practicing at least one or more CAM modalities inside or outside the conventional healthcare system) and (2) clinical experience working with supportive care and/or CAM modalities among children (0–9 years) and/or adolescents (10–19 years) [23]with cancer.

Recruitment

Participants were recruited using purposive sampling [33] and were contacted through email and telephone. The researchers had no prior relationships with the individual participants. The Norwegian participants were recruited through the University Hospital of North Norway (UNN) ($n=5$); the Norwegian Healer Association ($n=2$); the Norwegian Homeopathy Association ($n=1$); the Acupuncture Association ($n=1$) and Norwegian Association for Psychotherapy ($n=1$). The providers outside of Norway were recruited through the research team's professional networks in Canada ($n=1$), Germany ($n=1$), the Netherlands ($n=3$), and the United States ($n=7$).

Participants

Before completing the interviews, the researchers informed the participants about the aim of the study and the purpose and content of the interview. Written and verbal informed consent was obtained from all participants. The study participants were informed that they could withdraw from the study for any reason at any time. The study was approved by the Norwegian Center for Research Data, reference number 978969. None of the participants dropped out.

Data collection

Interviews were semi-structured, and an interview guide was developed by the investigators based on an review of the existing literature [34] and their knowledge of the field. Eight interviews were conducted face-to-face at workplaces ($n=7$) and a private home ($n=1$). Fourteen were conducted via Teams (a cloud-based video conferencing platform). The interviews were audio-recorded with the consent of the participants. Most of the interviews took between 30–60 min to complete. The first author (DCM) performed the interviews ($n=12$) in English, while the last author (TS), who is Norwegian, performed the Norwegian interviews ($n=10$) in Norwegian. To ensure the anonymity of each participant, they received an identification number (ID#). Field notes were taken during the interviews. The interviewers had previous experience conducting qualitative research [35–38], both interviewers are females and worked conducting research related to CAM at the time of the interviews.

Data analysis

The interviews were transcribed verbatim into English by the first author (DCM). All the Norwegian interviews were transcribed verbatim by a professional service and translated into English by the senior author (TS). The analysis was conducted using conventional content analysis [39]. The success of content analysis depends on the coding process and in this study the codes were defined during the data analysis. The data were coded inductively, the codes were generated after DCM and TS carefully read the interviews. The data were entered and coded into Nvivo 1.61 [40]. After reviewing the coding both authors discussed any

disagreements. The themes were developed by the first and the senior authors after reading and reviewing the interviews separately. Three themes were identified: (1) Perceptions of supportive care (2) Implementation of supportive care (3) the Empowerment of parents and overall care for the family. After identifying the three themes, six subthemes were developed (Table 1). Transcripts were not returned to participants for comment and/or correction. The consolidated criteria for reporting qualitative studies (COREQ) [41] were followed to ensure the methodological quality of the study. All methods were carried out in accordance with relevant guidelines and regulations.

Results

Twenty-two pediatric oncology experts, conventional health care providers, and CAM providers were recruited. Most participants were female with a mean age of 45 years (range 25–68 years). Over 70% of the participants ($n=17$) had ten or more years of experience in clinical practice (Table 2).

Fifteen of the participants were conventional pediatric oncology providers or other conventional providers (6 were pediatric oncologists, 5 were nurses, 4 were other conventional health care providers (i.e., physiotherapists (1), nutritionists (2), play therapist—in Norway, play therapists are licensed conventional healthcare providers (1)).

Almost one-third ($n=4$) were self-employed (healers, homeopath, massage therapist), and nine ($n=9$) were employed in the public health care sector (nurse, physiotherapist, pediatrician, music and play therapist). One participant worked both inside and outside the official sector (physiotherapist and psychodrama therapist). Nine participants worked for private hospitals.

All the participants had experience working with pediatric oncology patients (aged 0–19 years old), and 18 worked in pediatric oncology settings. Five participants had training in both conventional care and CAM.

Table 1 Overview of the main themes and subthemes

Themes	Subthemes
Perceptions of supportive care	- Clinical practice - Effect of supportive care - Supportive care for adverse effect management - Supportive care for palliative care
Implementation of supportive care	- Adverse effects management
Family empowerment and overall care for the family	-Providing agency, comfort, and relief

Participants were recruited from five countries (Canada $n=1$, Germany $n=1$, Netherlands $n=3$, Norway $n=10$, United States $n=7$) (Table 2).

Perceptions of supportive care

Through this theme, insight into the clinical practices of participants is gained, as well as what perceptions oncology experts and conventional providers have of supportive care. Four subthemes emerged: clinical practice, supportive care for palliative care, effect of supportive care, and supportive care for adverse effect management.

Clinical practice

Most of the participants (ID 1, 2, 5–9, 11–13, 15) stated that the cancer diagnosis they treated most often was leukemia (acute lymphocytic leukemia (ALL) or acute myeloid leukemia (AML)). In Norway, patients with cancer are diagnosed and treated at one of the main four hospitals in the country: Oslo University Hospital, Haukeland University Hospital, St. Olav's Hospital, and University Hospital of North Norway. According to one participant (ID 11), patients most often have chemotherapy or surgery. If the child has a rare tumor or needs special surgery, they are referred to the main hospital, in Oslo or they might be sent to other countries for treatment. Outside Norway, participants also stated that most children are treated with chemotherapy, radiation, or surgery (ID 1,5, 6, 8–10, 22, 23). The symptoms from cancer treatment most often reported in the interviews were nausea, mental health issues such as anxiety, lack of socialization, and depression. In addition, pain, vomiting, fatigue, neuropathy, mucositis, constipation, decrease appetite, and insomnia are also common. Even though the medical systems varied from country to country, all the participants (ID 1–18, 22, 23) who worked in hospitals said that the supportive care modalities (e.g., play therapy, acupuncture, and music therapy) offered at the hospital are free for the patient, but parents must pay out-of-pocket for any modalities performed outside of the hospital (e.g., acupuncture, healing, and massage).

All the conventional care providers interviewed outside of Norway had experience working in integrative medicine settings and had positive beliefs about CAM to various degrees. One oncologist (ID 22) stated that "a lot of CAM treatments would be okay to use but there is just not enough research". However, another pediatric oncologist (ID 9) was more skeptical about the modalities, he stated, "I'm not very much in favor, let's be clear, I'm not in favor of prescribing these things [modalities], which cost a lot and are not proven."

A program manager and CAM provider in the United States (ID 2) stated that, in her program, they view

Table 2 Demographic data of the participants

Health care providers	Total ($n=22$)	Oncology Experts ($n=11$)	Conventional[a] ($n=4$)	CAM providers[a] ($n=7$)
	n (%)	n (%)	n (%)	n (%)
Gender				
Female	18 (82)	8 (73)	4 (100)	6 (86)
Male	4 (18)	3 (27)	0 (0)	1 (14)
Age (mean)	45.5	48.3	46.5	51.6
18 – 40 years of age	6 (27)	3 (27)	2(50)	1 (14)
41—60 years of age	10 (45)	6 (55)	1 (25)	4 (57)
61 years and older	6 (27)	2 (18)	1 (25)	2 (29)
Years in practice				
0–10 years	5 (23)	2 (18)	2(50)	1 (14)
11–20 years	8 (36)	3 (27)	0 (0)	4 (57)
21–30 years	4 (18)	3 (27)	1(25)	1 (14)
More than 31 years	5 (23)	3 (27)	1 (25)	1 (14)
Training[a]				
Acupuncturist[a]	5(18)	3 (27)	0 (0)	2 (14)
Anthroposophic medicine[a]	1 (5)	1 (9)	-	-
Healer	3 (14)	1 (9)	-	2 (14)
Homeopath	1 (5)	-	-	1 (7)
Nurse[a]	5 (23)	3 (27)	-	2 (14)
Massage therapist	1 (5)	-	-	1 (7)
Music therapist	1 (5)	-	-	1 (7)
Nutritionist	2 (9)	-	2 (50)	-
Pediatric oncologist[a]	6 (27)	3 (27)	-	3 (21)
Physiotherapist[a]	1 (5)	-	1 (25)	-
Play therapist	1 (5)	-	1 (25)	-
Psychodrama therapist[a]	1 (5)	-	-	1 (7)
Sector				
Public sector	9 (45)	6 (55)	2 (50)	1 (14)
Private sector	9 (36)	5 (45)	2 (50)	2 (29)
Self-employed:	4 (18)	-	-	4 (57)
Country				
Canada	1 (5)	1 (7)	-	-
Germany	1 (5)	1 (7)	-	-
The Netherlands	3 (14)	2 (13)	-	1 (14)
Norway	10 (45)	4 (36)	2 (50)	4 (57)
United States	7 (32)	3 (27)	2 (50)	2 (29)

[a] These providers were trained as both conventional and CAM providers

supportive patient care through three different lenses. These lenses are prevention, mitigation of adverse effects, and long-term effects. The treatment plan for the different supportive care modalities is discussed among the provider, the parents, and the child, depending on the diagnosis, conventional treatment, and most importantly the immediate (daily) needs of the child. The conventional care team is not usually involved unless there is a specific question or someone in the conventional care team is trained as a CAM provider. In one program, consultations with the CAM provider often happen soon after diagnosis to focus on prevention and mitigation of symptoms from conventional cancer treatment. An acupuncturist (ID 3) explained that her job at the time of consultation, given all the other treatment the child was enduring, was to "have a flexible toolbox and prevent things from happening but also mitigate what is going on in the moment and just support [the patient] in the moment. …the overriding goal is just to help in the moment if possible."

Even in integrative programs, integrative medicine is not offered/discussed with all of the patients. In most programs, supportive care modalities including CAM (such as acupuncture, massage, or reiki) are only offered if the parents or patient asks for it or if someone in the oncology treatment team recommends integrative care for that patient.

Effect of supportive care

Providers also believe that it is okay to use CAM and are willing to recommend it as long as it does not add extra burden for patients. A provider (ID 15) stated "There must be evidence of effect of CAM. I think that the treatment must not cause additional suffering for the child just so the parents can feel that they have tried it…If the treatment has effect and does not harm the child, I could recommend it." Other providers (ID 4, 22) who recommend CAM to manage adverse effects from cancer treatment believe that some modalities are flagged on the conservative end but that many modalities would be fine to use, there is just evidence lacking. A providers (ID 4) stated "… there is evidence supporting the use [of CAM] in patients in outpatient setting, but there is very little data."

Supportive care for adverse effect management

For all the participants supportive care is used to help children manage adverse effects from cancer treatment not to treat cancer itself. As an oncologist (ID 1) stated, "So, we don't ever treat the cancer directly. We treat the adverse effects of the cancer, and we try to approach the patient at diagnosis and at initiation of treatment."

Two pediatric oncologists (ID 5, 22) also stated that they recommend supportive care as a non-pharmacological treatment to manage symptoms. An oncologist (ID 5) expressed that the last thing patients want to do to manage symptoms is to take another pill. She stated that "there are symptoms like fatigue, anxiety, insomnia, that we just don't have the interventions for. I am thinking there has got to be a better way to make people feel better as they're going through their cancer treatments that doesn't just involve asking, particularly children, to take more medicines".

Supportive care for palliative care

Conventional healthcare providers and oncology experts interviewed are more open to supportive care for those in palliative care. A nurse (ID 12) stated, "When the story ends, the parents should be left feeling that they did whatever they could for their child. It has never been a problem to get a healer to come here [at the hospital], upon request from the parents". Likewise, a pediatric oncologist (ID 22), while discussing the use of supplements, stated that she recommends certain treatments depending on the prognosis. For example, for ALL she does not recommend taking extra substances [herbs or supplements] due to concerns of decreasing the chemotherapy efficacy or increasing the toxicity. However, if the child is at the end of life she stated, "I'm much more liberal with that [using supplements]. I would be like yes, if that's not going to hurt you, fine."

In Norway specifically, most of the conventional care nurses are skeptical about supportive care modalities, especially CAM. They all had limited knowledge of CAM and agreed it should be used as a last resource when nothing else has worked to enable parents to give the best care for their child.

Implementation of supportive care

Throughout this theme, the participants describe various modalities they used and how they helped the child cope with adverse effects from conventional cancer treatments.

Adverse effects management

Most of the modalities mentioned by the participants are recommended and used to manage the adverse effects of cancer treatment. Among the modalities mentioned in the interviews were acupuncture, healing, massage/aromatherapy, nutrition (herbs, dietary changes, and supplements), and mental health (art, music, play therapy, and psychodrama).

Acupuncture According to the participants (ID1, 2, 3, 4, 5, 10, 22), acupuncture is one of the modalities often used and recommended in the United States. In pediatric oncology, the modality is mostly used to reduce symptoms from conventional cancer treatment, and it is considered safe. In one program, acupuncture is offered to the patients depending on the chemotherapy regimen the patient is receiving and the potential adverse effects that might be derived from that treatment (ID 2, 3). All acupuncturists use needles, acupressure, ear seeds, laser, or acupuncture bands. A Norwegian acupuncturist working in private practice stated that because children have simple patterns of imbalance, not many needles are needed. When treating children, thin short needles are used as they are gentler. Acupuncturists, pediatric oncologists, and nurses said that they use acupressure points to relieve nausea in their patients. For example, a pediatric oncologist (ID 22) says that she recommends acupressure for children who have refractory nausea and vomiting. An acupuncturist (ID 18) who works in an integrative program stated, "you should not treat children as adults" and noted that an individual assessment should always be made. Most providers agreed that babies, younger

children, and teenagers tolerate needles, so they are often used. According to the participants, children between 5–12 years are more afraid of needles, and acupressure or laser are more often used with that age group as they are not as invasive. Acupuncture is also recommended for pain, functional limitation due to neuropathy, musculoskeletal limitation, anxiety, relaxation, and constipation.

Nutrition Some of the symptoms that are addressed through nutrition are vomiting and nausea. Providers use herbal teas such as peppermint or ginger and add fresh ginger to smoothies to aid with nausea and vomiting symptoms. For those with mouth sores, providers recommend soft and bland foods and avoiding hot spicy foods. As described by the nutritionist (ID 6) below:

> *"Kids do better when they are able to sip on something through a straw throughout the day than having to actually eat."*

Children who lack appetite can try small protein pack snacks throughout the day (proteins can include dairy, meat, nut butter, and legumes). Commonly available sources of proteins for children can be milk, yogurt, and cheese. They can also try smoothies that are calorie and protein dense. For those who, due to chemotherapy, are sensitive to smells, the nutritionist recommends eating foods that are cold or at room temperature. Nutritionists (ID 6, 7) counsel parents based on food preferences, family eating patterns, accessibility to different foods, and cultural food practices.

According to nutritionists (ID 6, 7), avoiding foods with concentrated sugars or carbohydrates and having a source of healthy fat (e.g., olive oil, avocado oil, fatty fish, seeds, nuts) or protein and complex carbohydrates such as oatmeal or whole grains can help children with fatigue. The nutritionists also talk to parents about tube-feeding formulas. After addressing the basics when selecting a formula (does the child tolerate it? do they need elemental -broken down, hydrolyzed for easier digestion- or intact?), the nutritionist tries to involve the parents as much as possible to select the formula that is tolerated best by the child. They involve the parents by reviewing the ingredients and reviewing previous experiences based on knowledge from other parents and patients.

Healing/Reiki Participants referred to healing, reiki, and healing touch in the interviews. According to the Norwegian Law of Alternative Treatment [42], healers and other CAM providers are not allowed to treat cancer itself, but the healing may be used to strengthen the body and to treat the adverse effects of cancer and treatment. This is illustrated in the quotation below:

> *"Parents are interested in healing that strengthens the immune system and provides children with enough energy to face what they must go through (ID 12)."*

A participant (ID 20), who works as a healer, prepares herself before treating the child by processing her emotions, meditating, and asking for the power to help perform the healing of the child. Most of the children treated by the healer are diagnosed with leukemia and brain tumors. For the healers (ID 12, 20), included in this study, the primary focus is to provide trust, strengthen the child's energy and aura, and relieve pain. The treatments are only given during the children's breaks from chemotherapy or radiation. Healers do not treat the area in which the tumor lies, but the areas around it. Sometimes, the participant (ID 20), treats both the parents and the child.

Massage/Aromatherapy Providers also recommend modalities such as massage and play therapy for general well-being and to make the stay at the hospital or home with a sick child as normal as possible. Modalities often used for this purpose are massage and aromatherapy. According to an oncologist (ID 1), chemotherapy and radiation therapy cause muscle tension and dryness of the muscles and the joints; massage is recommended for loosening the muscles and tendons in the body. According to a massage therapist, massage is used to help the child relax and loosen the body, and to decrease anxiety, stress, and fatigue. Another factor that is taken into consideration when performing massage is the physiological and emotional impact of a cancer diagnosis on the family. Different providers (ID 3, 8, 10, 13) stated that they teach the parents message so that they can help their children. In addition, it is used for sleep problems, to reduce head and neck pain, and musculoskeletal complaints. A massage therapist (ID 23) stated that she works under the principle that *less is more*. During treatment, the massage sessions last 20—30 min maximum and can only be done on part of the body. However, the first session often lasts only 10 min to make sure it is safe, depending on the patient and their health history. Apart from using needles, acupuncturists use tui na massage (tui na follows the assumptions of Chinese medicine, it is a system of massage, manual acupuncture point stimulation, and manipulation) [43]. One acupuncturist (ID 3) used tui na to help constipated children. One of the chemotherapy drugs (Vincristine®) causes constipation. A new dose cannot be administered until children have a bowel movement, so the acupuncturist uses tui na and acupressure to help calm the nervous system and move

the bowel. In many cases, this massage has reportedly been effective.

Aromatherapy is also offered in integrative programs in the United States and Germany because, like massage, it has been shown to mitigate chemotherapy's effects and be safe. According to the participants, it is more often used for improving nausea, vomiting, sleep, and anxiety. The programs that offer this modality have trained personnel who prescribe the oils and make personalized nasal inhalers for the children. The oils are sometimes used with massage or acupressure for relaxation and constipation (ID 3). Ginger, lemon balm, and peppermint teas are incorporated together with deep breathing to help the children manage nausea caused by chemotherapy in one of the programs (ID 7). Lavender extract is also used to massage children's feet and lower extremities to help children sleep (ID 8).

Play, psychodrama, and music therapy Diverse modalities like play, psychodrama therapy, music, and virtual reality programs are often used for stress management, to divert the attention of children from painful procedures, treatment regimens, and the burden of having a cancer diagnosis. At the hospital, children play to process emotions, and through role-play, they cope with their situation. Using techniques such as role-play, the provider helps children process their emotions. The playroom is a safe space where doctors and nurses are not allowed and where both patients and parents can unfold their emotions. In Norway, the play therapist can also collaborate with other providers (e.g., the physiotherapist) to help children practice motor skills and language development.

Psychodrama is another strategy offered to help pediatric oncology patients express their emotions. Psychodrama is implemented by following three pillars: mirroring, role-playing, and duplication. Children use play to mirror their emotions. As stated by the therapist (ID 17), "Whatever the children have experienced will be symbolically expressed in the play." For example, the feeling of being powerless is often expressed in play when the child gets sleepy, disappears, or becomes dizzy. Children can go quickly in and out of roles; through role-play, the child can regain mental and physical control. For instance, a child with cancer expressed her feelings of powerlessness during therapy. In the session, she played a guard that captured a prisoner [the therapist], provided lousy food to the prisoner, and told her she would be in prison forever. The child wanted the therapist to feel/experience the same feelings as she did during cancer treatment, and through that, the child processed her own feelings.

Music therapy is used for distraction, relaxation, and as a means of visualization. A provider (ID 16), for example, can listen to music with the patient and while the music is playing the patient is guided to relaxation. Music therapy is also used for parents, by playing music parents can express their emotions, including the realization that they are scared by their child's diagnosis, but, at the same time, they need to be the safety net to comfort the child. This is a dilemma for the parents. They need to be strong, but they are also afraid, something they try to hide from the child. As stated by the therapist during this time, "It is important to strengthen relations in the family." The provider works with different instruments, including piano, guitar, and flute sound sticks. Music is used to strengthen family relationships and allow the children to express their emotions. For example, the provider had a little girl who stopped talking after surgery. During a music therapy section a week after surgery, the music therapist and the girl were looking for the girl's voice. They found the voice inside the guitar by playing lullabies. Having found her voice, the girl started to talk again. The music therapist uses puppet dolls to help the children express their feelings. She has a crow who is moody, sad, and angry; she also has a kitten who is anxious and worried. The puppets give the child different conversation partners that help them open up and talk to the puppets about anything of interest.

Empowerment of parents

Lastly, a theme emerged that captured the providers' perceptions of the parent's role during the treatment of the child and how supportive care provides a way for parents to feel they are actively part of their child's care.

Providing agency, comfort, and relief

The high survival rates of childhood cancer are due to closely prescribed treatment protocols. These protocols are strictly implemented. The pediatric oncologist takes complete control, and the parents have limited agency in making decisions about their child's treatment, potentially creating a feeling of helplessness among the parents. It is the providers' impression that the parents often feel afraid because of their child's diagnosis, but at the same time, they feel the responsibility to provide safety and comfort and want to do everything in their power to help the child. As described by a pediatric oncologist (ID 8):

> *"Pediatric oncology is very passive [for the parents], parents sign the informed consent, and then we [pediatric oncologists] give to the children any drug or intervention. So, the parents, at some stage, just have to tolerate it."*

All participants expressed that parents experience a passive role and a loss of authority and control that can lead them to anxiety and worry. Given the lack of agency parents have during conventional cancer treatment of their children, all the providers agree that the use of supportive care, including CAM helps parents overcome some anxiety and gives them back control. One acupuncturist (ID 3) stated: "CAM gives a sense of control, a sense of contribution, which can be therapeutic. By educating them about all the ways that exist and can be used to mitigate or treat symptoms, parents are given back agency."

As discussed in the former results, supportive care modalities give parents the agency to establish a treatment plan together with the CAM provider. For example, by learning about acupressure, they can use specific points to manage nausea and vomiting at home.

Education is an important tool used by providers to give the parents agency, provide some comfort to the children, and provide a sense of normalcy to the family. Often using things daily that are helpful, and teaching and empowering parents and children to do some of those things (e.g., massage, acupressure) has a significant impact because providers can see those patients and their parents feel better. A pediatric oncologist (ID 1) stated:

> *"Parents feel involved because they can do these things. That is a huge win and that is an everyday thing. So, to me, those everyday things are bigger than any other big miraculous thing."*

Providing treatments such as acupuncture or massage to parents is another technique providers use to help parents cope with their child's cancer diagnosis and treatment. In the providers' perception offering these treatments to parents helps mitigate some of the fears or questions both the parents and patients have about supportive care modalities.

Discussion

The participants interviewed are a heterogeneous group with different years of experience, different professions, and from different countries; however, common themes emerged from their interviews. They spoke about improving the general well-being of the patients and their families by empowering them to take control of the cancer treatment using supportive care modalities. For example, parents are taught how to give massages to help their children go to sleep or help with constipation. They also shared details about their perceptions of supportive care including their clinical practice, such as how their programs are coordinated and what and how supportive care modalities are offered and implemented. Participants also reported having similar experiences and goals concerning the treatment of children with cancer and the use of supportive care. For instance, most providers recommended supportive care to manage symptoms from cancer treatment such as nausea, anxiety, and depression. The supportive care modalities most often mentioned to help mitigate these adverse effects were massage, nutrition, play therapy, and acupuncture.

Well-established programs in pediatric oncology that integrate CAM modalities and conventional treatments exist in different parts of the world, including Europe and North America. Programs at university hospitals in the United States [44] and Germany [45] offer acupuncture, anthroposophic medicine, aromatherapy, exercise and movement therapy, herbal and homeopathic remedies, massage, mind–body medicine, and art therapy. While they are becoming more common [46], integrative programs in pediatric oncology are limited [47]. A survey from Jacobsen et al., [48] reported that CAM was offered in 64.4% of the hospitals in Norway in 2013. In Norway, CAM is normally not offered in pediatric oncology settings. However, other supportive care modalities such as music therapy, art therapy, and play therapy are offered to varying degrees in all four main hospitals. No major differences were found between public and private, nor between non-psychiatric and psychiatric hospitals. Acupuncture (37.3%) was the most commonly offered modality followed by art and expression therapy (25.4%), massage (15.3%), and alternative diet (8.5%). On the other hand, music therapy was offered by 13.6% of the hospitals [48]. Music therapy is a popular modality among children and, according to the participants in this study, is commonly offered at pediatric oncology units in Norway. Art therapy, play therapy, and clowns are other supportive care modalities offered in children's wards (including oncology) in Norway [49–52]. Even though CAM is used by pediatric oncology patients [53], according to the literature, there is a lack of knowledge about CAM among pediatric oncologists [54–56].

The results of our study showed that although supportive care modalities are used, they are not routinely offered to all pediatric oncology patients. All the participants in our study reported open communication about supportive care, including CAM; however, children are referred to integrative programs only if parents ask about CAM. This mirrors a skeptical attitude toward these modalities among many healthcare providers, which is in line with the existing literature regarding the attitudes of conventional health providers about CAM. In a study about attitudes of pediatric oncologists, it is reported that only 41% of the oncologists raise the topic of CAM during the first consultation [55]. The same study [55] also reports that over 70% of the pediatric oncologists

agree somewhat or fully that CAM should be used when all conventional therapies fail, also supporting responses obtained through our interviews. The latter is consistent with perceptions reported in this study, where providers are more favorable of supportive care, including CAM, during palliative care.

According to the participants in this study, supportive care modalities are an important component of care that can guide future clinical practice. The goal of applying supportive care is to improve the quality of life of children with cancer and their families by treating the adverse effects caused by cancer treatment. Modalities such as acupuncture [15, 16, 57–59], massage [12], aromatherapy [60], healing [61], music [62], play therapy [63], and psychodrama [64] have beneficial outcomes in children [17, 65]. In general, we found that supportive care modalities are used to provide comfort and control to the patients and parents; this is in line with other studies [66–68].

Due to the strict childhood cancer treatment protocols, parents report very little control over the uncomfortable and painful procedures and treatments the child has to endure after receiving a cancer diagnosis [68]. An important topic that emerged from these interviews is the empowerment that the use of supportive care provides to children and adolescents with cancer and their parents. Using different supportive care modalities to treat symptoms and complaints at home helps the families get back to normal everyday life even though the child is ill. This sentiment is in line with what Masten [69], called *the power of the ordinary*. This sentiment states that "resilience comes from the everyday magic of the ordinary, it comes from normative human resources in the minds, brains, and bodies, of children, in their families and relationships, and their communities." [69] By creating daily routines with massage, taking control of the child's diet, or creating spaces where children can play, or listening to music, a sense of normalcy is created. This need for normalcy and family routines in times of adversity is in line with goals of parents found in a Norwegian study among parents who have children with cancer [35].

Strengths and limitations

The findings of this study should be interpreted considering its limitations. The study centered on a small group of oncology pediatric experts, conventional health care, and CAM providers who were interviewed once, and all the participants interviewed were from high-income countries. An error introduced when the study population does not represent the target population is understood as selection bias [70]. Ideally, the subjects in a study should be very similar to one another and to the larger population from which they are drawn. If there are important differences, the results of the study must be understood with caution, which is the case in this study. Different modalities of CAM are offered/used by children and adolescents with cancer [53] and it was not possible to interview a provider for each modality. If more healthcare providers had been interviewed, or if multiple interviews had been done with each participant, it could have been possible to gather additional information about their clinical practice and their experience; however, no new information was achieved after 20 interviews, demonstrating that saturation was reached [71].

To our knowledge, this is the first study that interviews pediatric oncology experts, conventional healthcare providers, and CAM providers employing supportive care modalities among children and adolescents with cancer. The results show similarities in perceptions of supportive care use, the implementation of supportive care, and their approach to empowering parents during cancer treatment. This is important because it offers further knowledge and understanding of how conventional medicine and CAM clinical practices are used in combination to improve well-being, give hope, and treat adverse effects of cancer treatment among these children.

Implications for practice

Understanding the implications that supportive care can have for children and their parents can help guide treatment protocols for children with cancer across different countries. Although countries have different healthcare systems, childhood cancer is a rare disease. In most high-income countries, the survival of childhood cancer has improved due to the integration of clinical research into front-line care from multidisciplinary specialists [72]. The ailments and needs of the children undergoing cancer treatment are similar across countries, particularly among children in high-income countries. Hence, the results of this research can offer modalities that focus on the overall well-being of the patients and their families. The information gained in this study can be used to inform other countries where supportive care is not integrated on how existing programs work, how they are integrated, and what modalities are used among this patient group. The results can also be used as evidence to generate practical guidelines, for example, in nursing to implement modalities such as massage and reiki. The finding regarding the empowerment of the parents can be used as a baseline to further investigate among parents how supportive care empowers and helps them during and after diagnosis and treatment.

Conclusion

The overall results of this study give providers, parents, and patients insight into how healthcare providers working in pediatric oncology perceive the role of supportive care modalities in this field. According to the participants, these modalities can be used to help manage adverse effects of cancer treatment, but they also act as an adaptational system to develop resilience and empower children and their families while undergoing cancer diagnoses and treatment. Through the development of resilience and empowerment, children can have better overall health outcomes that could lead to healthier, happier, and more productive lives during and after cancer treatment.

Abbreviations

CAM	Complementary and alternative medicine
RCT	Randomized controlled trials
ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia

Acknowledgements

We want to express our gratitude to the oncology experts, and CAM providers who kindly participated in this study. The publication charges for this article have been funded by a grant from the publication fund at UiT, The Arctic University of Norway, Norway.

Authors' contributions

TS conception; DCM & TS design of the work; DCM and TS acquisition of data; DCM, TS, analysis; DCM, TS interpretation of data; DCM & TS have drafted the work; DCM, MJ, SA, TA, AK, and TS substantively revised it. All authors have read and approved the manuscript.

Funding

Open access funding provided by UiT The Arctic University of Norway (incl University Hospital of North Norway) This research was funded by Ekhaga Stiftelsen (2020–76), Sweden, and the Childrens' Cancer Society in Troms and Finnmark, Norway.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was approved by the Norwegian Center for Research Data (NSD), reference number 978969. The NSD is a governmental entity with a board that assesses research projects involving personal data. NSD conducts a privacy protection review and assesses that the processing of personal data in research projects is in accordance with ethics and data protection legislation. Before completing the interviews, the researchers informed the participants about the aim of the study and the purpose and content of the interview. Written and verbal informed consent was obtained from everyone. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable. We have not published any information that can identify the participants.

Competing interests

The authors declare no competing interests.

Author details

[1]National Research Center in Complementary and Alternative Medicine (NAFKAM), Faculty of Health Science, Department of Community Medicine, UiT The Arctic University of Norway, Tromsø N-9037, Norway. [2]Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA. [3]Department of Family and Community Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.

Received: 15 August 2022 Accepted: 15 March 2023
Published online: 03 April 2023

References

1. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, Hesseling P, Shin HY, Stiller CA, Bouzbid S, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol. 2017;18(6):719–31.
2. Bhakta N, Force LM, Allemani C, Atun R, Bray F, Coleman MP, Steliarova-Foucher E, Frazier AL, Robison LL, Rodriguez-Galindo C, et al. Childhood cancer burden: a review of global estimates. Lancet Oncol. 2019;20(1):e42–53.
3. National Quality Register for Childhood Cancer, Annual Report 2020. The Cancer Registry [https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2021/arsrapport-nasjonalt-kvalitetsregister-for-barnekreft-2020.pdf] Accessed.
4. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, Trama A, Visser O, Brenner H, Ardanaz E, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. Lancet Oncol. 2014;15(1):23–34.
5. Jemal A, Vineis P, Bray B, Torre L, Forman D. The Cancer Atlas New-York: Cancer in Children. 2015.
6. Barnekreft. English: Pediatric cancer [https://www.barnekreftforeningen.no/barnekreft] Accessed 6 Oct 2019
7. Howard SC, Zaidi A, Cao X, Weil O, Bey P, Patte C, Samudio A, Haddad L, Lam CG, Moreira C, et al. The My Child Matters programme: effect of public–private partnerships on paediatric cancer care in low-income and middle-income countries. Lancet Oncol. 2018;19(5):e252–66.
8. Lissauer T, Clayden G. Pædiatri. English: Pedriatrics. Copenhagen: FADL's forlag; 2016.
9. Seneffekter etter behandling av kreft. English: Late effekts after cancer treatment [https://www.barnekreftforeningen.no/barnekreft/seneffekter] Accessed 4 May 2020
10. Fitch M. Supportive care framework. Can Oncol Nurs J. 2008;18(1):6–14.
11. Dictionary of Cancer Terms : Supportive Care [https://www.cancer.gov/publications/dictionaries/cancer-terms/def/supportive-care] Accessed 22 July 2022
12. Radossi AL, Taromina K, Marjerrison S, Diorio CJ, Similio R, Njuguna F, Afungchwi GM, Ladas EJ. A systematic review of integrative clinical trials for supportive care in pediatric oncology: a report from the International Society of Pediatric Oncology, T&CM collaborative. Support Care Cancer. 2018;26(2):375–91.
13. Wiesener S, Falkenberg T, Hegyi G, Hök J, Roberti di Sarsina P, Fønnebø V. Legal Status and Regulation of Complementary and Alternative Medicine in Europe. Complement Med Res. 2012;19(suppl 2)(Suppl. 2):29–36.
14. Kania-Richmond A, Metcalfe A. Integrative health care - What are the relevant health outcomes from a practice perspective? A survey. BMC Complement Altern Med. 2017;17(1):548–548.
15. Reindl TK, Geilen W, Hartmann R, Wiebelitz KR, Kan G, Wilhelm L, Lugauer S, Behrens C, Weiberlenn T, Hasan C, et al. Acupuncture against chemotherapy-induced nausea and vomiting in pediatric oncology Interim results of a multicenter crossover study. Support Care Cancer. 2006;14(2):172–6.
16. Gottschling S, Reindl TK, Meyer S, Berrang J, Henze G, Graeber S, Ong MF, Graf N. Acupuncture to alleviate chemotherapy-induced nausea and vomiting in pediatric oncology - a randomized multicenter crossover pilot trial. Klin Padiatr. 2008;220(6):365–70.
17. Mora DC, Overvåg G, Jong MC, Kristoffersen AE, Stavleu DC, Liu J, Stub T. Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young

adults: a systematic review and meta-analysis of randomized controlled trials. BMC Complement Med Ther. 2022;22(1):1–21.
18. Stub T, Arcury TA, Kristoffersen AE, Jong MC, Quandt SA: Parents of children with cancer: Strategies for managing care of sick child in the context of family life. Unpublished data 2019.
19. Brown PR, Alaszewski A, Swift T, Nordin A. Actions speak louder than words: the embodiment of trust by healthcare professionals in gynaeoncology. Sociol Health Illn. 2011;33(2):280–95.
20. Stub T, Quandt SA, Arcury TA, Sandberg JC, Kristoffersen AE. Attitudes and knowledge about direct and indirect risks among conventional and complementary health care providers in cancer care. BMC Complement Altern Med. 2018;18(1):44.
21. Dwyer JM. Is it ethical for medical practitioners to prescribe alternative and complementary treatments that may lack an evidence base? - No. Med J Aust. 2011;195(2):79.
22. Joyce P, Wardle J, Zaslawski C. Medical student attitudes towards complementary and alternative medicine (CAM) in medical education: a critical review. J Complement Integr Med. 2016;13(4):333–45.
23. Adolescent health [https://www.who.int/health-topics/adolescent-health#tab=tab_1] Accessed 28 Feb 2023
24. Quinn Patton M. Qualitative research & evaluation methods. In: Integrating theory and practice. California: SAGE publications, Inc; 2015.
25. Kvale S, Brinkmann S, Anderssen TM, Rygge JF. Det kvalitative forskningsintervju. English: The qualitative research interview. Oslo: Gyldendal akademiske forlag; 2009.
26. Fønnebø V, Grimsgaard S, Walach H, Ritenbaugh C, Norheim AJ, MacPherson H, Lewith G, Launsø L, Koithan M, Falkenberg T, et al. Researching complementary and alternative treatments - the gatekeepers are not at home. BMC Med Res Methodol. 2007;7(7):1–6.
27. Malterud K. Qualitative research: standards, challenges, and guidelines. Lancet. 2001;11(358 9280):483–8.
28. Magnussen J, Vrangbaek K, Saltman R. EBOOK: Nordic Health Care Systems: Recent Reforms and Current Policy Challenges: McGraw-Hill Education (UK). 2009.
29. Marchildon GP, Allin S, Merkur S. Canada: Health system review. Health Syst Transit. 2020;22(3):1–194.
30. OECD/European Observatory on Health Systems and Policies. Germany: Country Health Profile 2019. Paris: State of Health in the EU, OECD Publishing; 2019. https://doi.org/10.1787/36e21650-en.
31. OECD/European Observatory on Health Systems and Policies. Netherlands: Country Health Profile 2019. Paris/Brussels: State of Health in the EU, OECD Publishing/European Observatory on Health Systems and Policies; 2019. https://doi.org/10.1787/9ac45ee0-en.
32. World Health Organization. Regional Office for E, European Observatory on Health S, Policies, Rice T, Rosenau P, Unruh LY, Barnes AJ, Saltman RB, van Ginneken E. United States of America: health system review. Copenhagen: World Health Organization. Regional Office for Europe; 2013.
33. Patton MQ. Qualitative research & evaluation methods: Integrating theory and practice. California: Sage publications; 2014.
34. Stub T, Kristoffersen AE, Overvåg G, Jong MC. An integrative review on the information and communication needs of parents of children with cancer regarding the use of complementary and alternative medicine. BMC Complement Med Ther. 2020;20(1):90.
35. Stub T, Quandt SA, Kristoffersen AE, Jong MC, Arcury TA. Communication and information needs about complementary and alternative medicine: a qualitative study of parents of children with cancer. BMC Complement Med Ther. 2021;21(1):85.
36. Stub T, Kiil MA, Lie B, Kristoffersen AE, Weiss T, Hervik JB, Musial F. Combining psychotherapy with craniosacral therapy for severe traumatized patients: A qualitative study from an outpatient clinic in Norway. Complement Ther Med. 2020;49:102320.
37. Quandt SA, Sandberg JC, Graham A, Mora DC, Stub T, Arcury TA. Mexican Sobadores in North Carolina: Manual Therapy in a New Settlement Context. J Immigr Minor Health. 2017;19(5):1186–95.
38. Mora DC, Arcury TA, Quandt SA. Good job, bad job: Occupational perceptions among Latino poultry workers. Am J Ind Med. 2016;59(10):877–86.
39. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15:1277–88.
40. Richards L. Handling Qualitative Data: A Practical Guide. London: Sage Publications; 2005. (ISBN 0-7619-4259-9).
41. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349–57.
42. LOV-2003-06-27-64 Lov om alternativ behandling av sykdom mv. Act No. 64 2003 [Act relating to the alternative treatment of disease, illness, etc,] Helse og omsorgsdepartementet (Ministry of Health and Care Services). 2003. https://app.uio.no/ub/ujur/oversatte-lover/data/lov-20030627-064-eng.pdf. Accessed 15 July 2022.
43. Ergil KV, Micozzi MS. 5 - Qi in China's traditional medicine: the example of tuina. In: Mayor D, Micozzi MS, editors. Energy Medicine East and West. Edinburgh: Churchill Livingstone; 2011. p. 65–71.
44. Integrative Therapies [https://www.pediatrics.columbia.edu/about-us/divisions/hematology-oncology-and-stem-cell-transplantation/center-comprehensive-wellness/patient-care/integrative-therapies] Accessed 15 July
45. Department of Pediatric Oncology and Pediatric Hematology [https://www.gemeinschaftskrankenhaus.de/medizin-therapie-pflege/fachabteilungen/kinder-/jugendmedizin/kinderonkologie/uebersicht/] Accessed 15 July 2022
46. Rutert B, Stritter W, Eggert A, Auge U, Laengler A, Seifert G, Holmberg C. Development of an Integrative Care Program in a Pediatric Oncology Unit. Complement Med Res. 2021;28(2):131–8.
47. Längler A, Zuzak TJ. Complementary and alternative medicine in paediatrics in daily practice—A European perspective. Complement Ther Med. 2013;21:S26–33.
48. Jacobsen R, Fønnebø VM, Foss N, Kristoffersen AE. Use of complementary and alternative medicine within Norwegian hospitals. BMC Complement Altern Med. 2015;15(1):275.
49. Barnekreft (Childhood cancer) [https://unn.no/behandlinger/barnekreft#vardesenteret] Accessed 15 July 2022
50. Children's Department for Cancer and Blood Diseases [https://oslo-universitetssykehus.no/behandlinger/barnekreft?sted=barneavdeling-for-kreft-og-blodsykdommer#barne--og-ungdomsaktiviteter] Accessed 15 July 2022
51. Will invest in music therapy [https://stolav.no/korus/vil-satse-pa-musikkterapi] Accessed 15 July 2022
52. Children and young people in the hospital [https://helse-bergen.no/avdelinger/barne-og-ungdomsklinikken/barn-og-unge-pa-sjukehus#aktivitetar-for-barn-og-unge] Accessed 15 July 2022
53. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT. Prevalence of Complementary Medicine Use in Pediatric Cancer: A Systematic Review. Pediatrics. 2010;125(4):768–76.
54. Alnafia A, Binyousef FH, Algwaiz A, Almazyed A, Alduaylij T, Alolaiwi O, Alajlan A, Alsuhaibani M, Alenazi KA. Attitudes Towards Complementary and Alternative Medicine Among Pediatricians in Saudi Arabia. Cureus. 2021;13(12):e20486.
55. Langler A, Boeker R, Kameda G, Seifert G, Edelhauser F, Ostermann T. Attitudes and beliefs of paediatric oncologists regarding complementary and alternative therapies. Complement Ther Med. 2013;21(SUPPL.1):S10–9.
56. Roth M, Lin J, Kim M, Moody K. Pediatric Oncologists' Views Toward the Use of Complementary and Alternative Medicine in Children With Cancer. J Pediatr Hematol Oncol. 2009;31(3):177–82.
57. Varejao CDS, Santo F. Laser Acupuncture for Relieving Nausea and Vomiting in Pediatric Patients Undergoing Chemotherapy: A Single-Blind Randomized Clinical Trial. J Pediatr Oncol Nurs. 2019;36(1):44–54.
58. Jones E, Isom S, Kemper KJ, McLean TW. Acupressure for chemotherapy-associated nausea and vomiting in children. J Soc Integr Oncol. 2008;6(4):141–5.
59. Ghezelbash S, Khosravi M. Acupressure for nausea-vomiting and fatigue management in acute lymphoblastic leukemia children. J Nurs Midwifery Sci. 2017;4(3):75–81.
60. Evans A, Garretson C, Pedroja E, Malvar J, Margol A, Sposto R, Nelson MB. The use of aromatherapy to reduce chemotherapy-induced nausea in children with cancer; A randomized, double blind, placebo controlled trial. Neuro Oncol. 2016;18(Supplement 33):iii137.
61. Wong J, Ghiasuddin A, Kimata C, Patelesio B, Siu A. The Impact of Healing Touch on Pediatric Oncology Patients. Integr Cancer Ther. 2013;12(1):25–30.
62. Facchini M, Ruini C. The role of music therapy in the treatment of children with cancer: A systematic review of literature. Complement Ther Clin Pract. 2021;42:101289.

63. Ibrahim HA, Amal AA. The Effectiveness of Play Therapy in Hospitalized Children with Cancer: Systematic Review. J Nurs Pract. 2020;3(2):233–43.
64. Purrezaian M, Purrezaian H. Group psychodrama for children with leukemia: A brief report. J Psychosoc Oncol. 2022;40(1):131–5.
65. Mora DC, Kristoffersen AE, Overvåg G, Jong MC, Mentink M, Liu J, Stub T. Safety of Complementary and Alternative Medicine (CAM) treatment among children and young adults who suffer from adverse effects of conventional cancer treatment: A systematic review. Integr Cancer Ther. 2022;21:15347354221105564.
66. Molassiotis A, Fernadez-Ortega P, Pud D, Ozden G, Scott JA, Panteli V, Margulies A, Browall M, Magri M, Selvekerova S. Use of complementary and alternative medicine in cancer patients: a European survey. Ann Oncol. 2005;16(4):655–63.
67. King N, Balneaves LG, Levin GT, Nguyen T, Nation JG, Card C, Truant T, Carlson LE. Surveys of cancer patients and cancer health care providers regarding complementary therapy use, communication, and information needs. Integr Cancer Ther. 2015;14(6):515–24.
68. Truant T, Bottorff JL. Decision making related to complementary therapies: a process of regaining control. Patient Educ Couns. 1999;38(2):131–42.
69. Masten AS. Ordinary magic: Resilience processes in development. Am Psychol. 2001;56(3):227–38.
70. Delgado-Rodríguez M. Llorca J: Bias. J Epidemiol Community Health. 2004;58(8):635.
71. Malterud K. Kvalitative metoder i medisinsk forskning: en innføring: Universitetsforlaget. 2011.
72. Pritchard-Jones K, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G, Naafs-Wilstra MC, Steliarova-Foucher E. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. Lancet Oncol. 2013;14(3):e95–103.

Publisher's Note

Paper V

A qualitative study among healthcare providers on risks associated with the use of supportive care for cancer treatment-related symptoms in children and adolescents

A qualitative study among healthcare providers on risks associated with the use of supportive care for cancer treatment-related symptoms in children and adolescents.

Abstract

Introduction

Although more than 300,000 children and adolescents worldwide are diagnosed with cancer yearly, little research has been conducted investigating how healthcare providers consider risk and patient safety connected with supportive care (including complementary and alternative medicine (CAM)) in this age group. This study aimed to explore how different healthcare providers perceive and evaluate risk when patients combine supportive care and conventional medicine in clinical practice and how they communicate and inform parents about the use of these modalities.

Materials and Methods

In-depth semi-structured interviews were conducted with 22 healthcare providers with expertise in treating pediatric oncology patients from five countries. Systematic content analysis was conducted using Nvivo 1.61.

Results

The analysis resulted in three themes and eight subthemes. Generally, participants were cautious about implementing unproven new modalities or therapies when recommending supporting care modalities to parents of children and adolescents with cancer. The most important criterion when recommending a modality was evidence for safety based on a risk/benefit evaluation. Negative interactions with conventional medicine were avoided by using the half-life of a drug approach (the time it takes for the amount of a drug's active substance in the body to reduce by half). For patients with severe symptoms, less invasive modalities were used (ear seeds instead of ear needling). To enhance safety, participants practiced open and egalitarian communication with parents.

Conclusion

Healthcare providers reported using a variety of approaches to achieve a safe practice when parents wanted to combine supportive care and conventional cancer treatment. They emphasized that these modalities should be foremost safe and not become an extra burden for the patients. Providers highlighted patient-centered care to meet the individual's specific

health needs and desired health outcomes. A lack of national and regional standardized training programs for supportive care in pediatric oncology was considered a hazard to patient safety.
Keywords: CAM, communication, healthcare providers, integrative medicine, pediatric oncology, qualitative, supportive care modalities, safety.

Introduction

The Supportive Care Framework for Cancer Care was originally formulated by Fitch in 1994 [1]. The framework was created as a tool for oncology experts and program managers to conceptualize what type of support cancer patients might require and how planning for service delivery might be approached. The framework draws upon the constructs of human needs, cognitive appraisal, coping, and adaptation as a basis for conceptualizing how humans experience and deal with cancer [1]. The concepts within the framework have been validated through in-depth interviews with patients and survivors about their experiences with cancer, its treatment, and living with the aftermath of that treatment [2,3]. Complementary and Alternative Medicine (CAM) is another tool within supportive care that aims to improve the well-being of pediatric oncology patients, and
parents seek different CAM for their children as a tool to lessen the burden of cancer diagnosis and treatment [4].

Cancer is the leading cause of death worldwide in children (0-9 years) and adolescents (10-19 years) [5,6]. The overall incidence of childhood cancer among children and adolescents in Norway is 17 per 100,000 [7]. Similar rates have been reported in Europe [8].

The National Institutes of Health's National Center for Complementary and Integrative Health understand complementary therapies as being nonmainstream practices applied alongside conventional medicine. In contrast, integrative medicine merges evidence-based conventional and complementary modalities in a coordinated way. The philosophical basis for many of these modalities is holistic, focusing on treating the whole person rather than a single disease or organ system [9]. Alternative modalities refer to modalities that are used instead of conventional medicine [9]. This practice is not supported by evidence and occurs less frequently among patients with cancer [10]. The prevalence of the use of CAM in childhood cancer is 47% in Western countries [11]. Parents often consider CAM modalities, such as faith healing, herbs, diet and nutrition, homeopathy and prayer, to reduce cancer treatment-related symptoms in their children [4,12,13].
Generally, CAM is considered to be natural and, therefore, safe. However, many modalities are not independently tested by governmental agencies before being offered to the public [14,15]. In addition, some natural products may negatively interact with cancer treatment,

resulting in adverse effects and potentially negative outcomes [16]. It is, therefore, important to investigate the possible risks of these modalities when they are used alongside conventional medicine.

Medical science risks can be divided into direct and indirect risks [17,18]. A direct risk is due to the treatment itself. This dimension includes traditional adverse effects of an intervention, such as bleeding in response to acupuncture needling, nausea caused by chemotherapeutic medication, or an adverse effect of an herb [19]. Indirect risk is related to adverse effects of the treatment context, for example, the CAM provider rather than the medicine. A patient can be harmed by a care context, possibly preventing the patient from receiving the best possible treatment relevant to her or his health needs [20]. Patients often believe that the products they use are harmless or are unaware that the modality they use is considered CAM [21]. Conventional healthcare providers do not routinely initiate open and informed discussions about the possible outcomes of combining supportive care modalities, including CAM, and conventional cancer treatment. Studies indicate that the main reason for not initiating such conversations in clinical settings is a lack of knowledge, which can create a feeling of professional discomfort [22,23]. Discussing the use of evidence-based CAM modalities that complement conventional cancer treatment has been shown to promote its use [24]. Primary reasons patients gave for not informing health care providers of CAM use include health care providers not asking about CAM a feeling that health care providers were indifferent or opposed to the use of CAM and that the use of CAM was irrelevant to their conventional cancer treatment [25-27].

An integrative review of the information and communication needs of parents of children with cancer demonstrated that parents wanted high-quality and more reliable information about CAM from authoritative sources, primarily from conventional healthcare providers at the hospital where their child was being treated [25]. A survey of 49 parents of pediatric cancer patients found that receiving information about CAM gave parents a sense of control and provided additional supportive treatment options [28]. Giving parents a feeling that they were doing everything possible to support their child's recovery. Loss of hope created despondency or desperation, and parents needed to maintain a sense of hope and control to counteract the possibility of their child's death. The study highlighted the need for family autonomy when making CAM treatment decisions for their children.

Generally, the risk connected with the use of CAM in supportive cancer care is under-researched [29]. With this in mind, our research team initially investigated how adverse effects were reported in the scientific literature [30,31]. The main finding from these systematic reviews were that most of the studies included failed to report whether CAM modalities have any adverse effects. Hence it is important to investigate through research how healthcare providers handle possible adverse effects in clinical practice.

Aim

This study was conducted as part of the research team's efforts to develop an evidence-based decision aid for parents of children with cancer. As part of this work, we conducted this study with a twofold overall aim: I) to explore the perceptions healthcare providers have of risk and how they evaluate patient safety when patients combine CAM and other supportive care modalities with conventional medicine in clinical practice, and II) how they communicate and inform parents about the use of these modalities in childhood and adolescent cancer care.

Materials and Methods

Design

This study draws on qualitative data obtained through individual semi-structured interviews among pediatric oncology experts and CAM providers in Norway and internationally. The data obtained from the interviews were used for two studies. In one study we investigated the perception of supportive care use among different pediatric healthcare providers and in this present study, we investigate their perception of safety in clinical practice [32].

Qualitative methods may contribute to a better understanding and improved level of knowledge regarding important health and well-being issues [33]. There is a limited amount of previous knowledge regarding the combination of CAM and other supportive care modalities with conventional medicine in pediatric cancer care. It is important to understand the philosophical and medical context of these modalities [15]. Therefore, a qualitative design is suitable for generating such information [34]. In this study, each participant received an identification number (ID) to ensure anonymity.

Interview guide and individual semi-structured interviews

The developed interview guide was employed for two qualitative studies (see above). The interview guide was based on an integrative review of the literature and the research team's knowledge of the literature [25]. The interviews were semi-structured and included open-ended questions, allowing follow-up questions, and enabling the participants to give nuanced answers [33]. The interview guide was not pilot tested and is included as supplementary material.

Study area and setting

This study was initiated and designed in Norway; participants were healthcare providers from five countries: Canada, Germany, the Netherlands, Norway, and the United States. According to the Nordic health model all inhabitants in Norway have access to universal health care [35]. Similar universal healthcare systems are found in Canada, Germany and the Netherlands [36,37]. The United States has multiple healthcare systems that operate separately [38]. CAM modalities, without regard to country, are mostly offered outside conventional healthcare systems, and patients themselves generally cover the costs of these modalities.

Inclusion criteria

In this study, healthcare providers were included if they: (1) had clinical experience working with CAM and/or other supportive care modalities among children and/or adolescents with cancer and (2) were trained as pediatric oncology experts (such as doctors and nurses), conventional healthcare providers (such as a physiotherapist, play-therapist, and nutritionists), or CAM providers (practicing inside or outside the conventional healthcare system at least one or more CAM modalities).

Participants and recruitment

Purposive and snowball sampling methods were used in this study [39]. International healthcare providers were recruited through the researcher team's professional networks. Twenty-two healthcare providers were recruited from five different countries (Canada (n=1), Germany (n=1), the Netherlands (n=3), Norway (n=10), and the United States (n=7)). Five of the Norwegian participants were recruited through snowball sampling at the University Hospital of North Norway (UNN). In addition, requests were sent to CAM provider associations in Norway to identify providers with treatment experience in pediatric

oncology. Five CAM providers were recruited through the Healer Association (n=2), the Norwegian Homeopathy Association (n=1), the Acupuncture Association (n=1), and the Norwegian Association of Psychotherapy (n=1).

Data collection

A total of 22 interviews were completed in the study. Twelve (n=12) interviews were conducted on a web platform (Teams), enabling the participant and interviewer to see each other. Other interviews were conducted face-to-face at different workplaces (n=9), while one interview was conducted in a private home (n=1). The participants had no prior knowledge of the interviewer. Only the participant and the interviewer were present during the interviews. Most interviews lasted from 30 to 60 minutes. Field notes were taken by the researchers during the interviews. The last author (TS) performed the Norwegian interviews (n=10) in Norwegian. The first author (DCM) performed the international interviews (n=12) in English. No interviews were repeated. The last author holds a Ph.D. in medical science; she worked as a research professor when this study was carried out and is formally trained as an acupuncturist and homeopath. The first author holds a master's in public health; she worked as a research fellow when interviews were carried out. Participants did not provide feedback on the findings of this study.

Data analysis

The Norwegian interviews were transcribed verbatim by a professional service. The last author (TS) translated the interviews into English. The first author (DCM) transcribed the international interviews verbatim into English. The first and last authors read them several times and created codes based on information received from each participant. Disagreements were discussed between these two authors until a consensus was reached. Analysis of the material was conducted according to conventional qualitative content analysis allowing the themes and codes to emerge from the data, thus inductive coding was conducted [40]. The data was entered and coded into Nvivo 1.61 [41]. The success of content analysis depends on the coding process.

Ethics approval and consent to participate

This study is considered health service research and was registered at the Norwegian Centre for Research Data (NSD). The study was approved by NSD on 25 August 2021 (register no.

978969). Participants were informed both orally and in writing that participation in the study was voluntary. In addition, it was clear that participants could decline participation without explanation and withdraw at any time without stating a reason. Participants were further informed about the purpose and aim of the study and that data would be handled and later published and presented confidentially. Before conducting and recording the interviews, written and verbal informed consent was obtained from the participants. None of the recruited participants dropped out. The study was conducted in line with the Helsinki and reported according to the Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist Declaration [42,43]. (See supplementary material)

Results

In this study, the themes were organized into three main themes (Deliberation and reflections about risk evaluation; cause no harm; cultivating patient-provider communication), and eight subthemes (table 1).

Table 1. Overview of the main themes and subthemes

Themes	Subthemes
Deliberation and reflections on risk evaluation	Safety assessment Efficacy assessment
Causing no harm	Minimizing adverse effects Minimizing Interactions Lack of standardized training
Cultivating patient-provider communication	Building trust Patient centeredness Information needs

The participants

Twenty-two interviews were conducted among oncology experts (n=6), conventional healthcare (n=4), and CAM providers (n=12). Of these, six (n=6) were trained in both conventional medicine and CAM. Participant ages ranged from 25 to 68 years (mean= 45 years). Over two-thirds of the participants were females. They were trained in 12 different supportive and CAM modalities. The majority (n=17) had more than ten years of experience in clinical practice.

Table 2. Demographic data of the participants

Healthcare providers	**Total (n=22) n (%)**
Age (mean)	45.5
18 – 40 years of age	6 (27)
41 - 60 years of age	10 (45)
61 years and older	6 (27)
Gender	
Female	18 (82)
Male	4 (18)
Years in practice	
0-10 years	5 (23)
11-20 years	8 (36)
21-30 years	4 (18)
More than 31 years	5 (23)
Training*	
Oncology experts and conventional health providers	
Nurse*	5 (23)
Nutritionist	2 (9)
Pediatric oncologist*	6 (27)
Physiotherapist*	1 (5)
Play therapist	1 (5)
CAM Providers	
Acupuncturist*	5(18)
Anthroposophic medicine provider*	1 (5)
Healer	3 (14)
Homeopath	1 (5)
Massage therapist	1 (5)
Music therapist	1 (5)
Psychodrama therapist*	1 (5)

*These providers were trained as both conventional and CAM providers.

Theme I: Deliberation and reflections on risk evaluation

This theme addresses how the participants deliberate about overall safety and consequences for clinical practice. The section also explores how they reflect on decision-making in their daily work.

Safety assessment

Safety precedence has been set by hospitals in the US offering integrative medicine.

Treatments offered include energy therapies, such as touch therapies and reiki, massage, and

in some instances, acupuncture - modalities that are considered safe when provided by professionals. Participant 4 emphasized that when deciding which treatments should be offered by integrative clinics, the most important factor was a proven safety record. This was confirmed by participant 7, who stated: "First and foremost, we want to make sure it [the modality] is safe before even worrying about efficacy". The principle was confirmed by participant 22, whose philosophy was to try out modalities with evidence for safety, even though evidence for efficacy was uncertain or lacking.

Sometimes participants had difficulties accessing information about specific modalities and when that happened the modalities were routinely assessed according to a risk/benefit evaluation. This evaluation was based on information from updated research before implementation. As explained by participants 1 and 22. A pediatric oncologist stated: "[if an] integrative therapist doesn't have information about a specific therapy, there is something called a 2 x 2 table of safety and efficacy". If a modality was considered safe and effective (according to research literature), the modality was recommended for use. Modalities were also recommended but carefully monitored if they were considered safe even though efficacy was unknown. In situations where a modality was effective but evidence on safety was inconclusive, the modality was recommended but closely monitored for safety. Lastly, if a modality was considered not effective and connected with serious risk, it was avoided.

Efficacy assessment

Participants found the lack of evidence for efficacy for many CAM modalities problematic. They reflected on the consequences of their clinical practice and as a result they were conservative in terms of treatment recommendations, especially for children. This is illustrated by participant 4:

"Well, a few things, number one we know that complementary therapies … there is evidence supporting the use in patients in outpatient settings but there is very little [scientific, author comment] data".

A solution to this dilemma (lack of evidence) was to suggest a substitute evidence-based modality when parents wanted to discuss a modality with a lack of evidence for an effect.

Most of the time, participants followed already established guidelines or outcomes from research published by the National Institute of Health. In addition, well-known

websites/databases, such as the one from the Memorial Sloan Kettering Cancer Center were used to gather safety and efficacy information about herbs and supplements that were unfamiliar to the participants. Although there is a lack of efficacy, providers agreed with its use if the modality is safe because it contributed to the well-being of patients and their families. Participant 7 believed that "the most therapeutic part of CAM is that it gives the parent or family a sense of contribution to the process". This sense of control was regarded as extremely therapeutic, an important element in a situation when a serious illness introduces a feeling of chaos to family life.

Theme II: Causing no harm

The participants emphasized the importance of preventing causing harm to patients by minimizing adverse effects and interactions of treatments. They also perceived insufficient standardized training for CAM providers as risky for patients.

Minimizing adverse effects

To minimize the risk of adverse effects the participants stated that treatment indication depended on the health status of the child. Participants 2 and 22 said that: "acupuncture with needles is not carried out if the patient's absolute neutrophil count (ANC) is less than 500 cells/μL or platelets are less than 20 [20,000/μL]. These levels are set to avoid infections in the child caused by acupuncture". Participant 2 also referred to a study conducted by their institution. She explained: "in patients with thrombocytopenia, no adverse events (including bleeding, bruising, or infections) were observed when clean needle technique protocols were employed by licensed acupuncturists who followed the safety guidelines from the National Institute of Health".

To avoid harming children, participants assessed the health status of the child and looked at the available evidence-based data. Providers used for example ear seeds or bands instead of needles when the immune system was compromised (participant 22). Participant 23, a massage therapist, found that "patients tend to be very tired after massage". She found reactions to massage difficult to predict and she often started with short treatments (only 10 minutes) to gauge how the body reacted.

According to participant 7, parents often asked about Reishi mushroom and there is a substantial body of research supporting its positive effects. Reishi (Ganoderma lucidum) is a

Chinese mushroom that has demonstrated anti-inflammatory, anticancer, and anti-metastatic activities in laboratory studies. However much of the research is either based on animal models or research in adults. She (participant 7) found it challenging to discuss the uncertainty of knowing whether the mushroom would produce the same results in a nine-year-old child as it did in 400 mice (animal studies). However, she said: “What these trials have the potential to show us, is possible adverse effects which is how we can deem safety”.

To ensure documentation on safety, participant 2, a trained acupuncturist, used the hospital's electronic medical record system to document treatment indication, frequency, and technique and to record adverse effects. The system provided access to laboratory results, including platelet and ANC count. “This documentation is in accordance with STRICTA” [standard guidelines for reporting interventions in clinical acupuncture trials, author comment] she explained.

Minimizing Interactions

Participant 1 used the half-life of a drug method to calculate when appropriate treatment interventions could be applied in cases where parents wanted to use an herb or supplement that might negatively interact with conventional treatment. The half-life of a drug is the time it takes for the drug's plasma concentration to be reduced to half its original value. Participant 1 explained: “a conventional drug with a 12-hour half-life (5x12) would no longer be present in the body after 60 hours, and at this point, the child could start taking the supplement”. This method allowed the participant to advise on when to start and stop taking the herb or supplement without affecting conventional drugs. Participants also advised parents about the advantages of using food as medicine and taking low-dose supplements. Participant 1 explained: “You can drink ginger tea, which is not going to interact with your chemo, but if you start taking 6 ginger capsules several times a day, that is not going to work with the chemo that the child is taking”.

Moreover, participant 5 explained that she will not recommend biologics (herbs) to patients who have a very good cure rate, because “I might be more nervous about offering them anything that could interfere with chemotherapy”.

Lack of standardized training

The major concern among the participants was the difficulty in assessing the qualifications of supportive care and CAM providers who worked outside hospitals. Different participants (2, 5, and 22) said that providers working at their respective institutions were certified professionals. “They followed evidence-based practices recommended by official entities such as the National Institutes of Health in the United States” said participant 2. However, finding a reliable CAM provider with established qualifications was difficult in most of the countries where participants were interviewed. It was especially hard in countries such as the United States and Canada, where certification requirements vary by state or province, and standardized training for CAM providers was lacking. Whether or not CAM providers had expertise in treating pediatric oncology patients was often unclear. Participant 8, who worked as an oncologist in Europe, said that “the availability of experienced complementary therapists specialized in pediatric oncology is very, very rare”.

Similarly, participant 12, a healer, believed that CAM providers need to know what to do if a patient wants to postpone or refrain from conventional treatment. “This requires training in ethics and knowledge about medical legislation”, she said (participant, 12).

According to the participants, properly trained providers decrease the possibility of putting patients at (indirect) risk, because they are trained to handle emotions and provide professional support for the child and the family to avoid medical trauma. Participant 7 believed that the most important is to have good training when working with children and cancer.

Participant 16 remembered an adolescent who became overwhelmed during a music session. Her emotions were related to her father's despair regarding her illness. When the therapist realized that the patient could not cope with the acute situation, she terminated the therapy session carefully, postponing it to a later date when the patient was less vulnerable. Thus, she was trained to handle severe emotional traumas derived from treatment.

Participant 14, previously educated as a preschool teacher, worked as a hospital play therapist, where her objective was to try to maintain a sense of normality for hospitalized children. She was trained to learn children how to cope with difficult situations. She explained that:” hospitalized children are exposed to a lot of painful procedures. Their lives

are turned upside down, routines are changed, many of them feel a loss of control, and they often become indecisive". The department encourages role-play such as doctors and nurses. Through play, the participant observed children processing what was happening to them. She describes:

"Once I had a boy who went in and out of roles. He quoted literally everything the doctor had told him ten minutes before. The next instant, he took off his doctor's coat and started playing with the toy train" (participant 14).

Participant 17 believed that many children with cancer try to protect their parents emotionally by pretending to be happy and smiling, even though they are crying inside. She observed parents suppressed emotions manifesting in children during psychodrama treatment. She remembered a girl who wanted to build houses, where each step of the process stimulated suppressed feelings of fear and sorrow. In this process, "it was important not to move forward too fast. It was all about the child being safe". She guided the child carefully through this process based on professional training and many years of working experience.

Healthcare providers with limited training in treating children with cancer and working outside hospitals, may therefore impose a risk on these patients.

Theme III: Cultivating patient-provider communication

In the context of pediatric cancer care, communication is the key to establishing treatment goals and realistic expectations related to health care. It is, therefore, important for parents to state their needs and concerns in consultations with their medical team. This section discusses the perceptions healthcare providers have about communication through building trust, patient-centeredness, and information needs.

Building trust

Healthcare providers expressed that what parents felt comfortable sharing and what they asked about, depended on the relationship they had with the healthcare providers. Participant 20, who worked as a healer, started to build trust with parents during a telephone consultation. As an experienced therapist, she knew that this initiation of contact by the parents meant that they needed to talk, so she listened. She explained: "Sometime I ended up treating both the parents and the child".

Participants (1, 7, and 12) believed that some parents held back information about CAM use. According to the participants, the reason for nondisclosure could be that parents feared a negative response from the doctors who believed that using these modalities was a waste of money. If doctors did not include the topic of CAM modalities in conversations with patients, patients were reluctant to ask. Participant 1 believed that: "This lack of communication often leads to parents keeping quiet about treatments that had not been recommended at the hospital".

Participant 6 appreciated that their parents seemed to trust her and were willing to have conversations about their treatment needs, including what modalities were available at the hospital and what the risks and potential benefits were. At the end of the day, there were no guarantees that families intended to follow her recommendations, but at least they had received valuable information. She said: "I would never approach (a request about CAM) with judgment; they are just trying to help their kids". If the parents wanted to use CAM *instead of* conventional medicine for their children, participant 5 became very nervous. The reason for this was that most of the children she met had cancers that were usually cured by conventional medicine. To build trust, she was, however, "willing to go through the list of CAM modalities that could be used as a supplement to conventional medicine, together with the parents". Moreover, the participants believed that openness was the most important factor when talking to parents. Therefore, participants encourage the parents to give them information about their use of CAM. Based on that information they could check whether the modalities were safe to use alongside conventional treatment regimes.

Patient centeredness

The concepts of building trust and a patient-centeredness approach complement each other. The concept of patient-centeredness was brought up by participant 8 in the interviews. He said that the lack of using this approach was problematic. He thought that doctors must be educated to train the students and the trainees in parent centeredness medicine. "That means that one of the first things I must ask is What do you think? What are your options? and What are your thoughts?". Asking questions like that may contribute to more open and respectful patient-provider communication.

In line with patient-centered care, the play therapist's (participant 14) main focus was always to be present for the child at that very moment. She strived to be open and receptive to what the child needed at any specific time. Working with pediatric patients meant that the participant had to be flexible and not tied to a rigid treatment regime. “Having fun was an important element”, she said.

Information needs

Obtaining accurate and timely information about supportive care is an important factor in enhancing safety. Getting diagnosed and starting a treatment regime is a lot to cope with for the children and their parents. Receiving treatment at the hospital was described by participants 10 as: “getting on a run-away train, moving faster and faster. After about two weeks, things became calmer, allowing parents time to talk and received information about supportive care modalities”.

Appropriate distribution of information to families was brought up by participants. Participant 13 believed that “a web page would be useful to relieve parents of having to seek out treatment information on their own”. She emphasized the importance of making it clear that these modalities are not a substitute for conventional treatment and are not used in a curative capacity but as complementary therapy to conventional hospital treatments. Participant 15 from Norway said: “A web page should be published nationally, rather than being attached to a specific hospital or health region. She suggested that it could be located at Helsenorge.no” [National online health service in Norway, author comment].

The participants emphasized that the most important criterion for a modality to be included in such a web page is evidence for safety. Where information about the effect, if available, should also be included. This presents a problem because scientific information is often lacking, and for some modalities, internet information is misleading according to participant 6.

Participants suggested that for the most commonly used modalities, such as acupuncture, massage, healing, and supplements, a short description including pros and cons should be included. They emphasized the importance of presenting realistic information so as not to add any extra suffering, either to the child or the family. Participant 15 said:

“I would not recommend modalities that would harm the child or that are not in the child's best interest. If the treatment is effective and does not cause harm, I would recommend it”.

Participants suggested organizing a web page according to treatment modalities indicated for the most common symptoms associated with childhood and adolescent cancer modalities, for example, pain, obstipation, lack of appetite, and anxiety. They also pointed out the importance of including modalities that help a child cope with everyday life. Sick children still need to play, and play is an important tool that can be utilized to process emotions and painful experiences. Ways to facilitate and organize play activities were suggestions, as was practical and realistic advice about diets and nutrition. Participant 6 believed that: “Relevant advice should be tailored to different food cultures”.

Other suggestions included a list of competent CAM providers; information regarding financial support, including insurance companies or private funding; and where to find reliable information (where to go next - including a list of updated webpages).

Discussion

To the best of our knowledge, this study is the first to report how different pediatric healthcare providers reflect on and practice patient safety about supportive modalities, including CAM. The participants were conservative when recommending these modalities to parents, meaning they were cautious about implementing unproven modalities or therapies, to prevent overtreatment and harm to patients [44]. The participants were careful to communicate the benefits/harms of the modality for the individual.

The participants emphasized that the modalities should be foremost safe and not become an extra burden for the patients. Therefore, they recommended using less invasive modalities to treat the most vulnerable children. According to the participants, negative interactions with conventional medicine were avoided by using the half-life of a drug approach. Moreover, a lack of national and regional standardized training in pediatric oncology was perceived as a major t to patient safety. To meet patients’ needs and to establish a trustful relationship with parents, participants reported that they practiced open and egalitarian communication to encourage parents to delineate their use of CAM modalities. Based on this information, participants could take action to avoid negative interactions with conventional treatments.

Norwegian healthcare providers expressed similar views concerning safety in a previous study examining attitudes concerning risks among complementary and conventional healthcare professionals [45]. Seventy-four percent of the participants believed that safety was the most important criterion for recommending a CAM modality to cancer patients. Moreover, 89% of medical doctors and nurses believed that CAM modalities should be subjected to more scientific testing before being accepted by conventional healthcare providers. These findings are reflected by Maha et al. and Fønnebø et al. [15,46]. Fønnebø et al. proposed a five-phase research strategy for CAM interventions, where safety status is recommended before the assessment of efficacy. A strategy that would generate evidence relevant to clinical practice and acknowledge the important but subtle differences between CAM and conventional medical practice.

Negative interactions with conventional treatment are a direct risk in cancer care [47]. The participants reported using strategies such as the half-life of a drug approach to minimize the risk of interactions between conventional drugs and supplements. Using supplements in small doses was another strategy participants reported using with the aim to avoid interactions with conventional care treatment. According to the participants, information about these strategies was imperative for parents when planning and making decisions regarding the integration of conventional medicine and CAM, and other supportive modalities [22].

Based on a study among pediatric oncologists, Roth et al. recommended applying modalities that are considered safe in professional hands, such as music and art therapy, mindfulness, and yoga [48]. However, severe adverse effects were reported in connection with physical activities (n=1), yoga (n=1), and art therapy (n=1). A study by Goldberg et al. reported anxiety, traumatic re-experiencing, and emotional sensitivity following meditation [49]. Similar findings were reported by a participant in this study when a teenager was overwhelmed by emotions during music therapy. Professionally trained providers need skills to manage and guide patients in emotional situations and help them process emotions that arise during treatments [50]. This is especially true in pediatric oncology where children and adolescents are vulnerable, and where supportive care modalities should not add extra burden to their suffering [50].

The participants expressed difficulty assessing the qualifications of supportive care and CAM providers outside hospitals to refer patients. Currently, there are no standard training requirements for CAM providers working in cancer care and other healthcare settings in the EU [51]. Mackereth et al. surveyed CAM providers working in cancer care. The authors highlighted the need for training standardization for providers, where specific training regarding safe practice was considered essential [52]. A study from Switzerland confirmed increasing interest in integrative medicine among pediatricians, supporting the need for pre- and postgraduate pediatric training related to CAM and integrative oncology [53]. Pediatric healthcare professionals are trained to guide children through difficult treatment processes and handle emotions that arise. Healthcare providers without training may impose an indirect risk on children and their families. In Norway, there is a voluntary register for CAM providers who are members of a professional organization [54]. The register aims to increase patient safety and consumer rights for patients seeking CAM providers [55].

Cultivating provider-patient communication is the key to establishing patients' treatment goals and realistic expectations of health care. To establish fruitful relationships with patients, communication needs to be transparent and open. Patient-centeredness is a concept that facilitates a more egalitarian relationship between patients and their healthcare providers [23,56,57]. Participants suggested training doctors in this concept, to form a partnership with their patients. Facilitating equality is a prerequisite for good and effective communication [58]. Without this joint establishment of meaning, patients are at increased risk of adverse effects and harm during medical care. Accordingly, Frenkel et al. and others believe that an open and equal dialogue may decrease risks associated with malpractice, maximize positive treatment outcomes, and avoid adverse effects that may occur when combining conventional treatment and supportive care [23,57,59].

A review from 2020 concluded that there is a need for information about supportive care among parents of children with cancer [25]. According to relevant literature parents want information from authoritative sources such as oncologist experts at hospitals [12]. However, information sources most often consulted are family and friends and the media [25,60,61]. Nado et al. found that where an integrated program existed, more than half of the participants would use them [62]. In this study, providers agreed that it is important to provide practical,

realistic, and easy-to-implement information, with no extra burden on the suffering of the children.

Limitations and strengths

This study should be interpreted in light of its limitations. The study is based on data from a selected group of healthcare providers. They were recruited through the network of the research team. Therefore, the present findings are not representative of all healthcare providers working with supportive care and CAM for pediatric cancer patients. The qualitative analysis provides insight into how participants understand and interpret situations, but it cannot be used to establish associations. However, in-depth interviews facilitated abundant material. Moreover, the participants interviewed here showed striking similarities in their clinical experience, modalities, and concerns for their patients. Saturation was reached after 20 interviews as no new information was obtained. Another strength of this study is that the interviewed healthcare providers were from five different countries, distributed on two different continents. Although healthcare providers from different countries were interviewed, no substantial differences were found in the ways safety is assessed or in the way information should be communicated to parents. The lack of substantial differences might be because childhood cancer is a rare disease, and in high-income countries, treatment from front-line clinical research has been readily incorporated into care resulting in successful treatment protocols and high-survival rates [63].

Implications for practice and research

The findings of this study have significant implications for practice and research. In practice, our findings on safety can be used to develop information tools for patients and providers that will facilitate their decision-making process. This strategy will support open communication and enhance trust among patients and healthcare providers. Networks of supportive care providers can be developed and maintained at regional and national levels. Such networks can provide reliable information on supportive care which can be exchanged. This network can also develop a list of properly trained CAM providers with experience in treating children with cancer. These strategies may increase patient safety including direct and indirect risks associated with these practices. Furthermore, as demonstrated in this study more standardized training programs are needed for providers who work and are motivated to work in this field.

The results of this study, have important implications for research. The lack of safety and efficacy information may be due to a true lack of safety data, or lack of awareness of existing data. These differences may require different interventions such as data being developed, or training/data dissemination. More importantly, it highlights the need for funding sources to conduct further research.

Conclusions

The participants reported using a variety of approaches to safeguard their clinical practice. However, there is a lack of evidence for the effect, of many supportive care modalities in pediatric oncology, which is considered a direct risk. Moreover, there is a lack of CAM providers trained in pediatric oncology, an indirect risk. Both risks are considered a hazard to patient safety. Furthermore, participants agreed that it is important to have communication where trust is the main pillar of the provider-patient relationship to improve patient care but also to shield patients from using modalities that might not be safe.

Acknowledgments

We want to express our gratitude to the oncology experts and CAM providers who participated in this study.

Author contributions

This study was initiated and designed by TS. She and DCM drafted the manuscript. They collected, analyzed, and interpreted the data. JH, MJ, and AK contributed substantially to either data collection and/or data interpretation, and all in writing of the manuscript. All authors approved the final version to be published.

Declaration of conflict of interest

The authors declare that there is no conflict of interest.

Funding

This study was funded by Barnekreftforeningen (The Children's Cancer Society) in Troms og Finnmark county, Norway; Ekhagastiftelsen (2020-76), Stockholm, Sweden. The publication charges for this article have been funded by a grant from the publication fund at UiT, The Arctic University of Norway, Norway.

Availability of data materials

The raw dataset is not available publicly due to Norwegian privacy regulations. Applicants for any data must be prepared to conform to Norwegian privacy regulations. Researchers, who want to request the data, can contact the first author.

References

1. Fitch MI. Supportive care framework. *Can Oncol Nurs J*. Winter 2008;18(1):6-24. doi:10.5737/1181912x181614

2. Boon H, Stewart M, Kennard M, et al. Use of complementary/alternative medicine by breast cancer survivors in Ontario: prevalence and perceptions. *J Clin Oncol*. 2000;18(13):2515 - 2521.

3. Fitch MI, Gray RE, Greenberg M, Carroll J, Chart P, Orr V. Self-help groups: oncology nurses' perspectives. *Can Oncol Nurs J*. Spring 2001;11(2):76-81. doi:10.5737/1181912x1127681

4. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT. Prevalence of Complementary Medicine Use in Pediatric Cancer: A Systematic Review. *Pediatrics*. 2010;125(4):768-776. doi:10.1542/peds.2009-1775

5. Bhakta N, Force LM, Allemani C, et al. Childhood cancer burden: a review of global estimates. *Lancet Oncol*. 2019;20(1):e42-e53.

6. World Health Organization (WHO). Adolescent Health. World Health Organization. 28 Feb., 2023. Accessed 28 Feb, 2023.

7. Dahlen AH, Due-Tønnessen BJ, Ruud E, Bjørnland K, Lund B. *National Quality Register for Childhood Cancer, Annual Report 2020*. 2021. https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2021/arsrapport-nasjonalt-kvalitetsregister-for-barnekreft-2020.pdf

8. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *Lancet Oncol*. 2014/01/01/ 2014;15(1):23-34. doi:https://doi.org/10.1016/S1470-2045(13)70546-1

9. National Center for Complementary and Integrative Health. Complementary, alternative, or integrative health: What's in a name? 04. January, 2019. Accessed 04. January, 2019. https://nccih.nih.gov/health/integrative-health#hed1

10. Quandt S, Verhoef M, Arcury T, et al. Development of an international questionnaire to measure use of complementary and alternative medicine (I-CAM-Q). *J Altern Complement Med*. 2009;15(4):331 - 9.

11. Diorio C, Lam CG, Ladas EJ, et al. Global use of traditional and complementary medicine in childhood cancer: A systematic review. *J Glob Oncol*. 2017;3(6):791-800. doi:10.1200/jgo.2016.005587

12. Singendonk M, Kaspers GJ, Naafs-Wilstra M, Meeteren AS-van, Loeffen J, Vlieger A. High prevalence of complementary and alternative medicine use in the Dutch pediatric oncology population: a multicenter survey. *Eur J Pediatr*. 2013/01/01 2013;172(1):31-37. doi:10.1007/s00431-012-1821-6

13. Magi T, Kuehni CE, L. T, Wengenroth L, Lüer S, Frei-Erb M. Use of complementary and alternative medicine in children with cancer: A study at a Swiss university hospital. *PLoS One*. 2015;10(12)doi:10.1371/journal.pone.0145787

14. MacLennan A, Myers S, Taylor A. The continuing use of complementary and alternative medicine in South Australia: costs and beliefs in 2004. *Med J Aust*. 2006;184(1):27 - 31.

15. Fønnebø V, Grimsgaard S, Walach H, et al. Researching complementary and alternative treatments - the gatekeepers are not at home. *BMC Med Res Methodol*. 2007;7(7):1-6. doi:10.1186/1471-2288-7-7

16. Ambrosone CB, Zirpoli GR, Hutson AD, et al. Dietary Supplement Use During Chemotherapy and Survival Outcomes of Patients With Breast Cancer Enrolled in a Cooperative Group Clinical Trial (SWOG S0221). *J Clin Oncol*. Mar 10 2020;38(8):804-814. doi:10.1200/jco.19.01203

17. Fisher P, Dantas F, Rampes H. The safety of homeopathic products *J R Soc Med*. 2002;95(9):474-476.

18. Ernst E. Towards a scientific understanding of the placebo effects. In: Peters D, ed. *Understanding the Placebo Effect in Complementary Medicine*. Churchill Livingstone; 2001:17-29.

19. Stub T, Musial F, Quandt SA, et al. Mapping the risk perception and communication gap between different professions of healthcare providers in cancer care: a cross-sectional protocol. *BMJ Open*. Sep 3 2015;5(9):e008236. doi:10.1136/bmjopen-2015-008236

20. Wardle JL, Adams J. Indirect risks of complementary and alternative medicine. In: Adams J, Andrews GJ, Broom A, Magin P, eds. *Traditional, complementary and integrative medicine*. Palgrave Macmillian; 2012:212-219.

21. The Nuremberg Code, Research ethics guideline 2005. Last accessed August 8, 2009, [http://www.hhs.gov/ohrp/references/nurcode.htm].

22. Stub T, Quandt SA, Arcury TA, et al. Perception of risk and communication among conventional and complementary health care providers involving cancer patients' use of complementary therapies: a literature review. journal article. *BMC Complement Altern Med*. 2016;16(1):1-14. doi:10.1186/s12906-016-1326-3

23. Broom A, Adams J. Oncology clinician's accounts of discussing complementary and alternative medicine with their patients. *Health: An Interdisciplinary Journal for the Social Study of Health, Illness and Medicine*. 2009;13:317-336.

24. Salamonsen A. Doctor-patient communication and cancer patient's choice of alternative therapies as supplement or alternative to conventional care. *Scand J Caring Sci*. 2013;27(1):70-76.

25. Stub T, Kristoffersen AE, Overvåg G, Jong MC. An integrative review on the information and communication needs of parents of children with cancer regarding the use of

complementary and alternative medicine. *BMC Complement Med Ther*. 2020/03/17 2020;20(1):90. doi:10.1186/s12906-020-02882-y

26. Davis EL, ByeongsangOH, Butow PH, Mullan BA, Clarke S. Cancer Patient Disclosure and Patient-Doctor Communication of Complementary and Alternative Medicine Use: A Systematic Review. *Oncologist*. November 1, 2012 2012;17(11):1475-1481. doi:10.1634/theoncologist.2012-0223

27. Tasaki K, Maskarinec G, Shumay DM, Tatsumura Y, Kakai H. Communication between physicians and cancer patients about complementary and alternative medicine: exploring patients' perspectives. *Psychooncology*. May-Jun 2002;11(3):212-20. doi:10.1002/pon.552

28. Molassiotis A, Cubbin D. 'Thinking outside the box': complementary and alternative therapies use in paediatric oncology patients. *Eur J Oncol Nurs*. 2004;8(1):50-60.

29. Turner LA, Singh K, Garritty C, et al. An evaluation of the completeness of safety reporting in reports of complementary and alternative medicine trials. *BMC Complement Altern Med*. Aug 22 2011;11:67. doi:10.1186/1472-6882-11-67

30. Mora DC, Kristoffersen AE, Overvåg G, et al. Complementary and alternative medicine (CAM) modalities used to treat adverse effects of anti-cancer treatment among children: A systematic review and meta-analysis of randomized control trials. *BMC Complement Med Ther* 2022;22(97)

31. Mora DC, Overvåg G, Jong MC, et al. Safety of Complementary and Alternative Medicine (CAM) modalities among children with cancer who suffer from adverse effects of conventional cancer treatment: A systematic review of observational and qualitative studies. *Integr Cancer Ther*. 2022;21:1-22.

32. Mora DC, Jong MC, Quandt SA, Arcury TA, Kristoffersen AE, Stub T. Supportive care for cancer-related symptoms in pediatric oncology: a qualitative study among healthcare providers. *BMC Complement Med Ther*. Apr 3 2023;23(1):104. doi:10.1186/s12906-023-03924-x

33. Kvale S, Brinkmann S, Anderssen TM, Rygge JF. *Det kvalitative forskningsintervju. English: The qualitative research interview*. Gyldendal akademiske forlag; 2009.

34. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet*. 2001;11(358 9280):483-8.

35. Magnussen J, Vrangbaek K, Saltman R. *EBOOK: Nordic Health Care Systems: Recent Reforms and Current Policy Challenges*. McGraw-Hill Education 2009.

36. Marchildon GP, Allin S, Merkur S. Canada: Health System Review. *Health Syst Transit*. Nov 2020;22(3):1-194.

37. European Observatory on Health Systems and Policies (OECD). *Germany: Country Health Profile 2019, State of Health in the EU*. 2019.

38. World Health Organization. World Alliance for Patient Safety. Forward programme 2005. World Health Organization. February, 2013. Accessed February, 2013. www.int/patientsafety

39. Quinn Patton M. *Qualitative research & evaluation methods. Integrating theory and practice*. SAGE publications, Inc; 2015.

40. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15doi:10.1177/1049732305276687

41. Richards L. Using NVivo in Qualitative Research. 1999;

42. The World Medical Association (WMA). Declaration of Helsinki - Ethical principles for medical research involving human subjects 1964 The World Medical Association; 2013. 24. May, 2013. http://www.wma.net/en/30publications/10policies/b3/

43. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19(6):349-357.

44. Mandrola J, Cifu A, Prasad V, Foy A. The Case for Being a Medical Conservative. *Am J Med*. 2019;132(8):900-901. doi:10.1016/j.amjmed.2019.02.005

45. Stub T, Quandt SA, Arcury TA, Sandberg JC, Kristoffersen AE. Attitudes and knowledge about direct and indirect risks among conventional and complementary health care providers in cancer care. journal article. *BMC Complement Med Ther*. January 31 2018;18(1):44. doi:10.1186/s12906-018-2106-z

46. Maha N, Shaw A. Academic doctor's views of complementary and alternative medicine (CAM) and its role within the NHS: An exploratory qualitative study. *BMC Complement Altern Med*. 2007;7(17):1-11.

47. Kristoffersen AE, Stub T, Broderstad AE, Hansen AH. Use of traditional and complementary medicine among Norwegian cancer patients in the seventh survey of the Tromsø study. *BMC Complement Med Ther*. Nov 29 2019;19(1):341. doi:10.1186/s12906-019-2762-7

48. Roth M, Lin J, Kim M, Moody K. Pediatric Oncologists' Views Toward the Use of Complementary and Alternative Medicine in Children With Cancer. *J Pediatr Hematol Oncol*. 2009;31 (3):177-182.

49. Goldberg SB, Lam SU, Britton WB, Davidson RJ. Prevalence of meditation-related adverse effects in a population-based sample in the United States. *Psychother Res*. Mar 2022;32(3):291-305. doi:10.1080/10503307.2021.1933646

50. Kyngäs H, Mikkonen R, Nousiainen E-M, et al. Coping with the onset of cancer: coping strategies and resources of young people with cancer. *Eur J Cancer Care (Engl)*. 2001;10(1):6-11. doi:https://doi.org/10.1046/j.1365-2354.2001.00243.x

51. Wiesener S, Falkenberg T, Hegyi G, Hök J, Fønnebø V. Legal status and regulation of CAM in Europe. *Forsch Komplementmed*. 2012;19(suppl 2):29-36.

52. Mackereth P, Carter A, Parkin S, et al. Complementary therapists' training and cancer care: A multi-site study. *Eur J Oncol Nurs*. 2009;13(5):330-335. doi:http://dx.doi.org/10.1016/j.ejon.2009.04.009

53. Huber BM, Rodondi PY. Interest and need for continuing medical education in pediatric complementary and integrative medicine: a cross-sectional survey from Switzerland. *BMC Complement Med Ther*. Apr 13 2022;22(1):106. doi:10.1186/s12906-022-03581-6

54. Brønnøysundregistrene. Registrere alternativ behandler. In English: Register Complementary and Alternative Provider. Brønnøysundregistrene. 20. July, 2020. Accessed 20. July, 2020. https://www.brreg.no/person/registrering-av-utovere-av-alternativ-behandling/

55. FOR-2003-12-11-1500. Forskrift om frivillig registerordning for utøvere av alternativ behandling. English: Regulation on voluntary registry for alternative treatment practitioners. *The Norwegian government*. 2003;

56. Frenkel M, Ben-Arye E, Cohen L. Communication in Cancer Care: Discussing Complementary and Alternative Medicine. *Integr Cancer Ther*. June 1, 2010 2010;9(2):177-185. doi:10.1177/1534735410363706

57. Schiff E, Frenkel M, Shilo M, Levy M, Schachter L, Freifeld Y. Bridging the physician and CAM practitioner communication gap: suggested framework for communication between physicians and CAM practitioners based on a cross professional survey from Israel. *Patient Educ Couns*. 2011;85doi:10.1016/j.pec.2010.08.029

58. Levit L, Balogh E, Nass S, Ganz PA. Patient-centered communication and shared decision making. *Delivering high-quality cancer care: Charting a new course for a system in crisis*. National Academies Press (US); 2013.

59. Frenkel M, Ben-Arye E, Cohen L. Communication in cancer care: discussing complementary and alternative medicine. *Integr Cancer Ther*. 2010;9doi:10.1177/1534735410363706

60. Laengler A, Spix C, Seifert G, Gottschling S, Graf N, Kaatsch P. Complementary and alternative treatment methods in children with cancer: A population-based retrospective survey on the prevalence of use in Germany. *Eur J Cancer Care (Engl)*. 2008/10/01/ 2008;44(15):2233-2240. doi:https://doi.org/10.1016/j.ejca.2008.07.020

61. Valji R, Adams D, Dagenais S, et al. Complementary and alternative medicine: a survey of its use in pediatric oncology. *Evid Based Complement Alternat Med*. 2013;2013:527163. doi:10.1155/2013/527163

62. Ndao DH, Ladas EJ, Bao Y, et al. Use of complementary and alternative medicine among children, adolescent, and young adult cancer survivors: a survey study. *J Pediatr Hematol Oncol*. May 2013;35(4):281-8. doi:10.1097/MPH.0b013e318290c5d6

63. Pritchard-Jones K, Pieters R, Reaman GH, et al. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. *Lancet Oncol*. 2013/03/01/ 2013;14(3):e95-e103. doi:https://doi.org/10.1016/S1470-2045(13)70010-X

Appendix

1. NSD Approval Questionnaire

2. NSD Approval Provider Interviews

3. Consent Form for Questionnaire

4. Questionnaire

5. Consent Form for Healthcare Provider Interviews (English)

6. Consent Form for Healthcare Provider Interviews (Norwegian)

7. Interview Guide for Healthcare Providers (English)

NSD sin vurdering

Skriv ut

Prosjekttittel
En spørreundersøkelse blandt foreldre med barn som har kreft: Kartlegging av mestringsstrategier

Referansenummer
493228

Registrert
09.11.2020 av Trine Stub - trine.stub@uit.no

Behandlingsansvarlig institusjon
UIT – Norges Arktiske Universitet / Det helsevitenskapelige fakultet / Institutt for samfunnsmedisin

Prosjektansvarlig (vitenskapelig ansatt/veileder eller stipendiat)
Trine Stub, trine.stub@uit.no, tlf: 77649286

Type prosjekt
Forskerprosjekt

Prosjektperiode
01.01.2021 - 01.01.2022

Status
04.12.2020 - Vurdert

Vurdering (1)

04.12.2020 - Vurdert
BAKGRUNN Prosjektet er vurdert av Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK). REK vurderer at studien framstår som forskning, men ikke som medisinsk eller helsefaglig forskning. Prosjektet er følgelig ikke omfattet av helseforskningslovens saklige virkeområde, jf. helseforskningslovens §§ 2 og 4 (deres referanse 178081). Det er vår vurdering at behandlingen av personopplysninger i prosjektet vil være i samsvar med personvernlovgivningen så fremt den gjennomføres i tråd med det som er dokumentert i meldeskjemaet den 04.12.2020 med vedlegg, samt i meldingsdialogen mellom innmelder og NSD. Behandlingen kan starte. MELD VESENTLIGE ENDRINGER Dersom det skjer vesentlige endringer i behandlingen av personopplysninger, kan det være nødvendig å melde dette til NSD ved å oppdatere meldeskjemaet. Før du melder inn en endring, oppfordrer vi deg til å lese om hvilke type endringer det er nødvendig å melde:
https://www.nsd.no/personverntjenester/fylle-ut-meldeskjema-for-personopplysninger/melde-endringer-i-meldeskjema
Du må vente på svar fra NSD før endringen gjennomføres. TYPE OPPLYSNINGER OG VARIGHET Prosjektet behandler særlige kategorier av personopplysninger om helseforhold og alminnelige kategorier av personopplysninger frem til 01.01.2022. LOVLIG GRUNNLAG Prosjektet vil innhente samtykke fra de registrerte til behandlingen av personopplysninger. Vår vurdering er at prosjektet legger opp til et samtykke i samsvar med kravene i art. 4 nr. 11 og art. 7, ved at det er en frivillig, spesifikk, informert og utvetydig bekreftelse, som kan dokumenteres, og som den registrerte kan trekke tilbake. Lovlig grunnlag for behandlingen er dermed den registrertes uttrykkelige samtykke, jf. personvernforordningen art. 6 nr. 1 bokstav a, jf. art. 9 nr. 2 bokstav a, jf. personopplysningsloven § 10, jf. § 9 (2). PERSONVERNPRINSIPPER NSD vurderer at den planlagte behandlingen av personopplysninger vil følge prinsippene i personvernforordningen om: - lovlighet, rettferdighet og åpenhet (art. 5.1 a), ved at de registrerte får tilfredsstillende informasjon om og samtykker til behandlingen - formålsbegrensning (art. 5.1 b), ved at personopplysninger samles inn for spesifikke, uttrykkelig angitte og berettigede formål, og ikke viderebehandles til nye uforenlige formål - dataminimering (art. 5.1 c), ved at det kun behandles opplysninger som er adekvate, relevante og nødvendige for formålet med prosjektet - lagringsbegrensning (art. 5.1 e), ved at personopplysningene ikke lagres lengre enn nødvendig for å oppfylle formålet DE REGISTRERTES RETTIGHETER Så lenge de registrerte kan identifiseres i

datamaterialet vil de ha følgende rettigheter: åpenhet (art. 12), informasjon (art. 13), innsyn (art. 15), retting (art. 16), sletting (art. 17), begrensning (art. 18), underretning (art. 19), dataportabilitet (art. 20). NSD vurderer at informasjonen som de registrerte vil motta oppfyller lovens krav til form og innhold, jf. art. 12.1 og art. 13. Vi minner om at hvis en registrert tar kontakt om sine rettigheter, har behandlingsansvarlig institusjon plikt til å svare innen en måned. FØLG DIN INSTITUSJONS RETNINGSLINJER NSD legger til grunn at behandlingen oppfyller kravene i personvernforordningen om riktighet (art. 5.1 d), integritet og konfidensialitet (art. 5.1. f) og sikkerhet (art. 32). Nettskjema er databehandler i prosjektet. NSD legger til grunn at behandlingen oppfyller kravene til bruk av databehandler, jf. art 28 og 29. For å forsikre dere om at kravene oppfylles, må dere følge interne retningslinjer og eventuelt rådføre dere med behandlingsansvarlig institusjon. OPPFØLGING AV PROSJEKTET NSD vil følge opp ved planlagt avslutning for å avklare om behandlingen av personopplysningene er avsluttet. Lykke til med prosjektet! Kontaktperson hos NSD: Jørgen Wincentsen Tlf. Personverntjenester: 55 58 21 17 (tast 1)

NSD NORSK SENTER FOR FORSKNINGSDATA

NSD sin vurdering

Prosjekttittel

Experiences with complementary and alternative medicine (CAM). A qualitative study among peadiatric oncology experts and CAM providers

Referansenummer

978969

Registrert

25.08.2021 av Dana Catalina Mora - dana.c.mora@uit.no

Behandlingsansvarlig institusjon

UiT Norges Arktiske Universitet / Det helsevitenskapelige fakultet / Institutt for samfunnsmedisin

Prosjektansvarlig (vitenskapelig ansatt/veileder eller stipendiat)

Dana C. Mora, dana.c.mora@uit.no, tlf: +4777645660

Type prosjekt

Forskerprosjekt

Prosjektperiode

25.09.2021 - 01.12.2025

Status

17.09.2021 - Vurdert

Vurdering (1)

17.09.2021 - Vurdert

Det er vår vurdering at behandlingen vil være i samsvar med personvernlovgivningen, så fremt den gjennomføres i tråd med det som er dokumentert i meldeskjemaet 17.09.2021 med vedlegg. Behandlingen kan starte.

TYPE OPPLYSNINGER OG VARIGHET
Prosjektet vil behandle alminnelige kategorier av personopplysninger frem til 01.12.2025.

LOVLIG GRUNNLAG
Prosjektet vil innhente samtykke fra de registrerte til behandlingen av personopplysninger. Vår vurdering er at prosjektet legger opp til et samtykke i samsvar med kravene i art. 4 og 7, ved at det er en frivillig, spesifikk, informert og utvetydig bekreftelse som kan dokumenteres, og som den registrerte kan trekke tilbake.

Lovlig grunnlag for behandlingen vil dermed være den registrertes samtykke, jf. personvernforordningen art. 6 nr. 1 bokstav a.

TAUSHETSPLIKT
Deltagerne (i alle fall mange av dem) i prosjektet har taushetsplikt. Intervjuene må gjennomføres uten at det fremkommer opplysninger som kan identifisere pasienter.

PERSONVERNPRINSIPPER
NSD vurderer at den planlagte behandlingen av personopplysninger vil følge prinsippene i personvernforordningen:

- om lovlighet, rettferdighet og åpenhet (art. 5.1 a), ved at de registrerte får tilfredsstillende informasjon om og samtykker til behandlingen
- formålsbegrensning (art. 5.1 b), ved at personopplysninger samles inn for spesifikke, uttrykkelig angitte og berettigede formål, og ikke viderebehandles til nye uforenlige formål
- dataminimering (art. 5.1 c), ved at det kun behandles opplysninger som er adekvate, relevante og nødvendige for formålet med prosjektet
- lagringsbegrensning (art. 5.1 e), ved at personopplysningene ikke lagres lengre enn nødvendig for å oppfylle formålet.

DE REGISTRERTES RETTIGHETER
NSD vurderer at informasjonen om behandlingen som de registrerte vil motta oppfyller lovens krav til form og innhold, jf. art. 12.1 og art. 13.

Så lenge de registrerte kan identifiseres i datamaterialet vil de ha følgende rettigheter: innsyn (art. 15), retting (art. 16), sletting (art. 17), begrensning (art. 18) og dataportabilitet (art. 20).

Vi minner om at hvis en registrert tar kontakt om sine rettigheter, har behandlingsansvarlig institusjon plikt til å svare innen en måned.

FØLG DIN INSTITUSJONS RETNINGSLINJER
NSD legger til grunn at behandlingen oppfyller kravene i personvernforordningen om riktighet (art. 5.1 d), integritet og konfidensialitet (art. 5.1. f) og sikkerhet (art. 32).

Transkriptør, Skype og Teams er databehandler i prosjektet. NSD legger til grunn at behandlingen oppfyller kravene til bruk av databehandler, jf. art 28 og 29

For å forsikre dere om at kravene oppfylles, må dere følge interne retningslinjer og eventuelt rådføre dere med behandlingsansvarlig institusjon.

MELD VESENTLIGE ENDRINGER
Dersom det skjer vesentlige endringer i behandlingen av personopplysninger, kan det være nødvendig å melde dette til NSD ved å oppdatere meldeskjemaet. Før du melder inn en endring, oppfordrer vi deg til å lese om hvilke type endringer det er nødvendig å melde: nsd.no/personverntjenester/fylle-ut-meldeskjema-for-personopplysninger/melde-endringer-i-meldeskjema Du må vente på svar fra NSD før endringen

gjennomføres.

OPPFØLGING AV PROSJEKTET
NSD vil følge opp underveis (hvert annet år) og ved planlagt avslutning for å avklare om behandlingen av personopplysningene er avsluttet/pågår i tråd med den behandlingen som er dokumentert.

Kontaktperson hos NSD: Lene Chr. M. Brandt

Lykke til med prosjektet!

En spørreundersøkelse blant foreldre med barn som har kreft. Kartlegging av mestringsstrategier.

Informasjon og samtykke til å delta i studie

Dette spørreskjemaet er en del av et forskningsprosjekt som har som formål å undersøke hvilke mestringsstrategier foreldre med barn som har kreft benyttet da barnet var sykt. Vi vil undersøke hvilke strategier som ble benyttet for å hjelpe barnet med å håndtere bivirkninger av kreftbehandlingen samt å bedre barnets fysiske og psykiske helse. Du har blitt spurt om å delta fordi du er medlem av Barnekreftforeningen i Norge.

Hva skjer med informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Det vil ikke være mulig å identifisere deg i resultatene av evalueringen når eller hvis disse publiseres.

Frivillig deltakelse

Det er frivillig å delta. Du kan når som helst og uten å oppgi noen grunn trekke deg fra studien. Dersom du ønsker å delta, undertegner du samtykkeerklæringen. Har du spørsmål kan du kontakte Trine Stub 92 26 75 02.

Rett til innsyn og sletting av opplysninger om deg

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i opplysningene du har gitt oss. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har om deg. Dersom du trekker deg fra studien, kan du kreve å få slettet opplysninger, med mindre opplysningene allerede er inngått i analyser.

Hvis du kan identifiseres i datamaterialet, har du rett til: - innsyn i hvilke personopplysninger som er registrert om deg, - å få rettet personopplysninger om deg, - få slettet personopplysninger om deg, - få utlevert en kopi av dine personopplysninger

(dataportabilitet), og - å sende klage til personvernombudet eller Datatilsynet om behandlingen av dine personopplysninger."

"Hva gir oss rett til å behandle personopplysninger om deg? Vi behandler opplysninger om deg basert på ditt samtykke". Når prosjektet skal avsluttes slettes alle opplysningene vi har om deg (31.12.2021). Dette prosjektet er finansiert av Nasjonalt Forskningssenter innen Komplementær og Alternativ Medisin – NAFKAM, UiT Norges Arktiske Universitet, Tromsø.

Du gir ditt informerte samtykke (godkjenner deltakelse) i studien ved å krysse av for dette i begynnelsen av spørreskjemaet.

Med vennlig hilsen

Trine Stub

Ved spørsmål kontakt: Trine Stub (prosjektleder), PhD, seniorforsker NAFKAM.
Telefon: 776 49 286 mobil: 92 26 75 02

QUESTIONNAIRE
(The present version is a shortened version of the questionnaire)

Thank you for participating in this survey, we will start by asking you some general questions about you

1. Are you?
   ___ Man
   ___Woman

2. How old are you? _____

3. What was your household's (everyone you live with) total gross income last year (before tax)? (Include all income from work, social security, social assistance and similar assistance)

   _____ Under 150,000 kr
   _____ 150,000-250,000 kr
   _____ 251,000-350,000 kr
   _____ 351,000-450,000 kr
   _____ 451,000-550,000 kr
   _____ 551,000-750,000 kr
   _____ 751,000-1,000,000 kr
   _____ Over 1,000,000 kr
   _____ Do not know
   _____ Refuse to answer

4. What is the higher level of education you completed?
   _____ Primary education (up to 10 yrs)
   _____ Upper secondary education (11- 13 yrs)
   _____ Lower level of university or college (up to 4 yrs)
   _____ Higher level of university/ college (more than 4 yrs)
   _____ Do not know
   _____ Refuse to answer

5. Would you say you live in a:
   ____ City (>50,000 inhabitants)
   ____ Town (10,000-50,000 inhabitants)
   ____ Village (Less than 10,000 inhabitants)
   ____ Rural Area
   ____ Do not know
   ____ Refuse to answer

The following questions are about your child who was diagnosed with cancer.

6. Have you:
   ____ Had cancer as child
   ____ Had a child that has/had cancer

7. Is your child alive?
   ____ Yes
   ____ No

   7a. How old is your child now? [only asked of those who responded "yes" to Q79]
   _____years old

   7b. How old was your child when he/she died? [only asked of those who responded "no" to Q79]
   _____ years old

8. Is your child a :
   ____ Boy
   ____ Girl

9. How old was your child the first time he/she was diagnosed with cancer?
   _____
   _____

10. How old was your child when the cancer treatment ended.
   ____ Age of child_____
   ____ Cancer treatment has not ended
   ____ I do not know if the treatment has ended yet
   ____ It is not relevant the child died

11. What cancer diagnosis was/is your child treated for: (Please mark all that apply)
   ____ Leukemia (blood cancer)
   ____ Lymphoma
   ____ Neuroblastoma
   ____ Bone Cancer (osteosarcoma, Ewing's sarcoma)
   ____Wilms kidney tumor
   ____ Soft tissue sarcoma
   ____ Retinoblastoma (eye tumor)
   ____ Germ cell tumor
   ____ I do not know
   ____ Other, specify_____

12. What kind of treatment did your child receive? (Please mark all that apply)

____ Chemotherapy
____ Radiotherapy
____Cancer treatment with hormones
____Operation
____High-dose treatment with stem cell support / bone marrow transplantation
____Antibody Treatment
____Do not know
____Other, specify_____

13. Did your child experiences any of the following symptoms as a consequence of cancer treatment? (Please mark all that apply)

	Yes
a. Pain	
b. Fatigue (exhaustion)	
c. Nausea /vomiting	
d. Sleep disorders	
e. Feeling of worry (unrest)	
f. Shortness of breath	
g. Lack of appetite	
h. Feeling sad	
i. Sleepiness (drowsiness)	
j. Dry mouth	
k. Numbness/tingling in the body including hands and feet	
l. Weakened immune system	
m. Hormone changes	
n. Reduced fertility	
o. Heart / disease	
p. Lung problems	
q. Dental Problems	
r. Difficulty with memory and concentration	
s. Hearing problems	
t. Muscle cramps	
u. Neuralgia	
v. Osteoporosis (osteoporosis)	
w. Lymphedema (accumulation of fluid in, for example, arm, leg and other body parts)	
x. Psychological reactions	
y. Radiation damage to skin, connective tissue and muscles	
z. Other adverse effects of cancer treatment specify_____	

14. Has your child ever had a recurrence of cancer after being diagnosed with cancer for the first time?

____ Yes
____ No {SKIP TO Q15]
____ It is not relevant the child died

14b. If yes , was it :
____ The same type
____ I do not know
____ Other, please specify_____

15. In your opinion, how is your child's health in general now?
____ Very good
____ Good
____ Neither good nor bad
____ Bad
____ Very bad
____ It is not relevant the child died

16. In your opinion, how do you think your child's general health compares to others children his/her age?
____ Better health
____ Similar health
____ Poorer health
____ I do not know

17. Do you think that your child's education/social skills and cognitive development has been negatively influenced by the cancer treatment?
____Minimally
____To some extent
____Very much
____ I don't know

These questions are about treatments you might have used or are using to help your child with health problems of cancer diagnosis and cancer treatment.

18. Has the child used any of the following to help reduce health challenges resulting from cancer diagnosis/treatment? (Please, mark all that apply)

____Received treatment from a therapist (physiotherapist, acupuncturist, masseuse, homeopath, etc.) [GO TO Q18]
____Vitamins/minerals [GO TO Q19]
____Other supplements [GO TO Q20]
____Diets [GO TO Q21]
____Outdoor activities (cycling, playing) [GO TO Q22]
____Yoga/meditation [GO TO Q22]

____Art/music (for example paint or play an instrument) [GO TO Q22]
____Religious activities (prayer, going to church) [GO TO Q22]
____Have not used any of those treatments [SKIP to Q23]

18. Have you used any of the following therapies for your child? (Please mark all that apply)

	Yes, the child has use it
a. Acupuncture	
b. Chiropractic	
c. Healing / laying of hands	
d. Homeopathy	
e. Kinesiology	
f. Massage / Aromatherapy	
g. Naprapathy	
h. Osteopathy	
i. Physiotherapy	
j.Psychotherapy	
k. Reflexology / reflexology	
l. Other: Specify_____	

IF YOU ANSWERED NO TO ALL OF THE CHOICES IN QUESTION 18 GO TO QUESTION 19
[*Questions 18a to 18r were asked for every modality the participant reported using]

18a. For which of the following symptoms did you use [MODALITY] for your child? (Please mark all that apply)

	Yes
a. Pain	
b. Fatigue (exhaustion)	
c. Nausea /vomiting	
d. Sleep disorders	
e. Feeling of worry (unrest)	
f. Shortness of breath	
g. Lack of appetite	
h. Sleepiness (drowsiness)	
i. Dry mouth	
j. Feeling sad	
k. Numbness/tingling in the body including hands and feet	
l. Weakened immune system	
m. Hormone changes	
n. Reduced fertility	
o. Heart / disease	
p. Lung problems	

q. Dental Problems	
r. Difficulty with memory and concentration	
s. Hearing problems	
t. Muscle cramps	
u. Neuralgia	
v. Osteoporosis (osteoporosis)	
w. Lymphedema (accumulation of fluid in, for example, arm, leg and other body parts)	
x. Psychological reactions	
y. Radiation damage to skin, connective tissue and muscles	
z. Other adverse effects of cancer treatment specify_____	

18b. Did [MODALITY] have positive effects?

_____ No

_____ Yes

IF YES, Did the [MODALITY]:

____ Cured the symptoms

____ Improved the symptoms

____ Did not provide any change on the symptoms

____ I do not know

18c. Did your child experience any adverse effects from [MODALITY]?

____Yes, what kind of adverse effects: (Please mark all that apply)

_____ Fatigue

_____ Headache

_____ Muscle soreness

_____ Allergic reactions

_____ Nausea

_____ Other, please specify_____

____No

18d. Do you remember, how much approximately did you spend on these treatments?

_____ NOK when you used it

____Do not remember

We would like to know how you feel about the way these therapists (masseur, osteopath, acupuncturist) communicated with you during your child's treatment**.** The therapists do not include anyone from our medical team (i.e. doctors, nurses)
Please use this scale to rate communication during most of your child's visits.

How do you experience the communication?	Poor				Excellent
18e. Greeted us in a way that made us feel comfortable	1	2	3	4	5
18f. Treated us with respect	1	2	3	4	5

18g. Showed interest in our ideas about our child's health	1	2	3	4	5
18h. Understood our main health concerns	1	2	3	4	5
18i. Paid attention to us (looked at us, listened carefully)	1	2	3	4	5
18j. Let us talk without interruptions	1	2	3	4	5
18k. Gave us as much information as we wanted	1	2	3	4	5
181. Talked in terms we could understand	1	2	3	4	5
18m. Encouraged us to ask questions	1	2	3	4	5
18n. Involved us in decisions as much as we wanted	1	2	3	4	5
18o. Discussed next steps, including any follow-up plans	1	2	3	4	5
18p. Showed care and concern	1	2	3	4	5
18q. Spent the right amount of time with us	1	2	3	4	5

18o. How did you find information on [MODALITY]? (Please mark all that apply)

_____ Online (i.e. Facebook, Instagram, websites. etc)
_____ Media (radio, TV, newspaper, magazine)
_____ Use/have used the modality myself
_____ Friends/family
_____ Healthcare professionals (nurse, doctors, hospital, etc)
_____ Other, specify_____

18p. During what stage of the cancer treatment did you use [MODALITY]?? (Do we want to ask this for activities)

_____During the first 3 months
_____After the 1st year of cancer treatment
_____More than a year following cancer treatment
_____I do not know
_____Other _____

18q. Did you use [MODALITY]?

____ During active cancer treatment
____ After cancer treatment ended
____ During palliative care

18r. How did you make the decision to use this [MODALITY]? (Please mark all that apply)

____ Advice from friends
____ Tradition in the family
____ Advice from social media groups such as Facebook
____ Advice from other parents of children with cancer
____ As a last resource
____ Other, specify_____

19. Have you used the following vitamins for your child? (please mark all that apply)

	Yes, the child has use it
a. Multivitamins/Vitamin bjørner	
b. Vitamin B	
c. Vitamin C	
d. Vitamin D	
e. Vitamin E	
f. Other vitamin, specify:	

IF YOU ANSWERED NO TO ALL OF THE CHOICES IN QUESTION 19 GO TO QUESTION 20

[*Questions 19a to 19h were asked for every modality the participant reported using]

19a. For which of the following symptoms did you use the vitamins for your child? (Please mark all that apply)

	Yes
a. Pain	
b. Fatigue (exhaustion)	
c. Nausea /vomiting	
d. Sleep disorders	
e. Feeling of worry (unrest)	
f. Shortness of breath	
g. Lack of appetite	
h. Sleepiness (drowsiness)	
i. Dry mouth	
j. Feeling sad	
k. Numbness/tingling in the body including hands and feet	
l. Weakened immune system	
m. Hormone changes	
n. Reduced fertility	
o. Heart / disease	

p. Lung problems	
q. Dental Problems	
r. Difficulty with memory and concentration	
s. Hearing problems	
t. Muscle cramps	
u. Neuralgia	
v. Osteoporosis (osteoporosis)	
w. Lymphedema (accumulation of fluid in, for example, arm, leg and other body parts)	
x. Psychological reactions	
y. Radiation damage to skin, connective tissue and muscles	
z. Other adverse effects of cancer treatment specify_____	

19b. Did [VITAMIN] have positive effects?

____Yes

IF YES, Did [VITAMIN]:

____ Cured the symptoms

____ Improved the symptoms

____ Did not provide any change on the symptoms

____ No

____ I do not know

19c. Did your child experience any adverse effects from [VITAMIN]

____Yes, what kind of adverse effects: (please mark all that apply)

_____ Fatigue

_____ Headache

_____ Muscle soreness

_____ Allergic reactions,

_____ Nausea

_____ other, please specify_____

____No

19d. Do your remember how much approximately did you spend on [VITAMIN]?

_____ NOK when you used it

____Do not remember

19e. How did you find information on [VITAMINS]? (Please mark all that apply)

_____ Online (i.e. Facebook, Instagram, websites. etc)

_____ Media (radio, TV, newspaper, magazine)

_____ Use/have used the modality myself

_____ Friends/family

_____ Healthcare professionals (nurse, doctors, hospital, etc)

_____ Other, specify_____

19f. During what stage of the cancer treatment did you use [VITAMIN]?

_____During the first 3 months
_____After the 1st year of cancer treatment
_____More than a year following cancer treatment
_____ I do not know
_____Other _____

19g. Did you use this [VITAMIN]?
____ During active cancer treatment
____ After cancer treatment
____ During palliative care

19h. How did you make the decision to use [VITAMIN]? (Please mark all that apply)
____ Advice from friends
____ Tradition in the family
____ Advice from social media groups such as Facebook
____ Advice from other parents of children with cancer
____ As a last resource
____ Other, specify_____

20. Have you used the following supplements for your child? (Please mark all that apply)

	Yes, the child has use it
a. Cod liver oil/ Tran	
b. Omega 3	
c. Turmeric / Curcumin	
d. Ginger	
e. Aloe Vera	
f. Mistletoe / Iscador	
g. Shark cartilage	
h. Noni juice	
i. Garlic	
j. Solhatt / Echinesea	
k. Green tea	
l. Cannabis (oil, tea, etc.)	
m. Blueberry/ blueberry extract	
n. Q10	
o. Ginseng / Gerimax	
p. Rosenrot	
q. Other, specify:	

IF ANSWERED NO TO ALL OF THE CHOICES IN QUESTION 20 GO TO QUESTION 21

[*Questions 20a to 20h were asked for every modality the participant reported using]

20a. For which of the following symptoms did you use [SUPPLEMENT] for your child? (Please mark all that apply)

	Yes
a. Pain	
b. Fatigue (exhaustion)	
c. Nausea /vomiting	
d. Sleep disorders	
e. Feeling of worry (unrest)	
f. Shortness of breath	
g. Lack of appetite	
h. Sleepiness (drowsiness)	
i. Dry mouth	
j. Feeling sad	
k. Numbness/tingling in the body including hands and feet	
l. Weakened immune system	
m. Hormone changes	
n. Reduced fertility	
o. Heart / disease	
p. Lung problems	
q. Dental Problems	
r. Difficulty with memory and concentration	
s. Hearing problems	
t. Muscle cramps	
u. Neuralgia	
v. Osteoporosis (osteoporosis)	
w. Lymphedema (accumulation of fluid in, for example, arm, leg and other body parts)	
x. Psychological reactions	
y. Radiation damage to skin, connective tissue and muscles	
z. Other adverse effects of cancer treatment specify_____	

20b. Did [SUPPLEMENT] have positive effects?

____Yes

IF YES, Did [SUPPLEMENT]:

____ Improved the symptoms

____ Cured the symptoms

____ Did not provide any change on the symptoms

____ No

____ I do not know

20c. Did your child experience any adverse effects from [SUPPLEMENT]?

____Yes, what kind of adverse effects: (please mark all that apply)
_____ Fatigue
_____ Headache
_____ Muscle soreness
_____ Allergic reactions,
_____ Nausea
_____ other, please specify_____
____No

20d. Do you remember How much approximately did you spend on [SUPPLEMENT]?
_____ NOK when you used it
____Do not remember

20e. How did you find information on [SUPPLEMENT]? (Please mark all that apply)
_____ Online (i.e. Facebook, Instagram, websites. etc)
_____ Media (radio, TV, newspaper, magazine)
_____ Use/have used the modality myself
_____ Friends/family
_____ Healthcare professionals (nurse, doctors, hospital, etc)
_____ Other, specify_____

20f. During what stage of the cancer treatment did you use [SUPPLEMENT]?
_____During the first 3 months
_____After the 1st year of cancer treatment
_____More than a year following cancer treatment
_____ Do not know
_____Other _____

20g. Did you use [SUPPLEMENT]:
____ During active cancer treatment
____ After cancer treatment
____ During palliative care

20h. How did you make the decision to use [SUPPLEMENT]? (Please mark all that apply)
____ Advice from friends
____ Tradition in the family
____ Advice from social media groups such as Facebook
____ Advice from other parents of children with cancer
____ As a last resource
____ Other, specify_____

21. Have you used the following diets for your child? (Please mark all that apply)

	Yes, we have use it

a. Fish and vegetable based diet	
b. Low carb diet	
c. Vegetarian / vegan diet	
d. Fast	
e. Homemade food only	
f. Juice diet (carrot, beetroot, apricot, etc.)	
g. Organic food only	
h. Ketogenic diet	
i. Other, specify:	

IF ANSWERED NO TO ALL OF THE CHOICES IN QUESTION 21 GO TO QUESTION 22
[*Questions 21f to 21f were asked for every modality the participant reported using]

21a. For which of the following symptoms did you use [DIET] for your child? (Please mark all that apply)

	Yes
a. Pain	
b. Fatigue (exhaustion)	
c. Nausea /vomiting	
d. Sleep disorders	
e. Feeling of worry (unrest)	
f. Shortness of breath	
g. Lack of appetite	
h. Sleepiness (drowsiness)	
i. Dry mouth	
j. Feeling sad	
k. Numbness/tingling in the body including hands and feet	
l. Weakened immune system	
m. Hormone changes	
n. Reduced fertility	
o. Heart / disease	
p. Lung problems	
q. Dental Problems	
r. Difficulty with memory and concentration	
s. Hearing problems	
t. Muscle cramps	
u. Neuralgia	
v. Osteoporosis (osteoporosis)	
w. Lymphedema (accumulation of fluid in, for example, arm, leg and other body parts)	
x. Psychological reactions	

y. Radiation damage to skin, connective tissue and muscles	
z. Other adverse effects of cancer treatment specify_____	

21b. Did [DIET] have positive effects?

Yes

IF YES, Did [DIET]:

____ Cured the symptoms
____ Improved the symptoms
____ Did not provide any change on the symptoms
____ I do not know
____ No

21c. How did you find information on [DIET]? (Please mark all that apply)

_____ Online (i.e. Facebook, Instagram, websites. etc)
_____ Media (radio, TV, newspaper, magazine)
_____ Use/have used the modality myself
_____ Friends/family
_____ Healthcare professionals (nurse, doctors, hospital, etc)
_____ Other, specify_____

21d. During what stage of the cancer treatment did you use [DIET]?

_____During the first 3 months
_____After the 1st year of cancer treatment
_____More than a year following cancer treatment
_____ Do not know
_____Other _____

21e. Did you use [DIET]:

____ During active cancer treatment
____ After cancer treatment
____ During palliative care

21f. How did you make the decision to use [DIET]? (Please mark all that apply)

____ Advice from friends
____ Tradition in the family
____ Advice from social media groups such as Facebook
____ Advice from other parents of children with cancer
____ As a last resource
____ Other, specify_____

The following set of questions asks about activities you used to help your child cope mentally and physically with the cancer diagnoses and treatment.

22. Which of the following activities have you used? (Please mark all that apply)

	Yes, we use it
a. Playing	
b. Walking outdoors	
c. Going to the cabin	
d. Physical exercise/ sport (such as biking, playing ball)	
e. Riding a horse	
f. Yoga	
g. Meditation/mindfulness	
h. Drawing/handcrafts	
i. Listening to music, playing an instruments, participating in school orchestra	
j. Religious activities (praying and going to church)	
k. Other, specify:	

[*Questions 22a to 22g were asked for every modality the participant reported using]

22a. Did [ACTIVITY] have positive effects?

_____No

_____Yes

IF YES, Did [ACTIVITY]:

____ Helped you keep a normal routine

____ Helped the family to think about something else

____ Provided a pause from illness/hospital

____ Beneficial for the child

____ I do not know

22c. Do you remember how much approximately did you spend on [ACTIVITY]?

_____ NOK

____Do not remember

22f. Did you use [ACTIVITY]:

____ During active cancer treatment

____ After cancer treatment

____ During palliative care

22d. How did you find information on about [ACTIVITY]? (Please mark all that apply)

_____ Online (i.e. Facebook, Instagram, websites. etc)

_____ Media (radio, TV, newspaper, magazine)

_____ Use/have used the modality myself

_____ Friends/family

_____ Healthcare professionals (nurse, doctors, hospital, etc)

_____ Other, specify_____

22g. How did you make the decision to use [ACTIVITY]? (Please mark all that apply)

____ Advice from friends and family
____ Tradition in the family
____ Normal activity in the community
____ Popular activity among friends
____ Advise from other parents of children with cancer
____ Other specify_____

23. Do you have any other information you would like to give us or the questionnaire itself

_____

_____

Thank you for participating in the survey!

Experiences with complementary and alternative medicine (CAM). A qualitative study among pediatric oncology experts and CAM providers

Information and consent to participate in the study

The main purpose of this study is to conduct in-depth interviews with oncology experts and CAM providers in Norway and internationally to ask them about their experiences with the use of CAM among children with cancer. You are been asked to participate because you are a pediatric oncology expert (doctors, nurses) or CAM provider. If you chose to take part in the project, you will be interviewed face to face or through a video conferencing platform such as Skype or Teams. It will take between 30-60 minutes. Your answers will be recorded electronically and transcribed by a professional transcription service.

What happens to the information about you?

The information registered about you should only be used as described for the purpose of the study. All information will be processed without name or other directly recognizable information. It will not be possible to identify you in the results of the evaluation when or if these are published.

Participation is voluntary

Participation in the project is voluntary. If you chose not to participate, you can withdraw your consent at any time without giving a reason.

Your rights

So long as you can be identified in the collected data, you have the right to:

- access the personal data that is being processed about you
- request that your personal data is deleted
- request that incorrect personal data about you is corrected/rectified
- receive a copy of your personal data (data portability), and send a complaint to the Data Protection Officer or The Norwegian Data Protection Authority

What gives us the right to process your personal data?

We will process your personal data based on your consent. Based on an agreement with The National Research Center for Complementary and Alternative Medicine - NAFKAM, UiT Norwegian Arctic University, Tromsø, NSD – The Norwegian Centre for Research Data AS has assessed that the processing of personal data in this project is in accordance with data protection legislation. The project is scheduled to end December 01, 2025.

Where can I find out more?

If you have questions about the project, or want to exercise your rights, contact:

The National Research Center for Complementary and Alternative Medicine - NAFKAM, UiT Norwegian Arctic University, Tromsø via Dana C. Mora by email dana.c.mora@uit.no or by telephone +47 77 64 56 60 or Trine Stub by email trine.stub@uit.no or by telephone +47 77 64 92 86.
Data Protection Officer: Joakim Bakkevold by telephone +47 77 64 63 22

UiT / NORGES ARKTISKE UNIVERSITET

nafkam

NSD – The Norwegian Centre for Research Data AS, by email: (personverntjenester@nsd.no) or by telephone: +47 55 58 21 17.

Yours sincerely,

Dana C. Mora, MPH
(Researcher/Dr. Philos candidate)

Trine Stub, PhD
(Researcher professor /supervisor)

Consent form

I have received and understood information about the project and have been given the opportunity to ask questions. I give consent to participate in the interview. I give permission to for my information to be used until the end of the project.

(Signed by participant, date)

nafkam

Nasjonalt forskningssenter innen
komplementær og alternativ medisin

Erfaringer med bruk av alternative behandling ved barnekreft: En kvalitativ studie blant helsepersonell og alternativ behandlere

Informasjon og samtykke til å delta i studie

Hensikten med denne studien er å innhente informasjon fra helsepersonell og alternative behandlere om deres erfaringer med bruk av alternative behandling hos barn med kreft. Du har blitt spurt om å delta i studien fordi du er kreftlege, sykepleier eller alternativ behandler som har erfaring med å arbeide med barn som har kreft. Som deltaker i studien vil du bli intervjuet ansikt til ansikt eller via Skype eller Teams. Intervjuet vil vare mellom 30 og 60 minutter. Intervjuet vil bli tatt opp og transkribert av en profesjonell aktør.

Hva skjer med informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og eller andre direkte gjenkjennende opplysninger. Det vil ikke være mulig å identifisere deg i resultatene av evalueringen når eller hvis disse publiseres.

Frivillig deltakelse

Det er frivillig å delta. Du kan når som helst og uten å oppgi noen grunn trekke deg fra studien. Dersom du ønsker å delta, undertegner du samtykkeerklæringen.

Rett til innsyn og sletting av opplysninger om deg

Hvis du kan identifiseres i datamaterialet, har du rett til:
- innsyn i hvilke personopplysninger som er registrert om deg,
- å få rettet personopplysninger om deg,
- få slettet personopplysninger om deg,
- få utlevert en kopi av dine personopplysninger (dataportabilitet), og
- å sende klage til personvernombudet eller Datatilsynet om behandlingen av dine personopplysninger."

Hva gir oss rett til å behandle personopplysninger om deg?

Vi behandler opplysninger om deg basert på ditt samtykke. Når prosjektet skal avsluttes slettes alle opplysningene vi har om deg (01.12.25). Dette prosjektet er finansiert av Nasjonalt Forskningssenter innen Komplementær og Alternativ Medisin – NAFKAM, UiT Norges Arktiske Universitet, Tromsø.

NSD – Norsk senter for forskningsdata AS har vurdert at behandlingen av personopplysninger i dette prosjektet er i samsvar med personvernregelverket.

Hvor kan jeg finne ut mer?

NAFKAM – Nasjonalt forskningssenter innen komplementær og alternativ medisin
Institutt for samfunnsmedisin – Det helsevitenskapelige fakultet – UiT Norges arktiske universitet
Adresse: Postboks 6050 Langnes, 9037 Tromsø | Telefon: 77 64 66 50 | Faks: 77 64 68 66
E-post: nafkam@helsefak.uit.no | Web: www.nafkam.no

Hvis du har spørsmål om studien, kan du ta kontakt med:
Nasjonalt forskningssenter innen komplementær og alternativ medisin - NAFKAM, UiT Norges arktiske universitet, Tromsø via Dana C. Mora e-post dana.c.mora@uit.no telefon +47 77 64 56 60
Trine Stub på epost trine.stub@uit.no eller på telefon +47 77 64 92 86.
Personvernombudet UiT: Joakim Bakkevold telefon +47 77 64 63 22
NSD – Norsk senter for forskningsdata AS på e-post (personverntjenester@nsd.no) eller på telefon: 55 58 21 17.

Med vennlig hilsen

Dana C. Mora, MPH
(Forsker/stipendiat)

Trine Stub, PhD
(Forsker I/veileder)

Samtykkeerklæring

Jeg har mottatt og forstått informasjon om prosjekt og har fått anledning til å stille spørsmål. Jeg samtykker til intervju. Jeg samtykker til at mine opplysninger behandles frem til prosjektet er avsluttet

---

(Signert av prosjektdeltaker, dato)

Children with cancer and self-management strategies: Providers Interview Guide

Introduction

- Can you please tell me about yourself and your professional background?
  - What is your profession?
  - How long have you been working in your field?
  - How long have you been working with pediatric cancer patients?

Cancer

- What type of cancer would you say you most often treat?
- What is the most common cancer treatment among your patients? (Chemotherapy, radiation, surgery?)
- What cancer treatment-induced symptoms do your pediatric cancer patients most often complain about?

Self-management strategies (SMS) and CAM

- Do you recommend SMS/CAM to your patients?
- How long have you been working with the modality?
- When do you recommend the modality?
- Why do you recommend SMS/CAM (your philosophy)
- What are the reasons parents inquired about this modality?
- What modalities have you used/recommended to your pediatric cancer patients? Acupuncture/Acupressure? Hypnosis? Supplements? Art music therapy? physiotherapy
- For what group of children do you recommend this treatment?
- For what symptoms/diagnoses do you recommend this modality? (CINV, Mucositis, Pain? Health-related quality of life? Mental health?
- At what stage did you recommend/use this modality?
- What are the disadvantages of the modality?
- What obstacles do your patients have accessing the treatments?

Safety and efficacy

- Do you think the modality is safe? Risks?
- Did your patient have any adverse effects from the strategy?
- Do you know about the interaction of conventional medicine with products? (Herbs, vitamin/supplement)
- Doctor delay contact- do you have experience with this
- Experience with children/parents who decline conventional medicine/ guidelines to follow in this case
- Did the strategy have any beneficial effects?
- Do you think SMS/CAM is effective?
- Can you tell me about the efficacy and safety of modalities your patients have used but which you did not necessarily recommend?

- Can you tell me about the most promising clinical practice case concerning cancer treatment and SMS/CAM?
- Where do you get information about these modalities? Scientific literature? Self-experience? Colleagues?

Communication/Information

- Do you ask your patients about SMS/CAM strategies? If they use it?
- Do you feel you have enough knowledge about these strategies to recommend or discuss this with parents?
  - Is this knowledge lacking from your medical education?
- What would you like to learn about CAM?
- How/where did you learn about SMS/CAM?
- Where do you gather scientific information/resources about these modalities?
- What information do you need? / What SMS/CAM information do you think is missing?"
- Apart from the modalities we have already discussed, are there other CAM or SMS you often recommend to your patients?
- Do you have any communication with other healthcare providers regarding your patient?
  - If communication with other healthcare providers exists, how is this communication?
- What is the best way to provide information to parents of pediatric patients that interested in SMS/CAM?
- Do you present these modalities as a complementary treatment, or do you present these treatment possibilities once the parents inquire about them?
- What do you feel is the biggest obstacle for those parents that are interested in learning more about SMS/CAM in accessing further information and possible treatments?
- Do you feel your patients are comfortable addressing CAM information/treatments with you?
- What information should be included on a web page for SMS/CAM in pediatric oncology?

CAM Providers

- How often do you treat children with cancer?
- What are their treatment goals? what modalities do they recommend?
- What products do you prescribe?
- How do these products interact with conventional treatment?
- Have they experienced any adverse effects from the treatments you recommended?
- How is the communication with conventional healthcare providers?