UiT – The Arctic University of Norway
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Body height and risk of cancer: The Tromsø Study

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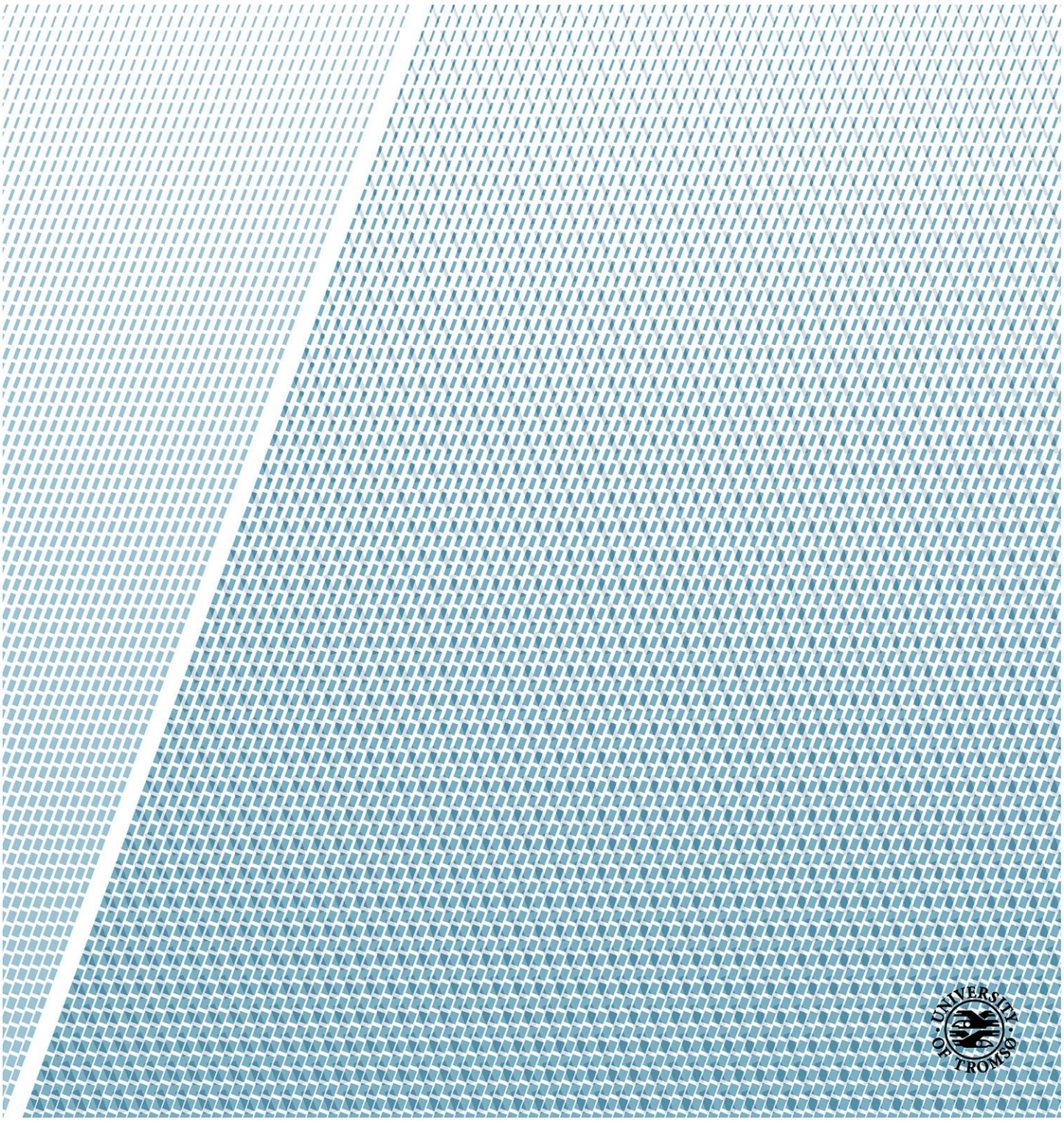

Preface

The association between body height and several malignancies is well established. The main aim of this master thesis was to investigate the association between measured body height and cancer among the inhabitants of the municipality of Tromsø. Further, as high BMI is known to increase cancer risk, we also aimed to investigate the combined effect of body height and body mass index (BMI) on cancer risk as additional analysis.

My interest in research was generated from attending the research program for medical students at the University of Tromsø, where a year was dedicated to research and PhD Courses. As a student in the research group K.G. Jebsen – Thrombosis Research and Expertise Center, I was assigned a project to investigate different risk factors for VTE in cancer patients. This work led to an increased interest in different diseases and medical conditions, especially so in cancer. Further, this project was created for my master thesis.

The project received no external funding using the resources available from the University Library at the University of Tromsø and collected data from the Tromsø Study and the Cancer Registry of Norway.

The work of this thesis began in August 2018 when I collected literature. I worked with this thesis during my fifth year as a medical student in clinical rotation, but the main work of analyses and writing was done in the period designated to the master thesis, from March to June 2019.

Finally, I would like to thank my two supervisors, Professor John-Bjarne Hansen and Professor Sigrid Brækkan, for their contribution to this work by continuous close supervision, support, the constrictive feedback when proofreading my manuscript and help with statistical analyses. You are my greatest inspiration in the field of research. Thank you, for never giving up on me and for always motivating me to continue even when things are tough.

Hanne Skille, May 2019

Table of contents

Summary

Background: The association between several anthropometric measures and malignancy is established, both for total cancer risk and for several individual cancers. However, no previous study have investigated the association between measured body height and cancer risk in North-Norway. Further, the combined effect of body height and body mass index (BMI) on cancer risk is scarcely investigated.

Aim: We aimed to i) investigate the association between measured body height and cancer in the Tromsø municipality, and ii) investigate whether there was a biological interaction between body height and BMI on cancer risk.

Methods: Subjects (n=30 586) were recruited from the fourth, fifth and sixth surveys of the Tromsø study (end of follow-up 31 December 2012). Subjects not consenting to medical research (n=181), not officially registered as Tromsø-residents at study enrollment (n=23), with a history of cancer (n=858) or missing values on body height (n=38) were excluded. We further excluded men with a height <161cm (n=141) and women <150cm (n=295). Body height was categorized into quartiles (Q1-Q4) and also used as a continuous variable per 10 cm increase. BMI was divided according to definitions of normal weight, overweight and obesity. Cox regression was used to determine hazard ratios (HRs) for cancer by body height and BMI. We further calculated the interactions between body height and BMI on cancer risk.

Results: During a median follow-up of 17.6 years, 3145 cancers occurred. The HR was 1.23 (95% CI 1.06-1.43) for cancer in tall men (Q4), when compared to men in Q1. The HR for cancer were 1.34 (95% CI 1.15-1.56) for women in Q4 compared to Q1. The risk of cancer increased per 10 cm increase in height. No biological interaction was found between body height and BMI on cancer risk.

Conclusion: Subjects of tall stature have an increased risk of cancer.

Abbreviations

AP – Attributable proportion

BMI – Body mass index

BSA – Body surface area

CRN – The Cancer Registry of Norway

HR – Hazard ratio

IR – Incidence rate

OR – Odds ratio

RR – Relative risk

RERI – Relative excess risk due to interaction

SD – Standard deviation

WHO – World Health Organization

1. Introduction

1.1. Cancer

Cancer is the collective term for more than a hundred different malignancies that can occur if a cells normal cell cycle is disturbed. Cancer can develop almost anywhere in the human body. Cells are the basic components of humans, which grow continuously and divide into new cells as the necessity and stimulation of cell division are present. Normally, cells die (apoptosis) after a certain period or amount of damage, and new cells arise in their place. Cancer develops when genetic alterations interfere with these regulated processes and cells begin to grow deviated from the normal control, which can form tumors that can invade surrounding tissue or metastasize to other parts of the body. Cancers are classified by either the cancer primary site (the location where the cancer first develops) or the histological degree (the type of body tissue in which the cancer originates). Treatment of cancer depends on cancer type and cancer stage. The traditional treatment composes of surgery, radiation and chemotherapy. Additionally, immunotherapy with monoclonal antibodies have been used the last decades and the use is likely to increase in future treatment regimen.

1.1.1. Epidemiology

The incidence and mortality of cancer are rapidly growing worldwide, which is partly due to the growing and aging population (1, 2). According to the estimates from the World Health Organization (WHO) in 2015, cancer was in 2018 still the first or second leading cause of death before the age of 70 years in many countries worldwide (2). A report by Bray et al. presented the global burden of cancer in 2018 (GLOBOCAN estimates) and estimated 17.0 million new cases of cancer and 9.6 million cancer deaths last year, when excluding non-melanoma skin cancers (2). Lung, prostate, colorectal, stomach and liver cancer has been reported as the most commonly diagnosed cancers in men, with lung cancer being the leading cause of cancer deaths (2). Further, in women, breast, colorectal, lung, cervix and thyroid cancer has been the most frequently diagnosed cancers, were breast cancer has been reported as responsible for most cancer deaths (2). Different cancers' incidence and mortality vary both in and between countries, depending on economic development, nutrition, sun exposure and life style. Markedly, cancer registries of high quality are not

obtainable in many countries of low- and middle income and therefore, data regarding cancer (frequency and mortality) in these countries are incomplete (2).

In Norway, cancer registration is mandatory by law. An evaluation of the Norwegian Cancer Registry shows a completeness and a validity of 98% with 94% of the cancer diagnoses being microscopically verified (3). In 2016, 32 827 new cases of cancer were registered in Norway, of which 17 763 (54%) were men (4). There was an increase in the overall cancer incidence of 1.2% when compared to the previous year. The most frequent cancers diagnosed in Norway in 2016 were prostate, breast, lung, colon cancer and melanomas (4).

1.1.2. Pathophysiology

Cancer is a genetic disorder caused by mutations of the DNA due to acquired spontaneous alterations or environmental impact (5). These alterations can be passed down to daughter cells at cell division, resulting in Darwinian selection where these cells outlive other cells (5). Finally, an accumulation of mutations give rise to a set of properties that facilitates growth and survival of the mutated cells, the hallmarks of cancer (Supplementary figure 1) (6). The six hallmarks presented by Hanahan and Weinberg in 2000 include 1) self-sufficiency in growth signals, 2) lack of response to growth inhibitory signals, 3) evasion of cell death, 4) limitless replicative potential, immortality of cells, 5) angiogenesis development to sustain growth and 6) metastatic and invasive abilities (6). Further, the authors added four new hallmarks eleven years later, introducing 7) evasion of the immune system, 8) tumor-promoting inflammation, 9) genomic instability and mutation and 10) the ability to deregulate cellular energetics (Supplementary figure 2) (7). Through knowledge on cells' and molecules' abnormalities, cancer treatment can further develop. The deeper understanding introduced by Hanahan and Weinberg was groundbreaking and essential in the field of targeting treatment in cancer.

By the presence of some hallmarks, a benign tumor can occur. If the cells additionally develop the remaining hallmarks, giving the ability for tissue invasion, the tumor becomes malignant. Malignant tumors can further spread through blood or lymph and form secondary tumors (i.e. metastases) at other sites (5, 6). In this thesis, only malignant tumors are included.

1.1.3. Risk factors

Malignancies are complex and multifactorial of nature. Although the causes of cancer are not completely understood, it is estimated that 5-10% of cancer cases arise from inherited factors, and the remaining percentage from acquired origins (5).

Genetics

It is commonly known that several cancers are heritable. Genetics contribute to cancer risk, but vary across different cancer sites and the genetic alterations are often tumor specific. The implication of genetics in i.e. cervical and lung cancer are negligible, however, genetics account for up to 27% and 42% of breast and prostate cancers, respectively (8). Other cancers associated with heritability are colorectal and ovarian cancer. In breast cancer, approximately 10% of the genetic cancer risk can be attributed to the rare and highly penetrant variations in BRCA1, BRCA2, and TP53 (9-11). The BRCA genes are also associated with increased ovarian cancer risk (12). Subjects with two or more first- or second-degree relatives with colorectal cancers, make up for around 20% of all colorectal cancer patients (13). Colorectal cancer of the distal colon are often more aggressive cancers associated with mutations of the adenomatous polyposis coli gene (APC), p53 and K-ras genes (14). Mutations of the TP53 gene are associated with Li-Fraumeni syndrome (various tumors), mutations of p16INK4A with melanoma, and MSH2, MLH1 and MSH6 with hereditary nonpolyposis colon cancer (5). Currently, research on the individual contribution of genetic variants in breast, ovarian and prostate cancer, have identified less than half of the genetic sources for these cancers, and more research in this field is needed (15-17).

Physical activity

Physical inactivity is a growing health problem worldwide. Around 300 epidemiologic studies have described the link between physical activity and cancer risk. The evidence of causal association of physical activity and cancer is found to be strong for colon cancer, with physical activity giving an overall reduced risk of 20-30% (18). In a review by Kruk et al. the average risk reduction for breast cancer and endometrial cancer due to physical activity was found to be 20-30% in different studies, and varying from 10-20% for prostate cancer, 20-40% for lung cancer, 10-20% for ovarian cancer, 40-50% for pancreatic cancers and finally, 30% for gastric cancers (19).

Age

Age is essential when speaking of cancer risk. In general, the frequency of cancer increases with age. Between 2005 and 2015, cancer incidence increased by 33%, with population aging contributing to 16% (20). Most cancer deaths occur in subjects aged from 55 to 77, and the rates thereafter decline due to the reduced population in elderly. The rising cancer incidence with age may be explained by the increased amount of somatic mutations and decrease in immune competence (5).

Tobacco smoking

The research on the association between tobacco smoking and cancer begun several decades ago, were the association between smoking and lung cancer was established in the 1950's (21-23). A meta-analysis by Gandini et al. presented the relative risks (RRs) of cancer in current smokers, with the highest risks presented in; lung (RR 8.96), laryngeal (RR 6.98) and pharyngeal (RR 6.76), upper digestive tract (RR 3.57) and oral (RR 3.43) cancers.

Alcohol use

Malignancy is one of the most severe consequences of alcohol consumption, and approximately 3.6% of all cancer-related cases worldwide can be attributed to alcohol intake (24). Further, 3.5% of all cancer deaths are related to chronic alcohol use (24). A use of alcohol is associated with risk of malignant tumors of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast cancer (25). A daily intake of approximately 50g of alcohol results in a 2-3 fold increased cancer risk, when compared to teetotalers (25).

Sunlight

Sun exposure or exposure to ultraviolet (UV) light, more outdoor activities, lighter clothing, longer longevity, genetics and diseases causing immune suppression are factors affecting the rising incidence of melanoma and non-melanoma skin cancers (NMSC) (26). Both the incidence of melanomas and non-melanomas are increasing worldwide, but the mortality rates are stable (27, 28). A study of UK population by Parkin et al. showed that 90% of melanomas in men and 82% of melanomas in women were attributed to excessed solar irradiation (29). Subjects with light skin, numerous moles and a family history of NMSC have an increased risk of skin cancer when exposed to UV radiation (30-32).

Air pollution

In 2013, air pollution was found to be associated with an increased risk of cancer, especially lung cancer (33). There are several matters in the air that affect cancer risk, i.e. second-hand smoking (34) and radon (35), which influence lung cancer risk.

Viruses

Seven viruses have been found to cause 10-15% of malignancies in humans, and it is estimated that one of five cancers can be attributed to infection, mainly due to viruses (36, 37). The cancers caused by viruses are of an extra burden in immunosuppressed populations in developing countries (38). The Epstein-Barr virus (EBV, also known as human herpesvirus 4) has been found to be associated with most Burkitt's lymphoma and nasopharyngeal carcinoma, some non-Hodgkin's and Hodgkin's diseases as well as other lymphomas (39). Hepatitis B virus (HBV) and hepatitis C virus (HCV) were first described in 1965 and 1989, respectively, as a cause of some hepatocellular carcinoma (40, 41). For cervical, anal and penile cancers, high-risk human papillomaviruses (HPV), mainly HPV 16 and HPV 18, are large contributors to cancer risk and are now included in the vaccination program in many countries worldwide (42-46). Further, other viruses such as Human T-lymphotropic virus-1 (HTLV-1) (47), Merkel cell polymavirus (MCV) (48) and Kaposi's sarcoma herpesvirus (KSHV, also known as human herpesvirus 8) (49), have been found to be associated with different cancers.

Inflammation

Inflammation is a critical component of tumor progression where inflammatory cells are involved in neoplastic processes, proliferation and both survival and migration of tumor cells. It is estimated that infectious diseases and chronic inflammation contribute to about 25% of malignancies (50). An inflammatory environment over time leads to genomic instability and further to cancer. This is due to an accumulation of reactive nitrogen, oxygen, aldehydes as well as reactive cytokines, growth factors and chemokines, which are the elements that normally alter the biological processes that maintain normal homeostasis of cells (50). Evidence implicate several pathways related to the development and progress of cancer (50). These pathways are of importance, as they can provide targeted detection and treatment.

Diet

Several studies have investigated the role of diet on cancer risk, i.e. in esophageal (51), gastric (52), colorectal (53) and breast cancer (54). In a review by Grosso et al. published in 2017, the association between diet and cancer was reported using 93 studies including more than 85000 cases and 100000 controls (55). The authors reported significant results from prospective cohorts showing an association between healthy dietary patterns and decreased risk of colon, lung and breast cancer, and further between unhealthy diets and elevated cancer risk, especially of colon cancer (55). Healthy diets have been found to be associated with an overall healthier lifestyle, which may be a contributor to explain the protective effect (55). Unhealthy diet is associated with higher BMI, suggesting a mediating effect of obesity on cancer risk (55).

Overweight and obesity

One of the easiest anthropometric indices of adiposity to understand is weight adjusted for stature. Since the eighties, indices of weight adjusted for height have given estimates for adiposity (regardless of body height) that can be used to compare populations (56). There is no doubt that the most popular and frequently used of the indices is the body mass index (BMI), which is also known as the Quetelet's index (57). BMI and indices of weight-for-height are all based on the hypothesis that true adiposity is unrelated to height, and studies have shown that among these indices, BMI is the one that correlates least with height (57, 58). Meaning that BMI represent the body fat consumption rather than the body height, and the strength of BMI as a measure for adiposity is further supported by BMIs association with obesity-related risk factors (i.e. blood triglycerides, total cholesterol, blood pressure and fasting glucose levels) (57). The World health Organization (WHO) has classified overweight and obesity according to values of BMI giving underweight a BMI <18.50, normal rage equals BMI between 18.50 and 24.99, subjects with a BMI ≥25 defined as overweight, and a BMI ≥30 as obese (59). There are also three classes of obesity defined, i.e. moderate (grade 1), severe (grade 2) and very severe (grade 3), with the popular description as morbid obese if the BMI is ≥40.0 (59).

Obesity (BMI ≥30) affects one third of all adults in the USA (60). Studies have consistently demonstrated a relation between increased BMI and an increase in cancer incidence and worsened prognosis for many cancers (56, 61-63). The evidence are strongest

for breast, colorectal, endometrial, gallbladder, kidney, pancreas, and gastric cardia cancer and esophageal adenocarcinoma (58, 64). Obesity, followed by smoking, is the most significant preventable lifestyle risk factor for cancer mortality (65). It has been estimated that 15-20% of all cancer deaths in the United States can be attributed to overweight and obesity (56). There are several mechanisms linking obesity and cancer, i.e. metabolic and endocrine effects of obesity, i.e. insulin resistance and resultant chronic hyperinsulinemia. The alarming trends of obesity growth in the population, combined with obesity associated with cancer, composes a huge burden on public health. Successful intervention strategies for weight loss and maintenance after weight loss are desirable both on an individual and community level to reduce the risk of malignancies.

1.2. Body height

Body height in adults is determined by several elements and seemingly, the combination of mainly genetic factors and the impact of nutrition, infections and socioeconomic status the first twenty years of life is important (66). Being of tall stature is associated with higher life expectancy, higher income, lower risk of respiratory and cardiovascular diseases, lower risk of pregnancy complications, and further, a higher risk of cancer (67-76).

Men's height trends have been analyzed for 250 years in Europe, USA and Japan (77-82). The trends of height in women are more scarcely studied. In a report published in 2016 by NCD Risk Factor Collaboration (NCD-RisC) international population-based data have been used to estimate the height of adult men and women born during a whole century worldwide (83). The analysis by NCD-RisC revealed large differences in body height between countries the last 100 years, with the tallest men being born the last decade in the Netherlands, yielding an average height of 183 cm and the shortest men were born in 1896 in Laos with an average adult height of only 152.9 cm (83). Swedish women, with an average adult height of 160.3 cm, were the tallest women a century ago and 20 cm taller than women in Guatemala born in 1896, which are registered as the shortest women the last century (with an average height of 140 cm) (83). People of different countries grow to different statures, which may be partly due to individuals' genetics but also due to malnutrition and severe diseases. The gap between the tallest and shortest men and women have been found to be around 20 cm, with the tallest men (average ≥181 cm) born in the

Netherlands, Belgium, Estonia, Latvia and Denmark and the tallest women (average ≥168 cm) living in Latvia, the Netherlands, Estonia and Czech Republic (83). A century ago, Norwegian men and women were on average ≥171 cm and ≥158 cm, respectively, being approximately 20 cm taller than the shortest men and women worldwide (83).

1.3. Body height and cancer risk

The association between body height (standing stature) and different cancers has been studied for several decades (84-86), and to date, body height is considered a risk factor for most types of cancer (69, 87). The incidence of cancer events increases with increasing adult height and has been reported for all cancers combined and for several malignancies alone such as ovarian, prostate, skin, lung, colorectal, breast and kidney cancer (67-74). A prospective cohort of one million UK women reported an increased incidence of cancer by increased height for most cancer sites, with no variation of cancer risk across subgroups of different years of birth, different socioeconomic origin, alcohol intake, body mass index (BMI), physical activity, use of oral contraceptives etc. (69). The Million Women Study showed a 16% increased risk of all cancers for every 10cm increase in height, and an especially increased risk for malignant melanomas (32%), kidney cancer (29%), leukemia (26%) and colon cancer (25%) (69).

As described above, the association between body height and cancer is well established, and body height seems to reflect several biological cancer cursors (70, 88, 89). However, the mechanism behind the association is unknown. A possible explanation for the relation is taller peoples increased amount of cells, larger organs and thereby more potential neoplastic origins (89). It is proposed that genes in relation to both height and oncogenic reaction pathways are the underlying factors. Growth hormones, such as insulin-like growth factors (IGFs), regulate body growth (90) and is a potential link between body height and malignancy. Circulating IGF-1 is found to be associated with an increased risk of cancer, including breast, prostate and colorectal cancer (91-93).

Total cancer risk

As previously mentioned, tall people are at increased risk of all cancers combined and for several common cancers (67-74, 87). The risk of cancer for every 10 cm increase in height

varies from 13%-16% to (69, 94) in women and is approximately 5% per 5cm increase in height in men (68, 87).

Breast cancer

Breast cancer is the number one cause of cancer morbidity and cancer mortality among women (95). Adult stature has been found to be positively associated with breast cancer in many epidemiological studies worldwide (69, 94, 96-99). The association found is mainly a dose-response relationship (69, 94, 96-99). The strongest relationship is found in postmenopausal women, and a lack of association is reported in premenopausal women (97). In a meta-analysis of 159 prospective cohorts by Zhang et al., the pooled relative risk of breast cancer was 1.17 (95% CI 1.15-1.19) per 10 cm increase in height. In the same meta-analysis, Mendelian randomization analysis provided evidence that genetic factors and biological pathways affecting body height have an important role in the etiology of breast cancer (99).

Colorectal cancer

Colorectal cancers (CRC) represents up to 10% of all cancers worldwide, being the third most common cancer in men, and the second most common in women (1). Colorectal cancer constituted almost 15% of all cancers in Norway in year 2000, having a greater increase of these cancers' incidence than comparing neighboring countries (100). In a Norwegian cohort of two million men and women, the relative risk of colorectal cancer for each 10 cm increase in height were 1.14 (95% CI 1.11-1.16) in men and 1.17 (95%CI 1-14-1.20) in women. A meta-analysis published in 2016 by Khankari showed a 12% increased risk (RR 1.12, 95% CI 1.10-1.15) of colorectal cancer per 10 cm of height. A nested case-control study by Boursi et al. demonstrated a significant association of body height and CRC both by height as a continuous variable and when comparing the highest quartile to the lowest quartile in both men and women (101).

Cutaneous melanoma

The incidence rate of cutaneous melanoma (CM) has increased dramatically the past decades, and CMs presents a large burden in fair-skinned populations (102, 103). CM has been found positively associated with several anthropometric factors, such as high BMI,

large body surface area (BSA) and tall stature (69, 94, 104-106). In a study by Stenehjem et al., body height displayed a positive significant association (p trends <0.001) in both sexes, and an exponential increase per quintile was found with more than 50% increased CM risk (men; HR 1.55, 95% CI 1.36-1.77, women; HR 1.52, 95% CI 1.31-1.76) for subjects in the fifth quintile when compared to subjects of quintile one (106).

Lung cancer

Lung cancer is one of the most common cancers in the terms of both incidence and mortality (95). Cigarette smoking and some occupational exposures are major known risk factors for this disease, however, the etiology of lung cancer is largely elusive (107). In a meta-analysis from year 2017 by Wang et al., in 15 prospective studies and one case-control study, the overall relative risk of lung cancer per 10 cm increase in height were 1.06 (95% CI 1.03-1.09) (108). Further, the risk increased (RR 1.15, 95% CI 1.04-1.26) in individuals with a high height compared to those with a low height (108).

Ovarian cancer

Representing approximately 239000 cases in 2012, ovarian cancer is the seventh most frequent cancer and the eight cause of cancer death in women worldwide (1). Due to late symptomatic development, ovarian cancer is often diagnosed late, in advanced stages and with poor prognosis (109, 110). In a meta-analysis of 12 cohort studies, women of height ≥170 cm had a pooled multivariate RR of 1.38 (95% CI 1.16-1.65) compared with those of height <160 cm (73). Further, several studies have found an increased risk of ovarian cancer by increasing body height (69, 94, 111, 112).

Pancreatic cancer

Pancreatic cancers cause significant morbidity and mortality worldwide. Studies investigating the relationship between body height and pancreatic risk show inconsistent results. Genkinger et al. found no association between height and pancreatic cancer using a pooled analysis of 14 cohorts in 2011 (113), which is similar to the majority of previously conducted studies (114-116). The EPIC study reported a significant positive association for height and pancreatic cancer risk, however, this trend was primarily due to a low risk in the lowest quartile, as when this group was excluded, the trend was no longer significant (117).

Prostate cancer

Studies on height and prostate cancer are inconsistent, with most pointing towards no association (118). Further, more recent studies have found an increased risk of prostate cancer with increasing height. In a study of 950000 Norwegian men, the tallest men (≥190 cm) had an RR of 1.72 (95% CI 1.46-2.04) compared to the shortest men (<160 cm). Additionally, in a resent meta-analysis by Khankari et al., the risk of prostate cancer were found to be 7% (RR 1.07, 95% CI 1.05-1.10) increased per each additional 10cm (119).

Cancer occurs frequently in elderly (4), and with an aging, growing population there is no doubt that cancer is a burden for the future on both the individual level and for society. It is essential that risk factors and mechanisms of cancer are mapped so prophylactic and facilitated treatment can be optimized of these patients. To the best of our knowledge, no previous study has investigated the association between measured body height and cancer in North-Norway. Further, the joint effect of body height and BMI on cancer risk is scarcely studied.

1.4. Aim of the thesis

We hypothesized that people of North-Norway, representing a general tall population compared to other populations worldwide, would confirm what previous studies have found on the association between body height and cancer. Further, we hypothesized that body height and BMI (as separate risk factors/exposures) would on more than an additive effect display a positive interaction on cancer risk.

The aims of the thesis were to i) investigate the association between measured body height and cancer in a large, population-based cohort of the inhabitants of Tromsø municipality, and further, for additional analysis, ii) investigate the combined effect of measured body height and body mass index (BMI) on cancer risk.

2. Methods

2.1. Body height and cancer – The Tromsø study

2.1.1. Study population

Participants were recruited from the fourth (1994-1995), fifth (2001-2002) and sixth (2007-2008) surveys of the Tromsø Study, a single-center, population-based cohort with repeated health surveys of the inhabitants of Tromsø, Norway. The Tromsø study was initiated in 1974 with an emphasis on cardiovascular disease with a primary aim to determine causes of the high cardiovascular mortality, and to develop preventative methods for heart attacks and strokes. However, the focus of the study has expanded over time and now includes a broad spectrum of diseases. To date, seven surveys have been conducted, the most recent carried out in 2015 to 2016. Further details about the Tromsø study can be found elsewhere (120). All inhabitants (Tromsø 4) above the age of 24 or parts of the population (Tromsø 5 and 6) above the age of 29 were invited to partake in these surveys. A personal invitation was sent two weeks prior to the suggested time of appointment, and the subjects were free to attend whenever suitable within the timeframe of the ongoing study. Those who did not attend were given one reminder. Overall, 30 586 individuals, aged 25 to 97, participated in at least one of the surveys. Attendance rates were high, ranging from 66% in Tromsø 6 to 77% in Tromsø 4, and finally, 79% in Tromsø 5. The Regional Committee of Medical and Health Research Ethics approved the study, and all participants gave their informed, written consent.

Subjects who did not consent to medical research (n=181), those not officially registered as residents of the municipality of Tromsø at the date of study enrollment (n=23), and subjects with a known pre-baseline history of cancer (n=858) were excluded. We also excluded subjects with missing values on body height (n = 38), men with a height of <161cm (n =141) and women <150cm (n=295) as per the Norwegian definition of short stature. Accordingly, our cohort consisted of 29 050 subjects, who were followed from date of study inclusion until the end of follow-up, 31 December 2012.

2.1.2. Baseline measurements and body height

Baseline data was obtained by physical examination, blood samples and self-administered questionnaires. Height and weight were measured with subjects wearing light clothing and no shoes. Weight were measured to the nearest 0.5 kg. Body height was measured to the nearest centimeter in Tromsø 4 and to the nearest mm in Tromsø 5 and 6. Information on measured body height in Tromsø 5 and 6 was used only if body height measurements were missing from Tromsø 4. Body mass index were calculated as weight in kilograms divided by the square of height in meters. Information on education level, daily smoking (never, former, current and duration in years) and physical activity was collected from questionnaires.

2.1.3. Cancer assessment

Information on malignancy, including the cancer diagnosis date, primary cancer site (ICD10 codes C00-96), tumor histology (ICO-3), cancer stage (localized, regional, distant, or unknown stage) and the initial planned treatment was obtained by linkage to the Cancer Registry of Norway (CRN) using the participants´ unique national civil registration number, which is assigned to all people residing in Norway. In Norway, cancer registration has been mandatory by law since 1952, and the CRN receive information from general practitioners, hospitals, pathological laboratories and death certificates nationwide (3). The cancer registry is also linked to the Norwegian National Cause of Death Registry as well as the patients discharge diagnosis registries. The CRN is considered a complete and valid registry, with a recent evaluation of data displaying a 98.8% completeness with 94% of the cases being histologically verified (3). Non-melanoma skin cancers (ICD 191.0-191.9) were classified as non-cancer due to the pathophysiology and nature of these cancer types.

2.1.4. Statistical analysis

For each participant, person-years of follow-up were accrued form date of study enrollment until the date of a cancer diagnosis, migration, death or to the end of study period (31th December 2012). Cancer status was defined as “no-cancer” or “cancer”. Men and women were categorized according to quartiles (Q1-Q4) of body height, giving Q1: ≤173 cm, Q2: >173-177 cm, Q3: >177-182 cm, Q4: ≥182cm for men and Q1: ≤160 cm, Q2: >160-164 cm, Q3: >164-168 cm, Q4: ≥168cm for women. The categories of men and women in Q1-

Q4 were used for analysis of baseline characteristics, as well as all categories combined (all participants) separated by sex.

We also modeled body height as a continuous variable and determined hazard ratios for cancer per 10-cm increase in body height. The risk per 10cm increase were measured for total cancers and different cancer sites i.e. colon and rectum, pancreas, lung, breast, gynecological cancers, prostate, urinary tract, cancers of the central nerve system, hematological and lymph cancers, upper GI and others (ear-nose-throat cancers, melanomas, endocrine cancers, sarcomas and unknown cancer site). Combined categories of BMI corresponded to the categories defined by WHO; subjects with a BMI <25 were considered "under- or normal weight", considered "overweight" with a BMI ≥25<30 and defined as "obese" if the BMI were 30 or higher (59).

Statistical analyses were carried out using STATA version 15.0 (Stata Corporation LP, College Station, TX, USA). Age-adjusted incidence rates (IRs) of cancer were calculated using Poisson regression and expressed as number of events per 1000 person-years at risk. Cox proportional hazard regression models were used to estimate age-adjusted hazard ratios (HR), with 95% confidence intervals (CIs) for cancer across quartiles of body height (Q1-Q4), categories of BMI (<25, ≥25<30 and ≥30), and per 10-cm increase in height. Analysis with hazard ratios for cancer across quartiles of height were also adjusted for other factors i.e. education level and the amount of hard physical activity more than once a week. Non-cancer subjects in the lowest quartile of body height and/or BMI <25 were used as reference group. Schoeneld's global test was used to confirm the proportional hazard assumption.

To investigate the interaction between body height and BMI on cancer risk, and whether a biological interaction between these two exposures was present, we calculated the relative excess risk attributable to interaction (RERI) and the proportion attributable to interaction (AP) with corresponding 95% CIs. The calculations were done according to Andersson et al. (121). Shortly, RERI can be understood as the part of the total effect that is attributable to the interaction (here of height and BMI), and the AP as the proportion of the combined effect that is attributable to interaction (122). A RERI and an AP value above zero (>0) suggest positive interaction or more than additivity, meaning that the effect of the combined exposure of two risk factors is greater than the sum of the two separate effects (121, 122).

2.2. GRADE

The Grading of recommendations, assessment, development and evaluations (GRADE) system is developed for systematic reviewers and guideline developers to evaluate articles´ quality of evidence on four levels (very low, low, moderate or high), and classify between two grades of recommendation (weak or strong) (123). The GRADE method was used for a thorough assessment of five articles describing the association between measured body height and different types of cancer in mainly Western populations. The evaluation of articles is presented in the final GRADE tables.

3. Results

3.1. Body height and cancer risk – Tromsø municipality

Of the 29050 participants included in our analysis, 48% (n=13930) were males and 52% (n=15120) were women. The mean age at recruitment was 45.9 (SD 13.8) years for men and 46.0 (SD 14.8) years and for women, respectively. The distribution of body height in men and women is presented in supplementary figure 3, showing a normal distribution in both sexes. The mean body height were 177.4 cm (SD±6.8cm) for male subjects and 164.1cm (SD±6.2cm) for female subjects.

Table 1 presents the baseline characteristics of the entire study population by four categories (quartiles) of body height measured at baseline in both sexes. Subjects of the fourth quartile (Q4) were younger of age (41.4, SD±11.4 vs 50.6, SD±15.2 in men, and 40.4, SD±10.8 vs 52.3, SD±16.6 in women), exercised strenuous more often (37.8% vs 30.0% for men, and 29.1% vs 17.5% for women) and were on average of higher education levels (45.4% vs 24.0% in men, and 46.2% vs 19.2% in women) than subjects of the lowest quartile (Q1) (Table 1). In men, the tallest subjects (Q4) smoked less than the shortest ones (32.7% vs 37.1%). The BMI was almost equal in the quartiles of men, and decreased narrowly by quartiles of women (Q1 25.7, SD±4.6 vs Q4 24.0, SD±3.9).

During a median follow-up of 17.6 years, 3145 subjects were diagnosed with incident cancer. The crude incidence rate (IR) of cancer were 8.03 (95% CI 7.75-8.31) per 1000 person-years in the total cohort, with IRs stratified by sex of 8.79 (95% CI, 6.98-7.72) per 1000 person-years in men and 7.34 (95% CI 8.37-9.22) per 1000 person-years in women.

The IRs and age-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for cancer risk by quartiles of body height are presented in Table 2, for men and women, respectively. In men, the IRs decreased by the increase in quartiles of body height, raging from 11.10 (95% CI 10.23-12.05) in Q1 to 6.87 (95% CI 6.12-7.72) in Q4. A tendency towards an increased cancer risk per increase in height quartiles of men was found. The risk of cancer was 23% higher (HR 1.23, 95% CI 1.06-1.43) for the tallest men (≥182cm (Q4)), when compared to men ≤173 cm (Q1). Further adjustments of the cox model by education level and exercise did not alter the risk estimates in men (table 2), and additional adjustments for daily smoking did not alter the risk estimates in the multi-adjusted model (data not shown). In women, the IRs were highest in the two lower quartiles (Q1-Q2) and decreased almost

equally in the two upper quartiles (Q3-Q4). The risk increased for subjects in Q2, were lower in Q3 when compared to Q2, and finally the risk of cancer were 34% higher (HR 1.34, 95% CI 1-15-1.56) for women ≥168 cm (Q4) than women ≤160 cm (Q1). The multi-adjusted model showed a slightly modified increase in cancer risk with an increase in all HRs in Q2-Q4. Further adjustments for daily smoking did not alter the risk estimates in the multi-adjusted model (data not shown).

Table 3 presents the risk of cancer by categories of BMI separated by sex. For both men and women, there were few subjects contributing to the upper BMI-category, and further, few cases when compared to the other BMI-categories. In men, the risk of cancer showed a tendency towards a decreased risk in subjects being overweight (BMI ≥25<30), although did not display significant risk estimates. In obese men (BMI ≥30), the risk increased by 28% (HR 1.28, 95%CI 1.10-1.49). In women, BMI displayed no significant risk estimates and no trend towards an increased risk by increasing BMI was found.

We also investigated the effect of body height and BMI on cancer risk (table 4). Male subjects of the obese category (BMI ≥30) showed a tendency towards an increased cancer risk through all categories of height (Q1-Q4). In women, no clear trend was found. Further, we investigated the combined effect of body height and BMI on cancer risk. No biological or positive interaction was found (RERI -0.07, 95% CI -0.61-0.48 and AP -0.05, 95% CI -0.51-0.40 in men, and RERI 0.03, 95% CI -0.47-0.54 and AP 0.03, 95% CI -0.43-0.49 in women).

Figure 1 presents the distribution of cancer by cancer site in the total population. Prostate, colorectal, breast and lung cancer were the most frequent occurring cancers. The distribution of cancers by sex are presented in Figure 2. Prostate, colorectal, lung and urological cancer were the most common cancer sites in men. In women, breast, colorectal, gynecological and lung cancer dominated the distribution of cancer site frequency.

Table 5 presents the cancer risk per 10cm increase in height for total cancer and 11 different cancer sites by sex. The HR for total cancer risk increased with 11% (HR 1.11, 95% CI 1.03-1.20) in men and 19% (HR 1.19, 95% 1.09-1.30) in women per 10cm increase in height. The separate analysis for the different cancer sites lacked statistical power, but a trend of increased risk was present for several sites, especially upper GI, pancreas and urinary tract in both men and women. Additionally, the risk of colorectal and gynecological cancers showed a tendency towards an increased risk per each additional 10cm in height in women, and an increased risk of cancers of the central nerve system (CNS) in men.

4. Discussion

In this thesis, we found that both men and women have an increased risk of cancer by increase in body height by quartiles and per additional 10 cm in stature. The risk of different cancers did not reach statistical significance, but showed a tendency towards an increased risk per 10 cm increase in body height for several cancers (i.e. upper GI, pancreas, urinary tract and CNS cancers in both sexes, CNS cancers in men and colorectal and gynecological in women). High BMI did not increase the risk of cancer in women, however, an increased cancer risk was seen in obese men. No association was found when investigating the interaction between body height and BMI on cancer risk. Our results indicate that body height itself is a risk factor of more importance than BMI for cancer, especially in women.

Since the increased cancer risk by increasing body height is well established, it was no surprise to us that our findings on the association between body height and total cancer risk in the population of the Tromsø municipality, confirmed what previous studies have found (67-74, 87), and giving a clear answer to what we hypothesized and aimed to investigate. We also observed an increased trend for some cancer sites, which correlates with previous findings, i.e. for CNS cancers in men (124), cancers of the urinary tract (69, 94, 125, 126), colorectal cancer in women (69, 94, 101, 127), and gynecological cancers (73, 94, 111, 112). However, surprisingly, no trend of an increased risk by height was found for colorectal cancer in men and breast cancer in women, were other epidemiological studies have confirmed these associations for years (69, 94, 96-99). We speculated whether this could be due to the younger population in our cohort, compared to other studies in addition to few cases in the subgroup analyses. The mean age of men and women in our study was approximately 45 years old, and vary from 47 to 68 years is other studies (69, 94, 96-99). There were also few obese subjects compared to normal weight.

Further, we failed to confirm that obesity increases cancer risk. Other studies have consistently demonstrated an association between BMI and cancer (56, 61-63), but our results did not point in the same direction, except from obese men. Finally, we were interested in the role of biological interaction between body height and BMI, but as BMI did not display an increased cancer risk in women and no great effect in men in our study, the results (RERI and AP) showed no positive interaction. Body height and BMI might display a

biological interaction in studies where BMI increases cancer risk, which would be interesting to investigate.

The underlying mechanisms of height in cancer is debated and argued to be related to several biological cursors (70, 88, 89). A tall stature, meaning more cells, equals a larger amount of neoplastic origins, however, the growth of height affected by genes and hormones has been proposed as potential explanations for the association between height and malignancy (91-93). Our study does not contribute in a large amount to a further understanding in the underlying mechanisms, and thus, we continue speculating and further studies are needed to gain knowledge on this field. In the future, body height might have clinical implication for cancer detection, but it is unlikely that it would affect targeting treatment.

The main strengths of our study are its prospective study design, the large number of participants which were recruited from the general population, the long follow-up time of the cohort, the high attendance rates of each survey, the measurements of body height and weight and the assessment of cancer. Measuring of the exposure (body height) has been reported to have great importance when studying cancer risk (128). In a study by Park et al., the self-reported height did not show statistical significance on cancer risk, but the measured height did (128).

However, our study has some limitations. First, the variables of physical activity, smoking and socioeconomic status are all self-reported and thus might be misclassified. Second, we did not have information on i.e. diet, alcohol consumption, use of hormones and other risk factors for cancer that might vary between quartiles of body height, causing a potential residual confounding. Third, we lacked statistical power in the subgroup-analysis, i.e. for specific cancer sites and in the combined categories of body height and BMI.

5. Conclusion

We conclude that people of tall stature have a greater risk of cancer, and that the risk of cancer increases by each 10 cm increase in body height. Further, our study showed no biological interaction between body height and BMI on cancer risk, which might be due to the fact that we failed to confirm the same trend as other studies has reported regarding BMI and cancer. More studies are needed to conclude whether body height and BMI interact on more than an additive scale on cancer risk.

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7. Tables and figures

Table 1. Baseline characteristics by quartiles of height in the Tromsø Study

Characteristics at recruitment	Body height quartiles*				All participants
	Q1	Q2	Q3	Q4	
Men	**n=3954**	**n=3104**	**n=3699**	**n=3173**	**n=13930**
Mean age, years (SD)	50.6 (15.2)	46.8 (13.7)	44.0 (12.6)	41.4 (11.4)	45.9 (13.8)
Education level of college or university, n (%)	951 (24.0)	946 (30.5)	1414 (38.2)	1439 (45.4)	4750 (34.1)
Body-mass index, mean (SD)	25.9 (3.4)	25.9 (3.5)	25.8 (3.5)	25.5 (3.4)	25.8 (3.4)
Strenuous exercise, n (%) once a week or more	1188 (30.0)	1045 (33.7)	1368 (37.0)	1199 (37.8)	4800 (34.5)
Current smokers, n (%)	1468 (37.1)	1113 (35.6)	1280 (34.6)	1039 (32.7)	4900 (35.2)
Women	**n=4382**	**n=3646**	**n=3389**	**n=3703**	**n=15120**
Mean age, years (SD)	52.3 (16.6)	46.3 (14.4)	43.6 (13.1)	40.4 (10.8)	46.0 (14.8)
Education level of college or university, n (%)	840 (19.2)	1063 (29.2)	1229 (36.3)	1710 (46.2)	4842 (32.0)
Body-mass index, mean (SD)	25.7 (4.6)	24.9 (4.2)	24.6 (4.2)	24.0 (3.9)	24.9 (4.3)
Strenuous exercise, n (%) once a week or more	765 (17.5)	761 (20.9)	882 (26.0)	1079 (29.1)	3487 (22.6)
Current smokers, n (%)	1504 (34.3)	1358 (37.2)	1233 (36.4)	1309 (35.3)	5404 (35.7)

* Men and women were categorized according to quartiles (Q) of body height, giving Q1: ≤173 cm, Q2: >173-177 cm, Q3: >177-182 cm, Q4: ≥182 cm for men and Q1: ≤160 cm, Q2: >160-164 cm, Q3: >164-168 cm, Q4: ≥168 cm for women.

Table 2. Crude incidence rates (IRs), harzard ratios (HRs) and 95% confidence intervals (CIs) for total cancer incidence, by categories of measures body height in men and women

Body height by quartiles	N	Incident cancers	IR (95% CI)	HR (95% CI)†	HR (95% CI) ‡
Men					
≤173 cm	3954	568	11.10 (10.23-12.05)	Ref.	Ref.
>173-177 cm	3104	379	9.10 (8.22-10.06)	1.02 (0.89-1.16)	1.02 (0.89-1.17)
>177-182 cm	3699	392	7.77 (7.04-8.58)	1.11 (0.97-1.27)	1.11 (0.97-1.27)
≥182cm	3173	289	6.87 (6.12-7.72)	1.23 (1.06-1.43)	1.22 (1.04-1.42)
Women					
≤160 cm	4382	498	8.35 (7.65-9.12)	Ref.	Ref.
>160-164 cm	3646	416	8.25 (7.49-9.08)	1.28 (1.12-1.46)	1.31 (1.15-1.50)
>164-168 cm	3389	291	6.20 (5.53-6.96)	1.10 (0.95-1.28)	1.14 (0.98-1.32)
≥168 cm	3703	312	6.29 (5.63-7.03)	1.34 (1.15-1.56)	1.39 (1.18-1.61)

N, number of subjects; CI, confidence intervals; IR, incident rates

† Age adjusted

‡ Adjusted for age, education level and strenuous exercise once a week or more

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer by categories of body mass index (BMI) in men and women

BMI categories	Men			Women		
	N	Incident cancers	HR (95% CI)*	N	Incident cancers	HR (95% CI)*
BMI <25	6131	658	Ref.	8887	825	Ref
BMI ≥25<30	6282	748	0.93 (0.83-1.03)	4457	465	0.86 (0.77-0.97)
BMI ≥30	1517	222	1.28 (1.10-1.49)	1776	227	1.01 (0.87-1.17)

N, number of subjects; CI, confidence intervals;
* Age adjusted

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer by categories of measures body height and BMI in men and women

	Men		Women	
Quartiles of body height	**Incident cancers**	**HR (95% CI)***	**Incident cancers**	**HR (95% CI)***
Q1				
BMI <25	239	Ref.	251	Ref.
BMI ≥25<30	250	0.79 (0.66-0.94)	152	0.70 (0.57-0.86)
BMI ≥30	79	1.25 (0.97-1.61)	95	0.88 (0.70-1.12)
Q2				
BMI <25	146	0.88 (0.72-1.09)	207	1.08 (0.89-1.30)
BMI ≥25<30	182	0.91 (0.75-1.10)	139	1.07 (0.87-1.32)
BMI ≥30	51	1.26 (0.93-1.71)	70	1.31 (1.01-1.72)
Q3				
BMI <25	157	1.01 (0.82-1.24)	163	0.96 (0.78-1.17)
BMI ≥25<30	177	0.96 (0.79-1.67)	90	0.91 (0.72-1.16)
BMI ≥30	58	1.29 (0.97-1.72)	38	1.05 (0.75-1.48)
Q4				
BMI <25	116	1.07 (0.85-1.34)	207	1.19 (0.98-1.44)
BMI ≥25<30	139	1.16 (0.94-1.41)	84	1.14 (0.89-1.46)
BMI ≥30	34	1.25 (0.87-1.79)	24	1.09 (0.72-1.67)

BMI, body mass index; CI, confidence intervals; IR, incident rates

Quartiles (Q) of body height; Q1: ≤173 cm, Q2: >173-177 cm, Q3: >177-182 cm, Q4: ≥182 cm for men and Q1: ≤160 cm, Q2: >160-164 cm, Q3: >164-168 cm, Q4: ≥168 cm for women.

* Age adjusted

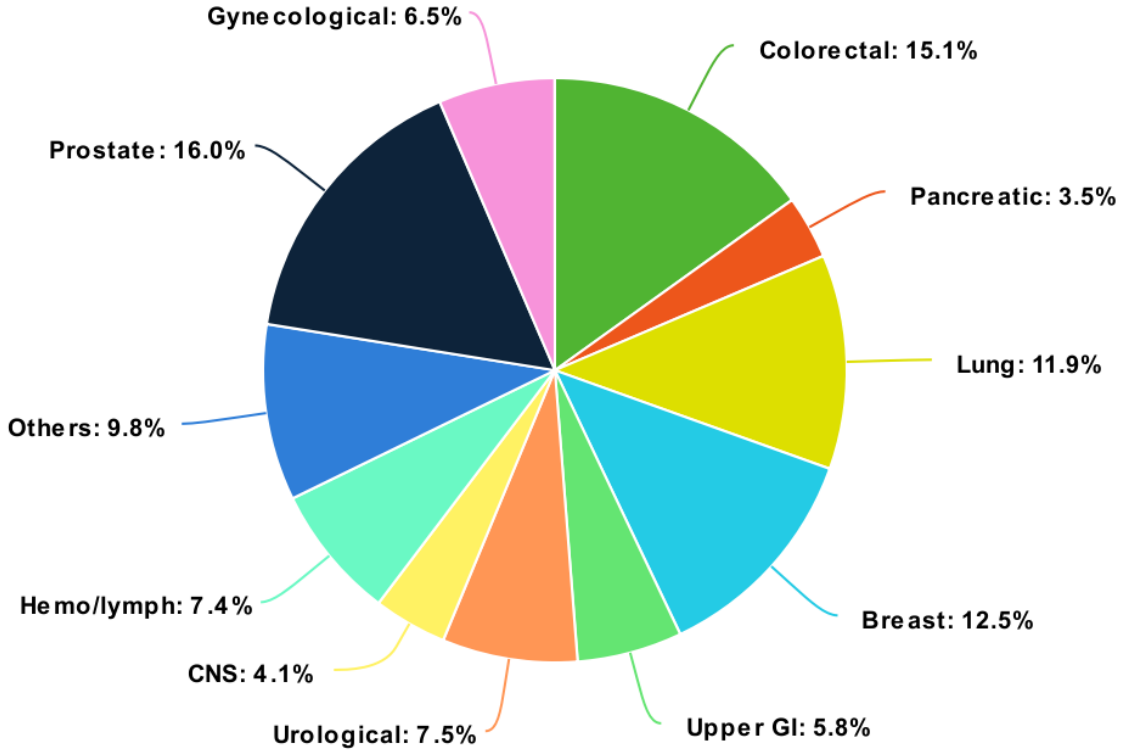
Table 5. Hazard ratios (HRs) and 95% confidence intervals (CIs) per 10 cm increase in height, for incident cancers at 11 different sites and for total cancer in men and women

Cancer	Men		Women	
	Number of incident cancers	HR (95% CI)	Number of incident cancers	HR (95% CI)
Upper GI	106	1.20 (0.89-1.60)	77	1.20 (0.90-1.60)
Colorectal	251	1.00 (0.81-1.21)	224	1.11 (0.87-1.42)
Lung	218	0.98 (0.78-1.24)	155	0.81 (0.60-1.08)
Pancreas	49	1.22 (0.72-2.06)	61	1.22 (0.78-1.91)
Urinary tract	174	1.10 (0.87-1.39)	62	1.14 (0.70-1.87)
Lymph- and hematological	124	1.05 (0.79-1.40)	110	0.75 (0.51-1.11)
Breast	NA	NA	390	0.98 (0.81-1.17)
Gynecological	NA	NA	203	1.14 (0.90-1.47)
CNS	65	1.13 (0.72-1.79)	63	0.89 (0.52-1.49)
Prostate	503	1.05 (0.91-1.22)	NA	NA
Other and unspecified*	137	1.01 (0.77-1.31)	170	1.12 (0.86-1.45)
Total	**13912**	**1.11 (1.03-1.20)**	**15113**	**1.19 (1.09-1.30)**

NA, not applicable; CNS, central nerve system.

* Ear, nose and throat cancers, melanomas, endocrine cancers, sarcomas and unknown cancer site.

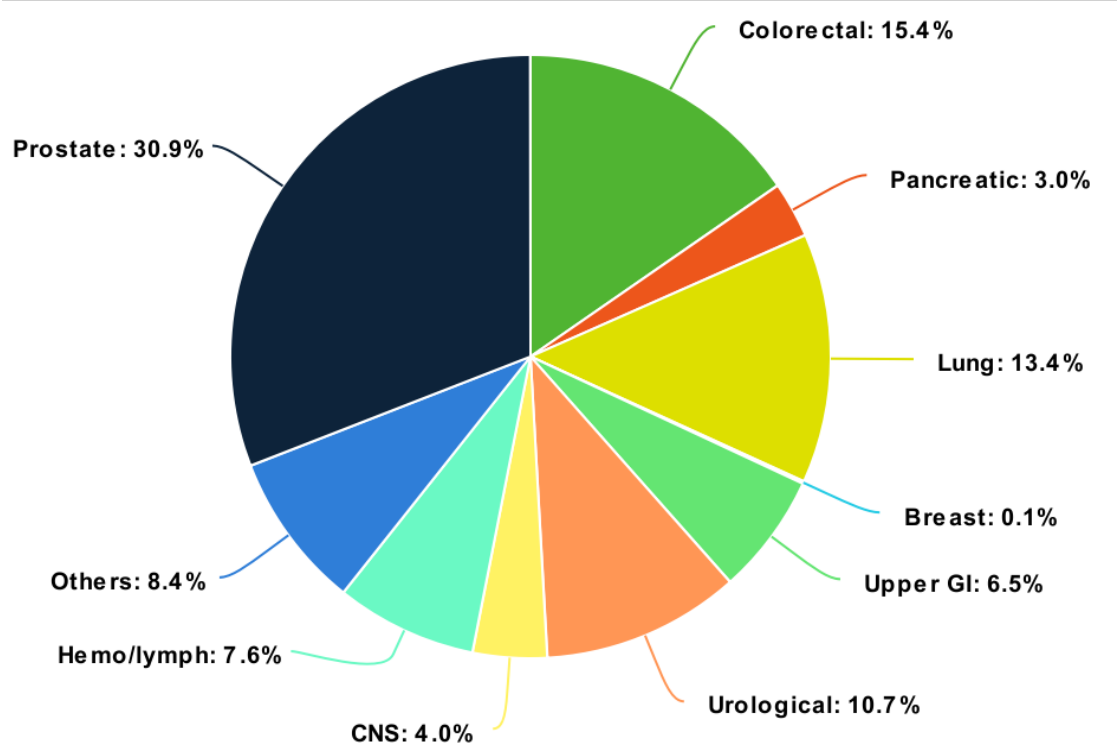
Figure 1. Distribution of cancer by cancer site in the total population: The Tromsø Study



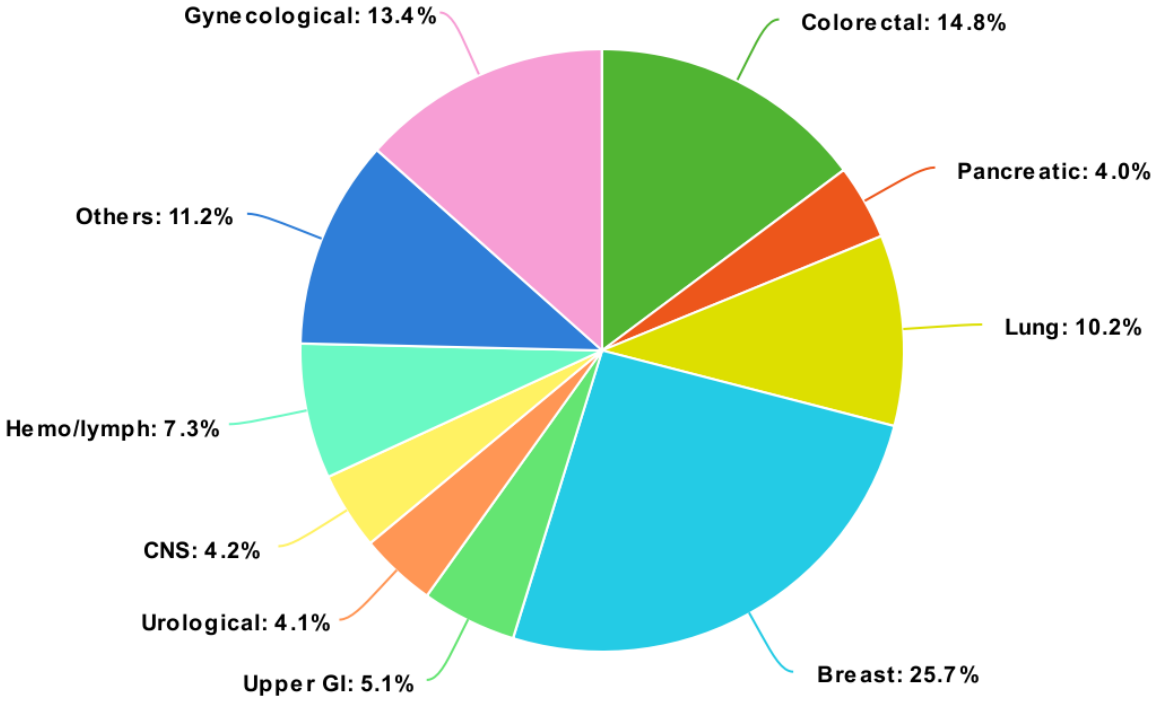
«Others» indicating ear, nose and throat cancers, melanomas, endocrine cancers, sarcomas and unknown cancer site.

Figure 2. The distribution of cancer by cancer site in men and women: The Tromsø Study

Men



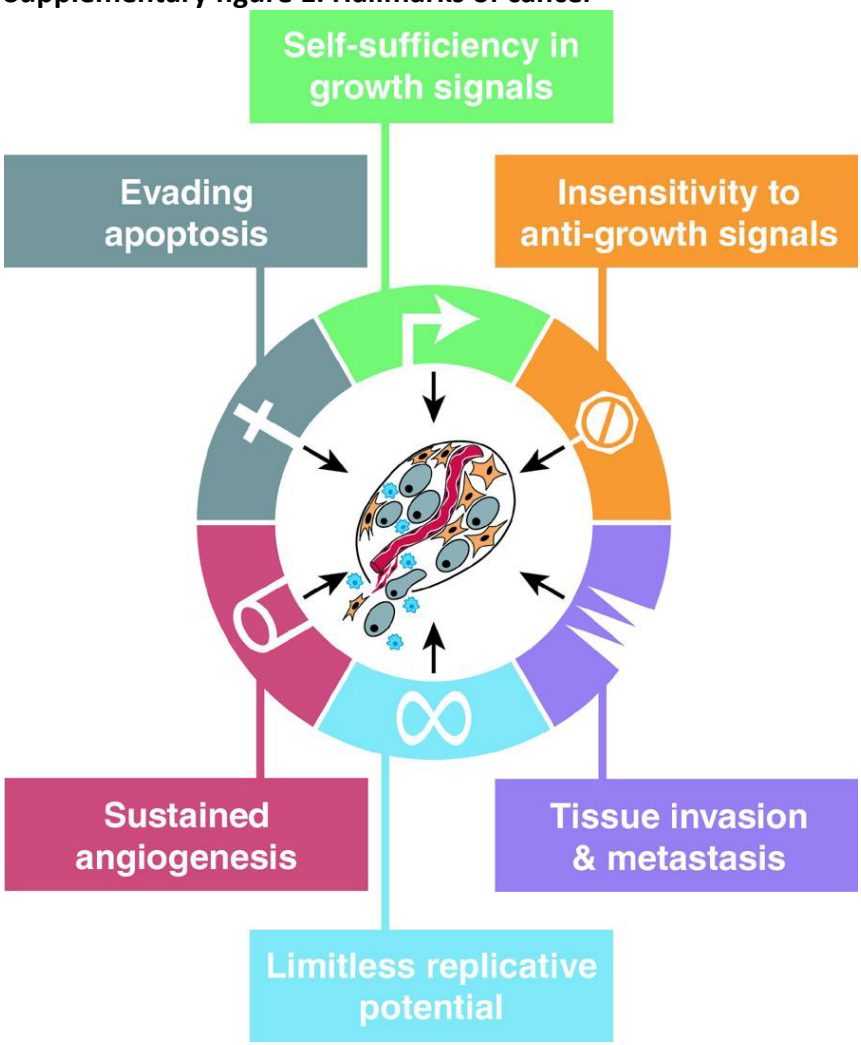
Women



«Others» indicating ear, nose and throat cancers, melanomas, endocrine cancers, sarcomas and unknown cancer site.

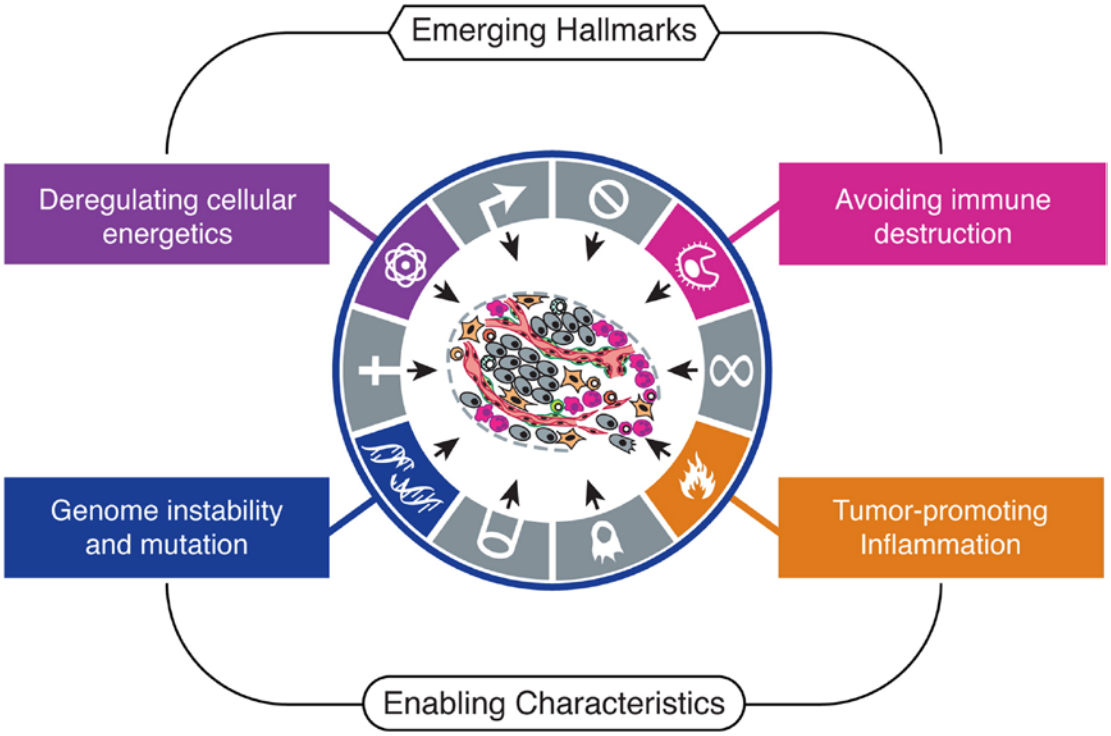
8. Supplementary

Supplementary figure 1. Hallmarks of cancer



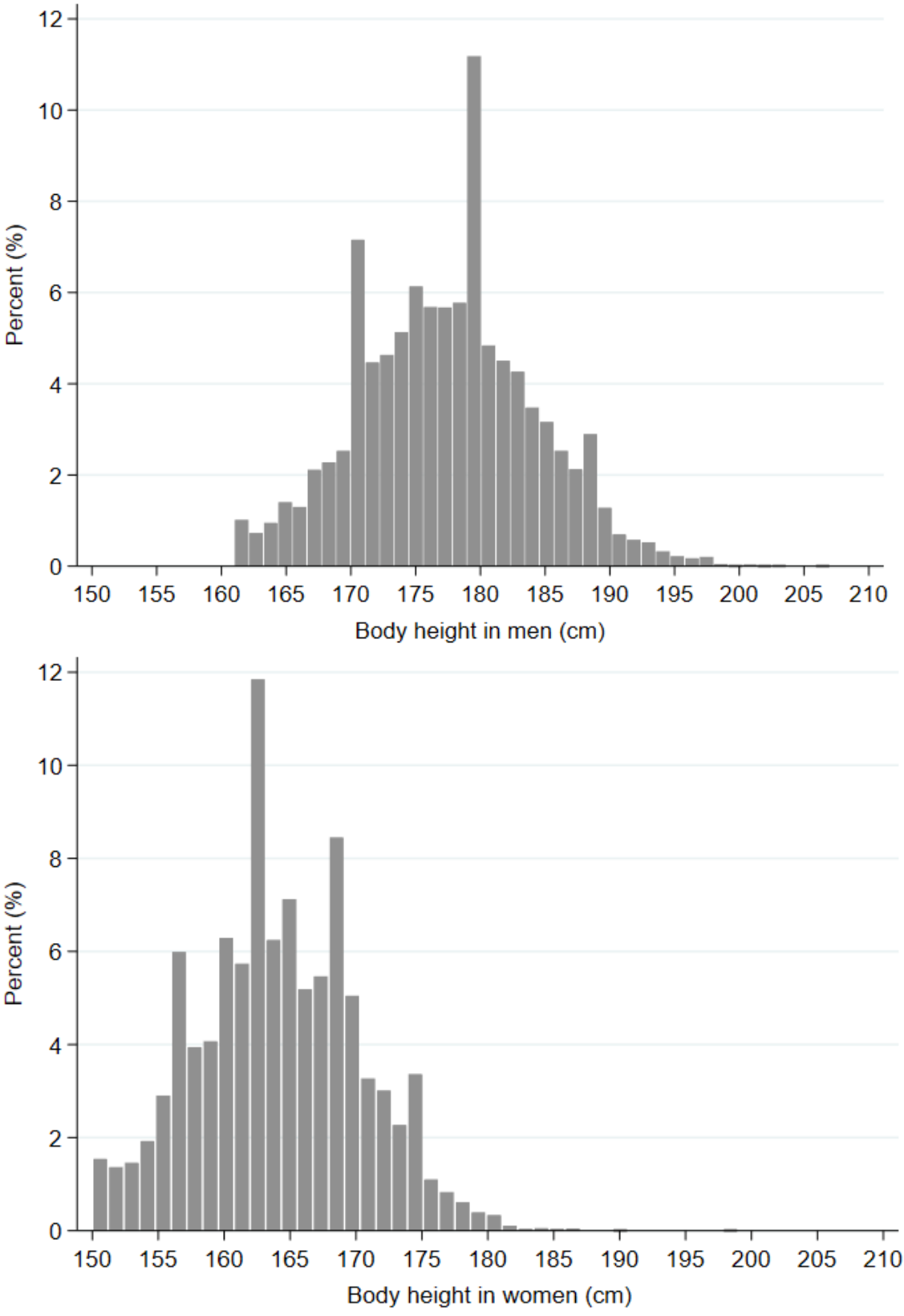
Most cancer cells aquire these properties during their development, typically by mutations in the relevant genes.
(From Hanahan D, Weinberg RA: The hallmarks of cancer. Cell, 2000)

Supplementary figure 2. Hallmarks of cancer: The next generation



Four new hallmarks of cancer added to the original figure (Supplementary figure 1).
(From Hanahan D, Weinberg RA: Hallmarks of cancer: The next generation. Cell, 2011)

Supplementary figure 3. The distribution of subjects (%) by measured body height (cm) in men and women



9. GRADE Tables

Reference:
Stenehjem JS, Veierod MB, Nilsen LT, Ghiasvand R, Johnsen B, Grimsrud TK, et al. Anthropometric factors and cutaneous melanoma: Prospective data from the population-based Janus Cohort. Int J Cancer. 2018;142(4):681-90.

Study design: Population-based cohort	
Level of evidence	**IIb**
GRADE	**B**

Aim	Material and Methods	Results	Discussion/Comments
Examine the risk of cutaneous melanoma (CM) adjusted for UVR indicators, according to measured BMI, body surface area (BSA), height, weight and weight change. **Conclusion** BMI, BSA, height and weight are positively associated with CM in males, an exponential increased risk. The first study to report that men may benefit from weight loss in order to decrease CM risk. In women, dose-response associations for CM risk were found with BSA and height. **Country** Norway **Year Data Collection** 1972-1973, 1974-1978, 1977-1983, 1985-1988, 1981-1999, 1985-1999, 2001-2003	**Data foundation:** The Janus serum bank cohort. **Exclusion criteria:** CM not histologically verified, irregular vital status, CM diagnosed pre-baseline, death or emigration, missing residence, no additional weight measurement, CM during weight change assessment period. **Data material:** 291 602 individuals available for analysis of CM risk after exclusions, in relation to BMI, BSA, weight and height. Five surveys between 1972 and 2003. Baseline was defined as the year of the second weight measurement conducted between 1985 and 1988. End of follow-up December 31, 2014. **Information collection:** Data from health examinations, measured anthropometry, questionnaires. Linkage to the Cancer Registry of Norway and Norwegian National Population Register. **Exposure:** BMI, BSA, weight and body height. **Outcome:** First incident CM diagnosis. **Validation of exposure and outcome:** Measured height to the nearest cm, weight to the nearest 0,5kg, BMI and BSA calculated. CM identified by linkage to different registries (see above). **Confounders:** Hormone use, was not considered in the analyses. **Statistical methods:** Linear trends across categories in regression models. Proportional-hazards assumption was evaluated by Schoenfeld residuals log-log plots. Tests for significance were two-sided, p-values of <0.05 were considered to rep. significance. Stata 14.2.	**Main findings:** 3000 first primary CM cases identifies, average age at baseline was 42 years. In men, 59% of the CMs were located on the trunk, while in women the most common location was the lower limbs. In men, CM risk increased significantly with increasing levels of BMI, BSA, height and weight (ptrends < 0.001). The exposure-response curves indicated an exponential increase in risk for all anthropometric factors. Weight loss of more than 2 kg in men was associated with a 53% lower risk (HR 0.47, 95% CI: 0.39, 0.57). In women, CM risk increased with increasing BSA (ptrend 5 0.002) and height (ptrend < 0.001). The shape of the height- CM risk curve indicated an exponential increase. In both sexes the risk of CM increased over 50% in Quintile 5 of height compared to Quintile 1. **Table** HR, 95% CI of CM according to quintiles (Q1-Q5) of height Height / Men* HR (95% CI) / Women* HR (95% CI) Per 5cm: 1.13 (1.09-1.17) / 1.18 (1.07-1.17) Q1: Ref. / Ref. Q2: 1.04 (0.90-1.21) / 1.28 (1.12-1.47) Q3: 1.24 (1.01-1.52) / 1.23 (1.06-1.43) Q4: 1.27 (1.09-1.49) / 1.25 (1.05-1.48) Q5: 1.55 (1.36-1.77) / 1.52 (1.31-1.76) p-values <0.001. * Adjusted for age (as time scale), ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education, smoking status. *Chosen to include a table showing only the exposure body height as it is the main focus of this master thesis.*	- Did the study address a clearly focused issue? Yes - Was the cohort recruited in an acceptable way? Yes - Was the exposure accurately measured to minimize bias? Yes - Was the outcome accurately measured to minimize bias? Yes - Have the authors identified all important confounding factors and taken them into account? No. Identified but not accounted for. - Was the follow up of subjects complete enough? Yes - Was the follow up of subjects long enough? Yes - Do you believe the results (using Hills criteria)? Yes - Can the results be applied to the general population? Yes - Do the results of this study fit with other available evidence? Yes - What are the implications of this study for practice? Men may benefit from weight loss in order to decrease CM risk. Further, by inspection of the BMI-CM risk curve in women, they found indications of confounding by sun tanning habits, which in turn warrants further study with meticulous UVR adjustment by use of individual and repeated UVR exposure data for an assessment of possible time-dependent effects. **Strengths:** Prospective design, long follow-up period, 3000 cases, pre-diagnostic measurements of height and weight by standardized protocol. **Limitations:** Lack of individual information on sun tanning habits and hormone use, which are potential cofounders.

Reference:
Boursi B, Haynes K, Mamtani R, Yang YX. Height as an independent anthropomorphic risk factor for colorectal cancer. Eur J Gastroenterol Hepatol. 2014;26(12):1422-7.

Study design: Nested case-control	
Level of evidence	IIIb
GRADE	C

Aim

To evaluate the association between height and colorectal cancer (CRC) using population-based medical records database, while controlling for known risk factors for CRC.

Conclusion

Increasing height is an independent risk factor for CRC in both men and women. Major risk scores for CRC currently do not include height as part of their nomogram, and only one model in the Korean population include height as a risk factor in women. If confirmed, height should be included in future risk score models for both sexes.

Country

United Kingdom (UK)

Year Data Collection

1995-2013

Material and Methods

Data foundation: Nested case-control study using The Health Improvement Network (THIN), a large population-based electronic medical records database from the UK.

Information collection:
Medical records on approximately 10 million patients treated by general practitioners. Each medical diagnosis is defined using Read diagnostic codes.

Exclusion criteria: History of familial CRC syndromes, inflammatory bowel disease or prevalent CRC. Missing documented height before index date. Subjects diagnosed with CRC within 183 days after initiation of the follow-up.

Cases: All individuals in the cohort that were given at least one or medical Read code for CRC during follow-up period and were more than 40 years old at the time of diagnosis.

Controls: Based on incidence density sampling. Up to four eligible controls were matched with each case in regards to age (categories of 5 years), sex, practice site, duration and calendar period follow-up.

Exposure: Body height measured pre index

Outcome: CRC

Validation of exposure and outcome:
Validated through medical records.

Confounders: Adjusted for.

Statistical methods: Multivariable conditional logistic regression to estimate the odds ratios (OR) and 95% CI.

Results

Main findings

The study included 9,978 CRC patients and 26,847 matched controls. For both men and women, univariate analysis demonstrated a significant increase in CRC risk associated with height both as a continuous variable and by quartiles (Table). The effect estimates were generally unchanged in the multivariable analysis (Table). The adjusted OR for CRC when comparing the highest height quartile to the lowest height quartile was 1.25(95%CI: 1.14-1.37) for males and 1.25 (95%CI 1.12-1.39) for females. The adjusted ORs for CRC associated for every 10cm increase in height was modestly higher for females (OR 1.16, 95%CI: 1.10-1.23) compared to males (OR 1.10, 95%CI: 1.05-1.15).

Table

Height Q= quartiles	Males Unadjusted OR (95% CI)	Males Adjusted* OR (95% CI)
Q1	Ref.	Ref
Q2	1.12 (1.03-1.22)	1.11 (1.02-1.22)
Q3	1.09 (0.99-1.19)	1.08 (0.98-1.19)
Q4	!.26 (1.15-1.38)	1.25 (1.14-1.37)
Per 10cm	1.10 (1.05-1.15)	1.10 (1.05-1.15)
Height Q = quartiles	Females Unadjusted OR (95% CI)	Females Adjusted* OR (95% CI)
Q1	Ref.	Ref.
Q2	1.08 (0.97-1.19)	1.08 (0.97-1.19)
Q3	1.29 (1.16-1.43)	1.28 (1.15-1.42)
Q4	1.25 (1.13-1.39)	1.25 (1.12-1.39)
Per 10cm	1.17 (1.10-1.23)	1.16 (1.10-1.23)

* Adjusted to diabetes mellitus, ischemic heart disease, connective tissue diseases, BMI, smoking history alcohol consumption, chronic use of Aspirin/NSAIDs, and performance of screening colonoscopy.

Discussion/Comments

- Did the study address a clearly focused issue? Yes
- Is case-control a suitable study design for this purpose? Yes
- Was the cases recruited in an acceptable way? Yes
- Was the exposure accurately measured to minimize bias? Yes, but 11 012 cases with missing height
- Was the outcome accurately measured to minimize bias? Yes
- Where there any major differences between cases and controls? No
- Have the authors identified all important confounding factors and taken them into account? Some
- Was the follow up of subjects complete enough? Yes
- Was the follow up of subjects long enough? Yes
- Do you believe the results (using Hills criteria)? Yes
- Can the results be applied to the general population? Yes
- Do the results of this study fit with other available evidence? Yes
- What are the implications of this study for practice? If confirmed, height should be included in future risk score models for CRC in both sexes.

Strengths:
Height data are prospectively recorded and less likely to be impacted by recall or self-report bias.

Limitations:
The THIN database lacks information regarding diet composition, physical activity, pre malignant adenomas, tumor location and tumor stage. The study also suffered from missing data, for example, 11 012 cases had missing data on height and were excluded from the analyses.

Reference: Kabat GC, Anderson ML, Heo M, Hosgood HD, 3rd, Kamensky V, Bea JW, et al. Adult stature and risk of cancer at different anatomic sites in a cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2013;22(8):1353-63.	**Study design: Population-based cohort**	
	Level of evidence	**IIb**
	GRADE	**C**

Aim	Material and Methods	Results	Discussion/Comments
To examine the association of height, measured at baseline as well as during follow-up, with risk of incident cancer among postmenopausal women and the possible affection by confounding and effect modification. **Conclusion** Adult height showed a modest but statistically significant positive association with risk of any cancer and with risk of melanoma, multiple myeloma, and cancers of the thyroid, ovary, rectum, breast, colo-rectum, and endometrium. **Country** United States (US) **Year Data Collection** 1993-1998	**Data foundation:** Data from the Women's Health Initiative (WHI), a large, multicenter, multifaceted study. **Exclusion criteria:** Previous history of cancer, except nonmelanoma skin cancer and those with missing information on height. **Data material:** After exclusions there were 144 701 postmenopausal women available for analysis, among whom 20 928 had one or more invasive cancer diagnoses during follow-up. In the analysis of individual cancer sites/types, if a woman had more than one cancer diagnosis, they selected the earliest. **Information collection:** At study entry, self-administered questionnaires were used to collect information on demographics, medical, reproductive, and family history, and on dietary and lifestyle factors, smoking history, alcohol consumption and physical activity. All participants had their weight, height, waist and hip circumferences measured by trained staff. **Exposure:** Height measured to the nearest 0,1cm. **Outcome:** Cancer diagnosis **Validation of exposure and outcome:** Exposure validated. Outcome validated by in-person, mailed or telephone questionnaires, and then verifies by centralized review of medical records and pathology reports. **Confounders:** Age, hormone therapy, pack-years of smoking, alcohol intake, age at menarche, weight/height^x, education, ethnicity, and study allocation. **Statistical methods:** Cox proportional hazard models with different scaling	**Main findings** Mean age and BMI decreased across increasing quin- tiles of height, whereas mean weight, MET-hours/week, pack-years of smoking, and alcohol intake increased with increasing height. Height was significantly and positively associated with risk of all cancers combined in all models adjusting for various factors. In the age-adjusted model, the HR per 10 cm increase in height with all cancer was 1.15 (95% CI, 1.12–1.17). After adjustment for all important potential confounders the HR was 1.13 (95% CI, 1.11–1.16). Similar patterns were seen in women of different age groups (50–59, 60–69, and 70–79 years) and different income levels. In age-adjusted models, height was significantly positively associated with 7 cancer sites/types (HR1: colorectum, colon, breast, endometrium, thyroid, melanoma, and multiple myeloma). Several other cancers showed borderline associations [rectum, kidney, brain, ovary, non-Hodgkin's lymphoma (NHL), and multiple myeloma]. After adjustment for covariates not including body weight, height was significantly associated with 9 sites/types (colorectum, colon, rectum, breast, ovary, kidney, thyroid, melanoma, and multiple myeloma). When BMI was included in the multivariable model, 9 sites/types showed statistically significant associations with height (colorectum, colon, rectum, breast, endometrium, kidney, thyroid, melanoma, and multiple myeloma). When site-specific scaling of W/H^x was used, the same 9 sites plus ovarian cancer showed significant associations with height. In addition, cancers of the brain, lung (in ever smokers), and NHL showed borderline associations.	- Did the study address a clearly focused issue? Yes - Was the cohort recruited in an acceptable way? Yes - Was the exposure accurately measured to minimize bias? Yes - Was the outcome accurately measured to minimize bias? No - Have the authors identified all important confounding factors and taken them into account? Not all - Was the follow up of subjects complete enough? Yes - Was the follow up of subjects long enough? Yes - Do you believe the results (using Hills criteria)? Yes - Can the results be applied to the general population? Yes - Do the results of this study fit with other available evidence? Yes - What are the implications of this study for practice? Knowledge on risk factor for cancer and more specific cancer types, might be included in future risk models. **Strengths:** Prospective design, measurement of height and weight by trained staff according to protocol, the large number of incident cancer cases, the central adjudication of outcomes, detailed information collected at baseline. **Limitations:** The outcome collection by questionnaires. No men or premenopausal women included. Measurements of 2 components of height-leg length and sitting height were not available. They did not have information on all relevant confounding variables, such as risk factors for melanoma (skin color, eye color, hair color, sun exposure).

Reference:	Study design: Cohort and meta-analysis of prospective studies	
Green J, Cairns BJ, Casabonne D, Wright FL, Reeves G, Beral V, et al. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. Lancet Oncol. 2011;12(8):785-94.	**Level of evidence**	**IIa**
	GRADE	**B**

Aim	Material and Methods	Results	Discussion/Comments
Report on the relation between height and cancer incidence in a prospective cohort study of 1 million middle-aged women in the UK. We also did a meta-analysis of published results from prospective studies on the relation between height and total cancer incidence or mortality. **Conclusion** A clear and highly significant trend of increasing cancer risk with increasing height. **Country** The cohort: United Kingdom (UK) **Year Data Collection** The cohort: 1996-2001, body height measured in 2006-2009	**Data foundation:** The UK's National Health Service (NHS) Breast Screening Programme, a Million Women Study. *Meta-analysis:* Published prospective studies on adult height and risk of cancer up to April, 2011 (Medline, Embase). **Exclusion criteria:** Previous cancer. No reported height. Height <120cm or >200cm. **Data material:** *Meta-analysis:* Included studies with published age-adjusted RR and 95% CIs for total cancer per 10 cm increase in height, or with sufficient published data to allow estimation of such RRs. *Cohort*: 1297124 women, 97376 incident cancers. **Information collection:** Questionnaires, measured body height, all study participants have a unique NHS number connected to NHS registries. **Exposure:** Body height. **Outcome:** Incident invasive cancer at 17 individual sites with at least 1000 incident cases: mouth and pharynx, oesophagus, stomach, colon, rectum, pancreas, lung, malignant melanoma, breast, endometrium, ovary, kidney, bladder, central nervous system, non-Hodgkin lymphoma, multiple myeloma and leukemia. Included all other invasive cancers (the remaining ICD-10 C codes, except non-melanoma skin cancer as "other and unspecified" cancers. **Validation of exposure and outcome:** Yes. **Confounders:** Accounted for. **Statistical methods:** Cox regression models, RR.	**Main findings:** Mean age at recruitment 56.1 (SD 4.9)years. Median length of follow-up was 9.4 years per woman (IQR 8.4-10.2 years), for a total of 11.7 million person-years, during which 97376 incident cancers were notified. The RR for total cancer was of 1.16 (95% CI 1.14–1.17; p<0.0001) for every 10 cm increase in height. Risk increased for 15 of the 17 cancer sites we assessed, and was statistically significant for ten sites: colon (RR per 10 cm increase in height 1.25, 95% CI 1.19–1.30), rectum (1.14, 1.07–1.22), malignant melanoma (1.32, 1.24–1.40), breast (1.17, 1.15–1.19), endometrium (1.19, 1.13–1.24), ovary (1.17, 1.11–1.23), kidney (1.29, 1.19–1.41), CNS (1.20, 1.12–1.29), non- Hodgkin lymphoma (1.21, 1.14–1.29), and leukemia (1.26, 1.15–1.38). Breast cancer accounts for half of incident cancers in the study and the results for breast cancer therefore dominate the overall results. However, the overall RR of incident cancer in relation to height was not materially altered when breast cancer cases were excluded from our analysis (RR per 10 cm increase in height 1.15, 95% CI 1.13–1.16). *Meta-analysis:* The overall increase in RR per 10 cm greater height is 1·14 (95% CI 1·13–1·15). There was no significant heterogeneity between the results from studies in men ($I2$ for heterogeneity 0%, p=0·9) or between those in women ($I2$ for heterogeneity 31%, p=0·2), but there was a slightly lower height-associated RR in men than in women (1·10 *vs* 1·15, p for difference <0·0001). When we excluded the findings of our study, the summary RR in women was slightly reduced (summary RR per 10 cm greater height 1·13, 95% CI 1·10–1·16; $I2$ for heterogeneity 25%; p=0·2), and there was no longer significant heterogeneity between studies in men and those in women (p for difference=0·1).	- Did the study address a clearly focused issue? Yes - Was the cohort recruited in an acceptable way? Yes - Was the exposure accurately measured to minimize bias? Yes - Was the outcome accurately measured to minimize bias? Yes - Have the authors identified all important confounding factors and taken them into account? Yes - Was the follow up of subjects complete enough? Yes, over 99% of study participants - Was the follow up of subjects long enough? Yes - Do you believe the results (using Hills criteria)? Yes - Can the results be applied to the general population? Yes - Do the results of this study fit with other available evidence? Yes - What are the implications of this study for practice? The increase in adult height during the past century could thus have resulted in an increase in cancer incidence some 10–15% above that expected if population height had remained constant. This assumes, of course, that the effect of height is independent of changes in other risk factors. **Strengths:** Direct comparison across cancer site and between smokers and non-smokers. Large amount of subjects and incident cancers. Long follow-up. Measured body height. **Limitations:** Limited power to assess modification by height-related risk by factors such as age, region, socioeconomic status, alcohol intake, body-mass index, strenuous exercise, age at menarche, parity, and age at first birth. *Meta-analysis:* The findings need to be interpreted in the knowledge that other studies with relevant data might not have published their results (publication bias).

Reference:	Study design: Population-based cohort	
Park JY, Mitrou PN, Keogh RH, Luben RN, Wareham NJ, Khaw KT. Self-reported and measured anthropometric data and risk of colorectal cancer in the EPIC-Norfolk study. Int J Obes (Lond). 2012;36(1):107-18.	Level of evidence	IIb
	GRADE	C

Aim	Material and Methods	Results	Discussion/Comments
The aim of this study was to examine the association of colorectal cancer risk with anthropometric data obtained by self-report and by direct measurement from the same participants using data from the EPIC–Norfolk study. **Conclusion** Measured height, waist circumference and WHR were strongly associated with colorectal cancer risk in women, whereas any significant associations with those measures were significantly attenuated when self-reported data were used. **Country** United Kingdom (UK) **Year Data Collection** 1993-1997	**Data foundation:** Age-sex registries of general practices in UK as part of the ten-country collaborative European Prospective Investigation Into Cancer and Nutrition (EPIC). **Exclusion criteria:** History of cancer at baseline. **Data material:** 25 639 individuals (11 607 men and 14 032 women) aged between 40 and 79 years at recruitment who were residing in Norfolk, UK. Followed until 31 December, 2006. **Information collection:** Baseline health examination, measurements, blood samples, questionnaires. **Exposure:** Body height, weight, body mass index (BMI), waist, hip, waist-to-hip ratio (WHR) and chest circumference. **Outcome:** Colorectal cancer (CRC) **Validation of exposure and outcome:** Anthropometric measures by trained personnel. Outcome: Routine record linkage with cancer registration and death certification. Incident CRC cases (International Statistical Classification of Diseases and Related Health Problems (ICD) 9th Revision, 153.0–153.9, 154.0 and 154.1) were ascertained by matching all participants to the Eastern Cancer Registration and Information Centre. **Confounders:** Adjusted for age, sex, smoking, alcohol, education, exercise, family history of CRC, energy intake, folate, fiber, total meat and processed meat, intakes. Waist and hip circumference and WHR. **Statistical methods:** Cox proportional hazards models to estimate hazard ratios (HR).	**Main findings** During 11 years of follow-up period, a total of 357 CRC cases (197 male and 160 female cases, average 64 years old) were identified. Of these cancers, 238 were located in the colon and 113 were located in the rectum. In both men and women height tended to be overestimated, whereas weight, waist and hip circumference tended to be underestimated, the magnitude of over- or underestimation being greater among participants with higher BMI. Chest circumference tended to be overestimated greatly among men with lower BMI, but greatly underestimated among women with higher BMI. We also found that participants who did not respond to the self-reported questions for height and weight tended to be heavier and to have higher measured waist and hip circumference than those who responded. In men: No significant association between anthropometric variables and CRC risk. In women: significant trend of increased risk of CRC across quintiles of measured height, (>166.1 cm vs <155.8 cm, HR 1.98; 95% CI, 1.19–3.28), waist circumference (>90.5 cm vs <73.0 cm, HR 1.65; 95% CI, 0.97–2.86) and WHR (>0.844 vs <0.739, HR 2.07; 95% CI, 1.17–3.67) after multivariable adjustment. These positive trends in women were not observed using self-reported height, waist circumference and WHR. However, a significant positive association was observed between self-reported BMI and CRC risk (X29.4 vs o22.6 kg m^2, HR 1.97; 95% CI, 1.18–3.30), whereas the association with measured BMI was weaker and the HR for those in the top versus bottom quintile was nonsignificant (>29.4 vs <22.6 kg m^2, HR 1.57; 95% CI, 0.91–2.73). For chest circumference, there was no statistically significant association with CRC risk in men or women, self-reported or measured values.	- Did the study address a clearly focused issue? Yes - Was the cohort recruited in an acceptable way? Yes - Was the exposure accurately measured to minimize bias? Yes - Was the outcome accurately measured to minimize bias? Yes - Have the authors identified all important confounding factors and taken them into account? Yes - Was the follow up of subjects complete enough? Yes - Was the follow up of subjects long enough? Yes - Do you believe the results (using Hills criteria)? Yes - Can the results be applied to the general population? Yes - Do the results of this study fit with other available evidence? Yes - What are the implications of this study for practice? The association of anthropometric measures with colorectal cancer risk was more apparent with directly assessed measures compared with self-reported measures, indicating that we should measure anthropometric in the future for concrete results when assessing risk of CRC. **Strengths:** The ability to investigate a range of self-reported and measured anthropometric information in association with CRC risk. Measures done by trained nurses using a standard protocol. General homogenous population, reducing possible role of residual confounders. **Limitations:** Small number of cases, not able to explore the effect of body size on proximal, distal colon and rectal cancer separately. All body size measures were available at baseline only, making it difficult to consider the effect of any long-term changes in body size on CRC risk throughout follow-up.