UiT The Arctic University of Norway

Faculty of health sciences

Weight change and cancer

The Norwegian Women and Cancer study

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A dissertation for the degree of Philosophiae Doctor…February 2020

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Acknowledgments

To begin with, epidemiology is a complicated word to say for many people. I, together with my peers and family, have stumbled upon pronouncing the word countless of times. One can hope that I have learnt more than just the correct way of saying the subject of my thesis but at least now, my closest and I can effortlessly say EPIDEMIOLOGY.

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Marisa da Silva

Abbreviations

BMI	Body mass index
DAG	Directed acyclic graph
IARC	International Agency for Research on Cancer
NOWAC	Norwegian Women and Cancer study
PAF	Population attributable fraction
WCRF	World Cancer Research Fund
WHO	World Health Organization

Brief definitions

Adiposity	The Latin term for obesity.
Adipose tissue	Body fat, which besides being a biological repertoire for storing and releasing energy, coordinates a variety of biological processes including energy metabolism, neuroendocrine function, and immune function.
Anthropometrics	Measurements of the size of the human body: for example, weight and height.

Body weight status	An individual’s weight status, which is most commonly defined by body mass index.
Incidence	The number of new cases of a disease in a defined population within a specific period.
Incidence rate	The number of new cases that occur in a population (incidence) divided by the number of people who are at risk of getting the disease in the same period. The rate is expressed per 100 000 persons per year.

List of papers

The thesis is based on the following papers, referred to in the text by their Roman numerals.

I. da Silva M, Weiderpass E, Licaj I, Rylander C. Factors associated with high weight gain and obesity duration: the Norwegian Women and Cancer (NOWAC) study. Obesity Facts. 2018;11(5):381-92.

II. da Silva M, Weiderpass E, Licaj I, Lissner L, Rylander C. Excess body weight, weight gain and obesity-related cancer risk in women in Norway: the Norwegian Women and Cancer study. Br J Cancer. 2018;119(5):646-56.

III. da Silva M, Laaksonen MA, Lissner L, Weiderpass E, Rylander C. Cancer burden attributable to weight gain: the Norwegian Women and Cancer study. (Manuscript)

Abstract

Background: The obesity prevalence has reached pandemic dimensions. The cancer incidence has also increased worldwide, and several cancers are related to body fatness. However, there are uncertainties weather the velocity and magnitude of weight gain, independent of body fatness, increase cancer risk. Moreover, there are few studies on short-term weight gain and site-specific cancers. Thus, our aim was to study weight change over 6–7 years in relation to all and specific body fatness-related cancers in women in Norway.

Methods: We used Cox proportional hazard models and restricted cubic splines to assess weight change and subsequent cancer incidence, in the Norwegian Women and Cancer study. Further, we calculated population attributable fractions to assess the impact of weight gain on the body fatness-related cancer burden.

Results: Short-term weight gain, independent of body weight status, was associated with increased risk of all body fatness-related cancers combined, and several site-specific cancers, in a non-linear dose-response manner. Women who gained more than 10kg had a two-fold increased risk of pancreatic cancer. Moreover, stable weight could have prevented 43% of pancreatic cancers cases in women in Norway diagnosed in 1998–2015, as well as 4299 postmenopausal breast cancer cases and 2798 colorectal cancer cases.

Conclusions: Avoiding weight gain has important implications for public health interventions, as several cancers seem to be preventable through weight maintenance. Our results on pancreatic cancer are novel and of upmost importance given the poor prognosis of the disease and increased rate in women, both in Norway and worldwide.

1 Introduction

1.1 Adult body weight development

Weight gain occurs when energy intake exceeds energy expenditure. Thus, interventions that target energy intake and/or energy expenditure will modify body weight. Although modifications as such are reasonable and the mathematics of weight imbalance is sound, in practice weight control and weight loss are often the contrary. Interventions to lose weight are frequently not successful in the long term [1]. In fact, most people gain weight through their adult life, with the largest weight gain in young adulthood and a somewhat stabilisation or even decline at the end of life [2, 3]. Adult weight trajectories are dependent on the speed of accumulated weight and starting age, where early and rapid weight gain is associated with steeper trajectories and greater risks for conditions related to body fatness [2].

1.2 Definition and scale of the obesity problem

Obesity is a consequence of weight gain in fat mass, and a multifaceted condition that is associated with social and physiological distress, as well as clinically adverse health [4]. Metabolic diseases (e.g. type 2 diabetes mellitus and fatty liver disease), cardiovascular diseases (hypertension, myocardial infarction and stroke), musculoskeletal disease (osteoarthritis), Alzheimer disease, depression, and some types of cancer (see later) are all related to obesity [1]. In addition, the World Obesity Federation and other organisations have declared obesity as a chronic progressive disease on its own, and not merely a risk factor for other diseases [5, 6]. Obesity is defined as abnormal or excessive fat accumulation in adipose tissue that present health risks [4]. Individuals with obesity differ regarding the amount of fat stored and how that fat is distributed within the body. Body mass index (BMI) is the most general way to measure body fatness in populations and is constructed by taking body weight

in kg divided by the square of height in meters (kg/m^2) [7]. The index was developed in the 19th century by a Belgian mathematician, Quetelet [8], and has since been validated to predict body fatness in different age, sex and racial groups. BMI has also been demonstrated to predict disease and mortality [9-11]. The World Health Organization (WHO) has adopted BMI as a standard measure of adiposity and clinicians and individuals have since used it as a common tool to identify body weight status. BMI is categorised as underweight ($<18.5kg/m^2$), normal weight (18.5 to $<25kg/m^2$), overweight (25 to $<30kg/m^2$), and obesity ($\geq 30kg/m^2$) [12]. The golden standard "normal weight" is the range for optimal body weight in relation to health risks and not a term that defines normal weight in a population. In addition, obesity can be further categorised into three classes: obesity I (30 to $<35kg/m^2$), obesity II (35 to $<40kg/m^2$), and obesity III ($\geq 40kg/m^2$) [4].

The NCD Risk Factor Collaboration[1], have demonstrated a global increase in obesity prevalence during the past four decades, which indicates that the attempts to halt the epidemic has failed [13]. Obesity has reached pandemic dimensions that induce considerable costs to public health [14]. In 2016, there were 671 million people living with obesity, of which 390 million were women [13]. The global obesity prevalence in women in 1975 was 7, compared to 16% in 2016. Although obesity prevalence increased in all countries, regional differences in the prevalence and trends exist. In high-income western countries including Norway, the obesity prevalence in women in 1975 was 12, compared to 30% in 2016. In Norway, several

[1] The NCD Risk Factor Collaboration (NCD-RisC) is a network of health scientists around the world that provides rigorous and timely data on risk factors for non-communicable diseases (NCDs) for 200 countries and territories. The group works closely with the World Health Organisation (WHO), through the WHO Collaborating Centre on NCD Surveillance and Epidemiology at Imperial College London.

regional population studies that measure weight and height through health examination have indicated an increase in obesity prevalence, both in women and men [3, 15]. The most recently published and largest regional study of obesity prevalence in women comes from the Nord-Trøndelag Health Study (HUNT), which reported an obesity prevalence of 13% in 1984–1986 compared to 23% in 2006–2008 [15]. In addition, Statistics Norway conduct a survey on living conditions every three years in a nationally representative sample of inhabitants aged 16 years or older, with self-reported weight and height [16]. Since 1998, the self-reported prevalence of obesity has increased, in both women and men, and reached 11% in women in 2015. In addition, the Norwegian Institute of Public Health, presented unpublished data from the latest regional population study, the Tromsø Study, in Northern Norway, indicating that the prevalence of obesity has increased steadily in men and women during 20 years, from 1994–1995 to 2015–2016 (Figure 1) [17]. Although there are differences in obesity prevalence according to age, region, rural/urban settlements and reporting method (self-report or examination), the obesity prevalence is a public health concern also in Norway.

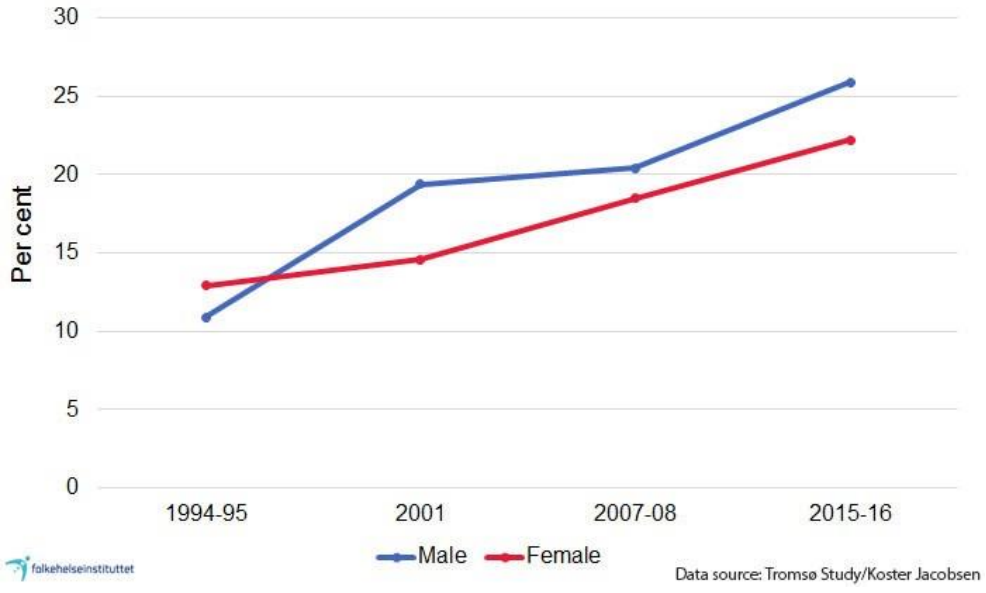

Figure 1. Obesity prevalence. The Tromsø Study. The Norwegian Institute of Public Health.

1.3 The cause of obesity

Obesity is a subject that evokes many presumptions and myths, whereby the scientific society has an important role to identify and distinguish these from knowledge built on sufficient scientific evidence [18]. Indeed, heritability play a role for the development of obesity, but there are to a greater extent environmental factors that can reduce and prevent obesity [18]. The two most commonly cited environmental risk factors of obesity, “the big two”, are food marketing practices that affect energy intake, and institutionally driven declines in physical activity that affect energy expenditure [19]. However, other behavioural, environmental, mechanistic, social-physiological, and reproductive factors may also drive the obesity epidemic. These modifiable and non-modifiable factors include among others, sleep deprivation, smoking cessation, increased use of manufactured chemicals hypothesized to disrupt endocrine function, unidentified gut microbiome mechanisms, economic disparity and insecurity, a psychological tendency towards smaller immediate rewards, and a possible increase of genotypes susceptible to obesity. Due to the numerous factors that influence obesity, the interventions to challenge the obesogenic environment has also to be multifactorial. To rely on the concept of “energy in – energy out” to describe and act upon obesity is simply not enough. The web of these factors and the unidentified interplay and order between them, impedes the construction of a theoretical framework applicable to describe the phenomena of obesity and weight imbalance. However, in an attempt to illustrate this web, the UK government constructed an obesity system map (Figure 2), with the aim to understand how to respond to rising levels of obesity in the UK [20]. The figure exemplifies the complexity of energy imbalance.

Foresight

Obesity System Map

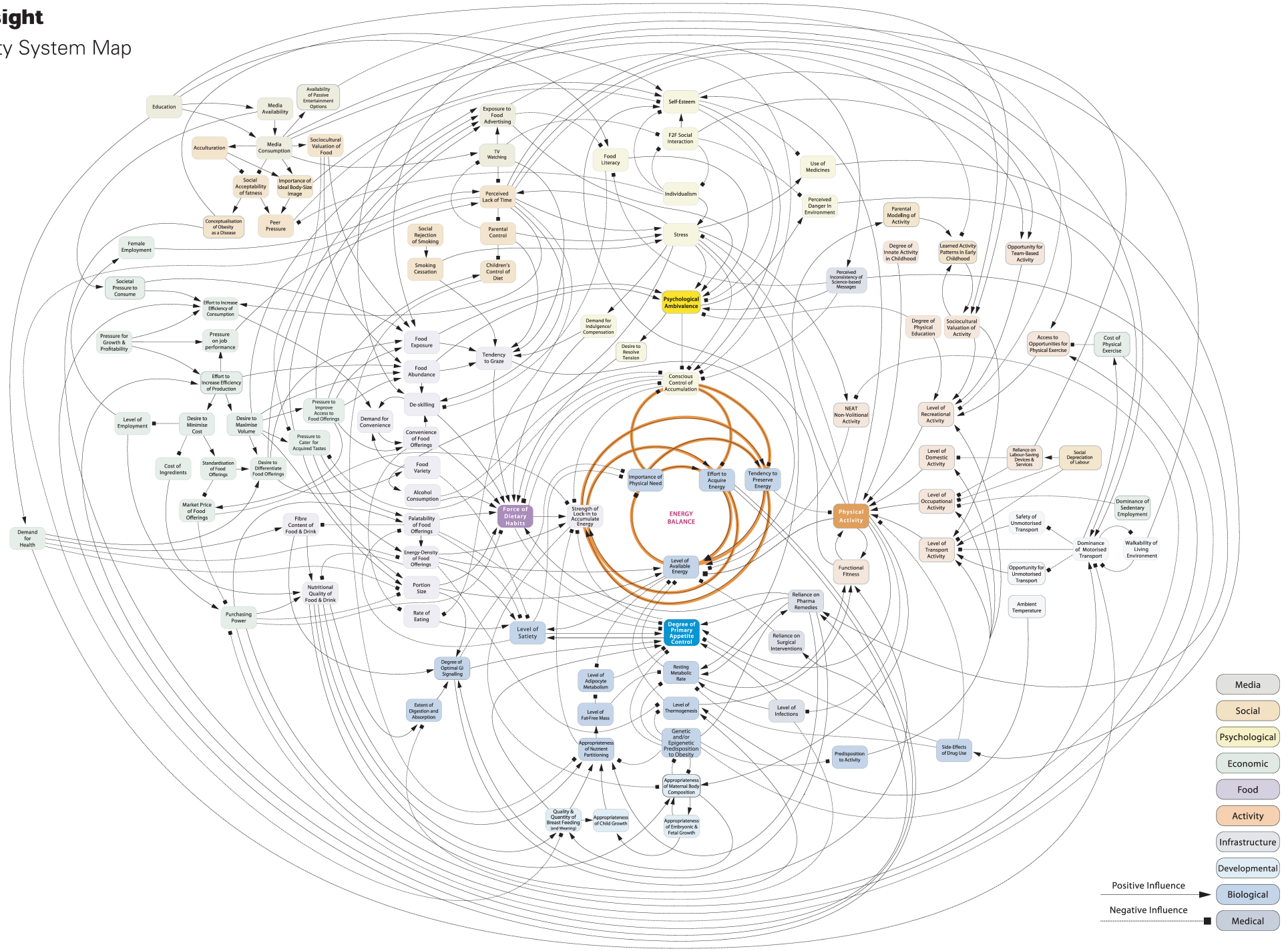

Figure 2. [Obesity system map](). Government Office for Science UK. Foresight projects.

1.4 The cancer process and burden

Cancer is a shared constellation of abnormal cell behaviours, characterised by rapid cell division, mutations, and invasion of surrounding tissue [21]. Cells have mechanisms to prevent the accumulation of such abnormalities, however, these mechanisms can also be damaged and fail to prevent the progression to cancer. In a successful attempt to facilitate the understanding of how normal cells evolve to malignant cells, Hanahan and Weinberg have provided a logical framework known as the "hallmarks of cancer" [22]. The framework consists of eight hallmark capabilities and two fundamental enabling characteristics (Figure 3). Epidemiological studies have showed that modifiable factors such as tobacco use, body fatness, and physical activity primarily determine cancer, whereas inherited genetic mutations play a major role in only 5–10% of cancer cases [21].

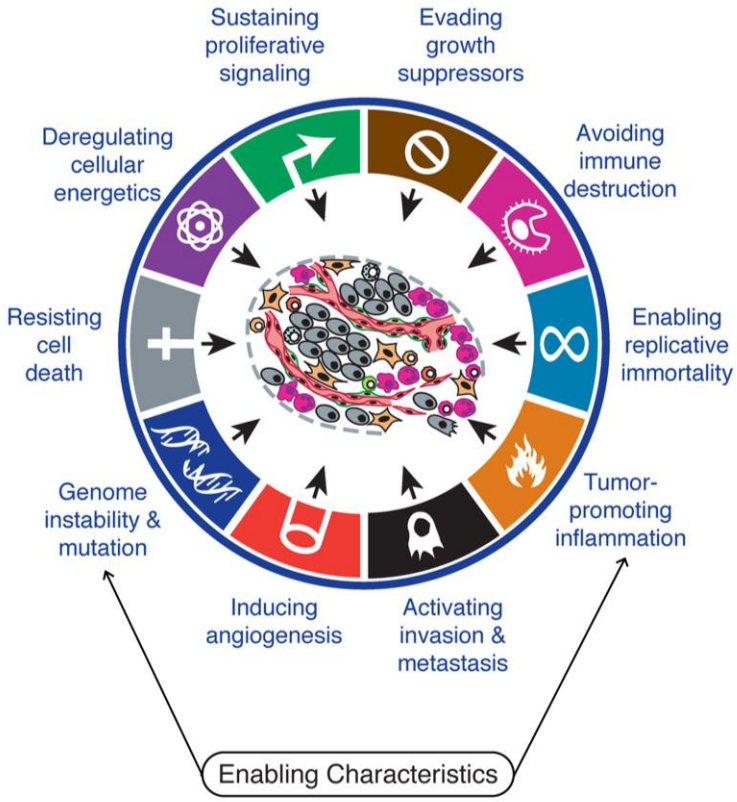

Figure 3. Hallmarks of cancer and enabling characteristics. Adapted from Cell, 144, Douglas Hanahan and Robert A. Weinberg, Hallmarks of Cancer: The Next Generation, 646-674, Copyright (2011), with permission from Elsevier.

Cancer incidence is rapidly increasing worldwide, due to aging and population growth, as well as changes in the prevalence and distribution of risk factors for cancer [23]. In 2018, there were an estimated 18.1 million incident cancer cases worldwide, of which 8.6 million occurred in women. The incidence rate in women was 183 cancer cases per 100 000 persons per year and varied almost four-fold between world regions, from 362 cancer cases per 100 000 persons per year in Australia/New Zealand to 96 cancer cases per 100 000 persons per year in South-Central Asia. Globally, the most common cancers in women were breast, colorectal, lung, cervical, and thyroid cancer. Among women in Norway in 2018, there were 15 869 incident cancer cases, with an incident rate of 311 cancer cases per 100 000 persons per year (world age-standardised) and 549 cancer cases per 100 000 persons per year (Norwegian age-standardised) [24]. The incidence rate of all cancer sites increased with 6% in women in Norway when comparing the last five-year period (2014-2018) with the previous one (2009-2013) and the most commonly diagnosed cancers were breast, colon, lung cancer, and melanoma of the skin.

1.5 Obesity and its relation to cancer

There are three main hypotheses of biological mechanisms to describe the association between obesity and cancer risk. In the setting of body fatness, (1) altered circulating levels of sex hormones, (2) increased insulin levels and higher bioavailability of insulin-like growth factor, and (3) elevated concentrations of adipokines and chronic inflammation, increase the risk of cancer development [25]. The sex hormone hypothesis applies predominately to breast, endometrial, and ovarian cancer. Suggestively, the association of body fatness with these cancers is through elevated oestrogen levels that occur from enhanced aromatisation in increased adipose tissue mass. For breast cancer, there are evidence from experimental studies that oestrogen indirectly and directly cause DNA damage, genetic instability, and mutations

in mammary tissue [26]. In addition, epidemiological studies have confirmed that increase in oestradiol levels with higher BMI largely explains the association between body fatness and postmenopausal breast cancer [27, 28].

The second hypothesis derives from evidence that circulating insulin levels correlates with increased body fatness and that many women with obesity are insulin resistant [25]. In detail, the state of elevated levels of insulin in the circulation (hyperinsulinemia) has been postulated to contribute to cancer development through two pathways; direct growth promoting signalling of elevated levels of insulin, and indirectly through higher bioavailability of insulin-like growth factor I (IGF1) [29]. Meta-analyses support the relationship between the latter pathway and the risk of prostate, colorectal and both pre- and postmenopausal breast cancer [30, 31]. However, in disfavour of this hypothesis, the therapeutic use of insulin in patients with diabetes mellitus does not increase cancer risk [31].

The third hypothesis relates to inflammatory markers. Adipose tissue is an endocrine organ, secreting hormones and other factors, collectively known as adipokines [32]. In the context of cancer, leptin (pro-inflammatory) and adiponectin (anti-inflammatory) are the most studied types of adipokines [25]. Circulating leptin concentrations are proportional to the level of body fat and is potentially relevant for cancer development through a substantial repertoire of mechanisms. In addition, body fatness is associated with a state of chronic (subclinical) inflammation [33]. However, there is inconsistency in the literature weather concentrations of leptin or chronic inflammation, increase cancer risk [25].

1.6 Body fatness-related cancer

The International Agency for Research on Cancer (IARC) has reviewed over 1000 studies, most of them observational, but also experimental in both humans and animals, and

mechanistic data. Consequently, the agency identified thirteen cancers with sufficient evidence of a positive association with body fatness (herein referred to as "body fatness-related"), including cancer of the breast (postmenopausal), colon-rectum, endometrium, ovary, pancreas, kidney, gallbladder, gastric cardia, liver, oesophagus (adenocarcinoma), meningioma, thyroid, and multiple myeloma [34]. However, the World Cancer Research Fund (WCRF) has a different list of body fatness-related cancers for which they claim there is strong evidence of increased risk by overweight and obesity throughout adulthood [35]. Their list does not include meningioma, thyroid, or multiple myeloma but instead include the cluster of mouth, pharynx, and larynx cancer and prostate cancer. Thus, there is an agreement of ten body fatness-related cancers. However, in this thesis, we will include body fatness-related cancers as per definition by IARC.

In 2012, the global fraction of body fatness-related cancer attributable to overweight and obesity was 15% in Northern Europe [36]. This implies that, given a causal relationship, 15% of body fatness-related cancer cases in Northern Europe could have been prevented, should women with overweight or obesity had had normal weight. In addition, a recent study in postmenopausal women reported that the duration of overweight and obesity was associated with greater risk of body fatness-related cancers [37]. A longer duration of obesity increased the risk of body fatness-related cancer by 10% for every 10 year with obesity. Worldwide, the most commonly diagnosed body fatness-related cancers in women are breast, colorectal, thyroid, endometrial, and ovarian cancer [23]. Below, I will briefly present the incidence and the increased risk related to higher BMI in the five most commonly diagnosed body fatness-related cancers in our study: breast, colorectal, endometrial, pancreatic, and kidney cancer.

Breast cancer is the most commonly diagnosed cancer in women, globally and in Norway [23, 24]. The risk of postmenopausal breast cancer increases with 12% per five BMI unit

increment [10]. Only postmenopausal breast cancer is associated with increased risk of body fatness.

Colorectal cancer is the second most commonly diagnosed cancer in women globally, and the third most commonly diagnosed cancer in women in Norway, after lung cancer [38, 39]. Of note, Norway has the highest incidence rate of colorectal and colon cancer in women in the world [23]. Compared to women in normal weight, women with obesity have 15% increased risk of colorectal cancer [40].

The endometrium is the lining of the uterus, and the majority of the cancers in corpus uteri are endometrial cancers [41]. Endometrial cancer is the six most commonly diagnosed cancer in women, globally and in Norway [38, 39]. The risk of endometrial cancer increases with 59% per five BMI unit increment [10]. It is the cancer with the strongest association with body fatness in a strong dose-response relationship, with 57% increased risk in overweight, more than two-fold increased risk in obesity class I, almost five-fold increased risk in obesity class II, and almost seven-fold increased risk in obesity class III [42].

Pancreatic cancer is the 12th most commonly diagnosed cancer in women in the world, and the 13th in women in Norway [38, 39]. Compared to women in normal weight, women with obesity have approximately 40% increased risk of pancreatic cancer [43]. What sets pancreatic cancer apart from many other cancers is the poor prognosis of the disease. The 5-year survival rate of pancreatic cancer in women in Norway is merely 10% [24].

Kidney cancer is the 14th most commonly diagnosed cancer in women in the world, and the 16th most commonly diagnosed cancer in women in Norway [38, 39]. Compared to women in normal weight, women with obesity have 95% increased risk of kidney cancer [44].

1.7 Weight change and its relation to cancer

There are fewer studies on weight change and cancer than there are of body weight status and cancer. In 2015, Keum and colleagues conducted a meta-analysis of weight gain and body fatness-related cancers wherein they reported that weight gain more than five kg increased the risk of postmenopausal breast cancer, endometrial, ovarian, and kidney cancer (only highest vs lowest level of weight gain) [45]. However, in the latest report from WCRF Continuous Update Project in 2018, the expert panel concluded that postmenopausal breast cancer was the only cancer for which there is evidence of an association with weight gain [35]. In addition to the meta-analysis by Keum and colleagues, a recent pooled European cohort study from last year reported that weight gain more than five kg in middle adulthood increased the risk of postmenopausal breast cancer and endometrial cancer [46].

Evidence of short-term weight gain and its effect on cancer is growing. These studies showed that short-term weight gain (four years) in pre- and postmenopausal women increased the risk of breast cancer [47, 48], while body fatness in premenopausal women decreased the risk of breast cancer [10]. The reasons for increased breast cancer risk related to the velocity in weight gain, and timing of body fatness, is not well understood.

Weight change also includes weight loss, with fewer studies than there are for weight gain and cancer, and with conflicting results [48-50]. However, two recent studies from last year demonstrated a decrease in cancer incidence in postmenopausal women following intentional weight loss, compared to women that maintained in stable weight [51, 52].

Keum and colleagues hypothesized that weight gain, as a time-integrated metric of accumulated body fatness, may be a greater predictor of cancer over BMI considering that cancer development spans over a long period [45]. On the other hand, Renehan and

colleagues concluded in a review on adiposity and cancer risk (after taking into account the meta-analysis by Keum) that it is unclear whether adult weight gain is more informative for assessing cancer risk than body weight status [25]. This as adult weight gain in most epidemiological studies are measured by using recalled weight from age 18 to cohort enrolment and correlates with enrolment BMI, which in its turn is the most used measure in BMI-cancer studies. Thus, it is not clear if weight gain is a superior measure of body fatness in relation to cancer incidence, or if the velocity and magnitude of weight gain, independent of body fatness, increase subsequent risk of cancer [53].

1.8 Aim

The aim of this thesis was to study weight change and its relation to all and specific body fatness-related cancers in middle-aged women in Norway. We studied both body weight status and weight change in order to investigate the role of weight change beyond that of body weight status.

Specific aims:

- Identify factors associated with body weight status and weight change (Paper I)
- Estimate the association of body weight status and weight change with all and specific body fatness-related cancers (Paper II)
- Estimate the fraction of all and specific body fatness-related cancers attributable to weight change (Paper III)

2 Material and methods

2.1 The Norwegian Women and Cancer study

The Norwegian Women and Cancer (NOWAC) study is a nationally representative prospective cohort, initiated in 1991 to investigate the aetiology of cancer [54]. The preliminary aim of the NOWAC study was to explore the hypothesis of oral contraceptives as a risk factor for breast cancer, in order to confirm or refute the results from earlier case-control studies, indicating that oral contraceptives increased breast cancer risk [55, 56]. Subsequently, prospective results from the NOWAC study confirmed the elevated breast cancer risk due to oral contraceptive use [57]. In addition, research from the NOWAC study have published results on diet, lifestyle, sun exposure, and socioeconomic gradients in relation to cancer. NOWAC also includes a post-genome cohort with collected blood samples allowing for molecular epidemiological studies related to cancer and relevant risk factors.

The NOWAC cohort constitutes of ~170 000 women who were randomly sampled from the National Registry and were mailed invitations to answer consecutive questionnaires. The comprehensive questionnaire included questions on anthropometrics, sociodemographic, lifestyle, and reproductive factors. Women aged 30–70 years were enrolled in separate waves of recruitment: 1991–92, 1996–97, and 2003–2005. The response rate in the NOWAC study varied between 48 and 57% at enrolment and 81% in the second questionnaire. The unique personal identity number assigned to every resident in Norway allowed for complete follow-up information on death, migration and cancer diagnosis through linkages to national registries [58]. The external validity in NOWAC is considered as high. The performed validation study showed that the distribution of exposures was independent of the response rate, i.e. there were no substantial differences in e.g. education, parity, and life-style factors

between responders and non-responders [59]. Moreover, the observed incidence rates for all cancer sites corresponded well to the national incidence rates in 2014 provided by the Cancer Registry of Norway (Figure 4) [54].

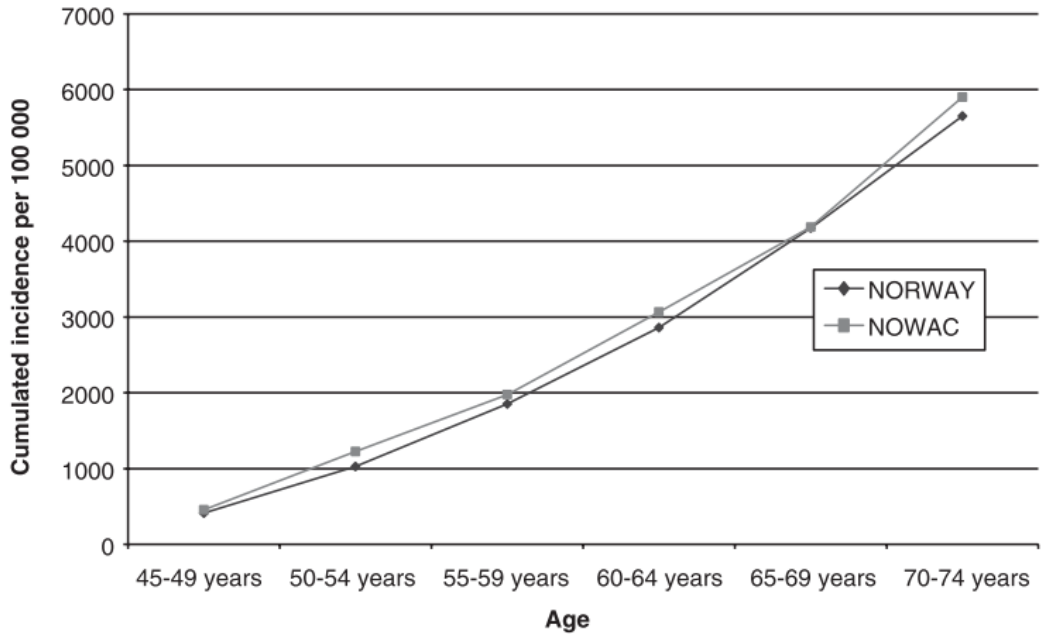

Figure 4. Age-specific cumulated incidence rates of all cancers 2004. The NOWAC study and national figures.

2.2 Study samples and design

All three papers included in this thesis were prospective cohort studies with separate study samples that we extracted from the NOWAC study. The cohort includes several waves of recruitment and consecutive surveys, and the development of study designs and statistical analyses in the included papers were dependent on number of questionnaires and follow-up time. In the body fatness-related cancer analysis in Paper II and Paper III, follow-up began at the time of the latest returned questionnaire. Women were followed-up until cancer diagnosis, death, emigration or the end of study, whichever occurred first. We identified cancer

diagnosis, death and emigration through linkage to the Cancer Registry of Norway, the Cause of Death Registry, and the National Registry of Norway.

In Paper I, we identified factors associated with high weight gain and duration of obesity. 89 749 women who returned an enrolment questionnaire between 1991 and 2005 and a second questionnaire 5–8 years later, were considered eligible for inclusion in the weight change analysis. Of these, 47 526 additionally returned a third questionnaire, 5–8 years after the second questionnaire, and were considered eligible for inclusion in the duration analysis. After exclusion of implausible and missing values of height and weight and missing information on important covariates, the weight change subsample included 60 911 women and the duration analysis subsample included 34 453 women.

In Paper II, we assessed BMI status and weight change and subsequent body fatness-related cancer. 145 658 women who returned an enrolment questionnaire between 1991 and 2005, were considered eligible for inclusion. We excluded women who had emigrated or died before the enrolment questionnaire was registered in the study database or were diagnosed with cancer (other than non-melanoma skin cancer) prior to enrolment and had less than 2 years of follow-up. Women with implausible and missing values of weight and height and implausible values of age at menopause were also excluded. After exclusions, 135 708 women were included in the BMI analysis subsample. In the weight change analysis, we additionally excluded women who did not return a second questionnaire, hence, 80 930 women were included in the subsample. In the site-specific analyses, we performed further exclusions; we excluded premenopausal women in the postmenopausal breast cancer analysis, women who reported hysterectomy in the endometrial cancer analysis, and women who reported bilateral oophorectomy in the ovarian cancer analysis. Follow-up in the BMI analysis began at the time of the registered enrolment questionnaire, while in the weight change

analysis follow-up began at the time of the second questionnaire. End of study was 31 December 2014. As we included all three waves of recruitment, the study follow-up time varied between 10–25 years in the BMI analysis, and between 4–17 years in the weight change analysis. Figure 5, and Figure 6, illustrates the study design in each analysis, respectively.

In Paper III, we calculated the fraction of the body fatness-related cancer burden, attributable to weight gain. 46 960 women who returned an enrolment questionnaire from the first wave of recruitment in 1991–1992 and a second questionnaire in 1998, were eligible for inclusion. We excluded women who had emigrated or died before the second questionnaire was registered in the study database or were diagnosed with cancer (other than non-melanoma skin cancer) prior to the second questionnaire, had missing weight values or implausible values of weight, height, or age at menopause. After exclusions, 44 114 women were included in the sample. Follow-up began at the time of the registered second questionnaire and ended 31 December 2015, corresponding to 18 years of follow-up. We included solely the first wave of recruitment to avoid the large variation in years of follow-up in order to facilitate the interpretation of the results. Figure 7, illustrates the study design of the weight change analysis.

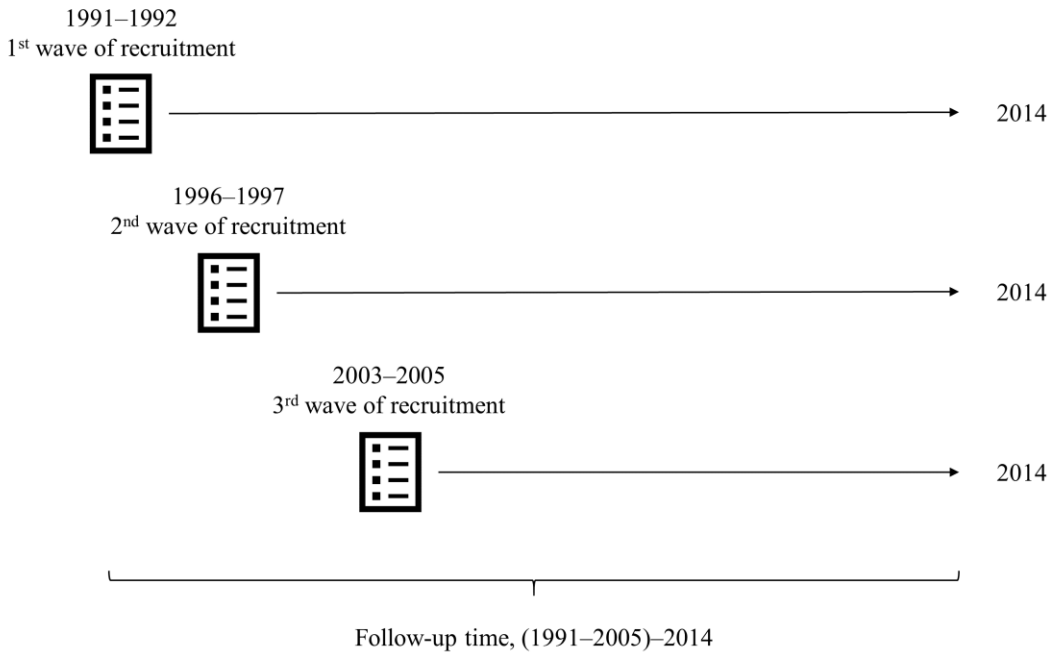

Figure 5. Paper II: recruitment and follow-up time in BMI analysis

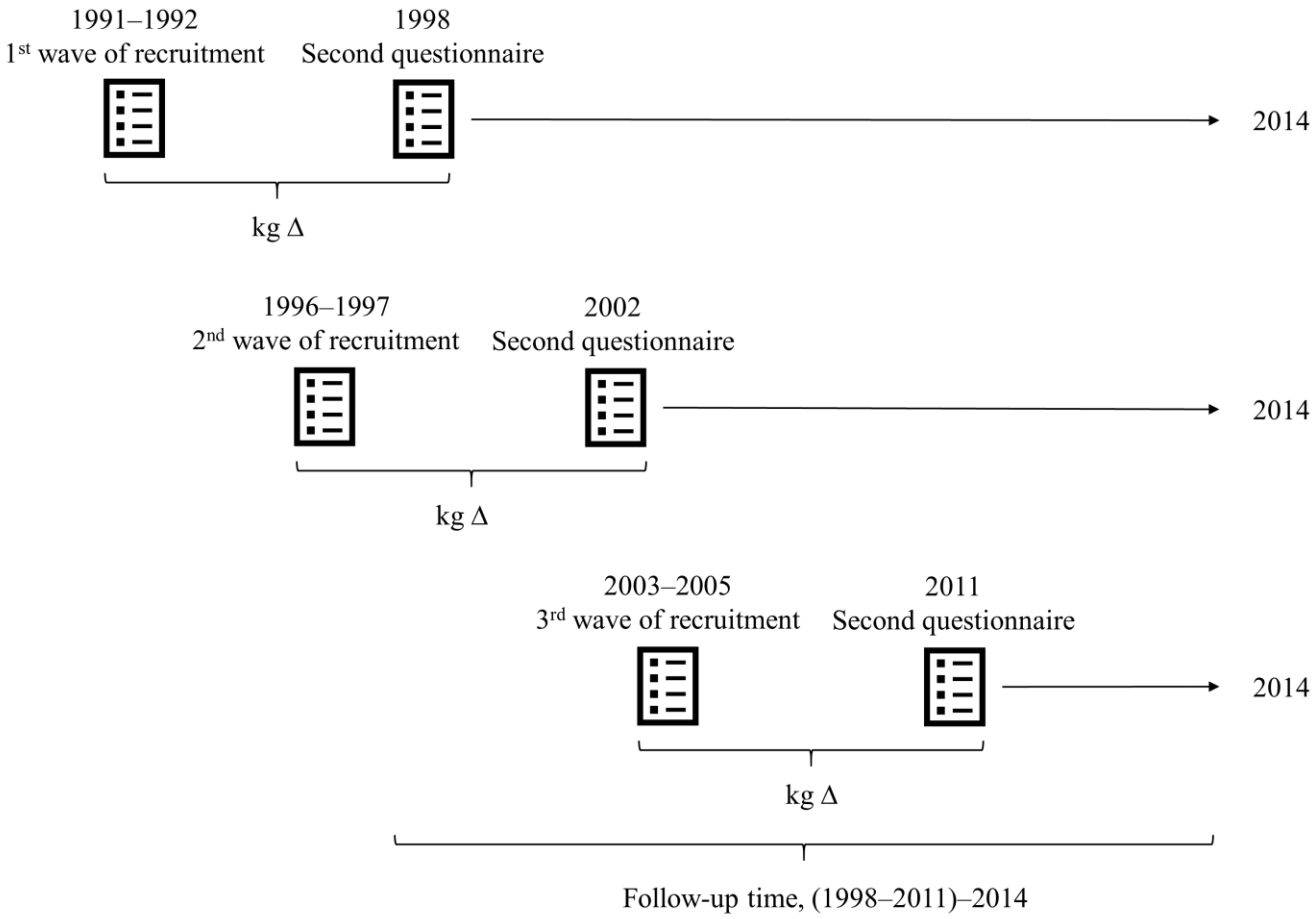

Figure 6. Paper II: recruitment, questionnaires, and follow-up time in weight change analysis

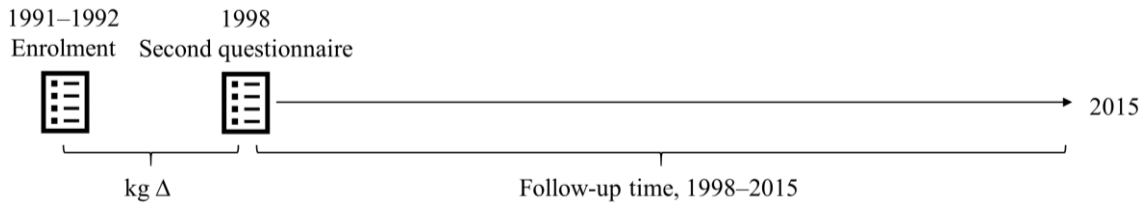

Figure 7. Paper III: enrolment, questionnaire, and follow-up time in weight change analysis

2.3 Exposures

2.3.1 Body weight status

We used self-reported weight and height to identify women's body weight status according to BMI, as defined by WHO [12]. We did not classify participants into obesity class I–III since there were too few women in each class that would limit the statistical power in stratified analyses. In addition, we assessed BMI continuously per five kg/m^2 increment. BMI was an exposure in Paper I and II and a covariate in Paper III. In Paper I, we introduced the concept of obesity duration as a measure of long-term obesity, which we defined as women who maintained in obesity ($\geq 30 kg/m^2$) in all three questionnaires during an average of 13 years. Normal weight was the reference category in all analyses.

There is a well-established tendency to underestimate weight and overestimate height that increases with age and BMI [60]. A validation study confirmed this tendency also in NOWAC, with misclassification due to underreporting in weight in women with overweight and obesity [61]. However, there was a substantial agreement between self-reports and objective measurements of weight and height and the distribution of body weight status did not differ between the two measurements. Thus, the authors concluded that self-reported weight and height was a valid ranking of BMI in middle-aged women in Norway.

2.3.2 Weight change

We used self-reported weight from the enrolment and second questionnaire to calculate weight change, which was categorised into five groups: weight loss (<–2kg), stable weight (–2 to <2kg), low weight gain (2 to <5kg), moderate weight gain (5 to <10kg), or high weight gain (≥10kg). There is no established definition of stable weight but researchers in several previous studies have used the chosen definition and similar categorization of weight change [62-68]. The enrolment and second questionnaire were parted by on average six years with a five to eight years range and did not differ substantially across weight change categories. In order to isolate the effect of weight change, we captured short-term weight change, as long-term change is more prone to weight cycling. Stable weight was the reference category in all analyses. In addition, we assessed weight change continuously per five kg increment.

In population-based studies, weight change is commonly measured by either weight change in kg or BMI change in unit. We chose to measure weight change in kg as BMI captures both lean mass and fat mass, whereas weight change in kg tends to capture increases in fat mass and is a more intuitive concept for public health messaging [7].

2.4 Outcomes

2.4.1 All body fatness-related cancers

The outcome of interest was first primary invasive cancer, for which evidence of a positive association with body fatness is considered sufficient according to IARC [34]. We identified these 13 body fatness-related cancers through linkage to the Cancer Registry of Norway, where they were classified according to the International Classification of Diseases, 10th Revision (ICD-10) and the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Table 1, presents the body fatness-related cancers and respective ICD-10

(topography) and ICD-O-3 (morphology) codes. Based on the topography and morphology codes, we classified endometrial cancer according to the WHO Classification of Tumours [69] and oesophagus adenocarcinoma as in Edgren [70]. In the analysis of all body fatness-related cancers, we considered women to have postmenopausal breast cancer if they reported postmenopausal status at enrolment (BMI analysis), or at enrolment or second questionnaire (weight change analysis), or had reached 53 years of age before or at breast cancer diagnosis. This age cut-off has been used previously in the NOWAC study [71] and is based on the Million Women Study convention [72], and represents ~80% of the women in our study population who reached natural menopause.

2.4.2 Specific body fatness-related cancers

We performed site-specific analysis in postmenopausal breast cancer, colon-rectal, endometrial, ovarian, pancreatic, and kidney cancer. Additional site-specific cancers (gallbladder, gastric cardia, liver, oesophagus, meningioma, thyroid, and multiple myeloma) were not analysed, owing to the small number of incident cases for each of these sites. In the site-specific analysis of postmenopausal breast cancer, only women who reported postmenopausal status at enrolment (BMI analysis) or at enrolment or second questionnaire (weight change analysis), were included. This differ from how we defined postmenopausal breast cancer in the analysis of all body fatness-related cancers. Women were at risk for any of the body fatness-related cancers and therefore their person-time were included regardless of menopausal status at enrolment (BMI analysis) or second questionnaire (weight change analysis), while in the site-specific analysis of postmenopausal breast cancer, premenopausal women were not at risk, hence excluded at enrolment (BMI analysis) or second questionnaire (weight change analysis).

Table 1. Body fatness-related cancers by ICD-10 and ICD-O-3 codes

	ICD-10	ICD-O-3
Cancer type:	Topography	Morphology
Breast (postmenopausal)	C50	
Colorectal	C18–20	
Endometrial	C54	8020, 8041, 8045, 8255, 8310, 8323, 8380, 8382, 8441, 8460, 8480, 8481, 8560, 8570
Ovarian	C56	
Pancreatic	C25	
Kidney	C64	
Gallbladder	C23–24	
Gastric cardia	C16.0	
Liver	C22	
Oesophagus (adenocarcinoma)	C15	8140–8573
Meningioma	C70–72, D42–43	
Thyroid	C73	
Multiple myeloma	C90	

2.5 Covariates

The comprehensive NOWAC questionnaire allowed us to assess several covariates as potential confounders. We did an *a priori* selection of covariates based on findings from previous studies on BMI/weight change and body fatness-related cancer, as well as previous reports from the NOWAC study. In the descriptive Paper I, we assessed all *a priori* selected

covariates to identify factors associated with high weight gain and obesity duration. In Paper II and Paper III, we assessed one set of covariates as potential confounders in the analysis of all body fatness-related cancers combined, plus additional outcome-specific covariates for each cancer site analysis. We extracted most covariates from the enrolment questionnaire.

2.5.1 Sociodemographic factors

Age was treated differently in each paper: In Paper I, we included age in the multivariable models as 5-year increments; In Paper II, we controlled for age as the underlying time metric in the Cox proportional hazard regression model; and in Paper III, we adjusted for age as a continuous variable in the piecewise constant hazard models. We categorised years of education into three groups (<10 years/10–12 years/>12 years). At the time when women in NOWAC attended school the compulsory school attendance in Norway was 7 and later 9 years, women with 10–12 years of education may had completed secondary school, while over 12 years of education corresponded to university studies [73].

2.5.2 Lifestyle factors

Physical activity was reported on an ordinal scale of 1–10 and collapsed into three categories: low (≤4), moderate (5–6), or high (≥7). In a validation study in a subsample of NOWAC participants, the physical activity scale showed a statistically significant agreement against a sensor that monitored heart rate and movement, but with a moderate correlation of 36–46% [74]. Smoking status was categorised as (never/former/current) and alcohol intake as (≤ median />median g/day). In addition, we categorised the transition from the enrolment to second questionnaire, in smoking status (no change/restart/cessation) and physical activity level (no change/decrease/increase).

2.5.3 Reproductive factors and intake of hormones

We defined menopausal status (pre-/peri-/post-menopausal/unknown) as per definition in the Million Women Study [72] based on questionnaire information on age, menstruation, hysterectomy, oophorectomy, age at menopause and hormone therapy use. Waaseth et al. validated the menopausal status in NOWAC by measuring plasma concentrations of sex hormones in a subsample of women [75]. The authors concluded that the study questionnaire provided valid information on menopausal status in women in Norway between 48 and 62 years old. Additional reproductive factors were age at menarche (≤ median />median), parity (nulliparous/1–2 children/≥3 children), age at first full-term pregnancy, parity and age at first full-term pregnancy (nullipara/unipara <29 years/unipara ≥30/multipara <29/multipara ≥30), oral contraceptive use (never/ever), and hormone therapy use (never/former/current). In addition, we categorised change in menopausal status as (no or unknown transition to menopause/transition to menopause).

2.5.4 Outcome-specific covariates

In the analysis of all body fatness-related cancers combined, we assessed education, physical activity, smoking status, and alcohol intake. In addition, we assessed smoking transition and physical activity change in all weight change analysis. In the site-specific analyses, we assessed additional covariates that were common for postmenopausal breast, ovarian and endometrial cancer, such as age at menarche, parity and age at first full-term pregnancy, oral contraceptive use, and hormone therapy use. In the postmenopausal breast cancer analysis, we also assessed maternal history of breast cancer (yes/no), and for endometrial and ovarian cancer, we assessed menopausal status. For colorectal cancer (as well as for colon and rectal cancer analysed separately) we additionally assessed dietary factors, such as intake of red and

processed meat, fruits, vegetables, fibre and calcium categorised into tertiles (low/medium/high).

2.6 Statistical analysis

We performed all statistical analysis using STATA (Stata Corp., College Station, TX, USA), except for the calculation of population attributable fraction (PAF), where we used SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

We used the "purposeful selection" approach described by Hosmer and Lemeshow, in order to evaluate which covariates to include in the final regression models [76]. First, we fitted univariable regressions for each covariate with potential for model inclusion and included those statistically significant at a 20% level in a multivariable model. Next, we excluded covariates that were no longer statistically significant in the full model using Wald statistics. In addition, we ascertained that the exclusion of a covariate did not change the coefficients of the remaining covariates in the model by more than 20%. We performed log-likelihood tests to compare goodness of fit between the reduced model and the full model. Thereafter, we reintroduced, on at the time, the covariates that were not included in the initial model based on the univariable regressions. This step was taken as some covariates may be statistically non-significant in univariable regressions but due to complicated confounding, can be statistically significant in multivariable regressions. Last, we listed biologically plausible interactions and tested them according to the steps for inclusion of covariates but with the traditional level of statistical significance of 5%. We aimed to include as large sample size of women as possible in each model, in order to conduct stratified analyses with sufficient cancer cases in each strata. By using set criteria for inclusion of covariates, we avoided exclusions of cases due to missing information on covariates not eligible for model inclusion.

In Paper I, we used multivariable logistic regressions to estimate odds ratios and 95% confidence intervals, to identify factors associated with high weight gain and obesity duration. In the final model, each factor was adjusted for all other factors. Women with missing information on the identified factors were excluded from the analysis.

In Paper II, we used Cox proportional hazard regression models with age as the underlying time metric [77] to estimate hazard ratios and 95% confidence intervals, for the associations of BMI and weight change with body fatness-related cancer. To account for the calendar and birth cohort effect, we constructed a variable based on wave of recruitment and birth year that was categorised into four groups (enrolled 1991–92, born 1943–65/enrolled 1996–97, born 1927–42/enrolled 1996–97, born 1943–65/enrolled 2003–06, born 1943–65). The variable was included in the Cox regression models with the "strata" command, which allowed the baseline hazard function to vary between the groups but with equal coefficients across groups. Women with missing information on any of the confounders were excluded from the analysis. Tests based on the Schoenfeld residuals showed no evidence of violation of the proportional hazard assumptions [78]. We fitted two models per outcome; Model 1 controlled only for age (by time in the Cox regression) and Model 2 (main model) with adjustments by purposeful selection of covariates for each outcome separately. Further, we tested for plausible interactions with loglikelihood ratio test, comparing models with and without the interaction term. In weight change analyses, we tested for interaction between BMI status and weight change. In site-specific analyses where hormone therapy use or menopausal status was assessed as a covariate, we tested for interactions between these and for each exposure separately. Moreover, we fitted restricted cubic spline transformations of the exposure variables in order to model potential non-linear dose-response relationships with 95% confidence intervals of BMI/weight change and risk of all and specific body fatness-related cancer [79]. We used four knots as recommended by Harrell, and evaluated non-linearity by

testing that the null hypothesis of the second and third spline coefficients jointly equalled to zero [80].

In Paper III, we used a recently developed method [81] and program [82] to estimate PAFs and their 95% confidence intervals of all and specific body fatness-related cancers attributable to weight gain. PAF estimates the proportion of disease (or other outcome) in a population, attributed to the causal effects of a risk factor or set of risk factors [83]. The PAF method that we used is the first that accounts for death as a competing risk, by combining weight gain and the risk of death, and weight gain and the risk of cancer, with the prevalence of weight gain in the population. We used a piecewise constant hazards model to estimate the strengths of the associations and expressed them as hazard ratios with 95% confidence intervals. The piecewise constant hazard function lets the baseline hazard vary between predefined time intervals and reduces the bias of a hazard ratio that extends over a long time [84]. We predefined five-year intervals during the 18 years of study follow-up. Moreover, we multiplied our PAF estimates by national incidence figures that occurred during the follow-up time, 1998–2015. This allowed us to estimate the absolute number of cancer cases in women in Norway attributable to weight gain during this time-period, for each statistically significant outcome separately.

2.7 Ethical considerations

The Regional Committee for Medical Research Ethics in Northern Norway (P REK NORD 141/2008) and the Norwegian Data Inspectorate approved The NOWAC study [54]. All participants provided written informed consent for participation and data linkage.

3 Results

3.1 Paper I:

In Paper I, we aimed to identify factors associated with high weight gain and obesity duration and to describe weight change and BMI status duration in respective subsample. 60 911 women were included in the weight change analysis with an average age of 46 years, average weight of 66kg, and average BMI of 24kg/m^2, at enrolment. Of these women, 28% reported a stable weight during the six-year study period, while 62% reported weight gain, and 9.4% reported weight loss. Women gained on average 0.5kg per year. The youngest women (34–40 years) gained the most weight, while the oldest women (61–70 years) gained the least. Lifestyle factors displayed the strongest associations with high weight gain (≥10kg). Women who stopped smoking between the two questionnaires had more than four-fold higher odds of high weight gain. Physical activity was also strongly associated with high weight gain; a high physical activity level lowered the odds of high weight gain with 70%. In addition, women who decreased their physical activity level between enrolment and the second questionnaire had more than two-fold higher odds of high weight gain. Further, already having obesity at enrolment was also associated with a two-fold increase in odds of high weight gain. Additional factors associated with high weight gain were being premenopausal which increased the odds of high weight gain, while old age, high education, being a current smoker, higher than median alcohol intake and higher than median age at menarche, decreased the odds of high weight gain.

34 453 women were included in the BMI status duration analysis. Over the 13-year study period, most women maintained in normal weight (46%), while 9% maintained in overweight, 4% in obesity, and 0.5% in underweight. Moreover, 41% changed their BMI status between

the surveys. Of these women, 80% changed to a higher BMI status, 6% changed to a lower BMI status, and 14% cycled. Physical activity displayed the strongest association with maintaining in obesity; a high physical activity level lowered the odds of maintaining in obesity with 83%. In addition, a higher than median age at menarche lowered the odds of obesity duration with 64%, and less years of education lowered the odds with 56%. Moreover, being a current smoker, higher than median alcohol intake, and ever use of oral contraceptives decreased the odds of obesity duration, while older age and having no children increased the odds of obesity duration.

3.2 Paper II:

In Paper II, we aimed to estimate the association of body weight status and weight change with all and specific body fatness-related cancers. 135 708 women were included in the BMI analysis with an average follow-up time of 17 years, during which 9328 body fatness-related cancers were diagnosed with an average age at diagnosis of 62 years. Women with overweight or obesity had an increased risk of body fatness-related cancer with 9 and 24%, respectively. In site-specific analyses, women with obesity had an almost three-fold increased risk of endometrial cancer, 95% increased risk of kidney cancer, and 20% increased risk of postmenopausal breast cancer. In addition, we found a dose-response relationship with increasing BMI for all body fatness-related cancers combined, endometrial, and kidney cancer, but not for postmenopausal breast cancer. The increased risk started at BMI 24 for all body fatness-related cancers and endometrial cancer, but just after BMI 30 for kidney cancer. Moreover, women with overweight had 12% increased risk of colorectal cancer and 21% increased risk of colon cancer, while there was no association between obesity and colorectal and colon cancer. In addition, there was no association between body weight status and rectal, ovarian, and pancreatic cancer.

80 930 women who also responded to the second questionnaire were included in the weight change analysis. The average study follow-up time was 13 years, during which 4831 body fatness-related cancers were diagnosed with an average age at diagnosis of 63 years. Weight gain was associated with increased risk of all body fatness-related cancers; low (2 to <5kg) and moderate (5 to <10kg) weight gain increased the risk with 14%, and high weight gain (≥10kg) with 16%. In the site-specific analyses, women who gained more than 10kg had nearly a two-fold increased risk of pancreatic cancer, 40% increased risk of endometrial cancer, and 36% increased risk of postmenopausal breast cancer. When we allowed for non-linearity, we found a dose-response relationship with increasing weight gain for all body fatness-related cancers combined, pancreatic, endometrial, and postmenopausal breast cancer. The risk of pancreatic cancer increased already with low weight gain, and the risk of postmenopausal breast cancer and endometrial cancer increased with moderate weight gain. As in the analysis of body weight status, low and moderate weight gain but not high weight gain was associated with colorectal cancer; low weight gain increased the risk with 11% and moderate weight gain increased the risk with 24%. For rectal cancer the associations with low and moderate weight gain was of borderline significance $p = 0.05$ and with high weight gain there was no association. In addition, there was no association between weight gain and colon, ovarian, and kidney cancer. However, weight loss increased the risk of colorectal cancer with 25% and displayed positive associations with all other body fatness-related cancers under study, although they did not reach statistical significance. We found no evidence of interaction between BMI status and weight change in relation to all and specific body fatness-related cancers, which was further confirmed in stratified analysis (Table 2).

Table 2. Hazard ratio (HR) with 95% confidence interval (CI) for body fatness-related cancer incidence by weight change category between the enrolment and second questionnaire, stratified by body weight status.

	Body weight status															
	Underweight				Normal weight				Overweight				Obesity			
	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI
Weight change category*																
Weight loss (<–2kg)	58	5	1.13	0.43–2.98	3191	161	1.04	0.88–1.24	2442	152	1.00	0.82–1.22	1195	88	1.36	0.99–1.89
Stable weight (–2 to <2kg)	557	30	1.00	Reference	14 863	754	1.00	Reference	4499	296	1.00	Reference	1031	62	1.00	Reference
Low weight gain (2 to <5kg)	609	22	0.75	0.43–1.32	15 091	915	1.19	1.08–1.31	3520	228	1.01	0.85–1.20	624	44	1.15	0.78–1.70
Moderate weight gain (5 to <10kg)	388	22	1.21	0.68–2.15	12 163	743	1.19	1.07–1.32	3817	238	0.98	0.82–1.17	834	66	1.39	0.98–1.96
High weight gain (≥10kg)	166	8	0.80	0.36–1.81	3940	235	1.19	1.03–1.39	1866	118	1.08	0.87–1.35	586	45	1.40	0.95–2.07
5kg increment	1778	87	1.19	0.75–1.19	49 248	2808	1.11	1.02–1.11	16 144	1032	1.07	0.95–1.07	4270	305	1.08	0.95–1.08

*Adjusted for age, physical activity, smoking status, and smoking transition

3.3 Paper III:

In paper III, we aimed to estimate the fraction of all and specific body fatness-related cancers attributable to weight gain while accounting for death as a competing risk. We used a smaller subsample than in Paper II by only including women from the first wave of recruitment, which allowed us to calculate absolute numbers of preventable cancer cases over 18 years. 44 114 women were included in the study sample with 3216 incident body fatness-related cancers and 2014 death observed during follow-up. The average follow-up time was 16 years and the average age at cancer diagnosis was 60 years.

As a first step in the PAF method, we estimated the strength of association between weight gain and cancer and the strength of association between weight gain and death. We had already reported on the association between weight gain and body fatness-related cancers in Paper II. The major difference between Paper II and Paper III was that the association between weight gain and endometrial cancer did not reach statistical significance in Paper III as it did in Paper II. When analysing the strength of association between death and body fatness-related cancer, we found no association between weight gain and death from other causes than body fatness-related cancers, except for women with high weight gain in the pancreatic cancer analysis subsample. These women had a 22% increased risk of death from other causes than pancreatic cancer.

The PAF of body fatness-related cancer attributable to weight gain in women in Norway was 9%, which is equivalent to 6795 cancer cases that could have been prevented, if women who gained weight had had stable weight. However, since weight gain was not associated with all site-specific body fatness-related cancers under study; the fraction and the absolute number of all body fatness-related cancer cases attributable to weight gain was attenuated. The fraction of pancreatic cancer that could have been prevented by avoiding weight gain was 43%, which

corresponds to 1371 cancer cases. Further, the fraction of postmenopausal breast cancer and colorectal cancer attributable to weight gain was both 16%, translating to 4299 and 2798 cancer cases, respectively.

4 Discussion

4.1 Summary of results

In this nationally representative prospective cohort, almost two thirds of women in middle adulthood gained weight over 6–7 years. Weight gain, independent of body weight status, was strongly associated, with all body fatness-related cancers combined, pancreatic, endometrial, and postmenopausal breast cancer in a dose-response manner. In detail, avoiding weight gain over seven years could have prevented over 43% of pancreatic cancer cases, 4299 postmenopausal breast cancer cases and 2798 colorectal cancer cases in women in Norway, diagnosed in 1991–2015. Among the site-specific cancers under study, body weight status and weight change differed in which of the two exposures that predicted increased risk and to what strength. Thus, body fatness and weight change are independently and differentially associated with several cancers, and given a causal relationship, many of the body fatness-related cancer cases could have been prevented, if women in Norway who gained weight had had stable weight.

4.2 Physical activity and smoking

Lifestyle factors, such as physical activity and smoking, were strongly associated with weight gain, which is in agreement with findings from the Tromsø Study in Norway [85]. In fact, low physical activity displayed the strongest association with obesity duration, and a decrease in physical activity increased the odds of high weight gain more than two-fold. These results indicate that effective interventions of increased physical activity can decrease the odds of negative weight development in women in Norway. Prevention of weight gain is more effective than weight loss strategies in reducing obesity rates [7]. However, there are inconsistent results concerning physical activity and the prevention of weight gain across

body weight statuses [86, 87]. In contrast to physical activity, the relationship between smoking and the studied outcomes was complex, since smoking both increased and decreased odds depending on status and transition. Current smoking decreased the odds of high weight gain (only after adjustment for smoking transition) and obesity duration, while smoking cessation between enrolment and second questionnaire displayed the strongest association with high weight gain, with four-fold increased odds. Indeed, smoking is associated with increased metabolic rate, decreased metabolic efficiency, and reduced appetite; however, there are uncertainties regarding the effect of smoking on weight control [88]. Nevertheless, smoking cessation should always be recommended, as immediate weight gain after cessation tends to attenuate [86] and smoking increases risk of several negative health outcomes [89]. The modifiable factor with the third strongest association with high weight gain was already having obesity, which is important to acknowledge as obesity and weight gain may independently be associated with negative health outcomes [10, 11, 45, 90-93].

4.3 The role and impact of weight change on cancer

4.3.1 All body fatness-related cancers

Weight gain was positively associated with all body fatness-related cancers combined in a clear dose-response relationship. This result was independent of BMI status and therefore may be of importance irrespective of body weight. Two recent pooled cohort studies also displayed a positive association between weight gain and all body fatness-related cancers [46, 94].

Importantly, weight gain is a modifiable risk factor that has a substantial impact on the body fatness-related cancer burden in women in Norway. However, the strength of association and our PAF estimate would have been higher, should we only had included body fatness-related

cancers with a statistically significant association with weight gain, instead of all those defined by IARC. This probable attenuation is important to stress in dissemination of the overall estimate, since PAF is a quantifier for planning and prioritising cancer prevention [95].

4.3.2 Pancreatic cancer

Weight gain but not body weight status predicted increased risk of pancreatic cancer, although the weight change analysis comprised of fewer cancer cases. In site-specific analyses, high weight gain was most strongly associated with increased risk of pancreatic cancer, and we observed the largest proportional impact of weight gain on the pancreatic cancer burden. Our finding of a positive association between weight change and pancreatic cancer is not consistent with other studies. WCRF conducted a systematic literature review on weight change and pancreatic cancer, which they recently updated in a revised report [96]. None of the included studies reported a statistically significant association, and the WCRF stated that weight gain was associated with pancreatic cancer, only as an interrelated aspect with other measures of body fatness, not independently. In addition, a meta-analysis of weight gain and several cancers was conducted in 2015, wherein the authors hypothesised that in the presence of strong risk factors such as smoking, weight gain was not able to establish itself as an individual risk factor for pancreatic cancer [45].

Our study differs from previous weight gain and pancreatic cancer studies on several aspects [97]. First, we have measured short-term weight gain to isolate the effect of change, instead of long-term weight change (ranging from ~20–50 years within each study separately), during which the effect of the actual change in weight may be lost. Second, we have showed an association between moderate and high weight gain with pancreatic cancer that remained after including smoking and smoking transition as potential confounders. In fact, there was no

substantial difference between the age-adjusted and multivariable model, suggesting that there is a robust association between weight gain and pancreatic cancer. Third, we showed a non-linear dose-response relationship with increased risk of pancreatic cancer by moderate and high weight gain. Instead, most other studies have forced the relationship between weight gain and pancreatic cancer to be linear by analysing five kg increments, which displayed no association with pancreatic cancer risk [45, 46]. Similarly, in our study, there was no risk of pancreatic cancer with weight gain per five kg increment. Thus, solely analysing weight gain and site-specific cancer associations by five kg increment might not reveal the full representation of a potential relationship. Nevertheless, a recent pooled Japanese cohort analysed weight change categories and reported no increased risk of pancreatic cancer in women [94].

In Paper III, the strength of association between weight gain and pancreatic cancer (as well as for the other statistically significant site-specific cancers under study) was stronger than in Paper II. The major difference between the two samples was that only women from enrolment were included (excluding women from the second and third waves of recruitment), which gives all participant a potential follow-up of 18 years. This is important as pancreatic cancer has one of the highest median age at diagnosis (72 years). A study with a large proportion of young women with short follow-up time will include person-time from individuals in a scenario where it is unlikely for them to have had the time to develop pancreatic cancer. For instance, in the European pooled study of weight gain and obesity-related cancer [46], almost half of the female sample was under 40 years at start of follow-up (second measurement) with a follow-up time ranging from zero to 39 years, and an average of 18 years. Thus, many individuals may have contributed with person-time without enough follow-up time to develop pancreatic cancer, which may have attenuated their result.

Despite of relatively few pancreatic cancer cases in our study sample (170 cases in the weight change analysis and 111 in the PAF analysis), which limited the precision of the estimates, our results show that stable weight has a large potential for primary prevention of pancreatic cancer. This novel finding is important due to the poor prognosis of the disease and given that the incidence of pancreatic cancer has steadily increased for decades in women in Norway [24].

Pancreatic cancer development may be related to increased insulin levels and higher bioavailability of insulin-like growth factor [98], in which weight gain, rather than body weight status, may play a more vital role. However, we have found no studies in animal models that assess short- or long-term weight gain and cancer incidence confirming or rejecting this mechanistic hypothesis. Our results suggest a possible role of weight change in the aetiology of pancreatic cancer, which must be confirmed by future studies, particularly in women.

4.3.3 Postmenopausal breast caner

Body weight status and weight gain were both associated with postmenopausal breast cancer, which is in accordance with previous studies [10, 45, 46]. The risk of postmenopausal breast cancer was higher in women experiencing weight gain than among women with obesity, suggesting that weight gain may be a stronger risk factor for postmenopausal breast cancer than body weight status. The only site-specific weight gain studies we found with PAF estimates were in postmenopausal breast cancer. The latest prospective cohort study that calculated fractions of postmenopausal breast cancer attributable to weight gain reported a PAF similar to our result, with comparable strength of association between weight gain and postmenopausal breast cancer, but a higher prevalence of weight gain [99]. As expected, in our study, postmenopausal breast cancer had the largest absolute number of cancers cases

attributable to weight gain, as it is the most commonly diagnosed cancer in women, both in Norway and worldwide [23, 24].

4.3.4 Endometrial cancer

Body weight status and weight gain were both associated with endometrial cancer, which is consistent with other studies [10, 42, 46, 100]. However, several studies on weight gain and endometrial cancer reported increased risk only for substantially higher weight gain categories than those included in our study, or only for the highest category [67, 94, 101, 102], whereas we reported an increased risk already at moderate weight gain (5 to <10kg). Though in Paper III, wherein we assessed a smaller subsample of women than in Paper II, the association between weight gain and endometrial cancer did not reach statistical significance. Nevertheless. the association for weight change was not as strong as that for body weight status; women with obesity had three-fold increased risk of endometrial cancer.

4.3.5 Colorectal cancer

There is inconsistency across studies on the association between weight change and colorectal cancer in women, with different results for colon and rectal cancers, but an overall indication of no association [45, 46, 50, 66, 94]. In this thesis, low and moderate weight gain but not high weight gain was associated with colorectal cancer, likewise, overweight but not obesity. Although we excluded the first two years of follow-up to minimize potential reverse causality, we cannot fully rule out that weight loss as a preclinical symptom of colorectal cancer, resulted in few colorectal cancer cases among women in the high weight gain category and among women in obesity. There are uncertainties of the magnitude and period in which unintentional weight loss occurs before colorectal cancer diagnosis [103], particularly, since colorectal cancer can develop over more than 10 years [104]. Although there was no dose-response relationship between weight gain and colorectal cancer, we calculated PAF.

Consequently, colorectal cancer had the second largest absolute number of cancer cases attributable to weight gain.

4.3.6 Weight loss

In site-specific analyses, weight loss displayed an increased risk although not statistically significant, other than for colorectal cancer. In addition, weight loss was associated with all body fatness-related cancers combined in Paper III but did not reach statistically significance in Paper II. These weight loss results are difficult to interpret since we cannot differentiate between intentional and unintentional weight loss. As with our colorectal weight gain results, we are uncertain to what extent our weight loss results are biased by reverse causality. Until recently, prospective cohort studies have not differentiated between intentional and unintentional weight loss in their weight change analysis, and have reported no associations between weight loss and cancer incidence [48, 105, 106]. On the other hand, studies of cancer incidence in women with obesity that undergone bariatric surgery have showed a decrease in all and female specific cancers, such as breast, endometrial, and ovarian cancer, compared to controls, suggesting that intentional weight loss decreased cancer risk [107-109]. Evidence for decreased risk with intentional weight loss has been building up in recent years [51, 52, 110, 111], which is a welcomed scientific contribution for public health messaging to motivate weight loss

4.3.7 Weight change vs. body weight status

We have investigated the association of body weight status and weight change with all and specific body fatness-related cancers in order to assess the role of weight change beyond that of body weight status in relation to cancer. Our results suggest that weight gain is not merely a better or worse measurement of body fatness; instead, body weight status and weight change may have different roles in cancer aetiology for different sites. These assumptions are based

on the following results, i) weight change and cancer associations were independent of body weight status, ii) there was no association between body weight status and pancreatic cancer, while high weight gain was associated with two-fold increased risk of pancreatic cancer, iii) in endometrial cancer, body weight status was the strongest predictor, while in postmenopausal breast cancer weight change was the strongest predictor.

4.4 Methodological considerations

4.4.1 Study design

Commonly, randomized control trials are the golden standard in casual inference [112]. However, in studies of weight gain and cancer incidence no other study design than observational is ethically sound. In addition, estimations of PAF assume a causal relationship between exposure and outcome [83]. Thus, our intention for the study designs in Paper II and Paper III, have been to explore causality, and draw attention to further research required to confirm or refute our findings [113].

In this observational study, we have had the possibility to adapt our study design to each paper and research question thanks to our large prospective cohort with repeated individual measures and virtual complete follow-up information on death, migration and cancer diagnosis. However, observational studies are recognised to be prone to three broad categories of systematic errors, such as selection bias, confounding, and information bias, discussed below [114].

4.4.2 Selection bias

In epidemiological studies, selection bias occurs when the relation between exposure and disease systematically differ between those who participated in the study and those who did

not participate [114]. In NOWAC, validation by linkage to national registers showed minor differences in education and parity between responders and the total sample of women [59]. In addition, a postal survey among non-responders showed no difference in lifestyle factors and anthropometrics between original responders and non-responders. Thus, the exposure and covariates did not substantially differ between participants and non-participants, and as earlier mentioned, the observed incidence rate and the national incidence rates of all cancer sites did not differ [54]. However, women who returned the second questionnaire were younger and weighed slightly less, compared to women who only returned the enrolment questionnaire. Overall, the potential selection bias in our study should be minimal, although we did not have the possibility to compare the exposure-outcome relation among responders and non-responders.

4.4.3 Confounding

Covariates that are associated with both outcome and exposure, and not on the causal pathway between the exposure and outcome, can cause confounding [115]. We used the purposeful selection approach to control for confounding in our multivariable regression models, as described in the methods section [76]. However, there are other procedures to select variables for model inclusion. In addition to the data-driven procedures such as the purposeful selection approach, the directed acyclic graph (DAG) solely relies on prior knowledge [116]. DAG is a graphical depiction of potential confounders and their association with e.g. an exposure and outcome. In our *a priori* selection of potential confounders to test for model inclusion, we discussed each potential confounder's association with the outcome and exposure before selection, although not by applying DAGs. There is an additional approach to deal with confounding in observational studies that has increased in popularity, namely propensity score methods [117]. In brief, these methods combine information on a number of potential

confounders into a single score for each individual in a data set. The score is equivalent to the probability of an exposure, given the characteristics measured at baseline. Thereafter, certain steps based on the score are taken to establish confounding. Nonetheless, in all our analyses there were no substantially difference between the age-adjusted models and the multivariable models, except for the analyses of postmenopausal breast cancer, which suggest little confounding by included variables.

Unmeasured confounders or the effects of measurement error in confounders can also confound the association between exposure and outcome [115]. The comprehensive questionnaire in NOWAC covers many potential confounders, and several core variables such as weight and height, physical activity, and menopausal status have been validated. However, the cause of weight change and cancer is multifaceted, and there can be unmeasured confounders that we have not been able to cover, or potential confounders that we were not able to properly measure to the level of detail necessary, in order to reveal confounding. For example, unmeasured medical conditions that affect both weight change and cancer, or time of initiation and frequency rather than status of measured potential confounders, may affect the weight change and cancer association. In our weight change and pancreatic cancer result, we explored additional smoking variables such as pack-year, and time since cessation, but it did not reveal any residual confounding. Moreover, we had to omit total energy intake as a potential confounder in our analyses, as the food frequency questionnaire was not provided to all women, leading to a large amount of missing data, and due to known biases related to under and over reporting [118, 119]. In our sample, women in underweight reported the highest total energy intake while women in obesity reported the lowest. Nonetheless, in our weight change analyses, the actual weight gain could function as a proxy for positive energy imbalance.

In all weight change analysis, we assessed potential confounding by body weight status at enrolment rather than weight. This as weight and weight change are dependent variables. Adjustment for weight at the enrolment or second questionnaire when assessing weight change is equivalent to measuring the association between weight at the enrolment or second questionnaire and cancer incidence, and thus the element of change would be lost [68].

4.4.4 Information bias

Information bias arise from measurement error or misclassification of an exposure, outcome, or covariate [120]. There is a well-established tendency to underestimate self-reported weight with increasing age and BMI, which we revealed also in NOWAC [60, 61]. However, we assume that the potential misclassification in our sample was non-differential between women with and without body fatness-related cancers, since we collected all information before cancer diagnosis. Thus, assuming non-differential, non-systematic errors, the potential misclassification would attenuate the estimate of the highest body weight status, but the test for trend would be valid [121]. Further, as we have several exposure categories and confounders in our multivariable models the potential misclassification can bias the estimates both toward and away from the null [122]. However, in the weight change analysis, we assume that the potential underestimation of weight was similar at the enrolment and second questionnaire, and therefore weight change was estimated accurately.

4.4.5 Interaction

Interaction occurs when the incidence of disease in the presence of two or more risk factors differs from the incidence expected to result from their individual effects [123]. We tested *a priori* selected potential interactions by the purposeful selection approach in similar fashion as with potential confounders. We found that menopausal status modified the effect of endometrial cancer with a statistical interaction between perimenopausal status and obesity.

However, there were few endometrial cancer cases among women in perimenopausal status and thus, we could not assume a biological or casual interaction, and therefore did not include the interaction term in our regression analysis [124]. Instead, we presented the association between body weight status and endometrial cancer stratified by menopausal status as recommended by Knol & VanderWeele [125].

5 Conclusion

In this observational study, we investigated the relationship between weight gain and cancer among women in Norway. Our results show that most women gained weight over 6–7 years. The cancer that was most strongly associated with weight gain was pancreatic cancer. Specifically, gaining more than 10kg was associated with almost two-fold increased risk of pancreatic cancer. We also noted an increased risk in all body fatness-related cancers combined, pancreatic, postmenopausal breast cancer, and endometrial cancer already at low and moderate weight gain. Moreover, avoiding weight gain could have prevented approximately 40% of pancreatic cancer cases, 4000 postmenopausal breast cancer cases and 3000 colorectal cancer cases in women in Norway diagnosed in 1998–2015. In addition, our results indicate that body weight status and weight change may have different roles in cancer aetiology for different sites

This study is the first to show a positive association between short-term weight gain and pancreatic cancer incidence. These results are of upmost importance due to the poor prognosis of pancreatic cancer and given the increase of pancreatic cancer incidence in women, both in Norway and worldwide. However, despite a statistically significant effect, our sample comprised of a relatively small number of women with pancreatic cancer. Therefore, more studies are needed in order to confirm our pancreatic cancer finding

To conclude, our findings demonstrate increased risk of cancer incidence with short-term weight gain regardless of body weight status. Our research makes a novel contribution to the literature on risk factors of pancreatic cancer and have important implications for public health interventions, as several site-specific cancers appear to be preventable through weight maintenance.

6 Public health implications and future perspectives

Our results suggest that clinicians and public health interventions should focus on weight maintenance as primary prevention for cancer. Therefore, a wider monitoring of weight change at population and individual level is needed.

We have reported the fraction of body fatness-related cancer burden attributable to weight gain, which is an estimate of the preventable proportion, given a hypothetical intervention. Although the mathematics to calculate this proportion is sound, the intervention to prevent body fatness-related cancer, i.e. in our study stable weight, must be achievable in the target population for the estimate to fit public health planning. Specifically, in our study, the intervention would be to avoid weight gain over 6–7 years during middle adulthood, which seems less challenging than weight maintenance from the weight of age18 throughout adulthood, as in most other studies. Thus, in comparison to previous estimates, our findings can be more easily translated to achievable interventions.

Epidemiological studies on short-term weight gain and cancer in both humans and animals are warranted to confirm our findings. Particularly, mechanistic data to reveal the potential role of short-term weight gain in the aetiology of pancreatic cancer in women, to confirm or refute or novel result. Large prospective cohort studies that can differentiate intentional and unintentional weight loss in weight change and cancer analyses are also called for in order to increase our understanding of weight loss, and the effect on cancer (especially in order to disentangle the effect of reverse causality).

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Appendix

Questionnaire

KVINNER, LIVSSTIL OG HELSE

KONFIDENSIELT

1 KLH/1991
60.000 34-49 år
1 – 59999
Skj-type I - 4 sider

Vi ber deg fylle ut spørreskjemaet så nøye som mulig, se orienteringen på brosjyren for nærmere opplysninger.

Sett kryss for JA i ruten ved siden av hvis du samtykker i å være med. Dersom du ikke ønsker å delta, sett kryss for NEI og returner skjemaet i vedlagte frankerte svarkonvolutt, så slipper du å bli purret på.

Med vennlig hilsen
Eiliv Lund
Professor dr. med.

Jeg samtykker i å delta i undersøkelsen JA ☐ NEI ☐

Forhold i oppveksten

I hvilke(n) kommune vokste du opp (0-7 år)?

.....

Hvem var forsørger i familien? (Sett ett kryss)

☐ far ☐ mor ☐ begge ☐ andre

Hvordan var de økonomiske forhold i oppveksten?

Meget gode	☐
Gode	☐
Dårlige	☐
Meget dårlige	☐

Kroppstype i 1. klasse. (Sett ett kryss)

☐ veldig tynn ☐ tynn ☐ normal ☐ tykk ☐ veldig tykk

Hvor mange års skolegang har du i alt, ta med folkeskole og ungdomsskole?

..... år

Hvilken yrkesutdannelse har du?

.....

Er din arbeidssituasjon: (Sett ett kryss)

☐ hjemmeværende ☐ deltids arbeid
☐ heltids arbeid utenfor hjemmet
☐ uførepensjon ☐ skolegang

Er du;

☐ gift ☐ samboer ☐ annet

Menstruasjonsforhold

Hvor gammel var du da du fikk menstruasjon første gang?

.....år

Hvor mange år tok det før menstruasjonen ble regelmessig?

☐ Ett år eller mindre ☐ Mer enn ett år ☐ Aldri
☐ Husker ikke

Hvor lang tid gikk det mellom 1. dag i en menstruasjonsblødning til 1. dag i neste menstruasjonsblødning da du var 18 år?

.....dager

Hvor lang tid gikk det mellom 1. dag i en menstruasjonsblødning til 1. dag i neste menstruasjonsblødning da du var 30 år?

.....dager

Har menstruasjonen noen gang vært borte mer enn en måned? (Se bort fra svangerskap) Ja ☐ Nei ☐

Hvis Ja;

	Ja	Nei	Hvis Ja; Hvor lenge Måneder
Spisevegring	☐	☐	
Etter slanking	☐	☐	
Etter p-pille bruk	☐	☐	
Ved stress i arbeidet (skift)	☐	☐	
Ved trening	☐	☐	
Andre årsaker	☐	☐	

Har du vanligvis før-menstruelle plager?

☐ ingen ☐ brystspreng ☐ depresjon ☐ annet

Har du hete- eller svettetokter som du mener skyldes overgangsalderen (klimakteriet)? (Sett ett kryss)

☐ Ingen ☐ Lette ☐ Plagsomme

Har du regelmessig menstruasjon fremdeles? Ja ☐ Nei ☐

Hvis Nei;

har den stoppet av seg selv?	☐
operert vekk eggstokkene?	☐
operert vekk livmoren?	☐
annet?	☐

Hvor gammel var du da menstruasjonen opphørte?

.....år

Hormonbehandling

Har du brukt hormontabletter i overgangsalderen? Ja ☐ Nei ☐

Hvis Ja, hvor gammel var du første gang du fikk det?

.....år

Hvor lenge har du i alt brukt hormontabletter?

.....mnd.....år

Graviditeter, fødsler og amming

Fyll ut for hvert barn opplysninger om fødselsår og antall måneder du ammet hvert barn (fylles ut også for dødfødte eller for barn som er døde senere i livet). I tillegg ber vi deg oppgi hvor mange kilo du la på deg i løpet av svangerskapet. Dersom du ikke har født barn fortsetter du ved neste spørsmål.

Barn	Fødselsår	Antall måneder med amming	Vektøkning i svangerskapet
1			
2			
3			
4			
5			
6			
7			

Har du hatt noe svangerskap som varte mindre enn seks måneder dvs. spontan abort eller selvbestemt abort? Ja ☐ Nei ☐

Hvis Ja, hvor gammel var du ved første abort?

.....år

Hvor mange aborter har du hatt i alt?

.....

Har du hatt svangerskap utenfor livmoren? Ja ☐ Nei ☐

Hvis Ja;
Hvor gammel var du første gang?

.....år

Har du noen gang prøvd i mer enn 1 år å bli gravid? Ja ☐ Nei ☐

Hvis Ja;
Hvor gammel var du?

.....år

Hvor lenge prøvde du?

.....år

P-Piller

Har du noen gang brukt p-piller, minipiller inkludert? Ja ☐ Nei ☐

Hvis Ja;
Hvor lenge har du brukt p-piller i alt?

.....år

Hvor gammel var du første gang du brukte p-piller?

.....år

Hvis du har født barn, brukte du p-piller før første fødsel? Ja ☐ Nei ☐

Bruker du p-piller nå? ☐ ☐

Har du fått p-piller av andre årsaker enn prevensjon? ☐ ☐

Har du blitt anbefalt å slutte med p-piller av medisinske årsaker? ☐ ☐

Vi vil be deg om å besvare spørsmålene om p-pille bruk mer nøye.
For hver periode med sammenhengende bruk av samme p-pille merke håper vi du kan si oss hvor gammel du var da du startet, hvor lenge du brukte det samme p-pille merket og navnet på p-pillene.
Dersom du har tatt opphold eller skiftet merke, skal du besvare spørsmålene for en ny periode. Dersom du ikke husker navnet på p-pille merket, sett usikker. For å hjelpe deg til å huske navnet på p-pille merkene ber vi deg bruke den vedlagte brosjyre som viser bilder av p-pille merker som har vært solgt i Norge. Vennligst oppgi også nummeret på p-pillen som står i brosjyren.

Periode	Alder ved start	Brukt samme p-pille sammenhengende år	måneder	P-pillene (se brosjyren) Nr.	Navn
Første					
Andre					
Tredje					
Fjerde					
Femte					
Sjette					
Syvende					
Åttende					

Annen prevensjon

Hvor ofte har du eller partner benyttet en av følgende prevensjonsmetoder, og hvor mange år?

	Aldri	Av og til	Ofte	Alltid	Antall år
Kondom					
Pessar					

Har du hatt spiral? Ja ☐ Nei ☐

Hvis Ja;
Hvor gammel var du første gang den ble satt inn?

.....år

Hvor mange år har du hatt spiral i alt?

.....år

Er du sterilisert? Ja ☐ Nei ☐

Hvis Ja;
Hvor gammel var du da du ble sterilisert? .....år

Sykdom

Har du hatt noen av følgende sykdommer?

	Ja	Nei	Hvis Ja; Alder ved start
Høyt blodtrykk	☐	☐	
Sukkersyke (diabetes)	☐	☐	
Årebetennelse	☐	☐	
Blodpropp i legg eller lår	☐	☐	
Hjerneslag, uansett type	☐	☐	
Hjerteinfarkt	☐	☐	
Reumatoid artritt (leddgikt)	☐	☐	
Crohns sykdom, ulcerøs colitt	☐	☐	
Psoriasis	☐	☐	
Fibromyalgi/Fibromyositt	☐	☐	
Deprimert mer enn 14 dager	☐	☐	

Allergi

Har du følgende allergiske sykdommer?

	Ja	Nei	Hvis Ja; Alder ved start
Eksem	☐	☐	
Høysnue	☐	☐	
Astma	☐	☐	

Er du allergisk overfor

	Ja	Nei
Bestemte typer mat	☐	☐
Pollen	☐	☐
Husdyr	☐	☐
Annet	☐	☐

Egen opplevelse av helse

Oppfatter du din egen helse som; (Sett ett kryss)

☐ meget god ☐ god ☐ dårlig ☐ meget dårlig

Brystkreft i nærmeste familie

Har noen nære slektninger hatt brystkreft;

	Ja	Nei	Vet ikke
mor	☐	☐	☐
søster	☐	☐	☐
mormor	☐	☐	☐
farmor	☐	☐	☐

Undersøkelser for kreft

Hvor ofte undersøker du brystene dine selv?
(Sett ett kryss)

Aldri	☐
Uregelmessig	☐
Regelmessig (Omtrent hver måned)	☐

Går du til regelmessig undersøkelse av brystene dine med mammografi? (Sett ett kryss)

Nei	☐
Ja, med 2 års mellomrom eller mindre	☐
Ja, med mer enn 2 års mellomrom	☐

Har du tatt kreftprøve fra livmorhalsen regelmessig?

Aldri	☐
Sjeldnere enn hvert 3. år	☐
Hver 3. år eller oftere	☐

Høyde og vekt

Hvor høy er du? ..... cm

Hvor mye veier du i dag? ..... kg

Hvor mye veide du da du var 18 år? ..... kg

Røykevaner

Har du noen gang røkt? Ja ☐ Nei ☐

Hvis Ja, ber vi deg om å fylle ut for hver fem års periode i livet hvor mange sigaretter du i gjennomsnitt røkte pr. dag i den perioden.

	Antall sigaretter hver dag						
Alder	0	1-4	5-9	10-14	15-19	20-24	25+
10-14							
15-19							
20-24							
25-29							
30-34							
35-39							
40-44							
45-49							

Bor du sammen med noen som røker? Ja ☐ Nei ☐

Hvis Ja, hvor mange sigaretter røker de til sammen pr. dag?

.....

Røkte noen av de voksne hjemme mens du var barn?

Ja ☐ Nei ☐

Hvis ja, røkte

☐ bare far ☐ bare mor ☐ far og mor ☐ andre

Fysisk aktivitet

Vi ber deg angi din fysiske aktivitet etter en skala fra svært liten til svært mye ved 14 års alder, ved 30 års alder og i dag. Skalaen nedenfor går fra 1-10. Med fysisk aktivitet mener vi både arbeid i hjemmet og i yrkeslivet samt trening og annen fysisk aktivitet som turgåing ol.

Alder	Svært lite									Svært mye
14 år	1	2	3	4	5	6	7	8	9	10
30 år	1	2	3	4	5	6	7	8	9	10
I dag	1	2	3	4	5	6	7	8	9	10

Har du drevet konkurranseidrett? Ja ☐ Nei ☐

Hvis Ja, hvor mange år i alt?

.....år

Kosthold

For hver matsort nedenfor ber vi deg krysse av i den ruten som passer hvor ofte du i gjennomsnitt i løpet av siste år har spist slik mat.

	6-10 pr dag	4-5 pr dag	2-3 pr dag	1 pr dag	5-6 pr uke	2-4 pr uke	1 pr uke	1-3 pr måned	Nesten aldri
Helmelk (glass)									
Skummet melk (glass)									
Lettmelk (glass)									
Kokekaffe (kopper)									
Traktekaffe (kopper)									
Pulverkaffe (kopper)									
Grov brød (skiver)									
Fint brød (skiver)									
Ost (skiver)									
Poteter									
Epler/pærer									
Appelsiner o.l.									

Middag	6-7 pr uke	4-5 pr uke	3 pr uke	2 pr uke	1 pr uke	2-3 pr måned	1 pr måned	Nesten aldri
Rent kjøtt								
Oppmalt kjøtt								
Fet fisk (makrell,laks o.l)								
Mager fisk (torsk ol.)								
Ris, spaghetti								
Gulerøtter								
Kål								
Kålrot								
Salat								
Broccoli/Blomkål								

Hva slags fett blir vanligvis brukt i din husholdning?

	På brød	Til matlaging
Smør eller hard margarin		
Myk (soft) margarin eller olje		
Smør/margarin blanding		

Hvor mye melk drakk du som barn hver dag?

☐ drakk ikke melk ☐ 1-3 glass ☐ 4-6 glass ☐ 7 glass eller mer

Hvor ofte spiste du grønnsaker til middag som barn?

☐ aldri ☐ 1 gang i uken eller mer sjelden

☐ 2-3 ganger i uken ☐ 4 eller flere ganger

Alkohol

Er du total avholdskvinne? Ja ☐ Nei ☐

Hvis Nei, hvor ofte og hvor mye drakk du i gjennomsnitt siste året?

	6-10 pr dag	4-5 pr dag	2-3 pr dag	1 pr dag	5-6 pr uke	2-4 pr uke	1 pr uke	1-3 pr måned	Nesten aldri
Øl (1/2 liter)									
Vin (glass)									
Brennevin (drinker)									

Solvaner

Dersom du i begynnelsen av sommeren soler deg kraftig, blir huden din; (Sett ett kryss)

☐ brun uten å først være rød ☐ rød

☐ rød med svie ☐ rød med svie og blemmer

Etter gjentatt og lenge soling, blir huden din; (Sett ett kryss)

☐ dypt brun ☐ brun ☐ lys brun ☐ aldri brun

Hvor mange uregelmessige føflekker større enn 5 mm har du sammenlagt på begge beina (fra tærne til lysken)?

(På siste side av brosjyren er det bilder som viser hva vi mener med uregelmessige føflekker.)

☐ 0 ☐ 1 ☐ 2-3 ☐ 4-6 ☐ 7-12 ☐ 13-24 ☐ 25+

Hvilken øyefarve har du? (Sett ett kryss)

☐ brun ☐ grå, grønn eller blanding ☐ blå

Hvilken hårfarve har du? (Sett ett kryss)

☐ mørkbrun, svart ☐ brun ☐ blond, gul ☐ rød

Hvor mange ganger pr. år er du blitt forbrent av solen slik at du har fått svie eller blemmer med avflassing etterpå? (Ett kryss for hver aldersgruppe)

Alder	Aldri	Høyst 1 gang pr.år	2-3 g. pr. år	4-5 g. pr. år	6 eller flere ganger
Før 10 år					
10-19 år					
20-29 år					
30-39 år					
40-49 år					

Hvor mange uker i gjennomsnitt pr. år har du vært på badeferie i syden eller i Norge?

Alder	Aldri	1 uke	2-3 uker	4-6 uker	7 uker eller mer
Før 10 år					
10-19 år					
20-29 år					
30-39 år					
40-49 år					

Hvor ofte har du solt deg i solarium?

Alder	Aldri	Sjelden	1 gang pr. mnd.	2 gang pr. mnd.	3-4 gang pr. mnd.	oftere enn 1 gang pr. uke
Før 10 år						
10-19 år						
20-29 år						
30-39 år						
40-49 år						

Takk for at du ville delta i undersøkelsen!

Paper I

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Research Article

Factors Associated with High Weight Gain and Obesity Duration: The Norwegian Women and Cancer (NOWAC) Study

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Keywords
Longitudinal studies · Obesity · Body weight changes · Risk factors

Abstract
Aim: To identify factors associated with high weight gain and obesity duration in a representative sample of Norwegian women. ***Methods:*** 66,618 Norwegian women aged 34–70 years at baseline were included in the analysis. Baseline and follow-up questionnaires completed in 1991–2011 provided information on height, weight as well as sociodemographic, lifestyle and reproductive factors. We assessed the association with multivariable logistic regression. ***Results:*** Women gained on average 0.5 kg/year (95% CI 0.5–0.5 kg/year) during 6 years of follow-up, and 3.5% maintained in obesity during 13 years of follow-up. The factors with strongest association with high weight gain (≥10 kg) were smoking cessation (cessation vs. no change, OR = 4.39, 95% CI 3.91–4.94) and decreased physical activity level (decrease vs. no change, OR = 2.40, 95% CI 2.21–2.61). Low physical activity level (high vs. low, OR = 0.17, 95% CI 0.14–0.20), higher than median age at menarche (over median vs. median or under median, OR = 0.36, 95% CI 0.31–0.41), and less than 10 years of education (>12 years vs. <10 years, OR = 0.44, 95% CI 0.37–0.51) were strongly associated with obesity duration. ***Conclusion:*** The modifiable factor with the strongest association with adverse weight development and potential for prevention was low or decreased physical activity level.

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Introduction

During the past 4 decades, the prevalence of obesity worldwide has surpassed the prevalence of underweight [1]. The increase in obesity prevalence is of great public health concern, as obesity and weight gain are independently associated with several negative health outcomes such as higher all-cause and cause-specific mortality, increased risk of cardiovascular disease, diabetes, and several types of cancer [2–8]. Long-term obesity (referred to as obesity duration) has also been associated with an increased risk of diabetes and obesity-related cancers [9, 10]. However, factors associated with weight gain and obesity duration, and the interplay between these, are less clear. To date, most studies of factors associated with body weight have been cross-sectional; however, to understand the increasing trends of obesity we also need to study factors associated with body weight development, and then a longitudinal study design with individual-level data is preferred. The latest regional health examination in Norway reported a prevalence of obesity of 23.1% in women in 2006–2008, which was a 10% point increase when compared with data from 1984–1986 [11]. In addition, Statistics Norway conducts a survey on living conditions every 3 years in a representative sample of inhabitants in Norway aged 16 years or older. Since 1998, the self-reported prevalence of obesity has increased in both women and men in Norway and reached 11% in women in 2015. Although there are differences in obesity prevalence according to age groups, region, rural/urban settlements, and reporting method (self-report or examination), the prevalence and increasing trends in obesity demonstrate that weight gain and obesity are major public health problems also in Norway. A deeper understanding of weight development and its underlying factors in various populations is needed to implement effective public health actions that could help control the obesity epidemic. In the present study, we assessed anthropometrics as well as sociodemographic, reproductive and lifestyle factors and the association with high weight gain and obesity duration. Additionally, we described short-term weight change and long-term BMI status among Norwegian women.

Material and Methods

Study Design, Participants, and Subcohorts

The Norwegian Women and Cancer (NOWAC) study is a nationally representative, population-based cohort study initiated in 1991. Women in NOWAC were randomly sampled from the Norwegian Central Population Register, which includes all Norwegian inhabitants. Details on the design, material, and procedures of the NOWAC study have been described elsewhere [12]. The NOWAC study was approved by The Regional Committee for Medical Research Ethics and The Norwegian Data Inspectorate, and all women provided written informed consent.

89,749 women, who returned a baseline questionnaire (Q1) and a follow-up questionnaire (Q2) 5–8 years later, were considered eligible for inclusion. Of these, 47,526 additionally returned a second follow-up questionnaire (Q3) 5–8 years after Q2. Women who returned Q2 were younger, weighed less, and were less likely to use hormone therapy (HT), compared to women who only returned Q1. Moreover, women who returned Q3 were also younger, weighed less, were less likely to use HT, and, further, had more years of education and were more likely to use oral contraceptives (OC), compared to women who only returned Q2.

We excluded 4 women with implausible values of weight (<30 or >200 kg) or height (<100 or >230 cm) in any of the questionnaires and women who had missing values of weight or height at Q1 or Q2 (n = 3,429). Women with missing information on important covariates at baseline (n = 19,698) were also excluded. Thus, our final analytical sample consisted of 66,618 women aged 34–70 years at baseline. Analyses of i) weight change and high weight gain and ii) duration of BMI status and obesity duration were carried out in subcohorts of the final analytical sample. In analyses of weight change and high weight gain, we excluded an additional 5,707 women with missing follow-up information on physical activity. There were no women with missing follow-up information on smoking status and menopausal status, which together with physical

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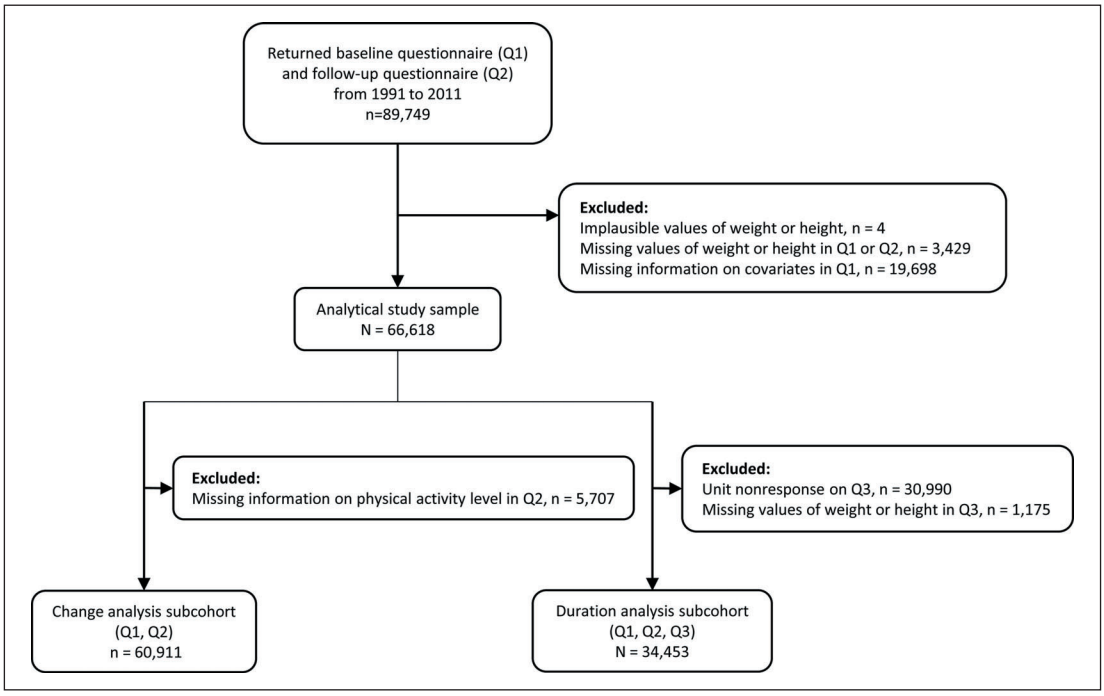

Fig. 1. Flowchart of study participants.

activity were the important transition factors. For analyses of duration of BMI status and obesity duration we excluded women who did not return Q3 (n = 30,990) or had missing information on weight or height in Q3 (n = 1,175) (fig. 1).

Outcome Measures and Covariates

Body weight change is commonly measured by either weight change in kilograms or BMI change, as BMI is a reasonably good measure of adiposity on a population level [13]. However, adults with stable height tend to follow upward weight trajectories, leading to increases in BMI until they reach the oldest age categories, when height decreases [14]. Weight change in kilograms tends to capture increases in fat mass more precisely than BMI change [13] and is also a more intuitive concept that can be communicated more effectively in public health recommendations. In order to capture short-term weight gain as long-term weight gain is more prone to weight cycling, we used self-reported weight from Q1 and Q2 to calculate weight change in kg. Weight change was categorized into five groups: weight loss <–2 kg), stable weight (–2 to <2 kg), low weight gain (2 to <5 kg), moderate weight gain (5 to <10 kg), or high weight gain (≥10 kg). The average absolute weight change was calculated by subtracting the weight in Q1 from the weight in Q2, and the average annual weight change was calculated by dividing the absolute weight change by years of follow-up time between Q1 and Q2. BMI was calculated as self-reported weight in kilograms divided by the square of self-reported height in meters and categorized according to the World Health Organization definition [15]: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5 to <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), or obesity (BMI ≥ 30 kg/m^2). Duration of BMI status was defined as women who maintained in the same BMI category in Q1, Q2, and Q3. Thus, obesity duration is defined as women who maintained in the obesity category in all three questionnaires.

Potential factors associated with the outcomes were selected based on a priori knowledge and, unless stated, extracted from Q1. In the multivariable analyses we assessed sociodemographic factors such as age (5-year increments) and education (<10 years / 10–12 years / >12 years). Lifestyle factors assessed were physical activity level based on an ordinal scale of 1–10 and collapsed into three categories: low (≤4), moderate (5–6), or high (≥7), smoking status (never/former/current) and alcohol intake (≤median / >median g/day). Further, we assessed reproductive factors such as menopausal status (pre-/peri-/post-

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menopausal/unknown) as per definition in the Million Women Study [16], age at menarche (≤median / >median), parity (nulliparous / 1–2 children / ≥3 or more children), OC use (never/ever), and HT use (never/former/current). In addition, for analyses of weight change we assessed BMI status at baseline (underweight / normal weight / overweight / obesity) and the transition factors from Q1 to Q2: i) physical activity level (no change / increase / decrease), ii) smoking status (no change / restart / cessation) with the small number of smoking initiators (n = 63) merged together with 'no change', and iii) menopausal status (no or unknown transition to menopause / transition to menopause).

Statistical Analyses

Characteristics of weight change and duration of BMI status were assessed using chi-square tests for categorical variables and one-way ANOVA or the Kruskal-Wallis test for continuous variables. We used multivariable logistic regressions to assess factor's association with high weight gain and obesity duration. The regression models were built according to the 'purposeful selection' approach [17]. Briefly, we performed univariable regressions for each covariate and included those significant at a 20% level in the multivariable model (the full model). Next, we excluded covariates that were no longer significant in the full model using Wald statistics. Log-likelihood tests were performed to compare goodness of fit between the reduced model and the full model. Finally, we tested for biological plausible interactions. The reduced final model is presented in tables 4 and 5, with the excluded covariates presented in the footnotes. All statistical analyses were performed using STATA version 14.0 (Stata Corp., College Station, TX, USA).

Results

Weight Change and Long-Term BMI Status

In total, 60,911 women were included in the weight change analyses: mean ± standard deviation (SD) age, weight and BMI was 46.1 ± 8.1 years, 65.5 ±10.7 kg and 23.6 ± 3.6 kg/m^2, respectively. The average follow-up time from Q1 to Q2 was 6.5 ± 0.8 years and did not differ substantially across weight change categories. Compared to other weight change categories, women who experienced high weight gain were younger, taller, more likely to be current smokers, premenopausal, nulliparous, ever users of OC and never users of HT (table 1). Moreover, between Q1 and Q2, they were more likely to stop smoking, decrease their physical activity level and transition to menopause. Women who lost weight were older, more likely to be overweight or have obesity, had lower education, lower physical activity level, lower alcohol intake, and were more likely to be former smokers, compared with the other weight change categories. Further, they were more likely to be postmenopausal, have three or more children, never use OC, use HT, increase their physical activity level, and restart smoking between Q1 and Q2. Overall, 28.4% of women reported stable weight (–2 to <2 kg), while 62.3% reported weight gain (≥2 kg), and 9.4% reported weight loss (<–2 kg). Women gained on average 3.1 kg between Q1 and Q2 (95 %confidence interval (CI): 2.0–3.1), which equals an average of 0.5 kg per follow-up year (95% CI 0.5–0.5 kg) (table 2). Young women (34–40 years) gained the most weight (0.6 kg/year, 95% CI 0.6–0.6), while old women (61–70 years) gained the least weight (0.1 kg/year, 95% CI 0.1–0.1).

34,453 women were included in the analysis of BMI status duration from Q1, Q2, and Q3. The average follow-up time between Q1 and Q3 was 13.1 ± 0.3 years. Compared to the other BMI duration categories, women that maintained in obesity had lower education, lower physical activity level, lower alcohol intake, and were more likely to be postmenopausal, report lower age at menarche than median, and never use OC (table 3). Women who maintained in the normal-weight category were taller, had higher education, higher physical activity level, higher alcohol intake, and were more likely to be premenopausal and more often use OC than women in the other BMI duration categories. Over the 13-year study period (Q1–Q3), most women maintained in the normal-weight category (46.4%), while 8.7% maintained in the overweight, 3.5% in the obesity, and 0.5% in the underweight category. Moreover, 40.9%

Table 1. Population characteristics by weight change category between baseline questionnaire (Q1) and follow-up questionnaire (Q2). The Norwegian Women and Cancer study, 1991–2011 (n = 60,911)

	Weight change category, kg				
	Weight loss (<–2 kg)	stable weight (–2 to <2 kg)	low weight gain (2 to <5 kg)	moderate weight gain (5 to <10 kg)	high weight gain (≥10 kg)
Number of women (%)	5,717 (9.4)	17,284 (28.4)	16,919 (27.8)	15,202 (25.0)	5,789 (9.5)
Baseline characteristics[a]					
Mean age, years (SD)	49.0 (8.6)	47.8 (8.6)	45.8 (7.8)	44.4 (7.1)	43.4 (6.7)
Mean weight, kg (SD)	72.3 (13.5)	64.7 (10.2)	63.3 (9.3)	65.3 (9.9)	68.3 (11.7)
Mean height, cm (SD)	166.5 (5.7)	166.2 (5.6)	166.2 (5.6)	166.7 (5.5)	167.2 (5.5)
BMI, %					
Underweight	1.0	2.7	3.2	2.2	2.4
Normal weight	46.2	71.1	76.2	71.3	60.9
Overweight	35.6	21.3	17.7	21.7	27.6
Obesity	17.2	5.0	3.0	4.8	9.1
Years of education, %					
<10	26.9	22.4	20.3	20.5	23.2
10–12	24.5	23.1	23.2	25.2	25.6
>12	48.6	54.5	56.6	54.2	51.3
Physical activity level, %					
Low	32.3	23.8	23.0	26.9	32.1
Moderate	39.7	42.9	43.2	42.8	38.5
High	28.1	33.3	33.9	30.4	29.5
Smoking status, %					
Never smoker	32.3	37.7	38.8	35.5	30.1
Former smoker	34.1	33.2	32.9	31.9	29.6
Current smoker	33.6	29.1	28.3	32.7	40.3
Median alcohol intake, g/day	1.5	1.9	1.9	1.8	1.6
Menopausal status, %					
Premenopausal	43.6	52.1	62.2	68.3	70.4
Perimenopausal	5.3	4.8	4.3	4.2	3.8
Postmenopausal	43.2	36.2	26.4	20.7	18.0
Unknown	8.0	6.9	7.1	6.9	7.8
Mean age at menarche, years (SD)	13.2 (1.4)	13.3 (1.4)	13.3 (1.4)	13.3 (1.4)	13.1 (1.4)
Parity, %					
Nulliparous	9.2	8.8	8.6	8.4	9.7
1–2 children	51.6	53.7	55.4	56.7	55.2
≥3 children	39.2	37.5	36.1	34.9	35.1
Oral contraceptive use, %					
Never	46.8	44.4	41.8	38.0	36.8
Ever	53.2	55.6	58.3	62.0	63.2
Hormone therapy use, %					
Never	77.1	80.0	84.2	86.9	87.7
Former	9.2	6.5	5.0	4.4	4.3
Current	13.7	13.5	10.8	8.7	8.1

Table 1 continued on next page

changed their BMI status between questionnaires. Of these women, 79.8% changed to a higher BMI category, 6.2% changed to a lower BMI category, and 14% cycled (data not shown).

Factors Associated with High Weight Gain and Obesity Duration

Smoking cessation displayed the strongest association with high weight gain, when compared to women in stable weight. Women who stopped smoking between Q1 and Q2 had more than four-fold higher odds of high weight gain (cessation vs. no change, OR = 4.39, 95% CI:3.91–4.94).

Table 1. Continued

	Weight change category, kg				
	Weight loss (<–2 kg)	stable weight (–2 to <2 kg)	low weight gain (2 to <5 kg)	moderate weight gain (5 to <10 kg)	high weight gain (≥10 kg)
Characteristics transition Q1 → Q2					
Physical activity level					
No change	50.4	52.7	52.3	50.7	47.9
Increase	28.8	23.9	21.6	20.7	16.7
Decrease	20.9	23.3	26.1	28.7	35.3
Smoking status					
No change	87.7	90.1	88.5	84.6	77.1
Restart	6.5	4.4	4.0	4.0	3.9
Cessation	5.8	5.4	7.5	11.5	19.0
Menopausal status					
No or unknown transition to menopause	52.1	43.8	34.2	28.3	26.7
Transition to menopause	47.9	56.2	65.8	71.7	73.3

SD = Standard deviation.
[a]Overall differences between weight change categories were significant for all variables ($p < 0.001$).

Table 2. Average absolute and annual weight change in kg with 95% confidence interval (CI) by age group. The Norwegian Women and Cancer Study, 1991–2011

	n	Follow-up time Q1 to Q2, years (95% CI)	Q1 to Q2, kg, mean (95% CI) [a]	
			absolute weight change	annual weight change
Age group at baseline, years[b]				
34–40	17,365	6.7 (6.7–6.7)	4.0 (4.0–4.1)	0.6 (0.6–0.6)
41–50	27,958	6.5 (6.5–6.5)	3.4 (3.3–3.4)	0.5 (0.5–0.5)
51–60	12,187	6.4 (6.3–6.4)	1.6 (1.5–1.7)	0.3 (0.3–0.3)
61–70	3,401	5.6 (5.6–5.6)	0.7 (0.5–0.8)	0.1 (0.1–0.1)
Total	60,911	6.5 (6.5–6.5)	3.1 (2.0–3.1)	0.5 (0.5–0.5)

Q1 = Baseline questionnaire; Q2 = follow-up questionnaire.
[a]The average absolute weight change was calculated by subtracting the weight in Q1 from the weight in Q2, and the average annual weight change was calculated by dividing the absolute weight change by years of follow-up time between Q1 and Q2.
[b]Overall differences between age groups were significant for absolute and annual weight change ($p < 0.001$).

Physical activity was also strongly associated with high weight gain, both the physical activity level in Q1 (high vs. low, OR = 0.30, 95% CI 0.27–0.33) and a decrease in physical activity level between Q1 and Q2 (decrease vs. no change, OR = 2.40, 95% CI 2.21–2.61). Further, already having obesity in Q1 was associated with a two-fold increase in odds of high weight gain (obesity vs. normal weight, OR = 2.06, 95% CI 1.80–2.35). Other factors significantly associated with high weight gain were being premenopausal which increased the odds of high weight gain, while young age, high education, being a current smoker, higher than median alcohol intake, and higher than median age at menarche decreased the odds of high weight gain (table 4).

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Table 3. Population characteristics by BMI duration category in baseline questionnaire (Q1), follow-up questionnaire (Q2) and second follow-up questionnaire (Q3). The Norwegian Women and Cancer Study, 1991–2010 (n = 34,453)

	BMI duration category, kg/m^2				
	stable underweight	stable normal weight	stable overweight	stable obesity	not stable
Number of women (%)	187 (0.5)	15,971 (46.4)	2,981 (8.7)	1,219 (3.5)	14,095 (40.9)
Baseline characteristics[a]					
Mean age, years (SD)	41.7 (4.6)	42.1 (5.1)	44.5 (5.1)	44.4 (5.3)	42.5 (5.1)
Mean weight, kg (SD)	48.3 (4.0)	59.1 (5.4)	73.3 (5.8)	91.3 (10.5)	66.2 (9.0)
Mean height, cm (SD)	166.2 (5.9)	166.9 (5.5)	166.5 (5.6)	165.7 (5.8)	166.5 (5.6)
Years of education, %					
<10	15.0	14.7	23.2	27.2	21.3
10–12	23.0	22.4	25.3	27.2	26.0
>12	62.0	63.0	51.5	45.6	52.7
Physical activity level, %					
Low	24.6	19.2	31.3	48.2	28.5
Moderate	38.0	43.4	43.6	35.6	42.4
High	37.4	37.5	25.1	16.2	29.2
Smoking status, %					
Never smoker	40.6	37.1	39.3	40.1	34.3
Former smoker	26.7	32.0	35.5	33.3	31.4
Current smoker	32.6	30.9	25.2	26.6	34.4
Median alcohol intake, g/day	1.6	1.9	1.6	0.9	1.7
Menopausal status, %					
Premenopausal	77.5	79.6	68.2	67.6	77.0
Perimenopausal	4.8	3.6	5.9	5.8	4.2
Postmenopausal	13.4	9.8	16.2	17.9	10.8
Unknown	4.3	7.0	9.8	8.7	8.0
Mean age at menarche, years (SD)	13.9 (1.4)	13.4 (1.4)	13.0 (1.3)	12.7 (1.4)	13.2 (1.4)
Parity, %					
Nulliparous	14.4	8.9	7.5	10.3	8.7
1–2 children	61.0	59.2	54.4	51.9	56.4
≥3 children	24.6	31.9	38.1	37.8	34.9
Oral contraceptive use, %					
Never	36.9	33.9	41.3	46.2	35.8
Ever	63.1	66.1	58.7	53.8	64.2
Hormone therapy use, %					
Never	93.6	91.9	86.6	87.5	91.0
Former	1.6	2.2	3.9	3.7	2.6
Current	4.8	5.8	9.6	8.8	6.4

SD = Standard deviation.
[a]Overall differences between BMI duration categories were significant for all variables ($p < 0.001$).

Low physical activity level displayed the strongest association with maintaining in obesity compared to maintaining normal weight from Q1 to Q3 (high vs. low, OR = 0.17, 95% CI 0.14–0.20). Higher than median age at menarche also decreased the odds of obesity duration (over median vs. median or under median, OR = 0.36, 95% CI 0.31–0.41) as well as high education (>12 years vs. <10 years, OR = 0.44, 95% CI 0.37–0.51). In addition, being a current smoker, higher than median alcohol intake, ever use of OC significantly decreased the odds of obesity duration, while older age and being nulliparous significantly increased the odds of obesity duration (table 5). We found no evidence of biological plausible interactions for any of the models.

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Table 4. Factors associated with high weight gain (n = 5,789) compared to stable weight (n = 17,284), with univariable and multivariable odds ratios (OR) and 95% confidence intervals (CI). The Norwegian Women and Cancer Study, 1991–2011

	High weight gain (≥10 kg)			
	univariable		multivariable[a]	
	OR	95% CI	OR	95% CI
Factors				
Age (5-year increments)	0.70	0.69–0.72	0.69	0.67–0.71
BMI category (kg/m^2)				
Underweight	1.08	0.97–1.34	0.87	0.71–1.08
Normal weight	1.00	reference	1.00	reference
Overweight	1.55	1.44–1.66	1.76	1.62–1.91
Obesity	2.14	1.90–2.40	2.06	1.80–2.35
Education				
<10 years	1.00	reference	1.00	reference
10–12 years	1.06	0.97–1.15	0.92	0.84–1.02
>12 years	0.89	0.82–0.96	0.78	0.71–0.85
Physical activity level				
Low	1.00	reference	1.00	reference
Moderate	0.66	0.62–0.71	0.43	0.39–0.47
High	0.65	0.60–0.71	0.30	0.27–0.33
Smoking status				
Never smoker	1.00	reference	1.00	reference
Former smoker	1.14	1.05–1.23	1.13	1.03–1.23
Current smoker	1.77	1.64–1.90	0.88	0.80–0.97
Alcohol intake (median = 1.7 g/day)				
≤1.7 g/day	1.00	reference	1.00	reference
>1.7 g/day	0.86	0.81–0.91	0.85	0.79–0.90
Menopausal status				
Premenopausal	2.65	2.45–2.86	1.24	1.11–1.39
Perimenopausal	1.60	1.36–1.89	1.09	0.91–1.31
Postmenopausal	1.00	reference	1.00	reference
Unknown	2.25	1.98–2.56	1.32	1.14–1.54
Age at menarche (median = 13 years)				
≤13 years	1.00	reference	1.00	reference
>13 years	0.74	0.69–0.79	0.88	0.82–0.94
Transition factors, Q1 → Q2				
Physical activity level				
No change	1.00	reference	1.00	reference
Increase	0.77	0.70–0.83	0.47	0.43–0.52
Decrease	1.66	1.55–1.78	2.40	2.21–2.61
Smoking				
No change	1.00	reference	1.00	reference
Restart	1.02	0.88–1.20	0.69	0.58–0.82
Cessation	4.08	3.71–4.49	4.39	3.91–4.94

Q1 = Baseline questionnaire; Q2 = follow-up questionnaire.

[a]Each variable was adjusted for all other variables shown in table. Potential covariates that did not reach statistical significance in the multivariable model were parity, oral contraceptive use, hormone therapy use and transition to menopause.

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Table 5. Factors associated with obesity duration (n = 1,219) compared to normal-weight duration (n = 15,971), with univariable and multivariable odds ratios (OR) and 95% confidence intervals (CI). The Norwegian Women and Cancer Study, 1991–2010

	Obesity duration (Q1, Q2 and Q3)			
	univariable		multivariable[a]	
	OR	95% CI	OR	95% CI
Factors				
Age (5-year increments)	1.55	1.46–1.64	1.49	1.39–1.59
Education				
<10 years	1.00	reference	1.00	reference
10–12 years	0.66	0.56–0.77	0.72	0.60–0.85
>12 years	0.39	0.34–0.45	0.44	0.37–0.51
Physical activity level				
Low	1.00	reference	1.00	reference
Moderate	0.33	0.29–0.37	0.33	0.29–0.38
High	0.16	0.14–0.19	0.17	0.14–0.20
Smoking status				
Never smoker	1.00	reference	1.00	reference
Former smoker	0.96	0.84–1.10	1.12	0.96–1.31
Current smoker	0.79	0.69–0.92	0.83	0.70–0.97
Alcohol intake (median = 1.9 g/day)				
≤1.9 g/day	1.00	reference	1.00	reference
>1.9 g/day	0.45	0.40–0.52	0.48	0.42–0.56
Age at menarche (median = 13 years)				
≤13 years	1.00	reference	1.00	reference
>13 years	0.39	0.34–0.44	0.36	0.31–0.41
Parity				
Nulliparous	1.33	1.09–1.62	1.43	1.15–1.78
1–2 children	1.00	reference	1.00	reference
≥ 3 children	1.36	1.20–1.54	1.14	0.99–1.30
Oral contraceptive use				
Never	1.00	reference	1.00	reference
Ever	0.60	0.53–0.67	0.79	0.70–0.91

Q1 = Baseline questionnaire; Q2 = follow-up questionnaire; Q3 = second follow-up questionnaire.

[a]Each variable was adjusted for all other variables shown in table. Potential covariates that did not reach statistical significance in the multivariable model were menopausal status and hormone therapy use.

Discussion

In the present study, we have described short-term weight change and long-term BMI status and identified factors associated with high weight gain and obesity duration in a representative, population-based Norwegian female cohort. Our results show that the mean adult body weight in Norwegian women increased during the study period and that younger women gained more weight than older, which is in accordance with other studies [18–21]. It is challenging to compare the mean annual weight change between studies, as population age distribution and follow-up time may differ considerably. A longer follow-up time and older population will result in a lower mean annual weight change, and vice versa. In accordance with our results, The Australian Longitudinal Study on Women's Health also reported an average annual weight gain of 0.5 kg with comparable follow-up time and mean population age [22].

Several lifestyle factors were significantly associated with high weight gain and obesity duration. Physical activity and smoking were the strongest lifestyle factors associated with high weight gain which is in agreement with findings from the Tromsø Study [23]. Low physical activity displayed the single strongest association with obesity duration, and a decrease in physical activity increased the odds of high weight gain more than two-fold. In the literature, the association between physical activity and prevention of weight gain has been inconsistent [20, 22, 24, 25], although there is strong agreement that physical activity can prevent obesity and lead to weight loss and other health benefits [26]. The relationship between smoking and the studied outcomes was complex, since it both increased and decreased the odds depending on smoking status or transition. Current smoking decreased the odds of obesity duration and high weight gain. However, smoking cessation between Q1 and Q2 displayed the strongest association with high weight gain, with four-fold increased odds, compared to women who did not change their smoking status. Smoking is associated with increased metabolic rate, decreased metabolic efficiency, and reduced appetite, but there are uncertainties regarding the effect of smoking on weight control [27]. On the other hand, cross-sectional studies have shown that heavy smoking is positively related to BMI [28, 29]. Smoking cessation is a well-established determinant of weight gain [27], and our result that smoking cessation was strongly correlated with weight gain is in accordance with those of other studies [22, 24]. The possibility of gaining weight can hamper the motivation to quit smoking, which is worrying, since smoking increases the risk of cardiovascular disease and cancer [30]. However, immediate weight gain after smoking cessation tends to attenuate [24], and smoking cessation should always be recommended regardless of any possible short-term weight gain. The factor with the third strongest association with high weight gain was already having obesity. Among the other factors significantly associated with high weight gain, only alcohol intake was a modifiable factor. Other prospective studies have found similar results that alcohol intake was negatively associated with weight gain [20, 22, 23, 31]. However, alcohol intake is not an effective weight control measure and is associated with other negative health outcomes, such as increased risk of certain types of cancer [32]. To the best of our knowledge, there are no other studies on factors associated with obesity duration (here defined as long-term obesity) with detailed information on sociodemographic, reproductive, and lifestyle factors. Thus, it is difficult to compare our results on factors associated with obesity duration with others in the literature.

The main strength of our study is that it includes a large, representative, population-based sample of Norwegian women. The comprehensive questionnaires enabled us to control for several covariates, and our longitudinal study design allowed us to use repeated measurements for outcome measures and transition covariates such as smoking, physical activity, and menopausal status. The importance of including transition variables in studies of weight change is exemplified in this study by smoking, as being a current smoker went from increasing to decreasing the odds of high weight gain after adjustment for smoking cessation. To the best of our knowledge, there has been no previous assessment of the average annual increase in body weight in a representative sample of women in middle adulthood in Norway. Nevertheless, this study has several limitations. Height and weight were self-reported, and there is a well-established tendency to underestimate height and weight, which increases with age and BMI [33]. A validation study of BMI in NOWAC was recently conducted and showed substantial agreement between self-reports and objective measurements values, although greater misclassification due to underreporting was observed in women with overweight and obesity [34]. Further, the physical activity scale in NOWAC was recently validated against a sensor that monitored heart rate and movement, showing a significant agreement but only moderate Spearman's rank correlation coefficients (0.36–0.46, $p < 0.001$) [35]. We had to omit total energy intake from the analyses as the food frequency questionnaire was not

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provided to all participants in this study, leading to a large amount of missing data, and because of known biases with respect to obesity [36]. However, the actual weight change could function as a proxy for positive energy imbalance in our weight change analyses.

In summary, over a period of 6 years of follow-up, women in middle adulthood gained on average 0.5 kg per year, and the largest increase in weight was among younger women. During 13 years of follow-up, 3.5% of women maintained in the obesity category. Lifestyle factors such as smoking cessation, physical activity decrease, and already having overweight and obesity were strongly associated with high weight gain. While for obesity duration, low physical activity, higher than median age at menarche, and less than 10 years of education displayed the strongest associations. Accordingly, physical activity can contribute considerably to the prevention of adverse weight development among Norwegian women in middle adulthood.

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Disclosure Statement

The authors declare no competing interests.

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Paper II

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ARTICLE

Epidemiology

Excess body weight, weight gain and obesity-related cancer risk in women in Norway: the Norwegian Women and Cancer study

Marisa da Silva[1], Elisabete Weiderpass[1,2,3,4], Idlir Licaj[1,5], Lauren Lissner[6] and Charlotta Rylander[1]

BACKGROUND: Excess body weight and weight gain have been reported to independently increase the risk of several cancers. There are few published studies in nationally representative populations of women on specific, 'obesity-related' cancers in relation to prior weight change and relevant confounders.

METHODS: Based on self-reported anthropometry, we prospectively assessed body mass index (BMI), weight change over 6 years and subsequent obesity-related cancer risk in the Norwegian Women and Cancer study. We used Cox proportional hazard models to calculate hazard ratios and restricted cubic splines to model potential non-linear dose–response relationships.

RESULTS: Excess body weight increased the risk of overall obesity-related cancer, postmenopausal breast, colorectal, colon, endometrial and kidney cancer, with endometrial cancer showing a threefold elevated risk. High weight gain (≥ 10 kg) increased the risk of overall obesity-related cancer, postmenopausal breast, endometrial and pancreatic cancer. The association between high weight gain and pancreatic cancer was strong, with 91% increased risk.

CONCLUSIONS: Maintaining stable weight in middle adulthood, irrespective of BMI category at baseline, and avoiding excess body weight are both important in the prevention of several obesity-related cancers in women. Our finding of increased risk of pancreatic cancer in women with moderate and high weight gain is novel.

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BACKGROUND

The prevalence of overweight and obesity has been increasing continuously worldwide over the past four decades.[1] Although body weight is a modifiable factor, the attempts to halt the obesity epidemic has failed. The global burden of cancer has increased alongside the obesity prevalence, with 13 cancer types defined as obesity-related.[2,3] The cancers with sufficient evidence of a positive association with overweight or obesity (also referred to as excess body weight) are cancer of the breast (postmenopausal), colon–rectum, endometrium, ovary, pancreas, kidney, gallbladder, gastric cardia, liver, oesophagus (adenocarcinoma), meningioma, thyroid and multiple myeloma. Weight gain is also associated with several obesity-related cancers independent of body composition.[4] However, nationally representative studies on weight gain and the risk of less-commonly diagnosed obesity-related cancers such as pancreatic and kidney cancer in women are rare. In fact, in the latest report from The World Cancer Research Fund's Continuous Update Project, the expert panel concludes that postmenopausal breast cancer is the only cancer for which there is strong evidence of an association with weight gain.[5] Thus, there is an evident research gap on weight gain and specific obesity-related cancers.

In accordance with global trends, there are indications of increased obesity prevalence in Norway. The latest regional health examination from Nord-Trøndelag (HUNT), carried out in 2006–2008, reported a prevalence of obesity of 23.1% in women. This represented a 10%-point increase from the previous HUNT report covering the period 1984–1986.[6] In addition, Statistics Norway conduct a survey on living conditions every 3 years in a representative sample of inhabitants in Norway aged 16 years or older.[7] Since 1998, the self-reported prevalence of obesity has increased in both women and men and reached 11% in women in 2015. Surely, there are differences in obesity prevalence according to age, region, rural/urban settlements and reporting method (self-report or examination), however, there is little doubt that increasing body weight is a public health concern also in Norway. Moreover, three of the five most commonly diagnosed cancers among women in Norway are obesity-related (breast, colon and endometrial cancer) and the overall cancer incidence rate has increased.[8]

In this study, we aimed to quantify separate risk estimates for body mass index (BMI) and short-term weight change in a nationally representative female cohort, for a large number of obesity-related cancers, including pancreatic and kidney cancer.

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MATERIALS AND METHODS

Study design, participants and subsamples

The Norwegian Women and Cancer (NOWAC) study is a nationally representative, population-based cohort study that was initiated in 1991, with the aim of investigating the aetiology of cancer among women in Norway. Women aged 30–70 years were randomly sampled from the Norwegian Central Population Register, which includes all Norwegian inhabitants, and invited to participate in the study during three separate waves of recruitment: 1991–1992, 1996–1997 and 2003–2005. Those who agreed to participate completed an enrolment questionnaire (Q1) and were invited to complete a follow-up questionnaire (Q2) 5–8 years after Q1. The response rate in the NOWAC study varied between 48 and 57% at enrolment, and was 81% at follow-up. The unique personal identity number assigned to every resident of Norway allowed for linkages to national registers for complete follow-up.[9] The external validity in NOWAC is considered high as the performed validation study showed that the distribution of exposures was independent of the response rate and the observed cumulative incidence of cancer vs expected national figures from the Cancer Registry of Norway showed no substantial differences.[10] Details on the design, materials and procedures of the NOWAC study have been described elsewhere.[11]

In the present study, 145,658 women who returned Q1 between 1991 and 2005 were considered eligible for inclusion (Fig. 1). We excluded women who had emigrated or died before Q1 was registered in the study database ($n = 30$), women who were diagnosed with cancer (other than non-melanoma skin cancer) prior to Q1 ($n = 5112$), and women with missing weight in both Q1 and Q2 ($n = 1678$). Women who reported implausible weight values (< 30 or > 200 kg), height values (< 100 or > 230 cm) ($n = 4$) or age at menopause (< 25 or > 60 years) ($n = 88$) in either questionnaire were also excluded. Thus, our final analytical study sample consisted of 138,746 women: 40% enroled in 1991–1992, 31% enroled in 1996–1997 and 29% enroled in 2003–2005. BMI and weight change analyses were carried out in subsamples of the final analytical study sample. In the BMI analysis, we excluded women with < 2 years of follow-up after Q1 to reduce the possible influence of reverse causality from the effects of pre-clinical cancer on weight ($n = 1\,565$), and women with missing weight or height in Q1 ($n = 1473$). In the weight change analysis, we excluded women who did not return Q2 ($n = 51\,637$). Women who returned Q2 were younger, had lower body weight and were less likely to use hormone therapy (HT) compared with women who completed only Q1. Furthermore, we excluded women who emigrated or died before Q2 was registered in the study database ($n = 8$). Women who had been diagnosed with cancer (other than non-melanoma skin cancer) prior to Q2 ($n = 2030$), had < 2 years of follow-up after Q2 ($n = 1174$), or had missing information on weight in Q1 or Q2 were also excluded ($n = 2967$).

In site-specific analyses, we excluded premenopausal women from the postmenopausal breast cancer analysis (BMI analysis, $n = 76{,}377$; weight change analysis $n = 34{,}222$), women who reported hysterectomy from the endometrial cancer analysis (BMI analysis, $n = 7394$; weight change analysis, $n = 5035$) and women who reported bilateral oophorectomy from the ovarian cancer analysis (BMI analysis $n = 2341$, weight change analysis $n = 1907$).

Follow-up and identification of cancer cases

Follow-up began at Q1 for the BMI analysis and at Q2 for the weight change analysis. Women were followed-up until cancer diagnosis, death, emigration or the end of follow-up (31 December 2014), whichever occurred first. Incidence of cancer, death and emigration were identified through linkage to the Norwegian Cancer Registry, the Cause of Death Registry and the Norwegian Central Population Register, respectively. The outcome of interest was first primary invasive cancer, for which evidence of a positive association with excess body weight is considered sufficient,[2] hereafter, referred to as 'obesity-related cancer'. These cancers were assessed as one combined outcome (overall obesity-related cancer) and as site-specific outcomes, and were classified according to the International Classification of Diseases, 10th

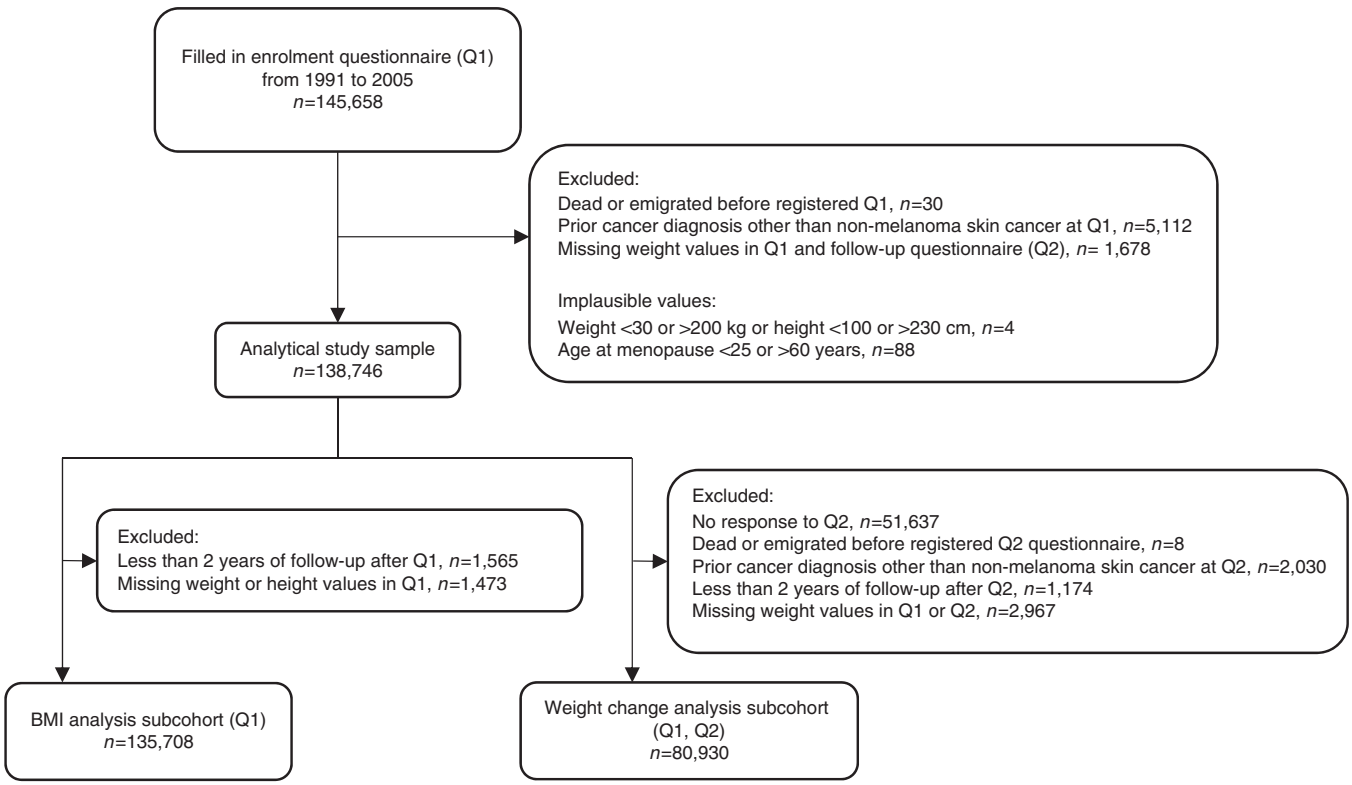

Fig. 1 Flowchart of study participants

Revision. They included cancer of the breast (postmenopausal) (C50), colon–rectum (C18–20), endometrium (C54), ovary (C56), pancreas (C25), kidney (C64), gallbladder (C23–24), gastric cardia (C16), liver (C22), oesophagus (adenocarcinoma) (C15), meningioma (C70–72), thyroid (C73) and multiple myeloma (C90). In the overall obesity-related cancer analysis, women were considered to have postmenopausal breast cancer if they reported being postmenopausal in Q1, or if they gave an age at menopause that was earlier than their age at breast cancer diagnosis. Women with unknown menopausal status or missing information on age at menopause were considered to have postmenopausal breast cancer if they had reached 53 years of age at or before the time of breast cancer diagnosis. This age cutoff has been used previously to classify women as postmenopausal in the NOWAC study[12] and represents ~80% of the women in our study population who reached natural menopause. We did not perform site-specific analyses for cancer of the gallbladder, gastric cardia, liver, oesophagus, meningioma, thyroid or multiple myeloma, owing to the small number of incident cases for each of these sites.

Assessment of BMI, weight change and covariates

BMI was calculated as self-reported weight in kg divided by the square of self-reported height in metres and categorised according to the World Health Organisation definition:[13] underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5 ≤ 25 kg/m^2), overweight (BMI 25 ≤ 30 kg/m^2), or obesity (BMI ≥ 30 kg/m^2). We used self-reported weight from Q1 and Q2 to calculate weight change, which was categorised into five groups: weight loss (≤ 2 kg), stable weight (−2– < 2 kg), low weight gain (2– < 5 kg), moderate weight gain (5– < 10 kg) or high weight gain (≥ 10 kg).

Information on covariates was extracted from Q1 for the BMI analysis, and Q1 or Q2 for the weight change analysis. An a priori selection of covariates was done, based on findings from previous studies on BMI or weight change and obesity-related cancer, as well as previous reports from the NOWAC study. Thus, the covariates education (< 10 years/10–12 years/ > 12 years), physical activity level (low/moderate/high), smoking status (never/former/current) and alcohol intake (≤ median/ > median g/day) were included in all analyses. In addition, we assessed smoking transition (cessation/restart/no change) and physical activity change (increase/decrease/no change) in all weight change analyses. The outcome-specific covariates that were common for postmenopausal breast, ovarian and endometrial cancer were age at menarche (≤ median/ > median age), parity/age at first full-term pregnancy (nullipara/unipara < 29 years/unipara ≥ 30/multipara < 29/multipara ≥ 30), oral contraceptive (OC) use (never/ever) and HT use (never/former/current). For postmenopausal breast cancer, maternal history of breast cancer (yes/no) was also included in the model, and for endometrial and ovarian cancer, menopausal status was also included in the model. Diabetes (yes/no) was evaluated as a potential confounder for endometrial, colorectal, pancreatic and kidney cancer; for colorectal cancer (as well as for colon and rectal cancer analysed separately) we assessed consumption of red and processed meat, fruits, vegetables, fibre and calcium categorised into tertiles (low/medium/high).

Statistical analysis

Population characteristics by BMI status and weight change category were assessed using χ^2 tests for categorical variables and one-way analysis of variance or Kruskal–Wallis test for continuous variables. We used Cox proportional hazard regression models with age as the underlying time metric[14] to estimate hazard ratios and 95% confidence intervals (CI) for the associations of BMI and weight change with obesity-related cancer risk. The reference groups were 'normal weight' and 'stable weight'. To account for the calendar and birth cohort effect, we constructed a variable based on wave of enrolment and birth year (categorised into four groups) that was included in the Cox regression models, and allowed the baseline hazard function to vary between the groups but with equal coefficients across groups. The Cox models were built according to the 'purposeful selection' approach.[15] In brief, we performed univariable Cox models for each covariate and included those that were significant at a 20% level in a multivariable model (the full model). Thereafter, we used Wald statistics to exclude covariates that were no longer significant in the full model, or did not change the coefficients of the exposure variable > 20%. Log-likelihood ratio tests were performed to compare goodness of fit between the reduced model and the full model. Covariates that remained in the reduced final models are presented in the footnotes of Tables 2 and 3. Participants with missing information on included covariates were excluded from the analyses. Tests based on Schoenfeld residuals showed no evidence of violation of the proportional hazard assumptions.[16] We fitted two models per outcome; Model 1 controlled only for age (by time in the Cox regression) and Model 2 (main model) with adjustments by purposeful selection of covariates for each outcome separately. We tested for plausible interactions with log-likelihood ratio test, comparing reduced models with and without the interaction term. In all weight change analyses, we tested for interaction between BMI status and weight change category. In site-specific analyses where HT use or menopausal status was included as a covariate, we tested for interactions between these and each exposure. In order to model potential non-linear dose–response relationships, we fitted restricted cubic spline transformations (four knots) of the exposure variables.[17] We evaluated non-linearity by testing the null hypothesis of equal spline coefficients. The knots were placed at equally spaced percentiles as recommended by Harrell (2001).[18] All statistical analyses were performed using STATA version 15.1 (Stata Corp., College Station, TX, USA).

RESULTS

In total, 135,708 women were included in the BMI analysis and 80,930 women who also responded to Q2 were included in the weight change analysis (Fig. 1). In the BMI analysis, average follow-up time was 16.9 (standard deviation (SD) = 5.8) years, during which 9328 obesity-related cancers were diagnosed, with a mean age at diagnosis of 61.9 (SD = 7.9) years. In the weight change analysis, average follow-up time was 13.1 (SD = 4.2) years, during which 4831 obesity-related cancers were diagnosed, with a mean age at diagnosis of 63.0 (SD = 7.7) years. The average response time between Q1 and Q2 was 6.3 years (SD = 0.9) and did not differ substantially across weight change categories.

Population characteristics

In the BMI analysis, the population mean (SD) age, weight and BMI were 48.2 (8.6) years, 66.7 (11.4) kg and 24.1 (3.9) kg/m^2, respectively. The majority of women were of normal weight (64.6%), followed by overweight (25.5%), obesity (7.7%) and underweight (2.2%) (Table 1). Compared with the other BMI categories, women with obesity were older, and had lower education, physical activity level and alcohol intake. They were more likely to be never or former smokers, report lower age at menarche, younger at first full-term pregnancy, have three or more children, less likely to use OC and more likely to report former use of HT.

In the weight change analysis, the population mean (SD) age, weight and BMI in Q2 was 52.4 (8.5) years, 68.6 (11.5) kg and 24.8 (3.9) kg/m^2, respectively. During the 6.3 years between Q1 and Q2, 9.7% of women lost weight, 29.3% had stable weight, 27.6% had low weight gain, 24.1% had moderate weight gain and 9.3% had high weight gain (Supplementary Information, Table S1). Population characteristics differed across these weight change

Table 1. Population characteristics by body mass index (BMI) category at enrolment

	BMI category (kg/m^2)				
	N[a]	Underweight	Normal weight	Overweight	Obesity
Number of women, *n* (%)	135,708	3022 (2.2)	87,595 (64.6)	34,656 (25.5)	10,435 (7.7)
Obesity-related cancer, *n*	9328	173	5689	2603	863
Characteristics at enrolment[b]					
Age (y), mean (SD)	135,708	44.1 (8.4)	46.9 (8.4)	50.8 (8.4)	51.5 (8)
Weight (kg), mean (SD)	135,708	49.3 (3.9)	61.4 (6.1)	74.2 (6.3)	91.0 (11.7)
Height (cm), mean (SD)	135,708	166.6 (5.6)	166.5 (5.6)	165.9 (5.7)	165.3 (5.8)
Education (y) %	128,948				
< 10		24.0	21.7	29.8	34.3
10–12		22.1	23.5	24.6	24.4
> 12		53.9	54.9	45.6	41.3
Physical activity level %	123,531				
Low		25.7	21.2	30.7	45.7
Moderate		37.5	42.2	42.6	37.0
High		36.8	36.7	26.7	17.4
Smoking status %	135,231				
Never smoker		27.2	34.4	37.8	40.0
Former smoker		21.3	31.8	35.7	36.2
Current smoker		51.6	33.8	26.5	23.8
Alcohol intake (g/day), median	128,046	1.6	1.9	1.5	0.9
Age at menarche (y), mean (SD)	133,625	13.7 (1.4)	13.4 (1.4)	13.2 (1.4)	12.9 (1.4)
Age at first full-term pregnancy (y), mean (SD)	123,592	24.7 (4.7)	24.1 (4.4)	23.6 (4.3)	23.4 (4.4)
Parity %	135,708				
Nulliparous		13.0	9.5	8.1	11.1
1–2 children		56.8	55.7	50.1	46.3
≥ 3 children		30.2	34.9	41.9	42.6
Oral contraceptive use %	131,415				
Never		38.2	40.6	49.8	54.4
Ever		61.8	59.4	50.2	45.6
Menopausal status %	135,708				
Premenopausal		64.0	55.3	37.1	31.6
Perimenopausal		4.2	4.8	5.6	6.6
Postmenopausal		25.9	32.9	50.1	54.7
Unknown		5.9	7.0	7.2	7.2
Age at menopause (y), mean (SD)	45,160	46.7 (5.9)	48.3 (4.8)	48.8 (4.7)	48.5 (5.2)
Hormone therapy use %	126,669				
Never		85.7	79.6	72.7	73.7
Former		5.6	8.2	12.9	14.4
Current		8.7	12.2	14.4	11.9

The Norwegian Women and Cancer study 1991–2005 ($n = 135, 708$)
[a]*N* is the total amount of responses for the specific variable
[b]Overall differences between weight change categories were significant for all variables ($p < 0.001$)
y years, *SD* standard deviation

categories. Women with high weight gain were younger and reported lower physical activity at Q1 compared with women with stable weight. Moreover, between Q1 and Q2, women with high weight gain were more likely to have stopped smoking, decreased their physical activity level and transitioned to menopause.

BMI and obesity-related cancer risk

Compared with normal-weight women, women with overweight or obesity had an increased obesity-related cancer risk, with HRs of 1.09 (95% CI: 1.03–1.14) and 1.24 (95% CI: 1.14–1.34) (Table 2). In site-specific analyses, endometrial cancer displayed a significant association with obesity, with an almost threefold increased risk (HR = 2.78, 95% CI: 2.30–3.35), as well as a significant association with overweight (HR = 1.45, 95% CI: 1.24–1.68). Furthermore, excess body weight increased the risk of postmenopausal breast cancer (overweight HR = 1.13, 95% CI: 1.00–1.27) and the association with obesity was of borderline significance (HR = 1.20, 95% CI: 1.00–1.44; $p = 0.05$). In addition, excess body weight was significantly associated with colorectal (overweight HR = 1.12, 95% CI: 1.01–1.25), colon (overweight HR = 1.21, 95% CI:

Table 2. Hazard ratio (HR) with 95% confidence interval (CI) for obesity-related cancer risk by body mass index (BMI) category at enrolment

	Model 1 age-adjusted				Model 2 multivariable			
	N	Cancer cases	HR	95% CI	*N*	Cancer cases	HR	95% CI
Overall obesity-related cancer[a]								
Underweight	3022	173	0.95	0.82–1.10	2626	149	0.92	0.78–1.08
Normal weight	87,595	5689	1.00	Reference	77,064	4961	1.00	Reference
Overweight	34,656	2603	1.10	1.05–1.15	29,517	2154	1.09	1.03–1.14
Obesity	10,435	863	1.26	1.17–1.35	8706	699	1.24	1.14–1.34
5 BMI unit increment	135,708	9328	1.11	1.08–1.14	117,913	7 963	1.10	1.07–1.13
Postmenopausal breast cancer[b]								
Underweight	899	27	0.96	0.66–1.41	650	19	0.98	0.62–1.55
Normal weight	32,831	1047	1.00	Reference	24,224	730	1.00	Reference
Overweight	19,270	638	1.04	0.95–1.15	14,079	448	1.13	1.00–1.27
Obesity	6331	206	1.07	0.92–1.24	4540	139	1.20	1.00–1.44
5 BMI unit increment	59,331	1918	1.03	0.97–1.08	43,493	1 336	1.07	1.00–1.15
Colorectal cancer[c]								
Underweight	3022	39	1.11	0.80–1.52	2902	38	1.10	0.80–1.52
Normal weight	87,595	1 146	1.00	Reference	83,411	1083	1.00	Reference
Overweight	34,656	585	1.12	1.02–1.24	32,511	544	1.12	1.01–1.25
Obesity	10,435	157	1.05	0.88–1.24	9744	140	1.01	0.84–1.20
5 BMI unit increment	135,708	1 927	1.05	0.99–1.11	128,568	1 805	1.04	0.98–1.11
Colon cancer[d]								
Underweight	3022	26	1.14	0.77–1.69	3017	26	1.13	0.76–1.67
Normal weight	87,595	746	1.00	Reference	87,355	743	1.00	Reference
Overweight	34,656	414	1.20	1.06–1.36	34,481	411	1.21	1.07–1.37
Obesity	10,435	104	1.05	0.85–1.29	10,378	103	1.06	0.86–1.30
5 BMI unit increment	135,708	1 290	1.06	0.99–1.14	135,231	1 283	1.07	0.99–1.14
Rectal cancer[e]								
Underweight	3022	13	1.05	0.60–1.82	2805	11	0.99	0.54–1.81
Normal weight	87,595	400	1.00	Reference	79,948	354	1.00	Reference
Overweight	34,656	171	0.98	0.82–1.18	30,665	153	1.02	0.84–1.24
Obesity	10,435	53	1.05	0.78–1.40	9189	44	1.03	0.75–1.42
5 BMI unit increment	135,708	637	1.03	0.93–1.14	122,607	562	1.04	0.93–1.16
Endometrial cancer[f]								
Underweight	2914	11	0.62	0.34–1.13	2594	10	0.63	0.34–1.18
Normal weight	83,620	539	1.00	Reference	74,239	489	1.00	Reference
Overweight	32,163	321	1.50	1.30–1.72	27,991	277	1.45	1.24–1.68
Obesity	9617	186	3.02	2.55–3.58	8326	156	2.78	2.30–3.35
5 BMI unit increment	128,314	1057	1.53	1.45–1.62	113150	932	1.51	1.42–1.60
Ovarian cancer[g]								
Underweight	2991	11	0.75	0.41–1.36	2851	10	0.71	0.38–1.33
Normal weight	86,442	429	1.00	Reference	81,300	404	1.00	Reference
Overweight	33,816	149	0.91	0.75–1.10	31,608	142	0.92	0.76–1.12
Obesity	10,118	53	1.13	0.85–1.51	9425	49	1.09	0.81–1.48
5 BMI unit increment	133,367	642	1.01	0.91–1.12	125,148	605	1.00	0.90–1.12
Pancreatic cancer[c]								
Underweight	3059	5	0.75	0.31–1.83	2902	4	0.55	0.20–1.48
Normal weight	88,480	213	1.00	Reference	83,411	202	1.00	Reference
Overweight	35,092	104	1.11	0.87–1.41	32,511	97	1.18	0.92–1.51
Obesity	10,574	28	1.05	0.70–1.56	9744	29	1.19	0.79–1.79
5 BMI unit increment	135,708	350	1.02	0.89–1.17	128,568	324	1.11	0.96–1.27
Kidney cancer[h]								
Underweight	3059	2	0.40	0.10–1.60	2295	2	0.50	0.12–2.04
Normal weight	88,480	158	1.00	Reference	68,745	120	1.00	Reference

Table 2 continued

	Model 1 age-adjusted				Model 2 multivariable			
	N	Cancer cases	HR	95% CI	*N*	Cancer cases	HR	95% CI
Overweight	35,092	94	1.41	1.08–1.82	26,124	62	1.32	0.96–1.81
Obesity	10,574	38	1.97	1.38–2.83	7502	27	1.95	1.26–3.02
5 BMI unit increment	135,708	292	1.34	1.18–1.51	104,666	211	1.33	1.15–1.54

[a]Model 2 for overall obesity-related cancer was adjusted for age, education, physical activity and smoking status
[b]Only in women who were postmenopausal at enrolment, model 2 for postmenopausal breast cancer was adjusted for age, education, alcohol intake, parity/age at first full-term pregnancy, oral contraceptive use, hormone therapy use and history of breast cancer in the mother
[c]Model 2 for colorectal and pancreatic cancer was adjusted for age, education and smoking status
[d]Model 2 for colon cancer was adjusted for age and smoking status
[e]Model 2 for rectal cancer was adjusted for age, education and alcohol intake
[f]Model 2 for endometrial cancer was adjusted for age, education, age at menarche, parity/age at first full-term pregnancy, oral contraceptive use and menopausal status
[g]Model 2 for ovarian cancer was adjusted for age, parity/age at first full-term pregnancy and oral contraceptive use
[h]Model 2 for kidney cancer was adjusted for age, smoking status and diabetes
The Norwegian Women and Cancer study, 1991–2014 ($n = 135{,}708$)

1.07–1.37) and kidney cancer (obesity HR = 1.95, 95% CI: 1.26–3.02). An increment of five BMI units was significantly associated with increased risk of overall obesity-related cancer, postmenopausal breast cancer, endometrial and kidney cancer. There was no significant association between excess body weight and increased risk of rectal, ovarian and pancreatic cancer.

Further, a clear dose–response relationship with increasing BMI was found for overall obesity-related cancer, endometrial and kidney cancer (Fig. 2). These dose–response relationships were statistically significant at different BMI; kidney cancer was statistically significant only after BMI 30, whereas overall obesity-related cancer and endometrial cancer were statistically significant at BMI 24 (Supplementary Information, Table S3–5). We found no statistically significant interactions between HT use and BMI; however, menopausal status modified the effect of BMI in relation to endometrial cancer risk with a statistically significant interaction between perimenopausal status and obesity. We performed stratified analysis by menopausal status (Supplementary Information, Table S2) but the subgroup analysis result should be interpreted with caution due to the low number of cases (58) in the perimenopausal status group.

Weight change and obesity-related cancer risk

Weight gain was significantly associated with increased obesity-related cancer risk, with associations observed among women with low weight gain (HR = 1.14, 95% CI: 1.05–1.23), moderate weight gain (HR = 1.14, 95% CI: 1.05–1.25) and high weight gain (HR = 1.16, 95% CI: 1.04–1.31), versus stable weight (Table 3). High weight gain was further significantly associated with nearly a twofold increased risk in pancreatic cancer (HR = 1.91, 95% CI: 1.11–3.30), also moderate weight gain increased the risk of pancreatic cancer (HR = 1.60, 95% CI: 1.03–2.47). Furthermore, weight gain increased the risk of postmenopausal breast cancer (moderate weight gain HR = 1.20, 95% CI: 1.01–1.43; high weight gain HR = 1.36, 95% CI: 1.08–1.71), as well as colorectal (moderate weight gain HR = 1.24, 95% CI: 1.05–1.48), rectal (low weight gain HR = 1.37, 95% CI: 1.00–1.86; moderate weight gain HR = 1.38, 95% CI: 1.00–1.91; $p = 0.05$) and endometrial cancer (moderate weight gain HR = 1.27, 95% CI: 1.01–1.61; high weight gain HR = 1.40, 95% CI: 1.04–1.88). Weight loss was significantly associated with an increased risk of colorectal cancer (HR = 1.25, CI: 1.01–1.55) and displayed positive associations with all obesity-related cancers under study, although they did not reach statistical significance. A 5 kg increase in weight was significantly associated with increased risk of overall obesity-related cancer, postmenopausal breast cancer and endometrial cancer. We found no significant association between weight change and the risk of colon, ovarian and kidney cancer.

When we allowed for non-linearity, we found a clear dose–response relationship with increasing weight gain for overall obesity-related cancer, postmenopausal breast cancer, endometrial and pancreatic cancer (Fig. 3). The increase in risk for these cancers was significant already with low or moderate weight gain (Supplementary Information, Table S6–9). There was no evidence of a significant interaction between BMI and weight change category in relation to overall and specific obesity-related cancer risk, which was further confirmed by the stratified analysis (Supplementary Information, Table S10). In addition, we found no significant interactions between HT use or menopausal status and weight change category.

DISCUSSION

In this study, we assessed the relationship between BMI, weight change and obesity-related cancer risk in a large and nationally representative cohort of women in Norway. We found that overweight and obesity increased overall obesity-related cancer risk by 9 and 24%. Furthermore, weight gain < 10 kg over 6 years, increased obesity-related cancer risk by 14%, whereas gaining 10 kg or more increased the risk by 16%, independent of BMI status at baseline. These findings highlight the health risks of excess body weight and increase in body weight among middle-aged women in Norway. Thus, maintaining stable weight is of utmost importance for the prevention of overall obesity-related cancer, especially as the increase in risk started at low levels of weight gain and most women gained weight. As in other studies, we found clear evidence of a significant association between excess body weight and postmenopausal breast, colorectal, colon, endometrial and kidney cancer,[2] but no significant association with rectal, ovarian or pancreatic cancer. In addition, we found significant associations between weight gain and postmenopausal breast, colorectal, rectal, endometrial and pancreatic cancer but not between weight gain and ovarian and kidney cancer. These results suggest a similar effect of excess body weight and weight gain on hormone-related cancers (postmenopausal breast, endometrial and ovarian cancer), but a differential effect on kidney, colon, rectal and pancreatic cancer. Excess body weight and weight gain may affect organs differently, depending on the mechanism of cancer development.[19] For instance, pancreatic cancer was not significantly associated with excess body weight, but there was a significant positive association with moderate and high weight gain.

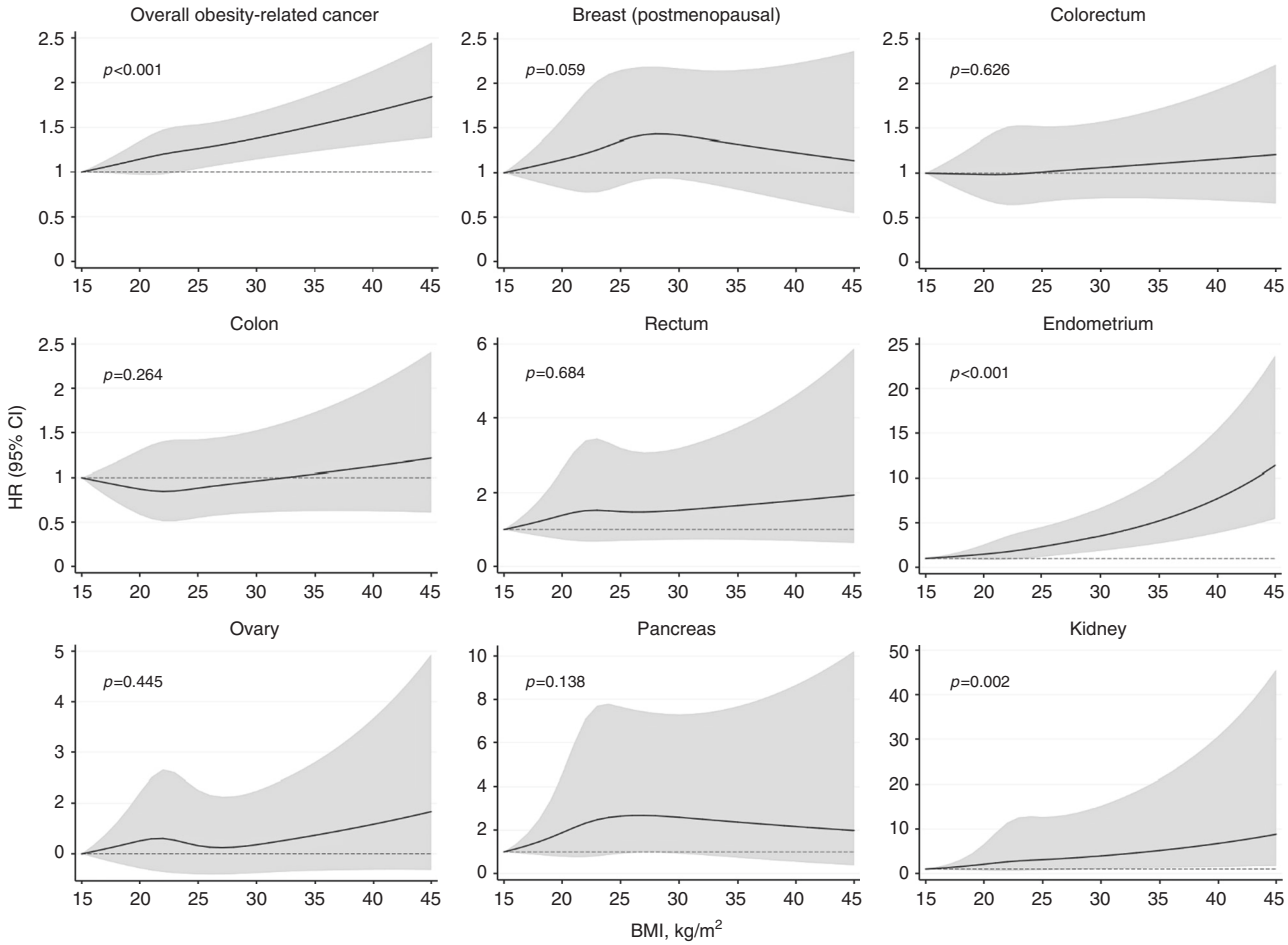

Fig. 2 Non-linear effects of BMI at enrolment and risk of specific and overall obesity-related cancers, with 95% CI. Restricted cubic splines were fitted with knots at BMI 19, 22, 25 and 31. *P* values are for non-linearity

Pancreatic cancer development could be related to increased insulin levels and higher bioavailability of insulin-like growth factor,[20] in which weight gain, rather than BMI, may play a more essential role. Our findings on weight gain and pancreatic cancer is novel. To the best of our knowledge, there has only been one previous study that included a separate analysis of pancreatic cancer and weight change in women, and it showed a non-significant, negative association.[21] Another study including both women and men, demonstrated a non-significant, positive association.[22] These two studies were included in a recent meta-analysis of weight gain and several cancers, wherein the authors hypothesised that in the presence of strong risk factors such as smoking, weight gain is not able to establish itself as an individual risk factor for pancreatic cancer.[4] Our study sample included 170 pancreatic cancer cases, and we showed a significant association of moderate and high weight gain with pancreatic cancer risk, which remained after including smoking and smoking transition as potential confounders. Thus, our results suggest a possible role of weight development in the aetiology of pancreatic cancer, which must be confirmed by future studies, particularly among women. Kidney cancer is also an obesity-related cancer less-commonly diagnosed and we found only one previous study on weight change and kidney cancer in women.[23] This aforementioned study showed no association with weight gain, consistent with our findings. On the contrary, obesity is reported as a strong predictor of kidney cancer,[2] which is in line with our results of a 95% increased risk of kidney cancer among women with obesity.

Obesity, moderate and high weight gain were significantly associated with increased risk of postmenopausal breast cancer, which is in accordance with previous studies.[4,24] The risk of postmenopausal breast cancer was higher in women experiencing moderate and high weight gain than among women with obesity, suggesting that weight gain may have an influence on postmenopausal breast cancer development beyond that of body composition. In our study, overweight, but not obesity, was associated with an increased risk of colorectal/colon cancer. This result may have been influenced by reverse causality, namely that weight loss was an early, pre-clinical symptom of colorectal cancer. There is inconsistency across studies on the association between weight change and colorectal cancer in women, with different results for colon and rectal cancers, but an overall indication of no association.[4,25] We found a positive significant association between weight loss and moderate weight gain and colorectal cancer, but there was no significant association between high weight gain and colorectal cancer. For rectal cancer, we found a significant association for low and moderate weight gain but not high weight gain. Although we excluded all women with follow-up < 2 years, we can still not entirely rule out reverse causality, as we cannot differentiate between intentional and unintentional weight loss. In fact, studies of cancer incidence in women with obesity who have undergone bariatric surgery, show a decrease in overall and female-specific (breast and gynaecological) cancer risk compared with controls, suggesting that intentional weight loss may decrease cancer risk.[26] However, large observational prospective cohort studies that can

Table 3. Hazard ratio (HR) with 95% confidence interval (CI) for obesity-related cancer risk by weight change category between the enrolment (Q1) and follow-up questionnaire (Q2)

	Model 1 age-adjusted				Model 2 Multivariable			
	N	Cancer cases	HR	95% CI	*N*	Cancer cases	HR	95% CI
Overall obesity-related cancer[a]								
Weight loss (< −2kg)	7876	478	1.15	1.04–1.28	6886	406	1.09	0.97–1.22
Stable weight (−2– < 2 kg)	23,711	1315	1.00	Reference	20,950	1 142	1.00	Reference
Low weight gain (2– < 5 kg)	22,362	1356	1.10	1.02–1.19	19,844	1 209	1.14	1.05–1.23
Moderate weight gain (5– < 10 kg)	19,495	1218	1.14	1.06–1.24	17,202	1 069	1.14	1.05–1.25
High weight gain (≥ 10 kg)	7486	464	1.19	1.06–1.32	6558	406	1.16	1.04–1.31
5 kg increment	80,930	4831	1.02	1.00–1.05	71,440	4 232	1.03	1.00–1.07
Postmenopausal breast cancer[b]								
Weight loss (< −2kg)	5456	128	1.00	0.82–1.22	4040	97	1.16	0.92–1.47
Stable weight (−2– < 2 kg)	14,997	388	1.00	Reference	11,605	277	1.00	Reference
Low weight gain (2– < 5 kg)	12,462	383	1.11	0.97–1.28	9858	293	1.16	0.98–1.36
Moderate weight gain (5– < 10 kg)	10,103	312	1.08	0.93–1.25	8025	254	1.20	1.01–1.43
High weight gain (≥ 10 kg)	3690	121	1.15	0.93–1.41	2924	102	1.36	1.08–1.71
5 kg increment	46,708	1 332	1.04	0.98–1.09	36,452	1023	1.08	1.02–1.14
Colorectal cancer[c]								
Weight loss (< −2kg)	7876	120	1.28	1.03–1.58	7874	120	1.25	1.01–1.55
Stable weight (−2– < 2 kg)	23,711	286	1.00	Reference	23,705	286	1.00	Reference
Low weight gain (2– < 5 kg)	22,362	273	1.11	0.94–1.31	22,361	273	1.11	0.94–1.32
Moderate weight gain (5– < 10 kg)	19,495	253	1.24	1.05–1.48	19,492	252	1.24	1.05–1.48
High weight gain (≥ 10 kg)	7486	75	1.04	0.8–1.34	7486	75	1.02	0.79–1.33
5 kg increment	80,930	1007	0.99	0.94–1.06	80,918	1006	1.00	0.94–1.06
Colon cancer[d]								
Weight loss (< −2kg)	7876	91	1.30	1.01–1.66	7872	91	1.26	0.98–1.61
Stable weight (−2– < 2 kg)	23,711	212	1.00	Reference	23,695	210	1.00	Reference
Low weight gain (2– < 5 kg)	22,362	181	1.01	0.83–1.24	22,355	181	1.03	0.84–1.26
Moderate weight gain (5– < 10 kg)	19,495	174	1.19	0.97–1.47	19,487	173	1.19	0.97–1.46
High weight gain (≥ 10 kg)	7486	52	1.01	0.74–1.38	7483	52	0.98	0.72–1.34
5 kg increment	80,930	710	0.98	0.91–1.05	80,892	707	0.98	0.91–1.05
Rectal cancer[e]								
Weight loss (< −2kg)	7876	29	1.22	0.80–1.88	7876	29	1.22	0.80–1.88
Stable weight (−2 to < 2 kg)	23,711	74	1.00	Reference	23,711	74	1.00	Reference
Low weight gain (2 to < 5 kg)	22,362	92	1.37	1.00–1.86	22,362	92	1.37	1.00–1.86
Moderate weight gain (5 to < 10 kg)	19,495	79	1.38	1.00–1.91	19,495	79	1.38	1.00–1.91
High weight gain (≥ 10 kg)	7486	23	1.11	0.69–1.78	7486	23	1.11	0.69–1.78
5 kg increment	80,930	297	1.03	0.92–1.15	80,930	297	1.03	0.92–1.15
Endometrial cancer[f]								
Weight loss (< −2kg)	7281	59	1.24	0.92–1.68	6813	55	1.03	0.75–1.41
Stable weight (−2– < 2 kg)	22,238	153	1.00	Reference	20,899	139	1.00	Reference
Low weight gain (2– < 5 kg)	20,998	136	0.94	0.75–1.19	19,798	127	0.99	0.78–1.26
Moderate weight gain (5– < 10 kg)	18,389	154	1.23	0.98–1.54	17,413	150	1.27	1.01–1.61
High weight gain (≥ 10 kg)	6989	69	1.51	1.13–2.01	6674	68	1.40	1.04–1.88
5 kg increment	75,895	571	1.10	1.02–1.19	71,597	539	1.12	1.04–1.20
Ovarian cancer[g]								
Weight loss (< −2kg)	7614	37	1.62	1.09–2.41	6650	30	1.52	0.99–2.34
Stable weight (−2– < 2 kg)	23,041	74	1.00	Reference	20,409	66	1.00	Reference
Low weight gain (2– < 5 kg)	21,890	90	1.25	0.92–1.71	19,497	84	1.29	0.93–1.79
Moderate weight gain (5– < 10 kg)	19,133	84	1.32	0.96–1.81	16,955	75	1.30	0.93–1.82
High weight gain (≥ 10 kg)	7345	25	1.05	0.66–1.66	6511	23	1.08	0.67–1.74
5 kg increment	79,023	310	0.96	0.86–1.06	70,022	278	0.98	0.87–1.10
Pancreatic cancer[h]								
Weight loss (< −2kg)	7876	25	1.84	1.12–3.02	7176	21	1.58	0.93–2.69

Table 3 continued

	Model 1 age-adjusted				Model 2 Multivariable			
	N	Cancer cases	HR	95% CI	*N*	Cancer cases	HR	95% CI
Stable weight (−2– < 2 kg)	23,711	42	1.00	Reference	21,697	39	1.00	Reference
Low weight gain (2– < 5 kg)	22,362	50	1.37	0.91–2.07	20,641	43	1.28	0.83–1.98
Moderate weight gain (5– < 10 kg)	19,495	48	1.59	1.04–2.43	18,124	46	1.60	1.03–2.47
High weight gain (≥ 10 kg)	7486	21	1.95	1.14–3.32	6971	21	1.91	1.11–3.30
5 kg increment	80,930	186	1.09	0.95–1.26	74,609	170	1.12	0.97–1.29
Kidney cancer[i]								
Weight loss (< −2kg)	7876	17	1.29	0.73–2.28	5750	10	1.08	0.52–2.27
Stable weight (−2– < 2 kg)	23,711	41	1.00	Reference	18,350	26	1.00	Reference
Low weight gain (2– < 5 kg)	22,362	40	1.07	0.69–1.66	17,697	27	1.14	0.66–1.96
Moderate weight gain (5– < 10 kg)	19,495	35	1.10	0.70–1.74	15,223	23	1.14	0.64–2.01
High weight gain (≥ 10 kg)	7486	15	1.31	0.72–2.38	5634	8	1.10	0.49–2.45
5 kg increment	80,930	148	1.05	0.90–1.23	62,654	94	1.09	0.90–1.31

The Norwegian Women and Cancer study, 1991–2014 ($n = 80,930$)
[a]Model 2 for obesity-related cancer was adjusted for age, BMI (Q1), physical activity (Q1), smoking status and smoking transition
[b]Only in women who were postmenopausal at Q2, model 2 for postmenopausal breast cancer was adjusted for age, education, parity/age at first full-term pregnancy, hormone therapy use and history of breast cancer in the mother
[c]Model 2 for colorectal cancer was adjusted for age and smoking status
[d]Model 2 for colon cancer was adjusted for age, BMI (Q1) and smoking status
[e]Model 2 for rectal cancer did not significantly differ from model 1 and was only adjusted for age
[f]Model 2 for endometrial cancer was adjusted for age, BMI (Q1), age at menarche, parity/age at first full-term pregnancy, oral contraceptive use and menopausal status
[g]Model 2 for ovarian cancer was adjusted for age, physical activity (Q1) and parity/age at first full-term pregnancy
[h]Model 2 for pancreatic cancer was adjusted for age, education and smoking status
[i]Model 2 for kidney cancer was adjusted for age, alcohol intake and diabetes

differentiate intentional and unintentional weight loss are warranted to improve our understanding of the effect of weight loss on cancer risk.

Endometrial cancer was strongly associated with obesity with a threefold elevated risk compared with women in normal weight. Moderate and high weight gain also increased the risk of endometrial cancer but the association for weight gain was not as strong as that for excess body weight. The evidence for a positive association between obesity, weight change and endometrial cancer risk is consistent with other studies.[24,27,28] However, many studies on weight gain and endometrial cancer risk reported an increased risk only for substantially higher weight gain categories than those included in our study,[29–31] whereas we report an increased risk starting at moderate weight gain.

The main strength of our study is its large, nationally representative, population-based sample of women in Norway with long follow-up time. The comprehensive questionnaires enabled us to control for important confounders such as anthropometric, sociodemographic, lifestyle, reproductive and menopausal factors, and the linkage with the Norwegian Cancer Registry provided us with virtually complete cancer case ascertainment. Thanks to the sample size and the extensiveness of the Norwegian Cancer Registry, we had the possibility to assess overall obesity-related cancer, and both common and less-common site-specific obesity-related cancers. There have been very few published articles on weight change and incidence of pancreatic and kidney cancer in women, and here we have added evidence to the current literature. Nevertheless, this study has several limitations. Height and weight were self-reported, and there is a well-established tendency to overestimate height as well as underestimate weight that increases with age and BMI.[32] In our study, we assume that the potential misclassification due to this information bias was non-differential between cases and non-cases. Therefore, our risk estimates may have been underestimated. Furthermore, a validation study of BMI has been conducted in the NOWAC study and showed substantial agreement between self-reports and objective measurements.[33] In addition, the covariate physical activity was also self-reported and displayed a moderate significant correlation with heart rate and movement in a previous validation study.[34] Total energy intake was omitted from the analyses because the food-frequency questionnaire was not provided to all participants in this study, leading to a large amount of missing data (61%), and because of known biases with respect to obesity.[35] Finally, as mentioned above, the lack of information on intentionality of weight loss to avoid reverse causality hampered the weight loss analysis.

The mean BMI in our study sample was 24.1. Thus, our study sample is slimmer than in many other high-income countries.[36] The generalisability of our study is restricted to women in Norway but it is unlikely that the association between excess body weight/weight gain and obesity-related cancer substantially differs across regions. However, the impact of our findings, i.e., the number of cancer cases attributable to excess body weight and weight gain (given a causal relationship) may potentially be larger in regions with higher prevalence of excess body weight or higher weight gain.

In summary, maintaining stable weight in middle adulthood, regardless BMI status, and avoiding excess body weight are important for the prevention of several obesity-related cancers. We found strong associations between obesity and endometrial cancer risk, and high weight gain and pancreatic cancer risk. Our findings on weight gain and pancreatic cancer risk are particularly interesting given the increasing incidence of pancreatic cancer in women in Norway, and the very poor prognosis of the disease.[8] If our findings are confirmed, avoidance of weight gain could be considered a potential preventive measure for pancreatic cancer.

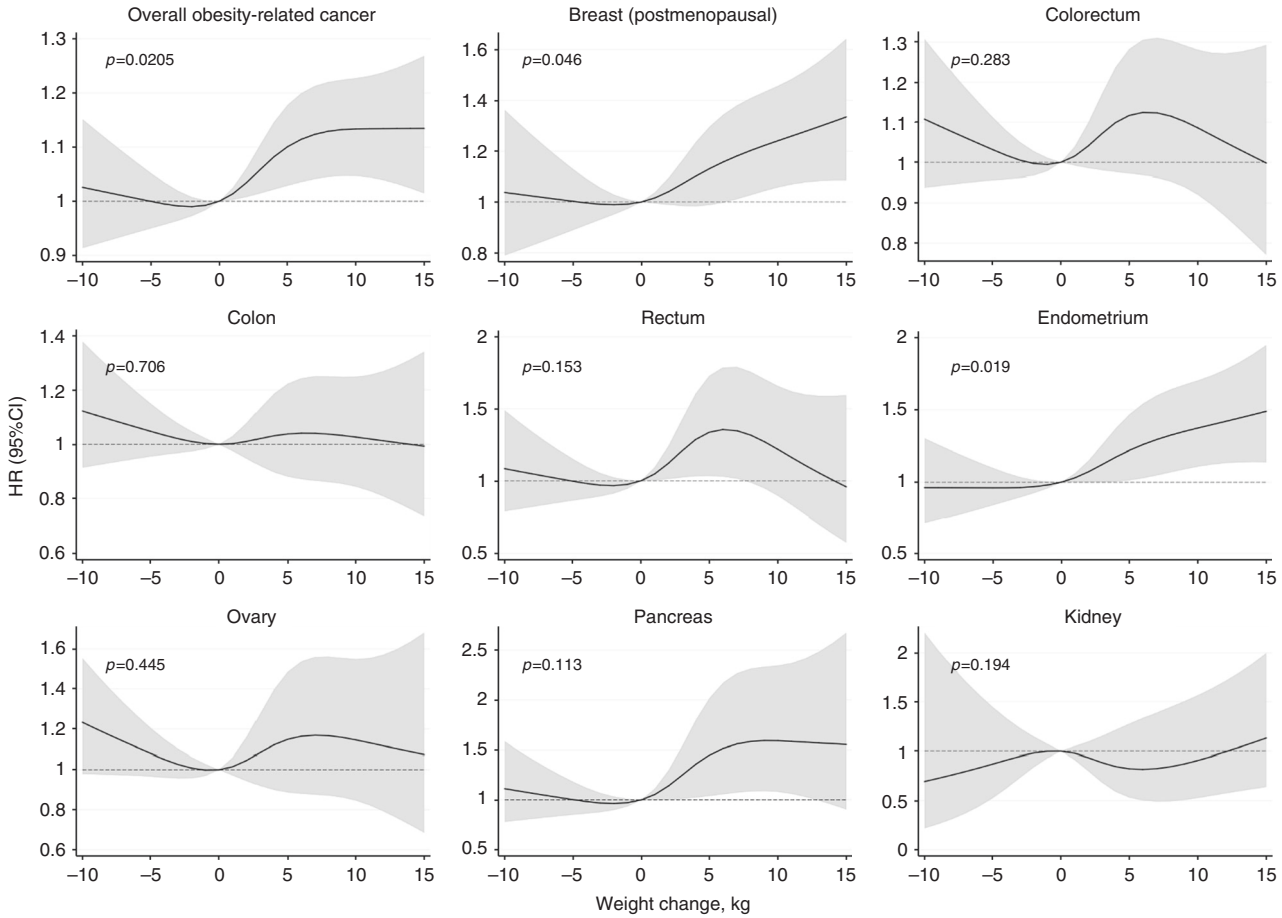

Fig. 3 Non-linear effects of 6 years weight change and risk of specific and overall obesity-related cancers, with 95% CI. Restricted cubic splines were fitted with knots at −5, 1, 4 and 11 kg. *P* values are for non-linearity

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AUTHOR CONTRIBUTIONS

M.d.S. performed the statistical analysis and drafted the manuscript. M.d.S., E.W., I.L. and C.R. developed the research plan. E.W., I.L., L.L. and C.R. critically revised the manuscript. All authors approved the final version of the manuscript.

ADDITIONAL INFORMATION

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Competing interests: The authors declare no competing interests.

Ethics approval and consent to participate: The NOWAC study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate (P REK NORD 141/2008), and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Availability of data and material: For the data supporting the presented results, please contact the person responsible for the NOWAC study—https://site.uit.no/nowac/contact-information/.

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Supplementary Information

Supplementary information Table 1 presents population characteristics by weight change category in PDF file format.

Table 1. Population characteristics by weight change category between enrolment questionnaire (Q1) and the follow-up questionnaire (Q2). The Norwegian Women and Cancer study, 1991-2011 (n=80 930)

		Weight change category (kg)				
	N†	Weight loss (<-2kg)	Stable weight (-2 to <2kg)	Low weight gain (2 to <5kg)	Moderate weight gain (5 to <10kg)	High weight gain (≥10kg)
Number of women. n (%)	80 930	7 876 (9.7)	23 711 (29.3)	22 362 (27.6)	19 495 (24.1)	7 486 (9.3)
Obesity-related cancer. n	80 930	478	1 315	1 356	1 218	464
Characteristics*						
Age (y). mean (SD)	80 930	55.3 (9.3)	53.9 (9.0)	52.0 (8.1)	50.8 (7.5)	49.8 (7.0)
Body mass index (kg/m). mean (SD) (Q1)	80 904	26.2 (4.8)	23.5 (3.5)	23.0 (3.1)	23.6 (3.4)	24.5 (4.0)
Education (y). %	77 415					
<10		31.1	25.4	22.6	23.3	25.7
10-12		23.7	22.9	23.3	25.0	25.3
>12		45.1	51.7	54.1	51.7	49.0
Physical activity level. % (Q1)	74 097					
Low		32.8	23.8	22.9	26.8	31.7
Moderate		39.5	42.6	43.0	42.5	38.9
High		27.7	33.6	34.0	30.7	29.4
Smoking status. %	80 918					
Never smoker		33.5	39.1	39.9	37.6	31.9
Former smoker		31.4	32.4	34.9	36.9	42.3
Current smoker		35.1	28.5	25.3	25.6	25.9
Alcohol intake (g/day). median	79 349	1.4	1.6	1.9	1.8	1.5
Age at menarche (y). mean (SD) (Q1)	79 788	13.2 (1.4)	13.4 (1.4)	13.3 (1.4)	13.3 (1.4)	13.1 (1.4)
Age at first full-term pregnancy (y). mean (SD)	74 062	23.7 (4.5)	24.2 (4.4)	24.1 (4.3)	24.0 (4.4)	23.7 (4.5)
Parity. %	80 930					
Nulliparous		8.3	8.3	7.9	7.6	9.1
1-2 children		49.0	51.3	53.2	54.6	53.0
≥ 3 children		42.8	40.4	38.9	37.8	37.8
Oral contraceptive use. %	80 004					
Never		48.7	45.7	42.4	39.4	38.1
Ever		51.3	54.3	57.6	60.6	61.9
Menopausal status. %	80 930					
Premenopausal		44.2	53.1	62.5	67.8	70.3
Perimenopausal		5.0	4.3	4.0	4.0	3.9
Postmenopausal		43.5	36.0	26.5	21.4	18.3
Unknown		7.3	6.7	6.9	6.8	7.6
Age at menopause (y). mean (SD)	45 881	48.7 (5)	49.0 (4.7)	48.9 (4.8)	48.6 (4.9)	47.9 (5.2)
Hormone therapy use. %	80 930					
Never		61.1	63.4	65.4	66.0	66.1
Former		18.2	14.1	12.3	12.0	13.2
Current		20.7	22.5	22.3	22.0	20.7

		Weight change category (kg)				
	N†	Weight loss (<-2kg)	Stable weight (-2 to <2kg)	Low weight gain (2 to <5kg)	Moderate weight gain (5 to <10kg)	High weight gain (≥10kg)
Characteristics transition Q1 → Q2						
Physical activity level. %	67 737					
Increase		29.6	24.3	21.9	20.6	16.6
Decrease		20.1	22.9	26.0	28.7	35.6
No change		50.3	52.9	52.0	50.7	47.8
Smoking status. %	78 008					
Cessation		5.4	5.7	7.8	11.8	19.3
Restart		7.0	4.6	4.2	4.1	4.1
No change		87.6	89.7	88.0	84.1	76.6
Menopausal status. %	80 930					
No transition to menopause		51.7	43.2	34.1	29.0	26.8
Transition to menopause		48.3	56.8	65.9	71.0	73.2

*Overall differences between weight change categories were significant for all variables ($p<0.001$)

†N is the total amount of responses for the specific variable

Abbreviations: y: years, SD: standard deviation

Supplementary Information

Supplementary information Table 2 presents stratified analysis of endometrial cancer risk and body mass index by menopausal status in PDF file format.

Table 2. Hazard ratio (HR) with 95% confidence interval (CI) for endometrial cancer risk by body mass index (BMI) and stratified by menopausal status. The Norwegian Women and Cancer study, 1991-2014 (n=113 150)*

	Menopausal status															
	Premenopausal				Perimenopausal				Postmenopausal				Unknown			
	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI
BMI category																
Underweight	1 766	7	0.65	0.30-1.37	115	0	0.00	0.00-0.00	619	3	0.80	0.25-2.50	2	0	0.00	0.00-0.00
Normal weight	44 204	297	1.00	Reference	3 663	25	1.00	Reference	22 663	146	1.00	Reference	3 709	21	1.00	Reference
Overweight	11 658	131	1.58	1.28-1.94	1 708	13	1.11	0.56-2.18	13 252	130	1.49	1.17-1.89	1 373	3	0.37	0.11-1.25
Obesity	2 994	46	2.12	1.54-2.91	595	20	4.74	2.56-8.78	4 330	85	3.12	2.37-4.10	407	5	2.25	0.82-6.15
5 BMI increment	60 622	481	1.42	1.28-1.58	6 081	58	1.70	1.42-2.03	40 864	364	1.55	1.43-1.69	5 583	29	1.29	0.88-1.88

* Adjusted for age, education, age at menarche, parity/age at first full-term pregnancy, and oral contraceptive use

Supplementary Information

Supplementary information Table 3-9 presents tables of specific and overall obesity-related cancers with a clear dose-response relationship and their respective hazard ratios and confidence intervals for selected values. The tables complement Figure 2 (body mass index analysis) and Figure 3 (weight change analysis) in the original research article and is presented in PDF file format.

Body mass index analysis

Table 3. Hazard ratio (HR) with 95% confidence interval (CI) for overall obesity-related cancer risk by body mass index (BMI) values, with fitted restricted cubic splines at knots BMI 19, 22, 25, and 31

Selected BMI values, kg/m^2	HR	95%CI
15	1.00	Reference
16	1.00	0.99-1.06
17	1.03	0.99-1.13
18	1.06	0.98-1.20
19	1.08	0.98-1.27
20	1.11	0.97-1.35
21	1.14	0.97-1.42
22	1.17	0.98-1.48
23	1.20	0.99-1.51
24	1.22	1.01-1.52
25	1.24	1.04-1.53
26	1.26	1.06-1.55
27	1.28	1.08-1.57
28	1.30	1.10-1.60
29	1.33	1.12-1.63
30	1.35	1.14-1.67
31	1.38	1.16-1.70
32	1.41	1.18-1.74
33	1.43	1.20-1.78
34	1.46	1.21-1.83
35	1.49	1.23-1.87
36	1.52	1.25-1.92
37	1.55	1.26-1.97
38	1.58	1.28-2.02
39	1.61	1.30-2.08
40	1.64	1.31-2.13
41	1.67	1.33-2.19
42	1.71	1.34-2.25
43	1.74	1.36-2.32
44	1.77	1.37-2.38
45	1.81	1.39-2.45

Table 4. Hazard ratio (HR) with 95% confidence interval (CI) for endometrial cancer risk by selected body mass index (BMI) values, with fitted restricted cubic splines at knots BMI 19, 22, 25, and 31, for selected values

Selected BMI values, kg/m^2	HR	95%CI
15	1.00	Reference
16	1.08	0.97-1.21
17	1.17	0.94-1.46
18	1.26	0.91-1.76
19	1.37	0.88-2.13
20	1.48	0.85-2.56
21	1.60	0.84-3.04
22	1.75	0.87-3.51
23	1.92	0.94-3.90
24	2.11	1.05-4.22
25	2.32	1.18-4.54
26	2.54	1.32-4.88
27	2.77	1.45-5.27
28	3.01	1.59-5.70
29	3.26	1.72-6.17
30	3.53	1.86-6.68
31	3.81	2.01-7.25
32	4.12	2.16-7.86
33	4.46	2.33-8.54
34	4.82	2.51-9.27
35	5.21	2.70-10.07
36	5.63	2.90-10.95
37	6.09	3.12-11.91
38	6.59	3.35-12.96
39	7.12	3.59-14.11
40	7.70	3.86-15.37
41	8.32	4.14-16.75
42	9.00	4.44-18.26
43	9.73	4.75-19.91
44	10.52	5.09-21.72
45	11.37	5.46-23.71

Table 5. Hazard ratio (HR) with 95% confidence interval (CI) for kidney cancer risk by selected body mass index (BMI) values, with fitted restricted cubic splines at knots BMI 19, 22, 25, and 31

Selected BMI values, kg/m^2	HR	95%CI
15	1.00	Reference
16	1.16	0.92-1.46
17	1.34	0.84-2.14
18	1.55	0.77-3.12
19	1.80	0.71-4.56
20	2.08	0.65-6.62
21	2.37	0.62-9.14
22	2.64	0.61-11.45
23	2.84	0.64-12.64
24	2.99	0.69-12.86
25	3.11	0.76-12.74
26	3.24	0.82-12.83
27	3.39	0.88-13.16
28	3.56	0.93-13.68
29	4.00	0.98-14.38
30	4.00	1.03-15.22
31	4.00	1.07-16.20
32	4.00	1.12-17.28
33	5.00	1.17-18.46
34	5.00	1.21-19.75
35	5.17	1.26-21.17
36	5.45	1.31-22.73
37	5.75	1.35-24.43
38	6.06	1.40-26.30
39	6.40	1.44-28.35
40	6.75	1.49-30.60
41	7.12	1.53-33.07
42	8.00	1.58-35.78
43	8.00	1.62-38.76
44	8.00	1.66-42.03
45	9.00	1.70-45.63

Weight change analysis

Table 6. Hazard ratio (HR) with 95% confidence interval (CI) for overall obesity-related cancer risk by selected weight change values, with fitted restricted cubic splines at knots -5, 1, 4, and 11 kg

Selected weight change values, kg	HR	95%CI
-10	1.03	0.91-1.15
-9	1.02	0.92-1.13
-8	1.02	0.93-1.11
-7	1.01	0.94-1.09
-6	1.00	0.94-1.07
-5	1.00	0.95-1.05
-4	0.99	0.96-1.03
-3	0.99	0.96-1.02
-2	0.99	0.97-1.01
-1	0.99	0.98-1.00
0	1.00	Reference
1	1.01	1.00-1.03
2	1.03	1.01-1.06
3	1.06	1.01-1.10
4	1.08	1.02-1.15
5	1.10	1.03-1.18
6	1.11	1.04-1.20
7	1.12	1.04-1.21
8	1.13	1.05-1.22
9	1.13	1.05-1.22
10	1.13	1.05-1.23
11	1.13	1.04-1.23
12	1.13	1.04-1.24
13	1.13	1.03-1.25
14	1.13	1.02-1.26
15	1.13	1.01-1.27

Table 7. Hazard ratio (HR) with 95% confidence interval (CI) for postmenopausal breast cancer risk by selected weight change values, with fitted restricted cubic splines at knots -5, 1, 4, and 11 kg

Selected weight change values, kg	HR	95%CI
-10	1.04	0.79-1.36
-9	1.03	0.81-1.31
-8	1.02	0.83-1.26
-7	1.02	0.85-1.22
-6	1.01	0.87-1.17
-5	1.00	0.89-1.13
-4	1.00	0.91-1.09
-3	0.99	0.93-1.06
-2	0.99	0.95-1.03
-1	0.99	0.97-1.01
0	1.00	Reference
1	1.02	0.99-1.04
2	1.04	0.99-1.10
3	1.07	0.98-1.17
4	1.10	0.98-1.24
5	1.13	0.99-1.30
6	1.16	1.00-1.34
7	1.18	1.01-1.38
8	1.20	1.03-1.41
9	1.22	1.04-1.43
10	1.24	1.06-1.46
11	1.26	1.07-1.48
12	1.28	1.08-1.52
13	1.30	1.08-1.55
14	1.32	1.08-1.60
15	1.33	1.08-1.64

Table 8. Hazard ratio (HR) with 95% confidence interval (CI) for endometrial cancer risk by selected weight change values, with fitted restricted cubic splines at knots -5, 1, 4, and 11 kg

Selected weight change values, kg	HR	95%CI
-10	0.96	0.71-1.30
-9	0.96	0.74-1.26
-8	0.96	0.76-1.22
-7	0.96	0.79-1.18
-6	0.96	0.81-1.14
-5	0.96	0.84-1.10
-4	0.96	0.87-1.06
-3	0.96	0.90-1.04
-2	0.97	0.92-1.01
-1	0.98	0.96-1.00
0	1.00	Reference
1	1.03	1.00-1.06
2	1.07	1.00-1.15
3	1.12	1.00-1.26
4	1.17	1.00-1.37
5	1.22	1.01-1.47
6	1.26	1.03-1.54
7	1.29	1.05-1.60
8	1.32	1.07-1.64
9	1.35	1.09-1.67
10	1.37	1.11-1.70
11	1.40	1.12-1.74
12	1.42	1.13-1.78
13	1.44	1.14-1.83
14	1.47	1.14-1.88
15	1.49	1.14-1.95

Table 9. Hazard ratio (HR) with 95% confidence interval (CI) for pancreatic cancer risk by selected weight change values, with fitted restricted cubic splines at knots -5, 1, 4, and 11 kg

Selected weight change values, kg	HR	95%CI
-10	1.11	0.78-1.59
-9	1.09	0.79-1.49
-8	1.07	0.81-1.41
-7	1.04	0.82-1.33
-6	1.02	0.84-1.25
-5	1.00	0.85-1.18
-4	0.98	0.86-1.12
-3	0.97	0.88-1.07
-2	0.96	0.90-1.03
-1	0.97	0.93-1.01
0	1.00	Reference
1	1.05	1.00-1.11
2	1.14	1.00-1.30
3	1.25	1.01-1.54
4	1.36	1.02-1.80
5	1.45	1.04-2.02
6	1.52	1.06-2.17
7	1.56	1.07-2.27
8	1.58	1.08-2.31
9	1.59	1.09-2.33
10	1.59	1.08-2.35
11	1.58	1.06-2.37
12	1.58	1.03-2.42
13	1.57	0.99-2.48
14	1.56	0.95-2.57
15	1.55	0.90-2.67

Supplementary Information

Supplementary information Table 10 presents stratified analysis of overall obesity-related cancer risk and weight change by body mass index status in PDF file format.

Table 10. Hazard ratio (HR) with 95% confidence interval (CI) for obesity-related cancer risk by weight change category between the enrolment (Q1) and follow-up questionnaire (Q2) stratified by body mass index (BMI) status (Q1). The Norwegian Women and Cancer study, 1991-2014 (n=71 440)*

	BMI category															
	Underweight				Normal weight				Overweight				Obesity			
	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI	N	Cancer cases	HR	95% CI
Weight change category																
Weight loss (<-2kg)	58	5	1.13	0.43-2.98	3 191	161	1.04	0.88-1.24	2 442	152	1.00	0.82-1.22	1 195	88	1.36	0.99-1.89
Stable weight (-2 to <2kg)	557	30	1.00	Reference	14 863	754	1.00	Reference	4 499	296	1.00	Reference	1 031	62	1.00	Reference
Low weight gain (2 to <5kg)	609	22	0.75	0.43-1.32	15 091	915	1.19	1.08-1.31	3 520	228	1.01	0.85-1.20	624	44	1.15	0.78-1.70
Moderate weight gain (5 to <10kg)	388	22	1.21	0.68-2.15	12 163	743	1.19	1.07-1.32	3 817	238	0.98	0.82-1.17	834	66	1.39	0.98-1.96
High weight gain (≥10kg)	166	8	0.80	0.36-1.81	3 940	235	1.19	1.03-1.39	1 866	118	1.08	0.87-1.35	586	45	1.40	0.95-2.07
5 kg increment	1 778	87	1.19	0.75-1.19	49 248	2 808	1.11	1.02-1.11	16 144	1 032	1.07	0.95-1.07	4 270	305	1.08	0.95-1.08

*Adjusted for age, physical activity (Q1), smoking status, and smoking transition

Paper III

Cancer burden attributable to weight gain: the Norwegian Women and Cancer study

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Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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Abstract

PURPOSE: To estimate the fraction of overall and site-specific body fatness-related cancers attributable to weight gain.

MATERIALS AND METHODS: We assessed self-reported weight gain over 7 years and its association with body fatness-related cancer risk in 44,114 women aged 34 to 49 years and followed up for 18 years from the Norwegian Women and Cancer study. We estimated the burden of body fatness-related cancers attributable to weight gain (≥2 kg) using a population attributable fraction method that accounts for death as a competing risk and statistical uncertainty.

RESULTS: In total, 3216 body fatness-related cancers and 2041 deaths were observed from 1998 to 2015. Preventing weight gain could have avoided 9.2% of body fatness-related cancer (95% confidence interval [CI], 3.5% to 14.6%). We observed the largest proportional impact of weight gain on pancreatic cancer (43.2% [95% CI, 13.7% to 62.6%]) and the highest absolute impact on postmenopausal breast cancer (4299 cancers or 16.4% [95% CI, 4.3% to 26.9%]), followed by colorectal cancer (2798 cancers or 16.4% [95% CI, 3.3% to 27.7%]). Notably, low, moderate, and high weight gain were associated with a two-fold risk of pancreatic cancer when compared to stable weight.

CONCLUSION: Maintaining a stable weight, independent of body weight status, could have prevented thousands of body fatness-related cancers and had a substantial impact on pancreatic cancer. This finding is of utmost importance given the increasing incidence of pancreatic cancer in women in Norway and worldwide, and the poor prognosis of the disease.

Introduction

The worldwide prevalence of obesity has increased to such an extent during the past four decades that obesity has been declared a global emerging epidemic that has negative consequences on health and the economy.[1,2] Body fatness has been causally associated with 13 cancers.[3] Most studies that have estimated the risk and burden of body fatness-related cancers have used body mass index (BMI) as a proxy, most often measured at one point in time.[3-5] However, weight gain has several advantages over BMI and may be a superior predictor of body fatness-related cancers. Indeed, weight gain is based on at least two repeated measurements and therefore is less prone to misclassification, tends to capture increases in fat mass more precisely, and is an intuitive concept for public health recommendations.[6] Weight gain has been shown to have an effect on several cancers independent of BMI.[4,7] Adults tend to follow upward weight trajectories through midlife, and those who experience early, rapid weight gain are more likely to follow a steeper trajectory and be at risk for body fatness-related conditions.[8] The cancer burden attributable to weight gain has only been evaluated for postmenopausal breast cancer,[9,10] and no studies have assessed the cancer burden attributable to short-term weight gain. We previously reported that weight gain ≥10 kg over seven years increased the risk of overall body fatness-related cancer, postmenopausal breast cancer, endometrial and pancreatic cancer among women in Norway.[7] To facilitate translation of these results into relevant public health measures[11], we here estimate the fraction of overall and site-specific body fatness-related cancers attributable to weight gain. We use a smaller sub-sample of Norwegian women than in our previous publication by only including women from the first wave of recruitment, which allow us to calculate absolute numbers of avoidable cancer cases over a period of 18 years.

Material and methods

Study population

The Norwegian Women and Cancer (NOWAC) study is a nationally representative prospective cohort, initiated to investigate the etiology of cancer.[12] Women were randomly sampled from the National Registry of Norway, and were invited to answer consecutive questionnaires that included questions on anthropometrics, sociodemographic, lifestyle, and reproductive factors. The unique personal identity number assigned to every resident in Norway allows for complete follow-up through linkages to national registries.[13] The NOWAC study was approved by the Regional Committee for Medical Research Ethics in Northern Norway (P REK NORD 141/2008) and the Norwegian Data Inspectorate, and it was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent for participation and data linkage. Details on the design of the NOWAC study have been described elsewhere.[12]

We included women who returned an enrollment questionnaire in 1991-1992 and a follow-up questionnaire in 1998. After exclusions, our final study sample consisted of 44,114 women, aged 34 to 49 years in 1992 (Figure 1). Women who returned the follow-up questionnaire did not differ considerably from women who did not, apart from being less likely to smoke (data not shown).

Follow-up and identification of cancer cases

Follow-up began in 1998 and continued until cancer diagnosis, death, emigration, or the end of the study (31 December, 2015), whichever occurred first. Incident, invasive, body fatness-related cancers[3] (breast (postmenopausal), colon-rectum, endometrium, ovary, pancreas, kidney (renal cell), gallbladder, gastric cardia, liver, esophagus (adenocarcinoma), thyroid, multiple myeloma, and meningioma) were identified through linkage to the Cancer Registry

of Norway, where they are classified according to the International Classification of Diseases 10th Revision. In the analysis of overall body fatness-related cancer, women were considered to have postmenopausal breast cancer if they reported postmenopausal status in the follow-up questionnaire or had reached 53 years of age before or at breast cancer diagnosis. This age cut off has been used previously in the NOWAC study and is based on the Million Women Study convention.[14,15] In the site-specific analysis of postmenopausal breast cancer, only women who reported postmenopausal status at the follow-up questionnaire were included. Dates of death and emigration were ascertained through linkage to the Cause of Death Registry and the National Registry of Norway, respectively.

Assessment of weight change and covariates

We used self-reported weight in kg from the enrollment and follow-up questionnaires to calculate short-term weight change over 7.1 (±0.6) years, which was categorized into five groups: weight loss (<–2 kg), stable weight (–2 to <2 kg), low weight gain (2 to <5 kg), moderate weight gain (5 to <10 kg), or high weight gain (≥10 kg). In all analyses, we tested potential confounding by BMI at the enrollment and follow-up questionnaires (underweight/normal weight/overweight/obesity). Adjustment for body weight at enrollment or follow-up is not recommended in weight change analysis, as body weight and weight change are dependent variables.[16] Such an adjustment would essentially be the same as assessing the association between body weight at either enrollment or follow-up and cancer incidence. Further, we assessed potential confounding by education (<10 years/10–12 years/ >12 years); physical activity (low/moderate/high); smoking status (never/former/current); alcohol intake at the enrollment questionnaire (≤median/ >median g/day); physical activity change (increase/decrease/no change) and smoking status change from the enrollment to the follow-up questionnaire (cessation/restart/no change).

In analyses on postmenopausal breast, ovarian, and endometrial cancer, the variables age at menarche (≤median/ >median age), parity/age at first full-term pregnancy (nulliparous/uniparous <29 years/ uniparous ≥30/ multipara <29/ multipara ≥30), oral contraceptive use (never/ever), and menopausal hormone therapy use (never/former/current) were tested to determine their inclusion as confounders. This was also done for the variables maternal history of breast cancer (yes/no) (for postmenopausal breast cancer) and menopausal status (for endometrial and ovarian cancer). We considered diabetes an intermediate variable in the potential causal pathway between weight change and cancer and not a potential confounder.

Statistical analysis

We used piecewise constant hazard models to estimate hazard ratios(HR) and their 95% confidence intervals (CI) to assess the strength of the association between weight change and body fatness-related cancer overall and by cancer site.[17] Observation time was used as time-scale.

Owing to the small number of incident cases, we did not perform site-specific analyses for cancers of the gallbladder, gastric cardia, liver, esophagus, and thyroid, nor for multiple myeloma and meningioma. We fitted two survival models for each outcome: an age-adjusted model and a multivariable model adjusted for additional confounders. We selected covariates a priori, based on findings from previous studies on BMI or weight change and obesity-related cancer, as well as previous reports from the NOWAC study. Further, we used the "purposeful selection" approach described by Hosmer and Lemeshow[18] to evaluate which covariates to include in the final multivariable models. Women with missing information on any of the included confounders were excluded from the analysis. By using set criteria for inclusion of covariates, we avoid exclusion of cases due to missing information on covariates not eligible for model inclusion. In addition, we tested for biologically plausible interactions between

weight change categories and BMI status, hormone therapy use or menopausal status with the likelihood ratio test, comparing models with and without the interaction term. In a sensitivity analysis, we excluded the first 2 years of follow-up to minimize potential reverse causality, as weight change may be a symptom of cancer prior to clinical diagnosis.

To calculate the population attributable fraction (PAF), we used a recently developed method[19] and program[20] that accounts for death as a competing risk and statistical uncertainty. The method combines the strength of the associations between weight gain and cancer, and weight gain and death, with the prevalence of weight gain, to estimate the fraction of cancer attributable to weight gain. Further, we multiplied PAF estimates by national incidence figures from 1998-2015, which allowed us to estimate the number of cancer cases attributable to weight gain for each statistically significant outcome. As the method accounts for death as a competing risk, the risk of overestimating PAFs is reduced.[19] All statistical analyses were performed using STATA version 15.1 (Stata Corp., College Station, TX, USA) and SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Population characteristics

In total, 3216 incident body fatness-related cancers and 2041 deaths were observed during 18 years of follow-up. The average follow-up time and age at diagnosis was 16.2±3.1 and 59.8±5.6 years. At enrollment, the average age and BMI were 41.1±4.3 years and 23.0±3.3 kg/m^2. Between the enrollment and follow-up questionnaires, 69.3% of women gained >2 kg, while 24.0% had a stable weight; the average weight change was 3.9±5.2 kg. Women with body fatness-related cancer were significantly older, heavier, more likely to have a low education level, low physical activity, and to gain weight compared to those without these cancers. There were no statistically significant differences in height, smoking status, physical

activity change, or smoking status change between women with and without body fatness-related cancers (Table 1).

Strength of association and attributable cancers

Low, moderate, and high weight gain were significantly associated with overall body fatness-related cancer (HR, 1.13; 95% CI, 1.02 to 1.25; HR, 1.13; 95% CI, 1.02, 1.26; and HR, 1.25; 95% CI, 1.09 to 1.42, respectively) and with pancreatic cancer (HR, 2.03; 95% CI, 1.11 to 3.73; HR, 2.18 to 95% CI, 1.19 to 3.98; HR, 2.45, 95% CI, 1.23 to 4.88, respectively) (Table 2). Moderate and high weight gain were significantly associated with postmenopausal breast cancer (HR, 1.36, 95% CI, 1.10 to 1.70; HR, 1.48; 95% CI, 1.14 to 1.93, respectively), and low and moderate weight gain with colorectal cancer (HR, 1.33; 95% CI, 1.05 to 1.68; HR, 1.30; 95% CI, 1.03 to 1.64, respectively). There was no significant association between weight gain and endometrial, ovarian, or kidney cancer. In addition, weight loss was significantly associated with an increased risk of overall body fatness-related cancer but not with any of the site-specific cancers under study. The results did not change substantially after adjustment for BMI at the enrollment or follow-up questionnaire, or in the sensitivity analysis that excluded the first 2 years of follow-up. There was no interaction between BMI and weight change in the analysis of overall body fatness-related cancer (Table S1 in the Supplementary Appendix). Furthermore, weight gain was not associated with death from causes other than body fatness-related cancers, with the exception of high weight gain in the pancreatic cancer analysis.

The fraction of overall body fatness-related cancer attributable to weight gain in Norway was 9.2% (95% CI, 3.5% to 14.6%), which is equivalent to 6795 cancer cases over 18 years (Table 3). Weight gain was not associated with all site-specific body fatness-related cancers under study. Hence, the number of overall body fatness-related cancers attributable to weight gain was attenuated and does not equal the sum of attributable site-specific body fatness-related

cancers. The proportion of pancreatic cancer that could be prevented by avoiding weight gain was 43.2% (95% CI, 13.7% to 62.6%), which corresponds to 1371 cancer cases. Maintaining stable weight could have prevented 16.4% of postmenopausal breast cancers (95% CI, 4.3% to 26.9%) and colorectal cancers (95% CI, 3.3% to 27.7%), translating to 4299 and 2798 cases, respectively.

Discussion

Weight gain is a modifiable risk factor that considerably impacts the body fatness-related cancer burden in women in Norway. We found that maintaining a stable weight could have prevented 9% of the body fatness-related cancers in our study sample, i.e., 6795 cancers diagnosed in 1998 to 2015. This result was independent of BMI and therefore may be of importance irrespective of body weight. These estimates would have been higher if we only assessed body fatness-related cancers that were significantly associated with weight gain, instead of all those defined by the International Agency of Research on Cancer.

We observed the largest proportional impact of weight gain on the pancreatic cancer burden and the highest absolute impact on the postmenopausal breast cancer burden. Our results indicate that over 40% of pancreatic cancers could have been prevented if women had avoided weight gain. Despite of relatively few pancreatic cancer cases in our study sample, which limited the precision of the estimates, our significant result show that stable weight has a large potential for primary prevention of pancreatic cancer. This novel finding is of special importance as the 5-year relative survival of women with pancreatic cancer in Norway is 9%, and the incidence of this cancer has steadily increased for decades.[21] In comparison, the fraction of pancreatic cancer attributable to body fatness in women in Northern Europe is 10%,[5] and our previous study found no statistically significant association between body fatness and pancreatic cancer.[7] The World Cancer Research Fund conducted a systematic

literature review on long-term weight change (ranging from ~20-50 years within each study) and pancreatic cancer risk, which they updated in a revised report. None of the included studies reported a statistically significant association[22,23], and they stated that weight gain is associated with pancreatic cancer, but as an interrelated aspect with other anthropometrics of body fatness, not independently. However, we report short-term weight gain, which was associated with an over two-fold, statistically significant, increased pancreatic cancer risk.

Our findings on pancreatic cancer may be explained by the hypotheses that: i) short-term weight gain captures body fatness more accurately than long-term weight gain or BMI, and therefore provides higher risk estimates for pancreatic cancer, ii) the prevalence of weight gain is higher than that of excess body weight, or iii) given a causal relationship, short-term weight gain may have unknown biological implications for cancer development. To-date, we have found no studies in animal models that assess short- or long-term weight gain and cancer risk to confirm or reject the latter hypothesis.

Postmenopausal breast cancer is the only cancer type with sufficient evidence for an independent association with weight gain including prospective studies.[4,9,10] The latest study reported a PAF of 19%, which is in line with our result of 16%, with comparable HRs but a higher prevalence of weight gain.[10] The fraction of postmenopausal cancer attributable to body fatness in women in Northern Europe is 12%.[5] As expected, postmenopausal breast cancer had the largest absolute number of cancers attributable to weight gain: over 4000 cases in 18 years, as it is the most commonly diagnosed cancer in women in Norway[21] and worldwide[24]. Colorectal cancer had the second largest absolute number of cancers attributable to weight gain with nearly 3000 cases. Women in Norway have among the highest colon cancer incidence rates in the Nordic countries, which could not be explained by established risk factors.[21] Although we excluded the first 2 years of follow-up in the sensitivity analyses in order to minimize potential reverse causality, we cannot fully rule out that the significant

results observed for low and moderate weight gain, but not high weight gain, were due to weight loss as a preclinical symptom of colorectal cancer. This may also be the case for our statistically significant result of increased risk of body fatness-related cancer related to weight loss, as we cannot differentiate between intentional and unintentional weight loss. Based on the non-significant associations between weight gain and ovarian and kidney cancer, as well as the borderline significant association with endometrial cancer in our previous study[7], the non-significant fractions of these cancers were probable in the present study.

The main strength of our study is its large, nationally representative sample of women in Norway. The external validity of NOWAC is considered high, as the distribution of exposures is independent of the response rate, and the cumulative incidence of cancer is not substantially different from national figures.[25] The comprehensive questionnaires enabled us to control for important confounders, and the long prospective follow-up time is important when investigating body fatness-related cancers, which some tend to be less common, develop later in life, and have various preclinical durations. The method that we used accounts for death as a potential competing risk, which ensures that PAFs are not overestimated.[19] In addition, we estimated short-term weight change from the enrollment to the follow-up questionnaire (7 years) in an attempt to isolate the impact of weight change. This is different from most studies that calculated weight change from recalled weight at the age of 18 and weight at enrollment, which may be prone to recall bias and misclassification as older women would have had a longer period of possible weight gain.

Nevertheless, this study has limitations. Weight was self-reported, and the well-established tendency to underestimate weight[26], which increases with age and BMI, has been confirmed in a validation study in NOWAC[27]. However, we assume that the potential misclassification was non-differential between women with and without body fatness-related cancers. Thus, our risk estimates may be underestimated. We can also assume that the potential underestimation

of weight was similar at the enrollment and the follow-up questionnaires, and therefore that weight change was measured accurately.

Our findings have implications for public health monitoring, clinical primary prevention, community interventions, and future research. We suggest that weight gain should be monitored more widely at the population and individual level, and that the importance of maintaining a stable weight be stressed by clinicians and through public health interventions. Additional epidemiological and biological studies on short-term weight gain and cancer risk confirming our novel results are warranted.

Contributions

MdS and CR designed the study. MdS performed the statistical analysis and drafted the manuscript. ML quality assured the statistical analysis. ML, LL, EW and CR critically revised the manuscript.

Declaration of interests

No competing interests.

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Figure 1. Flowchart of the study sample.

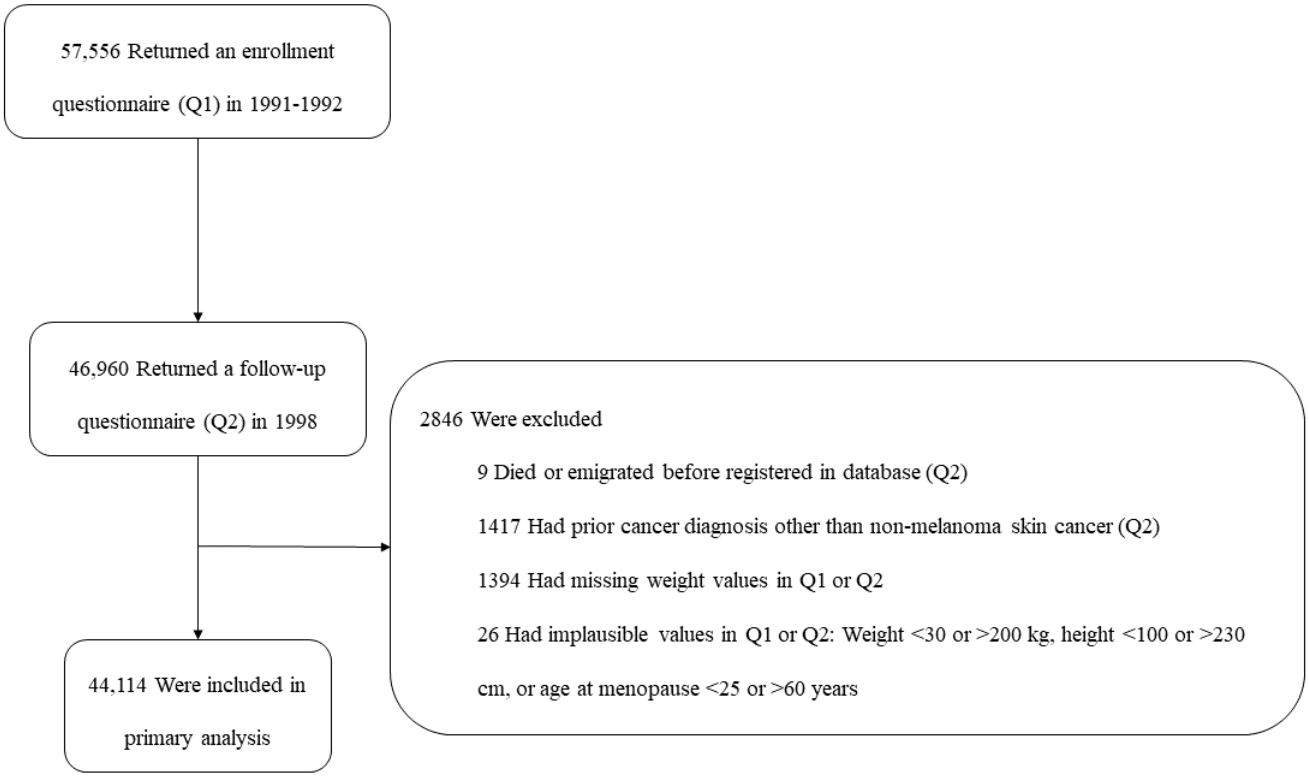

Table 1. Key characteristics of participants at enrollment questionnaire (Q1) and by change from Q1 to follow-up questionnaire (Q2), according to diagnosis of body fatness-related cancer*

	Body fatness-related cancer	
	Cases	Non-cases
Characteristics at Q1		
No. of women†	3216	40,898
Age (years)	42.7±4.1	41 ±4.3
Weight (kg)	65±10.3	63.7±10
Height (cm)	167±5.6	166.6±5.5
Body mass index (kg/m^2)	23.3±3.4	22.9±3.3
Body mass index (kg/m^2, %)		
Underweight	2.7	3.5
Normal weight	73.0	75.9
Overweight	19.1	16.6
Obesity	5.2	4.1
Education (%)		
<10 years	23.5	21.7
10-12 years	26.3	24.8
>12 years	50.3	53.5
Physical activity (%)		
Low	28.3	24.9
Moderate	41.0	42.1
High	30.7	33.0
Smoking status (%)		

Never smoker	33.0	34.4
Former smoker	30.4	30.7
Current smoker	36.6	34.9
Alcohol intake (g/day)	3.7±6.5	3.3±5.5
Changes from Q1 to Q2		
Weight change (%)		
Weight loss (<–2 kg)	6.8	6.7
Stable weight (–2 to <2 kg)	21.9	24.1
Low weight gain (2 to <5 kg)	28.6	28.6
Moderate weight gain (5 to <10 kg)	29.9	28.7
High weight gain (≥10 kg)	12.9	11.9
Physical activity change (%)		
No change	49.7	50.2
Decrease	28.1	27.0
Increase	22.2	22.8
Smoking status change (%)		
No change	82.8	83.5
Restart	5.9	6.1
Cessation	11.4	10.4

*Plus-minus values are means ± standard deviation (SD). †The numbers of women were 44,114 for the analysis of age, weight, smoking status, weight change and smoking status change; 44,106 for the analysis of height and body mass index; 43,537 for the analysis of education; 40,278 for the analysis of physical activity; 43,829 for the analysis of alcohol intake; and 38,295 for the analysis of physical activity change.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for body fatness-related cancer, according to weight change category*

	N	Cancer cases	Age-adjusted model HR (95% CI)	Multivariable model HR (95% CI)
Overall body fatness-related cancer†	38,295	2819		
Weight loss (<–2 kg)	2510	199	1.21 (1.03-1.42)	1.18 (1.00-1.38)
Stable weight (–2 to <2 kg)	9157	610	Reference	Reference
Low weight gain (2 to <5 kg)	11,003	812	1.13 (1.01-1.25)	1.13 (1.02-1.25)
Moderate weight gain (5 to <10 kg)	11,089	828	1.15 (1.04-1.28)	1.13 (1.02-1.26)
High weight gain (≥10 kg)	4536	370	1.31 (1.15-1.49)	1.25 (1.09-1.42)
Postmenopausal breast cancer‡	14,232	653		
Weight loss (<–2 kg)	1010	42	1.09 (0.77-1.54)	1.10 (0.78-1.56)
Stable weight (–2 to <2 kg)	3431	134	Reference	Reference
Low weight gain (2 to <5 kg)	4013	176	1.14 (0.91-1.43)	1.14 (0.91-1.43)
Moderate weight gain (5 to <10 kg)	4044	207	1.35 (1.09-1.68)	1.36 (1.10-1.70)
High weight gain (≥10 kg)	1734	94	1.47 (1.13-1.91)	1.48 (1.14-1.93)
Colorectal cancer∫	43,821	585		
Weight loss (<–2 kg)	2951	41	1.25 (0.87-1.78)	1.26 (0.88-1.81)
Stable weight (–2 to <2 kg)	10,497	118	Reference	Reference
Low weight gain (2 to <5 kg)	12,527	183	1.33 (1.05-1.67)	1.33 (1.05-1.68)
Moderate weight gain (5 to <10 kg)	12,609	178	1.30 (1.03-1.65)	1.30 (1.03-1.64)
High weight gain (≥10 kg)	5237	65	1.19 (0.88-1.61)	1.17 (0.86-1.59)
Endometrial cancer‖	31,419	243		

Weight loss (<–2 kg)	2005	19	1.41 (0.83-2.39)	1.09 (0.64-1.87)
Stable weight (–2 to <2 kg)	7534	51	Reference	Reference
Low weight gain (2 to <5 kg)	9108	54	0.89 (0.60-1.30)	0.94 (0.64-1.37)
Moderate weight gain (5 to <10 kg)	9098	79	1.31 (0.92-1.86)	1.29 (0.91-1.84)
High weight gain (≥10 kg)	3674	40	1.68 (1.11-2.55)	1.49 (0.98-2.27)
Ovarian cancer¶	36,862	187		
Weight loss (<–2 kg)	2460	18	1.60 (0.92-2.78)	1.59 (0.91-2.76)
Stable weight (–2 to <2 kg)	8863	41	Reference	Reference
Low weight gain (2 to <5 kg)	10,614	51	1.05 (0.70-1.58)	1.05 (0.70-1.59)
Moderate weight gain (5 to <10 kg)	10,619	59	1.23 (0.82-1.83)	1.22 (0.82-1.82)
High weight gain (≥10 kg)	4306	18	0.94 (0.54-1.63)	0.93 (0.53-1.62)
Pancreatic cancer**	44,106	111		
Weight loss (<–2 kg)	2972	7	1.68 (0.68-4.11)	1.53 (0.62-3.74)
Stable weight (–2 to <2 kg)	10,574	15	Reference	Reference
Low weight gain (2 to <5 kg)	12,600	34	1.95 (1.06-3.57)	2.03 (1.11-3.73)
Moderate weight gain (5 to <10 kg)	12,685	37	2.14 (1.17-3.90)	2.18 (1.19-3.98)
High weight gain (≥10 kg)	5275	18	2.60 (1.31-5.17)	2.45 (1.23-4.88)
Kidney cancer††	40,278	87		
Weight loss (<–2 kg)	2648	8	1.66 (0.72-3.81)	1.60 (0.69-3.68)
Stable weight (–2 to <2 kg)	9680	18	Reference	Reference
Low weight gain (2 to <5 kg)	11,576	20	0.94 (0.50-1.78)	0.95 (0.50-1.80)
Moderate weight gain (5 to <10 kg)	11,598	27	1.28 (0.71-2.33)	1.28 (0.70-2.32)
High weight gain (≥10 kg)	4776	14	1.66 (0.83-3.35)	1.60 (0.80-3.23)

*Analyses were from piecewise constant hazard models with death as a potential competing risk and included confounders by purposeful selection

†The multivariable model for overall body fatness-related cancer included physical activity, smoking status, and physical activity change

‡Only in women who were postmenopausal, the multivariable model for postmenopausal breast cancer included education, oral contraceptive use, history of breast cancer in the mother, parity/age at first full-term pregnancy, and menopausal hormone therapy use

∫The multivariable model for colorectal cancer included body mass index, smoking status, and alcohol intake

‖The multivariable model for endometrial cancer included body mass index, physical activity, oral contraceptive use, hormone therapy use, and menopausal status

¶The multivariable model for ovarian cancer included menopausal status

**The multivariable model for pancreatic cancer included height, smoking status, and smoking status change

††The multivariable model for kidney cancer included physical activity

Table 3. Population attributable fractions (PAF) and 95% confidence intervals (CI), and the absolute number of cancer cases attributable to weight gain in women in Norway in 1998 to 2015*

	Modification of weight gain (≥2 kg) to stable weight (-2kg to <2kg)		Data from the Cancer Registry of Norway, women aged 35-75 years, 1998-2015	
	PAF (%) (95% CI)	Attributable cancer cases†	Total no. of cancer cases in Norway	Age-adjusted incidence rate in Norway, per 100,000 person-years
Overall body fatness-related cancer	9.2 (3.5-14.6)	6795	73,754	376
Postmenopausal breast cancer	16.4 (4.3-26.9)	4299	26,211	268
Colorectal cancer	16.4 (3.3-27.7)	2798	17,069	87
Endometrial cancer	11.3 (–10.4-28.8)	NA	NA	NA
Ovarian cancer	6.4 (–18.8-26.3)	NA	NA	NA
Pancreatic cancer	43.2 (13.7-62.6)	1371	3173	16
Kidney cancer	11.7 (–27.0-38.6)	NA	NA	NA

*Attributable cancer cases were only calculated for outcomes with significant PAFs; † The number of attributable cancer cases for overall body fatness-related cancer is attenuated, as not all site-specific cancers were associated with weight gain; NA: not applicable

Table S1. Hazard ratios (HR) and 95% confidence intervals (CI) for body fatness-related cancer risk and weight change category, stratified according to body mass index*

	Body mass index											
	Underweight <18.5 kg/m^2			Normal weight 18.5 to <25 kg/m^2			Overweight 25 to <30 kg/m^2			Obesity ≥30 kg/m^2		
		Cancer			Cancer			Cancer			Cancer	
	N	cases	HR (95% CI)	N	cases	HR (95% CI)	N	cases	HR (95% CI)	N	cases	HR (95% CI)
Overall body fatness-related cancer†												
Weight loss (<–2 kg)	31	3	1.13 (0.34-3.79)	1298	85	1.01 (0.80-1.27)	817	70	1.21 (0.89-1.64)	364	41	1.78 (1.06-2.99)
Stable weight (–2 to <2 kg),	348	23	Reference	7152	465	Reference	1341	100	Reference	315	22	Reference
Low weight gain (2 to <5 kg)	490	26	0.84 (0.48-1.47)	9105	666	1.13 (1.01-1.28)	1220	103	1.14 (0.87-1.51)	185	17	1.41 (0.75-2.66)
Moderate weight gain (5 to <10 kg	313	15	0.74 (0.38-1.43)	8640	640	1.15 (1.02-1.30)	1798	143	1.08 (0.83-1.39)	335	30	1.26 (0.73-2.20)
High weight gain (≥10 kg)	137	10	0.93 (0.44-1.97)	2972	224	1.18 (1.01-1.39)	1113	107	1.41 (1.07-1.86)	314	29	1.45 (0.83-2.55)

* Analyses were from piecewise constant hazard models with death as a potential competing risk and included confounders by purposeful selection.

†The multivariable model for overall body fatness-related cancer included physical activity, smoking status, and physical activity change