Menopausal hormone therapy and breast cancer risk: effect modification by body mass through life

Marie Søfteland Sandvei[1,2,3] MD, PhD, marie.s.sandvei@gmail.com

Lars J. Vatten[1] MD, PhD, lars.vatten@ntnu.no

Elisabeth Krefting Bjelland[4,5] PhD, elisabeth.krefting.bjelland@ahus.no

Anne Eskild[4,6] MD, PhD, anne.eskild@medisin.uio.no

Solveig Hofvind[7] PhD, solveig.hofvind@kreftregisteret.no

Giske Ursin[7,8,9] MD, PhD, giske.ursin@kreftregisteret.no

Signe Opdahl[1] MD, PhD, signe.opdahl@ntnu.no

[1] Norwegian University of Science and Technology, Department of Public Health and Nursing, Trondheim, Norway

[2] Nordland Hospital Bodø, Department of Cancer and Palliative Care, Bodø, Norway

[3] University of Tromsø, Department of Clinical Medicine, Tromsø, Norway

[4] Akershus University Hospital, Department of Obstetrics and Gynecology, Lørenskog, Norway

[5] Uppsala University, Department of Public Health and Caring Sciences, Sweden

[6] University of Oslo, Institute of Clinical Medicine, Campus Ahus, Oslo, Norway

[7] Cancer Registry of Norway, Institute of Population-Based Research, Oslo, Norway

[8] University of Oslo, Institute of Basic Medical Sciences, Oslo, Norway

[9]Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California, USA

Corresponding author: Marie Søfteland Sandvei, NTNU, Fakultet for medisin og helsevitenskap, Institutt for samfunnsmedisin og sykepleie, Postboks 8905, N-7491 Trondheim, Norway.

Email: marie.s.sandvei@gmail.com

Phone: +47 41469825

Acknowledgements

We are indebted to the women who participated in the Norwegian Breast Cancer Screening Program (NBCSP) and provided the information that is used in this study.

Abstract

It is not known whether increased breast cancer risk caused by menopausal hormone therapy (HT) depends on body mass patterns through life. In a prospective study of 483,241 Norwegian women aged 50-69 years at baseline, 7,656 women developed breast cancer during follow-up (2006-2013). We combined baseline information on recalled body mass in childhood/adolescence and current (baseline) body mass index (BMI) to construct mutually exclusive life-course body mass patterns. We assessed associations of current HT use with breast cancer risk according to baseline BMI and life-course patterns of body mass, and estimated relative excess risk due to interaction (RERI). Within all levels of baseline BMI, HT use was associated with increased risk. Considering life-course body mass patterns as a single exposure, we used women who "remained at normal weight" through life as the reference, and found that being "overweight as young" was associated with lower risk (hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.76-0.94), whereas women who "gained weight" had higher risk (HR 1.20, 95% CI 1.12-1.28). Compared to never users of HT who were "overweight as young", HT users who either "remained at normal weight" or "gained weight" in adulthood were at higher risk than expected when adding the separate risks (RERI 0.52, 95% CI 0.09-0.95, and RERI 0.37, 95% CI -0.07-0.80), suggesting effect modification. Thus, we found that women who remain at normal weight or gain weight in adulthood may be more susceptible to the risk increasing effect of HT compared to women who were overweight as young.

Key words: breast cancer; menopausal hormone therapy; body-mass index; epidemiology; cohort study

The use of hormone therapy (HT) around menopause, particularly estrogen and progestogen in combination (EPT), increases the risk of breast cancer [1, 2]. Ideally, an individual risk-benefit assessment should be performed before prescribing HT for menopausal symptoms [3], but predicting individual breast cancer risk is difficult and has its limitations [3, 4]. One challenge is that the effect of HT use may be modified by other factors that influence risk [5-8]. Previously, it has been suggested that the risk increasing effect of HT is weaker in overweight than in normal weight women [1, 7, 9, 10], and that HT use may not contribute to additional risk in women who are overweight around menopause [5, 6]. However, in most previous studies, relative risks were compared directly between subgroups with different baseline risk, an approach that may not be appropriate to assess the importance of effect modification [11]. Instead, for public health purposes and in individual decision-making, the additive scale is preferable [12], where positive departure from additivity implies that the number of cases attributable to the combination of risk factors exceed the sum of cases attributable to each individual risk factor [13]. It is well known that overweight after menopause is positively associated with breast cancer risk [14-16], whereas overweight at younger ages is inversely associated with risk before menopause [15, 17]. In addition, there is accumulating evidence that overweight in childhood and adolescence is inversely associated with risk, both before and after menopause [15, 16, 18-24].

Thus, the complex role of body mass warrants closer examination of the combined effects of HT and body mass on breast cancer risk. If the effect of HT varies according to life course patterns of body mass, tailored recommendations for HT use may be a relevant option. Therefore, we studied body mass patterns from childhood until postmenopausal age, and assessed whether the association of HT use

with breast cancer risk could be modified by different patterns of body mass through life.

METHODS

Study population

The source of the study population was women who attended the Norwegian Breast Cancer Screening Program [25], to which all women 50 to 69 years of age with residence in Norway receive biennial invitations (for practical purposes, age at invitations ranges from 48 to 71 years). The program reached national coverage in 2005, and at each round, attendance has been stable at approximately 75%. Among all invited women, 84% participate at least once [25].

In the period 2006-2015, questionnaires were included with the invitations [26], and completion of the first questionnaire was defined as the baseline from when each woman was followed up for breast cancer. In addition to socio-demographic factors, the questionnaires covered age at menarche, use of hormonal contraception, age at first birth, number of pregnancies, information on smoking habits (never, former, current), and alcohol consumption. Information about current and previous health was included, as well as BMI at the time of participation (termed baseline BMI from here) [10]. The women were also asked to categorize their height and weight relative to their peers in childhood (age 7 years) and adolescence (age 15 years). These ages were selected to cover the period before and after age at menarche, which is an established breast cancer risk factor [27, 28]. Age 7 and 15 years correspond to the ages when women in the cohort started school and had their Christian confirmation ceremony, respectively, possibly improving recall accuracy.

Using the 11-digit personal identification number of Norwegian residents, we linked questionnaire data to information about all incident cases of invasive breast cancer registered at the Cancer Registry of Norway (International Classification of Diseases, 7th edition) [29], and to information on date of death and emigration from the Central Population Registry. Follow-up started at questionnaire completion (first attendance in the screening program after January 1, 2006), and ended at the date of breast cancer diagnosis, date of emigration, date of death from other causes than breast cancer, or at the end of follow-up, December 31, 2013, whichever occurred first.

A total of 488,112 women responded (86% of all screened women) [30]. Among them, we excluded 4,853 women with previously diagnosed breast cancer and 18 women who had emigrated or died within a month after screening participation. Thus, 483,241 women were followed up for incident breast cancer and included in the analyses.

The study was approved by the Regional Committee for Ethics in Medical Research in Norway (reference no. 2014/1711 REK south-east D).

Study variables

In the questionnaire, the participants were asked to categorize their body weight compared to their peers at the ages of 7 and 15 years as being “much below average”, “somewhat below average”, “average”, “somewhat above average”, or “much above average”. Due to few responses in the most extreme categories, we combined the responses at each age into “below average”, “average” or “above average”.

We used these categories in combination with baseline BMI to construct three life course patterns of body mass. We considered the results for weight in childhood and adolescence as sufficiently consistent to combine them into a single measure

(correlation coefficient 0.62), thereby reducing loss of power from missing values on one of the questions. Thus, we classified women who reported weight above average at either 7 or 15 years as being "overweight as young", regardless of their baseline BMI. This decision was supported by previous publications that show negative associations of similar strength for overweight at different ages early in life with breast cancer risk before and after menopause, independently of adult BMI [18]. Women who reported weight below or at average at 7 and 15 years of age (or at a single age if missing on the other age), and whose BMI was <25 kg/m² at baseline, were classified as "remained at normal weight" through life. Finally, women who reported weight below or at average at 7 and 15 years of age, but were overweight (BMI ≥25 kg/m²) at baseline, were classified as having "gained weight".

We excluded women who reported menarche before 8 or after 18 years of age [27], first pregnancy before 8 or after 55 years of age, baseline body weight less than 30 kg or more than 299 kg, or height less than 120 cm or more than 203 cm, from analyses of these factors, respectively. In analyses of age at natural menopause, women with a surgical menopause (i.e. hysterectomy and/or uni- or bilateral oophorectomy), or menopause before 15 or after 71 years of age (the oldest participant), were excluded [31, 32].

The questions about current and former use and duration of HT use indicated use of the following HT-formulations: estradiol-NETA (oral formulations: Kliogest, Activelle, Trisekvens, Novofem, and transdermal formulations: Sequidot, Estalis), estradiol-medroxyprogesterone (Indivina), estradiol-levonorgestrel (Cyclabil), tibolon (Livial), estriol (Ovesterin) and estradiol (Progynova (oral), Estradot and Evorel (transdermal)). In the analyses, we restricted HT use to systemic therapy in broad categories; either all types of HT or, more specifically, use of EPT. Among current

users of HT, 11% reported <2 years of use, 13% 2-5 years, 18% 5-10 years, and 31% ≥10 years, whereas 27% did not report duration of use.

Statistical analyses

Cox proportional hazards models were used to estimate associations (hazard ratios, HRs, with 95% confidence intervals, CIs) of single exposures, as well as the combination of exposures, with breast cancer risk. In all models, attained age was used as the timescale. Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals and by inspection of the log-log plots.

We assessed whether the association of all types of HT (or specifically, EPT) with breast cancer risk could be modified by body mass. Thus, we assessed effect modification of HT by baseline BMI and by life course patterns of body mass, and considered effect modification as present if the risk associated with both exposures departed from additivity [33, 34]. Thus, relative excess risk due to interaction (RERI) [35-37] was calculated as HR_{11}-HR_{10}-HR_{01}+HR_{00} where HR_{ij} is the hazard ratio for i = use of HT (0 = never, 1 = current) and j = BMI (0 = <25, 1 = ≥25) or weight/body mass pattern (0 = "overweight as young", 1 = "remained at normal weight" or 1 = "gained weight"). RERI corresponds to the excess risk due to effect modification, expressed as a proportion of the hazard in women who are free from both risk factors. The null-value of RERI, corresponding to additivity of risks, is zero.

HT use was the factor of primary interest, and therefore, we assessed potential confounding by factors associated with both HT use and breast cancer risk, according to recent recommendations [34]. Thus, we adjusted for the following potentially confounding factors: education (<9, 9, 12, >12 years), age at first birth (<20, 20-24, 25-29, 30-34, ≥35 years, nulliparous), number of children (0, 1, 2, 3, 4-14) and current alcohol consumption (abstainer, 1-5, 6-10, >10 units per month). In analyses

including relative weight in childhood or adolescence, we also adjusted for relative height at age 7 or 15 years (below average, average, above average) to account for variation in relative weight due to variation in height. Women with missing data on specific factors were excluded from the analyses where these factors were included as either exposures or as covariates.

In sensitivity analyses, we excluded 2,206 cases diagnosed within six months after start of follow-up to address potential bias from reverse causality (i.e. detection of advanced breast cancers that might have affected body weight at baseline). We also repeated analyses with body mass at younger ages based on the individual responses at age 7 and 15 years, rather than the combination of these two.

Other studies have evaluated effect modification of HT by BMI on a multiplicative scale [5, 6, 10]. To enable comparison with these studies, we also applied a multiplicative scale, and used likelihood-ratio tests to assess effect modification [38]. Some studies included data that allowed calculation of RERI, but did not present estimates of RERI. We therefore calculated RERI from these studies, using the formula referred to above [38, 39]. In these studies, only postmenopausal women were included in the analyses. To facilitate comparison, we therefore repeated our own analyses of effect modification according to baseline BMI for women <55 and ≥55 years, using age ≥55 years at baseline to approximate postmenopausal status. All analyses were performed using the statistical software Stata (Version 13.1; Stata Corp, College Station, TX, USA).

RESULTS

During 2,432,832 person-years, 7,656 incident cases of invasive breast cancer were diagnosed. Mean age at baseline was 57.0 years, and mean age at diagnosis was 61.0 years (range 48.6 to 76.7 years). Mean duration of follow-up was 5.0 years (median

5.8 years). Among cases, 44.5% (3,406) were stage I at diagnosis; 20.9% (1,601) were stage II; 3.2% (246) were stage III, 1.1% (82) were stage IV; 0.6% (47) were stage 0 (carcinoma in situ), and 29.7% (2,274) had unknown stage at the time of diagnosis.

Table 1 summarizes age-adjusted associations of well-known risk factors for breast cancer (age at menarche, age at first birth, parity, number of children, age at natural menopause), and shows that the results were all in the expected directions. Only 13% of participants reported that they still had menstrual cycles, whereas 6% were unsure and/or had irregular cycles. Among women who had never used HT, the corresponding percentages were 19% and 9%, respectively. The correlation coefficient between HT use and baseline BMI was -0.03, and 11% of women with BMI ≥25 kg/m^2 were current users of HT compared to 13% of women with BMI <25 kg/m^2.

Body mass patterns through life and use of HT as single exposures

Self-reported weight at 7 and 15 years of age were both inversely associated with breast cancer risk later in life (Table 2), whereas baseline BMI was positively associated with risk. The association of baseline BMI with breast cancer was somewhat stronger for women who were postmenopausal or ≥55 years at baseline, compared to women who were premenopausal or <55 years (Online Resource 1).

In the analysis of body mass patterns through the life course, we used women who had "remained at normal weight" as the reference, and found a lower risk of breast cancer in women who were "overweight as young" (HR 0.88, 95% CI 0.80-0.97). On the other hand, women who had "gained weight" (average or less at 7 and/or 15 years, but overweight between 50 and 69 years of age) were at higher risk

(HR 1.15, 95% CI 1.08-1.23) compared to women who had "remained at normal weight" through life.

Current use of HT was associated with a strong increase in risk. Thus, risk in current users was nearly two-fold (HR 1.92, 95% CI 1.80-2.05) compared to never users. The medication was dominated by EPT, and for current EPT users, the risk was slightly higher than for all HT users (HR 2.22, 95% CI 2.07-2.38), compared to never users (Table 2).

Effect modification of HT use related to baseline body mass and body-mass patterns through life

Table 3 shows effect modification of HT use by baseline BMI. Women who were either current users of HT (HR 2.09, 95% CI 1.90-2.30) or whose baseline BMI was ≥25 kg/m^2 (HR 1.20, 95% CI 1.11-1.29), had a higher risk of breast cancer compared to never users of HT whose BMI was <25 kg/m^2. The risk in women with both exposures (current HT use and overweight) was roughly the same as expected when adding the risks associated with each factor (RERI -0.11, 95% CI -0.37-0.15). Thus, the association of HT use with breast cancer risk did not appear to be modified by baseline BMI.

In Tables 4 and 5 and in Figure 1, we present effect modification of HT use by body mass patterns through life, with the combination of never use of HT and "overweight as young" as the common reference. We found that current HT users who were "overweight as young", were at higher risk (HR 1.68, 95% CI 1.32-2.14) compared to never users of HT who were "overweight as young". However, we found the highest risk in current HT users who had "remained at normal weight" (HR 2.25, 95% CI 1.93-2.62). Their risk was higher than expected when adding the risks

associated with each of the two factors (RERI 0.52, 95% CI 0.09-0.95), suggesting effect modification. Similarly (Table 5), the combination of current HT user and "gained weight" in adulthood (HR 2.28, 95% CI 1.94-2.67), also indicated effect modification (RERI 0.37, 95% CI -0.07-0.80).

In separate analyses, applying a method often used by other investigators, we tested whether HT use and body mass were associated with departure from multiplicativity of effects on breast cancer risk, using likelihood ratio tests. Thus, we found that hazard ratios of breast cancer for HT use differed between baseline BMI ≥25 kg/m^2 versus <25 kg/m^2, suggesting that associations were less than multiplicative (likelihood-ratio test $P = 0.04$). For the pattern "remained at normal weight" versus "overweight as young", departure from multiplicativity was less convincing ($P = 0.07$), and for "gained weight" versus "overweight as young", there were no indications of departure from multiplicativity($P = 0.54$).

The results for any use of HT and results restricted to use of EPT were nearly identical. Also, including adjustment for potentially confounding factors (Online Resources 2-4), the multivariable-adjusted estimates did not substantially differ from the age-adjusted results.

In sensitivity analysis, we excluded 2,206 cases detected within six months of the study baseline, but the results were nearly identical to the main results. Results were also similar when using weight only at age 7 years or only at age 15 years, instead of the combination of these, to define "overweight as young". We also compared women with and without missing information on body weight at 7 and/or 15 years of age, and found that baseline BMI was practically identical (25.9 kg/m² and 25.8 kg/m²).

In Online Resource 5, we use data available from previous studies, and present RERI as calculated from information about HT use and current BMI or weight gain, using a common reference category [15, 40-46]. Estimates of RERI varied greatly between studies, but were <0 in all except for one case-control study [41], suggesting possible effect modification on the additive scale in nearly all studies. In separate analyses according to age at baseline in the present cohort, RERI was -0.06 (95% CI 0.46-0.34) for women <55 years and -0.24 (95% CI -0.59-0.11) for women ≥55 years at baseline (Online Resource 6 and 7).

DISCUSSION

In this large population based study with follow-up for breast cancer among ever attendees in the Norwegian Breast Cancer Screening Program, we found that HT use was associated with increased breast cancer risk within all levels of baseline BMI. The results also suggest that the effect of HT may be modified by body mass patterns through life; thus, the excess risk associated with HT use was substantially higher in women who either remained at normal weight or gained weight in adulthood, compared to women who were overweight at a young age.

Major strengths of our study include the large population of women from all parts of Norway, complete follow-up for breast cancer incidence and total mortality, and high validity of the diagnoses recorded in the Cancer Registry of Norway [29].

HT use increased steeply in Norway in the 1990s, peaked around 2000 and decreased after the results from the Women's Health Initiative were published [47]. Since breast cancer follow-up in this study started in 2006, HT use among participants was essentially restricted to women with severe menopausal symptoms, and the estrogen content of the medication was lower than in the 1990s [47]. We compared HT use in our study population to data on dispensed prescriptions from the

Norwegian Prescription Database, and found that nationally, 6.6% in the relevant age group were current users of EPT in 2010. This corresponds well with the 6.4% of EPT users in our study population and suggests that HT use in this study is comparable to HT use in the background population, despite the fact that only women attending mammography screening were included in this study. In a study that compared women who did and did not attend the NBCSP during the period 2002-2007, self-reported BMI was similar for attenders and non-attenders [48]. However, we cannot exclude the possibility that the participants may differ from the background population with respect to other factors that are associated with breast cancer risk, or that the associations observed may differ from those in a non-screened population. BMI may predict menopausal symptoms, and a high current BMI may indicate a lower need for HT around menopause [49]. However, the weak correlation between baseline BMI and HT use in our study suggests that the two factors may be regarded as independent.

We had information on established risk factors for breast cancer, and it is important to note that adjustment for potential confounding by these factors did not materially influence the results. Self-reported information has some limitations, and recall of body weight at 7 and 15 years of age is vulnerable to misclassification. However, studies of other cohorts suggest that agreement between recall and objective measurements of body size is fairly good, and recalled comparisons with body size of peers at the same age appear to be reliable [50]. Still, constructing life-course patterns of body mass from two time-points is not likely to capture all relevant weight changes.

Our results confirm that overweight at a young age, indicated by self-reported weight at 7 or 15 years of age, is associated with a relative reduction in breast cancer

risk later in life. Similar findings have been reported by others [15, 16, 18-23, 51]. In addition, our findings suggest that HT use is associated with higher risk also in women who were overweight at a young age, but the association appears to be less pronounced than in HT users who either remained at normal weight through life or became overweight or obese as adults. Although plausible explanations may be difficult to identify, the lower breast density that has been observed in women who were overweight at a young age, may provide some clues [52-54]. It is also known that menopausal HT use increases breast density [55-57], and it seems conceivable that breast density may be of importance, both for the reduced risk of breast cancer associated with overweight at a young age, and for the increased risk associated with menopausal HT [58]. The relations of HT use, BMI and breast density are complex, and for example, the positive association of breast density with mammographic sensitivity may influence breast cancer detection [57].

It is well established that HT use is more strongly associated with hormone receptor positive breast cancer [10], whereas overweight at a young age may confer a lower risk for all breast cancer subtypes [23]. Unfortunately, detailed information about breast cancer subtypes was not available to us, but we acknowledge that an effect modification of HT by life-course body mass patterns, may be more relevant for some than for other subtypes of breast cancer.

The multiplicative scale is often used to assess potential effect modification, but the additive scale is preferable in situations where the excess number of cases due to the combination of exposures is of interest [11-13, 59]. We found that associations of HT use and baseline BMI were approximately additive (i.e. less than multiplicative), corresponding to a similar increase in absolute risk associated with HT use in both categories of baseline BMI. For HT use and life-course body mass

patterns, associations were more than additive, corresponding to a larger increase in absolute risk associated with HT use among women who either remained at normal weight or gained weight, compared to women who were overweight at a young age. For women who remained at normal weight, the associations were more than multiplicative, whereas for women who gained weight, the associations were approximately multiplicative.

In most previous studies of HT use and breast cancer risk, information on BMI was restricted to adult or current BMI, and effect modification was assessed on a multiplicative scale [1, 5-10, 60-75]. Two studies, using the additive scale, have quantified effect modification of HT use by current BMI [45, 76], but found no clear evidence for effect modification. Our results related to baseline BMI are consistent with those findings.

However, when applying an additive scale on results from previous studies of postmenopausal women [15, 40-46], we found some indication that the effect of HT use could be modified (i.e. weakened) by current BMI (RERIs from all but one study were negative). Our results for baseline BMI in mainly postmenopausal women (≥55 years) are in line with these results. However, it is important to note that a negative RERI does not in itself imply that HT can be used without further increasing breast cancer risk in overweight or obese women.

In summary, we found that HT use around menopause is associated with increased risk of breast cancer regardless of baseline BMI. However, women who were overweight at a young age had a lower excess risk associated with HT use compared to women who had either remained at normal weight or gained weight as adults. The two latter groups had the highest excess risk of breast cancer associated with HT, suggesting that these women may be more susceptible to the risk increasing

effect of HT use, and that particular care should be taken when considering the balance between relieving menopausal symptoms and breast cancer risk in these women.

Disclaimer

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Conflicts of interest

All authors report no conflicts of interest.

References

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet. 1997;350(9084):1047-59.

2. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA. 2003;289(24):3243-53.

3. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. 2015;100(11):3975-4011.

4. Moyer VA, U.S. Preventive Task Force. Medications to decrease the risk for breast cancer in women: recommendations from the U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;159(10):698-708.

5. Cui Y, Deming-Halverson SL, Beeghly-Fadiel A, et al. Interactions of hormone replacement therapy, body weight, and bilateral oophorectomy in breast cancer risk. Clin. Cancer Res. 2014;20(5):1169-78.

6. Hou N, Hong S, Wang W, Olopade OI, Dignam JJ, Huo D. Hormone replacement therapy and breast cancer: heterogeneous risks by race, weight, and breast density. J. Natl. Cancer Inst. 2013;105(18):1365-72.

7. Rosenberg L, Palmer JR, Wise LA, Adams-Campbell LL. A prospective study of female hormone use and breast cancer among black women. Arch. Intern. Med. 2006;166(7):760-5.

8. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA. 2000;283(4):485-91.

9. Reeves GK, Beral V, Green J, Gathani T, Bull D, Million Women Study C. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. The Lancet. Oncology. 2006;7(11):910-8.

10. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. Breast Cancer Res. 2017;19(1):10.

11. Rothman KJ, Greenland S, Lash TL. Concepts of Interaction. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. 3 ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 71-83.

12. Rothman KJ, Greenland S, Walker AM. Concepts of interaction. Am J Epidemiol. 1980;112(4):467-70.

13. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. Am J Epidemiol. 2009;169(6):756-60.

14. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer. 2001;91(3):421-30.

15. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA. 1997;278(17):1407-11.

16. Magnusson C, Baron J, Persson I, et al. Body size in different periods of life and breast cancer risk in post-menopausal women. Int. J. Cancer. 1998;76(1):29-34.

17. Willett WC, Browne ML, Bain C, et al. Relative weight and risk of breast cancer among premenopausal women. Am J Epidemiol. 1985;122(5):731-40.

18. Baer HJ, Colditz GA, Rosner B, et al. Body fatness during childhood and adolescence and incidence of breast cancer in premenopausal women: a prospective cohort study. Breast Cancer Res. 2005;7(3):R314-25.

19. Baer HJ, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. Am J Epidemiol. 2010;171(11):1183-94.

20. Fagherazzi G, Guillas G, Boutron-Ruault MC, Clavel-Chapelon F, Mesrine S. Body shape throughout life and the risk for breast cancer at adulthood in the French E3N cohort. Eur. J. Cancer Prev. 2013;22(1):29-37.

21. Bandera EV, Chandran U, Zirpoli G, et al. Body size in early life and breast cancer risk in African American and European American women. Cancer Causes Control. 2013;24(12):2231-43.

22. Hilakivi-Clarke L, Forsen T, Eriksson JG, et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br. J. Cancer. 2001;85(11):1680-4.

23. Warner ET, Hu R, Collins LC, et al. Height and Body Size in Childhood, Adolescence, and Young Adulthood and Breast Cancer Risk According to Molecular Subtype in the Nurses' Health Studies. Cancer Prev Res (Phila). 2016;9(9):732-8.

24. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. Int J Gynecol Cancer. 2006;16 Suppl 2:569-75.

25. Hofvind S, Tsuruda KM, Mangerud G, Zerener G. The Norwegian Breast Cancer Screening Program, 1996-2016: Celebrating 20 years of organised

mammographic screening. In: Cancer in Norway 2016 - Cancer incidence, mortality, survival and prevalence in Norway. Cancer Registry of Norway, Oslo, Norway. 2017. https://www.kreftregisteret.no/globalassets/cancer-in-norway/2016/mammo_cin2016_special_issue_web.pdf. Accessed 21 Feb 2018.

26. Tsuruda KM, Sagstad S, Sebuodegard S, Hofvind S. Validity and reliability of self-reported health indicators among women attending organized mammographic screening. Scand J Public Health. 2018:1403494817749393.

27. Ritte R, Lukanova A, Tjonneland A, et al. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: a cohort study. Int J Cancer. 2013;132(11):2619-29.

28. Collaborative Group on Hormonal Factors in Breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. The Lancet. Oncology. 2012;13(11):1141-51.

29. Larsen IK, Smastuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur. J. Cancer. 2009;45(7):1218-31.

30. Hofvind S, Sagstad S, Selbuødegård S, Holen ÅS. Mammografiprogrammet - Resultater fra prosessindikatorer, 2006-2013/14. Oslo: Kreftregisteret2015.

31. Rockhill B, Colditz GA, Rosner B. Bias in breast cancer analyses due to error in age at menopause. Am J Epidemiol. 2000;151(4):404-8.

32. Pike MC, Ross RK, Spicer DV. Problems involved in including women with simple hysterectomy in epidemiologic studies measuring the effects of hormone replacement therapy on breast cancer risk. Am J Epidemiol. 1998;147(8):718-21.

33. VanderWeele TJ. On the distinction between interaction and effect modification. Epidemiology. 2009;20(6):863-71.

34. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol. 2012;41(2):514-20.

35. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol. 2005;20(7):575-9.

36. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology. 1992;3(5):452-6.

37. Li R, Chambless L. Test for additive interaction in proportional hazards models. Ann Epidemiol. 2007;17(3):227-36.

38. VanderWeele T. Explanation in causal inference: methods for mediation and interaction: Oxford University Press; 2015.

39. Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

40. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). Int J Cancer. 2004;111(5):762-71.

41. Wu AH, Yu MC, Tseng CC, Pike MC. Body size, hormone therapy and risk of breast cancer in Asian-American women. Int J Cancer. 2007;120(4):844-52.

42. Ritte R, Lukanova A, Berrino F, et al. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. Breast Cancer Res. 2012;14(3):R76.

43. Canchola AJ, Anton-Culver H, Bernstein L, et al. Body size and the risk of postmenopausal breast cancer subtypes in the California Teachers Study cohort. Cancer Causes Control. 2012;23(3):473-85.

44. Rosenberg LU, Magnusson C, Lindstrom E, Wedren S, Hall P, Dickman PW. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. Breast Cancer Res. 2006;8(1):R11.

45. Hvidtfeldt UA, Tjonneland A, Keiding N, et al. Risk of breast cancer in relation to combined effects of hormone therapy, body mass index, and alcohol use, by hormone-receptor status. Epidemiology. 2015;26(3):353-61.

46. Lahmann PH, Schulz M, Hoffmann K, et al. Long-term weight change and breast cancer risk: the European prospective investigation into cancer and nutrition (EPIC). Br. J. Cancer. 2005;93(5):582-9.

47. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.

48. Lund E, Mode N, Waaseth M, Thalabard JC. Overdiagnosis of breast cancer in the Norwegian Breast Cancer Screening Program estimated by the Norwegian Women and Cancer cohort study. BMC Cancer. 2013;13:614.

49. Costas L, Sequera VG, Quesada P, et al. Hormonal contraception and postmenopausal hormone therapy in Spain: time trends and patterns of use. Menopause. 2015;22(10):1138-46.

50. Cairns BJ, Liu B, Clennell S, et al. Lifetime body size and reproductive factors: comparisons of data recorded prospectively with self reports in middle age. BMC Med Res Methodol. 2011;11:7.

51. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. N Engl J Med. 2004;351(16):1619-26.

52. Samimi G, Colditz GA, Baer HJ, Tamimi RM. Measures of energy balance and mammographic density in the Nurses' Health Study. Breast Cancer Res. Treat. 2008;109(1):113-22.

53. Andersen ZJ, Baker JL, Bihrmann K, Vejborg I, Sorensen TI, Lynge E. Birth weight, childhood body mass index, and height in relation to mammographic density and breast cancer: a register-based cohort study. Breast Cancer Res. 2014;16(1):R4.

54. Bertrand KA, Baer HJ, Orav EJ, et al. Body fatness during childhood and adolescence and breast density in young women: a prospective analysis. Breast Cancer Res. 2015;17:95.

55. McTiernan A, Martin CF, Peck JD, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. J. Natl. Cancer Inst. 2005;97(18):1366-76.

56. Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. J. Natl. Cancer Inst. 2003;95(1):30-7.

57. Couto E, Qureshi SA, Hofvind S, et al. Hormone therapy use and mammographic density in postmenopausal Norwegian women. Breast Cancer Res. Treat. 2012;132(1):297-305.

58. Rice MS, Bertrand KA, VanderWeele TJ, et al. Mammographic density and breast cancer risk: a mediation analysis. Breast Cancer Res. 2016;18(1):94.

59. Ahlbom A, Alfredsson L. Interaction: A word with two meanings creates confusion. Eur J Epidemiol. 2005;20(7):563-4.

60. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010;304(15):1684-92.

61. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004;291(14):1701-12.

62. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. JAMA. 2002;287(6):734-41.

63. Ursin G, Tseng CC, Paganini-Hill A, et al. Does menopausal hormone replacement therapy interact with known factors to increase risk of breast cancer? J. Clin. Oncol. 2002;20(3):699-706.

64. Beral V, Million Women Study C. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003;362(9382):419-27.

65. Chlebowski RT, Anderson GL, Aragaki AK, Prentice R. Breast Cancer and Menopausal Hormone Therapy by Race/Ethnicity and Body Mass Index. J. Natl. Cancer Inst. 2016;108(2).

66. Gertig DM, Fletcher AS, English DR, Macinnis RJ, Hopper JL, Giles GG. Hormone therapy and breast cancer: what factors modify the association? Menopause. 2006;13(2):178-84.

67. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J. Natl. Cancer Inst. 2000;92(4):328-32.

68. Lahmann PH, Lissner L, Gullberg B, Olsson H, Berglund G. A prospective study of adiposity and postmenopausal breast cancer risk: the Malmo Diet and Cancer Study. Int J Cancer. 2003;103(2):246-52.

69. Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol. Biomarkers Prev. 2002;11(7):593-600.

70. Beral V, Reeves G, Bull D, Green J, Million Women Study C. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J. Natl. Cancer Inst. 2011;103(4):296-305.

71. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. Int. J. Cancer. 1999;81(3):339-44.

72. Beral V, Banks E, Reeves G, Wallis M. Hormone replacement therapy and high incidence of breast cancer between mammographic screens. Lancet. 1997;349(9058):1103-4.

73. Brinton LA, Richesson D, Leitzmann MF, et al. Menopausal hormone therapy and breast cancer risk in the NIH-AARP Diet and Health Study Cohort. Cancer Epidemiol. Biomarkers Prev. 2008;17(11):3150-60.

74. White KK, Park SY, Kolonel LN, Henderson BE, Wilkens LR. Body size and breast cancer risk: the Multiethnic Cohort. Int J Cancer. 2012;131(5):E705-16.

75. Salagame U, Banks E, Sitas F, Canfell K. Menopausal hormone therapy use and breast cancer risk in Australia: Findings from the New South Wales Cancer, Lifestyle and Evaluation of Risk study. Int J Cancer. 2016;138(8):1905-14.

76. Shantakumar S, Terry MB, Paykin A, et al. Age and menopausal effects of hormonal birth control and hormone replacement therapy in relation to breast cancer risk. Am J Epidemiol. 2007;165(10):1187-98.

Figure legend

Figure 1

Effect modification of breast cancer risk related to use of HT and the life-course body mass patterns “remained at normal weight” versus “overweight as young” Among 468,736 Norwegian Women 2006-2013

RERI (relative excess risk due to interaction) equals excess risk due to interaction (yellow box) divided by risk in the common reference group with none of the risk factors (blue box, overweight as young and never HT)

Abbreviations: CI = confidence interval; HT = menopausal hormone therapy

Overweight as young: Participants reporting weighing above average at 7 and/or 15 years of age, regardless of baseline BMI

Remained at normal weight: Participants reporting weighing below the average or average at 7 and 15 years of age and having BMI <25 kg/m^2 at baseline