HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2017 July 26.

Published in final edited form as:

Int J Cancer. 2016 June 01; 138(11): 2602–2615. doi:10.1002/ijc.29994.

WCRF/AICR recommendation adherence and breast cancer incidence among postmenopausal women with and without non-modifiable risk factors

Sarah J. O. Nomura[1], **Maki Inoue-Choi**[2], **DeAnn Lazovich**[3,4], and **Kim Robien**[5]

[1]Georgetown Lombardi Comprehensive Cancer Center

[2]National Cancer Institute, Division of Cancer Epidemiology and Genetics

[3]University of Minnesota-School of Public Health

[4]Masonic Cancer Center

[5]Milken Institute School of Public Health, George Washington University

Abstract

Taller height, family history of breast cancer, greater number of years of potential fertility and nulliparity are established non-modifiable risk factors for postmenopausal breast cancer. Greater adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) diet, physical activity and body weight recommendations has previously been shown to be associated with lower breast cancer risk. However, no prior studies have evaluated whether women with non-modifiable risk factors receive similar benefits from recommendation adherence compared to women without these risk factors. In the Iowa Women's Health Study prospective cohort, we investigated whether associations of WCRF/AICR recommendation adherence differed by the presence/absence of non-modifiable breast cancer risk factors. Baseline (1986) questionnaire data from 36,626 postmenopausal women were used to create adherence scores for the WCRF/AICR recommendations (maximum score=8.0). Overall and single recommendation adherence in relation to breast cancer risk (n=3,189 cases) across levels of non-modifiable risk factors were evaluated using proportional hazards regression. Mean adherence score was 5.0 points (range: 0.5–8.0). Higher adherence scores (score ≥6.0 vs. ≤3.5, HR=0.76, 95% CI=0.67–0.87), and adherence to the individual recommendations for body weight and alcohol intake were associated with a lower breast cancer incidence. While not statistically significant among women with more non-modifiable risk factors (score ≥6.0 vs. ≤3.5, HR=0.76, 95% CI=0.36–1.63), hazard ratios were comparable to women with the no non-modifiable risk factors (score ≥6.0 vs. ≤3.5, HR=0.74, 95% CI=0.49–0.93) (p-interaction=0.57). WCRF/AICR recommendation adherence is associated with lower breast cancer risk, regardless of non-modifiable risk factor status.

Corresponding Author Information: Sarah J. O. Nomura, Lombardi Comprehensive Cancer Center, Georgetown University, 1000 New Jersey Ave SE, Washington, DC 20003, sjo36@georgetown.edu, Phone: 202-687-3957, Fax: 202-687-1368.

COMPETING INTERESTS

None of the authors have any competing interests.

Keywords

Breast Cancer; Diet; Body Weight; Physical Activity; Cancer Prevention

INTRODUCTION

An estimated one in eight women will develop breast cancer in her lifetime,[1] and two in three invasive breast cancer cases occur among women 55 years and older.[2] While several modifiable risk factors for breast cancer have been identified (including oral contraceptive use, hormone replacement use, alcohol consumption, physical activity and being overweight or obese[2]), several non-modifiable risk factors have also been established. Taller height, family history of breast cancer, younger age at menarche and older age at menopause have all been associated with increased risk of breast cancer.[2–5] Nulliparity has also been shown to be associated with breast cancer risk, and may also be considered a non-modifiable risk factor because it is unlikely women will only choose to have children to prevent cancer.[6, 7] Women with non-modifiable breast cancer risk factors may be especially motivated to make diet and physical activity changes to reduce their breast cancer risk. While few non-modifiable risk factors and lifestyle habits have been previously evaluated, current research suggests women at higher risk of breast cancer, due to a family history of breast cancer, are not more likely to adhere to diet, physical activity and body weight recommendations.[33, 34] Whether these women derive equal, or potentially greater, benefit from healthy behaviors compared to women without these non-modifiable breast cancer risk factors is unclear.

Studies evaluating evidence-based guidelines that have been developed specifically to address cancer prevention, such as the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) guidelines,[8–13] the European Code Against Cancer,[14] and the American Cancer Society recommendations,[10, 15–17] have generally observed that greater adherence to recommendations is associated with lower cancer incidence and/or cancer mortality.[8, 9, 11, 12, 14, 15] Higher adherence was also associated with a lower incidence of breast cancer in previous studies.[9–11, 13, 16, 17] Fewer studies have evaluated the benefits of adherence to the individual recommendations.[9–11, 13, 16] Results from these studies have been generally inconsistent, but adherence to the alcohol intake recommendation has been consistently associated with reduced breast cancer incidence. The WCRF/AICR Breast Cancer Continuous Update Project (CUP) Report indicates that adherence to alcohol, body composition and physical activity recommendations are likely to confer the greatest benefit in reducing breast cancer risk.[18]

In 2007, the WCRF/AICR released diet, physical activity and weight management recommendations for cancer prevention (Table 1),[19] which have been most often evaluated in previous studies. No previous studies have assessed whether benefits of adherence differ among population sub-groups, such as women who may be at an increased risk for breast cancer due to non-modifiable risk factors. In this analysis, we evaluated whether the association between adherence to the 2007 WCRF/AICR recommendations and postmenopausal breast cancer incidence in the Iowa Women's Health Study (IWHS) differs between women with and without non-modifiable risk factors, including taller height, total

years of potential fertility, parity, family history of breast cancer, and a combined risk score that encompasses all these non-modifiable risk factors.

MATERIALS AND METHODS

Study Population

The IWHS is a prospective cohort study designed to investigate diet and lifestyle factors with risk of cancer and other chronic diseases among postmenopausal women ages 55 – 69 years at enrollment in 1986.[20] Women were identified using the Iowa Department of Transportation drivers' license lists; 41,836 women (42% response rate) provided information on demographic, anthropometric, medical, reproductive, and family history, lifestyle factors and dietary intake data via a self-administered questionnaire. The final analytic cohort included 36,626 postmenopausal women, after excluding women who left >30 items blank on the dietary intake section of the questionnaire, had implausible estimated caloric intake (<600 or >5,000 kcal/day) (n = 2,712), were not postmenopausal at baseline (n = 569), or reported a previous mastectomy (n = 1,884) or cancer diagnosis (except for non-melanoma skin cancer) at baseline (n = 3,830). Incident cancers in the IWHS are identified through annual linkage with the State Health Registry of Iowa, a member of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Since annual migration from Iowa among cohort members is <1%, identification of incident cancers is nearly complete.[21] The IWHS has been approved by the Institutional Review Boards at the University of Minnesota and the University of Iowa.

Data Collection

The Harvard food frequency questionnaire (FFQ) was used to assess usual intake frequency of 127 food items at baseline.[22, 23] This questionnaire has been validated in the IWHS population.[24] Grams of intake of food groups (total fruit and vegetable intake, red and processed meat intake) and individual nutrients (fiber, sodium) were computed based on reported serving numbers and portion sizes for each item. Grams of sugar sweetened beverage intake included (i) Coke, Pepsi, or other cola with sugar; (ii) caffeine-free Coke, Pepsi or other cola with sugar; (ii) other carbonated beverage with sugar (e.g. 7-up); (iv) Hawaiian Punch, lemonade, or other non-carbonated fruit drink. For physical activity, women were categorized as "high" (≥2 times/week vigorous or ≥5 times/week moderate activities), "moderate" (2–4 times/week moderate or once/week both vigorous and moderate activities) or "low" (all other activity levels).[25] Women also reported their age at menarche, age at menopause, number of live births, family history of cancer, height and weight. Body mass index (BMI) was calculated as kilograms/meter.^{2}

WCRF/AICR Guideline Adherence Score

The guidelines and scoring system are outlined in Table 1. Adherence scores for the WCRF/AICR cancer prevention guidelines were calculated according to baseline measures of BMI (normal BMI: 18.5 – <25; overweight BMI: 25 – <30; obese or underweight BMI: ≥30 or <18.5 kg/m^2), physical activity (high activity levels; moderate activity levels; low activity levels), and intake of fruits and vegetables (≥400, 200 – <400, <200 grams/day), fiber (≥25; 12.5 – <25; <12.5 grams/day), alcohol (≤10; >10 – 20; >20 grams/day) (standard single

serving of alcohol = 10 grams), red and processed meat (<500 grams/week total red and processed and < 3 grams/week processed; <500 grams/week total red and processed and 3 – <50 grams/week processed; ≥500 grams/week total red and processed or ≥50 grams/day processed), sugar sweetened beverages (0 grams/day; <250 grams/day, ≥250 grams/day) and sodium (<1500 mg/day; 1500 – 2400 mg/day, >2400 mg/day). When specific cut-points were specified in the WCRF/AICR recommendations, these were used in score creation. Given the age of this cohort of postmenopausal women, we chose a lower sodium intake cut-point (<2400 mg/d) for our analysis, based on the United States Dietary Guidelines recommendation for people ≥ 51 years of age.[26] These cut-points have been used in several previous published IWHS analyses.[27, 28] The recommendation to limit energy dense foods was not included due to a lack of data on caloric intake by food gram. The dietary supplement recommendation was excluded due to a lack of information on whether supplement usage was medically indicated or elective. For each individual recommendation, 1 point was assigned for complete adherence, 0.5 points for partial adherence and 0 points for non-adherence. Scores for each of the individual recommendations were then summed to a total WCRF/AICR recommendation adherence score (maximum score: 8 points). Three levels were used instead of met/did not meet to be better able to assess differences between those who were most adherent compared to those who were least adherent. Additionally, a diet adherence score was created by summing scores for the six diet recommendations (maximum score: 6 points).

Statistical Analysis

Person-years of follow-up time for each participant were computed from the date of the return of baseline questionnaire to 1) date of first breast cancer diagnosis, 2) date of emigration for Iowa, 3) date of death, or 4) December 31, 2010, whichever came first.

Associations between risk factors, demographic and lifestyle characteristics and the WCRF/AICR adherence scores overall and by individual recommendation were evaluated using Pearson correlations, chi-square tests and ANOVA. The WCRF/AICR adherence score was evaluated as a continuous variable and as categorical (≤3.5 points, 4.0 – 4.5 points, 5.0 – 5.5 points, ≥6.0 points). Four categorical levels were chosen to clearly differentiate between those with high vs. low adherence centered on a median score of 4.5 points and assess the benefits of adhering to at least half the recommendations compared to adherence to less than or more than half the recommendations. Cox proportional hazards regression was used to calculate unadjusted and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between WCRF/AICR adherence scores and breast cancer incidence. Associations between WCRF/AICR adherence scores and breast cancer risk were evaluated in the total population and in each stratum of the following non-modifiable risk factors: height (tertiles), family history of breast cancer (none, history of breast cancer in grandmother only, history of breast cancer in mother/sister), parity (none, 1–2, ≥ 3 children) and total years of fertility (age at menopause – age at menarche) (tertiles). Since the effects of age at menopause and age at menarche are hypothesized to be due to the number of lifetime menstrual cycles (in combination with parity), these variables were combined into a total number of years of potential fertility. The choice of non-modifiable risk factors were

chosen *a priori* based on factors previously shown to be associated with breast cancer risk.[2–7]

To evaluate whether there were differences among women whom had a larger number of non-modifiable risk factors compared to women who had one or none of the non-modifiable risk factors we created a combined number of risk factors variable. The number of non-modifiable risk factors for which a participant was in the highest risk category (defined based on previously published research[2–7]) for the individual factors were summed. The highest risk category for each individual non-modifiable risk factor as follows: parity – nulliparous; height (tertiles) - ≥ 166 cm; family history –first-degree relative; total years of potential fertility (duration from age at menarche to age at menopause tertile) - ≥ 39 years (highest). Based on their number of non-modifiable risk factors women were assigned to one of four categories: No non-modifiable risk factors, one risk factor, two risk factors, at least 3 risk factors.

Associations between the non-modifiable risk factors and breast cancer incidence were evaluated using Cox proportional hazards regression. Analyses stratified by non-modifiable risk factors and combined number of risk factors were performed in the regression models to evaluate the benefits of adherence across risk factor levels. A test for interaction was performed in the Cox regression models by adding an interaction term with WCRF/AICR score (continuous and categorical) and the individual (3 categories) or combined (four categories) non-modifiable risk factors. Covariates were included in final models if they were known risk factors for breast cancer or were significantly associated with the WCRF/AICR adherence score. All adjusted models included age (continuous), smoking status (current, former, never), education (< high school, high school, some college/vocational, college), and hormone replacement therapy usage (yes/no). Additional covariates included family history of breast cancer (none, grandmother, mother/sister, multiple relatives), menarche age (continuous), menopause age (continuous), and parity (yes/no) except in models where associations were evaluated according to that non-modifiable risk factor. Similarly, BMI/alcohol/physical activity variables were included in models where BMI/alcohol/physical activity score were not the exposure of interest.

We also evaluated associations between adherence to diet recommendations only (continuous and categorical: ≤2.5, 3.0 – 4.0, ≥ 4.5) and individual WCRF/AICR recommendations (continuous and categorical: 0 points, 0.5 points, 1 point) and breast cancer incidence using Cox proportional hazards regression. Diet category cut-points were chosen to reflect low adherence, adherence to at least half, and high adherence. In addition to the covariates listed above, the analyses of associations between adherence to each dietary recommendation and breast cancer risk were adjusted for BMI and/or alcohol, depending on the recommendation being evaluated.

Multivariate adjusted absolute risk difference was calculated for the overall score and individual recommendations in the overall cohort using the approach outlined by Spiegelman and Hertzmark.[29] Analyses were performed with SAS (version 9.2; SAS Institute, Inc.). Statistical significance was defined as $p < 0.05$ (two-sided).

RESULTS

A total of 3,189 women were diagnosed with incident breast cancer from baseline through December 31, 2010. The mean WCRF/AICR adherence score was 5.0 (range 0.5 – 8.0), and 32.9% of participants had a score of 4.0 or 4.5 (Table 1). Participants were least likely to meet the physical activity recommendation (47.3%) and most likely to follow the alcohol intake recommendation (88.2%). Except for adherence to fiber intake and fruit and vegetables recommendations ($r=0.60$, $p<0.001$) and adherence to sodium intake in relation to adherence to red and processed meat intake ($r=0.29$, $p<0.001$) and fruit and vegetable intake ($r=-0.35$, $p<0.001$), adherence to any one individual recommendation was generally not strongly correlated (positively or inversely) with adherence to any other recommendation (range: $r=-0.11$ to 0.17). Older age, higher levels of education, and no history of smoking were associated with higher adherence scores ($p < 0.001$) (Table 2). Age at menopause, parity, and height were also significantly associated with the WCRF/AICR adherence score, but no clear pattern to the HRs was observed across adherence score levels. In unadjusted models, all factors included in this risk score (parity, taller height, family history for breast cancer and years of fertility) were significantly associated with breast cancer incidence in this study population (Supplementary Table 1). In adjusted models, parity was no longer significantly associated with breast cancer risk. Since study results did not differ, risk factors were chosen *a priori*, and parity was previously shown to be associated with number of live births in the IWHS we included parity in presented study results.[7] Similarly, in the Cox regression analysis, increasing numbers of non-modifiable risk factors was positively associated with breast cancer incidence and associations were strongest among women at least three non-modifiable risk factors.

A higher adherence score on the continuous scale was associated with lower breast cancer risk (HR=0.94, 95% CI: 0.90 – 0.97 per 0.5 point increase in adherence score) (data not shown). Using a categorical scale of the adherence score, women who adhered to six or more out of eight recommendations had the lowest risk of breast cancer (adjusted HR=0.76, 95% CI: 0.67–0.87) compared with women who adhered to less than half of the eight recommendations (Table 3). Absolute risk difference (RD) for higher adherence compared to lower adherence was small, but statistically significant for the overall score (>6 vs. <3.5 recommendations RD=−0.022 (−0.033, −0.012, $p<0.001$) (Supplementary Table 2). Regardless of height, adherence to a larger number of recommendations was associated with lower breast cancer incidence, although the association was weaker among the women in the tallest tertile (p-interaction = 0.50). The pattern was similar for years of fertility, where the hazard ratios and confidence intervals were similar for the lowest (adjusted HR for the highest vs. lowest score categories: 0.72, 95% CI: 0.57–0.91) and middle tertiles (adjusted HR for the highest vs. lowest score categories: 0.74, 95% CI: 0.59–0.92), but slightly weaker among women with the most years of fertility (adjusted HR for the highest vs. lowest score categories: 0.81, 95% CI: 0.65–1.01, p-interaction = 0.66). Benefits of adherence were similar among women with no children and women with one to two children. While greater adherence was still protective in women who had three or more children, the association was weaker compared with the other parity categories (p-interaction = 0.09). Despite a non-significant interaction (p-interaction = 0.60), associations between the WCRF/AICR

adherence score and breast cancer risk were stronger among women with no family history of breast cancer (adjusted HR for the highest vs. lowest score categories=0.70, 95% CI: 0.60–0.82), while higher adherence was not significantly associated with breast cancer incidence among women with first or second-degree relatives with a history of breast cancer. The test for interaction between WCRF/AICR adherence score and combined number of risk factors was not significant (p=0.57). Among women with the fewest non-modifiable risk factors higher adherence was statistically significantly association with lower breast cancer incidence (adjusted HR for the highest vs. lowest score categories: 0.74, 95% CI: 0.59–0.93). While not statistically significant, higher adherence was also inversely associated among women with the greatest number of non-modifiable risk factors (adjusted HR for the highest vs. lowest score categories: 0.76, 95% CI 0.36–1.63).

Individual Recommendation Adherence Scores

Regardless of non-modifiable risk factors, adherence to a greater number of the six dietary recommendations was not associated with lower breast cancer risk (Table 4). In the combined number of risk factors analysis, moderate or higher adherence was non-significantly associated with elevated breast cancer incidence but should be interpreted with caution due to small numbers of low adherence women. More than 60% of women adhered to between 3 and 4 diet recommendations, while less than 9% adherence to less than 3 recommendations. In the highest risk category and lowest diet adherence category there where 43 non-cases and 3 breast cancer cases. Higher adherence to the recommendation to limit alcohol drinks was moderately associated with lower risk of breast cancer in the overall cohort (HR for the highest vs. lowest score = 0.84, 95% CI = 0.71 – 1.00, p-trend=0.01). Adherence to other dietary recommendations was not associated with breast cancer risk. Adherence to the BMI recommendation was significantly associated with lower breast cancer risk (HR for the highest vs. lowest score = 0.78, 95% CI = 0.70 – 0.85, p-trend < 0.001), while higher adherence to the physical activity recommendation was associated with a borderline, statistically non-significant, lower breast cancer risk (HR for the highest vs. lowest score = 0.93, 95% CI = 0.84 – 1.02, p-trend=0.23) (Table 5). When stratified by non-modifiable risk factors, associations were generally weaker and did not differ by the presence or absence of non-modifiable risk factors. Adherence to the BMI recommendation tended to be more strongly associated with breast cancer risk in the lower levels of the non-modifiable risk factor categories and the combined risk score, but none of the interactions was significant (p-interaction = 0.40 – 0.81). Greater adherence to the alcohol recommendation appeared to be more strongly associated with a lower breast cancer incidence among women with three or more non-modifiable risk factors, however, tests for interaction were non-significant (p-interaction = 0.61) and non-adherence to the alcohol recommendation was very low (<5%) in the study population. Adherence scores for other individual recommendations listed in Table 1 were not statistically significant in the overall or stratified analyses (data not shown). Absolute risk difference for adherence vs. non-adherence was statistically significant only for the body weight recommendation (RD= −0.022, 95% CI: −0.030, −0.014, p<0.001).

DISCUSSION

Our results suggest that better adherence to the WCFR/AICR cancer prevention guidelines is associated with a lower risk of postmenopausal breast cancer, regardless of a woman's non-modifiable risk factors. However, the association was weaker among women who had more non-modifiable risk factors compared with those with fewer non-modifiable risk factors. Our study findings also confirmed the WCRF/AICR CUP report's statement that adherence to the recommendations to limit alcohol intake and to maintain a healthy body weight may be the most important recommendations of the WCRF/AICR guidelines for prevention of postmenopausal breast cancer. Conversely, adherence to diet recommendations was unassociated with breast cancer incidence, while higher physical activity was non-significantly inversely associated in this population.

To our knowledge, no previous studies have evaluated whether relationships between dietary, body weight and physical activity recommendations and risk of postmenopausal breast cancer differ by the presence or absence of multiple non-modifiable risk factors. Dietary habits, especially alcohol consumption, body composition and physical activity are hypothesized to contribute to variability in hormone levels, which could contribute to cancer risk, especially in women who are already at risk for breast cancer due to non-modifiable factors.[30–33] Previous research indicates that women at high risk for breast cancer, due to a family history of breast cancer, are no more likely to adhere to cancer prevention recommendations.[34, 35] Consistent with prior studies, when individual non-modifiable risk factors were evaluated, such as family history, benefits of adherence did not appear to differ by the presence/absence of a non-modifiable risk factor.[36–38] However, among women with multiple non-modifiable risk factors, higher adherence to cancer prevention recommendations was not associated with breast cancer risk. One possible explanation for the somewhat weaker association among women with multiple non-modifiable risk factors may be that the effects of the non-modifiable risk factor moderate the benefits of adherence. For example, a higher body weight has been shown to be associated with risk of postmenopausal hormone receptor positive (HR+) breast cancer.[39, 40] Similarly, younger age at menarche, older age at menopause and being nulliparous are also more strongly associated with HR+ breast cancer.[40, 41] In both examples, sex hormone levels are considered to have a role in development of HR+ breast cancer, and it may be that having several sex hormone-related risk factors counters the effects of maintaining a normal body weight.[39, 41] However, it is also important to note that tests for interaction were non-significant, adherence was generally still associated with lower cancer incidence and is likely beneficial for overall health and prevention of other types of cancer among women who have non-modifiable risk factors.

Despite differences in analytic approaches in previous studies, adherence to cancer prevention guidelines has been consistently associated with a lower risk of breast cancer. Consistent with our results, five prior studies observed that adhering to cancer prevention guidelines was associated with lower incidence of breast cancer.[9–11, 13, 16] A previous study in the IWHS found that adherence to the 1997 WCFR/AICR recommendations was associated with lower risk of all cancer, but a clear dose-response pattern to the association was not observed.[8] Absolute risk difference for adherence to more recommendations

compared to fewer recommendations was small, but it is important to note that these guidelines are intended to reduce the burden of cancer overall and some recommendations would not be expected to be associated with breast cancer risk based on previous research and biological mechanisms. In support of the goal of overall cancer reduction, the risk difference was larger in the previously published IWHS analysis that evaluated all cancers combined.[8]

This previous study did not evaluate specific cancer types, and the WCFR/AICR guidelines have evolved over time to incorporate more recent research. Two other previous analyses evaluated cancer survivors in the IWHS cohort and found that greater adherence to the 2007 WCRF/AICR guidelines was associated with lower all-cause mortality[28] and higher mental and physical health-related quality of life.[27, 28]

No previous studies have evaluated combined diet adherence and breast cancer incidence; however, our results for the adherence to individual dietary recommendations and breast cancer risk are largely consistent with previous studies. Similar to our findings, all of three previously published studies evaluating adherence to individual recommendations in cancer prevention guidelines and breast cancer incidence reported that adherence to alcohol intake recommendations was associated with lower breast cancer incidence.[9, 10, 13] Additionally, higher alcohol intake[42, 43] is an established risk factor for postmenopausal breast cancer risk.[18] Ethanol is an established carcinogen, which may disrupt folate metabolism and influence DNA repair and DNA methylation patterns.[44] Additionally, ethanol is associated with elevated levels of sex hormones, which is linked with increased breast cancer risk.[45, 46] Meanwhile, associations with other dietary factors, such as fruit and vegetable intake and red and processed meat intake have not been consistently associated with breast cancer risk.[19, 43, 47] Reasons for differences in associations with adherence to other dietary factors may include differences in pre- and post-menopausal breast cancer etiology, possible heterogeneous associations by breast cancer subtypes, variances in analytic approaches, regional dietary differences (e.g., Iowa versus Washington), and temporal changes in dietary habits (e.g., IWHS baseline questionnaire 1986, VITAL baseline questionnaire 2000 – 2002).

Among the non-dietary recommendations, one prior study found adherence to the body weight recommendation to be associated with postmenopausal breast cancer incidence, which is in agreement with our results.[9] The two studies that found no association evaluated pre- and postmenopausal breast cancer combined,[10, 13] which may explain the differing results. Body fatness has been more strongly associated with increased postmenopausal risk while it may be inversely associated with premenopausal breast cancer risk.[18] One proposed mechanism behind pre- and postmenopausal differences is contribution of adipose tissue to levels of circulating estrogens. Among postmenopausal women, adipose tissue becomes an important contributing source of estrogen and higher circulating estrogen levels have been positively associated with postmenopausal breast cancer risk.[39] While higher levels of physical activity may be associated with lower risk for breast cancer;[25, 48, 49] consistent with our findings, the three prior adherence studies[9, 10, 13] and a previous report in the IWHS population did not find an association between physical activity and breast cancer risk.[50]

Some strengths of this study include the more than 23 years of follow-up and the large number of incident breast cancer cases, which allowed us to stratify the analyses to evaluate whether adherence to guidelines and breast cancer risk differed according to established risk factors for breast cancer. A majority of women in this study adhered to at least four and less than six recommendations. The relatively similar diet and other lifestyle exposures among these women may limit the ability to observe differences at extreme ends of the exposure spectrum in the interaction analyses, particularly in the risk score analysis, where numbers of women with multiple risk factors is smaller. The cut point for our height analysis was based on the height distribution within our cohort and among women in the general population of the United States, and may not reflect a true point at which risk of breast cancer truly differs between the two categories. However, results did not differ when different cut points were used or when data were evaluated as quartiles. It is also important to note that this is an observational study so residual confounding or unknown related factors may influence associations and direct effects of adherence cannot be ascertained.

Overall, our results indicate that better adherence to the 2007 WCRF/AICR cancer prevention guidelines may reduce postmenopausal breast cancer risk. This finding was apparent, regardless of the presence of non-modifiable risk factors. These results also suggest that maintaining normal body weight and limiting alcohol consumption may be particularly helpful recommendations for decreasing risk of postmenopausal breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Iowa Women's Health Study is funded by National Cancer Institute R01 CA039742. At the time of the analysis, SJON was supported by National Cancer Institute T32 CA132670.

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Novelty and Impact

Women with non-modifiable breast cancer risk factors may be especially motivated to make diet and physical activity changes to reduce their breast cancer risk. However, whether these women derive equal, or potentially greater, benefit from healthy behaviors compared to women without these non-modifiable breast cancer risk factors is unclear. This article contributes important data on the benefits of adherence to the WCRF/AICR cancer prevention guidelines among women at higher risk for breast cancer.

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Table 1

WCRF/AICR Guidelines and Adherence Scores

WCRF/AICR Recommendation	IWHS Baseline Data	Categories	Score	Cohort N (%)	Cases N (%)
Be as lean as possible without becoming underweight.	BMI (kg/m^2)	18.5 – < 25	1	14,108 (38.5)	1,082 (33.9)
		25 – < 30	0.5	13,545 (37.0)	1,262 (39.6)
		≥ 30 or < 18.5	0	8,973 (24.5)	845 (26.5)
Be physically active, for at least 30 minutes every day.	Physical activity level [1]	High	1	9,015 (25.1)	739 (23.6)
		Moderate	0.5	9,907 (27.6)	900 (28.7)
		Low	0	16,994 (47.3)	1,498 (47.8)
Limit energy-dense food intake. + Avoid sugary drinks.	Not included [2]	---	---	---	---
	High sugar beverage intake (g/d)	0	1	16,705 (45.6)	1,434 (8.58)
		< 250	0.5	17,077 (46.6)	1,524 (47.8)
		≥ 250	0	2,844 (7.8)	231 (7.24)
Eat more vegetables, fruits, whole grains, and legumes such as beans.	Total fruit and vegetable intake (servings/d) 5 servings = 400 g 3 servings = 200 g	≥ 5	1	23,009 (62.8)	2,014 (63.2)
		3 – < 5	0.5	10,125 (27.7)	889 (27.9)
		< 3	0	3,492 (9.5)	286 (8.97)
	Dietary fiber intake (g/d)	≥ 25	1	7,791 (21.3)	678 (21.3)
		12.5 – < 25	0.5	22,634 (61.8)	1,982 (62.1)
		< 12.5	0	6,201 (16.9)	529 (16.6)
Limit red meat intake and avoid processed meats.	Total red and processed meat (RP) intake (g/wk) and processed meat (P) intake (g/wk)	< 500 RP and < 3 P	1	6,509 (17.8)	531 (16.7)
		< 500 RP and 3 – < 50 P	0.5	22,933 (62.6)	2,042 (64.0)
		< 500 RP or ≥ 50 P	0	7,184 (19.6)	616 (19.3)
Limit alcohol drinks to 2 for men and 1 for women a day, if consumed at all.	Alcohol intake (g/d) (1 standard alcohol serving = 10 g)	≤ 10	1	32,320 (88.2)	2,773 (87.0)
		> 10 – 20	0.5	2,700 (7.4)	258 (8.09)
		> 20	0	1,606 (4.4)	158 (4.95)
Limit intake of salty foods and foods processed with salt.	Sodium intake (mg/d)	≤ 1500	1	7,528 (20.6)	666 (20.9)

WCRF/AICR Recommendation	IWHS Baseline Data	Categories	Score	Cohort N (%)	Cases N (%)
		>1500 – 2400	0.5	17,023 (46.5)	1,433 (44.9)
		> 2400	0	12,075 (32.9)	1,090 (34.2)
Don't use supplements to protect against cancer.	Not included[3]	---	---	---	---
Overall Adherence Score	Sum of Scores (Max score = 8)	6.0 – 8.0	---	6,597 (18.4)	501 (16.0)
		5.0 – 5.5		11,626 (32.4)	1,050 (33.5)
		4.0 – 4.5		11,818 (32.9)	1,040 (33.1)
		0 – 3.5		5,875 (16.4)	546 (17.4)
Diet Adherence Score	Sum of Dietary Scores (Max score = 6)	4.5 – 6.0	---	10,719 (29.3)	917 (28.8)
		3.0 – 4.0		22,768 (62.2)	2,025 (63.5)
		0 – 2.5		3,139 (8.57)	247 (7.75)

[1] "High" if reported ≥2 times/week vigorous (e.g., jogging, racket sports, swimming, aerobics, strenuous sports) or ≥5 times/week moderate activities (e.g., bowling, golf, light sports, or physical exercise, gardening, taking long walks), "Moderate" if they reported 2–4 times/week moderate or once/week vigorous and moderate activities, or otherwise "Low"

[2] Data on caloric intake by food gram was not available.

[3] Insufficient data on supplement usage were collected.

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Table 2

Population Characteristics According to WCRF/AICR Score Group

	Breast Cancer Status		p[1]	WCRF/AICR Score Group				p[2]
	IWHS Cohort	Breast Cancer Cases		Group 1 (0 − 3.5)	Group 2 (4.0 − 4.5)	Group 3 (5.0 − 5.5)	Group 4 (6.0 − 8.0)	
Age (mean ± SD)	61.7 ± 4.2	61.6 ± 4.1	0.06[3]	61.1 ± 4.1	61.6 ± 4.2	61.9 ± 4.2	62.0 ± 4.2	<0.001[3]
Calories (mean ± SD)	1,785 ± 614	1,787 ± 615	0.26[3]	1,882 ± 648	1,835 ± 648	1,769 ± 593	1,649 ± 518	<0.001[3]
Level of Education (%)			<0.001[4]					<0.001[4]
<High school graduate	7,062 (19.3)	519 (16.3)		1,463 (25.0)	2,409 (20.8)	1,998 (13.9)	912 (13.9)	
High school graduate	15,262 (41.8)	1,325 (41.6)		2,681 (45.8)	5,046 (43.5)	4,816 (40.9)	2,464 (37.4)	
Some college/vocational	9,668 (26.5)	905 (28.4)		1,279 (21.8)	3,007 (25.9)	3,307 (28.1)	1,950 (29.6)	
College graduate	4,538 (12.4)	437 (13.7)		436 (7.44)	1,133 (9.77)	1,665 (14.1)	1,259 (19.1)	
Smoking Status (%)			0.04[4]					<0.001[4]
Never	23,772 (65.9)	2,208 (66.9)		3,282 (56.7)	7,501 (65.4)	7,998 (68.7)	4,501 (69.2)	
Former	6,941 (19.24)	623 (19.8)		1,120 (19.3)	2,098 (18.3)	2,203 (18.9)	1,426 (21.9)	
Current	5,357 (14.9)	420 (13.3)		1,388 (24.0)	1,878 (16.4)	1,443 (12.4)	579 (8.9)	
Age at Menarche (%)			0.39[4]					0.19[4]
≤ 12 years	15,425 (42.6)	1,382 (43.7)		2,508 (43.2)	4,939 (43.0)	4,937 (42.2)	2,768 (42.3)	
13 years	10,738 (29.7)	931 (29.4)		1,728 (29.8)	3,299 (28.7)	3,501 (29.9)	1,984 (30.3)	
≥ 14 years	10,051 (27.8)	852 (26.9)		1,568 (27.0)	3,244 (28.3)	3,267 (27.9)	1,788 (27.3)	
Age at Menopause (%)			<0.001[4]					<0.001[4]
≤ 46 years	12,196 (34.5)	1,001 (32.3)		2,046 (36.1)	3,950 (35.1)	3,874 (33.9)	2,087 (32.8)	
47–50 years	10,433 (29.5)	860 (27.8)		1,684 (29.7)	3,274 (29.1)	3,376 (29.5)	1,904 (29.9)	
≥ 51 years	12,763 (36.1)	1,234 (39.9)		1,937 (34.2)	4,024 (35.8)	4,195 (36.7)	2,378 (37.2)	
Potential Fertility Years			0.002[4]					0.001[4]
≤ 33 years	12,009 (34.2)	978 (31.8)		2,001 (35.5)	3,912 (35.0)	3,808 (33.5)	2,055 (32.4)	

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	Breast Cancer Status		p[1]	WCRF/AICR Score Group				p[2]
	IWHS Cohort	Breast Cancer Cases		Group 1 (0 − 3.5)	Group 2 (4.0 − 4.5)	Group 3 (5.0 − 5.5)	Group 4 (6.0 − 8.0)	
34–38 years	12,177 (27.6)	1,062 (27.9)		1,929 (34.2)	3,821 (34.2)	4,009 (35.3)	2,207 (34.8)	
≥ 39 years	23,009 (62.8)	2,014 (63.2)		1,703 (30.2)	2,435 (30.8)	3,552 (31.2)	2,079 (32.8)	
Parity (%)			0.64[4]					<0.001[4]
None	3,272 (11.1)	292 (11.0)		481 (10.7)	1,002 (10.9)	1,088 (11.3)	642 (11.5)	
1–2 children	11,702 (39.8)	1,074 (40.6)		1,728 (38.4)	3,582 (39.0)	3,841 (39.9)	2,323 (41.7)	
3 or more	14,437 (49.1)	1,277 (48.3)		2,289 (50.9)	4,600 (50.1)	4,690 (48.8)	2,600 (46.7)	
Height (%)			<0.001[4]					<0.001[4]
≤160 cm	9,873 (27.0)	742 (23.3)		1,681 (28.6)	3,140 (26.9)	3,177 (26.9)	1,677 (25.4)	
>160–<165 cm	16,113 (44.0)	1,400 (43.9)		2,550 (43.4)	5,184 (43.9)	5,184 (43.9)	2,887 (43.8)	
≥ 165 cm	10,640 (29.0)	1,047 (32.8)		1,644 (28.0)	3,457 (29.3)	3,457 (29.3)	2,033 (30.8)	
Family History[5]			<0.001[4]					0.71[4]
None	26,766 (76.6)	2,137 (70.0)		4,293 (76.7)	8,537 (76.7)	8,657 (76.6)	4,826 (76.4)	
Second degree	3,946 (11.3)	392 (12.8)		622 (11.1)	1,242 (11.2)	1,316 (11.7)	710 (11.2)	
First degree	4,232 (12.1)	523 (17.1)		686 (12.3)	1,359 (12.2)	1,322 (11.7)	783 (12.4)	
Combined Factors (%)			<0.001					<0.001[4]
None	11,861 (38.8)	968 (33.0)		2,152 (40.1)	4,175 (39.1)	4,138 (38.1)	2,149 (35.5)	
1 risk factor	12,979 (42.5)	1,241 (42.3)		2,230 (41.6)	4,505 (42.2)	4,615 (42.5)	2,648 (43.7)	
2 risk factors	5,059 (16.6)	627 (21.3)		877 (16.3)	1,776 (16.6)	1,841 (17.0)	1,103 (18.2)	
3+ risk factors	651 (2.1)	101 (3.4)		107 (2.0)	218 (2.1)	255 (2.4)	158 (2.6)	

[1] Compares cases to non-cases in cohort

[2] Compares WCRF/AICR score categories

[3] p-value from ANOVA test

[4] p-value from x^2 test for categorical variables

[5] Breast cancer

Table 3

Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer incidence in relation to WCRF/AICR adherence score

		Reference	WCRF/AICR Adherence Scores Unadjusted HR					WCRF/AICR Adherence Scores Multivariable Adjusted HR				
	N Cases/N Total	Group 1 (0 − 3.5)	Group 2 (4.0 − 4.5)	Group 3 (5.0 − 5.5)	Group 4 (6.0 − 8.0)	P_{trend} [1]	P_{int}	Group 2 (4.0 − 4.5)	Group 3 (5.0 − 5.5)	Group 4 (6.0 − 8.0)	P_{trend} [1]	P_{int}
Overall [2]	3,189/36,626	1.0 (ref)	1.01 (0.91–1.12)	1.04 (0.93–1.15)	0.90 (0.80–1.02)	0.07	---	0.92 (0.83–1.03)	0.90 (0.81–1.00)	0.76 (0.67–0.87)	<0.001	---
Height [2,3]							0.78					0.50
≤160 cm	742/9,873	1.0 (ref)	1.06 (0.86–1.32)	1.10 (0.89–1.36)	0.86 (0.67–1.12)	0.20		0.98 (0.78–1.22)	0.98 (0.78–1.23)	0.73 (0.55–0.96)	0.08	
>160–<165 cm	1,400/16,113	1.0 (ref)	0.96 (0.83–1.13)	0.95 (0.81–1.11)	0.88 (0.74–1.06)	0.59		0.85 (0.72–1.00)	0.79 (0.67–0.93)	0.73 (0.60–0.89)	0.008	
≥ 165 cm	1,047/10,640	1.0 (ref)	1.02 (0.85–1.23)	1.10 (0.91–1.32)	0.92 (0.75–1.14)	0.31		0.99 (0.81–1.20)	1.02 (0.83–1.24)	0.84 (0.67–1.05)	0.24	
Fertility Years [3,4,5]							0.70					0.66
≤ 33	978/12,009	1.0 (ref)	1.03 (0.86–1.23)	1.04 (0.86–1.24)	0.85 (0.68–1.06)	0.22		0.93 (0.77–1.13)	0.93 (0.77–1.13)	0.72 (0.57–0.91)	0.03	
34–38 years	1,062/12,177	1.0 (ref)	1.02 (0.86–1.22)	0.96 (0.80–1.15)	0.95 (0.77–1.17)	0.82		0.90 (0.75–1.08)	0.78 (0.65–0.95)	0.74 (0.59–0.92)	0.02	
≥ 39 years	1,040/10,969	1.0 (ref)	0.94 (0.78–1.13)	1.04 (0.87–1.25)	0.88 (0.71–1.09)	0.28		0.92 (0.76–1.12)	0.98 (0.81–1.19)	0.81 (0.65–1.01)	0.18	
Parity [6]							0.12					0.09
None	292/3,272	1.0 (ref)	1.18 (0.84–1.67)	0.95 (0.67–1.35)	0.73 (0.48–1.10)	0.05		1.08 (0.75–1.57)	0.78 (0.53–1.14)	0.66 (0.42–1.05)	0.04	
1–2 children	1,074/11,702	1.0 (ref)	0.91 (0.76–1.09)	1.05 (0.88–1.25)	0.80 (0.65–0.99)	0.02		0.81 (0.66–0.98)	0.89 (0.74–1.08)	0.68 (0.54–0.85)	0.004	
3 or more	1,277/14,437	1.0 (ref)	1.07 (0.91–1.27)	1.04 (0.88–1.23)	0.97 (0.80–1.18)	0.66		1.02 (0.86–1.22)	0.94 (0.79–1.12)	0.83 (0.68–1.02)	0.13	
Family History [7,8]							0.69					0.60
None	2,137/26,766	1.0 (ref)	0.97 (0.85–1.10)	0.99 (0.88–1.13)	0.86 (0.75–1.00)	0.16		0.86 (0.76–0.98)	0.84 (0.74–0.96)	0.70 (0.60–0.82)	<0.001	
Second Degree	392/3,946	1.0 (ref)	1.30 (0.95–1.78)	1.31 (0.96–1.78)	1.14 (0.79–1.63)	0.30		1.20 (0.86–1.66)	1.18 (0.85–1.64)	1.01 (0.69–1.48)	0.54	
First Degree	523/4,232	1.0 (ref)	1.07 (0.83–1.38)	1.08 (0.83–1.39)	0.96 (0.71–1.29)	0.80		0.99 (0.76–1.29)	0.99 (0.75–1.30)	0.88 (0.64–1.21)	0.83	
Combined Factors [9]							0.40					0.57
None	968/11,861	1.0 (ref)	1.02 (0.85–1.23)	0.96 (0.80–1.16)	0.94 (0.75–1.17)	0.41		0.92 (0.76–1.11)	0.81 (0.67–0.99)	0.74 (0.59–0.93)	0.001	
1 risk factor	1,241/12,979	1.0 (ref)	0.88 (0.75–1.04)	1.00 (0.85–1.18)	0.78 (0.64–0.95)	0.12		0.82 (0.70–0.98)	0.89 (0.75–1.05)	0.69 (0.56–0.84)	0.003	
2 risk factors	627/5,059	1.0 (ref)	1.18 (0.92–1.51)	1.12 (0.88–1.44)	1.09 (0.82–1.44)	0.57		1.14 (0.89–1.47)	1.05 (0.81–1.35)	0.99 (0.74–1.31)	0.81	
3+ risk factors	101/651	1.0 (ref)	1.19 (0.63–2.27)	1.11 (0.59–2.08)	0.75 (0.35–1.58)	0.56		1.08 (0.57–2.08)	1.13 (0.60–2.16)	0.76 (0.36–1.63)	0.84	

[1] Score evaluated as a continuous variable Cox regression model.

[2] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, menarche age, menopause age, and parity.

[3] Tertiles.

[4] Age at menopause – age at menarche = years of potential fertility.

[5] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, and parity.

[6] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, menopause age, and menarche age.

[7] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, menopause age, menarche age, and parity.

[8] Breast cancer; second degree = grandmother only, First degree = history in mother/sister.

[9] Unadjusted and adjusted for age, smoking, education and hormone replacement therapy.

Table 4

Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer incidence in relation to diet recommendation adherence score

	Reference	Diet Adherence Score Unadjusted HR				Diet Adherence Score Multivariable Adjusted HR			
	0–2.5	3.0–4.0	4.5–6.0	p_{trend}[1]	p_{int}	3.0–4.0	4.5–6.0	p_{trend}[1]	p_{int}
Overall[2,4]	1.0 (ref)	1.24 (1.24–1.41)	1.25 (1.09–1.44)	0.005	---	1.11 (0.97–1.28)	1.06 (0.91–1.24)	0.22	---
Height[3,4]					0.87				0.87
≤160 cm	1.0 (ref)	1.32 (1.00–1.74)	1.26 (0.94–1.69)	0.14		1.20 (0.89–1.60)	1.07 (0.78–1.47)	0.28	
>160–<165 cm	1.0 (ref)	1.27 (1.04–1.56)	1.30 (1.05–1.62)	0.05		1.16 (0.93–1.45)	1.12 (0.88–1.41)	0.37	
≥165 cm	1.0 (ref)	1.14 (0.91–1.42)	1.18 (0.93–1.50)	0.38		1.02 (0.81–1.29)	1.01 (0.79–1.31)	0.98	
Fertility Years[3,5,6]					0.23				0.36
≤33 years	1.0 (ref)	1.61 (0.77–3.34)	1.13 (0.51–2.50)	0.18		0.97 (0.77–1.22)	0.91 (0.77–1.22)	0.64	
34–38 years	1.0 (ref)	1.10 (0.88–1.37)	1.06 (0.83–1.34)	0.65		1.00 (0.79–1.26)	0.95 (0.79–1.22)	0.80	
≥39 years	1.0 (ref)	1.15 (0.92–1.44)	1.22 (0.96–1.55)	0.25		1.51 (1.14–2.01)	1.47 (1.09–1.98)	0.02	
Parity[7]					0.48				0.37
None	1.0 (ref)	1.16 (0.77–1.75)	1.02 (0.66–1.59)	0.56		0.96 (0.61–1.51)	0.83 (0.51–1.36)	0.59	
1–2 children	1.0 (ref)	1.11 (0.89–1.39)	1.10 (0.86–1.39)	0.65		1.00 (0.79–1.26)	0.94 (0.73–1.21)	0.73	
3 or more	1.0 (ref)	1.41 (1.13–1.75)	1.42 (1.13–1.78)	0.007		1.31 (1.04–1.65)	1.24 (0.97–1.58)	0.06	
Family History[8,9]					0.31				0.46
None	1.0 (ref)	1.15 (0.98–1.34)	1.18 (0.99–1.34)	0.16		1.04 (0.88–1.23)	0.99 (0.83–1.18)	0.61	
Second Degree	1.0 (ref)	1.81 (1.17–2.81)	1.83 (1.16–2.88)	0.02		1.47 (0.94–2.28)	1.45 (0.91–2.32)	0.24	
First Degree	1.0 (ref)	1.29 (0.92–1.82)	1.20 (0.83–1.72)	0.29		1.25 (0.87–1.79)	1.14 (0.78–1.68)	0.40	
Combined Factors[10]					0.22				0.33
None	1.0 (ref)	1.30 (1.02–1.66)	1.21 (0.94–1.58)	0.91		1.15 (0.90–1.46)	1.00 (0.76–1.30)	0.02	
1 risk factor	1.0 (ref)	1.05 (0.86–1.29)	1.15 (0.93–1.42)	0.46		0.97 (0.79–1.19)	0.99 (0.80–1.24)	0.42	
2 risk factors	1.0 (ref)	1.48 (1.06–2.08)	1.50 (1.05–2.13)	0.09		1.42 (1.01–2.00)	1.36 (0.95–1.95)	0.45	
3+ risk factors	1.0 (ref)	2.31 (0.73–7.36)	1.71 (0.52–5.62)	0.65		2.14 (0.67–6.85)	1.59 (0.48–5.30)	0.55	

[1] Score evaluated as a continuous variable in Cox regression model.

[2] Combined dietary recommendations (score range 0 – 6.0).

[3] Tertiles.

[4] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, menarche age, menopause age, parity, BMI and physical activity.

[5] Age at menopause – age at menarche = years of potential fertility.

[6] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, parity, BMI and physical activity.

[7] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, menopause age, menarche age, BMI and physical activity.

[8] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, menopause age, menarche age, parity, BMI and physical activity.

[9] Breast cancer; second degree = grandmother only, First degree = history in mother/sister.

[10] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, BMI and physical activity.

Table 5

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer incidence and adherence to alcohol, body weight, and physical activity recommendations

	Reference	Alcohol Recommendation				Body Weight Recommendation				Physical Activity Recommendation			
	0	0.5	1.0	p_{trend}[1]	p_{int}	0.5	1.0	p_{trend}[1]	p_{int}	0.5	1.0	p_{trend}[1]	p_{int}
Overall[2]	1.0	0.99 (0.81–1.22)	0.84 (0.71–1.00)	0.01	---	0.96 (0.97–1.05)	0.78 (0.70–0.85)	<0.001	---	1.00 (0.91–1.09)	0.93 (0.84–1.02)	0.23	---
Height[3,4]					0.77				0.40				0.76
≤160 cm	1.0	1.00 (0.65–1.55)	0.82 (0.57–1.18)	0.23		0.98 (0.81–1.17)	0.76 (0.62–0.92)	0.008		0.94 (0.78–1.12)	0.86 (0.71–1.05)	0.35	
>160–<165 cm	1.0	1.02 (0.74–1.40)	0.94 (0.72–1.23)	0.73		0.97 (0.84–1.11)	0.73 (0.63–0.84)	<0.001		0.99 (0.86–1.13)	0.94 (0.81–1.08)	0.64	
≥165 cm Fertility	1.0	0.95 (0.67–1.35)	0.75 (0.56–1.00)	0.03		0.94 (0.79–1.12)	0.86 (0.72–1.02)	0.20		1.06 (0.91–1.24)	0.96 (0.82–1.13)	0.52	
Years[3,5]					0.94				0.81				0.95
≤33 years	1.0	1.36 (0.95–1.94)	0.90 (0.66–1.23)	<0.001		0.96 (0.82–1.14)	0.79 (0.67–0.94)	0.009		0.98 (0.84–1.15)	0.96 (0.82–1.14)	0.90	
34–38 years	1.0	0.86 (0.61–1.21)	0.76 (0.58–1.00)	0.11		0.91 (0.78–1.07)	0.71 (0.60–0.83)	<0.001		1.00 (0.86–1.16)	0.89 (0.76–1.04)	0.30	
≥39 years	1.0	0.85 (0.58–1.24)	0.92 (0.67–1.27)	0.68		0.99 (0.85–1.16)	0.84 (0.71–0.99)	0.04		0.99 (0.85–1.16)	0.92 (0.79–1.08)	0.55	
Parity[6]					0.91				0.44				0.55
None	1.0	1.33 (0.69–2.55)	0.91 (0.52–1.59)	0.24		0.84 (0.62–1.15)	0.67 (0.49–0.93)	0.05		0.91 (0.68–1.22)	0.78 (0.57–1.07)	0.31	
1–2 children	1.0	1.14 (0.81–1.61)	0.89 (0.67–1.19)	0.08		0.93 (0.78–1.09)	0.76 (0.64–0.90)	0.002		1.08 (0.93–1.25)	0.96 (0.82–1.13)	0.42	
3 or more	1.0	1.00 (0.72–1.39)	0.85 (0.65–1.12)	0.21		1.02 (0.88–1.18)	0.85 (0.73–0.99)	0.02		0.94 (0.82–1.08)	0.88 (0.76–1.02)	0.21	
Family History[7,8]					0.71				0.81				0.63
None	1.0	1.06 (0.82–1.36)	0.90 (0.73–1.11)	0.11		0.96 (0.86–1.07)	0.75 (0.67–0.84)	<0.001		0.97 (0.87–1.08)	0.89 (0.80–1.00)	0.13	
Second Degree	1.0	0.77 (0.43–1.38)	0.69 (0.43–1.09)	0.26		0.92 (0.71–1.20)	0.86 (0.66–1.13)	0.55		0.98 (0.77–1.26)	1.07 (0.83–1.39)	0.82	
First Degree	1.0	0.91 (0.57–1.46)	0.70 (0.44–1.11)	0.24		0.95 (0.76–1.19)	0.82 (0.65–1.03)	0.17		1.10 (0.90–1.36)	0.97 (0.77–1.22)	0.54	
Combined Factors[10]					0.61				0.73				0.70
None	1.0	0.96 (0.71–1.44)	0.83 (0.61–1.12)	0.07		1.00 (0.86–1.18)	0.79 (0.67–0.94)	0.004		0.92 (0.78–1.07)	0.94 (0.81–1.12)	0.42	
1 risk factor	1.0	0.98 (0.71–1.35)	0.85 (0.65–1.11)	0.11		0.90 (0.78–0.83)	0.71 (0.62–0.83)	<0.001		1.03 (0.90–1.18)	0.87 (0.76–1.01)	0.11	
2 risk factors	1.0	1.23 (0.77–1.95)	1.03 (0.69–1.54)	0.61		1.03 (0.84–1.27)	0.89 (0.72–1.09)	0.20		1.03 (0.85–1.25)	0.97 (0.79–1.18)	0.80	
3+ risk factors	1.0	0.39 (0.14–1.05)	0.39 (0.18–0.83)	0.04		0.91 (0.55–1.52)	1.03 (0.61–1.75)	0.88		1.20 (0.74–1.93)	1.15 (0.71–1.87)	0.54	

[1] Score evaluated as a continuous variable in Cox regression model.

[2] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, menarche age, menopause age, parity and BMI/alcohol/physical activity in model where BMI/alcohol/physical activity score were not exposure of interest.

[3] Tertiles.

[4] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, menarche age, menopause age, parity and BMI/alcohol/physical activity in model where BMI/alcohol/physical activity score were not exposure of interest.

[5] Age at menopause – age at menarche = years of potential fertility.

[6] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, parity, menarche age, menopause age, parity and BMI/alcohol/physical activity in model where BMI/alcohol/physical activity score were not exposure of interest.

[7] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, family history of breast cancer, menopause age, menarche age, menarche age, menopause age, parity and BMI/alcohol/physical activity in model where BMI/alcohol/physical activity score were not exposure of interest.

[8] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy, menopause age, menarche age, parity, menarche age, menopause age, parity and BMI/alcohol/physical activity in model where BMI/alcohol/physical activity score were not exposure of interest.

[9] Breast cancer; second degree = grandmother only, First degree = history in mother/sister.

[10] Unadjusted and adjusted for age, smoking, education, hormone replacement therapy and menarche age, menopause age, parity and BMI/alcohol/physical activity in model where BMI/alcohol/physical activity score were not exposure of interest.