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Lifetime grain consumption and breast cancer risk

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Abstract

Aims—We evaluated individual grain-containing foods and whole and refined grain intake during adolescence, early adulthood, and premenopausal years in relation to breast cancer risk in the Nurses' Health Study II.

Methods—Grain-containing food intakes were reported on a baseline dietary questionnaire (1991) and every 4 years thereafter. Among 90,516 premenopausal women aged 27 to 44 years, we prospectively identified 3235 invasive breast cancer cases during follow-up to 2013. 44,263 women reported their diet during high school, and from 1998 through 2013, 1347 breast cancer cases were identified among these women. Cox proportional hazards regression was used to

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estimate relative risks (RR) and 95% confidence intervals (95% CI) of breast cancer for individual and total grain-containing foods.

Results—After adjusting for known breast cancer risk factors, adult intake of whole grain-foods was associated with lower premenopausal breast cancer risk (highest vs lowest quintile: RR=0.82; 95%CI=0.70–0.97; P_{trend}=0.03), but not postmenopausal breast cancer. This association was no longer significant after further adjustment for fiber intake. The average of adolescent and early adulthood whole grain-food intake was suggestively associated with lower premenopausal breast cancer risk (highest vs lowest quintile: RR=0.74; 95%CI=0.56–0.99; P_{trend} =0.09). Total refined grain-food intake was not associated with risk of breast cancer. Most individual grain-containing foods were not associated with breast cancer risk. The exceptions were adult brown rice which was associated with lower risk of overall and premenopausal breast cancer (for each 2 servings/week: RR=0.94; 95%CI=0.89–0.99 and RR=0.91; 95%CI=0.85–0.99, respectively) and adult white bread intake which was associated with increased overall breast cancer risk (for each 2 servings/week: RR=1.02; 95%CI=1.01–1.04), as well as breast cancer before and after menopause.

Conclusion—Our results suggest that high whole grain-food intake may be associated with lower breast cancer risk before menopause. Fiber in whole grain-foods may mediate the association with whole grains.

Introduction

Breast cancer is the most frequently diagnosed cancers and the second leading cause of cancer deaths among women in the United States [1]. The potential influence of dietary factors on breast cancer development has received considerable attention from scientists and the public alike, because modifiable risk factors could help prevent breast cancer. Grains are major components of the diet and contribute to daily intake of carbohydrate, protein and dietary fiber [2]. Whole grains, in addition to fiber, contain many nutrients and bioactive components that may offer significant health benefits. While epidemiological evidence supports a protective effect of whole grain intake against type 2 diabetes [3, 4], cardiovascular diseases [4], and some cancers [5], the relation between whole grain food intake and breast cancer has been examined in only a few studies [6–8] and no clear association has been seen. However, these studies generally evaluated grain intake during midlife and later. Studies of women who survived the atomic bombing in Hiroshima and Nagasaki, or who underwent radiation treatment for lymphoma, provide evidence that carcinogenic exposures in early life may be critical in subsequent breast cancer risk [9–11]. Consistent with this, in our previous work in the Nurses' Health Study II (NHSII), high intake of fiber during adolescence and early adulthood was associated with lower risk of breast cancer [12]. Further, different grains may be differently associated with risk of breast cancer and an understanding of the role of each grain on breast carcinogenesis is needed. NHSII is a prospective cohort study in which we could evaluate the importance of timing of grain consumption, given the large sample size and validated data on dietary intake, as well as information on lifestyle and breast cancer risk factors during both adolescent and adult life. The overall goal of this analysis was to investigate the intake of whole grain and refined grain foods as well as individual grain-containing foods during adolescence, early adulthood

and premenopausal periods in relation to subsequent risk of pre- and postmenopausal breast cancer in the NHSII. The analyses also included consideration of tumor hormone receptor status.

SUBJECTS AND METHODS

Study Population

The NHSII was established in 1989 with a total enrollment of 116,430 female registered nurses aged 25 to 42 years. Our analyses included women who returned the 1991 self-reported food-frequency questionnaire (FFQ) (n=97,813). We excluded participants with extreme total energy intake (<600 or >3500 kcal/day); more than 70 food items left blank in the FFQ; postmenopausal status in 1991, missing information on age, or with a diagnosis of cancer (except non-melanoma skin cancer) in 1991 or before. The primary analyses included 90,516 women. The follow-up rate was over 96 percent of total potential person-years from 1991 through 2013.

In 1997, participants were asked about their willingness to complete a supplemental FFQ about diet during high school (HS-FFQ). Among the 47,355 women who returned the HS-FFQ in 1998, we excluded women if they had cancer (except non-melanoma skin cancer) before 1998, extreme total energy intake (<600 or ≥5000 Kcal) or more than 70 food items left blank in the HS-FFQ. Thus, the adolescent diet analyses included 44,263 women. The follow-up rate was over 98 percent of total potential person-years from 1998 through 2013.

This study was approved by the Human Subjects Committee at Brigham and Women's Hospital and Harvard School of Public Health (Boston, MA, United States).

Dietary Assessment

In 1991 and every 4 years thereafter, validated semi-quantitative FFQs with approximately 130 items were sent to participants to report their usual dietary intake during the past year (available at http://www.nurseshealthstudy.org/participants/questionnaires). We asked women how often they consumed grain foods in 9 categories ranging from “never or less than once per month” to “6 or more times per day”. Whole and refined grain foods listed on the FFQ are presented in Supplementary Table S1. Validity of repeated questionnaires to assess long term intake was evaluated by comparison with diet records collected 6 years later; the average correlation for dietary nutrient intakes, corrected for variation in diet records, was 0.83 [13]. In addition, higher intake of whole grain foods assessed by this questionnaire has been associated with lower risks of total mortality [14] and type 2 diabetes [15], indirectly supporting the validity of the FFQ.

Adolescent diet was evaluated using a 124-item FFQ that included foods typically consumed between 1960 and 1980 when participants were in high school (HS-FFQ, see Supplemental Table S2). Among 80 young women, the validity of the HS-FFQ was assessed. Women completed three 24-hour recalls and two FFQ during high school with the HS-FFQ administered 10 years later; the mean of corrected correlation coefficients for energy-adjusted nutrient intakes was 0.45 for the HS-FFQ and the earlier 24-hour recalls and 0.58 for the HS-FFQ and the earlier FFQ’s [16]. Validity was also come from comparing

adolescent diet reported by 272 of NHSII participants with their diet reported by their mothers; the mean correlation for nutrients was 0.40 [17].

Assessment of Breast Cancer Cases

In the biennial follow-up questionnaires, participants reported diagnosis of breast cancer and the date of diagnosis. When a case of breast cancer was identified, we asked the participant (or next of kin for those who had died) for permission to review their medical records and pathology reports. Because accuracy was high for self-reporting (99%), diagnoses with unavailable medical records (n=547) were included in the analysis. Estrogen and progesterone receptors status of tumors was extracted from medical records. Deaths were identified by reports of next of kin, the postal service in response to the follow-up questionnaires or by searching the National Death Index.

Assessment of covariates

In the biennial NHSII questionnaires, we inquired about potential risk factors for breast cancer including age, history of benign breast disease, family history of breast cancer, smoking, race, menopausal status, menopausal hormone use, oral contraceptive use, height, and weight. These data were updated to the most recent information, if available. Body mass index (BMI) at age 18 and adolescent alcohol consumption were obtained from the 1989 questionnaire. Women were considered premenopausal if they still had periods. Women were considered postmenopausal if they reported natural menopause, or had undergone bilateral oophorectomy. We defined women of unknown menopausal status or who had hysterectomy without bilateral oophorectomy as premenopausal if they were younger than 46 years for smokers or younger than 48 years for nonsmokers and as postmenopausal if they were 54 years or older for smokers or 56 years or older for non-smokers [18].

Statistical Analysis

We calculated premenopausal cumulative average of dietary intakes by using the 1991, 1995, 1999, 2003, 2007 and 2011 dietary intake data, stopping updating after reporting menopause. Grain-food intakes reported on the baseline FFQ (1991), when participants were 27–44 years of age, were considered early adulthood dietary intake. To evaluate adult diet and breast cancer, participants contributed person-years from the date of return of the 1991 questionnaire until the date of any cancer diagnosis except non-melanoma skin cancer, death, or end of follow-up period (June 1, 2013), whichever was earlier. For adolescent grain-food intake, participants contributed person-years similarly except that follow-up began with return of the adolescent diet questionnaire in 1998. Participants were divided into quintiles according to their dietary intake. Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (95% CI) for each category, using the lowest quintile of intake as the reference category. To control for confounding by age, calendar time, or any possible two-way interactions between these two time scales, we stratified by age in month and 2-year time periods. Multivariable models also simultaneously adjusted for various confounding factors including race, history of breast cancer in mother or sisters, history of benign breast disease, smoking, height, BMI at age 18, weight change since age 18, age at menarche, parity and age at first birth, oral contraceptive use, menopausal status, menopausal hormone use, age at menopause, physical activity and

intakes of alcohol and energy. For adolescent grain-food intake and breast cancer risk, multivariable models adjusted additionally for adolescent alcohol intake and adolescent energy intake instead of adult energy intake. Test for trend was performed by assigning the median value for each quintile and modeling as a continuous variable. We also calculated the average of adolescent and early adulthood (1991) intakes of whole grain and refined grain foods among those with available information for both periods.

To examine if the observed associations were independent of a generally healthy dietary pattern, we additionally adjusted for a modified Alternate Healthy Eating Index (AHEI) [19] score that excluded the scores for whole grain foods to avoid redundancy with our primary variables. We also examined the associations after additional adjustment for total red meat, fruits and vegetables, or fiber (12, 20–22). To better represent adolescent intakes and determine whether these associations were independent of adulthood dietary intakes, we adjusted for dietary intake during adult life (cumulative average of dietary intakes). To examine whether the associations between whole grain-food intake and breast cancer risk were modified by BMI at age 18 (<21 or >= 21 kg/m^2), a cross-product term of the ordinal score for this variable and whole grain-food intake was included in the multivariable model. Tests for interactions were obtained from a likelihood ratio test. We evaluated the effects of whole grain and refined grain food intake in relation to breast cancer risk by tumor hormone receptor status using Cox proportional cause-specific hazards regression model with a duplication method for competing risk data. This method permits estimation of separate associations of diet for tumors that are both estrogen and progesterone receptors positive and both receptors negative, and is used to assess whether a risk factor has statistically different regression coefficients for different tumor subtype [23]. All *P* values were two-sided. SAS version 9.3 (SAS Institute, Inc., Cary NC) was used for all analyses.

Results

During 22 years of follow-up, 3235 women developed invasive breast cancers for the adult dietary analyses, among which there were 1347 invasive breast cancers for the adolescent dietary analyses. At the time of dietary assessment (1991 for adult and 1998 for adolescent diet), higher consumption of whole grain foods in adulthood and adolescence was associated with a lower prevalence of smoking, lower consumption of animal fat, and higher consumption of fiber, fruits and vegetables (Tables 1 and S3). Women with higher consumption of whole grain food during adulthood were also less likely to drink alcohol. Higher intake of refined grain during adult was associated with higher intake of fiber, total red meat, fruit and vegetables and lower intake of animal fat (Table 1). Women with high intake of refined grain during adult life were less likely to smoke, to use oral contraceptive pills, and to be nulliparous. Higher adolescent refined grain intake was associated with higher adolescent intake of alcohol, total red meat, fruit and vegetables and lower intake of fiber and animal fat (Table S3).

Adult grain-food intake and breast cancer risk

Cumulative average of premenopausal intake of whole grain-foods was associated with lower risk of breast cancer before menopause (highest vs lowest quintile RR=0.82;

95%CI=0.70–0.97; P_{trend}=0.03), but not overall or postmenopausal breast cancer (Table 2). This association was attenuated after further adjustment for fiber (highest vs lowest quintile RR=0.89; 95%CI=0.73–1.07; P_{trend}=0.31), red meat intake (highest vs lowest quintile RR=0.84; 95%CI=0.71–1.00; P_{trend}=0.07) or AHEI (highest vs lowest quintile RR=0.85; 95%CI=0.72–1.01; P_{trend}=0.09). Cumulative average of premenopausal refined grain-food intake was not significantly associated with risk of overall breast cancer (highest vs lowest quintile RR=0.88; 95%CI=0.76–1.01; P_{trend}=0.06), premenopausal breast cancer or postmenopausal breast cancer (Table 2). With mutual adjustment for whole grain and refined grain foods, the association among refined grain-food intake was not materially changed (for overall breast cancer RR=0.88; 95%CI=0.77–1.02; P_{trend}=0.07).

Most individual grain-containing foods were not significantly associated with risk of breast cancer (Figure 1). However, cumulative average of premenopausal white bread intake was associated with increased risk of overall breast cancer (for each 2 servings/week: RR=1.02; 95%CI=1.01–1.04), as well as before menopause (for each 2 servings/week: RR=1.03; 95%CI=1.00–1.05) and after menopause (for each 2 servings/week: RR=1.03; 95%CI=1.00–1.06). Cumulative average of brown rice intake during premenopausal adult life was inversely associated with risk of overall breast cancer (for each 2 servings/week: RR=0.94; 95%CI=0.89–0.99) and premenopausal breast cancer (for each 2 servings/week: RR=0.91; 95%CI=0.85–0.99), but not postmenopausal breast cancer (for each 2 servings/week: RR=0.98; 95%CI=0.90–1.07) (Figure 1). These associations were slightly attenuated after further adjustment for fiber intake (each 2 servings/week for overall breast cancer: RR=0.95; 95%CI=0.90–1.01; for premenopausal breast cancer: RR= 0.93; 95%CI=0.86–1.01; for postmenopausal breast cancer: RR= 0.99; 95%CI=0.91–1.08). The associations were materially unchanged after additional adjustment for fruits and vegetable, red meat intake or AHEI (data not shown). Cumulative average of premenopausal white rice intake was not associated with overall or premenopausal breast cancer. However, an inverse association between white rice and postmenopausal breast cancer was noted (for each 2 servings/week: RR=0.95; 95%CI=0.90–1.00). A similar association was observed when Asian women (n=1435) were excluded from analysis (data not shown). Cumulative average of pasta intake before menopause was also inversely associated with overall breast cancer (for each 2 servings/week: RR=0.97; 95%CI=0.94–1.00), but not premenopausal or postmenopausal breast cancer (Figure 1).

Grain-food intakes reported on the baseline FFQ (1991) were considered early adulthood dietary intake. Early adulthood intakes of whole grain or refined grain foods were not associated with risk of breast cancer (Table 3). When early adulthood specific grain-containing food intake was examined, an inverse association was observed between brown rice intake and overall and premenopausal breast cancer, but not postmenopausal breast cancer (data not shown).

Adolescent grain-food intake and breast cancer risk

Adolescent intakes of whole grain or refined grain foods were not associated with risk of breast cancer (Table 4). Adolescent white bread, dark bread or rice intake was not also associated with risk of breast cancer. Adolescent cold breakfast cereal was inversely

associated with risk of postmenopausal breast cancer (for each 2 servings/week: RR=0.93; 95%CI=0.87–0.99), but not premenopausal or overall breast cancer (Figure 1). No other significant association was observed.

Average adolescence and early adulthood grain-food intake and breast cancer risk

Adolescent and early adult (1991) whole grain-food intakes were only modestly correlated (r=0.28). Among women with both early adulthood and adolescent dietary data (n=41,092), we observed an inverse association between average adolescent and early adulthood intake of whole grain food and premenopausal breast cancer (highest vs lowest quintile: RR=0.74; 95%CI=0.56–0.99; P_{trend}=0.09), but not overall breast cancer (highest vs lowest quintile: RR=0.88; 95%CI=0.73–1.06; P_{trend}=0.13), or postmenopausal breast cancer (highest vs lowest quintile: RR=0.94; 95%CI=0.71–1.23; P_{trend}=0.30). We observed inverse associations between average adolescent and early adulthood intake of refined grain food and postmenopausal breast cancer (highest vs lowest quintile: RR=0.72; 95%CI=0.53–0.98; P_{trend}=0.04), but not overall (RR=0.82; 95%CI=0.66–1.01; P_{trend}=0.07) or premenopausal breast cancer risk (RR=0.97; 95%CI=0.70–1.33; P_{trend}=0.83).

Breast cancer subtypes and subgroups

The inverse association with adolescent whole grain-food intake was stronger for both estrogen and progesterone receptors negative (ER-/PR-) cancers (HR=0.60; 95%CI=0.38–0.96, each serving/day) compared to ER+/PR+ cancers before menopause (HR=0.97; 95%CI=0.81–1.17) ($P_{for\ difference\ by\ receptor\ status}$ =0.046). Adolescent refined grain-food intake was suggestively associated with higher risk of ER+/PR+ cancers (HR=1.07; 95%CI=0.95–1.20, each serving/day) and with lower risk of ER-/PR- cancers among premenopausal women (HR=0.80; 95%CI=0.64–1.01, each serving/day) ($P_{for\ difference\ by\ receptor\ status}$=0.01) (Table S4). Associations between whole grain and refined grain food intake and breast cancer risk did not differ significantly by BMI at age 18 for either cumulative average, early adulthood or adolescent diets (data not shown).

Discussion

Our findings suggest that higher adult whole grain-food intake may be associated with lower premenopausal breast cancer risk. Further, an inverse association was observed between average adolescent and early adulthood intake of whole grain food and premenopausal breast cancer risk. However, these associations were somewhat mediated with fiber intake. No single food or type of grain appeared to account for these findings. The exceptions were consumption of brown rice during adulthood that was associated with lower risk of breast cancer and white bread consumption that was associated with higher risk. We also noted that high whole grain intake during adolescence is associated with reduced premenopausal risk of both estrogen and progesterone receptors negative tumors.

The association between whole grain intake and breast cancer has been evaluated in few prospective studies [6–8]. Intake of whole grain foods was not associated with risk of postmenopausal breast cancer in Danish and US women [6, 8]. High intake of high-fiber bread was associated with lower risk of breast cancer in Malmo Diet and Cancer cohort [7].

Compared with refined grain foods, whole grain foods have a high content of many nutrients and bioactive components as well as fiber that may offer significant health benefits. Our previous analysis within the NHSII indicated that high intake of fiber during adolescence and early adulthood was associated with decreased risk of breast cancer in later life [12]. We noted non-significant association between whole grain-food intake and premenopausal breast cancer after additionally adjustment for fiber, suggesting that fiber or correlated constituents of whole grains may account for the association with whole grain foods.

Rice is an important source of arsenic exposure in the U.S. diet, and arsenic levels are higher in brown rice than in white rice [24, 25]. While health concerns about arsenic in some rice products have been recently raised in the United States [26], we observed that adult brown rice was associated with lower risk of breast cancer. However, this finding is reassuring regarding concerns over arsenic in brown rice. As we examined many relationships between specific foods and breast cancer, this inverse association could be due to chance and needs confirmation. Only a few epidemiological studies have investigated whether a high intake of rice is associated with risk of breast cancer. We earlier reported a lower risk of breast cancer with high lifetime intake of rice in the same NHSII cohort [27]. In contrast, among women in Nurses' Health Study cohort, high intake of total rice was not associated with risk of breast cancer [27]. However, it is not clear whether the significant findings in NHSII were due to early age at dietary assessment or the relatively young age of women at diagnosis of breast cancer. Similarly, lower risk of breast cancer was also reported with high intake of brown rice in a cross-sectional study in South Korean postmenopausal women [28].

Potential limitations need to be considered. The participants were restricted to nurses and predominantly white women that could reduce generalizability; however, it is unlikely that the biology underlying these associations differs by race or education. Residual confounding is also possible as women with high whole grain consumption may have healthier lifestyles. However, we controlled for a variety of potential confounders, including intakes of red meat, and modified AHEI, which had minimal effects on associations between brown rice and breast cancer. Adolescent diet may be misclassified because assessments were done when women were 33–52 years old. However, the associations were largely independent of adult diet, and evidence of validity came from comparisons of diet recorded during adolescence and our questionnaire administered 10 years later [16, 17]. Further, because diet was assessed before diagnosis, misclassification would tend to be non-differential and may dilute the associations.

Our study has several strengths. The large sample size and dietary assessments during adolescence, early adulthood, and cumulatively over the premenopausal period allowed examination of exposures during specific periods of life. We were also able to examine breast cancers by menopausal and hormone receptor status.

In summary, our findings suggest that higher intake of whole grain-foods intake may play a role in prevention of premenopausal breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The authors' responsibility were as follows: MSF, EC, WYC, AHE and WCW: designed the research; MSF: analysis and wrote the manuscript; and WCW: had primary responsibility for the final content of the manuscript; and all authors: provided critical input in the writing of the manuscript and read and approved the final manuscript. The authors assume full responsibility for analyses and interpretation of these data.

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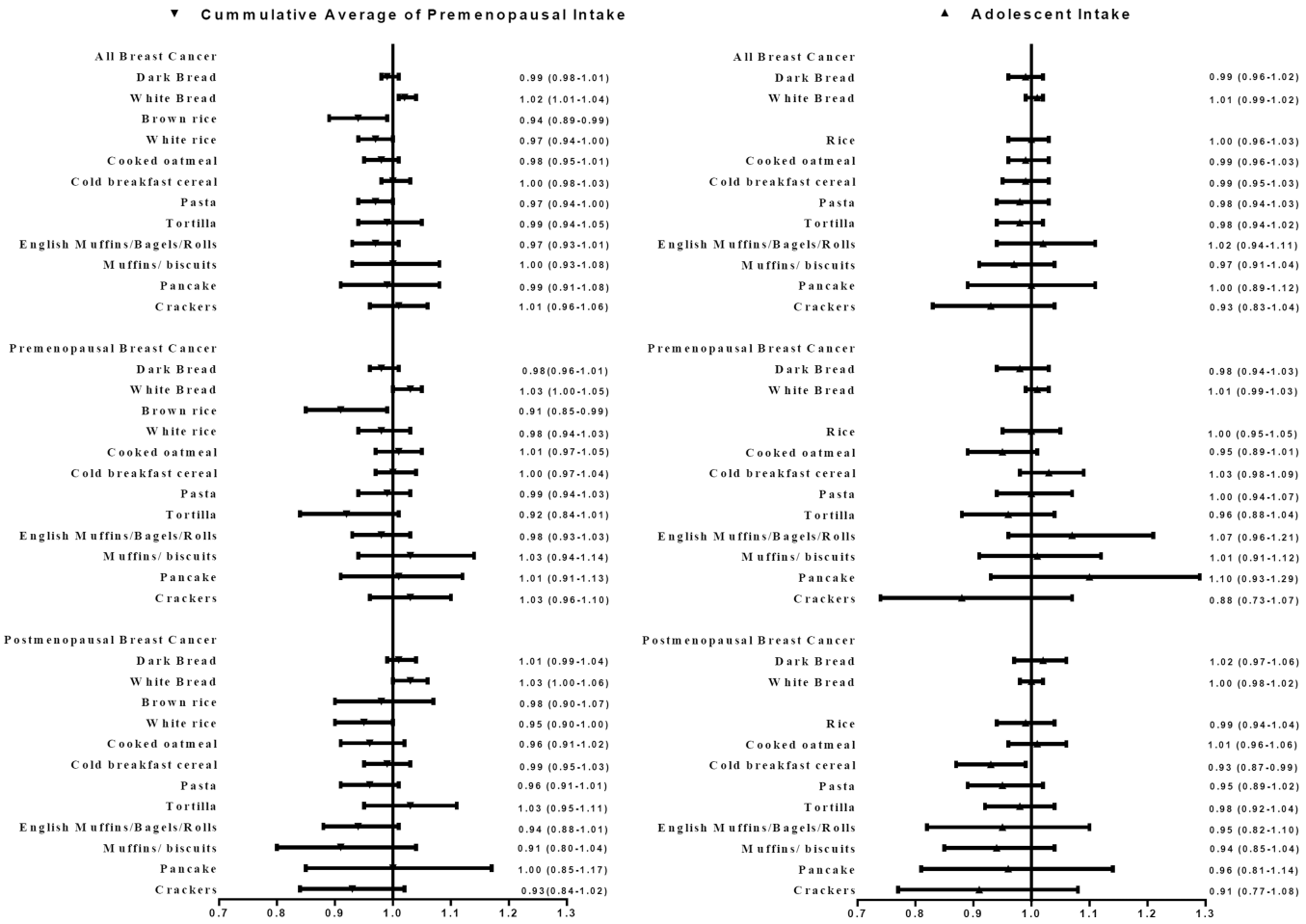

Figure 1. Multivariate relative risks (RRs) and 95% confidence intervals (95%CI) for every 2 servings/week specific grain-containing food intake during adolescence and adulthood and breast cancer risk

Model 2 was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking (never, past, current 1 –14/ day, current 15–24/day, current ≥25/day), race (white/non-white), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth ≥30 years, parity 3–4 and age at first birth <25 years, parity 3–4 and age at first birth 25–<30 years, parity 3–4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), height (<62, 62–<65, 65–<68, ≥68 inches), BMI at age 18 years (<18.5, 18.5–<22.5, 22.5–<25, 25.0–<30, ≥30.0 kg/m2), weight change since age 18 (continuous, missing indicator), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past, current), adult alcohol intake (nondrinker, <5, 5–<15,≥15 g/day), physical activity (quintile), energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users), age at menopause (<45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal

current users, unknown menopausal status) and, age at menopause (premenopausal, unknown menopause, <45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years). For adolescent grain intake, we additionally adjusted for adolescent alcohol intake (nondrinker, <5, ≥5 g/day) and adolescent energy intake (instead of adult energy intake).

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Table 1

Age and age-standardized other characteristics in 1991 according to intake of whole grain and refined grain foods during early adulthood among women enrolled in the Nurses' Health Study II

	Whole grain, quintile			Refined grain, quintile		
Number	**Q1 18,020**	**Q3 17,970**	**Q5 18,062**	**Q1 18,161**	**Q3 18,070**	**Q5 18,045**
Mean±SD						
Age, years	37± 5	37±5	37±5	37±5	36±5	36±5
Whole grain intake, serving/day	0.1± 0.07	0.6±0.07	1.6±0.6	0.5±0.5	0.7±0.5	0.9±0.7
Refined grain intake, serving/day	1.9±1.0	2.2±0.9	2.5±1.1	1.0±0.3	2.1±0.1	3.7±0.8
Total energy intake, kcal	1525±506	1793±511	2074±538	1305±378	1766±407	2336±490
Alcohol consumption, g/day	3.1±6.9	3.2±6.0	3.0± 5.3	3.1±6.7	3.1±5.9	3.2±5.8
Total fiber intake, g/day	15.0±4.4	17.8±4.3	22.7±6.4	17.9± 6.5	18.3±5.2	18.6±5.0
Animal fat intake, % energy	19.5±4.9	17.7± 4.2	15.0±4.2	18.8±5.1	17.5± 4.3	16.1±4.2
Total red meat intake, serving/day	0.8±0.6	0.8±0.5	0.7±0.5	0.6±0.5	0.8±0.5	1.0±0.6
Total fruit intake, serving/day	0.7±0.7	1.0±0.8	1.5±1.0	0.9±0.8	1.1±0.8	1.3±1.0
Total vegetable intake, serving/day	2.3±1.5	2.9±1.6	3.8±2.2	2.4±1.7	2.9±1.7	3.7±2.1
Adult body mass index, kg/m^2	24.9±5.7	24.7±5.3	24.0± 4.8	24.6±5.3	24.5±5.3	24.8±5.6
Body mass index at age 18, kg/m^2	21.3±3.5	21.3±3.3	21.2±3.2	21.5±3.5	21.2±3.3	21.2±3.4
Age at first birth, years	25.5±4.1	25.8±4.1	26.3±4.3	25.4±4.3	26.0±4.1	26.2±4.1
Age at menarche, years	12.4±1.4	12.4±1.4	12.4±1.4	12.4±1.5	12.4±1.4	12.4±1.4
%						
Current smokers	19	11	7	16	11	9
Current oral contraceptive use	11	11	10	12	11	10
History of benign breast disease	10	9	9	10	9	9
Family history of breast cancer in mother or sisters	15	15	16	15	16	15
Nulliparous	27	26	29	35	25	22

Table 2

Relative risks (RR) and 95% confidence intervals (95%CI) for breast cancer according to quintile of cumulative average of premenopausal whole grain and refined grain foods intake among women in the Nurses' Health Study II

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Cumulative average of premenopausal total whole grain-food intake						
All cases						
Median intake, serving/day	0.2	0.5	0.7	1.0	1.5	
No. of cases/person-years	673/375,194	642/377,729	617/377,311	647/377,992	656/377,630	
Age-adjusted RR (95%CI)	1	0.99 (0.89–1.10)	0.95 (0.85–1.06)	1.01 (0.90–1.12)	1.01 (0.90–1.12)	0.76
Multivariable RR (95%CI)[†]	1	0.92 (0.83–1.03)	0.87 (0.77–0.97)	0.91 (0.81–1.02)	0.91 (0.81–1.03)	0.25
Premenopausal cases						
Median intake, serving/day	0.2	0.5	0.7	1.00	1.5	
No. of cases/person-years	386/234,866	339/236,307	343/236,657	322/236,936	329/236,277	
Age-adjusted RR (95%CI)	1	0.89 (0.77–1.03)	0.90 (0.77–1.04)	0.85 (0.74–0.99)	0.86 (0.74–1.00)	0.06
Multivariable RR (95%CI)[†]	1	0.88 (0.76–1.02)	0.87 (0.75–1.02)	0.83 (0.71–0.97)	0.82 (0.70–0.97)	0.03
Postmenopausal cases						
Median intake, serving/day	0.2	0.5	0.7	1.0	1.6	
No. of cases/person-years	223/105,700	243/106,194	216/106,298	233/106,309	254/106,231	
Age-adjusted RR (95%CI)	1	1.11 (0.92–1.33)	0.99 (0.82–1.20)	1.07 (0.89–1.29)	1.14 (0.95–1.37)	0.21
Multivariable RR (95%CI)[†]	1	1.05 (0.87–1.26)	0.91 (0.75–1.11)	0.99 (0.81–1.21)	1.06 (0.87–1.30)	0.61
Cumulative average of premenopausal total refined grain-food intake						
All cases						
Median intake, serving/day	1.2	1.7	2.2	2.7	3.5	
No. of cases/person-years	684/376,472	677/377,439	642/377,614	638/377,317	594/377,014	
Age-adjusted RR (95%CI)	1	1.03 (0.92–1.14)	0.99 (0.89–1.10)	1.00 (0.89–1.11)	0.93 (0.83–1.03)	0.12
Multivariable RR (95%CI)[†]	1	0.97 (0.86–1.08)	0.92 (0.81–1.03)	0.93 (0.81–1.05)	0.88 (0.76–1.01)	0.06
Premenopausal cases						

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Median intake, serving/day	1.3	1.8	2.2	2.7	3.5	
No. of cases/person-years	365/235,558	370/236,446	337/236,531	338/236,476	309/236,032	
Age-adjusted RR (95%CI)	1	1.03 (0.89–1.20)	0.98 (0.84–1.13)	0.99 (0.86–1.15)	0.92 (0.79–1.07)	0.20
Multivariable RR (95%CI)[†]	1	1.03 (0.88–1.20)	0.97 (0.83–1.15)	0.99 (0.83–1.18)	0.91 (0.75–1.11)	0.31
Postmenopausal cases						
Median intake, serving/day	1.2	1.7	2.1	2.6	3.4	
No. of cases/person-years	250/105,946	239/106,239	230/106,239	221/106,186	229/106,069	
Age-adjusted RR (95%CI)	1	0.97 (0.82–1.16)	0.94 (0.79–1.13)	0.92 (0.76–1.10)	0.93 (0.77–1.11)	0.34
Multivariable RR (95%CI)[†]	1	0.92 (0.76–1.11)	0.84 (0.69–1.03)	0.81 (0.65–1.00)	0.83 (0.66–1.04)	0.10

[†]Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), race (white/non-white), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth ≥30 years, parity 3–4 and age at first birth <25 years, parity 3–4 and age at first birth 25–<30 years, parity 3–4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), height (<62, 62–<65, 65–<68, ≥68 inches), BMI at age 18 years (<18.5, 18.5–<22.5, 22.5–<25, 25.0–<30, ≥30.0 kg/m2), weight change since age 18 (continuous, missing indicator), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past, current), adult alcohol intake (nondrinker, <5, 5–<15,≥15 g/day), physical activity (quintile), energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users), age at menopause (<45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status) and, age at menopause (premenopausal, unknown menopause, <45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years).

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Table 3

Relative risks (RR) and 95% confidence intervals (95%CI) for breast cancer according to quintile of intake of whole grain and refined grain foods during early adulthood among women in the Nurses' Health Study II

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Early adulthood total whole grain-food intake						
All cases						
Median intake, serving/day	0.1	0.4	0.6	0.9	1.4	
No. of cases/person-years	665/374,554	669/380,529	625/374,930	642/379,035	634/376,807	
Age-adjusted RR (95%CI)	1	1.00 (0.89–1.11)	0.95 (0.85–1.06)	0.98 (0.87–1.09)	0.95 (0.85–1.06)	0.34
Multivariable RR (95%CI)[†]	1	0.97 (0.87–1.09)	0.92 (0.82–1.03)	0.93 (0.83–1.05)	0.91 (0.81–1.02)	0.11
Premenopausal cases						
Median intake, serving/day	0.2	0.4	0.6	0.9	1.5	
No. of cases/person-years	367/235,540	354/237,799	316/236,259	343/236,473	339/234,973	
Age-adjusted RR (95%CI)	1	0.95 (0.82–1.10)	0.85 (0.73–0.99)	0.93 (0.80–1.08)	0.91 (0.79–1.06)	0.34
Multivariable RR (95%CI)[†]	1	0.93 (0.80–1.08)	0.84 (0.72–0.98)	0.90 (0.77–1.06)	0.88 (0.75–1.03)	0.19
Postmenopausal cases						
Median intake, serving/day						
No. of cases/person-years	0.1	0.3	0.6	0.9	1.4	
Age-adjusted RR (95%CI)	1	1.00 (0.84–1.21)	1.11 (0.93–1.33)	0.99 (0.82–1.19)	0.99 (0.82–1.19)	0.75
Multivariable RR (95%CI)[†]	1	0.99 (0.82–1.19)	1.06 (0.88–1.28)	0.95 (0.78–1.15)	0.95 (0.78–1.16)	0.45
Early adulthood total refinedgrain-food intake						
All cases						
Median intake, serving/day	1.1	1.6	2.1	2.6	3.5	
No. of cases/person-years	671/377,164	693/377,147	603/377,366	672/377,181	596/376,998	
Age-adjusted RR (95%CI)	1	1.06 (0.95–1.18)	0.93 (0.83–1.04)	1.04 (0.93–1.15)	0.92 (0.83–1.03)	0.13
Multivariable RR (95%CI)[†]	1	1.01 (0.90–1.12)	0.86 (0.76–0.97)	0.97 (0.86–1.10)	0.89 (0.77–1.02)	0.10
Premenopausal cases						

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Median intake, serving/day	1.1	1.6	2.1	2.6	3.5	
No. of cases/person-years	351/236,306	377/236,163	300/236,428	363/236,090	328/236,056	
Age-adjusted RR (95%CI)	1	1.07 (0.93–1.24)	0.86 (0.73–1.00)	1.04 (0.90–1.20)	0.95 (0.82–1.11)	0.46
Multivariable RR (95%CI)[†]	1	1.04 (0.89–1.21)	0.83 (0.70–0.98)	1.01 (0.85–1.20)	0.94 (0.78–1.14)	0.57
Postmenopausal cases						
Median intake, serving/day	1.0	1.6	2.0	2.5	3.4	
No. of cases/person-years	235/106,060	255/106,200	220/106,178	243/106,114	216/106,181	
Age-adjusted RR (95%CI)	1	1.11 (0.93–1.32)	0.96 (0.80–1.16)	1.07 (0.89–1.28)	0.93 (0.77–1.12)	0.35
Multivariable RR (95%CI)[†]	1	1.05 (0.87–1.26)	0.87 (0.71–1.07)	0.97 (0.78–1.19)	0.86 (0.68–1.08)	0.14

[†]Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), race (white/non-white), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth ≥30 years, parity 3–4 and age at first birth <25 years, parity 3–4 and age at first birth 25–<30 years, parity 3–4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), height (<62, 62–<65, 65–<68, ≥68 inches), BMI at age 18 years (<18.5, 18.5–<22.5, 22.5–<25, 25.0–<30, ≥30.0 kg/m2), weight change since age 18 (continuous, missing indicator), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past, current), adult alcohol intake (nondrinker, <5, 5–<15,≥15 g/day), physical activity (quintile), energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users), age at menopause (<45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status) and, age at menopause (premenopausal, unknown menopause, <45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years).

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Table 4

Relative risks (RR) and 95% confidence intervals (95%CI) for breast cancer according to quintile of intake of whole grain and refined grain foods during adolescence among women in the Nurses' Health Study II

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Adolescent total whole grain-food intake						
All cases						
Median intake, serving/day	0.2	0.4	0.6	0.9	1.5	
No. of cases/person-years	270/134,593	270/134,862	286/134,501	259/134,628	262/134,488	
Age-adjusted RR (95%CI)	1	1.02 (0.86–1.21)	1.08 (0.92–1.28)	0.98 (0.82–1.16)	1.01 (0.85–1.20)	0.88
Multivariable RR (95%CI)[≠]	1	1.01 (0.85–1.20)	1.06 (0.89–1.26)	0.96 (0.80–1.14)	0.98 (0.81–1.17)	0.57
Premenopausal cases						
Median intake, serving/day	0.2	0.4	0.7	0.9	1.5	
No. of cases/person-years	126/69,635	118/69,585	113/69,549	113/69,509	106/69,439	
Age-adjusted RR (95%CI)	1	0.95 (0.73–1.22)	0.89 (0.69–1.15)	0.90 (0.69–1.16)	0.86 (0.67–1.12)	0.28
Multivariable RR (95%CI)[≠]	1	0.97 (0.75–1.26)	0.89 (0.68–1.16)	0.91 (0.69–1.18)	0.85 (0.65–1.13)	0.25
Postmenopausal cases						
Median intake, serving/day	0.2	0.4	0.6	0.9	1.4	
No. of cases/person-years	129/53,409	124/53,411	139/53,181	120/53,396	128/53,316	
Age-adjusted RR (95%CI)	1	0.97 (0.75–1.24)	1.10 (0.86–1.39)	0.93 (0.72–1.19)	1.00 (0.78–1.28)	0.92
Multivariable RR (95%CI)[≠]	1	0.93 (0.72–1.20)	1.03 (0.81–1.32)	0.89 (0.68–1.15)	0.94 (0.72–1.23)	0.61
Adolescent total refined grain-food intake						
All cases						
Median intake, serving/day	1.5	2.1	2.7	3.3	4.3	
No. of cases/person-years	295/134,819	259/134,283	268/135,101	263/133,935	262/134,936	
Age-adjusted RR (95%CI)	1	0.89 (0.75–1.05)	0.94 (0.80–1.11)	0.95 (0.80–1.12)	0.95 (0.80–1.12)	0.78
Multivariable RR (95%CI)[≠]	1	0.88 (0.74–1.05)	0.94 (0.78–1.12)	0.95 (0.78–1.15)	0.97 (0.78–1.21)	0.98
Premenopausal cases						

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Median intake, serving/day	1.5	2.2	2.7	3.3	4.3	
No. of cases/person-years	129/69,801	111/69,158	104/69,717	115/69,410	117/69,632	
Age-adjusted RR (95%CI)	1	0.89 (0.69–1.15)	0.82 (0.63–1.07)	0.95 (0.73–1.22)	0.98 (0.76–1.26)	0.91
Multivariable RR (95%CI)[‡]	1	0.92 (0.70–1.20)	0.88 (0.66–1.17)	1.02 (0.75–1.38)	1.09 (0.78–1.53)	0.47
Postmenopausal cases						
Median intake, serving/day	1.4	2.1	2.6	3.2	4.2	
No. of cases/person-years	147/53,464	124/53,274	122/53,428	126/53,262	121/53,284	
Age-adjusted RR (95%CI)	1	0.85 (0.67–1.09)	0.83 (0.65–1.06)	0.87 (0.69–1.11)	0.85 (0.67–1.09)	0.28
Multivariable RR (95%CI)[‡]	1	0.79 (0.61–1.02)	0.77 (0.59–1.00)	0.80 (0.60–1.06)	0.78 (0.57–1.08)	0.21

[†]Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), race (white/non-white), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth ≥30 years, parity 3–4 and age at first birth <25 years, parity 3–4 and age at first birth 25–<30 years, parity 3–4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), height (<62, 62–<65, 65–<68, ≥68 inches), BMI at age 18 years (<18.5, 18.5–<22.5, 22.5–<25, 25.0–<30, ≥30.0 kg/m2), weight change since age 18 (continuous, missing indicator), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past, current), adolescent alcohol intake (nondrinker, <5, ≥5 g/day), adult alcohol intake (nondrinker, <5, 5–<15,≥15 g/day), physical activity (quintile), adolescent energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users), age at menopause (<45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status) and, age at menopause (premenopausal, unknown menopause, <45 years, 45 to 46 years, 47 to 48, 49 to 50 years, 51 to 52 years, ≥53 years).