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Total Energy Intake and Breast Cancer Risk in Sisters: the Breast Cancer Family Registry

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Abstract

Energy restriction inhibits mammary tumor development in animal models. Epidemiologic studies in humans generally do not support an association between dietary energy intake and breast cancer risk, although some studies suggest a more complex interplay between measures of energy intake, physical activity and body size. We examined the association between total energy intake jointly with physical activity and body mass index (BMI) and the risk of breast cancer among 1,775 women diagnosed with breast cancer between 1995 and 2006 and 2,529 of their unaffected sisters enrolled in the Breast Cancer Family Registry (BCFR). We collected dietary data using the Hawaii-Los Angeles Multiethnic Cohort food frequency questionnaire. Using conditional logistic regression to estimate the odds ratios (OR) and 95% confidence intervals (CI) associated with total energy intake, we observed an overall 60% -70% increased risk of breast cancer among women in

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the highest quartile of total energy intake compared to those in the lowest quartile (Q4 vs. Q1: OR =1.6, 95% CI: 1.3-2.0; $P_{\text{trend}} < 0.0001$); these associations were limited to pre-menopausal women or women with hormone receptor positive cancers. Although the associations were slightly stronger among women with a higher BMI or lower level of average lifetime physical activity, we observed a positive association between total energy intake and breast cancer risk across different strata of physical activity and, BMI. Our results suggest that within sisters, high energy intake may increase the risk of breast cancer risk independent from physical activity and body size. If replicated in prospective studies, these findings suggest that reductions in total energy intake may help modify breast cancer risk.

Keywords

Breast cancer; energy balance; energy intake; physical activity; body mass index

Introduction

Animal models provide strong support that restricting caloric intake inhibits mammary tumor development [1]. However, human studies report inconsistent findings regarding the association between dietary energy intake and breast cancer risk [2-28]. In humans, physical activity and body composition are important determinants of energy intake [29]. The balance between energy intake and expenditure rather than energy intake *per se* may be etiologically important in affecting breast cancer risk. In fact, increasing food consumption and body weight are both observed in female rats exposed to exercise training, suggesting an interaction between energy intake, expenditure, and body size [30-32].

Energy intake, physical activity, and body size are three determinants of energy balance, which may work jointly affecting several biological pathways involved in cancer initiation such as insulin resistance, elevated levels of insulin-like and other growth factors, elevated levels of sex steroid hormones, pro-inflammatory state, and altered adipokines [33-35]. For example, in a large randomized controlled trial of exercise and weight loss interventions, McTiernan *et al* reported significant reductions in sex steroid hormones associated with exercise intervention in post-menopausal women, but the effect was seen primarily among women who also lost body weight during the intervention [36]. Some earlier trials found that a seven-day dietary energy restriction (1,000-1,200 kcal/day) reduced serum concentration of insulin-like growth factor-1 (IGF-1) by 38% in normal weight individuals [37], but had no effect in obese subjects [38]; on the other hand, dietary energy restriction led to a more profound increase in sex hormone binding globulin (SHBG) in obese post-menopausal women than in normal weight women [39]. These findings, although far from conclusive, suggest that energy intake, body composition, and physical activity may work interactively in breast carcinogenesis.

Although associations between excessive energy intake, obesity, and sedentary lifestyle and breast cancer risk have been examined, their joint effect has not been adequately addressed in epidemiologic studies, which requires a large sample size to achieve sufficient statistical power. In addition, previous breast cancer studies of energy balance have been primarily

conducted in the general population at average risk for breast cancer. Less is known about whether energy intake is also associated with breast cancer risk for women at higher risk of breast cancer due to their family history. In this study, we examined the effect of energy intake jointly with physical activity and body mass index on breast cancer risk in 4,304 women enrolled in the Breast Cancer Family Registry.

Material and Methods

Study population

The Breast Cancer Family Registry (BCFR) recruited families from six sites in the USA, Canada, and Australia, either through population-based cancer registries (in the San Francisco Bay Area, California, USA; Ontario, Canada; and Melbourne and Sydney, Australia) or through clinical settings and community outreach (in New York City, Philadelphia, and Salt Lake City; for details see [40]). The study was approved by the Institutional Review Board at each participating site. In this analysis, we include participants from the five North American BCFR sites that used the same dietary questionnaire.

Of full sisters with or without breast cancer who enrolled in the BCFR, 12,843 completed questionnaires that assessed family history and epidemiologic risk factors. Usual dietary intake was assessed using a food frequency questionnaire (FFQ). To minimize information bias on self-reported diet after diagnosis, we excluded 1,172 women who completed the FFQ > 2 years after their breast cancer diagnosis. We also excluded 127 women with potentially unreliable dietary energy intake, defined as energy intake exceeding three standard deviations above or below the mean value of the natural log transformed energy intake among unaffected sisters. These exclusions left 11,644 women of whom 5,490 had a personal history of breast cancer (i.e., cases) and 6,154 were unaffected (i.e., controls). After excluding women without sisters and concordant sister sets (both unaffected or both unaffected), the final analysis was based on 1,755 affected and 2,529 unaffected sisters who are discordant sister sets (i.e., sets from families that had both affected and unaffected sisters).

Energy intake

Participants completed the Hawaii-Los Angeles Multiethnic Cohort Food Frequency Questionnaire which asked about usual consumption of 108 food items during the year prior to diagnosis for the affected women and the year prior to the completion of the questionnaire for the unaffected women. For each food item, the FFQ assessed frequency of consumption (never or hardly ever, once a month, 2-3 times a month, once a week, 2-3 times a week, 4-6 times a week, once a day and 2+ times a day) and portion size. This FFQ has been previously validated with three 24-hours dietary recalls and showed generally high correlations [41]. Quartiles of dietary energy intake were created based on the distribution of energy intake in the sisters unaffected with breast cancer.

Recreational pphysical activity

Participants answered questions about the frequency (months per year) and duration (hours per week) of strenuous and moderate exercise performed in the past three years and at

various times in life. Examples of strenuous activities included swimming laps, aerobics, calisthenics, running, jogging, basketball, cycling on hills, and racquetball. Examples of moderate activities included brisk walking, golf, volleyball, cycling on level streets, recreational tennis, and softball. For both strenuous and moderate activities, we asked questions about the average number of months of exercising per year (1-3, 4-6, 7-9 and 10-12 months/year) and exercise duration (none, 0.5, 1, 1-1.5, 2, 3, 4-6, 7-10 and 11 hours/week). Average lifetime moderate or strenuous physical activity (hours/week) was estimated by averaging physical activities performed at different age periods (at ages 12-17, 18-24, 25-34, 35-44, 45-54 and 55 years). A binary variable was created for both moderate and strenuous physical activity to reflect whether a woman's level of average lifetime physical activity meets the U.S. Department of Health and Health Services 2008 Guidelines of Physical Activity for Americans (i.e., moderate physical activity 2.5 hours/week or strenuous physical activity 1.75 hours/week). (www.health.gov/paguidelines).

Body mass index (BMI)

We calculated body mass index (BMI kg/m^2) based on self-reported height and weight during the year prior to diagnosis (affected sisters) or questionnaire completion (unaffected sisters).

Menopausal status and other variables

Women who reported having a menstrual period or giving birth within a year of the reference age were considered pre-menopausal and women who had not had a menstrual period within this time or reported having both ovaries removed were considered post-menopausal. Reference age was defined as age at diagnosis for the affected sisters and age at questionnaire completion for unaffected sisters. Women who had a hysterectomy without oophorectomy or who started using menopausal hormone therapy before they stopped menstruating were considered having an unknown menopausal status unless their reference age was 55 years in which case they were considered post-menopausal. Women with an unknown menopausal status and a reference age <55 years were considered pre-menopausal. For alcohol consumption, usual intake of beer, wine, and liquor prior to reference age was summed to estimate the total number of alcoholic drinks consumed per week. For smoking status, women were categorized as never, former, and current smokers based on current smoking status and age of starting and stopping smoking. Self-reported race/ethnicity was categorized as non-Hispanic white, Hispanic, African American, Asian American or Pacific Islander, and other. Because fewer than 5% of the women were Hispanics, they were combined with the other racial/ethnic group.

Statistical methods

We first compared the demographic and epidemiologic risk factors of breast cancer between 1,755 affected and 2,529 unaffected sisters. We then analyzed the association between energy intake and breast cancer risk among sister sets (N:M matching by family) using conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) [42]. We adjusted all models for reference age as a continuous variable. We then examined an *a priori* set of confounders, including education (high school or less, some

college or college graduate, graduate degree), menopausal status (pre-menopausal, post-menopausal), BMI (<25, 25-29.9, 30 kg/m²), whether meeting physical activity guidelines for average lifetime physical activity (yes, no), smoking status (never, former, current smokers), usual lifetime alcohol consumption (0, <7, 7 drinks/week), age at menarche (<12, 12 years), parity (number of full-term pregnancies, continuous), age at first live birth (continuous), oral contraceptive use (ever, never), menopausal hormone therapy use (ever, never), and history of benign breast disease (yes, no). Only adjustment for history of benign breast disease altered the parameter estimates for energy intake by more than 10%. All analyses were done by sister sets so that the following factors were controlled by design rather than by adjustment: race/ethnicity, study site, and family history of breast cancer.

Effect modification by BMI (<25; 25 kg/m²), average lifetime moderate physical activity (<2.5, 2.5 hours/week), average lifetime strenuous physical activity (<1.75, 1.75 hours/week), and menopausal status (post-menopausal, pre-menopausal) at the multiplicative level was evaluated by comparing the log-likelihood statistic for models that included a multiplicative interaction using indicator terms and models without interaction terms [42]. We further considered whether effect estimates differed for breast tumors defined by estrogen receptor (ER) and progesterone receptor (PR) status (ER+ and/or PR+ versus ER-PR- disease).

Results

There were 1,775 affected and 2,529 unaffected sisters coming from 1,693 unique families who were included in the analyses. Demographic and other characteristics are shown in Table 1. The average age was 48.1 years and most participants were non-Hispanic white (72.5%) and pre-menopausal (62.1%). Compared to unaffected sisters, affected sisters were slightly younger, received higher levels of education, had an older age at first live birth, were less likely to have two or more children, were more likely to have a history of benign breast diseases, and had a higher level of total energy intake, but slightly lower BMI. Affected and unaffected sisters did not differ in menopausal status, age at menarche, smoking status, usual alcohol consumption, oral contraceptive use, menopausal hormone therapy use, and levels of moderate or strenuous physical activity.

The mean and median energy intakes in affected and unaffected women were 1,958 and 1,788 kcal/day, respectively. Total energy intake was associated with increased breast cancer risk. With adjustment for age and history of benign breast disease, high total energy intake was associated with a 60% increased risk of breast cancer (Quartile 4 [Q4] vs. Q1: OR = 1.6, 95% CI: 1.3-2.0; $P_{\text{trend}} < 0.0001$) (Table 2). Additional adjustment for BMI, physical activity and other breast cancer risk factors (i.e., education, menopausal status, smoking, alcohol consumption, age at menarche, parity, age at first live birth, use of oral contraceptives and use of menopausal hormone therapy) did not alter the results (Q4 vs. Q1: OR = 1.7, 95% CI: 1.3-2.2).

In stratified analyses, the association between total energy intake and breast cancer risk was similar for all strata, but slightly stronger among women with a BMI ≥ 25 kg/m² compared to those with a BMI <25 kg/m², and among women with lower moderate physical activity

(<2.5 hours/week) compared to those with higher moderate physical activity (>2.5 hours/week). The multiplicative interaction terms by BMI and by physical activity were statistically significant only for strenuous physical activity ($P_{\text{interaction}} = 0.01$). The positive association between total energy intake and breast cancer risk in the adjusted model was overall stronger in women with <1.75 hours/week of strenuous activity (Q4 vs. Q1: OR=1.7, 95% CI: 1.1-2.7; Q3 vs. Q1: OR=1.8, 95% CI: 1.2-2.8; Q2 vs. Q1: OR=1.6, 95% CI: 1.1-2.4) as compared to those with ≥1.75 hours/week of strenuous activity (Q4 vs. Q1: OR=1.5, 95% CI: 0.9-2.5; Q3 vs. Q1: OR=1.0, 95% CI: 0.6-1.6; Q2 vs. Q1: OR=1.0, 95% CI: 0.6-1.6).

When stratified by menopausal status, the association between high energy intake and breast cancer risk was significant in pre-menopausal women (Q4 vs. Q1: OR=1.4, 95% CI: 1.0-2.0, $P_{\text{trend}} = 0.01$), but not in post-menopausal women (Q4 vs. Q1: OR=1.5, 95% CI: 0.9-2.4, $P_{\text{trend}} = 0.23$). Similarly, the association was only significant in women with hormone receptor positive cancers (ER+PR+, ER+PR- or ER-PR+) (Q4 vs. Q1: OR=2.0, 95% CI: 1.4-2.8, $P_{\text{trend}} < 0.001$), but not in women with hormone receptor negative cancers (ER-PR-) (Q4 vs. Q1: OR=1.7, 95% CI: 0.9-3.5, $P_{\text{trend}} = 0.23$) (Table 3).

When total energy intake, physical activity, and BMI were considered jointly, women who had energy intake greater than the median (>1,788 kcal/day), were physically inactive (<2.5 hours/week of moderate activity and <1.75 hours/week of strenuous activity), and were overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$) (i.e., those with the least favorable energy balance profile) had a 50% increased risk of breast cancer compared to those who had a low level of total energy intake, were physically active, and had a healthy weight (i.e., women with the most favorable energy balance profile) (OR=1.5, 95% CI: 1.0-2.2) (Table 4). The three-way interaction was not statistically significant ($P = 0.21$).

Discussion

We examined the association between dietary energy intake and breast cancer risk individually and jointly with physical activity and BMI in sister sets. Overall, we found a 60-70% increased risk of breast cancer associated with high energy intake and the association was dose-dependent; these results were limited to pre-menopausal women or women with hormone receptor positive cancers. Although the associations appeared to be slightly stronger among women who were more sedentary or women who were overweight or obese compared to those who were active or had a healthy weight, an overall trend of an increased breast cancer risk with high energy intake was apparent across different strata of physical activity and BMI.

The individual effect of energy intake on breast cancer risk has been examined in previous studies. One cohort study followed Swedish women diagnosed with anorexia who therefore had very low energy intake and found a 53% lower breast cancer incidence compared to age-matched controls [43]; however, studies that examined women exposed to the 1944-1945 Dutch famine found a significantly higher risk of breast cancer in exposed women than those who were not exposed [44]. Among 15 case-control studies and 12 cohort studies that examine a range of energy intake compatible with healthy intake, seven case-

control studies [4, 12, 14, 18, 23, 25, 27] and four cohort studies [2, 3, 5, 22] reported a positive association between higher energy intake and breast cancer risk, whereas the other 16 studies showed either no association or an inverse association [6-11, 13, 15-17, 19-21, 24, 26, 28].

The positive association between energy intake and breast cancer risk can be explained by the greater absolute intake of energy or by components of diet that typically constitute higher versus lower energy intake. Fat and alcohol provide higher energy per unit than carbohydrate and protein. Therefore it is possible that the observed association was due to high fat consumption or dietary patterns that are high in fat and low in fruits and vegetables. However, we did not find differences in percent of energy from fat or in dietary patterns between affected and unaffected sisters. Alcohol consumption was not associated with breast cancer risk in sisters [45]. Although further confirmation is needed, our results suggest that greater intake of energy rather than the source of energy contributes to an increased risk of breast cancer in sisters.

One case-control study [19] and three cohort studies [3, 22, 46] examined associations with the three components of energy balance (i.e., energy intake, physical activity, and body mass index) individually and jointly. These studies reached different conclusions regarding the individual effect of energy intake, BMI, and physical activity: two reported a 20% increased risk of breast cancer associated with high energy intake (>2,000 kcal/day) but not with low physical activity [3, 22], and the other two reported an inverse association between high physical activity (>4 hours/week) and breast cancer risk but no association with energy intake [19, 46]. Nevertheless, four studies consistently identified an increased breast cancer risk associated with the least favorable energy balance profile: high energy intake, high body size, and low physical activity. Excessive energy intake and physical inactivity significantly increased breast cancer risk, in particular among women with a BMI ≥ 25 kg/m² [19, 46]. We found an overall 60-70% increased risk of breast cancer associated with high levels of energy intake when comparing breast cancer cases to their unaffected sisters, all of whom were relatively young. Our results also indicated that the association between energy intake and breast cancer risk was slightly stronger among overweight or obese women than women with healthy weight, and among sedentary women than among active women, although the statistical interaction was significant only for strenuous physical activity. In addition, women with the least favorable energy balance profile had an increased risk of breast cancer compared to women with the most favorable energy balance profile.

Previous studies suggest that the association between energy balance and breast cancer risk may depend on menopausal status. The different effect of body size on breast cancer risk in pre-menopausal and post-menopausal women has been consistently observed [47-49]. An increased risk associated with high BMI among post-menopausal women may be explained by elevated levels of free estradiol produced by the adipose tissue of obese post-menopausal women. In contrast, obesity-related anovulation may explain a small decreased risk of breast cancer in pre-menopausal women [35]. Physical activity seems to confer a stronger protective effect on breast cancer among post-menopausal than pre-menopausal women [49, 50]. When body size is also taken into consideration, however, prior studies produced conflicting results regarding whether the joint effect between physical activity and body

mass index differs by menopausal status [50]. Few studies examined the integrated effect of energy balance on breast cancer risk in pre-menopausal and post-menopausal women separately [19, 22] and results are mixed. A stronger association between unfavorable energy balance profile and breast cancer risk was found in pre-menopausal women in one study [22], but in post-menopausal women in another study [19]. In our study population of which 60% were pre-menopausal women, we found significant associations between high energy intake and breast cancer risk and a significant trend in pre-menopausal women but not in post-menopausal women. More research is needed to elucidate the effect of energy balance on breast cancer risk by menopausal status.

Estrogen and progesterone receptors are important characteristics of breast tumors and it has been shown that reproductive and other hormonal risk factors are more closely related to ER +PR+ breast tumors than ER-PR- tumors [51, 52]. Whether energy balance exerts a heterogeneous effect on breast cancer risk by hormone receptor status has been not evaluated in other studies, although obesity, physical activity, and energy intake were each examined in a few studies, but results are inconclusive [51-58]. We found the association between energy intake and breast cancer risk, although elevated in both hormone receptor positive and negative cancers, was only statistically significant in hormone receptor positive cancers.

Our study has several strengths. The study sample size allows for the evaluation of an integrated effect of energy intake, BMI, and physical activity on breast cancer risk. In addition, nearly 80% of the affected sisters had information available on tumor hormone receptor status, which made it feasible to examine the association between energy balance and hormone receptor defined breast cancer risk. Although many investigations have been carried out to examine risk factors of breast cancer in the general population, few have examined the impact of behavioral risk factors within families. The sister set design allows for partial control of genetic influence on breast cancer because similar genes are shared by sisters. It also allows for control of fixed-level family effects such as parental body size and environmental factors that are likely to be shared within families. However, the sister set design may also be less powerful to study the effect of diet on breast cancer risk if sisters tend to be similar in early life nutrition and/or lifetime dietary habits [59].

Evaluating the effect of energy balance is challenging because measures of energy intake, body size, and physical activity in observational studies are subject to measurement errors. In particular, under-reporting of energy intake and body weight and over-reporting of physical activity has been observed among individuals who are overweight or obese, which may result in misclassification of energy balance and lead to biased results [60-62]. More objective measures have been developed to assess energy intake and expenditure such as doubly labeled water, 24-hour physical activity diary, and covert weighted food intake [63]. However, these methods cannot easily be implemented in large-scale epidemiologic studies due to the considerable cost and inconvenience. Assessing energy balance through questionnaires still represents one of the most practical ways to evaluate the association between energy balance and breast cancer risk in observational studies. The FFQ used in this study has been previously validated in a multi-ethnic population and showed satisfactory correlations with multiple 24-hour dietary recalls [41]. For physical activity, we collected

data on recreational activities but did not include questions on occupational or household activities; total physical activity is therefore likely to be underestimated. We did not ask information about specific types of exercise so that the metabolic equivalents (MET) of physical activity could not be calculated. However, the most consistent evidence on the protective effect of physical activity was observed for recreational activities [50] and the questionnaire used in this study captured the frequency and duration of both strenuous and moderate recreational physical activity over the life time. Therefore, our study provides a comprehensive assessment of energy balance. Because diet was assessed after cancer diagnosis, in a case-control design recall bias can be a concern if cases and controls recall their energy intake differently. However, because the Breast Cancer Family Registry administered a questionnaire to assess a comprehensive list of genetic and environmental influences on breast cancer, not only diet, it is unlikely that cases reported greater energy intake than controls because they were aware of the specific dietary hypotheses we investigated. Another concern is that cases may have changed their dietary habits due to cancer diagnosis. We excluded women who completed the FFQ more than two years after their breast cancer diagnosis in order to prevent reverse causation given that dietary intake was not measured prospectively.

In summary, we found an increased risk of breast cancer associated with high energy intake and the association was dose-dependent. Although the association between energy intake and breast cancer risk appeared to be stronger among women who performed less than 15 minutes per day of strenuous physical activity compared to those who did, the overall trend of an increased risk of breast cancer with high energy intake was observed across different strata of physical activity and BMI. This association was limited to pre-menopausal women or women with hormone receptor positive cancers. Future prospective studies are needed to replicate our findings and to further examine the role of energy balance in breast cancer development. Such knowledge is of public health and clinical importance because energy intake and expenditure are modifiable behaviors and behavioral modification may potentially reduce the incidence of breast cancer in the general population as well as in women at increased risk of breast cancer due to their family history of breast cancer.

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References

1. Dirx MJ, Zeegers MP, Dagnelie PC, van den Bogaard T, van den Brandt PA. Energy restriction and the risk of spontaneous mammary tumors in mice: a meta-analysis. *Int J Cancer*. 2003; 106:766–770. [PubMed: 12866038]

2. Barrett-Connor E, Friedlander NJ. Dietary fat, calories, and the risk of breast cancer in postmenopausal women: a prospective population-based study. *J Am Coll Nutr.* 1993; 12:390–399. [PubMed: 8409101]
3. Chang SC, Ziegler RG, Dunn B, Stolzenberg-Solomon R, Lacey JV Jr, Huang WY, Schatzkin A, Reding D, Hoover RN, Hartge P, Leitzmann MF. Association of energy intake and energy balance with postmenopausal breast cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:334–341. [PubMed: 16492925]
4. Franceschi S, Favero A, Decarli A, Negri E, La Vecchia C, Ferraroni M, Russo A, Salvini S, Amadori D, Conti E, Montella M, Giacosa A. Intake of macronutrients and risk of breast cancer. *Lancet.* 1996; 347:1351–1356. [PubMed: 8637339]
5. Gaard M, Tretli S, Loken EB. Dietary fat and the risk of breast cancer: a prospective study of 25,892 Norwegian women. *Int J Cancer.* 1995; 63:13–17. [PubMed: 7558440]
6. Graham S, Hellmann R, Marshall J, Freudenheim J, Vena J, Swanson M, Zielezny M, Nemoto T, Stubbe N, Raimondo T. Nutritional epidemiology of postmenopausal breast cancer in western New York. *Am J Epidemiol.* 1991; 134:552–566. [PubMed: 1951261]
7. Graham S, Zielezny M, Marshall J, Priore R, Freudenheim J, Brasure J, Haughey B, Nasca P, Zdeb M. Diet in the epidemiology of postmenopausal breast cancer in the New York State Cohort. *Am J Epidemiol.* 1992; 136:1327–1337. [PubMed: 1336931]
8. Holmberg L, Ohlander EM, Byers T, Zack M, Wolk A, Bergstrom R, Bergkvist L, Thurfjell E, Bruce A, Adami HO. Diet and breast cancer risk. Results from a population-based, case-control study in Sweden. *Arch Intern Med.* 1994; 154:1805–1811. [PubMed: 8053747]
9. Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, Hankinson SE, Speizer FE, Rosner B, Willett WC. Association of dietary intake of fat and fatty acids with risk of breast cancer. *Jama.* 1999; 281:914–920. [PubMed: 10078488]
10. Howe GR, Friedenreich CM, Jain M, Miller AB. A cohort study of fat intake and risk of breast cancer. *J Natl Cancer Inst.* 1991; 83:336–340. [PubMed: 1995917]
11. Ingram DM, Nottage E, Roberts T. The role of diet in the development of breast cancer: a case-control study of patients with breast cancer, benign epithelial hyperplasia and fibrocystic disease of the breast. *Br J Cancer.* 1991; 64:187–191. [PubMed: 1854621]
12. Iscovich JM, Iscovich RB, Howe G, Shiboski S, Kaldor JM. A case-control study of diet and breast cancer in Argentina. *Int J Cancer.* 1989; 44:770–776. [PubMed: 2583858]
13. Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, Hoover R, Taylor PR. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *J Natl Cancer Inst.* 1987; 79:465–471. [PubMed: 3476789]
14. Katsouyanni K, Trichopoulou A, Stuver S, Garas Y, Kritselis A, Kyriakou G, Stoikidou M, Boyle P, Trichopoulos D. The association of fat and other macronutrients with breast cancer: a case-control study from Greece. *Br J Cancer.* 1994; 70:537–541. [PubMed: 8080743]
15. Katsouyanni K, Willett W, Trichopoulos D, Boyle P, Trichopoulou A, Vasilaros S, Papadiamantis J, MacMahon B. Risk of breast cancer among Greek women in relation to nutrient intake. *Cancer.* 1988; 61:181–185. [PubMed: 3334945]
16. Knekt P, Albanes D, Seppanen R, Aromaa A, Jarvinen R, Hyvonen L, Teppo L, Pukkala E. Dietary fat and risk of breast cancer. *Am J Clin Nutr.* 1990; 52:903–908. [PubMed: 2239766]
17. Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, Folsom AR. Dietary fat and postmenopausal breast cancer. *J Natl Cancer Inst.* 1992; 84:1092–1099. [PubMed: 1619683]
18. Levi F, La Vecchia C, Gulie C, Negri E. Dietary factors and breast cancer risk in Vaud, Switzerland. *Nutr Cancer.* 1993; 19:327–335. [PubMed: 8346081]
19. Malin A, Matthews CE, Shu XO, Cai H, Dai Q, Jin F, Gao YT, Zheng W. Energy balance and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1496–1501. [PubMed: 15941962]
20. Miller AB, Kelly A, Choi NW, Matthews V, Morgan RW, Munan L, Burch JD, Feather J, Howe GR, Jain M. A study of diet and breast cancer. *Am J Epidemiol.* 1978; 107:499–509. [PubMed: 665664]
21. Rohan TE, McMichael AJ, Baghurst PA. A population-based case-control study of diet and breast cancer in Australia. *Am J Epidemiol.* 1988; 128:478–489. [PubMed: 3414656]

22. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Energy balance and breast cancer risk: a prospective cohort study. *Breast Cancer Res Treat.* 2006; 97:97–106. [PubMed: 16319973]
23. Toniolo P, Riboli E, Protta F, Charrel M, Cappa AP. Calorie-providing nutrients and risk of breast cancer. *J Natl Cancer Inst.* 1989; 81:278–286. [PubMed: 2913325]
24. van den Brandt PA, van't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJ, Sturmans F. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. *Cancer Res.* 1993; 53:75–82. [PubMed: 8416752]
25. Van't Veer P, Kok FJ, Brants HA, Ockhuizen T, Sturmans F, Hermus RJ. Dietary fat and the risk of breast cancer. *Int J Epidemiol.* 1990; 19:12–18. [PubMed: 2351506]
26. Velie E, Kulldorff M, Schairer C, Block G, Albanes D, Schatzkin A. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: a prospective cohort study. *J Natl Cancer Inst.* 2000; 92:833–839. [PubMed: 10814679]
27. Yu SZ, Lu RF, Xu DD, Howe GR. A case-control study of dietary and nondietary risk factors for breast cancer in Shanghai. *Cancer Res.* 1990; 50:5017–5021. [PubMed: 2379166]
28. Yuan JM, Wang QS, Ross RK, Henderson BE, Yu MC. Diet and breast cancer in Shanghai and Tianjin, China. *Br J Cancer.* 1995; 71:1353–1358. [PubMed: 7779738]
29. Willett, WC. *Nutritional Epidemiology.* Oxford University Press; New York: 1998.
30. Applegate EA, Upton DE, Stern JS. Food intake, body composition and blood lipids following treadmill exercise in male and female rats. *Physiol Behav.* 1982; 28:917–920. [PubMed: 7048359]
31. Nance DM, Bromley B, Barnard RJ, Gorski RA. Sexually dimorphic effects of forced exercise on food intake and body weight in the rat. *Physiol Behav.* 1977; 19:155–158. [PubMed: 11803679]
32. Pitts GC. Body composition in the rat: interactions of exercise, age, sex, and diet. *Am J Physiol.* 1984; 246:R495–501. [PubMed: 6720924]
33. Hursting SD, Lashinger LM, Colbert LH, Rogers CJ, Wheatley KW, Nunez NP, Mahabir S, Barrett JC, Forman MR, Perkin SN. Energy balance and carcinogenesis: underlying pathways and targets for intervention. *Curr Cancer Drug Targets.* 2007; 7:484–491. [PubMed: 17691908]
34. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc Nutr Soc.* 2001; 60:91–106. [PubMed: 11310428]
35. Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. *Proc Nutr Soc.* 2001; 60:81–89. [PubMed: 11310427]
36. McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, Sorensen B, Rudolph RE, Bowen D, Stanczyk FZ, Potter JD, Schwartz RS. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. *Cancer Res.* 2004; 64:2923–2928. [PubMed: 15087413]
37. Smith AT, Clemmons DR, Underwood LE, Ben-Ezra V, McMurray R. The effect of exercise on plasma somatomedin-C/insulinlike growth factor I concentrations. *Metabolism.* 1987; 36:533–537. [PubMed: 3587016]
38. Snyder DK, Clemmons DR, Underwood LE. Treatment of obese, diet-restricted subjects with growth hormone for 11 weeks: effects on anabolism, lipolysis, and body composition. *J Clin Endocrinol Metab.* 1988; 67:54–61. [PubMed: 3379136]
39. O'Dea JP, Wieland RG, Hallberg MC, Llerena LA, Zorn EM, Genuth SM. Effect of dietary weight loss on sex steroid binding sex steroids, and gonadotropins in obese postmenopausal women. *J Lab Clin Med.* 1979; 93:1004–1008. [PubMed: 571447]
40. John EM, Hopper JL, Beck JC, Knight JA, Neuhausen SL, Senie RT, Ziogas A, Andrulis IL, Anton-Culver H, Boyd N, Buys SS, Daly MB, O'Malley FP, Santella RM, Southey MC, Venne VL, Venter DJ, West DW, Whittemore AS, Seminara D. The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. *Breast Cancer Res.* 2004; 6:R375–389. [PubMed: 15217505]
41. Stram DO, Hankin JH, Wilkens LR, Pike MC, Monroe KR, Park S, Henderson BE, Nomura AM, Earle ME, Nagamine FS, Kolonel LN. Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. *Am J Epidemiol.* 2000; 151:358–370. [PubMed: 10695594]
42. Hosmer, DW.; Lemeshow, S., editors. *Applied logistic regression.* John Wiley & Sons; New York: 1989.

43. Michels KB, Ekblom A. Caloric restriction and incidence of breast cancer. *Jama*. 2004; 291:1226–1230. [PubMed: 15010444]
44. Elias SG, Peeters PH, Grobbee DE, van Noord PA. Breast cancer risk after caloric restriction during the 1944–1945 Dutch famine. *J Natl Cancer Inst*. 2004; 96:539–546. [PubMed: 15069116]
45. Terry MB, Knight JA, Zablotska L, Wang Q, John EM, Andrulis IL, Senie RT, Daly M, Ozelik H, Briollais L, Santella RM. Alcohol metabolism, alcohol intake, and breast cancer risk: a sister-set analysis using the Breast Cancer Family Registry. *Breast Cancer Res Treat*. 2007; 106:281–288.10.1007/s10549-007-9498-7 [PubMed: 17268812]
46. Dirx MJ, Voorrips LE, Goldbohm RA, van den Brandt PA. Baseline recreational physical activity, history of sports participation, and postmenopausal breast carcinoma risk in the Netherlands Cohort Study. *Cancer*. 2001; 92:1638–1649. [PubMed: 11745243]
47. Trentham-Dietz A, Newcomb PA, Storer BE, Longnecker MP, Baron J, Greenberg ER, Willett WC. Body size and risk of breast cancer. *Am J Epidemiol*. 1997; 145:1011–1019. [PubMed: 9169910]
48. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, Fraser G, Goldbohm RA, Graham S, Kushi L, Marshall JR, Miller AB, Rohan T, Smith-Warner SA, Speizer FE, Willett WC, Wolk A, Hunter DJ. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*. 2000; 152:514–527. [PubMed: 10997541]
49. World Cancer Research Fund/American Institute for Cancer Research (ed). *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. AICR; Washington DC: 2007.
50. Monninkhof EM, Elias SG, Vlems FA, van der Tweel I, Schuit AJ, Voskuil DW, van Leeuwen FE. Physical activity and breast cancer: a systematic review. *Epidemiology*. 2007; 18:137–157. [PubMed: 17130685]
51. Cotterchio M, Kreiger N, Theis B, Sloan M, Bahl S. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. *Cancer Epidemiol Biomarkers Prev*. 2003; 12:1053–1060. [PubMed: 14578142]
52. Potter JD, Cerhan JR, Sellers TA, McGovern PG, Drinkard C, Kushi LR, Folsom AR. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: how many kinds of breast cancer are there? *Cancer Epidemiol Biomarkers Prev*. 1995; 4:319–326. [PubMed: 7655325]
53. Adams SA, Matthews CE, Hebert JR, Moore CG, Cunningham JE, Shu XO, Fulton J, Gao Y, Zheng W. Association of physical activity with hormone receptor status: the Shanghai Breast Cancer Study. *Cancer Epidemiol Biomarkers Prev*. 2006; 15:1170–1178. [PubMed: 16775177]
54. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. *J Natl Cancer Inst*. 2004; 96:218–228. [PubMed: 14759989]
55. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from two case-control studies. *Cancer Epidemiol Biomarkers Prev*. 2000; 9:681–687. [PubMed: 10919738]
56. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *Am J Epidemiol*. 2000; 151:703–714. [PubMed: 10752798]
57. Britton JA, Gammon MD, Schoenberg JB, Stanford JL, Coates RJ, Swanson CA, Potischman N, Malone KE, Brogan DJ, Daling JR, Brinton LA. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20–44 years of age. *Am J Epidemiol*. 2002; 156:507–516. [PubMed: 12225998]
58. Kushi LH, Potter JD, Bostick RM, Drinkard CR, Sellers TA, Gapstur SM, Cerhan JR, Folsom AR. Dietary fat and risk of breast cancer according to hormone receptor status. *Cancer Epidemiol Biomarkers Prev*. 1995; 4:11–19. [PubMed: 7894319]
59. Milne RL, John EM, Knight JA, Dite GS, Southey MC, Giles GG, Apicella C, West DW, Andrulis IL, Whittemore AS, Hopper JL. The potential value of sibling controls compared with population controls for association studies of lifestyle-related risk factors: an example from the Breast Cancer Family Registry. *Int J Epidemiol*. 2011; 40:1342–1354.10.1093/ije/dyr110 [PubMed: 21771852]

60. Johansson L, Solvoll K, Bjorneboe GE, Drevon CA. Under- and overreporting of energy intake related to weight status and lifestyle in a nationwide sample. *Am J Clin Nutr.* 1998; 68:266–274. [PubMed: 9701182]
61. Braam LA, Ocke MC, Bueno-de-Mesquita HB, Seidell JC. Determinants of obesity-related underreporting of energy intake. *Am J Epidemiol.* 1998; 147:1081–1086. [PubMed: 9620052]
62. Lichtman SW, Pisarska K, Berman ER, Pestone M, Dowling H, Offenbacher E, Weisel H, Heshka S, Matthews DE, Heymsfield SB. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med.* 1992; 327:1893–1898. [PubMed: 1454084]
63. Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. *J Appl Physiol.* 1982; 53:955–959. [PubMed: 6759491]

Table 1

Demographics and risk factors of breast cancer among affected and unaffected sisters, Breast Cancer Family Registry

		Affected Sisters (N=1,775)	Unaffected Sisters (N=2,529)
		Mean (SD)	
Age, yrs		47.3 (9.6)	48.7 (10.8)
		N (%)	
Race/Ethnicity	Non-Hispanic White	1,303 (73.4)	1,819 (71.9)
	African American	220 (12.4)	328 (13.0)
	Asian American/Pacific islander	193 (10.9)	288 (11.4)
	Hispanic and others	59 (3.3)	94 (3.7)
Education	High school graduate or less	651 (36.8)	1,061 (42.2)
	Some college or college graduate	868 (49.1)	1,126 (44.8)
	Graduate degree	248 (14.0)	328 (13.0)
Menopausal status	Pre-menopausal	1,170 (65.9)	1,503 (59.4)
	Post-menopausal	605 (34.1)	1,026 (40.6)
		Mean (SD)	
Age at first live birth, yrs		24.8 (5.4)	24.1 (5.3)
		N (%)	
Parity	0	100 (6.7)	127 (5.8)
	1	851 (56.9)	1,164 (53.4)
	2	546 (36.5)	887 (40.8)
Age at menarche, yrs	< 12	371 (21.1)	518 (20.7)
	12	1,390 (78.9)	1,991 (79.4)
Use of oral contraceptives	Never	431 (24.3)	637 (25.2)
	Ever	1,340 (75.7)	1,888 (74.8)
Use of menopausal hormone therapy	Never	1,261 (71.2)	1,771 (70.4)
	Ever	509 (28.8)	744 (29.6)
History of benign breast disease	No	1,146 (65.5)	1,840 (73.3)
	Yes	607 (34.5)	669 (26.7)
		N (%)	
Smoking status	Never smokers	1,041 (58.9)	1,513 (59.9)
	Former smokers	470 (26.6)	661 (26.2)
	Current smokers	256 (14.5)	350 (13.9)
Usual alcohol consumption, drinks/wk	None	982 (56.4)	1,421 (57.3)
	< 7	516 (29.6)	707 (28.5)
	7	243 (14.0)	353 (14.2)
		Mean (SD)	
Total energy intake, kcal/d		2,071 (972.9)	1,940 (939.4)
		Mean (SD)	
BMI, kg/m ²		26.1 (5.5)	26.7 (5.9)
		N (%)	

	Affected Sisters (N=1,775)	Unaffected Sisters (N=2,529)
<25	905 (51.0)	1,180 (46.7)
25-29.9	527 (29.7)	749 (29.6)
30	343 (19.3)	600 (23.7)
	Mean (SD)	
Average lifetime moderate physical activity, <i>hrs/wk</i>	3.6 (3.3)	3.6 (3.4)
	N (%)	
< 2.5	883 (50.5)	1,276(51.0)
2.5	865(49.5)	1,227(49.0)
	Mean (SD)	
Average lifetime strenuous physical activity, <i>hrs/wk</i>	2.6 (3.0)	2.7 (3.0)
	N (%)	
<1.75	943 (54.2)	1,294 (52.2)
1.75	797 (45.8)	1,186 (47.8)

Table 2

The association between total energy intake and breast cancer risk among sister sets by body mass index and physical activity, Breast Cancer Family Registry

Total energy intake, kcal/d	Affected sisters N (%)	Unaffected sisters N (%)	OR (95% CI) ^a	OR (95% CI) ^b
All women				
Q1 (< 1359.2)	411 (23.2)	717 (28.4)	1.0	1.0
Q2 (1359.2 - 1788.2)	391 (22.0)	609 (24.1)	1.2 (1.0-1.4)	1.3 (1.0-1.6)
Q3 (1788.2 - 2341.6)	446 (25.1)	576 (22.8)	1.4 (1.2-1.7)	1.4 (1.1-1.8)
Q4 (< 2341.6)	527 (29.7)	627 (24.8)	1.6 (1.3-2.0)	1.7 (1.3-2.2)
			<i>P</i> _{trend} < .0001	<i>P</i> _{trend} < 0.0001
Women with BMI <25 kg/m²				
Q1 (< 1359.2)	212 (23.4)	320 (27.1)	1.0	1.0
Q2 (1359.2 - 1788.2)	211 (23.3)	294 (24.9)	1.1 (0.8-1.6)	1.0 (0.7-1.6)
Q3 (1788.2 - 2341.6)	239 (26.4)	309 (26.2)	1.1 (0.8-1.6)	0.9 (0.6-1.5)
Q4 (< 2341.6)	243 (26.9)	257 (21.8)	1.6 (1.1-2.3)	1.5 (0.9-2.4)
			<i>P</i> _{trend} = 0.02	<i>P</i> _{trend} = 0.23
Women with BMI ≥ 25 kg/m²				
Q1 (< 1359.2)	199 (22.9)	397 (29.4)	1.0	1.0
Q2 (1359.2 - 1788.2)	180 (20.7)	315 (23.4)	1.2 (0.9-1.7)	1.3 (0.9-1.8)
Q3 (1788.2 - 2341.6)	207 (23.8)	267 (19.8)	1.5 (1.1-2.0)	1.3 (0.9-1.9)
Q4 (< 2341.6)	284 (32.6)	370 (27.4)	1.6 (1.1-2.2)	1.7 (1.2-2.5)
			<i>P</i> _{trend} = 0.002	<i>P</i> _{trend} = 0.007
Women with average lifetime moderate PA <2.5 hrs/wk				
Q1 (< 1359.2)	253 (28.7)	434 (34.0)	1.0	1.0
Q2 (1359.2 - 1788.2)	222 (25.1)	315 (24.7)	1.5 (1.1-2.0)	1.5 (1.1-2.3)
Q3 (1788.2 - 2341.6)	203 (23.0)	270 (21.2)	1.5 (1.1-2.2)	1.8 (1.2-2.9)
Q4 (< 2341.6)	205 (23.2)	257 (20.1)	1.6 (1.1-2.4)	1.9 (1.1-3.2)
			<i>P</i> _{trend} = 0.01	<i>P</i> _{trend} < 0.01
Women with average lifetime moderate PA ≥ 2.5 hrs/wk				
Q1 (< 1359.2)	156 (18.0)	280 (22.8)	1.0	1.0
Q2 (1359.2 - 1788.2)	164 (19.0)	285 (23.2)	1.1 (0.8-1.6)	0.9 (0.6-1.4)
Q3 (1788.2 - 2341.6)	234 (27.1)	297 (24.2)	1.7 (1.2-2.4)	1.2 (0.8-1.8)
Q4 (< 2341.6)	311 (36.0)	365 (29.8)	2.0 (1.4-2.9)	1.5 (1.0-2.2)
			<i>P</i> _{trend} < 0.0001	<i>P</i> _{trend} = 0.03
Women with average lifetime strenuous PA <1.75 hrs/wk				
Q1 (< 1359.2)	250 (26.5)	439 (33.9)	1.0	1.0
Q2 (1359.2 - 1788.2)	226 (24.0)	324 (25.0)	1.3 (1.0-1.8)	1.6 (1.1-2.4)
Q3 (1788.2 - 2341.6)	246 (26.1)	260 (20.2)	1.7 (1.2-2.3)	1.8 (1.2-2.8)
Q4 (< 2341.6)	221 (23.4)	271 (20.9)	1.5 (1.1-2.2)	1.7 (1.1-2.7)
			<i>P</i> _{trend} = 0.008	<i>P</i> _{trend} = 0.01
Women with average lifetime strenuous PA ≥ 1.75 hrs/wk				

Total energy intake, kcal/d	Affected sisters N (%)	Unaffected sisters N (%)	OR (95% CI) ^a	OR (95% CI) ^b
Q1 (< 1359.2)	156 (19.6)	265 (22.3)	1.0	1.0
Q2 (1359.2 - 1788.2)	151 (19.0)	272 (22.9)	0.9 (0.6-1.4)	1.0 (0.6-1.6)
Q3 (1788.2 - 2341.6)	193 (24.2)	304 (25.6)	1.2 (0.8-1.7)	1.0 (0.6-1.6)
Q4 (2341.6)	297 (37.3)	345 (29.1)	1.5 (1.0-2.3)	1.5 (0.9-2.5)
			<i>P</i> _{trend} = 0.01	<i>P</i> _{trend} = 0.06

^a Adjusted for age and history of benign breast disease.

^b Additionally adjusted for education, menopausal status, BMI, average lifetime physical activity, smoking, usual alcohol consumption, age at menarche, parity, age at first live birth, ever use of oral contraceptives, and ever use of menopausal hormone therapy.

Table 3

The association between total energy intake and breast cancer risk among sister sets by menopausal status and hormone receptor status, Breast Cancer Family Registry

Total energy intake, <i>kcal/d</i>	Affected sisters (N=1,775)	Unaffected sisters (N=2,529)	OR (95% CI) ^a	OR (95% CI) ^b
N (%)				
Pre-menopausal women				
Q1 (< 1359.2)	258 (22.1)	386 (25.7)	1.0	1.0
Q2 (1359.2 - 1788.2)	248 (21.2)	371 (24.7)	1.0 (0.8-1.3)	0.9 (0.6-1.2)
Q3 (1788.2 - 2341.6)	297 (25.4)	353 (23.5)	1.2 (0.9-1.6)	1.2 (0.9-1.7)
Q4 (2341.6)	367 (31.2)	393 (26.2)	1.5 (1.2-2.0)	1.4 (1.0-2.0)
			<i>P</i> _{trend} = 0.001	<i>P</i> _{trend} = 0.01
Post-menopausal women				
Q1 (< 1359.2)	153 (25.3)	331 (32.3)	1.0	1.0
Q2 (1359.2 - 1788.2)	143 (23.6)	238 (23.2)	1.5 (1.1-2.3)	1.6 (1.0-2.5)
Q3 (1788.2 - 2341.6)	149 (24.6)	223 (21.7)	1.5 (1.0-2.1)	1.2 (0.7-1.9)
Q4 (2341.6)	160 (26.5)	234 (22.8)	1.7 (1.1-2.5)	1.5 (0.9-2.4)
			<i>P</i> _{trend} = 0.02	<i>P</i> _{trend} = 0.23
Any hormone receptor positive tumors (ER+PR+, ER+PR-, or ER-PR+)				
Q1 (< 1359.2)	209 (23.1)	717 (28.4)	1.0	1.0
Q2 (1359.2 - 1788.2)	192 (21.2)	609 (24.1)	1.1 (0.9-1.5)	1.3 (1.0-1.9)
Q3 (1788.2 - 2341.6)	237 (26.2)	576 (22.8)	1.4 (1.1-1.9)	1.5 (1.0-2.1)
Q4 (2341.6)	266 (29.4)	627 (24.8)	1.7 (1.3-2.3)	2.0 (1.4-2.8)
			<i>P</i> _{trend} < 0.001	<i>P</i> _{trend} < 0.001
ER-PR- tumors				
Q1 (< 1359.2)	56 (21.7)	717 (28.4)	1.0	1.0
Q2 (1359.2 - 1788.2)	70 (27.1)	609 (24.1)	1.7 (1.0-2.9)	1.9 (1.0-3.4)
Q3 (1788.2 - 2341.6)	53 (20.5)	576 (22.8)	1.7 (1.0-3.0)	1.4 (0.7-2.9)
Q4 (2341.6)	79 (30.6)	627 (24.8)	2.1 (1.2-3.6)	1.7 (0.9-3.5)
			<i>P</i> _{trend} = 0.01	<i>P</i> _{trend} = 0.23

^c Adjusted for age and history of benign breast disease.

^d Additionally adjusted for education, menopausal status, BMI, average lifetime physical activity, smoking, usual alcohol consumption, age at menarche, parity, age at first live birth, ever use of oral contraceptives, and ever use of menopausal hormone therapy.

Table 4

The joint effect of total energy intake, physical activity and body mass index on breast cancer risk, Breast Cancer Family Registry

Total energy intake, kcal/day	Physically active ^c	BMI (kg/m ²)	Affected sisters (N=1,775)	Unaffected sisters (N=2,529)	OR (95% CI) ^a	OR (95% CI) ^b
Low (<1788.2)	Yes	< 25	247 (13.9)	375 (14.8)	1.0	1.0
High (1788.2)	Yes	< 25	345 (19.4)	391 (15.5)	1.4 (1.1-1.8)	1.3 (1.0-1.8)
Low (<1788.2)	Yes	25	167 (9.4)	348 (13.8)	0.8 (0.6-1.1)	0.8 (0.6-1.1)
High (1788.2)	Yes	25	320 (18.0)	442 (17.5)	1.3 (1.0-1.7)	1.1 (0.8-1.5)
Low (<1788.2)	No	< 25	176 (9.9)	239 (9.5)	1.2 (0.9-1.6)	1.1 (0.8-1.5)
High (1788.2)	No	< 25	137 (7.7)	175 (6.9)	1.2 (0.9-1.7)	1.3 (0.9-1.9)
Low (<1788.2)	No	25	212 (11.9)	364 (14.4)	1.0 (0.8-1.4)	1.0 (0.7-1.5)
High (1788.2)	No	25	171 (9.6)	195 (7.7)	1.5 (1.1-2.0)	1.5 (1.0-2.2)

^a Adjusted for age and history of benign breast disease.

^b Additionally adjusted for education, menopausal status, BMI, average lifetime physical activity, smoking, usual alcohol consumption, age at menarche, parity, age at first live birth, ever use of oral contraceptives, and ever use of menopausal hormone therapy.

^c Physically active was defined as having average lifetime moderate physical activity 2.5 hrs/wk or having average lifetime strenuous physical activity 1.75 hrs/wk.