Published in final edited form as:

Breast Cancer Res Treat. 2014 June ; 145(2): 461–470. doi:10.1007/s10549-014-2953-3.

Adolescent Dietary Fiber, Vegetable Fat, Vegetable Protein, and Nut Intakes and Breast Cancer Risk

Ying Liu¹, Graham A. Colditz^{1,2}, Michelle Cotterchio^{3,4}, Beatrice A. Boucher^{3,5}, and Nancy Kreiger^{3,4,5}

¹Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO

²Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, MO

³Prevention and Cancer Control, Cancer Care Ontario, Toronto, Canada

⁴Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

⁵Department of Nutritional Sciences, University of Toronto, Toronto, Canada

Abstract

Purpose—The importance of early-life exposures in breast cancer development is increasingly recognized. However, limited research has evaluated the relationship between adolescent diet and subsequent risk of breast cancer and reported inconsistent results. This population-based case-control study investigated the associations of dietary fiber, vegetable protein, vegetable fat, and nuts consumed during adolescence with adult breast cancer risk.

Methods—Women, ages 25–74 years, who were diagnosed with first primary breast cancer between 2002 and 2003 were identified using the Ontario Cancer Registry. Controls were identified through random digit dialing and age-frequency matched to cases. Diet at ages 10–15 was assessed with a 55-item food frequency questionnaire among 2,865 cases and 3,299 controls. Logistic regression was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—Inverse associations were found between intakes of dietary fiber, vegetable protein, vegetable fat, and nuts during adolescence and breast cancer risk, which persisted after controlling for adult intakes. The ORs (95% CI) for the highest versus the lowest quintile of intake were 0.66 (0.55 to 0.78; $P_{\text{trend}} < 0.0001$) for fiber, 0.80 (0.68 to 0.95; $P_{\text{trend}} = 0.01$) for vegetable protein, 0.74

Correspondence to: Graham A. Colditz, MD, DrPH, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, 660 S. Euclid Ave, Campus Box 8100, St. Louis, MO 63110 (colditzg@wustl.edu).

Author Contributions: Dr. Liu had access to the de-identified study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Liu, Colditz.

Acquisition of data: Cotterchio, Boucher, Kreiger.

Analysis and interpretation of data: Liu, Colditz, Cotterchio, Boucher, Kreiger.

Drafting of the manuscript: Liu, Colditz.

Critical revision of the manuscript for important intellectual comment: Liu, Colditz, Cotterchio, Boucher, Kreiger.

Statistical analysis: Liu, Colditz.

Conflict of Interest Disclosures: The authors declare that they have no conflict of interest.

(0.63 to 0.87; $P_{\text{trend}}=0.002$) for vegetable fat, 0.76 (0.61 to 0.95 for 1 serving/day versus <1 serving/month intake; $P_{\text{trend}}=0.04$) for nuts. The reduced risk for adolescent intakes of fiber, vegetable protein and nuts was largely limited to postmenopausal women ($P_{\text{interaction}}=0.05$).

Conclusions—Dietary fiber, vegetable protein, vegetable fat, and nuts consumed during adolescence were associated with reduced breast cancer risk.

Keywords

Breast cancer; Diet; Adolescence; Nutrition

It is increasingly recognized that early-life exposures can influence a lifetime risk of breast cancer [1–4]. Breast cancer risk accumulates across the life course with the highest rate of increase from menarche to first pregnancy [5–8]. Both human and animal data have demonstrated that environmental exposures during preadolescence, adolescence and early adulthood are more important in breast cancer development than exposures later in life [2, 4, 9–13]. There may be a critical period of increased biologic vulnerability from menarche, when breast tissue undergoes rapid proliferation, until the completion of the first pregnancy, when multiple physiologic changes in the breast occur and render epithelial cells less susceptible to malignant transformation [13–17]. This is well exemplified by the observed higher risk of breast cancer among female atomic bomb survivors in Hiroshima and Nagasaki who were less than 20 years old at the time of bombing [2].

Although the role of adolescent exposures in the etiology of breast cancer is increasingly evident, few epidemiologic studies have assessed the associations between adolescent diet and breast cancer risk. Among women in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII), two separate cohorts of US female nurses, adolescent vegetable fat intake was associated with a significant reduction in breast cancer risk, and adolescent dietary fiber intake was related to a non-significant decreased risk [18, 19], though these analyses were controlled for benign breast disease (BBD) which might be on the etiologic pathway [20, 21]. In addition, dietary fiber, vegetable fat, vegetable protein, and nuts consumed during adolescence have been inversely related to risk of proliferative BBD [20–22] among the participants in the NHSII and their daughters. It remains unclear if the results are specific to these populations with similar characteristics or applicable to a diverse population of women. Although adolescent soy food and/or soy protein intake has been associated with significantly reduced risk of breast cancer [4, 10], vegetable protein intake per se during adolescence in relation to adult breast cancer risk has not been evaluated.

We, therefore, examined the associations of dietary fiber, vegetable protein, vegetable fat, and nuts consumed in adolescent years with risk of breast cancer in a large, population-based case-control study. We also evaluated the associations by menopausal status, adult body mass index (BMI), and family history of breast cancer at cancer diagnosis.

Methods

Breast Cancer Cases and Controls

The Ontario Women's Diet and Health Study is a population-based case-control study of exposures across the life course and breast cancer risk, which was described in detail elsewhere [23, 24]. Briefly, women diagnosed with histologically confirmed, first primary invasive breast cancer at ages 25–74 between June 2002 and April 2003 were identified through the Ontario Cancer Registry. Controls were selected from Ontario households by random-digit dialing and frequency matched to cases within 5-year age groups. Between 2003 and 2004, cases and controls were mailed questionnaires including information on a variety of health conditions and behaviors, including diet during adolescence and adulthood.

Dietary Assessment

Diet during adolescence (defined as ages 10–15) was collected using a food frequency questionnaire (FFQ) including 55 food items that were considered relevant to phytoestrogen intake among adolescent females in North America. Participants indicated their average frequency of consumption in terms of the specified serving size by checking one of four frequency categories ranging from “never or hardly ever” to “at least once a day”. The nutrient database for fiber, vegetable protein, and vegetable fat was developed using the US Department of Agriculture National Nutrient Database for Standard Reference, Release 25 [25]. The average daily nutrient intake from a given food was calculated by multiplying its assigned portion size by the number of servings per day and its nutrient content. The daily nutrient intake for each participant was then estimated by summing across all relevant food items.

A modified 178-item Block FFQ was used to measure dietary intake during adulthood [23]. Women were asked to report both the frequency and portion size of each food/supplement item consumed two years before study enrollment to reduce any bias due to changes in diet after cancer diagnosis. The frequency of consumption of each food was multiplied by reported portion size to obtain the amount of daily intake, which was then multiplied by the nutrient content of that food. Average daily intakes of nutrients and total energy were calculated using Block Dietary Data Systems with nutrient values from the US Department of Agriculture National Nutrient Database for Standard Reference and national data on food consumption (third National Health and Nutrition Examination Survey and the Continuing Survey of Food Intake by Individuals II) [26]. In a random sample of Ontario women, the modified Block FFQ has been demonstrated to have moderate to high reliability and validity overall (for dietary fiber: Pearson correlation coefficient=0.84 and 0.62, respectively) [27].

Statistical Analyses

Overall, 3023 (74%) of 4109 eligible breast cancer cases and 3420 (83%) of 4102 eligible controls completed and returned the questionnaires. Cases and controls with more than 10 missing food items on the adolescent FFQ were excluded from the analysis (158 (5.2%) cases; 121 (3.5%) controls). For participants with 1–10 blank food items, intakes for missing foods were imputed using the median value among controls [28].

Adolescent fiber, vegetable protein, and vegetable fat intakes were categorized into quintiles based on the distributions of intakes in controls. Two nut items on the adolescent FFQ (peanuts or peanut butter; other nuts) were used to determine categories for servings of peanuts and peanut butter, other nuts, and total nuts (combined), based on their distributions in controls; those with small numbers of participants were combined to improve stability of the estimates. We used student t-tests and χ^2 tests to compare the distributions of breast cancer risk factors between cases and controls. Unconditional logistic regression analyses were used to compute odds ratios (ORs) and 95% confidence intervals (CIs). In multivariable models we controlled for breast cancer risk factors, including age at diagnosis for cases and age on November 15, 2002 for controls, age at menarche (<12, 12, 13, 14 years, or unknown), education (high school or lower, higher than high school, or unknown), race (white, nonwhite, or unknown), recent adult BMI (<18.5 kg/m², 18.5–24.9 kg/m², 25.0–29.9 kg/m², 30 kg/m², or unknown), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal non-user, postmenopausal user, or unknown), family history of breast cancer in mother or sister(s) (yes, no, or unknown), oral contraceptive use (never use, ever use, or unknown), adult alcohol consumption two years before study enrollment (none, <7 drinks/week, 7 drinks/week, or unknown), parity and age at first birth (nulliparous; 1–2 pregnancies, age at first birth <25 years; 1–2 pregnancies, age at first birth 25–29 years; 1–2 pregnancies, age at first birth 30 years; 3 pregnancies, age at first birth <25 years; 3 pregnancies, age at first birth 25–29 years; 3 pregnancies, age at first birth 30 years; or unknown), and breastfeeding (yes, no, or unknown). The models were further adjusted for adult intakes of dietary fiber and vegetables (servings) two years before study enrollment to reduce the confounding effect of adult dietary intakes. Tests for trend were performed by using the median value for each category of dietary intakes of interests as a continuous variable in the multivariable model. The interactions between adolescent diet intakes, menopausal status, adult BMI, and family history of breast cancer were assessed by entering cross-product terms in multivariable models. The statistical significance of an interaction term was evaluated by using the likelihood ratio test. All statistical analyses were performed by SAS (version 9.3; SAS Institute, Cary, NC). $P < 0.05$ were considered statistically significant, and all statistical tests were two-sided.

Results

Table 1 shows comparisons of 2,865 cases and 3,299 controls on demographic, reproductive, and lifestyle factors. Compared with controls, cases were slightly older, younger at menarche, and reported higher levels of alcohol and dietary fiber intakes two years before enrollment but lower levels of fiber and vegetable fat intakes during adolescence. Cases were more likely than controls to be nulliparous and postmenopausal and have a family history of breast cancer among their first-degree relatives. Among parous participants, cases were older at first pregnancy than controls. Among postmenopausal women, cases had menopause at older age and were more likely to report postmenopausal hormone use than controls.

Multivariable-adjusted associations between adolescent diet and breast cancer risk are shown in Table 2. The risk of breast cancer was lower among women who consumed more fiber during adolescence; the OR comparing the highest with the lowest quintile of intake

was 0.69 (95% CI=0.59 to 0.82; $P_{\text{trend}} < .0001$). Adolescent fiber intake was mildly correlated with adult dietary fiber intake two years before enrollment ($r=0.3$), and further adjustment for adult fiber intake slightly reduced the OR to 0.66 (95% CI=0.55 to 0.78; $P_{\text{trend}} < .0001$) for the highest versus the lowest quintile of adolescent fiber intake. We also observed a statistically significant inverse association for adolescent vegetable fat intake ($\text{OR}_{\text{Q5-Q1}}=0.74$; 95% CI=0.62 to 0.87; $P_{\text{trend}}=0.001$). Adjustment for adult vegetable intake did not change this association ($\text{OR}_{\text{Q5-Q1}}=0.74$; 95% CI=0.63 to 0.87; $P_{\text{trend}}=0.002$). Higher adolescent vegetable protein intake showed a significant trend toward an inverse association with breast cancer ($\text{OR}_{\text{Q5-Q1}}=0.80$; 95% CI=0.68 to 0.95; $P_{\text{trend}}=0.01$), which remained unchanged after additional adjustment for adult vegetable intake ($P_{\text{trend}}=0.01$).

The associations between adolescent nut intake and breast cancer risk are shown in Table 3. Daily consumption of ≥ 1 serving of total nuts (including peanuts, peanut butter, and other nuts) during adolescence was associated with 24% reduced risk ($\text{OR}=0.76$; 95% CI=0.61 to 0.95; $P_{\text{trend}}=0.04$) compared with consumption of <1 serving of nuts per month. Breast cancer risk tended to decrease with the increase in adolescent intake of peanuts and peanut butter ($\text{OR}=0.78$ for ≥ 1 serving/day vs. <1 serving/month; 95% CI=0.64 to 0.95; $P_{\text{trend}}=0.08$). Higher intake of nuts other than peanuts during adolescence was also associated with lower risk of breast cancer ($\text{OR}=0.76$ for ≥ 1 serving/week vs. <1 serving/month; 95% CI=0.65 to 0.88; $P_{\text{trend}}=0.001$).

We further analyzed the associations between adolescent diet and breast cancer risk by menopausal status (Table 4), as well as by BMI, and family history of breast cancer. The significantly reduced risk associated with adolescent intakes of fiber, vegetable protein, total nuts, and peanuts and peanut butter was largely limited to postmenopausal breast cancer (for fiber: $\text{OR}_{\text{Q5-Q1}}=0.58$; 95% CI=0.47 to 0.72; $P_{\text{interaction}}=0.04$; for vegetable protein: $\text{OR}_{\text{Q5-Q1}}=0.71$; 95% CI=0.58 to 0.88; $P_{\text{interaction}}=0.05$; for total nuts: $\text{OR}=0.68$ for ≥ 1 serving/day vs. <1 serving/month; 95% CI=0.52 to 0.88; $P_{\text{interaction}}=0.02$; for peanuts and peanut butter: $\text{OR}=0.69$ for ≥ 1 serving/day vs. <1 serving/month; 95% CI=0.54 to 0.88; $P_{\text{interaction}}=0.01$) than for premenopausal breast cancer (for fiber: $\text{OR}_{\text{Q5-Q1}}=0.84$; 95% CI=0.64 to 1.12; for vegetable protein: $\text{OR}_{\text{Q5-Q1}}=0.99$; 95% CI=0.76 to 1.30; for total nuts: $\text{OR}=0.92$; 95% CI=0.61 to 1.37; for peanuts and peanut butter: $\text{OR}=0.97$; 95% CI=0.68 to 1.39). For vegetable fat and other nut intakes during adolescence, comparable inverse associations were observed for premenopausal and postmenopausal breast cancer. There was no significant interaction of adolescent diet with BMI or family history of breast cancer (data not shown).

DISCUSSION

This large, population-based case-control study showed that adolescent dietary fiber, vegetable protein, vegetable fat, and nut intakes were each associated with a reduced risk of breast cancer. The risk was significantly decreased by 34%, 26%, and 20% for women in the highest quintile of adolescent fiber, vegetable fat, and vegetable protein intakes compared with those in the lowest quintile, respectively. Moreover, these inverse associations persisted after adjustment for adult dietary intakes. Adolescent nut intake was also associated with a 22%-24% reduced risk. The inverse associations with adolescent intakes of vegetable fat and

nuts other than peanuts was not modified by menopausal status, while the decreased risk associated with adolescent fiber, vegetable protein, total nut, peanut and peanut butter intakes were stronger for postmenopausal compared with premenopausal breast cancer. Therefore, dietary fiber, vegetable protein, vegetable fat, and nut intakes during adolescence may convey lifelong protection against breast cancer.

The relationship between adolescent fiber intake and breast cancer risk has been evaluated in four independent studies. A case-control analysis of adolescent diet and breast cancer risk among participants in the NHS, which included 843 cases diagnosed between study enrollment and the return of the high-school diet questionnaire, showed that the highest versus lowest quintile of fiber intake was related to a non-significantly decreased risk ($OR_{Q5-Q1}=0.78$; $P_{trend}=0.09$) [19], which was similar to the result of a retrospective analysis of breast cancer cases identified before the completion of the high-school diet questionnaire in the NHSII cohort ($RR_{Q5-Q1}=0.81$; $P_{trend}=0.11$) [18]. There was no significant association between adolescent fiber intake and breast cancer risk in a prospective analysis of premenopausal women in the NHSII cohort [29]. Additionally, in a small study including 172 breast cancer cases and 190 controls, higher fiber intake during adolescence was associated with an increased risk for postmenopausal breast cancer [30]. Most of these analyses controlled for BBD [18, 19, 29] that might be on the etiologic pathway [21]. In this regard, the NHSII study observed that women in the highest quintile of adolescent fiber intake had a significantly 25% lower risk of proliferative BBD compared with those in the lowest quintile [21]. A meta-analysis of 16 prospective studies concluded that breast cancer risk was reduced by 7% (95% CI=2% to 11%) for the highest compared with the lowest dietary fiber intake during adulthood [31]. Further adjustment for adult fiber intake did not appreciably change the association between adolescent fiber intake and breast cancer risk in our study, suggesting an important, independent role of adolescent dietary fiber intake in modulating breast cancer development.

The biological mechanism for the observed inverse association of dietary fiber intake with breast cancer risk remains unclear. Dietary fiber could inhibit the intestinal reabsorption and increase the fecal excretion of estrogens [32], thus reducing their bioavailability. In a dietary intervention study, preadolescent girls (ages 8–10) were randomly assigned to usual care or to an intervention group with a low-fat and high-fiber diet and showed lower serum estradiol and progesterone levels in the intervention group during adolescence [33]. However, such differences did not persist during the transition of adolescence to young adulthood [34]. An inverse association between fiber intake and breast cancer risk may operate through modulating the insulin-like growth factor (IGF) system. In adolescent girls, dietary fiber intake has been positively related to IGF binding protein 3 that has antiproliferative and proapoptotic effects in breast cancer cells [35].

Our study confirmed a significant inverse association between vegetable fat intake in teenage years and adult breast cancer risk that was reported in the NHS and the NHSII. A prospective analysis of participants in the NHSII showed a 42% reduced risk of breast cancer for the highest intake of vegetable fat during adolescence [18]. Breast cancer risk was reduced by 15% for the highest compared with the lowest adolescent vegetable fat intake in a nested case-control study of participants in the NHS [19]. In addition, Baer et al. [22]

retrospectively analyzed the association between adolescent diet and subsequent risk of proliferative BBD in the NHSII. Those in the top quartile of vegetable fat consumption had a 27% reduced risk of proliferative BBD. The Growing Up Today Study (GUTS) prospectively collected childhood and adolescent diet and physical activity information from girls (ages 9–15), daughters of NHSII participants. In that study, vegetable fat intake at age 11, but not at age 14, was related to a reduced risk of subsequent biopsy-confirmed BBD with an OR of 0.72 for every 10-g daily intake [20].

Childhood and adolescent soy food or soy protein intake among Asians and Asian Americans has been shown to have a greater or additive protective effect on breast cancer risk compared to adult intake alone [10, 36]. In these studies vegetable protein intake was not reported. In the GUTS, a reduced risk of biopsy-confirmed BBD was observed in young women who consumed higher vegetable protein at age 14, but not at age 11 [20]. In our study, vegetable protein intake at ages 10–15 was inversely associated with breast cancer risk, which was more pronounced for postmenopausal breast cancer. More epidemiologic and experimental studies are needed to clarify vegetable protein consumed in teenage years in relation to breast cancer development.

Nuts are rich in unsaturated fatty acids, particularly monounsaturated fatty acids, and also sources of other bioactive compounds, such as vegetable protein, fiber, and phytosterols [37]. We observed a 24% lower risk of breast cancer for women who consumed one or more serving (1 serving=4 tablespoons) of nuts per day at ages 10–15 compared with those who consumed less than a serving per month, which was consistent for peanuts and peanut butter, and other nuts, separately or in combination (as total nuts). In the NHSII cohort, women who ate two or more small bags (1 bag=1 oz.) of peanuts and other nuts per week in high school had a 36% lower risk of proliferative BBD [21]. Peanut butter and nut intakes at ages 11 and 14 was also significantly associated with a reduced risk of BBD in young women from the GUTS [20]. However, there was no association between adult nut intake and breast cancer risk in the Malmo Diet and Cancer cohort [38]. These results suggest that nut intake during adolescence may be more relevant to breast carcinogenesis as compared with nut intake in adult life.

This study had several limitations. First, the validity of dietary information at ages 10–15 that was recalled 10–59 years later is unknown, although recall of adolescent diet by young adults has been reported to be valid and reproducible [39, 40]. Second, the 55-item FFQ was designed to capture phytoestrogen intake and might not provide a complete record for other dietary factors. Although nuts and dietary fiber were fairly well represented on the FFQ, the list of vegetable fat and vegetable protein sources was incomplete, excluding items such as snack foods (e.g. crackers/chips), added fats, baked goods, and pasta [41, 42]. This may be a reason for a lower level of estimated intakes of these nutrients in our study as compared with the literature [20, 21]. Another limitation is the possibility of differential measurement errors because adolescent diet was asked after cancer diagnosis. However, previous analyses of phytoestrogen intake and breast cancer risk in our sample showed a significant decrease in the risk for adolescent phytoestrogen intake [24] but results were less consistent for adult phytoestrogen intake [23]. In the current analysis, adult fiber intake was not significantly associated with breast cancer risk ($OR_{Q5-Q1}=1.08$; 95% CI=0.91 to 1.28; $P_{trend}=0.07$). Thus,

differential misclassification could not be an explanation for the inverse association of adolescent diet with breast cancer risk.

In summary, our study adds further evidence that intakes of dietary fiber, vegetable protein, vegetable fat, and nuts during adolescence are associated with a lower risk of breast cancer. This supports other evidence for the important role of dietary exposures during a critical period in life, when breast tissue is likely at its most vulnerable stage in breast cancer development. These results, if further substantiated, suggest that increasing intakes of fruits, vegetables, and grains as recommended by the American Cancer Society [43] with addition of nuts to diets of adolescent girls may represent an important opportunity for breast cancer prevention.

Acknowledgments

Funding/Support: YL and GAC are supported by the Barnes-Jewish Hospital Foundation, St. Louis, Missouri. GAC is also supported by the Breast Cancer Research Foundation. This research was funded by the Canadian Breast Cancer Research Alliance with special funding support of the Canadian Breast Cancer Foundation Ontario Chapter (CBCRA grant no. 13572 to M. Cotterchio).

Role of Sponsor: The funding agency had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. *Cancer Epidemiol Biomarkers Prev.* 1995; 4:567–571. [PubMed: 7549816]
2. Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, Tokuoka S. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. *Radiat Res.* 2003; 160:707–717. [PubMed: 14640793]
3. Trichopoulos D, Adami HO, Ekblom A, Hsieh CC, Laggiou P. Early life events and conditions and breast cancer risk: from epidemiology to etiology. *Int J Cancer.* 2008; 122:481–485. [PubMed: 18022897]
4. Wu AH, Wan P, Hankin J, Tseng CC, Yu MC, Pike MC. Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. *Carcinogenesis.* 2002; 23:1491–1496. [PubMed: 12189192]
5. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol.* 2000; 152:950–964. [PubMed: 11092437]
6. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. *Nature.* 1983; 303:767–770. [PubMed: 6866078]
7. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. *J Natl Cancer Inst.* 1996; 88:359–364. [PubMed: 8609645]
8. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. *Am J Epidemiol.* 1994; 139:819–835. [PubMed: 8178795]
9. Anderson LN, Cotterchio M, Boucher BA, Kreiger N. Phytoestrogen intake from foods, during adolescence and adulthood, and risk of breast cancer by estrogen and progesterone receptor tumor subgroup among Ontario women. *Int J Cancer.* 2013; 132:1683–1692. [PubMed: 22907507]
10. Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng W. Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. *Am J Clin Nutr.* 2009; 89:1920–1926. [PubMed: 19403632]
11. Liu Y, Colditz GA, Rosner B, Berkey CS, Collins LC, Schnitt SJ, Connolly JL, Chen WY, Willett WC, Tamimi RM. Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. *J Natl Cancer Inst.* 2013; 105:1571–1578. [PubMed: 23985142]

12. Maruti SS, Willett WC, Feskanich D, Rosner B, Colditz GA. A prospective study of age-specific physical activity and premenopausal breast cancer. *J Natl Cancer Inst.* 2008; 100:728–737. [PubMed: 18477801]
13. Russo IH, Russo J. Pregnancy-induced changes in breast cancer risk. *J Mammary Gland Biol Neoplasia.* 2011; 16:221–233. [PubMed: 21805333]
14. Meier-Abt F, Milani E, Roloff T, Brinkhaus H, Duss S, Meyer DS, Klebba I, Balwierz PJ, van Nimwegen E, Bentires-Alj M. Parity induces differentiation and reduces Wnt/Notch signaling ratio and proliferation potential of basal stem/progenitor cells isolated from mouse mammary epithelium. *Breast Cancer Res.* 2013; 15:R36. [PubMed: 23621987]
15. Medina D. Pregnancy protection of breast cancer: new insights reveal unanswered questions. *Breast Cancer Res.* 2013; 15:103. [PubMed: 23659596]
16. Bernstein L, Pike MC, Ross RK, Judd HL, Brown JB, Henderson BE. Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. *J Natl Cancer Inst.* 1985; 74:741–745. [PubMed: 3857369]
17. Musey VC, Collins DC, Musey PI, Martino-Saltzman D, Preedy JR. Long-term effect of a first pregnancy on the secretion of prolactin. *N Engl J Med.* 1987; 316:229–234. [PubMed: 3099198]
18. Frazier AL, Li L, Cho E, Willett WC, Colditz GA. Adolescent diet and risk of breast cancer. *Cancer Causes Control.* 2004; 15:73–82. [PubMed: 14970737]
19. Frazier AL, Ryan CT, Rockett H, Willett WC, Colditz GA. Adolescent diet and risk of breast cancer. *Breast Cancer Res.* 2003; 5:R59–R64. [PubMed: 12631400]
20. Berkey CS, Willett WC, Tamimi RM, Rosner B, Frazier AL, Colditz GA. Vegetable protein and vegetable fat intakes in pre-adolescent and adolescent girls, and risk for benign breast disease in young women. *Breast Cancer Res Treat.* 2013; 141:299–306. [PubMed: 24043428]
21. Su X, Tamimi RM, Collins LC, Baer HJ, Cho E, Sampson L, Willett WC, Schnitt SJ, Connolly JL, Rosner BA, Colditz GA. Intake of fiber and nuts during adolescence and incidence of proliferative benign breast disease. *Cancer Causes Control.* 2010; 21:1033–1046. [PubMed: 20229245]
22. Baer HJ, Schnitt SJ, Connolly JL, Byrne C, Cho E, Willett WC, Colditz GA. Adolescent diet and incidence of proliferative benign breast disease. *Cancer Epidemiol Biomarkers Prev.* 2003; 12:1159–1167. [PubMed: 14652275]
23. Cotterchio M, Boucher BA, Kreiger N, Mills CA, Thompson LU. Dietary phytoestrogen intake--lignans and isoflavones--and breast cancer risk (Canada). *Cancer Causes Control.* 2008; 19:259–272. [PubMed: 17992574]
24. Thanos J, Cotterchio M, Boucher BA, Kreiger N, Thompson LU. Adolescent dietary phytoestrogen intake and breast cancer risk (Canada). *Cancer Causes Control.* 2006; 17:1253–1261. [PubMed: 17111256]
25. U.S. Department of Agriculture, Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 25. Nutrient Data Laboratory Home Page, <http://www.ars.usda.gov/services/docs.htm?docid=8964>. 2007.
26. Anderson LN, Cotterchio M, Vieth R, Knight JA. Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women. *Am J Clin Nutr.* 2010; 91:1699–1707. [PubMed: 20392891]
27. Boucher B, Cotterchio M, Kreiger N, Nadalin V, Block T, Block G. Validity and reliability of the Block98 food-frequency questionnaire in a sample of Canadian women. *Public Health Nutr.* 2006; 9:84–93. [PubMed: 16480538]
28. Thompson, FE.; Subar, AF. Dietary assessment methodology. In: Coulston, AM.; Rock, CL.; Monsen, ER., editors. *Nutrition in the prevention and treatment of disease*. 2nd. San Diego, CA: Academic Press; 2001.
29. Linos E, Willett WC, Cho E, Frazier L. Adolescent diet in relation to breast cancer risk among premenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2010; 19:689–696. [PubMed: 20200427]
30. Pryor M, Slattery ML, Robison LM, Egger M. Adolescent diet and breast cancer in Utah. *Cancer Res.* 1989; 49:2161–2167. [PubMed: 2539254]

31. Aune D, Chan DS, Greenwood DC, Vieira AR, Rosenblatt DA, Vieira R, Norat T. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Ann Oncol.* 2012; 23:1394–1402. [PubMed: 22234738]
32. Forman MR. Changes in dietary fat and fiber and serum hormone concentrations: nutritional strategies for breast cancer prevention over the life course. *J Nutr.* 2007; 137:170S–174S. [PubMed: 17182821]
33. Dorgan JF, Hunsberger SA, McMahon RP, Kwiterovich PO Jr, Lauer RM, Van Horn L, Lasser NL, Stevens VJ, Friedman LA, Yanovski JA, Greenhut SF, Chandler DW, Franklin FA, Barton BA, Buckman DW, Snetselaar LG, Patterson BH, Schatzkin A, Taylor PR. Diet and sex hormones in girls: findings from a randomized controlled clinical trial. *J Natl Cancer Inst.* 2003; 95:132–141. [PubMed: 12529346]
34. Dorgan JF, Liu L, Klifa C, Hylton N, Shepherd JA, Stanczyk FZ, Snetselaar LG, Van Horn L, Stevens VJ, Robson A, Kwiterovich PO Jr, Lasser NL, Himes JH, Pettee Gabriel K, Kriska A, Ruder EH, Fang CY, Barton BA. Adolescent diet and subsequent serum hormones, breast density, and bone mineral density in young women: results of the Dietary Intervention Study in Children follow-up study. *Cancer Epidemiol Biomarkers Prev.* 2010; 19:1545–1556. [PubMed: 20501774]
35. Kerver JM, Gardiner JC, Dorgan JF, Rosen CJ, Velie EM. Dietary predictors of the insulin-like growth factor system in adolescent females: results from the Dietary Intervention Study in Children (DISC). *Am J Clin Nutr.* 2010; 91:643–650. [PubMed: 20089725]
36. Korde LA, Wu AH, Fears T, Nomura AM, West DW, Kolonel LN, Pike MC, Hoover RN, Ziegler RG. Childhood soy intake and breast cancer risk in Asian American women. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:1050–1059. [PubMed: 19318430]
37. Kris-Etherton PM, Hu FB, Ros E, Sabate J. The role of tree nuts and peanuts in the prevention of coronary heart disease: multiple potential mechanisms. *J Nutr.* 2008; 138:1746S–1751S. [PubMed: 18716180]
38. Sonestedt E, Borgquist S, Ericson U, Gullberg B, Landberg G, Olsson H, Wirfalt E. Plant foods and oestrogen receptor alpha- and beta-defined breast cancer: observations from the Malmo Diet and Cancer cohort. *Carcinogenesis.* 2008; 29:2203–2209. [PubMed: 18711147]
39. Frazier AL, Willett WC, Colditz GA. Reproducibility of recall of adolescent diet: Nurses' Health Study (United States). *Cancer Causes Control.* 1995; 6:499–506. [PubMed: 8580297]
40. Maruti SS, Feskanich D, Rockett HR, Colditz GA, Sampson LA, Willett WC. Validation of adolescent diet recalled by adults. *Epidemiology.* 2006; 17:226–229. [PubMed: 16477265]
41. Keast DR, Fulgoni VL 3rd, Nicklas TA, O'Neil CE. Food sources of energy and nutrients among children in the United States: National Health and Nutrition Examination Survey 2003–2006. *Nutrients.* 2013; 5:283–301. [PubMed: 23340318]
42. Phillips S, Jacobs Starkey L, Gray-Donald K. Food habits of Canadians: food sources of nutrients for the adolescent sample. *Can J Diet Pract Res.* 2004; 65:81–84. [PubMed: 15217526]
43. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin.* 2012; 62:30–67. [PubMed: 22237782]

Table 1

Characteristics of breast cancer cases and controls.

	Cases n=2,865		Control n=3,299		P
	Mean	SD	Mean	SD	
Age ^a (years)	56.4	10.2	55.1	11.0	<.0001
Adult body mass index (kg/m ²)	26.7	5.6	26.5	5.4	0.24
Age at menarche (years)	12.7	1.6	12.8	1.6	0.02
Total dietary fiber intake two years ago (g/day)	17.9	9.6	17.5	9.0	0.053
Vegetable intake two years ago (servings/day)	3.6	2.3	3.5	2.2	0.34
Adolescent fiber intake (g/day)	9.4	5.6	9.8	5.5	0.001
Adolescent vegetable protein intake (g/day)	7.0	5.9	7.2	5.5	0.07
Adolescent vegetable fat intake (g/day)	10.1	9.2	10.7	9.1	0.02
	N	%	N	%	
Parity					<.0001
Nulliparous	510	18.1	380	11.7	
1	388	13.7	395	12.2	
2	1,927	68.2	2,465	76.1	
Missing	40		59		
Age at first pregnancy ^b , years					0.02
< 25	1,226	53.0	1,618	56.6	
25–30	698	30.2	820	28.7	
30	391	16.9	422	14.8	
A history of breastfeeding ^b					0.73
No	807	41.8	1,057	42.3	
Yes	1,124	58.2	1,441	57.7	
Missing	384		362		
Ever used oral contraceptive					0.17
No	1,407	49.6	1,565	47.8	
Yes	1,430	50.4	1,708	52.2	

	Cases n=2,865		Control n=3,299		P
	Mean	SD	Mean	SD	
Missing	28		26		
Menopausal status					.0001
Premenopausal	918	32.1	1,206	36.6	
Postmenopausal	1,944	67.9	2,088	63.4	
Missing	3		5		
Age at menopause ^c , years					<.0001
< 45	520	27.5	680	33.5	
45–49	473	25.1	517	25.4	
50	895	47.4	836	41.1	
Missing	56		55		
Postmenopausal hormone use ^c					0.02
Never use	960	50.2	1,109	54.0	
Ever use	951	49.8	943	46.0	
Missing	33		36		
Family history of breast cancer in mother or sisters					<.0001
No	2,207	78.9	2,828	87.7	
Yes	591	21.1	396	12.3	
Missing	67		75		
Education					0.21
High school or lower	1,264	44.4	1,406	42.8	
Higher than high school	1,586	55.7	1,881	57.2	
Missing	15		12		
Race					0.07
White	2,554	89.4	2,981	90.8	
Nonwhite	302	10.6	302	9.2	
Missing	9		16		
Alcohol consumption two years ago (drinks/week)					0.04
0	1,111	42.6	1,256	41.8	
< 7	983	37.7	1,220	40.6	

	Cases	Control	P
	n=2,865	n=3,299	
	Mean	Mean	SD
7	513	528	17.6
Missing	258	295	

^a Age at diagnosis for cases and age on November 15, 2002 for controls.

^b Among 5,175 women who had a history of at least one full-term pregnancy (>7 months gestation).

^c Among 4,032 postmenopausal women.

Table 2

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer by quintiles of intakes of dietary fiber, vegetable protein, and vegetable fat during adolescence (ages 10–15 years).

	Intake level (g/day)		Cases	Controls	OR (95% CI) ^a	OR (95% CI) ^b
	Median	Range				
Dietary fiber						
Quintile 1 (low)	4.0	<5.2	676	672	1.00 (Reference)	1.00 (Reference)
Quintile 2	6.5	5.2–7.6	575	635	0.87 (0.74, 1.02)	0.86 (0.73, 1.01)
Quintile 3	8.8	7.7–10.0	577	662	0.86 (0.73, 1.01)	0.84 (0.72, 0.99)
Quintile 4	11.4	10.1–13.3	556	660	0.83 (0.71, 0.97)	0.80 (0.68, 0.94)
Quintile 5 (high)	16.4	13.4	481	670	0.69 (0.59, 0.82)	0.66 (0.55, 0.78)
Per 10-g/day increase			2,865	3,299	0.77 (0.68, 0.87)	0.73 (0.65, 0.84)
					$P_{\text{trend}} < .0001$	$P_{\text{trend}} < .0001$
Vegetable protein						
Quintile 1 (low)	2.7	<3.5	638	659	1.00 (Reference)	1.00 (Reference)
Quintile 2	4.1	3.5–4.7	617	660	0.94 (0.80, 1.10)	0.94 (0.80, 1.10)
Quintile 3	5.4	4.8–6.2	570	662	0.86 (0.73, 1.01)	0.86 (0.73, 1.01)
Quintile 4	7.5	6.3–9.9	519	659	0.78 (0.66, 0.91)	0.78 (0.66, 0.91)
Quintile 5 (high)	15.1	10.0	521	659	0.80 (0.68, 0.95)	0.80 (0.68, 0.95)
Per 5-g/day increase			2,865	3,299	0.92 (0.87, 0.98)	0.92 (0.87, 0.98)
					$P_{\text{trend}} = 0.01$	$P_{\text{trend}} = 0.01$
Vegetable fat						
Quintile 1 (low)	2.9	<5.1	646	659	1.00 (Reference)	1.00 (Reference)
Quintile 2	6.1	5.1–7.1	578	660	0.84 (0.71, 0.98)	0.84 (0.71, 0.99)
Quintile 3	8.3	7.2–9.4	589	661	0.86 (0.74, 1.01)	0.87 (0.74, 1.02)
Quintile 4	10.1	9.5–12.9	563	659	0.85 (0.72, 1.00)	0.85 (0.72, 1.00)
Quintile 5 (high)	27.6	13.0	489	660	0.74 (0.62, 0.87)	0.74 (0.63, 0.87)
Per 10-g/day increase			2,865	3,298	0.86 (0.79, 0.94)	0.86 (0.79, 0.95)
					$P_{\text{trend}} = 0.001$	$P_{\text{trend}} = 0.002$

^aORs were adjusted for age, family history of breast cancer in mother and sisters, age at menarche, parity, age at first birth, education, ethnicity, oral contraceptive use, adult BMI, breastfeeding, menopausal status, hormone replacement therapy, and alcohol consumption two years before study enrollment.

^b ORs for dietary fiber intake during adolescence were further adjusted for total dietary fiber intake two years before study enrollment; ORs for intakes of vegetable protein and vegetable fat during adolescence were further adjusted for vegetable intake two years before study enrollment.

Table 3

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer for nut intake during adolescence (ages 10–15 years).

	Cases	Controls	OR (95% CI) ^c
Total nuts (servings ^a)			
< 1/month	307	291	1.00 (Reference)
1–3/month	864	1,003	0.86 (0.71, 1.04)
1–6/week	1,363	1,564	0.86 (0.72, 1.04)
1/day	331	441	0.76 (0.61, 0.95)
			$P_{\text{trend}} = 0.04$
Peanuts and peanut butter (servings ^b)			
< 1/month	489	491	1.00 (Reference)
1–3/month	778	912	0.86 (0.73, 1.01)
1–6/week	1,281	1,477	0.87 (0.75, 1.02)
1/day	317	419	0.78 (0.64, 0.95)
			$P_{\text{trend}} = 0.08$
Other nuts (servings ^a)			
< 1/month	1,091	1,081	1.00 (Reference)
1–3/month	1,303	1,604	0.82 (0.73, 0.92)
1/week	471	614	0.76 (0.65, 0.88)
			$P_{\text{trend}} = 0.001$

^aTotal nuts includes peanuts/peanut butter and other nuts combined; a serving is equal to ¼ cup.

^bA serving is equal to ¼ cup for peanuts and two tablespoons for peanut butter.

^cORs were adjusted for age, family history of breast cancer in mother and sisters, age at menarche, parity, age at first birth, education, ethnicity, oral contraceptive use, adult BMI, breastfeeding, menopausal status, hormone replacement therapy, and alcohol consumption two years before study enrollment.

Table 4

The associations between dietary intakes during adolescence and breast cancer risk by menopausal status at cancer diagnosis.

	Premenopausal women			Postmenopausal women			<i>P</i> _{interaction}
	cases	control	OR (95% CI) ^a	cases	control	OR (95% CI) ^a	
Dietary fiber (g/day)							
<5.2	231	267	1.00 (Reference)	445	405	1.00 (Reference)	
5.2–7.6	169	233	0.82 (0.63, 1.08)	406	401	0.88 (0.72, 1.07)	
7.7–10.0	192	244	0.90 (0.69, 1.17)	385	418	0.81 (0.66, 0.99)	
10.1–13.3	165	248	0.75 (0.57, 0.99)	389	411	0.81 (0.66, 0.99)	
13.4	161	214	0.84 (0.64, 1.12)	319	453	0.58 (0.47, 0.72)	
Per 10-g/day increase	918	1,206	0.87 (0.70, 1.08)	1,944	2,088	0.67 (0.57, 0.78)	
			<i>P</i> _{trend} =0.20			<i>P</i> _{trend} <0.0001	0.04
Vegetable protein (g/day)							
<3.5	238	290	1.00 (Reference)	400	369	1.00 (Reference)	
3.5–4.7	196	228	1.03 (0.79, 1.34)	421	431	0.90 (0.74, 1.09)	
4.8–6.2	152	226	0.80 (0.61, 1.06)	416	435	0.88 (0.72, 1.08)	
6.3–9.9	144	232	0.75 (0.57, 0.99)	375	427	0.78 (0.64, 0.96)	
10.0	188	230	0.99 (0.76, 1.30)	332	426	0.71 (0.58, 0.88)	
Per 5-g/day increase	918	1,206	1.00 (0.91, 1.11)	1,944	2,088	0.88 (0.82, 0.95)	
			<i>P</i> _{trend} =0.98			<i>P</i> _{trend} =0.0001	0.05
Vegetable fat (g/day)							
<5.1	276	324	1.00 (Reference)	370	333	1.00 (Reference)	
5.1–7.1	153	221	0.80 (0.61, 1.04)	425	438	0.85 (0.69, 1.04)	
7.2–9.4	174	199	1.04 (0.80, 1.35)	413	462	0.79 (0.64, 0.97)	
9.5–12.9	144	218	0.78 (0.59, 1.02)	418	439	0.87 (0.71, 1.07)	
13.0	171	244	0.85 (0.65, 1.10)	318	415	0.68 (0.55, 0.84)	
Per 10-g/day increase	918	1,206	0.93 (0.80, 1.08)	1,944	2,087	0.83 (0.74, 0.93)	
			<i>P</i> _{trend} =0.34			<i>P</i> _{trend} =0.0001	0.23
Total nuts (servings ^b)							
< 1/month	75	77	1.00 (Reference)	232	214	1.00 (Reference)	
1–3/month	271	355	0.78 (0.54, 1.12)	592	646	0.89 (0.71, 1.11)	

	Premenopausal women			Postmenopausal women			<i>P</i> _{interaction}
	cases	control	OR (95% CI) ^a	cases	control	OR (95% CI) ^a	
1–6/week	443	623	0.73 (0.52, 1.04)	918	939	0.94 (0.76, 1.16)	
1/day	129	151	0.92 (0.61, 1.37)	202	289	0.68 (0.52, 0.88)	
			<i>P</i> _{trend} = 0.46			<i>P</i> _{trend} = 0.002	0.02
Peanuts and Peanut butter (servings ^c)							
< 1/month	112	127	1.00 (Reference)	377	363	1.00 (Reference)	
1–3/month	252	337	0.81 (0.59, 1.10)	525	574	0.88 (0.73, 1.07)	
1–6/week	432	597	0.80 (0.60, 1.06)	847	878	0.92 (0.77, 1.10)	
1/day	122	145	0.97 (0.68, 1.39)	195	273	0.69 (0.54, 0.88)	
			<i>P</i> _{trend} = 0.31			<i>P</i> _{trend} = 0.004	0.01
Other nuts (servings ^b)							
< 1/month	352	353	1.00 (Reference)	738	725	1.00 (Reference)	
1–3/month	423	625	0.67 (0.55, 0.82)	878	977	0.90 (0.78, 1.03)	
1/week	143	228	0.63 (0.48, 0.82)	328	386	0.84 (0.70, 1.00)	
			<i>P</i> _{trend} = 0.003			<i>P</i> _{trend} = 0.07	0.15

^aORs were adjusted for age, family history of breast cancer in mother and sisters, age at menarche, parity, age at first birth, education, ethnicity, oral contraceptive use, adult BMI, breastfeeding, menopausal status, hormone replacement therapy, and alcohol consumption two years before study enrollment. ORs for dietary fiber intake during adolescence were further adjusted for total dietary fiber intake two years before study enrollment; ORs for intakes of vegetable protein and vegetable fat during adolescence were further adjusted for vegetable intake two years before study enrollment.

^bTotal nuts includes peanuts/peanut butter and other nuts combined; a serving is equal to ¼ cup.

^cA serving is equal to ¼ cup for peanuts and two tablespoons for peanut butter.