Association Between Diet During Preadolescence and Adolescence and Risk for Breast Cancer During Adulthood

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Article history: Received May 3, 2012; Accepted August 31, 2012

Keywords: Preadolescent diet; Adolescent diet; Adult breast cancer

ABSTRACT

It is increasingly evident that diet during preadolescence and adolescence has important consequences for breast cancer during adulthood. However, only a few epidemiologic studies have been conducted on the relationship between diet during preadolescence and adolescence, and cancer during adulthood. This situation is partly because of methodological challenges such as the long latency period, the complexity of breast cancer, the lack of validated diet assessment tools, and the large number of subjects that must be followed, all of which increase costs. In addition, funding opportunities are few for such studies. Results from the small number of epidemiologic studies are inconsistent, but evidence is emerging that specific aspects of the diet during preadolescence and adolescence are important. For example, during preadolescence and adolescence, severe calorie restriction with poor food quality, high total fat intake, and alcohol intake tend to increase risk, whereas high soy intake decreases risk. Research on preadolescent and adolescent diet is a paradigm shift in breast cancer investigations. This research paradigm has the potential to produce transformative knowledge to inform breast cancer prevention strategies through dietary intervention during preadolescence and adolescence, rather than later in life, as is current practice, when it is perhaps less effective. Methodological challenges that have plagued the field might now be overcome by leveraging several existing large-scale cohort studies in the U.S. and around the world to investigate the role of diet during preadolescence and adolescence in risk for adult breast cancer.

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early-life exposures and events, including during preadolescence and adolescence, can affect breast cancer risk.

Clues from epidemiologic studies of cardiovascular disease (CVD) indicate that early-life diet affects later risk for CVD. In 1989, Barker and colleagues [1] published data showing that men with the lowest weights at birth and at 1 year of age had the highest death rates from ischemic heart disease, and that increasing weight was associated with a graded decrease in risk. Barker et al proposed that an environment that induces poor fetal and infant growth will be followed by high risk of ischemic heart disease during adulthood. This idea has been validated by several prospective cohort studies. For example, studies in Sweden [2], Finland [3], Denmark [4], Norway [5], England [6], and Scotland [7] found that mortality from ischemic heart disease was inversely associated with birth weight. In the U.S. [8,9] and India [10], a strong inverse association between birth weight and nonfatal coronary heart disease was reported. A recent systematic review of 17 published studies concluded that low birth weight increases risk for ischemic heart disease [11]. If indeed early-life exposures affect CVD risk, by logical extension and because of similar pathways, such exposures may also affect risk for breast cancer. For example, a single acute exposure to radiation to those who were in utero or in early childhood at the time of the atomic bombings of Hiroshima and Nagasaki resulted in significantly elevated risk of malignancies decades later [12]. In addition, studies of migrant populations show that rates of breast cancer change after migration and primarily affect the next generation [13,14], which supports the idea that early-life exposures have a role. In Asia, breast cancer incidence rates are much lower than in the U.S., but when Asian women migrate to the U.S., their breast cancer risk increases gradually over several generations and eventually approaches that of U.S. white women [13]. Early studies suggest that the increased breast cancer risk among Asians did not appear until the second generation was born in the U.S. [15]. These studies [13,15] and other early studies [16,17] prompted the hypothesis that exposure to western diet and lifestyle at an early age was critical to breast cancer development.

In 2006, a review was published on early-life diet and the risk for adult breast cancer [18]. The focus was not on the epidemiological evidence, but on postulated mechanistic links between early-life diet and breast cancer development. For this review, we used Pub Med to search for all published epidemiologic studies of preadolescent and adolescent diet in relation to adult breast cancer risk, and reviewed the evidence. In this article, we discuss a possible mechanistic link, and the challenges to and opportunities for elucidating the role of preadolescent and adolescent diet and adult breast cancer.

**Preadolescent and Adolescent Diet**

**Calories**

In 1988, deWaard and Trichopoulos [19] proposed that an energy-rich diet during puberty and adolescence stimulates the growth of mammary glands and increases the occurrence of precancerous lesions in the breast. It is well established that energy restriction in animal models leads to reduced cancer incidence. Prospective data from the Nurses’ Health Study II (NHS II) cohort study of adolescent total caloric intake and breast cancer risk showed a significant trend for increased risk with increased levels of total calories consumed [21]. A retrospective cohort study using the Swedish Cancer Registry found that younger women with anorexia nervosa (before age 40 years) have lower risk of breast cancer compared with women in the Swedish general population [22]. Anorexia nervosa, an illness that occurs generally during adolescence or early adulthood, is an indicator of caloric restriction. On the contrary, early-life caloric restriction coupled with malnutrition or famine increases risk for breast cancer development. For example, women who were in the pubertal phase of life during World War II and exposed to caloric restriction without substantially poor diets had decreased risk of subsequent breast cancer compared with women exposed to severe calorie restriction and poor food quality [23]. Birth cohorts of subjects exposed to severe calorie restriction and poor diet quality such as experienced by European Jews who had potentially been exposed to the Holocaust and then migrated to Israel had substantially increased breast cancer risk [24]. The strongest increased breast cancer risk occurred in the youngest birth cohort of European Jews, which suggests that early-life exposure had a major role [24], and affirms that timing of the exposure is clearly important. The Netherlands Cohort Study, in which a proxy was used to assess adolescent energy restriction during the Hunger Winter (1944–1945), found evidence that severe food restriction during the Hunger Winter significantly increased risk for adult breast cancer in the western rural areas, but not in the western city areas [25]. Thus, the Netherlands Cohort Study data did not provide clear evidence to support the hypothesis that energy restriction resulting from severe famine leads to significantly increased breast cancer risk.

Surrogate indicators of caloric consumption and, more generally, energy balance such as childhood growth, body fatness at young age, and adolescent body size all point to a role in breast cancer development. An advantage of presenting data on anthropometry is that it is a time-integrated measure of energy balance, whereas variability in total caloric intake may represent variability in physical activity, which makes it difficult to interpret some of the findings presented. Prospective data from a British cohort in which 2,547 girls were observed from birth in 1966 to the end of 1999 showed that adult height was positively associated with age at menarche and breast cancer. Overall, the breast cancer cases were taller and slimmer throughout childhood. Women who grew faster in childhood and reached adult height above the average for their menarche category were at the highest risk for breast cancer [26]. In a prospective analysis of NHS (1988–2004) and NHS II (1989–2005) among 188,860...
women (7,582 breast cancer cases) who recalled their body fatness at ages 5, 10, and 20 years, it was reported that body fatness at young ages had a strong and independent inverse association with both premenopausal and postmenopausal breast cancer [27]. Several studies have found that childhood and adolescent body size is inversely associated with both premenopausal and postmenopausal breast cancer risk [28–32].

Fat

A recent analysis from the NHS II, based on 39,268 premenopausal women who completed a 124-item food frequency questionnaire about their diet during high school (participants were 34–53 years of age at the time they were surveyed in 1998) found that the highest intake of total fat compared with the lowest during adolescence was associated with significantly increased risk for premenopausal breast cancer (relative ratio = 1.35; 95% confidence interval [CI], 1.00–1.81; p trend = .05). However, when data on consumption of saturated, mono-unsaturated, polyunsaturated, trans, animal, and vegetable fat were analyzed separately, the associations were null [33]. In an earlier retrospective analysis of 47,355 participants in the NHS II, no association was found between adult breast cancer risk and adolescent intake of total, animal, saturated, monounsaturated and polyunsaturated fats, although a significantly reduced risk was observed for the highest intake of vegetable fat [21]. Case-controls studies show inconsistent results [34,35]. In a nested case-control study of participants within the NHS II cohort, women who consumed a high level of vegetable fat during adolescence had a lower risk of breast cancer [34]. A small Utah case-control study found that adolescent consumption of total fat (or fat from milk, cheese, and yogurt) was not associated with adult breast cancer risk [35].

The effect of adolescent fat consumption on adult mammographic breast density, a marker of breast cancer risk, was also studied. In that study, women (1,142 premenopausal women and 451 premenopausal women) in the Minnesota Breast Cancer Family cohort who had mammograms but had no breast cancer were asked to report on diet consumption during their adolescence (age 12–13 years). Fat consumption was not associated with mammographic breast density among the women [36]. Whether the women later developed breast cancer was not assessed.

An intervention study that randomly assigned 8–10-year-olds (n = 286) to one of two groups—(1) usual care or (2) a behavioral intervention that promoted a reduced fat diet—reported that modest reductions in fat intake lowered serum concentrations of estradiol (29.8%; 95% CI, 5.4%–47.9%), non—sex hormone-binding globulin—bound estradiol (30.2%; 95% CI, 7.0%–47.7%), estrone (20.7%; 95% CI, 4.7%–34.0%), and estrone sulfate (28.7%; 95% CI, 5.1%–46.5%) in the follicular phase and increased testosterone (27.2%; 95% CI, 5.7%–53.1%) in the luteal phase of the menstrual cycle in blood samples at the Year 5 visit [37]. During this time, girls in the intervention group consumed significantly less total and saturated fat. These results indicate that modest reductions in adolescent fat intake reduce hormone concentrations consistent with reductions in breast cancer risk. However, a follow-up of the participants at age 25–29 years found that serum estradiol concentrations were significantly higher in the behavioral intervention group, which indicates that modest reductions in adolescent fat consumption is unlikely to lower breast cancer risk [38].

Red meat

An analysis of NHS II data showed that increasing adolescent consumption of red meat was associated with a nonsignificant trend toward increased breast cancer risk [21]. However, a more recent analysis of premenopausal women in NHS II showed that increased levels of red meat consumed during adolescence was associated with a significant linear trend for increased premenopausal breast cancer risk [39].

A recent case-control study of Chinese immigrant women reported that high consumption of red meat during adolescence, but not during adulthood, was associated with significantly higher adult mammographic breast density [40]. This finding is important despite the low level of red meat consumed by Chinese immigrants compared with western populations. Data from another case-control study found that frequent intake of ground beef during preadolescence was associated with a nonsignificant 44% increased risk of adult breast cancer [41].

French fries

A nested case-control study of 582 women with breast cancer and 1,569 control subjects, all selected from participants in the NHS and NHS II, assessed the preschool diet of nurses at ages 3–5 years by collecting information from the mothers of the participants. Results showed that frequent consumption of french fries during the preschool age was associated with significantly increased risk for breast cancer later in life. For every one additional serving of french fries per week during their preschool years, adult breast cancer risk increased by 27% [41]. No other data on preadolescent or adolescent french fry consumption and adult breast cancer have been published.

Vegetables, fruit, and fiber

Prospective data from the Boyd Orr cohort of 4,999 men and women who had been children in the households participating in a survey of family diet and health, after 60 years of follow-up (483 incident malignant neoplasms; 82 incident breast cancers), reported that increased childhood fruit consumption but not vegetable intake was associated with significantly reduced risk of incident cancer [42]. A nested case-control analysis of participants in the NHS to assess diet during high school and breast cancer, in which 843 eligible cases were diagnosed between the start of the study (1976) and before the return of the high school diet questionnaire (1986), reported that women who consumed a higher level of dietary fiber during adolescence had a lower risk for breast cancer than those who consumed a low level of fiber [34]. Similarly, in an analysis of the NHS II, the highest quintile of adolescent dietary fiber intake was associated with a significant 25% lower risk of adult proliferative benign breast disease (BBD) (n = 682 cases) than was those in the lowest quintile. High intakes of nuts and apples during adolescence also were associated with significantly reduced risk for BBD. Adolescents who consumed less than two servings of nuts per week had a 36% lower risk for BBD than adolescents who ate more than one serving per month [43]. However, an analysis of participants in the NHS II of diet during high school in 1998, at which time the participants were 34–53 years of age and observed for 7 years (1998–2005), during which time 455 invasive premenopausal breast cancer cases were diagnosed, showed that dietary fiber intake during adolescence was not significantly associated with
premenopausal breast cancer development [33]. Similarly, in a previous analysis of NHS II data, adolescent intake of total vegetables or total fruit did not affect breast cancer development [21]. A nested case-control analysis of NHS and NHS II data reported null findings for the association between high school dietary intakes of vegetable, fruit, and fiber and breast cancer development [41]. A population-based case-control study (1,647 cases and 1,501 controls) of diet during adolescence and breast cancer in which participants were identified by random-digit dialing reported that high versus low consumption of fruits and vegetables during adolescence was associated with a nonsignificantly reduced risk of breast cancer [44]. In a much smaller case-control (172 cases and 190 controls) study of adolescent diet and breast cancer in Utah, the higher quartile of fiber intake produced a significantly elevated odds ratio for increased postmenopausal breast cancer risk [35].

**Bean (soy)**

Evidence from in vitro animal studies and a few epidemiological studies has been accumulating to suggest that consumption of soy foods contributes to reductions in breast cancer risk. Table 1 shows the results of studies that investigated the association between childhood or adolescent soy intake and risk for adult breast cancer. A recent population-based case-control study [45] of 579 first primary breast cancer cases and 966 matched control subjects reported that increasing childhood (12 years old or younger) and adolescent (12–19 years old) soy intakes were associated with substantial reductions in risk for later breast cancer among Asian-American women. Adult soy intake was also associated with reduced breast cancer risk in this population, but the strongest and most consistent association was with childhood intake [45]. Soy intake was associated with significantly reduced breast cancer risk among women who consumed the highest level of soy during either childhood (odds ratio \( \text{OR} = .42; 95\% \text{ CI}, .20–.90; p \text{ trend} = .02 \)) or adolescence (\( \text{OR} = .77; 95\% \text{ CI}, .57–1.04; p \text{ trend} = .08 \)) [45]. Four other studies (Table 1)—one of Asian-American women [46]; one of non-Asians, mostly white Canadian women [47]; and the other two of Chinese women [48,49]—reported that increased soy intake during adolescence reduced risk for adult breast cancer. In general, when soy consumption in these studies is compared, the daily median intake of soy is lower among Asian-Americans and whites than Asians or Chinese women in Shanghai.

**Whole milk and dairy**

In addition to their findings on french fries, data from the NHS II (a nested case-control study of 582 women with breast cancer and 1,569 controls) [41] also found that consuming whole milk at age 3–5 years was associated with a significant 10% decreased risk for adult breast cancer. However, the Boyd Orr prospective cohort study found that milk, total dairy and cream intake during childhood were not associated with breast cancer risk after 65 years of follow-up [50]. In contrast, the Norwegian Women and Cancer prospective cohort study reported that childhood milk consumption was protective against breast cancer [51], but a subsequent analysis with longer follow-up showed no association between childhood milk consumption and breast cancer [52]. Similarly, other large studies in North America found no significant association between childhood dairy consumption and risk for breast cancer [21,44].

**Adolescent Drinking**

Good evidence suggests that high alcohol consumption during late adolescence continues into adulthood [53]. Because adult alcohol consumption is a known risk factor for breast cancer, it seems logical that adolescent alcohol consumption would have similar effects. However, results of only one prospective study of alcohol intake assessed during adolescence, rather than retrospectively recalled years later, and risk of benign breast disease, a risk factor for breast cancer development, have been published [54]. The study found that the risk of biopsy-confirmed benign breast disease increased with the amount of alcohol consumed among girls at ages 9–15 years. Girls who drank 6 or 7 days per week had a 5.5 times higher risk of having benign breast disease compared with those who did not drink or had less than one drink per week [54]. These results are consistent with those of a retrospective study in which adults recalled alcohol consumption at age 18–22 years. Alcohol consumption of 15 g/day or more at age 18–22 years, but not at 15–17 years, was associated with significant increased risk for benign breast disease [55]. In the NHS I and II cohorts, high alcohol consumption during adolescence was associated with a nonsignificant increased risk for adult breast cancer [30,56]. To date, results from case-control studies of adolescent alcohol consumption and breast cancer risk have been inconsistent [57–60].

**Discussion**

Limited research has been done on the role of preadolescent and adolescent diet in risk for adult breast cancer. This situation is partly because of methodological challenges such as the long latency period for breast cancer development, which requires epidemiologic studies of preadolescent and adolescent dietary...
exposures to have a long follow-up and be large and expensive. Other challenges include the lack of validation of most of the currently used dietary assessment tools for pre-adolescence and adolescence dietary consumption and the fact that dietary recall is prone to bias. Most studies have used questionnaires developed for dietary exposure assessment in adults. Errors in assessing diet during preadolescence and adolescence because of the lack of valid measurement tools, lack of adequate dietary range of intake, and the unique characteristics of study populations in different geographic locations contribute to the inconsistent results from prospective, retrospective, and case-control studies, although few studies have been conducted overall. There is a need to validate the questionnaires used in the existing cohort studies that have engaged in the retrospective collection of early-life dietary data as a scientific building up of research resources. Although some effort at validation has been undertaken, it is inadequate and inconsistent in its implications. For example, in the data from the Fels Study established in 1929, although some individual dietary factor were reasonably recalled, it was found that the food frequency questionnaire did not validly measure overall preschool diet when completed by mothers 4 decades later [61], or overall adolescent diet when completed by middle-aged and older adults 48 years after adolescence [62]. However, validation studies using the NHS II suggest that the food frequency questionnaire can reasonably capture diet recalled by mothers [63] and by young adults [64].

In addition, there are no established biomarkers correlated with diet exposures during preadolescence and adolescence and cancer development many years later in adulthood. Because few epidemiologic studies of preadolescent and adolescent diet and risk for adult breast cancer have been conducted, enormous gaps in knowledge are evident not only in the epidemiology, but also in studies attempting to understand biological mechanisms. An example of a research gap is the lack of understanding of diet—gut microbiome interactions during critical periods of growth such as preadolescence and adolescence, and adult breast cancer risk. Evidence is emerging that gut bacteria that feed on healthy foods amplify the nutritional benefits, but also amplify the harmful effects of unhealthy foods [65]. For example, adolescent soy consumption is associated with reduced risk for adult breast cancer, but there is some inconsistency in the findings. One possible reason for inconsistent findings could be the individual differences in how gut bacteria metabolize soy isoflavones. Other gaps include a lack of understanding about how dietary patterns during the elementary, middle, and high school years affect risk for adult breast cancer. During these periods of preadolescent and adolescent development, dietary changes are typical, and because diet induces phenotypic and molecular changes, the impact on later breast cancer risk could be important. In addition, it remains unclear how diet during preadolescence and adolescence affects markers for adult breast cancer risk, such as hormonal profiles. Evidence from a randomized, controlled clinical trial [37] suggests that a modest reduction in fat consumption during adolescence lowers concentrations of estradiol, non—sex hormone-binding globulin—bound estradiol, estrone, and estrone sulfate during the follicular phase of the menstrual cycle, consistent with changes expected to reduce risk for breast cancer. Efforts at unraveling clear phenotypic and molecular mechanisms to explain the impact of preadolescent and adolescent dietary exposures on the development of adult breast cancer would be greatly valuable in preventing breast cancer earlier (during preadolescence and adolescence) rather than later in life. Research must also address the interactions diet, adiposity, inflammation, and immunity during preadolescence and adolescence, and breast cancer development during adulthood. The ideal epidemiologic study design would be prospective studies starting from the in utero period, with long follow-up for breast cancer outcomes. These types of prospective studies would be costly, but the impact could be substantial. Several birth cohorts around the world could be collectively harnessed to answer important questions regarding the role of preadolescence and adolescence diet and adult breast cancer risk [66].

Current evidence points to a trend in which aspects of diet during preadolescence and adolescence either increase or decrease risk for adult breast cancer. Several methodological issues such as dietary recall bias may affect the validity of the current evidence. Therefore, it is crucial that research opportunities target the development of tools that would accurately aid in both the prospective and retrospective collection of dietary data in early life, such as in preadolescence and adolescence. However, because of the emerging evidence, it is not too early to consider issuing voluntary advice to adolescents regarding risk and potential benefits in preventing later breast cancer development. Such advice regarding healthier diet would be useful, not harmful, to good health in general and might potentially offset a percentage of the breast cancer risk attributable to dietary exposures at the age 8–18 range. This should be useful because preadolescents and adolescents typically consume inadequate daily amounts of unprocessed foods such as fruits, vegetables, and whole grains, and consume excessive amounts of processed foods that are high in sugar, corn syrup, fat, and salt [67].

References


