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Review article

Preadolescent and Adolescent Risk Factors for Benign Breast Disease

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A B S T R A C T

Purpose: It is well established that exposures during childhood and adolescence affect breast cancer risk much later in life. Recently, studies have begun to evaluate whether early life exposures might also impact the risk of developing benign breast disease (BBD). A diagnosis of proliferative BBD independent of other breast cancer risk factors also increases the subsequent risk of breast cancer; therefore, understanding how to decrease the incidence of BBD may have important implications for primary breast cancer prevention.

Methods: We reviewed several studies from prospective cohort studies that have investigated the relationship between risk factors during childhood and adolescence, such as anthropometric and reproductive characteristics as well as diet and other behaviors, and subsequent risk of BBD.

Results: Higher intake of vegetable oils, nuts, vitamin E, and fiber and lower consumption of animal fat, red meat, and alcohol are associated with reduced risk of BBD. Childhood weight and adolescent body mass index are inversely associated with BBD risk, whereas a greater peak height velocity during adolescence is associated with a higher risk of BBD. There was no association between age of menarche and risk of BBD.

Conclusion: Early life exposures and behaviors appear to impact BBD risk. The current body of evidence further supports the importance of a life-course approach to breast cancer prevention.

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CONTRIBUTION

These findings support a life-course approach to preventing breast cancer. Interventions during adolescence could reduce the risk for breast cancer later in life.

With more than 200,000 new cases of invasive breast carcinoma reported each year, breast cancer is the most commonly diagnosed malignancy among women in the United States [1]. Identifying opportunities for prevention of this disease by actions earlier in life are warranted. It has become widely accepted that exposures during childhood and adolescence can “set the stage” for breast cancer development later in life [2–4]. Some of the earliest work on the epidemiology of breast cancer established the importance of adolescent life events, such as age of menarche, age at first birth, childhood body fat, and adolescent

body mass index (BMI) in determining subsequent risk of breast cancer [2,5–8]. These observations led to the suggestion that there might be a window of biologic vulnerability between the onset of menarche, when the breast tissue begins to proliferate monthly, until the completion of the first pregnancy, when breast tissue undergoes terminal differentiation into milk-producing cells [4]. Certainly, the vulnerability of the breast to irradiation is inversely related to age at exposure; this observation has been borne out not only among girls who survived the atomic bomb explosions in Hiroshima or Nagasaki but also among female survivors of Hodgkin's disease who underwent chest irradiation as part of their treatment [4]. In addition, findings from some studies suggest that women who begin drinking or smoking at younger ages are at increased risk for breast cancer [4,9].

The impact of early life exposures on breast cancer development is supported by animal model data. In a series of classic experiments, Russo and Russo demonstrated that rats with

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mammary glands that were “pubertal” and not fully differentiated were more likely to develop breast tumors when exposed to chemical carcinogens than rats whose mammary glands had gone through terminal differentiation [10].

So-called benign breast disease (BBD) is a condition diagnosed in women beginning in the late teenage years. BBD is not a precursor lesion to breast cancer in the same way that a polyp is a precursor to colon cancer. A polyp is a dysplastic lesion that if left in situ has a high likelihood of acquiring additional mutations that will cause it to progress to colorectal cancer. BBD is instead a marker of a proliferative state of the breast that is a “herald” or “early warning sign” that a cancerous process may initiate elsewhere within the breast. Although many studies have shown that a higher proportion of breast cancers will subsequently develop in the same breast in which the BBD was diagnosed, the diagnosis of atypical BBD lesions also confer an increased risk of cancer in the contralateral breast [11,12].

BBD is generally classified into three types of lesions: (1) non-proliferative (without atypia); (2) proliferative without atypia; and (3) atypical hyperplasia [13]. The degree of risk conferred by BBD has been quantified by grading the amount of proliferation and atypia in the BBD lesion [14,15]. Likelihood of developing cancer is dependent on these pathologic categorizations: relative risks (RR) for breast cancer range from approximately 60% increase in risk for nonproliferative BBD without atypia among women with a family history positive for breast cancer, to greater than a fourfold increased risk of breast cancer among women with atypical hyperplasia [12]. Thus, the risk conferred by a diagnosis of BBD is analogous to the much more recognized risk of having a family history of breast cancer (RR of 1.5–3.0) for a mother or sister with breast cancer [12]. Given this strong association, understanding how to decrease the incidence of BBD may have important implications for primary breast cancer prevention.

Study Population

Much of the evidence that has emerged on the relation between adolescent risk factors and BBD is based on data from several large studies: (1) the Women’s Health Initiative (WHI); (2) the Nurses’ Health Study II (NHS); and the (3) Growing Up Today Study (GUTS). The WHI included a series of randomized control trials, with more than 68,000 postmenopausal women enrolling into the WHI between 1993 and 1998 [16,17]. At baseline, women enrolled in the WHI trials were surveyed about past health and reproductive behaviors [17]. The NHS II cohort was established in 1989, enrolling 116,671 women, aged 25–44, who are sent surveys that ask about a wide range of medical and lifestyle issues, every 2 years [18]. The GUTS cohort comprises the offspring of the women in the NHS II; GUTS was initiated in 1996 and enrolled 9,037 girls, aged 9–15 [19]. GUTS has prospectively collected comprehensive childhood and adolescent diet and lifestyle information whereas the NHS II, in contrast, must rely on adult recall of adolescent diet and behavior. Several studies, however, have demonstrated that diet, alcohol use, and physical activity can be measured with reasonable levels of reproducibility and validity many years later [20–22].

Although BBD cases are initially identified in both the NHS II and GUTS by self-report (including a question about whether the diagnosis was “biopsy-confirmed”) on biannual surveys, both studies ask for consent from participants for study pathologists to collect and review the biopsy specimens [22]. BBD samples have been collected in sequential studies in the NHS II. In an

initial study of dietary factors and BBD in the NHS II, 91% of women consented to pathology review and investigators were able to access and review 94% of these samples [18]. In the study of early life factors and BBD, fewer women (77%) consented; however, among this subset, 91% of samples were available for review [22]. A validation study conducted within the NHS II reported high concordance (95%) between self-report of BBD and pathology-confirmed cases [19]. A similar process of pathologic verification is currently underway in GUTS. The pathology review by NHS II pathologists also allows for the lesions to be classified as proliferative or nonproliferative and also notes the presence or absence of atypia, which as detailed previously, has important implications for breast cancer risk.

Anthropometric Factors

Body mass index and weight

In the GUTS cohort, higher BMI as measured during middle school and high school was associated with a slightly decreased BBD risk [23]. Girls with a BMI in the upper two quintiles of BMI had less than half the risk (OR: .46 95% CI: .26–.81) compared with those with a BMI in the lower three quintiles [23]. This is consistent with results from the NHS II, which found that body fat composition measured in children between the ages 5 and 10 to be inversely related to proliferative BBD (P-BBD) risk, with the heaviest children having the lowest risk of BBD (RR: .61, 95% CI: .44–.86) [22]. This protective effect was apparent in later adolescence as well: a BMI ≥ 25 at age 18 was associated with a 33% reduction in BBD risk [22]. These results support the well-documented relationship between higher BMI and reduced risk of premenopausal breast cancer [2,24].

Growth velocity and height

In the GUTS cohort, Berkey et al. reported that a faster rate of growth was associated with BBD risk; girls with peak height velocity > 8.9 cm/year were nearly twice as likely to develop BBD relative to the girls whose peak height velocity was ≤ 7.6 cm/year [23]. Attained adult height (reported at ages 18–27), however, was not associated with BBD in the GUTS cohort [23]. Similarly, Baer et al. did not find any association between height and premenopausal P-BBD, suggesting that rate of growth rather than attained height is the more important factor relating to premenopausal BBD development [22]. Similarly, a study in Denmark that linked school health records with breast cancer registry data reported a RR of breast cancer of 1.17 (95% CI: 1.09–1.25) for each 5-cm increase in height among peripubertal 8- to 14-year-old girls [3].

Age at Menarche and Other Reproductive Factors

In their analysis of risk factors for premenopausal P-BBD in the NHS II, Baer et al. analyzed a range of reproductive characteristics. With the exception of a slightly elevated risk seen among women who were younger at first birth (before age 25) and reported only one to two pregnancies, there were no other significant predictors of a P-BBD diagnosis after adjusting for other covariates [22]. In the GUTS cohort, Berkey et al. did not find any association between age of menarche and BBD risk [23,25]. These findings are consistent with other studies that also have failed to find any relationship between early age of

menarche and P-BBD [17,26,27]. Interestingly, Tamimi et al. reported a differential impact of the pathologic subtype of BBD on the relationship between age at menarche and subsequent breast cancer risk among women in the NHS II [28]. Among women with P-BBD and atypia, those who experienced menarche at age 15 had a risk of .83 (95% CI: .73–.93) relative to those who experienced menarche at age 11 [28]. Women with P-BBD without atypia also had a lower risk of breast cancer (RR: .93, 95% CI: .86–.99), whereas women with nonproliferative BBD who were age 15 at menarche had a higher risk (RR: 1.16, 95% CI: 1.08–1.24) compared with women who were age 11 at menarche [28].

Dietary Factors

Fats, meats, and dairy

In their study of adolescent diet and subsequent P-BBD risk among the NHS II cohort, Baer et al. investigated the association between type of fat and BBD. Those who were in the top quartile of animal fat consumption had a 33% increased risk of P-BBD, whereas those women who were in the highest quartile of vegetable fat consumption had a 27% reduced risk of P-BBD [18]. The highest quartile of monounsaturated fat consumption was associated with a relative risk of 1.52 [18]. No association with total fat consumption was found [18].

Baer et al. also reported an elevated risk of P-BBD (RR: 1.50, 95% CI: 1.01–2.22) among women who ate three or more portions of any meat per day during adolescence, compared with women who ate <1.5 portions of meat per day; specifically, red meat was associated with a 33% increased risk of P-BBD in women who consumed at least two portions/day compared with women who consumed less than a single serving a day [18]. There were no significant associations found between milk or dairy product consumption and BBD [18].

Many of these results are consistent with findings from analyses of adolescent diet and breast cancer risk. In an analysis of the NHS II, Frazier et al. reported a reduced risk (RR: .58, 95% CI: .38–.86) among those in the highest quintile of vegetable fat consumption compared with the first quintile [29,30]. In an updated analysis of adolescent diet and breast cancer in the NHS II, Linos et al. did report that an association with total fat, after controlling for red meat, was no longer significant [30]. Although some studies have reported protective trends associated with increased dairy and milk product consumption during adolescence, these have generally not been significant [29,30]. Michels et al. have examined the impact of early childhood diet, as recalled by the mother, on risk of breast cancer. In her analysis, eating French fries between the ages of 3 and 5 was associated with an increased risk (OR: 1.27, 95% CI: 1.12–1.44), whereas drinking milk was associated with a decreased risk (OR: .90, 95% CI: .82–.99) [31].

Fiber, fruits/vegetables, and nuts

In the NHS II cohort, those in the fourth (highest) quartile of adolescent fiber consumption had a 25% decreased risk of P-BBD compared with those in the bottom quartile [18]. A similar risk reduction (HR: .75, 95% CI: .59–.96) attributed to fiber was reported by Su et al. in an updated analysis of the NHS II data [32]. Although total fiber intake conferred a protective effect, there was little evidence of an association between eating fiber derived

from produce (fruits and vegetables) and P-BBD [18,32]. Eating at least one to three apples a month, however, was associated with almost a 40% reduction in risk (relative to eating less than one per month) [32]. In contrast to BBD, adolescent fiber, fruit, or vegetable consumption have not been associated with subsequent breast cancer risk [29,30].

In the NHS II cohort, women who ate the most nuts (two or more small bags or at least 1 oz. per week) had the lowest risk (HR: .64, 95% CI: .48–.85) of BBD [32]. In an analysis of specific types of nuts, women who had at least one serving of peanuts per week had about 1/3 of the risk of P-BBD compared with women who ate less than one serving a month [32]. Consumption of other types of nuts also showed a similar affect but the amount required was larger: eating two or more servings per week compared with less than one serving a month was associated with a hazard ratio of .62 (95% CI: .44–.88) [32].

Vitamins and micronutrients

In the analysis of adolescent diet and P-BBD risk in the NHS II cohort, there was a significant protective trend for vitamin E and vitamin A [18]. Vitamin E intake during adolescence also appears to be an important factor in relation to risk of breast cancer; in the NHS II, women in the 5th quintile had a relative risk of .61 (95% CI: .42–.89), compared with the first quintile [29]. There was no association between P-BBD and any of the other vitamins and micronutrients examined, including lycopene, retinol, carotene (α and β), vitamin C, and folate [18]. Calcium and vitamin D intake was not reported in this analysis; however, a recent randomized control trial of calcium+D supplementation conducted within the WHI (a postmenopausal population) did not find a lower risk of proliferative BBD among women who were in the intervention arm [33]. Because this study investigated supplementation in an older population of women, these findings do not preclude the possibility that calcium intake during childhood and adolescence might affect BBD. Further studies are needed to better elucidate early life calcium and vitamin D intake/supplementation and BBD risk.

Lifestyle Factors

Alcohol

Berkey et al. assessed the frequency, amount, and binge drinking among females ages 16–23, and diagnosis of BBD [19]. In this analysis, more than a fivefold risk of BBD was associated with drinking 6 to 7 days per week and more than a threefold increased risk associated with drinking 3 to 5 days per week, relative to women who drank less than once a week or did not drink at all [19]. No effect was seen for binge drinking. Baer et al. also reported a slightly increased risk of premenopausal P-BBD in women who drank between the ages of 18 and 22, although risk was not dose-dependent [22]. Compared with nondrinkers, women in the NHS II who drank ≥ 10 grams alcohol per day between ages 18 and 22 had a RR of 1.25 (95% CI: 1.02–1.54), women who drank 5 to 9.9 g/day had an RR of 1.31 (95% CI: 1.07–1.60), women who drank 1.5 to 4.9 g/day had an RR of 1.23 (95% CI: .95–1.60), and women who drank .1 to 1.4 g/day had an RR of 1.23 (95% CI: 1.01–1.50) [22].

A recent analysis examining the relationship between several risk factors for BBD among those with a family history of breast cancer suggests that alcohol might be an important modifier of

BBD risk in this population [25]. Alcohol consumption was not associated with an increased risk of BBD in women without a family history of either breast cancer or BBD; however, among women with a mother, aunt, or grandmother with breast cancer, drinking seven alcoholic beverages each week during adolescence was associated with an increased risk of BBD (OR: 2.28, $p = .01$) relative to women who did not report any alcohol consumption [25]. Among women with a family history of either maternal BBD or breast cancer, those who were in the uppermost quartile of alcohol use for their specific age (one or more servings/week at age 16, two servings/week at age 18, three servings/week at age 19) had an increased risk of BBD (OR: 2.27, $p = .03$) compared with women with a negative family history who did not consume alcohol [25].

Lifetime alcohol consumption is one of the most well-established lifestyle factors associated with an increased breast cancer risk [34,35]. However, the evidence linking adolescent alcohol intake to breast cancer later in life is mixed. Although some studies have reported an increased risk associated with alcohol use at younger ages, the relative contribution of adolescent alcohol consumption is still unclear [4]. In the NHS II, there was no association between alcohol use between the ages of 15 to 17 or 18 to 22 and breast cancer [36]. A recent case-control study assessing alcohol consumption between the ages of 15 and 20 also did not find women had an increased risk of breast cancer diagnosed before the age of 50 [37].

Physical activity

There is little evidence that physical activity (PA) during childhood and adolescence has a meaningful impact on BBD development. Baer et al. detected a protective effect (RR: .65, 95% CI: .50–.84) in women who performed “strenuous” PA 4 to 6 months a year while they were in high school; however, this effect was not apparent in women who reported more frequent strenuous activity during this time [22]. A recent analysis conducted within NHS II explored lifetime PA, including frequency, duration, and type, reported a relationship between increased PA, and decreased P-BBD risk [38]. The primary exposure in this study, however, was lifetime PA and not early life PA. Although PA during adolescence was incorporated in the composite PA metric, it is unclear to what degree adolescent PA contributed to the protective trend, relative to and in combination with, activity during adulthood. The beneficial impact of PA during childhood and adolescence on breast cancer risk is also uncertain; although some studies have found that increased PA does reduce risk, many of analyses fail to properly adjust for BMI a potential confounder [39].

Smoking

Although the overall association linking smoking to breast cancer risk is weak, there are some studies that suggest that women who initiate smoking many years before their first pregnancy do in fact have an increased risk of breast cancer [9]. Given this evidence, it is plausible that BBD risk might be increased in women who start smoking during adolescence. In their study of P-BBD risk in premenopausal women, after adjusting for several other risk factors, Baer et al. did not find any significant association between smoking and BBD risk [22]. These results are consistent with those from an analysis in the WHI, in which the authors reported no increased risk of postmenopausal,

benign proliferative epithelial disorder among women who began smoking as teenagers [40].

Adolescent risk factors for BBD risk for the most part mimic the effects observed for breast cancer. However, among those factors that are modifiable, a reduced rate of BBD may herald a reduced incidence of breast cancer in later life and therefore BBD may be an important surrogate in prevention intervention trials. Potentially modifiable dietary intake may include higher intake of vegetable oils, nuts, vitamin E, and fiber and lower consumption of animal fat, red meat, and alcohol. Increased physical activity may also reduce risk. However, these findings should be interpreted cautiously given some of the methodologic challenges that exist, including exposure and outcome misclassification, both differential (mainly from bias related to recall of exposures from many years earlier) and nondifferential. Additionally, studies often use analysis-specific categorizations (i.e., quartiles based on the distribution of the exposure in a particular cohort) or define key covariates differently (i.e., definitions of physical activity), which can make it difficult to compare results across studies. Some studies have only identified cases of BBD among premenopausal women. It is possible that several early life factors might confer either a protective or harmful effect on postmenopausal BBD; continued follow-up in these studies will better appreciate any differences between pre- versus postmenopausal risk. However, a life-course framework for interventions that recognizes the importance of healthy choices during adolescence offers some promise of making some inroads into the hardship and premature death associated with the diagnosis of breast cancer.

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