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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.

IMPLICATIONS AND 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) nonproliferative (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 $\geq$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 $\leq$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 heath 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