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Commentary

The contribution of the environment (especially diet) to breast cancer risk

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Abstract

Environmental factors play an important role in breast carcinogenesis. Opportunities for prevention are limited, however, because most of the known or suspected risk factors are not targets for modification. Dietary factors have generally not emerged as crucial contributors to mammary tumor causation. We still appear to be missing a critical piece of the breast cancer puzzle because we can only explain a moderate proportion of international and national variation in breast cancer rates. Research needs to pursue new avenues, focusing on exposure windows that have not yet been sufficiently explored, such as events between conception and adolescence, and on modifiable risk factors that show large variation within or between populations.

Keywords: diet, epidemiology, estrogens, growth factors, nutrition

Introduction

What do we know about the causes of breast cancer at the beginning of the third millennium? Relatively little – disappointingly little. Despite the number of smart minds and research dollars invested in breast cancer research, we have disentangled amazingly little of the maze of breast cancer causation. Known or suspected risk factors explain only a modest proportion of the international and within-population variation in worldwide breast cancer rates, less than for other diseases including some other cancers [1]. Worse than this is that, although we know little about modifiable risk factors, these very factors may be our best hope for successful preventive efforts.

Although genetic factors undoubtedly play a role in mammary carcinogenesis, and susceptibility genes such as *BRCA1* and *BRCA2* have been identified, environmental factors must also contribute to breast cancer etiology. How do we arrive at this insight? Migrant studies have taught us that a change in environment affects risk for breast cancer. Breast cancer rates among immigrants are similar to those observed in their newly adopted host country, even if substantially different from their native country. The timeframe of adjustment remains unclear; some studies suggest that breast cancer rates change within the same generation, whereas others indicate that it takes a generation for rates to conform to those of the new host country. This inconsistency may be a function of women's age at migration; if migration occurs during childhood and adolescence, then the chances may be greater that the adjustment is triggered within the same generation.

What we think we know

To the best of our current knowledge, reproductive factors such as early menarche, nulliparity, older age at first birth, and older age at menopause play important roles in the formation of mammary tumors [2,3]. Although these may be the most important factors in breast cancer etiology we have thus far identified, they are not targets for preventive

strategies. Reproductive risk factors point toward endogenous estrogens as likely players in the initiation, progression, or promotion of breast cancer. Other important factors identified in breast carcinogenesis are indicators of growth, including height, birth weight, adult weight gain, body mass index, and waist circumference [4–6]. Obesity and weight gain are associated with high estrogen levels (which in turn may explain the association with breast cancer risk), but accelerated fetal growth and tall height may indicate an important role for other growth factors, such as insulin-like growth factors, in the etiology of mammary carcinoma. In contrast, among premenopausal women, high body mass index has been related to a reduced risk for breast cancer [7]. Although the underlying mechanisms have not yet been disentangled, it is possible that compromised ovarian function among obese women contributes to this effect.

Exogenous hormones appear to affect mammary tumor formation only after endogenous levels begin to decrease. Oral contraceptives do not appear to impact on breast cancer risk. Postmenopausal hormone use, however, has been associated with a modest but consistent increase in breast cancer incidence [8]. Exogenous replacement of steroid hormones appears to elevate risk for breast cancer to the level that would be expected if endogenous production had not decreased. The opposed hormone regimen of estrogen plus progesterone appears to increase the risk beyond that of estrogen alone. The decision to use postmenopausal hormones, however, should be based on the presence of menopausal symptoms rather than on possible effects on cancer or cardiovascular disease, and thus postmenopausal hormone use is not a suitable target for breast cancer prevention.

Some possible modifiable environmental risk factors for breast cancer have not evolved as major players in the causal web after careful scrutiny. Among such factors are smoking and physical activity, which could become prevention targets, but evidence to support their role in mammary carcinogenesis is inconsistent.

The role of diet

Given the high incidence of breast cancer and the fear that many women have of such a diagnosis, dietary risk factors would be ideal candidates for modification and prevention efforts. Unfortunately, diet during adult life appears to play a minor role if any in breast cancer etiology. Although fat intake had been suspected to influence breast cancer risk, this hypothesis has largely been disproved by large observational studies [9]. Evidence regarding whether any of the subtypes of fat may affect mammary carcinoma is inconclusive. No foods, specific nutrients, or vitamin supplements were implicated by repeated testing in epidemiologic studies, and no dietary factors have been convincingly linked to breast cancer incidence [10]. Phytoestrogens have been studied because of their antiestrogenic effect, and some studies have shown a reduced risk for breast cancer associated with soy intake [11]. Phytoestrogens also have estrogenic effects, however, and may increase breast tissue proliferation [12]. Before we can encourage women to stock up on tofu and soymilk, more convincing evidence is needed.

The only fairly well established dietary risk factor for breast cancer is alcohol; small but consistent increase in risk has been associated with regular consumption [13]. Similarly evident, but not yet as frequently studied, is the modification of the effect of alcohol by folate. Several studies have shown that, among women with high folate intake, the alcohol–breast cancer association is weakened further. With the recent adoption of folic acid fortification of grains in the USA, any major deficits in the population should be reduced, but higher doses of folate might be required to achieve the desired effect. Small relative risk estimates, however, such as that for the alcohol–breast cancer link, may be the result of residual confounding, even if consistent across studies. Women who consume alcohol are likely to differ in many aspects from women who do not, and it is almost impossible to account sufficiently for these differences in statistical analyses.

Circulating insulin levels and hyperinsulinemia with insulin resistance increase the risk of breast cancer independent of adiposity [14,15]. Plasma insulin regulates bioavailable insulin-like growth factor-I concentrations and affects plasma estrogen [16]. To what extent diet and physical activity (in particular early in life) may influence these pathways and provide opportunities for breast cancer prevention remains to be explored [16].

The importance of obesity and weight gain in mammary tumorigenesis indicates that a positive energy balance increases risk. Whether diet composition modifies this association is not clear. The work of Ellison and coworkers [17,18], however, indicates that a negative energy balance can compromise ovarian function independent of nutritional status via high energy expenditure. Conversely, it is likely that severe caloric restriction, which has been shown in the animal model to reduce cancer rates, will reduce breast cancer incidence.

The general lack of association between diet and breast cancer in epidemiological studies has to be interpreted cautiously, because diet is assessed with considerable measurement error in observational studies, and our current diet assessment instruments may not provide sufficiently valid and reliable data to detect small to moderate associations with disease. Similarly, variation in diet within the populations studied may not be sufficiently large to overcome the measurement error that is inherent in self-reported dietary information.

Furthermore, inferences cannot be made for dietary regimens more extreme than vegetarianism or high fruit, vegetable, and fiber consumption. Most participants in epidemiologic studies follow a diet without major restrictions. Thus, it is not known whether a more restricted diet might have a profound effect on breast cancer incidence. Such dietary regimens are more common in Europe and largely prescribe the use of fresh, 'living', and whole foods, including freshly ground whole grains, plant proteins, and a large variety of organic raw vegetables and fruit [19–22].

New avenues

Although the search for dietary risk factors for breast cancer during adulthood has been disappointing, this does not preclude a possible association between breast cancer and diet earlier in life. Perhaps we have focused on the wrong window of exposure. For example, the consistent correlation of height with breast cancer incidence points toward an earlier origin of breast cancer than we have thus far studied in depth. Height is partly genetically determined, but much variation is due to environmental factors such as maternal nutrition during pregnancy and diet during childhood and adolescence. The importance of the intrauterine environment is also supported by accumulating evidence on the role of birth weight in breast carcinogenesis [23,24]. It is likely that such factors operate via growth factors, in particular insulin-like growth factors.

Thus, data are needed on diet during childhood and adolescence and its relation to mammary carcinoma [25]. Dietary information early in life is difficult to collect, however. Retrospective data may be affected by considerable differential and non-differential measurement error. Linking prospectively assessed diet information to breast cancer incidence data exceeds the working life of an epidemiologist. Nevertheless, although fat intake during adult life has largely been dismissed as an important risk factor for mammary tumors, fat intake during childhood or adolescence, for example, might be of relevance. This has not yet been sufficiently studied.

Similarly, other factors assessed in adult life that were not related to breast cancer risk might well affect risk at earlier stages. Physical activity in childhood and adolescence, for example, might be of greater relevance than that during adult life.

Conclusion

Environmental factors must play an important role in breast cancer causation. Reproductive factors and growth trajectories have been identified as fundamental contributors to breast carcinogenesis. Although the search for risk factors has been vigorous, we are still missing some important pieces of the puzzle. Of particular interest is the identification of potentially modifiable risk factors. Dismissing outright the role of adult diet as an important contributor to breast cancer risk should be considered with caution, given the power of the inherent measurement error in diet assessment to obscure small but important associations. Future research efforts should focus on under-studied windows of opportunity for exposure, such as the perinatal phase, childhood, and adolescence. Because cancer is a multifactorial process, the first seeds might be sown earlier in life than we have thus far appreciated.

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