Review

Towards an integrated model for breast cancer etiology

The lifelong interplay of genes, lifestyle, and hormones

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Abstract

While the association of a number of risk factors, such as family history and reproductive patterns, with breast cancer has been well established for many years, work in the past 10–15 years also has added substantially to our understanding of disease etiology. Contributions of particular note include the delineation of the role of endogenous and exogenous estrogens to breast cancer risk, and the discovery and quantification of risk associated with several gene mutations (e.g. *BRCA1*). Although it is difficult to integrate all epidemiologic data into a single biologic model, it is clear that several important components or pathways exist. Early life events probably determine both the number of susceptible breast cells at risk and whether mutations occur in these cells. High endogenous estrogens are well established as an important cause of breast cancer, and many known risk factors appear to operate through this pathway. Estrogens (and probably other growth factors) appear to accelerate the development of breast cancer at many points along the progression from early mutation to tumor metastasis, and appear to be influential at many points in a woman's life. These data now provide a basis for a number of strategies that can reduce risk of breast cancer, although some strategies represent complex decision-making. Together, the modification of nutritional and lifestyle risk factors and the judicious use of chemopreventive agents could have a major impact on breast cancer incidence. Further research is needed in many areas, but a few specific arenas are given particular mention.

Keywords: breast cancer, epidemiology, etiology, prevention

Introduction

The search for specific breast cancer risk factors has been stimulated by the large differences in rates of the disease observed among countries [1], and by changes in rates in migrating populations [2,3] and within countries over time [4,5].

Several breast cancer risk factors have been known for many years [6,7]. Increasing age is one of the strongest risk factors. Having a family history of breast cancer increases a woman's own risk; an earlier age at diagnosis and greater number of affected relatives augments her risk. Early age at menarche, late age at menopause, nulliparity and late age at first birth modestly, but consistently, increase risk [8]. Breastfeeding, particularly for long durations, is associated with lower risk [9]. Both height and postmenopausal body mass index are positively associated with disease, while premenopausal obesity is inversely associated, at least in Western populations [10]. A personal history of benign breast disease, particularly with atypia [11,12], and having dense breasts on a mammogram [13] are both associated with substantial increases in breast cancer. Alcohol intake, the only dietary factor currently well established, also is associated with an increase in risk, although the relationship is modest [14].

Over the past 10–15 years substantial additional progress has been made in delineating risk factors for breast cancer. Contributions of particular note include the discovery of several gene mutations (e.g. in *BRCA1*, *BRCA2* and *PTEN* genes) and quantification of the risk

associated with them [15,16]. Although long proposed [17], both observational studies and randomized trials have confirmed and quantified the important role of estrogens, both exogenous and endogenous, in breast cancer etiology. Specifically, circulating estrogen levels in postmenopausal women are positively associated with risk [18], and the use of therapies, such as tamoxifen, that block the binding of estrogen to the estrogen receptor at the breast decrease the risk of disease [19–21]. The use of postmenopausal estrogens, particularly when combined with a progestin, also increases the disease risk in women [22–25]. Furthermore, risk increases with duration of use of postmenopausal hormones. Although factors have long been suspected to influence breast carcinogenesis during early life, the hypothesis that even *in utero* exposures influence risk is much more recent [26] and has been increasingly supported [27,28]. However, many methodologic challenges exist in confirming these ideas. Finally, progress has been steady in further delineating the probable protective role of physical activity [29] and in evaluating more recent dietary hypotheses such as folate intake [30].

Known and suspected risk factors are presented in Table 1, and approximate strengths of association are provided for specific comparisons. Note, however, that these comparisons are somewhat arbitrary because many of these risk factors are continuous variables and the relative risks will depend on the magnitude of the contrasts chosen for comparison (e.g. a 5-year difference versus a 10-year difference in age at menopause). While many of these risk factors are established with a high degree of certainty, some, such as high prolactin levels and low physical activity, will require further research for confirmation.

Table 1

Epidemiology of breast cancer: abbreviated risk factor summary

Risk factor	Direction of effect[a]
Well-confirmed risk factors	
Family history in first-degree relative or genetic predisposition (e.g. *BRCA1*)	↑↑
Height	↑
Benign breast disease	↑↑
Mammographically dense breasts	↑↑
Parity	↓
Age at first birth > 30 years versus at < 20 years	↑↑
Lactation (longer durations)	↓
Menopause at > 54 years versus at < 45 years	↑↑
High endogenous estrogen levels	↑↑
Postmenopausal hormone use	↑
Ionizing radiation exposure in childhood	↑↑
Menarche at < 12 years versus at > 14 years	↑
High body mass index (postmenopausal)	↑
High body mass index (premenopausal)[b]	↓
Alcohol use (~ 1 or more drinks/day)	↑
Probable relationship exists, based on substantial data	
Current oral contraceptive use	↑
Physical activity	↓
Limited study to date	
High prolactin levels	↑↑
High premenopausal insulin-like growth factor I levels	↑↑
In utero exposures	↑
Nonsteroidal anti-inflammatory drug use	↓

[a] Arrows indicate approximate magnitude of the relationship: ↑, slight to moderate increase in risk; ↑↑, moderate to large increase in risk; ↓, slight to moderate decrease in risk; ↓↓, moderate to large decrease in risk.
[b] In Western countries – data are less consistent in other lower risk populations.

A biologic model of breast cancer etiology

Mechanisms linking risk factors to the development of breast cancer are known with varying levels of certainty. Although it is difficult to integrate all epidemiologic data into a single biologic model, it is clear that several important pathways or components exist. Of critical importance in breast cancer etiology is the timing of exposure in a woman's life. For example, exposures that occur early in life can have an influence on risk that is quite different from that resulting from the same exposure occurring years later (e.g. radiation exposure [31,32]). In addition, a single exposure can have opposing influences on risk at different times in life (e.g. parity [33]).

Early life events probably determine both the number of susceptible breast stem cells at risk and whether mutations occur in these cells. The relatively consistent positive association of risk with birthweight and the well-confirmed association with height (a marker of childhood nutritional status and associated growth factors) strongly suggest an influence of early events, perhaps even those occurring *in utero*, to subsequent risk. Mammographic breast density may, at least in part, be a marker of the number of at-risk cells in the breast. Mutations in these cells can be inherited (e.g. mutations in *BRCA1* or *p53*) or acquired, such as by exposure to ionizing radiation. Oxidative damage from endogenous metabolism is hypothesized to contribute to DNA damage [34] but the importance of this mechanism to breast carcinogenesis is not clear. To the extent that oxidative damage is important, dietary antioxidants might reduce risk and their role may be particularly important

early in life. Low availability of folate (and its cofactors such as vitamin B6 and B12), particularly in conjunction with high alcohol intake, can lead to abnormal DNA synthesis and repair and aberrant DNA methylation [35], and hence may play a role in breast carcinogenesis.

Pregnancy has a particularly complex influence on subsequent breast cancer risk. For about a decade after the pregnancy, risk is increased, probably due to the hormonal stimulation of already initiated breast epithelial cells [33]. In contrast, risk is reduced over the long term, possibly by rendering the breast substantially less susceptible to somatic mutations [36]. An earlier age at first pregnancy also is associated with a reduction in risk as it may shorten the time (from menarche to first birth) when the breast is particularly susceptible to mutations.

As already noted, high endogenous estrogen levels in postmenopausal women are now well established as an important cause of breast cancer, and many known risk factors appear to operate through this pathway. The additional contribution of cyclical estrogen exposure (as opposed to continuously high levels) is less clear, and much evidence indicates that progestins add to breast cancer risk [22–25]. Factors that increase lifetime exposure to estrogens and progesterone include early age at menarche, regular ovulation, and late age at menopause. Breastfeeding and being overweight during the woman's young adult life decrease the ovulatory frequency, and this probably accounts, at least in part, for their protective effects. In addition to its role in folate absorption and metabolism, alcohol intake increases endogenous estrogen levels that may contribute to the observed increase in risk among regular drinkers [37,38]. The modest increase in risk of breast cancer among current or recent users of oral contraceptives is probably due to their estrogenic (and probably progestational) effects [39]. In postmenopausal women, both adiposity and the use of postmenopausal hormones are primary determinants of estrogen exposure, and also increase breast cancer risk. Increases in physical activity can delay the onset of menarche and can also reduce the risk of breast cancer by helping to control weight gain and by modifying bioavailable hormone levels. Other growth factors in addition to estrogens, particularly insulin-like growth factor I [40] and prolactin [41], are also likely to contribute to breast cancer risk, although these relationships are less firmly established.

Importantly, estrogens (and probably other growth factors), by their mitotic effects on breast cells, appear to accelerate the development of breast cancer at many points along the progression from early mutation to tumor metastasis. By increasing cell proliferation, estrogens may also increase the probability that DNA damage is not repaired, resulting in mutations [42]. In addition, estrogens may be directly genotoxic, through their reactive metabolites [43], although evidence for this mechanism is more limited. Although exposure to high estrogen levels early in life increases risk decades later, reduction in levels late in life can reduce risk rather quickly, whether this exposure is via oophorectomy, cessation of postmenopausal hormones, or the administration of anti-estrogens. This broad outline of breast carcinogenesis, generally similar to that previously described by other scientists (see, for example [44,45]), seems unlikely to change substantially in the future, although further research will certainly fill in details of the aforementioned relationships and will identify other contributing factors. For example, we will probably identify genetic polymorphisms that contribute to variation in endogenous levels of, or responsiveness to, estrogens and other growth factors. Also, other molecular mechanisms such as DNA repair and apoptosis are thought to be important in carcinogenesis in general, but the extent to which exogenous factors influence these processes in the context of human breast cancer is not yet known.

Current opportunities for primary prevention of breast cancer

A number of breast cancer risk factors are now well established and a subset of them, such as reproductive factors and postmenopausal obesity, account for a large part of the high breast cancer rates seen in affluent Western populations [46–48]. However, this knowledge does not necessarily translate easily into strategies for breast cancer prevention. Several risk factors (such as age at menarche or family history), while well established, are difficult or impossible to modify; some (such as alcohol intake) are well established but carry complex risks and benefits; and other risk factors (such as high vegetable and fruit consumption) are not as proven, but have other important benefits that justify the strategy, with reduction in breast cancer being a possible additional benefit. Known risk factors for breast cancer are also modest in magnitude, with relative risks generally in the range of 1.3–1.8 for attainable changes. Although these associations are not strong, they remain important. When considering primary prevention, even modest changes at the individual level can produce substantial changes in the population rates of disease [49].

Encouraging physical activity early in life is desirable and, through a modest delay in age at menarche [50,51], should contribute to some reduction in breast cancer risk. Avoiding weight gain during adult life plays an important role in reducing the risk of postmenopausal breast cancer, as well as many other chronic diseases. Individual women can minimize weight gain by exercising regularly and moderately restraining caloric intake. It is important to note that while some strategies for breast cancer prevention, such as weight control, can be implemented by individuals

themselves, the health system, governments, and society as a whole also can, and should, play a role. For example, the incorporation of increased physical activity into daily life would be greatly facilitated for both children and adults if far greater emphasis was placed on daily physical activity in schools and the provision of safe and easily accessible exercise facilities and environments (e.g. cycle paths) in the community and at the workplace.

Alcohol consumption has a complex mix of desirable and adverse health effects, one of which is an increase in breast cancer. Individuals should make decisions considering all the risks and benefits, but for a middle-aged woman who drinks alcohol on a daily basis, reducing intake is one behavioral change that is likely to reduce the risk of breast cancer. No other specific aspects of diet are well established to influence breast cancer risk. However, several dietary habits, such as high consumption of fruits and vegetables and the replacement of saturated fats and trans fats with monounsaturated fat, are important for reducing risk of heart disease [52], and could also prove to modestly decrease the risk of breast cancer.

Postmenopausal hormone use involves a complex trade-off of benefits and risks. From the standpoint of breast cancer, the best strategy would be to use estrogens for only a few years for menopausal symptoms, if at all. In particular, the combined use of estrogen plus progestin, associated with a greater risk increase, should be avoided or minimized. The range of other pharmacologic options to treat osteoporosis has been rapidly expanding, several of which (e.g. raloxifene [20,53]) may simultaneously reduce the risk of breast cancer. Few, if any, similarly effective options exist for alleviating menopausal symptoms, however, and research is needed to provide alternatives to currently available hormone therapy.

With the demonstration that tamoxifen, and probably other selective estrogen receptor modulators (SERMs), can be effective in the primary prevention of breast cancer [19,20], chemoprevention has become an option for women at elevated risk. A number of other pharmacologic agents, such as aromatase inhibitors [54], are being evaluated at present and are likely to increase the alternatives in the relatively near future. Identifying who would most benefit from these agents, all of which to date have potential adverse consequences associated with their use, remains an important issue.

In summary, available evidence provides a basis for a number of strategies that can reduce risk of breast cancer, although some of these represent complex decision-making. Together, the modification of nutritional and lifestyle risk factors and the judicious use of chemopreventive agents should have a major impact on incidence of this important disease.

Future research in breast cancer etiology

Further research is needed in many areas, but a few specific arenas deserve particular note. During most of the past several decades, epidemiologists have largely focused on adulthood exposures and risk of breast cancer. With increasing recognition that early life exposure also plays a role, a continued and expanded emphasis needs to be placed on the prenatal period through the premenopausal years. A number of innovative studies have been conducted [55,56]; more are needed, however, as is a greater commitment to the conduct of very long-term prospective studies that start early in life. An emphasis on the validation of early exposure assessments is also needed.

The continued incorporation of advances in genetics and molecular biology into epidemiologic studies is a priority. The evaluation of gene polymorphisms and haplotypes, particularly in conjunction with environmental and other lifestyle exposures, will further our understanding of the causal nature of a number of observed associations, as well as our understanding of breast cancer etiology more generally. In addition, while most early studies considered breast cancers as a single disease entity, several studies [57,58] have shown that risk factors vary by estrogen receptor status and progesterone receptor status of the tumor. Further molecular characterization of breast tumors will again provide substantial insight into etiology and a greater understanding of certain exposure/breast cancer relationships (e.g. an exposure that is weakly or inconsistently associated with breast cancer risk overall may be strongly associated with a particular tumor subtype). Many of these efforts, however, will require very large studies, or the pooling of data across studies.

The availability of effective chemopreventive agents, such as SERMs, has raised many questions about the optimal criteria for use of these drugs; that is, how to determine which women are at high risk and hence the best candidates for their use. Until recently, risk has been primarily based on an evaluation of family and reproductive history and a history of benign breast disease [59]. New information on risk based on genotype, mammographic density [13], and serum hormone levels [18,53] should now allow a much more powerful prediction of risk for an individual woman – development and validation of these models is critical.

A number of other possible candidates for (chemo)prevention exist. For example, a preventive role for aspirin and other nonsteroidal anti-inflammatory medications has been suggested [60]. Further assessment of these associations with breast cancer risk, as well as intermediates such as mammographic density, may provide further avenues for prevention. The role of diet, such as folate and vitamin D intake, needs further evaluation. Other

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areas of emphasis should include the identification of lifestyle factors that can improve, and biologic markers that can predict, breast cancer prognosis.

Competing interests

None declared.

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