Breast Cancer Prevention Strategies

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The ultimate goal of breast cancer prevention strategies is to reduce the incidence of this disease in populations. Greater understanding of recently identified associations of lactation, alcohol, exercise, and diet with breast cancer.

Introduction

Apparent continuing increases in the incidence of breast cancer have stimulated interest in gaining a greater understanding of the development of this disease so that it may be possible to prevent it.[1] At present, considerable attention is being focused on the inherited genetic changes that play important roles in perhaps 10% of cases of breast cancer among American women. Although investigation of the functional implications of these changes should provide useful information about broad developmental processes in breast cancer, a more general focus on our emerging understanding of this process is critical to addressing the ultimate public health goal of breast cancer prevention: the reduction of the incidence of breast cancer in the entire American population.

A broad strategy to address this goal is clear: to identify, understand, and act broadly on manipulable causes of breast cancer. Pursuit of this strategy requires that the following challenges be addressed:

1. Identification of (new) specific manipulable causes. For example, dietary factors and exercise appear to be important causes, but exactly which dietary constituents are important and when in the developmental causal sequence these constituents and exercise exert their effects are unknown.
2. Greater understanding of the developmental causal sequence. More inclusive, more comprehensive models are needed, along with targeted studies to explain how apparent causes (eg, lactation, alcohol) fit these models. This understanding is critical to manipulating usual physiology to prevent clinical cancers.
3. The development of sound biologic, behavioral, and social data as bases for broad action.

This article will explore each of these challenges in turn.

Manipulable Causes of Breast Cancer

A discussion of manipulable factors associated with the development of breast cancer serves to introduce and emphasize the importance of hormonal physiology in the pathogenesis of this disease and especially in its prevention.

Three Initiators

Known manipulable risk factors--in particular, three that act as initiators--are relevant for a minority of the population. Specifically, inherited genetic susceptibility appears to be important in approximately 10% of cases, and thus, manipulation of these changes and their functions (when defined) is likely to be of limited benefit in the general population. For example, the extreme intervention of prophylactic mastectomy is acceptable only in genetically at-risk individuals.

Radiation is a second well-described initiator of breast cancer,[2] and limitation of exposure, particularly of the prepubertal breast through judicious use of therapeutic radiation for malignancy,[3] is an important preventive strategy. Again, however, this strategy can be applied to only small numbers of women. Nevertheless, there remains the possibility that excess sensitivity to lower doses of diagnostic radiation may be an important initiator of breast cancer in larger numbers of women.

Finally, cigarette smoking seems to be a likely initiator.[4] For many health reasons, major efforts to reverse the upward trend in smoking among younger female age groups are well justified.

More Recently Identified Associations
Four more recently identified associations have potentially greater application to populations. Lactation for total periods of more than 6 months appears to be associated with a reduced risk for premenopausal breast cancer. This association has obvious widespread application, and is particularly intriguing because of its physiologic mechanism of action (discussed further below).

It appears likely that the basis for the associations of alcohol and exercise with breast cancer is hormonal modulation, whereas the possible basis for the association of fresh fruits and vegetables with breast cancer is uncertain. There appear to be broad health benefits and risks of both alcohol and exercise, and thus, the specifics of how these factors work in breast cancer are more important.

The possibility that certain dietary constituents (fruits and vegetables) are protective is also of significant interest because of their direct applicability to public health. Although these associations for alcohol, exercise, and fruits and vegetables are not strong (twofold increased risk for high alcohol intake and a halving of risk for exercise and for high fruit and vegetable consumption), they are worthy of attention because they can be altered.

**Developmental Biology of Breast Cancer**

There has been a long-standing emphasis on the observation that many breast cancers in individual Western women occur in the absence of attributable risk factors. Brinton suggested that only half of the disease can be explained on the basis of widely accepted risk factors. This perspective has left the impression that little is known about the development of breast cancer, and this impression has been reinforced by the fact that comprehensive models have rarely been presented or discussed.

Despite these circumstances, it is becoming clearer that we do have a broad understanding of the major physiologic factors in breast cancer, which provides a sound basis for prevention strategies. The initiation, promotion, progression model from skin carcinogenesis experiments appears to be a less useful model for breast cancer than is a physiologic model. The basic skin-derived model, however, is useful in emphasizing the multistep nature of malignancy development and the prolonged multiyear nature of the process.

There now appear to be two key physiologic variables in breast cancer: breast lobular maturation and hormone exposure of breast tissue. Together, these variables provide a rational model that can account for many epidemiologic observations and that can form the basis for prevention strategies. Although the importance of lobular maturation and hormonal exposure has been recognized increasingly over the last 20 years, there remains the perception that these variables (and their associated risk factors) do not provide a complete or satisfying explanation for the disease.

Perhaps the major reason for this perception is the fact that, in a majority of breast cancer cases, no exposure can be identified that is considered critical in initiating the malignant transformation of breast epithelia. Inherited genetic changes, radiation, and perhaps cigarette smoking, described earlier, may each represent such exposures or act as initiators, but together they appear to play a role in only a minority of cases. (Clearly, the details and extent of impact of these factors deserve further intense study.) This unidentified exposure-cause may not be as critical numerically as has been suggested. Some experts suggest that, together with spontaneous mutation rates, these exposures provide adequate explanation for observed rates.

**Lobular Maturation**

The first critical physiologic variable—lobular maturation—was so recognized by Russo and Russo in animal studies. The supporting observation in humans, however, preceded this laboratory work by a decade. Based on international data, MacMahon et al clearly laid out the powerful relationship of age at first full-term pregnancy and breast cancer risk later in life. How powerful a risk factor this age is found to be clearly depends on the referent group. In a relative risk of 1.0 is assigned to nulliparous women. Note that a woman completing her first pregnancy at age 15 has approximately 25% the risk of a similar woman who completes her first pregnancy at age 35. Perhaps the obvious occurrence of significant hormonal perturbations during and after pregnancy (which do have a recognizable impact on breast cancer risk) has detracted from an appreciation of the explanation for this strong relationship recognized by the Russos. In elegant work following the suggestion that lobular maturation and permanent differentiation of breast terminal end-bud cells were critical events in susceptibility to breast malignancy in animals, the Russos studied the process in human tissues. The coherent picture suggested by their work is very compelling. Four types of breast lobules are seen in human breasts. Lobule 1, which is the dominant type in women before a pregnancy (and in nulliparous women throughout their premenopausal
years), is an undifferentiated structure with only several ductules. Cells in these lobules appear to exhibit increased sensitivity to malignant transformation, and appear to be the cells of origin of the most common breast cancers of the ductal type. The hormonal proliferative stimulation of menstrual cycles causes some type 1 lobule cells to begin to differentiate; prior to pregnancy, young women have a mixture of types 1 and 2 lobules, but the majority are type 1. The profound and sustained hormonal stimulation of a full-term pregnancy results in differentiation of the cells in most breast lobules to semidifferentiated (lobule 2) or fully differentiated (lobule 3) states. Although lobular structures with the appearance of types 1 and 2 are seen in postmenopausal women, these are, in fact, terminally differentiated structures without the sensitivity to malignant transformation of these types seen in younger women. This theory of lobular development clearly suggests that a full-term pregnancy is a defining event for breast cancer risk expressed perhaps 2 decades later. It is noteworthy that during the 10 to 20 years following a first pregnancy, breast cancer risk is first greater and then lower than that for nulliparous women (Figure 2); consequently, for premenopausal women, age at first full-term pregnancy is not an obvious risk factor.[15]

**Hormonal Exposure**

The second critical physiologic variable in breast cancer is hormonal exposure.[12] The specific details are unclear, particularly with respect to the interactive effects of estrogenic and progestogenic hormones (and this has detracted from an appreciation of the broad significance of hormonal perturbations). However, a coherent picture has emerged (Table 1). The basic critical observations are shown in Figure 3. On a logarithmic scale, there is a linear increase in breast cancer incidence until menopause, after which a less pronounced increase continues. The message from the bend in the curve is clear: Menstrual cycling significantly affects the incidence of breast cancer (reducing the rate of increase seen prior to menopause). Using epidemiologic data demonstrating the protective effect of early or artificial menopause, Pike et al developed the branches seen on the incidence curve (Figure 3).[16] What other messages can be derived from this curve are less clear. Given the long natural history of breast cancer--10+ years--the establishment of a rapid increase in incidence by the third decade of life suggests that events in women's lives before age 20 set the stage for disease appearance 1 to 3 decades later.

Studies suggest that most of the benefit from ovariectomy is not lost with postsurgical estrogen replacement therapy.[16] The log/log incidence curves for breast cancer before menopause are linear in different populations (when good data are available) but have profoundly different slopes. Looked at in another way, using average incidence figures, there are large differences, with Asian populations showing a relatively low incidence (Figure 4).[17] A rational physiologic explanation for these Western-Eastern differences in incidence is found in the results of hormonal studies of different designs, which clearly demonstrate that Asian women have lower estradiol levels. (Figure 5). [18-21] The impact of such differences early in life offers a reasonable explanation for the difference in slopes of the age-incidence curves.

Various other risk factors for breast cancer are associated with similar hormonal changes, usually increases in estradiol (Table 1). It has been clear for some time that breast cancer risk is related to the number of years of menstrual activity, influenced accordingly by age at menarche (strongly) and age at menopause; each of these is a relatively strong risk factor for the disease. The effects of early age at menarche increase markedly with each year earlier that this milestone occurs. Inversely, as noted above, early age at menopause, like artificial menopause, is associated with a significant decrease in breast cancer incidence (Figure 3).

Other epidemiologic observations are also consistent with the interpretation that exposure to increased levels of estradiol increases breast cancer risk. In particular, observations about pregnancy are fitting together in a now more obviously rational way (Figure 2).[15] As might be expected, the major hormonal increases during pregnancy are associated with increased risk in the years immediately following the pregnancy, but the lobular-differentiating effects of these same changes are associated with decreased overall risks beginning about a decade later (Figure 2). Pregnancy also results in a down-regulation of baseline prolactin levels, which logically is believed to be important in breast epithelial proliferation.[22]

Within the breast, the effects of hormonal changes are somewhat more evident in the stroma, with increases in fluid content in the second half of the cycle. However, there also is corroborating evidence of the significance of hormonal effects with increased proliferative activity of the epithelia in the second half of the cycle.[23] Interestingly, a distinct minority of normal breast epithelial cells appear to have estrogen-receptor proteins.[24]

How the risk factors listed in Table 1 themselves develop deserves some discussion because of their
relationship to manipulable factors important in prevention. The Eastern-Western differences in hormonal profile and breast cancer risk are believed to be based primarily on lifestyle differences, most likely, variations in diet and physical activity throughout the life span. Age at menarche appears to be later in Asian women, possibly reflective of nutritional effects during the prepubertal and pubertal years. Physical activity during these same years and later may significantly affect ovarian activity.[8]

Although total caloric content and fat content have received the greatest attention with respect to their relationship to breast cancer risk, it seems that specific dietary constituents may play protective roles, and the evidence supporting these roles is becoming more persuasive.[9] For example, accumulating data suggest that, taken together, diets with high levels of fruits and vegetables are protective.[9] With respect to the Asian diet, the increased phytoestrogens in commonly consumed soy products are thought to be weak estrogen agonists, thereby acting to protect breast epithelium from more potent estrogens.[25] Dietary factors in cruciferous vegetables increase 2-alpha-hydroxylation of estrogens (with decreased formation of genotoxic 16-alpha-hydroxylation metabolites).[26]

Although the relationship of overall dietary fat intake to breast cancer risk is uncertain, excess caloric intake that results in postmenopausal obesity is clearly important, acting as a modulator of hormonal metabolism.[27] Distribution of body fat, however, differs among individuals, and for as yet unclear reasons, central or abdominal adiposity appears to be more important than the peripheral form.[28] At what age weight change occurs is also important, perhaps because body mass influences the hormonal system differently in premenopausal and postmenopausal women, with a disruption of normal cycling in younger women.

Two more recently suggested novel risk factors also are postulated to act through hormonal mechanisms. Excess electrical field exposure is suggested to increase levels of estrogens and prolactin.[29] Exposure to organochlorides may also be important, with these compounds acting as superestrogens.[30]

A final piece of evidence supporting the contention that hormonal exposure is a key variable in breast cancer development comes from therapeutic studies of the estrogen antagonist tamoxifen (Nolvadex). When tamoxifen has been given as adjuvant therapy for unilateral invasive breast cancer, a 39% reduction in the occurrence of second, contralateral breast cancers has been observed.[31] What is most remarkable about this observation is the limited duration of therapy--1 or 2 years--in many of the trials contributing data that led to this overall conclusion.

Implications of Developmental Data

This article has focused on pulling together ideas about the development of breast cancer because successful prevention strategies obviously must be well-grounded in such concepts. Current understanding of the interactions among and timing of many variables is incomplete, and further study of the factors themselves and their mechanisms of action are needed. Nevertheless, the broad outline developed thus far provides some clear guidance for currently applicable, rational prevention strategies and for strategies genuinely worthy of comprehensive study.

Currently Applicable Prevention Strategies

Since other recent reviews have discussed the management of women at presumed or laboratory-documented increased risk for breast cancer,[32-34] this subject will not be discussed here. Avoidance of cigarette smoking, particularly greater efforts to reduce development of addiction among women in the second decade of life, should be a general health promotion strategy and may possibly be a successful breast cancer prevention tactic. Limitation of diagnostic and therapeutic radiation to the breasts in younger women also deserves more attention.

Further continuing the focus on younger women (which follows from the earlier suggested interpretation of Figure 3), a moderate level of exercise should be advocated.[8] Alcohol consumption should be discouraged, and following childbirth, lactation should be encouraged. These latter two strategies, in particular, seem unlikely to have any adverse effects. Limited caloric intake, again critically in the prepubertal years, appears to be a worthwhile strategy. Throughout life, consumption of a diet that is high in fruits and vegetables seems likely to be protective. During middle age (ie, the fourth and fifth decades of life), ovariectomy and hormone replacement therapy are likely to be associated with significantly decreased risk.[12] It is difficult to advocate this strategy in the absence of other indications for ovarian or uterine body gynecologic surgery, but it deserves more consideration.
Finally, at menopause, the risks and benefits of estrogen or combined hormone replacement therapies warrant balanced consideration. It is difficult to escape the conclusion that over the longer term, ie, more than 5 to 10 years, estrogen therapy alone is associated with a modest increase in breast cancer risk.[35] However, the effects of shorter-term treatment are uncertain.

**Preventive Strategies Worthy of Study**

The thrust of research efforts must be to identify technologically simple, practical (ie, nontoxic, low cost), and effective preventive strategies. At the outset, comprehensive models are needed. These models should be able to project specific effects of a preventive strategy on breast epithelial tissue and, at a minimum, an absence of other tissue effects, particularly toxic effects. The absence of toxicity is critical, given that preventive interventions are for healthy people and may involve long-term application. In these circumstances, any toxicity is likely to be associated with low acceptance of the intervention.

The studies of the Russos[6] suggest that exploration of a brief hormonal intervention to achieve the same profound lobular maturational effects as occur during a full-term pregnancy should be pursued. The physical, emotional, and biologic challenges of defining and investigating such an intervention are great, but the developmental data are compelling.

Strategies that address the hormonal exposure variable (discussed in detail above) need to consider the multisystem impact of hormonal changes. The proposal by Pike and colleagues for an oral contraceptive that creates a less stimulatory milieu for the breast deserves the careful exploration that this group is undertaking.[16] Again, the comprehensive model of the biology of breast cancer developed thus far makes a striking case for this suggestion.

A direct breast (cancer) cell estrogen antagonist intervention, such as tamoxifen, is currently under study in randomized trials in the United States, the United Kingdom, and Italy. The direct and indirect multiorgan effects of tamoxifen, the occurrence of symptomatic toxicities in a large fraction of treated women, and the complexities of obtaining data on multiple end points of interest that occur at different times in the treatment sequence all suggest that even if tamoxifen proves to be effective in suppressing breast cancer in a particular group or groups of women, its use will be limited to small numbers of women who are members of unique, high-risk subpopulations. Thus, this strategy likely will have a minimal impact on public health.

Increasing attention is being directed to the stroma in which breast cancers arise and to possible modulation of stromal growth factors that influence breast epithelial growth. The basic science and clinical pilot studies in this area may ultimately lead to even more useful strategies for preclinical breast cancer control than those suggested above.

**Dietary Changes and Chemoprevention Strategies**

At present, hypotheses about other interventions likely to suppress the appearance of clinical breast cancers are less well-developed, and thus, do not merit large studies. To bring ideas about retinoids,[36] limonene,[37] and selenium[38] to such clinical trials, considerably more information is needed that establishes well-understood roles for these factors in the development of breast cancer. In addition, as mentioned above, it will need to be shown that these factors have effects that are specifically targeted to breast tissue and that are nontoxic to other tissues.

The apparent increases in breast cancer incidence and the perception that little is understood about the causes and development of this disease have combined to create intense pressure to take action. They also have fostered greater hope that a simple "magic bullet" intervention can be identified to prevent a large fraction of breast cancer cases. It is important to emphasize that the complexity and hormonal aspects of the biology of this disease make identification of such an intervention unlikely.

Chemoprevention and dietary modification studies in breast cancer should be seen as ways to help increase our understanding of disease biology and less as ways of identifying possibly useful public health strategies.

**Breast Cancer Prevention in Populations**

The recent interest in genetic biology and the development of the field of chemoprevention have focused significant attention on the biology of breast cancer. The attainment of the public health goal stated at the outset of this article--decreased incidence of breast cancer in the US population--however, will require a major emphasis on behavioral and social issues. Each of the currently implementable prevention approaches and the strategies under active study require individual behavioral and often broad lifestyle changes. The attainment of these lifestyle changes for
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populations, particularly the heterogeneous populations of the United States, is daunting. Consider two such lifestyle changes: exercise and (costly) dietary modifications. The changing economic conditions and lifestyles of Americans—e.g., greater numbers of families with two working parents, more fragmented families, and considerably greater numbers of underinsured or uninsured individuals—all will make broad application of these prevention strategies difficult. Nevertheless, if the public health goal is to be attained, these strategies must somehow be implemented on a wide scale.

Hurowitz has suggested that considerably more attention must be focused on social policy as it affects health.[39] Our greater understanding of the developmental biology of breast cancer has numerous implications for potential preventive strategies. However, understanding this biology alone, without considerable progress in the behavioral and social sciences, will yield little benefit for the total population.

References:


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