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Women's Expectations for Breast Cancer Prevention and Early Detection: High Expectations Can Be Achieved

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Disclosures of potential conflicts of interest may be found at the end of this article.

In his commentary titled "Breast Cancer Prevention: Can Women's Expectations Be Met?" [1], Dr. Ponzone raises an important and timely question. Dr. Ponzone asks whether breast "cancer prevention" and "early detection" are attainable goals and whether these phrases have the same meaning to women at risk of breast cancer as to health professionals. This is a critically important issue, because researchers and health care providers strive to reduce the incidence and mortality from breast cancer by working to develop safe and effective methods to prevent breast cancer.

As Dr. Ponzone points out, mammography "is not without its drawbacks" [1]. Mammography, although associated with reduced breast cancer-specific mortality in some studies [2, 3], has not been found to reduce breast cancer-specific mortality in others [4]. In addition, mammograms can detect noninvasive cancers, some of which might not evolve to invasive breast cancer (the problem of overdiagnosis) [5]. However, I believe it is misguided to conclude that "preventive measures for a given individual might have only modest impact" and that "efforts of cancer specialists should focus more on improving the length and quality of life of patients through therapeutic advances." Although cancer specialists should work to develop more effective therapies for women with all stages of breast cancer, the greatest impact on breast cancer incidence and mortality will come from appropriately applying risk-based cancer preventive and early detection strategies.

The word "prevention" is often interpreted differently by the general population and health care providers. For health care experts, interventions that reduce the incidence of disease (in this case, cancer), even if incompletely, are considered to have prevented the disease in some individuals. However, for most of the general population, interventions that "prevent" disease are considered to be 100% effective (i.e., to reduce the incidence to zero) and to have minimal toxicity. The common perception is that an individual receiving preventive treatment will have no side effects and will never develop the disease to be prevented (cancer, in this case). The common example of such a "preventive intervention" is that of the polio vaccine given in childhood with minimal toxicity and almost 100% efficacy [6]. Other acceptable "preventive interventions" include treatment with statins to reduce cholesterol levels to prevent heart disease [7], antihypertensive drugs to prevent strokes [8], and bisphosphonate drugs to prevent bone fractures [9]. However, in each of these cases, the intervention is neither 100% effective nor risk-free. It is remarkable that the general population accepts medical intervention to prevent heart disease, strokes, and bone fractures but often does not accept "preventive interventions" to prevent cancer.

There are currently available interventions that clearly prevent many breast cancers in high-risk women. These include bilateral prophylactic mastectomy, which prevents up to 90% of breast cancers in very high-risk women [10, 11]; antiestrogen preventive therapy (with anti-estrogen selective estrogen receptor modulators, such as tamoxifen or raloxifene), which prevents approximately 50% of breast cancers [12]; and aromatase inhibitors, which prevent up to 70% of breast cancers in moderately high-risk women [13]). These interventions prevent breast cancer in many women but are often not accepted because of the possible side effects. The behavioral interventions that Dr. Ponzone mentions (avoidance of environmental carcinogens and lifestyle factors such as diet and exercise) likely also prevent some cancers; however, these highly tolerable interventions are less effective than the surgical or medical interventions mentioned. In clinical practice, these various preventive interventions are being used in a tiered fashion according to risk. Thus, for women at extremely high risk of breast cancer (such as those carrying *BRCA1* or *BRCA2* mutations), bilateral prophylactic mastectomies are considered and frequently performed. For women at moderately high risk (e.g., those with precancerous lesions such as atypical ductal hyperplasia), preventive therapy with tamoxifen, raloxifene, or an aromatase inhibitor is being prescribed and accepted by many women. The remaining women (those at low to moderate risk of breast cancer) might benefit from behavioral interventions such as exercise, diet, and alcohol avoidance alone. The current interest in healthy lifestyles has led Dr. Graham Colditz to suggest that by avoiding exposure to carcinogens, receiving vaccination for oncogenic viruses, and implementing lifestyle measures to minimize tobacco use and obesity, it is possible to reduce cancer incidence by 50% or more [14]. Although it is currently difficult to determine whether an individual woman will benefit from these behavioral interventions, such measures are generally healthful and thus should be recommended.

Dr. Ponzone also cites the recent report by Tomasetti and Vogelstein as evidence that cancer prevention interventions

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are unlikely to be generally useful. Drs. Tomasetti and Vogelstein investigated the relationship between the lifetime risk of specific cancer types and the total number of divisions of "normal self-renewing cells" [15]. These investigators reached the provocative conclusion that only one third of cancer risk can be attributed to inherited predispositions or environmental factors, with the remaining two thirds of cancer risk attributable to random DNA mutations occurring in normal, noncancerous cells. These investigators attributed this random DNA mutation rate as "bad luck" and concluded that such findings suggest that cancer preventive interventions such as avoiding environmental or endogenous carcinogens will do little to reduce the risk of these cancers. The conclusion that much of cancer risk can be attributed to DNA mutations is certainly correct; however, the conclusion that the rate of DNA mutation has little to do with endogenous and exogenous exposure to carcinogens and mutagens is unlikely to be true.

The report by Drs. Tomasetti and Vogelstein has been criticized by others [16–18]. However, it is important to point out several major issues with their analysis here. Central to the study by Tomasetti and Vogelstein is the hypothesis that cancer risk can be directly related to the number of stem cell divisions in normal tissue [15]. In their report, they showed a positive linear relationship between the lifetime risk of cancer (abstracted from incidence data from the Surveillance, Epidemiology, and End Results Program database) and the number of stem cell divisions in normal tissues over an average lifetime (estimated from immunostaining for stem cell markers or from biologic studies). However, they carefully selected the tumor types to include in their study. Tomasetti and Vogelstein left out important common cancers that might not fit their linear relationship (e.g., breast, prostate, and ovary) [15]. Equally problematic is the "expansion" of some tumors into nontraditional subsets that are treated as separate tumors (e.g., splitting osteosarcomas into five different subtypes, each equally weighted as esophageal, testicular, and head and neck cancer). This process of selecting specific tumors that fit their hypothesis, and leaving out those that do not, greatly weakens the validity of their conclusion and does not allow their analysis to be generally applicable to many cancer types.

Dr. Ponzone also cites problems with the "early detection" of breast cancer. Mammograms are certainly able to detect breast cancer at an early stage. However, the current debate has been focused on whether mammograms detect too many cancers that are not life-threatening [2–5]. This problem of "overdiagnosis" of nonlethal cancers is a major focus of current early detection research. Similar to "prevention," the phrase "early detection" often implies to the general population a test that is 100% effective in detecting cancer (i.e., is 100% sensitive), with no false-positive results (i.e., 100% specific). However, no screening test will be 100% sensitive and 100% specific. Although mammograms will not detect all breast cancers, currently, with computer-aided detection, mammograms are 85% sensitive and 92% specific [19]. Thus, mammography remains the reference standard breast screening test. However, a need certainly exists to develop breast screening tests that more effectively detect lethal cancers without identifying nonlethal cancers.

The concept of breast cancer "early detection" is also evolving. Clinicians now use a risk-based approach to detect breast cancer. For low- to average-risk women, the generally accepted screening guidelines for the general population are being used. Although debate is ongoing concerning at what age mammographic screening should start (40 or 50 years old or older) and whether mammograms should be obtained yearly or every other year [20–23], such screening approaches should only be applied to those women with the population or average risk. For high-risk women, more aggressive screening approaches are generally used (and are authorized for payment by Medicare and insurance companies). For women with a lifetime risk of 20%–25% or higher, including women with *BRCA1* or *BRCA2* mutations, annual mammograms and annual breast magnetic resonance imaging scans have been recommended. Bilateral breast ultrasonography is also often added to mammography for breast cancer screening in women with lobular premalignant lesions (e.g., atypical lobular hyperplasia and lobular carcinoma in situ). Thus, a risk-based approach is also now being used for breast cancer screening.

So, are women's expectations for breast cancer prevention and early detection being met? For the highest risk women, the answer appears to be yes. However, for most women (in particular, those at low to moderate risk), the answer is clearly no. For such women, it is clear that additional research is needed to improve the ability to detect life-threatening cancer at an early curable stage and to prevent the development of these cancers. Many research groups are working to discover more effective and safer methods to detect and prevent life-threatening breast cancers. Promising prevention strategies include using novel medical therapies such as drugs targeting precancerous cells [24], natural products [25], cancer vaccines [26], and combinations of exercise, diet, and antidiabetic drugs such as metformin [27, 28]. Novel early detection strategies are also being developed that use blood-based DNA, RNA, or protein markers to detect life-threatening cancer [29]. The results from such research studies will ultimately allow women's expectations for breast cancer prevention and early detection to be met.

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