

Breast Cancer Prevention: Can Women's Expectations Be Met?

RICCARDO PONZONE

Gynecological Oncology, Candiolo Cancer Institute-FPO, IRCCS, Candiolo, Italy

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

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The recent publication of a landmark paper on cancer etiology by Cristian Tomasetti and Bert Vogelstein in the journal *Science* instantly generated a great amount of media interest in how and why cancer arises and fueled similar discussions in the scientific community [1]. The key message of the paper, that most types of cancer are due to bad luck rather than lifestyle or genes, is likely responsible for the broad coverage of the paper [2], although the authors' rather conflicting comments deserve more in-depth reflection.

Undoubtedly, "prevention" and "early detection" are key messages delivered by doctors and health authorities to construct the hope that cancer can be defeated. Screening mammography has been associated with a reduction in breast cancer-specific mortality in selected age groups, but it is not without its drawbacks [3, 4]. Furthermore, the promise to avoid an occurrence of cancer is certainly more appealing than a reasonable chance of cure by effective (but toxic) treatments administered once the cancer has been discovered.

As a consequence, the attention of both the media and the scientific community has recently shifted to breast cancer prevention and, in particular, to the possibility that environmental factors [5] and lifestyle modification [6] play a significant role in reducing the risk of developing breast cancer. However, ionizing radiation is the only well-recognized environmental factor linked to breast cancer incidence, with the risk inversely correlated with the age of the woman at the time of exposure [7], and no clear influence has been demonstrated to date for any specific chemical carcinogen. In contrast, consistent epidemiological evidence has associated physical activity with breast cancer risk reduction [8] and a better prognosis in breast cancer patients [9], as well as associated postmenopausal obesity with increased breast cancer risk [10] and a worse prognosis in breast cancer patients [11]. Several protective diets (i.e., rich in vegetables, fruit, and fiber and low in fat) have been proposed [12, 13], although alcohol consumption is the only dietary risk factor convincingly associated with a moderate increase in breast cancer risk [14].

Exposure to sex hormones might exert a procarcinogenic effect on breast cells, as demonstrated by the epidemiological correlation between breast cancer risk and age at menopause and menarche, age at and number of pregnancies, breastfeeding, and the use of exogenous sex hormones. Among these

variables, the use of postmenopause hormone replacement therapy (HRT) is the only truly modifiable risk factor. Indirect evidence has suggested that the decrease in HRT use among American women beginning in 2003 after the first report of the Women's Health Initiative Study [15] might have been associated with a decrease in the annual age-adjusted breast cancer incidence [16, 17]. Nevertheless, combined HRT use might be responsible for only 8 breast cancer cases of 10,000 women treated over 1 year. Furthermore, the increased risk declines markedly soon after discontinuation of therapy, and no difference in breast cancer mortality between HRT users versus nonusers has ever been observed [18].

It is well known that modifiable risk factors explain just a small fraction of the overall attributable breast cancer risk and that the influence of other nonmodifiable risk factors such as family history, age, and sex is much stronger. Still, even considering both modifiable and nonmodifiable risk factors, a large piece of the picture is missing, and current models of risk prediction might not be accurate [19].

Given this context, it is not surprising that Tomasetti and Vogelstein [1] found that only one third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions and that random mutations arising during DNA replication in normal, noncancerous stem cells are responsible for most cancer. Breast cancer was not included in their study, because the data on stem cell division rates in the breast are still contradictory and could be subjected to significant variations according to the age and reproductive phase of the patient. Their ongoing work will inform us whether stochastic factors ("replicative" tumors) or environmental/inherited factors ("deterministic" tumors) play a predominant role in the development of breast cancer. The existence of both inheritable and environmental risk factors has been well demonstrated; however, most breast cancer patients do not have such factors. Therefore, one could speculate that breast cancer might lie in between the two clusters of "replicative" and "deterministic" tumors [1].

Such knowledge will help to clarify what proportion of cumulative breast cancer risk can be attributed to hereditary, environmental, and lifestyle characteristics. This will allow cancer researchers to calculate the magnitude of the average benefit that can be derived from acting on modifiable risk

Correspondence: Riccardo Ponzone, M.D., Ph.D., Gynecological Oncology, Candiolo Cancer Institute-FPO, IRCCS, Strada Provinciale 142, km 3.95, Candiolo 10060, Italy. Telephone: 39-011-993-3036. E-Mail: riccardo.ponzone@ircc.it Received April 25, 2015; accepted for publication November 2, 2015; published Online First on December 14, 2015. ©AlphaMed Press 1083-7159/2015/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2015-0169>

factors, such as sedentary lifestyle, obesity, alcohol intake, HRT use, and radiation exposure, or by adopting chemoprevention strategies (tamoxifen, aromatase inhibitors). A deeper understanding of the inheritable component of breast cancer risk could likewise help target those individuals with the greatest genetic risk for whom prophylactic surgery would be of most benefit.

Nevertheless, according to what Tomasetti and Vogelstein [1] have described, a precise risk estimation for each individual will never be possible owing to the major stochastic influence on the probability of developing most types of cancer. Furthermore, if the lifetime number of divisions of stem cells within each organ really is the major determinant of our cumulative cancer risk, any type of primary prevention could well be out of reach. In fact, stem cells are responsible for the

development and maintenance of a tissue's architecture, and, thus, even if technically feasible, any intervention on their replication rate in normal tissues could seriously endanger the vitality and normal functioning of the tissues themselves.

In conclusion, the important insights reported by Tomasetti and Vogelstein [1] provide convincing evidence that cancer preventive measures for a given individual might have only modest impact compared with stochastic factors. Therefore, although healthful behaviors must be encouraged by the medical community, we believe the efforts of cancer specialists should focus more on improving the length and quality of life of patients through therapeutic advances.

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