

EDITORIAL

## Avenues for the Primary Prevention of Breast Cancer in the Second Millennium

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Breast cancer (BC) has recently surpassed lung cancer as the most frequently diagnosed cancer worldwide, with an estimated 19.3 million new cases and almost 10 million deaths occurring in 2020.<sup>1</sup> A steady ascension in BC incidence has been a remarkable feature in cancer epidemiology for almost a century, and has been reported in richer as well as poorer communities all over the world. This trend is no doubt associated with the ageing of the global population: “Each one-year increase of population ageing (is) associated with a nearly ½ year increase of age at BC diagnosis. Population demographics explain forty-two percent of the age variance for BC.”<sup>2</sup> The association with global ageing is obviously not amenable to preventive interventions, but many other avenues exist, to modify risk factors leading to BC. Less than 1% of all BC cases occur in men, therefore, this paper will be limited to those avenues likely to prevent BC incidence in women only.<sup>3</sup>

Besides ageing, another known BC-specific risk factor that is not always avoidable is the increase in breast tissue exposure to estrogen, itself associated with changes in patterns of the reproductive life of contemporary women. Improvement in women's socioeconomic status all over the world has led to delays in age at first pregnancy and decreased parity and breast-feeding intensity, which have prolonged the lifetime physiological exposure to estrogen.<sup>1</sup> In contrast with unavoidable sociological changes, age at menarche is a reproductive determinant which may be a good candidate for prevention. Age at menarche has decreased in all girls in the past century, thus prolonging the interval of physiological breast exposure to estrogen. The decrease was first spotted in more affluent nations, and is now being reported also in less developed ones.<sup>4,6</sup> It has been suggested that better nutrition and early weight gains in younger girls are main contributors to early sexual maturity.<sup>4</sup>

These findings indicate that early intervention to prevent premature weight gain in childhood may be an important avenue for reducing BC risk. Reliable guidelines exist to help parents and educators address

the issue of weight control with children while avoiding psychological distress, stigma and body image distortion. Tools are being developed and validated in various cultural contexts to respond to that crucial balancing act.<sup>7-8</sup>

Excess adipose tissue increases estrogen levels also in post-menopausal women.<sup>9</sup> Weight loss among perimenopausal women has been found to be associated with significant decrease in risk for BC primary incidence, and for recurrence after a primary resection.<sup>10</sup> There is limited evidence that food items rich in carotenoids and calcium may provide some protection against BC, while charred and processed meats contribute to its incidence. Inasmuch as sedentary lifestyles promote weight gain, physical activity can contribute to BC prevention. Many studies have shown that as little as 75 to 150 minutes of brisk walking each week can lower the risk of BC in all women.<sup>11</sup>

Other lifestyle-associated factors may also present important opportunities for primary prevention. Several studies indicate that alcohol raises estrogen levels in the body, in addition to contributing to weight gain. A pooled analysis of data from 53 studies found that for each alcoholic drink consumed per day, the relative risk of breast cancer increased by about 7 percent. In developing countries, where alcohol consumption is less prevalent, its effect on BC incidence is relatively negligible. This same meta-analysis found that smoking, a known risk factor for several types of cancers, has little or no independent effect on BC risk in women with low or no alcohol use.<sup>12</sup>

In recent years, there has been increased interest in assessing the impact of outdoor and indoor environmental factors on cancer in general, and on BC in particular. Some pollutants are already known to be carcinogens, but those with particular importance on BC are mostly endocrine disrupting compounds (EDCs), whose impact is mediated through alterations of the activity of endocrine tissues. These EDCs include natural estrogen products such as genestien, a compound found in soja, or in industrial products:

organochlorine pesticides such as DDT, parabens in hygiene products or the ubiquitous bisphenol A (BPA) found in plastic items of daily use. Pathological mechanisms follow a variety of toxicological or epigenetic paradigms. The pre-existence of some particular mutations, such as *BRC1* and *BRC2*, optimize the interaction between these compounds and the genome, leading to changes in mammary tissue development with an increased likelihood of the later development of BC. Genetic research is on-going to identify new genetic markers of environmental vulnerability, while other compounds, and also medical and non-medical radiations, are being tested *in vitro* and *in vivo* to elicit their respective contribution to BC.<sup>13</sup>

A full review of modifiable risk factors of BC cannot be concluded without considering the issue of synthetic estrogen prescribed for medical indications. A first link was found with diethylstilbestrol pills (DES) which was prescribed to millions of pregnant women to prevent miscarriages and other complications of pregnancy between 1940 and 1971. The DES was banned after exposure was associated with an increased risk of BC in the mothers and an increased risk of a rare vaginal clear-cell adenocarcinoma in daughters exposed in-utero.<sup>14</sup> Numerous studies have demonstrated an increased risk of BC among current and recent users of oral contraceptives (OC), particularly those who have used them for more than 5 years, and initiated use at a young age.<sup>15-17</sup> Most of what we know about the association between hormone replacement therapy (HRT) and risk for BC comes from the Women's Health Initiative (WHI). This large randomized controlled trial (N = 16,608 women) was designed to explore the risks and benefits of combined estrogen and progestin HRT in post-menopausal women. The trial had to be interrupted in 2002, 5 years after its initiation and midway within its planned course, when researchers found a significantly increased BC risk in women in the combination arm. On the other hand, BC risk was decreased in women in the progestin-only arm.<sup>18</sup> These findings were corroborated in 2003, in the UK Million Women Study (MWS), which reported that the current use of all types of post-menopausal HRT significantly increased the risk of BC.<sup>19</sup> The implications of these results on HRT prescription practices were drastic.

In conclusion, this review clearly indicates that avenues for primary prevention of BC are extremely numerous. They include:

1. Behavioral change regarding healthy diet, physical exercise, alcohol intake and weight control.
2. Changes in clinical practices of OC and HRT, and better counseling during gynecological visits.

3. Legislation to decrease the exposure of populations to known carcinogens, and to modify industrial processes to decrease adverse exposures.
4. Further research into genomic markers of vulnerability especially among women with a family history of BC, which may lead to pre-emptive, tailored gene therapy in the future.<sup>20</sup>

Public health practitioners all over the world are invited to continue their advocacy and lobbying efforts with governments, community organizations and international agencies, to slow down the continuously upward trend in BC incidence, as we move into a new millennium.

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