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## Putting Together the Pieces of the Mosaic - What Do We Know About Potential Environmental and Social Risk Factors for Breast Cancer?

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## ABSTRACT

**Background:** The human breast undergoes processes of proliferation and involution, especially during puberty, pregnancy, and menopause. During these dynamic phases, some specific environmental factors play important roles, including pro-carcinogenic effects. In addition to the usual breast tumor, its pathologic characteristics, and genetic variants, different environmental and social factors create additional challenges to the accurate comprehension of breast cancer (BC) risk, diagnosis, prophylaxis, and treatment.

**Methods:** This mini-review is based on Medline database search for recent clinical studies on BC risk factors, development, and prevention, particularly at the time of puberty, pregnancy, and menopause.

**Results:** Based on the medical literature review, some insights were provided into how external environmental factors influence BC risk, incidence, and mortality. Also, in an attempt to answer this key question, the selected chemical and physical components of the environment, as well as the large spectrum of social and behavioral elements, were analyzed.

**Conclusion:** It has been suggested that a broad spectrum of established and potential environmental elements have been related to BC etiology. Furthermore, a modern transdisciplinary approach to research studies, including epidemiological, biological, toxicological, pathological, genetic, social, and behavioral factors should help provide the “whole picture” of the environmental risk factors and causes for BC. This is particularly valid to medical personnel involved in women's health to facilitate preventive efforts, especially for those who are at the highest risk for this common and devastating malignancy.

### Introduction

Breast cancer (BC), as the most frequent neoplasm and the largest mortality cause among malignancies in females around the globe, usually attack during the most vital periods of women's personal and professional life.<sup>1</sup> As a consequence, BC profoundly influences the women's general health status and

quality of life, and can affect many aspects of their family dynamics. Despite unquestionable preventive, diagnostic, and therapeutic advances, the BC incidence has increased in all ethnic groups (except whites).<sup>2</sup> It is very challenging to distinguish numerous factors that can be responsible for BC. A puzzling difference in the BC incidence, across various countries, cannot be simply attributed to genetic reasons. Therefore, further research needs to focus on various environmental factors.<sup>3</sup> For instance, it has been reported that many female immigrants, mostly from the underdeveloped countries, with low BC incidence, have subsequently experienced higher BC incidence rates, typical for the highly industrialized

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countries (e.g., the U.S.), where they had migrated. Such data suggest that certain environmental factors may augment the BC rates in genetically connected women (such as mothers and daughters from immigrant families).<sup>4</sup> Unquestionably, reproductive factors play some role in this scenario, due to the cyclic estrogen (E) and progesterone (P) stimulations of the breast tissue.<sup>5</sup>

In addition, other possible causal factors, particularly from the external environment (e.g., toxic chemical agents), represent one of the research priorities.<sup>6</sup> To explore these topics in detail, it is mandatory to evaluate the cumulative environmental risk, simultaneously from several sources, using various, precise instruments, and biomarkers (e.g., in areas of molecular biology, genetics, toxicology, endocrinology, and epidemiology).<sup>7</sup> It is very challenging to find causality between BC and potentially toxic environmental exposures. For instance, with regard to case-control studies, a recall bias is a common inconvenience, and for many longitudinal studies, the unavailability of the toxic chemicals in tissue specimens, represent frequent disadvantages. In an attempt to overcome such methodological difficulties, mapping cumulative toxic effects from the environment, and monitoring the burden of disease, are reasonable approaches. As a consequence, these strategies can help women with BC or at high risk for BC, make individual lifestyle choices and BC management-related decisions.<sup>8</sup>

### Methods

This mini-review is based on Medline database search for clinical studies on BC risk factors, development, and prevention, particularly in the periods of puberty, pregnancy, and menopause. The main timeframe for this search was set for the last 25 years. Also, the search was supplemented with some information from the relevant cross-references. Publications focused on clinical trials, investigating puberty, pregnancy, and menopause, and target populations of women exposed on specific BC risk factors, often derived from social, built, chemical, and physical environment were analyzed.

### Results and Discussion

Based on the medical literature review, some insights have been provided into how external environmental factors influence BC risk, incidence, and mortality. Also, in an attempt to answer this key question, the selected chemical and physical components of the environment, as well as the large spectrum of social and behavioral elements, have been analyzed.

This narrative review outlines several environmental factors for BC, which have been frequently correlated with BC, or could have caused it. Such factors can exert some direct or indirect effects on BC, particularly, when acting through

certain mediating circumstances, like early onset of puberty, obesity, and endocrine or metabolic derangements.

Moreover, a comprehensive evaluation of cumulative environmental effects should be useful in a deeper understanding of the interconnected causes of BC, in real-life dynamic scenarios. In this way, a transdisciplinary approach (e.g., epidemiological, biological, toxicological, pathological, genetic, social, and behavioral) to research on BC that incorporates a balanced constellation of environmental risk factors and causes should be considered for prevention and management of this common and devastating female cancer. The interpretation of current findings in this area of BC research has been outlined in the consecutive sections of this article, and summarized accordingly.

#### *Why the traditional models of BC causation are insufficient?*

Several BC risk factors typically interact with each other, and their combination, after some period of time, can lead to BC in susceptible women.<sup>9</sup> In this situation, a transdisciplinary study on the impact of the environmental exposures on BC etiology is of utmost importance.<sup>9</sup> This offers a potential to disentangle a conglomerate of risk factors and pinpoint the most important causal components for BC. In general, the American Cancer Society (ACS) recommendations for BC prevention emphasize reducing alcohol intake, maintaining a healthy body mass, performing regular physical activity, and avoiding post-menopausal hormone therapy (HT).<sup>10</sup> However, for many women, who follow the ACS guidelines, several BC risk factors still remain unclear, and the ACS recommendations appear insufficient.<sup>11</sup>

At this point, observations of female immigrants (e.g., arriving from the underdeveloped to industrialized Western countries), research on nuclear bomb survivors and epidemiological studies can shed some light on the idea of those toxic exposures, at some specific periods in a women's life course, that can be crucial to the later BC risk.<sup>12, 13</sup> Moreover, prenatal exposures to carcinogens (e.g., synthetic estrogens) can have detrimental effects on adult women's health, several years later.<sup>14</sup> These so-called windows of susceptibility (WOS), involving the prenatal, pubertal, pregnancy, and menopausal transition periods, correspond with certain "milestones", during which the mammary glands undergo anatomical and functional transformations.<sup>15</sup> In fact, BC etiology is related to ongoing changes in the breast tissue and alterations of the mammary gland environment. Therefore, when some toxic chemical agents, derived from the environment, such as endocrine-disrupting chemicals (EDC), as well as certain therapeutics (e.g., applied for the coexisting



medical conditions) can influence the BC risk, development, course, and prognosis.<sup>15</sup>

*What are the key non-genetic risk factors or causes of BC?*

To address the main non-genetic causes of BC, a universal term: “population attributable risk” (PAR) (representing the percentage of excess cases, which may be related to a particular exposure) can be helpful with regard to the BC.<sup>12</sup> However, PAR is often difficult to accurately determine, with regard to many BC risk factors, both internal (e.g., genetic or biological)<sup>16</sup> and external (e.g., occupational, residential, social, or cultural).<sup>17</sup> At this point, it is useful to introduce a working definition of the environment, which means “anything that is not genetic” and includes the social (socioeconomic/sociocultural), built, and toxicological/chemical/physical components.<sup>12</sup>

Interestingly, the BC risk is often elevated in women with higher socioeconomic status (SES) (measured by the education level, residential standard, employment rate, and income level).<sup>18</sup> This phenomenon may be explained, to some degree, by certain reproductive patterns, often linked to typical sociocultural values.<sup>19</sup> Moreover, the neighborhood SES has also been related to a higher BC risk for women with the highest SES, compared to the ones with the lowest SES, across all ethnic groups.<sup>20</sup>

The built environment encompasses the purposeful human actions to create and affect the physical surroundings (e.g., spaces for living, working, shopping, eating, exercising, relaxing, and entertaining), which can be beneficial (e.g., availability of fresh food, clean air/water, safe recreation/sports facilities) or dangerous to health (e.g., the overwhelming presence of fast food, alcoholic beverages, tobacco products, and lack of safe areas for physical exercises).<sup>20</sup> Both the social and built environment characteristics of community neighborhoods appear to influence the BC risk. Hopefully, an analysis of this impact, across various populations, will help explain the relevant ethnic discrepancies in BC risk, incidence, prevalence, or management.<sup>20</sup> Moreover, it should be noted that the multiethnic communities with lower SES and unhealthy features of the built environment are often more obesogenic, prone to diabetes mellitus type 2, metabolic syndrome, or cardiovascular diseases, as well as to the higher risk of postmenopausal BC.<sup>20</sup> Also, it is conceivable that the dangerous combination of highly processed, poor nutritional value food and beverages, with predominant sedentary activities can be associated with excessive energy intake among young girls, and a subsequent adverse impact on their development, including endocrine and reproductive functions.<sup>21</sup> In contrast, there is an inverse correlation between the physical activity (usually associated with good access to safe recreational areas in the neighborhood, and healthy

nutrition) and BC incidence.<sup>22</sup>

Over the last few decades, relations between exposures to common chemical agents, which represent a large part of toxicological and chemical/physical environment, and the BC risk and incidence (or some intermediate outcomes related to BC, such as an age at the onset of menarche) have been intensely studied.<sup>23</sup> In practical terms, environmental exposures can be categorized as modifiable lifestyle factors (or consequences of individual or societal behaviors), and EDC (mostly found in many industrial and agricultural chemical agents, as well as in numerous commercial and personal care products). It should be noted that many behavioral factors are driven by both personal choices and dominant surrounding societal trends. Such pressures are often beyond individual control, and thus, only the well-designed interventions, at the community and public health levels are urgently needed. In fact, promptly addressing the specific, hazardous environmental exposures, and rectifying the situation for the endangered populations, are necessary to counterbalance the possible BC risk, incidence, and adverse outcomes.

*What are the modifiable lifestyle risk factors for BC? - How can women apply personal choices for BC prevention more effectively?*

*A. Obesity - a new look at energy intake and expenditure rather than traditional approaches to diet and physical exercises*

Obesity shares some common factors with the built environment.<sup>24</sup> Excessive body mass, including being overweight and obesity, has traditionally been measured via body mass index (BMI). Elevated BMI (e.g., above 25) has been associated with an increased risk of postmenopausal BC, a decreased risk of premenopausal BC, and an earlier age at menarche.<sup>25</sup> However, BMI is not the most accurate parameter to assess body fat content. In fact, abdominal (central) fat is metabolically important, with regard to insulin resistance and potential malignancy risk. The paradoxical relationship of obesity (e.g., BMI above 30) in pre- versus postmenopausal women can be explained by the differential frequency of estrogen receptor-positive/progestin receptor-positive (ER+/PR+) tumors, which can occur in these two age groups.<sup>26</sup> ER+/PR+ tumors, which are more frequent among postmenopausal women, are more sensitive to estrogen (E) that is produced by the adipose tissue. In contrast, ER-/PR- tumors are more common in the premenopausal population, and can be related to some other risk factors. In addition, adipose tissue can serve as a reservoir for EDCs (which are lipophilic and can be stored in the body for prolonged periods of time), playing an obesogenic role.<sup>27,28</sup>

It is very difficult to demonstrate definite associations between BC and dietary factors in females with excessive body weight. In fact, BC



incidence, in various countries worldwide, can be related to high energy intake (e.g., mostly due to the quantity and quality of fats and carbohydrates consumption) and low energy expenditure (e.g., secondary to sedentary behaviors and lack of physical exercises). Such a combination often contributes to prepubertal obesity and weight gain among midlife women.<sup>29</sup> In general, physical activity (regardless of its kind) as a modifiable environmental factor in favor of BC prevention, has protective effects, predominantly for postmenopausal BC, mainly due to decreasing the body adiposity and E levels.<sup>30</sup>

#### *B. Alcohol*

Alcohol use is a causal factor in BC that acts via the formation of genotoxins (e.g., acetaldehyde) or by the alteration of hormones (e.g., E) and hormone receptors (e.g., ER).<sup>31</sup>

#### *C. Tobacco*

Tobacco smoke includes over twenty carcinogenic components.<sup>32</sup> These toxins can be detected in the breast tissue of women who smoke (in an active and passive manner).<sup>33</sup> Based on international epidemiologic studies, there is a causal relationship between BC and active tobacco smoking, especially in women, who started smoking before their first full-term pregnancy. Moreover, such a relationship exists also in females, who have a genetic trait, N-acetyltransferase 2 (NAT2) slow acetylator (slowing the metabolism and detoxification of carcinogens).<sup>34,35</sup> Exposure to secondhand smoke has also been related to increased risk of BC in never smokers (e.g., especially among premenopausal women).<sup>36</sup>

#### *D. Exogenous female hormones - oral contraception (OC), hormone replacement therapy (HT), and diethylstilbestrol (DES)*

In general, BC as a hormonally dependent malignancy is sensitive to oral contraceptives (OC) and hormone replacement therapy (HT). Certainly, individual variability and clinical context always should be considered before the possible use of OC or HT.

Oral contraceptives (OCs) are applied for birth control or some other medical reasons (e.g., irregular menstrual cycles or dysmenorrhea) by approximately 16% of women within the age range 15–44 years, in the U.S.<sup>37</sup> OCs have carcinogenic properties, but the risk decreases after 4 years from the termination of their use.<sup>38</sup> Since OCs are mostly being used by young females, in whom the risk of BC is low, and this risk also remains low at the population level. A combined estrogen-progestin hormone therapy (HT) for menopausal women had been used, until the Women's Health Initiative (WHI) study revealed an augmented risk of BC, which was not offset by other medical advantages (related to cardiovascular disease, osteoporosis, or cognitive functions) in

postmenopausal population.<sup>39</sup> At present, HT is used to control menopausal symptoms with great caution, under constant medical supervision, for a short time, depending on an individual clinical context.

Diethylstilbestrol (DES) is an estrogenic agent, which had been applied for miscarriages prevention. Unfortunately, it was found that daughters of women who took DES during pregnancy, subsequently developed adenocarcinomas of the vagina<sup>40</sup>, and thus, the use of DES was terminated. In addition, it was noted that as the females who took DES were getting older, they experienced higher BC incidence.<sup>41</sup>

#### *E. Light at night*

Shift work that has been related to elevated BC rates is typically combined with exposure to light at night.<sup>42</sup> In this way, the suppression of melatonin, a hormone which physiologically increases in the darkness of night and has anti-estrogenic actions contributes to elevated BC risk.<sup>43</sup> In addition to necessary shift work in certain areas (e.g., health care, emergency or military services, communication, transport, and industrial infrastructure), a light at night may be overused by students, workers using electronic equipment, or persons who excessively watch TV or engage in entertainment at night time. Therefore, a reasonable (e.g., very limited) use of electric and electronic devices, for unnecessary reasons, especially during the late hours should be encouraged.

#### *F. Ionizing radiation*

Ionizing radiation has demonstrated carcinogenicity for BC, which was reported in survivors of the atomic bomb explosions.<sup>44</sup> Currently, diagnostic radiological imaging (e.g., radiography, fluoroscopy, and computed tomography CT) represents a common source of ionizing radiation.<sup>12</sup> Therefore, the most reasonable and cautious use of the diagnostic radiation should be promoted to reduce the unnecessary risk related to this exposure.<sup>45</sup>

#### *G. Endocrine disrupting chemicals (EDC) – How can we improve conscious control over personal care products, commercial, industrial, and agricultural chemical agents?*

In addition to endogenous and exogenous hormones, which influence the BC risk, multiple synthetic chemical agents often mimic or disrupt the endocrine actions (e.g., estrogen signaling). At present, such agents with estrogenic activity, known as EDCs, are commonly used in a plethora of industrial, commercial, and agricultural compounds (or their byproducts), as well as in personal care products.<sup>6</sup> It should be emphasized that the most dangerous EDCs frequently encountered by women at their home or neighborhood and workplace include the following toxic substances: organochlorines (such as polychlorinated biphenyls (PCBs), dioxins (e.g.,



2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and dichlorodiphenyltrichloroethane (DDT) (a pesticide), organohalogenated compounds (e.g., polybrominated diphenyl ethers (PBDE)), per- and poly-fluoroalkyl substances (PFAS), perfluorooctanoic acid (PFOA), phenols (e.g., bisphenol A (BPA)), parabens, phthalates (e.g., butyl benzyl phthalate (BBP)), polycyclic aromatic hydrocarbons (PAH), benzene, ethylene oxide, and certain metals (e.g., cadmium).<sup>6</sup> Brief characteristics of the selected EDCs, and the key messages from the most relevant studies in this area are outlined below.

Organochlorines are lipophilic compounds, which are resistant to biodegradation. Although their use was prohibited in the 1970s due to their toxicity, organochlorines can still be present in the environment and biological samples.

Polychlorinated biphenyls (PCBs) are organochlorine compounds, characterized by various biological effects, which had been used as industrial coolants, insulators, and lubricants, until their use was banned, in 1979, in the U.S. PCBs have been related to BC in some epidemiologic studies.<sup>46</sup> In addition, gene-environment interactions with *CYP1A1* that have been reported in some studies (e.g., elevated levels of PCB and increased expression of *CYP1A1*) support an increased BC risk related to the PCB exposure.<sup>47,48</sup> For instance, in a trial, which assessed serum PCB levels, among females during early postpartum period, in 1959 - 1967 (a time of culmination of the PCB use), women with a higher proportion of PCB 203 (the most toxic PCB type) to the sum of PCBs 167 and 187 (the less toxic PCB types) had a higher probability to be diagnosed with BC by the age of 50.<sup>49</sup>

Dioxins, including 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), are very toxic organochlorines, obtained during a process of combustion or metal processing, and various chemical technologies. Similar to PCBs, they remain for a long term in the environment, contributing to neoplastic, reproductive and endocrine disorders.<sup>50</sup> The Environmental Protection Agency (EPA) considers TCDD to be a carcinogen for several malignancies, including BC. In particular, in the Seveso Women's Health Study, the relationship between dioxin exposure and BC risk has been investigated in a large population of women living around and working in a chemical plant which was a source of exposure to TCDD. After over thirty years of follow-up, thirty three BC cases were diagnosed, and the BC risk was elevated among females with higher blood levels of TCDD.<sup>51</sup> Also, relations of organochlorines with earlier age at menarche have been observed in some studies.<sup>52,53</sup>

Dichlorodiphenyltrichloroethane (DDT) is another toxic organochlorine used in the past as a pesticide. It should be noted that the p,p'-DDT and its metabolite p,p'-DDE were addressed in research. For instance, in a study using serum samples from women

participating in the Child Health and Development Studies (CHDS), at the time of their childbirth, it was noted that 129 of such females subsequently developed BC before menopause (e.g., before 50 years of age).<sup>54</sup> Interestingly, those who were in the highest tertile of p,p'-DDT exposure were almost three times as likely to develop BC as were those in the lowest tertile. In addition, this relation was stronger among females who were younger than 14 years at the time of their exposure. These data are convergent with the idea that the timing of exposure, such as an early development period, can be critical for EDC (e.g., p,p'-DDT) to contribute to the carcinogenic action in the breast.<sup>55</sup> Similarly, there are some supportive results derived from the Sister Study, in which it was reported that young girls (e.g., before age 18 years), who were exposed to fogger truck or plane spraying of DDT were at an increased risk for premenopausal BC.<sup>56</sup>

Polybrominated diphenyl ethers (PBDEs) (also known as polybrominated biphenyls (PBBs)) are commonly used flame retardants, which can persist in the environment for a long time (e.g., in the house dust).<sup>57</sup> Interestingly, in the Breast Cancer and the Environment Research Program (BCERP) study of PBDEs, the elevated serum levels of PBDE were detected in 70% of girls from California and Ohio, in the U.S., and such levels were higher for participants from California.<sup>58</sup>

Perfluoroalkyl substances (PFASs) represent per- and polyfluorinated agents that have EDC properties, and have been used in many industrial and commercial products (e.g., perfluorooctanoic acid (PFOA) - in Teflon and Gore-Tex materials).<sup>59</sup> The Danish National Birth Cohort study has reported an increased probability of BC among the participants in the highest compared to the lowest quintile of perfluorooctanesulfonamide (PFOSA) (which is metabolized to perfluorooctane sulfate (PFOS)), and the results of this follow-up study have been pending.<sup>60</sup>

Phenols, such as a bisphenol A (BPA), are weakly estrogenic agents, often used industrially in polycarbonate plastic and epoxy resins manufacturing. Hazardous exposure takes place when BPA is leached from plastic-lined food and beverage cans.<sup>61</sup> BPA can exert some abnormal effects on body mass (e.g., weight gain), puberty, and reproductive functions, in both females and males.<sup>62</sup> For instance, according to a study of prepubertal 6-7-year-old girls, participating in the BCERP in the U.S., 94% of the tested urinary samples contained elevated BPA levels.<sup>63</sup>

Parabens act like weak estrogens (Es) that bind to the estrogen receptors (Ers). Parabens can serve as antimicrobial preservatives, often used in personal care products (e.g., underarm cosmetics, deodorants, etc.). They have been found in urine samples and in BC tissue specimens<sup>64</sup>, and can also stimulate BC cell proliferation in vitro.<sup>65</sup> According to a large study, in which the urine paraben levels were measured in a



group of 1,151 6-8-year-old girls, it was revealed that paraben levels (that often occurred together with benzophenone-3 (BP-3), a phenol present in sunscreens) were higher in the summer time, and among a white group of girls.<sup>66</sup>

Phthalates are widespread, hormonally active pollutants that can alter pubertal timing. Exposures to phthalates may either accelerate or delay pubertal development depending on the age of exposure and some other factors (e.g., obesity).<sup>66</sup> Phthalates can be contained in different personal care products, such as cosmetics, together with parabens and organic solvents.<sup>67</sup> For instance, butyl benzyl phthalate (BBP) is an estrogenic agent and a partial agonist for the ER. BBP is frequently used in food wraps, cosmetic formulations, and plastics. Studies of pubertal timing in 30 Taiwanese girls with premature thelarche (breast development) were compared to 26 girls with central precocious puberty, and 33 normal controls. The girls with premature thelarche were found to have higher levels of monomethyl phthalate (MMP) than the control group.<sup>68</sup> Similarly, a study from the BCERP assessed a panel of nine phthalate metabolites. In a group of 1,149 girls, the investigators noted a relationship between the phthalate metabolites and the pubertal onset (measured by either breast or pubic hair development).<sup>66</sup> According to this study, high-molecular-weight phthalates (HMWP) levels were inversely associated with pubic hair development.<sup>66</sup> In addition, increased low-molecular-weight phthalates (LMWP) levels were associated with BMI and waist circumference (WC) gain, among girls in another study.<sup>69</sup> Therefore, it appears that exposure to phthalates may be indirectly related to the BC risk, especially in early stages of the female developmental process.

#### *H. Hazards of Air Pollution and Polycyclic Aromatic Hydrocarbons (PAHs)*

Many genotoxins and estrogenic or antiestrogenic agents contribute to widespread air pollutions that are cancerogenic. Among them, polycyclic aromatic hydrocarbons (PAHs) have been related to BC.<sup>6</sup> PAHs are carcinogenic chemical compounds that are produced during the incomplete combustion of different kinds of fuel (e.g., coal, oil, and gas). In addition, exposure to dietary products (e.g., grilled meats or fish) and contaminated ambient air (e.g., by tobacco smoke, active or passive) poses BC risk, due to the genotoxic properties.<sup>70</sup> Some PAHs have weakly estrogenic properties, and thus can influence BC risk.<sup>71</sup> Since air pollution is different in various neighborhoods, there can be an interaction between the PAH exposure and some social environmental components that may create particular hazards in more disadvantaged local communities.<sup>72</sup> In the ESCAPE Project that included 15 European groups of postmenopausal females, elevated BC risk related to nitrogen oxides

(NO<sub>2</sub>) (a marker of air pollution) and nickel (a marker of oil combustion and various industrial procedures) was documented.<sup>73</sup> Similarly, findings of the U.S. Sister Study revealed an increased risk of ER+/PR+ breast tumors, correlated with NO<sub>2</sub> exposure.<sup>74</sup> Moreover, the results of the California Teachers Study found associations between ER+/PR+ breast tumors and certain carcinogens, as well as between ER-/PR- breast tumors and benzene, cadmium, and arsenic.<sup>75, 76</sup> Furthermore, research on work and residential settings-related exposures to PAHs indicates possible relations between ambient air pollutions and BC. For instance, in a study from New York, women with increased exposure to total suspended particulates (TSP) at their birth location had an elevated BC risk later in life. In addition, the TSP levels were related to the 2.4-fold increased BC risk in these women.<sup>77</sup> Another study from the same group, examined exposure to traffic emissions, in females with BC, in which the residence was considered to be an indirect exposure parameter. This study examined exposures at different times in the life cycle of the participating females (e.g., the age at menarche). In particular, an increased BC risk was noted for exposures at the time of menarche and the age at first childbirth among females with postmenopausal BC.<sup>78</sup>

Convergent with these findings, a recent study from the longitudinal BCERP has shown an association between andrenarche and living in the proximity to traffic-related air pollution exposure.<sup>79</sup> In agreement with that result, a case-control study has revealed that women with detectable PAH levels had a twofold increase in their BC risk compared to the ones without detectable PAH levels. In addition, a dose-response relationship was reported among women with elevated PAH levels who had over fourfold increase in the BC risk.<sup>80</sup> Also, a study of female employees in Canada reported that the increased risk of BC was related to a longer employment period in some facilities, which were exposed to a higher vehicle exhaust (e.g., especially, if such exposure began when these women were younger than 36 years of age).<sup>81</sup> Interestingly, in the Long Island Breast Cancer Study that explored interactions with more than a dozen gene variants, an association between a higher BC risk and PAH-DNA adducts was observed.<sup>6</sup> This elevated BC risk was observed particularly in the case of higher levels of PAH-DNA adducts, in women with gene variants related to poor cell repair abilities.<sup>6</sup> Although the Long Island Breast Cancer Study linked the elevated PAH-DNA adducts levels with the increased BC risk, the exact role of PAHs in BC etiology still requires an intense research investigation.<sup>82</sup>

Notably, benzene, a very common industrial agent, is an established carcinogen for BC.<sup>83</sup> For instance, as a combustion product of gasoline and natural gas, benzene is widely present in the environment, and exposure to it should be reduced



due to hazardous consequences.<sup>12</sup> Similarly, 1,3-butadiene, a gas present in petroleum products and cigarette smoke, is a carcinogen. According to some occupational studies, 1,3-butadiene has been connected to various hematopoietic malignancies. Even though no human studies of its effects on BC in women are available, some animal studies (like in the case of benzene) have revealed elevated rates of mammary tumors and genotoxic damages.<sup>85</sup> Likewise, ethylene oxide, a compound that has been used mostly for medical equipment sterilization, presents the biggest BC hazard to women working in the relevant hospital facilities.<sup>85</sup> For instance, a large U.S. epidemiologic study, conducted among women in the hospital occupational setting, reported an increased risk of BC which remained elevated, even after adjustment for the number of childbirths and family history of BC.<sup>86</sup>

#### *F. Metals*

Metals derived from natural and industrial sources are practically unavoidable environmental components. For instance, cadmium, arsenic, beryllium, chromium, and nickel have been considered carcinogenic.<sup>87</sup> In particular, cadmium has revealed estrogenic properties and has been related to elevated BC risk.<sup>88</sup>

#### *How to advance BC prevention? - Directions for future research projects examining possible correlations between common environmental factors and BC*

It should be pointed out that integrating various factors from the biological, behavioral, social, and physical domains, in order to expand practical knowledge about risk, prevention and, management of BC is superior to analyzing them in isolation. In fact, a recent comprehensive, transdisciplinary approach proposes the multilevel etiology of postmenopausal BC.<sup>89</sup> For instance, in this design, the main parameters included the patient's age, ethnicity, age at the onset of menarche, the birth of the first child, menopause, as well as obesity (assessed by BMI), alcohol or tobacco use, financial income, hormone therapy (HT), and BRCA1/2 genotype. This study has shown that the decrease in HT and BMI, as well as the increased age at menarche, were beneficial for BC prevention. On the one hand, modification of these factors can only modestly affect the BC risk estimates. However, on the other hand, such hormonal and anthropometric modifications (HT and BMI) may influence the absolute number of women affected by BC. In addition, this approach emphasizes the complex BC etiology, shows methodological challenges, and indicates some directions for further studies. Consequently, after completing a pilot project called "Race and Ethnicity in Stage-specific Breast Cancer Survival" (2008), future BC studies are planned to

explore the impact of contextual factors (e.g., body size, physical activity, and various co-morbidities) on ethnic differences in BC survival in detail.<sup>90</sup> Furthermore, with regard to the urgent need for advancing the primary BC prevention, the novel structured approach has been developed by the Breast Cancer Prevention Partners (BCPP).<sup>91</sup> In short, the BCPP is a strategic plan that integrates scientific data with community perspectives, focusing on measurable objectives to reduce the incidence of BC in the future.<sup>91</sup> Unfortunately, despite increases in screening and advances in treatment, BC continues to be the most common cancer and cause of cancer mortality among women worldwide. Since BC rates have remained steady for several years, special efforts need to be re-directed and concentrated on the population-level primary prevention. For instance, to address the complexity of the BC at this level, the California Breast Cancer Research Program (CBCRP) has promoted some innovative BC preventive concepts for research studies in many high-priority areas.<sup>91</sup>

In order to develop practical recommendations for the safe use of multiple chemical substances, in the context of BC (and other hormonally-influenced cancers), some important aspects of the commercial agents' testing as well as epidemiology and toxicology investigations need to be applied.<sup>92</sup> Moreover, in an analysis of the environmental exposures, novel statistical approaches will be used to explain the roles of multiple interacting factors, which can influence BC risk and development. In this way, many variables (e.g., demographics) could be investigated simultaneously to better understand disparities between certain ethnic groups of women with BC. For instance, an analysis of the immigrant experiences and BC risk among Asian women in the U.S. may elucidate the patterns, in which some social factors (e.g., discrimination) may influence the BC risk, and particular patterns, which can show how this risk oscillates during the lifespan of these women in the community (Table 1).<sup>92,93</sup>

Considering insufficient progress in BC prevention, the CBCRP intends to apply current scientific knowledge about BC into primary prevention, at the population level, whenever feasible.<sup>93</sup> In particular, involvement in the community-based participatory research (CBPR), as well as dissemination, and implementation of research findings are needed. If such efforts succeed, the next challenge will be to translate the CBCRP interventions, targeted at the specific BC risk factors and relevant, protective strategies, into evidence-informed interventions (EIIs). Furthermore, the Californians Linking Action with Science for Prevention of Breast Cancer (CLASP-BC) is planned to detect, spread, and implement population-based prevention strategies, aimed at reducing the risk of BC (or other malignancies and



**Table 1.** Exemplary etiologic risk factors for breast cancer (demographic, social, occupational, behavioral, or personal) - perspectives for ongoing and future research studies<sup>92, 93</sup>

Geographical Migration	Women born and raised in the U.S. are more likely to acquire BC than newly arrived immigrant women (except the ones from Northern and Western Europe)	Detect what the particular differences are between the immigrant women from various ethnic groups, which make their BC rates lower. Determine why the chances of immigrant women to acquire BC increase after living in the U.S. Explore the ways in which adopting of the U.S./Western culture influences survival after a diagnosis of BC in various ethnic groups of women.
Urban Living	Women living in cities are more likely to get BC than women living in rural areas	Establish efficient collaboration between medical personnel, researchers, social and environmental scientists, community leaders, public health policy makers, and urban planners, to study the local neighborhood environments. Apply models of multiple stressors and cumulative BC risk to answer the research question.
Socioeconomic Status Income Level Education Level Neighborhood Status	BC is a rare health problem that is more commonly found in well-educated or affluent women than in uneducated/poor ones; BC is more often seen in high-income neighborhoods than low-income ones	Examine what is different about high socioeconomic status women and high socioeconomic status neighborhoods that correlate with higher BC rates. Explore the relative and joint roles of individual and neighborhood socioeconomic status. Investigate how individual and neighborhood socioeconomic status influences the BC risk of women from various ethnic groups
Occupation	BC risk varies by occupation	Examine long-term BC risk of the women exposed to pesticides, industrial chemicals, solvents, and heavy metals at work. Explore why women performing some professions (e.g., teachers or nurses) have a higher-than-average incidence of BC. Examine BC rates in women performing certain types of work (e.g., cleaning, agriculture, electronics, and cosmetic services), related to exposure to environmental toxins
Ionizing Radiation	Ionizing radiation is a proven cause of BC	Evaluate the use of radiation in mammograms for populations of women, who may be particularly susceptible to its harmful effects (e.g., flying air-lines personnel, especially during long intercontinental flights). Examine how genes affect radiation-related BC risk
Light at Night	Working at night raises a woman's chance of getting BC, probably due to the increased exposure to light at night	Study sleep behaviors (e.g., timing, number of hours, and amount of light in the bedroom) that can influence a woman's hormones in ways which can contribute to or help prevent BC. Examine the link of night-time light exposure with the BC risk. Explore whether exposure to light at night during a mother's pregnancy affects her daughter's risk of BC
Disabilities	Research addressing questions about the BC risk in women with disabilities should be expanded	Investigate the BC-related experiences of women with different disabilities. Explore barriers to BC prevention, detection, and treatment, as well as strategies for overcoming these barriers among women with various disabilities
Sexual Orientation	Research on the BC risk and sexual orientation is needed	Select study populations of sexual minority women for participation in BC research. Study the BC rate of transgender individuals, who use long-term hormonal therapies (e.g., estrogen preparations)
Timing of Exposure	Exposure to toxic chemicals at critical time periods in reproductive life (e.g., prenatal, puberty, and pregnancy) may increase a woman's BC risk many years later, when she is an adult	Investigate exposure to chemicals that act similarly to the female hormone estrogen. Find out if exposure to such chemicals at levels actually found in babies' blood can increase the risk that the laboratory animals will get mammary cancer. Develop better methods for measuring toxic exposures to environmental causes of BC through the woman's life course. Investigate exposures to real-life mixtures of pesticides/other toxins, at critical points in the life course, when these exposures are most likely to increase BC risk (e.g., during development in the womb, at puberty, and before childbearing)
Childbearing Breastfeeding	Having children at younger ages and breastfeeding are protective against BC; after a full-term pregnancy, breast cells are less sensitive to carcinogenesis with the lifetime risk of BC decreased in a half	Investigate multiple aspects of culture and tradition that influence childbearing practices (e.g., age of having children & breastfeeding). Conduct pilot projects to test policies to encourage breastfeeding in low income communities
Vitamin D	Higher levels of vitamin D in the blood are protective against BC	Directly measure vitamin D levels in women's blood and find out how these levels affect BC risk. Investigate whether vitamin D from sun exposure, in conjunction with dietary supply, can reduce the risk of getting BC and can increase BC survival



chronic illnesses, with similar risk factors) especially among local ethnic minorities or vulnerable populations of women.<sup>93</sup>

In conclusion, promoting research that not only increases knowledge but also points towards practical solutions will facilitate future BC prevention and therapeutic management. At this point, gathering detailed information about certain groups of women, who carry a greater burden of BC, as well as detecting the connections between BC and environmental or social circumstances are certainly merited. Steering future BC research in such directions will hopefully lead to decreasing BC mortality among the most vulnerable ethnic groups of women with high death rates of BC.

In summary, the practical goal for both the researchers and clinicians is to apply pertinent clues from the basic or clinical sciences and public health studies to design the most reasonable “action plans”, in various medical and personal contexts for women at the risk for BC or suffering from BC.

#### Conflict of Interests

None.

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