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RESEARCH ARTICLE

Breast Cancer: An Environmental Disease

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KEY MESSAGE

Breast cancer is a major health problem that is not adequately addressed through the current seek and destroy approach. It requires a systemic environmental approach – one that recognizes breast cancer as an environmental disease and therefore a disease that can be prevented by implementing changes to the environment.

Breast Cancer Incidence

Despite decades of intense research focus, the threat that breast cancer plays on the health of women is increasing. Breast cancer became the most common cancer in the world as of 2020, accounting for 12% of all new annual cancer cases worldwide among men and women. When looking at women only, breast cancer is not only the most common cancer, at 25% of their cancer diagnoses, but also the most common cause of cancer death at 16%.[1]

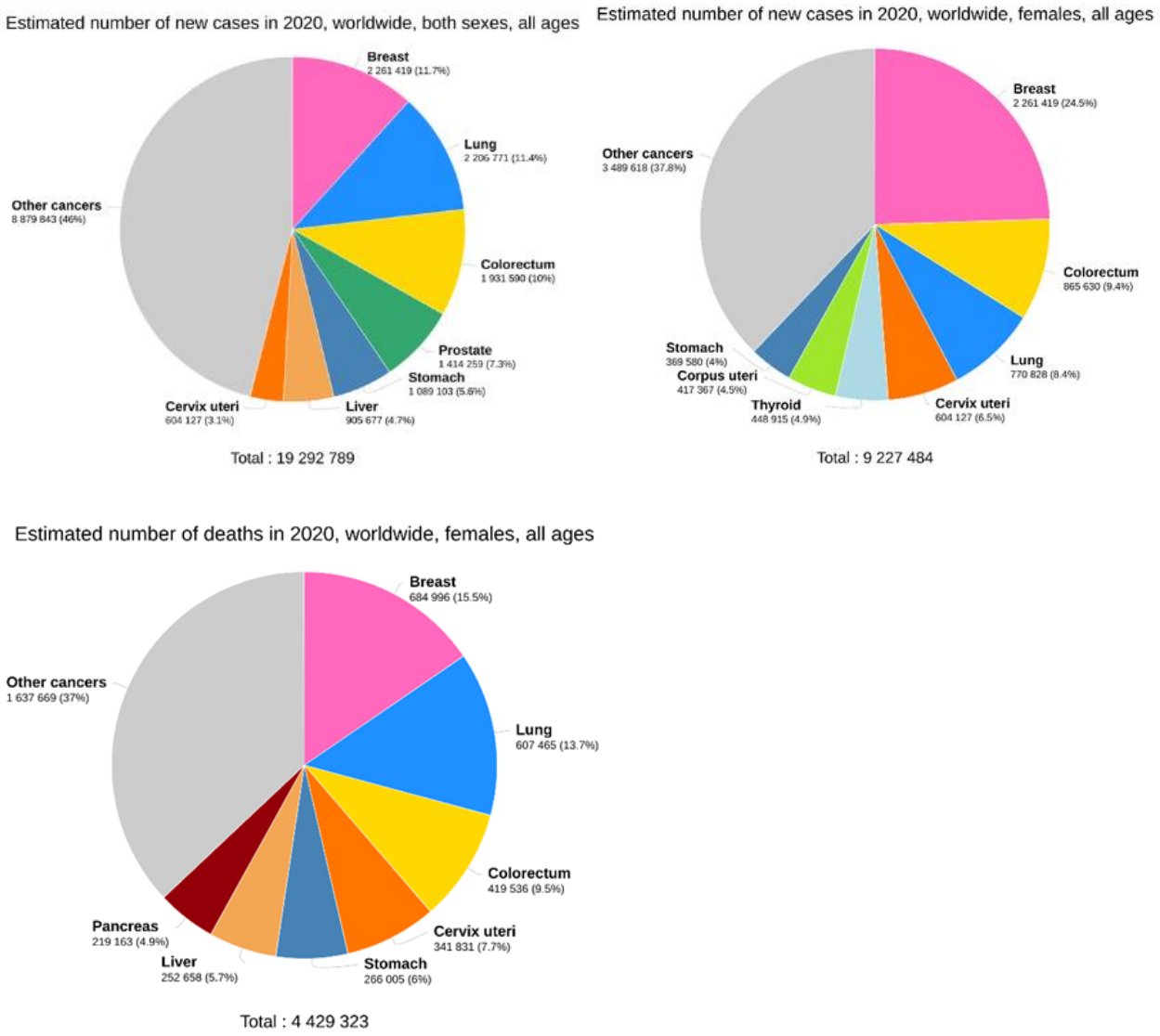

Figure 1 Worldwide Cancer data 2023 showing breast cancer accounts for 12% of all cancer worldwide and is the major cause of cancer incidence and mortality among women. [1-2]

Evidence of Breast Cancer as an Environmental Disease

Many people, including clinicians and scientists, think of breast cancer as a genetic disease. In reality, less than 10% of breast cancer cases are hereditary or familial, and many of those will carry a deleterious mutation in BRCA1 and BRCA2 (De Silva et al., 2019). [3] In addition, although family history is a recognized risk factor for breast cancer, at most 15% of breast cancer is linked to familial origins; most of those diagnosed with breast cancer have no family history (Haber et al., 2012). [4] Thus, most of the burden of breast cancer is sporadic and due to nongenetic, nonfamilial factors.

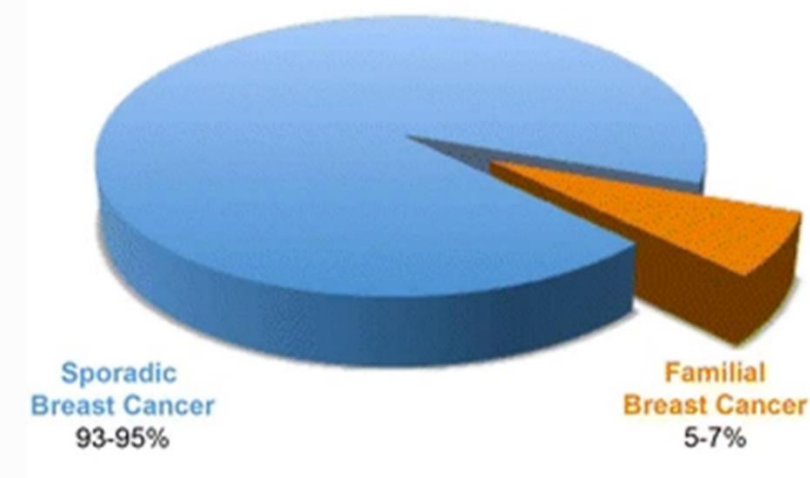

Figure 2. Most breast cancers are sporadic and cannot be attributed to genetic inheritance. [4-6]

Further evidence that breast cancer is an environmental disease is the penetrance of the known breast cancer mutations over time. Even for the small percentage of breast cancers that are due to genetic mutations, the expression of those mutations as breast cancer varies based on the environment in which they are found. Figure 3 demonstrates the diagnosis patterns of two populations of women with these mutations – one cohort born prior to 1940 and one born after. [6]

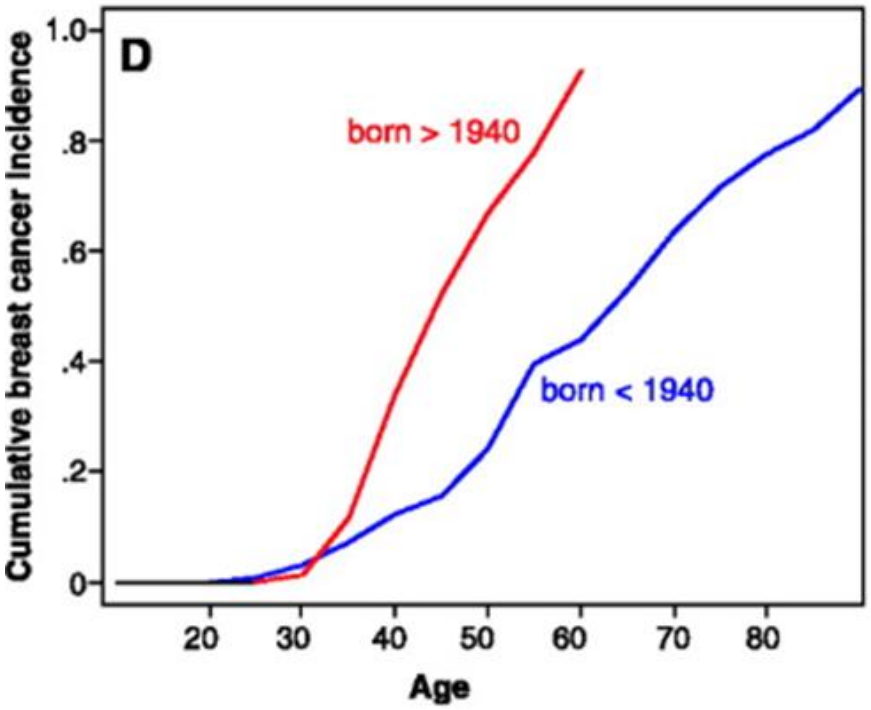

Figure 3. "…nongenetic factors may significantly influence the penetrance even of high-penetrance mutations. Breast cancer risk in women {carrying BRCA1 and 2] born before 1940 is high, but risk is even higher for women born after 1940."[6]

Something other than the gene mutations is causing an earlier and higher penetrance in the more recent cohort than in the earlier cohort. Nongenetic, environmental, factor(s) increased the occurrence of cancers even in those with known mutations.

In summary, most breast cancers are not caused by gene mutations and occur in people with no family history of the disease. Even for those who carry BRCA1 and 2 mutations, their risk is increasing due to environmental causes.

Another factor suggesting that breast cancer is an environmental disease is the temporal change in rates.

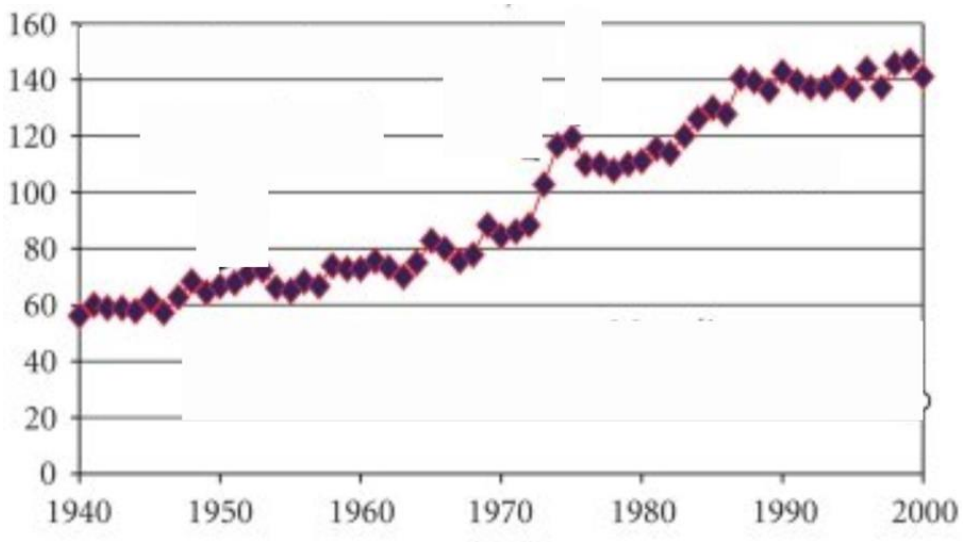

Figure 4. Breast cancer incidence and mortality in the US over time

Figure 4 illustrates that, in the US, the incidence of breast cancer has more than doubled, increasing from 60 per 100,000 to 140 per 100,000 since the 1940s. A portion of this rise can be attributed to increased awareness and detection of the disease, but this is not the whole story – there has been an absolute increase in disease over this century. [7]

This dramatic increase has led to decades of intense research, but we have failed to make a dent in the incidence of the disease. Three time periods have been circled in figure 5 where there has been a shift in incidence rates. [8] The first, circle in yellow, is referred to as the Betty blip- a time period shortly after Betty Ford and Happy Rockefeller went public with their diagnoses and encouraged women to get screened. [10] This helped to destigmatize the traditional silence that came when talking about breast cancer.

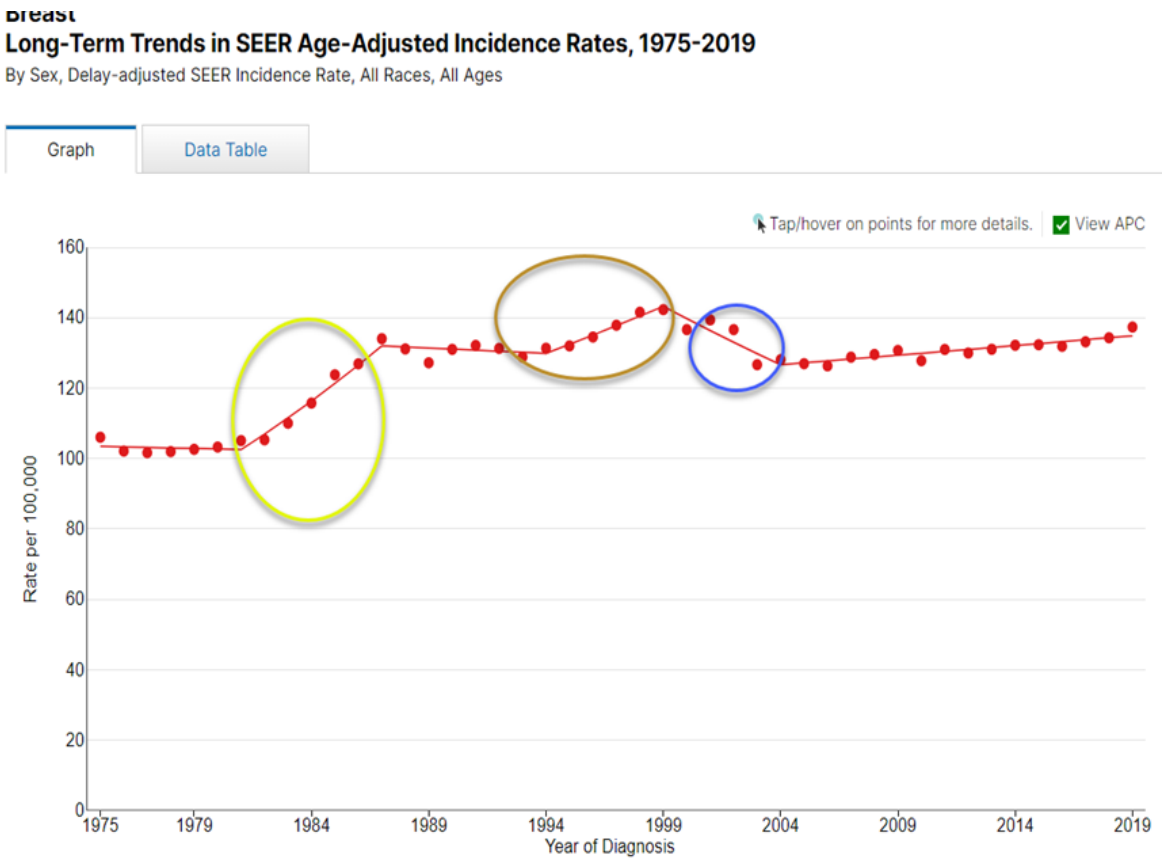

Figure 5. Historical shifts in breast cancer rates. [8]

The orange circle is a period of extensive public awareness of breast cancer and the creation of the national screening program. The national screening program allowed more diagnoses, theoretically helping those affected by breast cancer to have earlier detections, but also increasing the incidental detection of indolent breast cancers. [10]

Finally, the blue circle shows a finding that was not expected. This rapid decrease in incidence rates came after the Women's Health Initiative was halted due to its findings of increased breast cancer risk with post-menopausal hormones.[11] The findings explained a cause-and-effect correlation between post-menopausal hormone use and breast cancer incidence, with estrogen and progestin treatments being linked to a doubling in incidence rates. When the results were publicized, women responded by voluntarily discontinuing their postmenopausal hormone use, and breast cancer rates started falling. [12-13] This is a significant real-life example and proof that we can actually undertake research that can lead to a reduction in disease.

Breast cancer rates also vary over the globe, again suggesting it is an environmental disease. The map in Figure 6 shows the breast cancer rates across the globe, with higher rates in darker colors. Breast cancer rates vary nearly 13-fold across different regions of the world. In general, the higher income, more industrialized countries have higher incidence than the lower income, less industrialized countries. [14] For example, the United States, Canada, Europe and Australia have the highest incidence rates in the world.

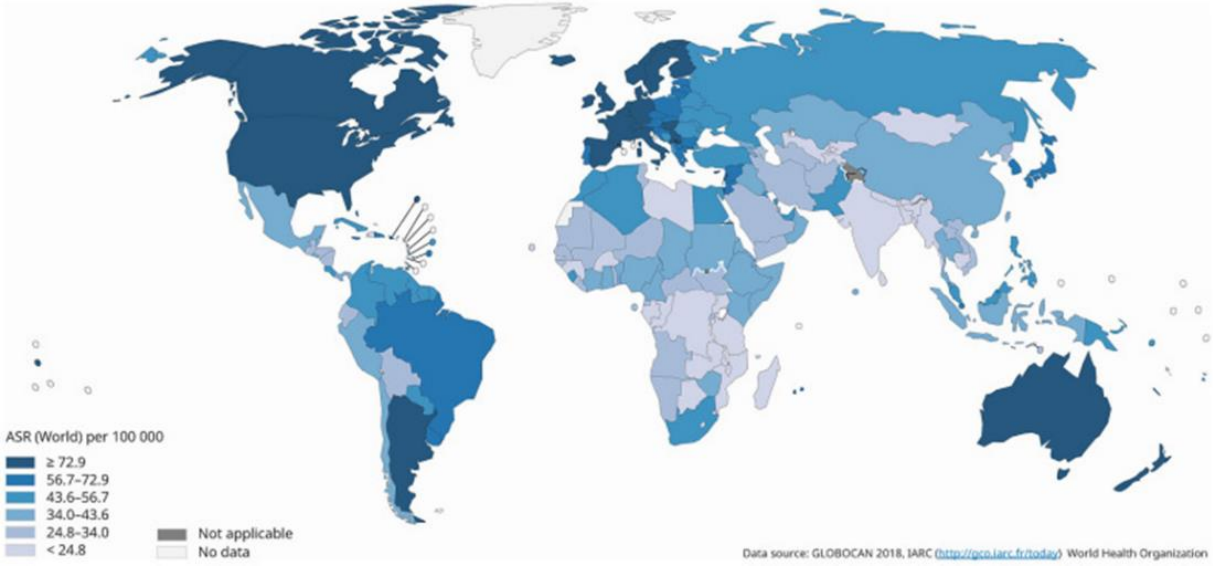

Figure 6: Variation in breast cancer incidence rates across the world.[14]

Not only does the rate vary across countries, but migration from one country to another can impact breast cancer incidence in the women who migrate, in their children and in their grandchildren. One study revealed that Japanese American women living in the U.S. had breast cancer rates two times greater than women living in Japan. [15] The same finding has been demonstrated in other populations, such as immigrants from Mexico and from Asia . [16] Another study focusing on foreign born vs U.S born Hispanics, showed that immigrants who moved from low to high incidence regions such as Mexico to the United States experienced greater risk, with the risk increasing the longer they remained in the U.S. This demonstrates the profound impact that the physical and social environment can have on breast cancer development. There is little that can change the context of people's lives more than immigrating from one country to another. The fact that breast cancer rates vary so much simply by moving to a different country tells us that breast cancer can be caused and prevented by a change in environment.

Preventing Breast Cancer by Changing the Environment

Recognition that breast cancer is an environmental disease as opposed to one of genetic inheritance has implications for how we study, prevent and treat it. Rather than focusing research and treatment efforts on genetics and individual-level treatments, prevention should be focused on changing the environment.

History tells us that the most impactful public health interventions are those that create system-level

changes, influencing a whole population and providing the context for individuals to lead healthier lives. The health impact pyramid reproduced in Figure 7 sorts interventions with different level of impact. [17] The different intervention levels consist of socioeconomic factors, changing the context to make individuals' default decisions healthy, long-lasting protective, clinical, counseling and education interventions. An intervention targeting socioeconomic factors incorporates environmental aspects like the social and physical environments and hazardous living conditions.

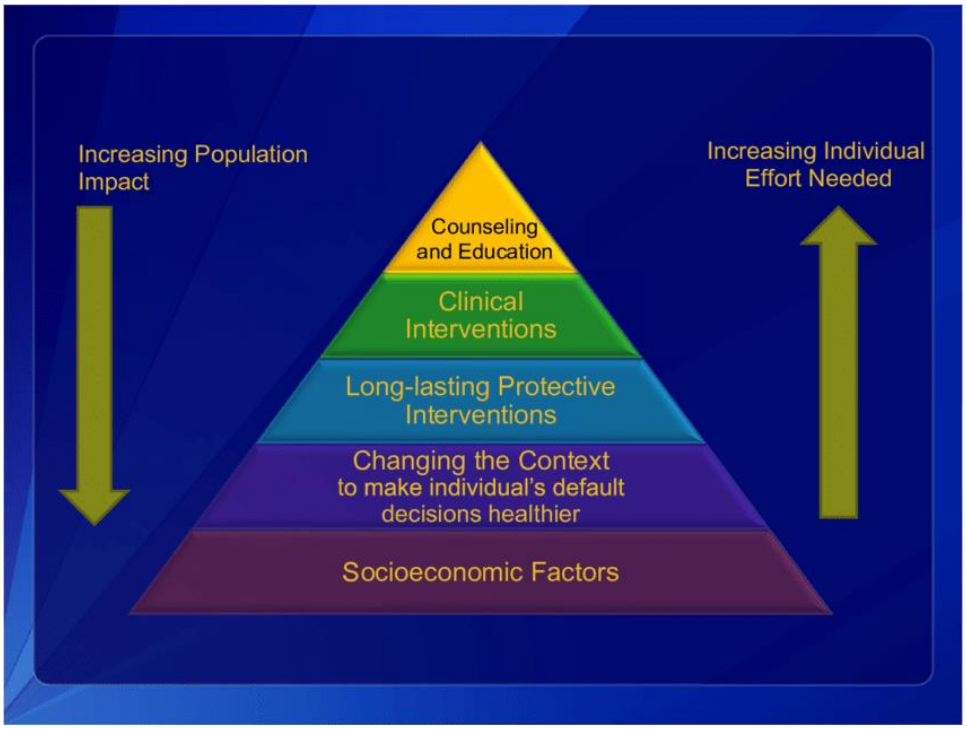

Figure 7: Health Impact Pyramid[17]

Many of the commonly recognized breast cancer risk factors are ones that we try to change by educating and coaching individuals to change their lifestyle; in other words, by counseling and behavioral interventions. These include alcohol consumption, obesity and physical activity.[18] However, we often don't even teach about these well.

Alcohol intake can have up to a 50% increase in the risk of breast cancer and also negatively impact the recurrence and survival rates of those who have breast cancer.[19] Only about one in four women ages 15 to 44 knows that alcohol is a risk factor for breast cancer. [20]

The story of obesity and breast cancer is complex and can be boiled down to this: those with the lowest risk of breast cancer are those who had the highest BMI at age 18 and the lowest BMI at age 50. [23] In a study conducted around Taiwanese women and their BMI in relation to breast cancer it was found that, in postmenopausal women obesity can be a promoter of late-onset breast cancer. It was also found that in early adulthood a higher BMI had reduced risk for break cancer for premenopausal women.[22-23] Despite these rather paradoxical findings, public health messages about breast cancer prevention routinely caution to avoid obesity despite its protective effect for pre-menopausal breast cancer. [23-24] Physical activity also plays a significant role in the prevalence of breast cancer, with an average 25% lower risk in women that have active lifestyles.[21-22] This risk reduction is correlated with biological pathways like hormones and inflammation, both which can be balanced through regular physical activity. In the exploration of 73 worldwide studies, it was found that the frequency of physical activity from moderate to intense had an average reduction of 15% in breast cancer risk. Most significant was the promise it showed for post-menopausal women who benefited from a risk reduction of 31%. While the least efficient interventions of education and counseling still promote physical activity for girls and women, the more effective environmental interventions such as universal physical education and sports in schools is declining.[27]

We live in an environment where we are bathed in chemicals day and night, in our air, our water and in the products we interact with. We know that hundreds of chemicals have been identified in our everyday environment and measured in people. A significant number of chemicals have been identified as suspected breast carcinogens.[28]

Making a connection between a chemical and breast cancer is complicated by many factors, including differing effects during different windows of susceptibility, which mandates knowing not only the dose of the exposure, but also its timing. Latency between exposure during a window of susceptibility and the development of cancer calls out for intermediate markers of disease and measuring impact on known pathways and endpoints.

The fruitful studies on chemicals and their impact on breast cancer that have been done to date – each examining one agent in isolation, have given us critical proof of principle for mechanisms and single-agent effects. Studies of such agents as DDT, DES, and air pollution have revealed the connections between breast cancer and our day-to-day exposure to chemicals. Studies have shown that girls born to women who ingested DES during their pregnancy developed breast cancer at higher rates later in life.[29-30] Additionally, in a study done in Long Island, exposure to polycyclic aromatic hydrocarbons (PAHs) increased breast cancer risk with the highest exposed groups having upwards of a 50% greater risk.[31] Cohn et al found that women exposed to high levels of DDT carry a five-fold risk of pre-menopausal breast cancer for women if they were exposed prior to puberty, with even greater risk if their exposure occurred by 4 years of age.[33] Later studies revealed that women exposed to DDT in utero had a nearly four-fold increased risk for pre-menopausal breast cancer while women first exposed before age 3 years had an increased risk of pre-menopausal breast cancer only, those exposed from ages 3 to 13 years had increased risk of both pre- and post-menopausal breast cancer and women first exposed after age 13 years had an increased risk of postmenopausal breast cancer only. Thus, intrauterine and infant DDT exposure increases risk of premenopausal breast cancer, whereas DDT exposure after infancy increases breast cancer risking the early postmenopausal years.[34]

These studies emphasize the magnitude of the effect that chemicals in the environment have on the development of breast cancer. However, we cannot rely on these chemical-by-chemical methods to tick through the hundreds of chemicals we are exposed to. None of us will be alive long enough to see that approach through. In addition, that approach gives us no insight into such possibilities as additive effects, synergistic effects, antagonistic effects, or multiple insults to common pathways.

Conclusion

The research described above has demonstrated the profound impact of the physical and social environment on breast cancer causation, as well as preventive impact of changes in the environment. New tools, including high resolution mass spectrometry, metabolomics and exposomics, offer promises to uncover new causes as well as risk prediction and protective public policy.

We will not make real progress towards breast cancer until we find ways to go beyond simply detecting breast cancer earlier and instead determine how to markedly decrease the incidence of breast cancer once and for all. We will not accomplish that by staying at the top of the health impact pyramid, impacting one woman at a time, or by examining one chemical at a time. Instead, we must view breast cancer as an environmental disease and discover the environmental factors that are so conducive to the development of breast cancer. Only by changing our environment and working to remove those factors from the environment can we hope to make progress against the disease.

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