NAT'S BLOG ON CANCER AND MEDICINE

Cancer precursor project - breast cancers with precursor lesions - part 6a

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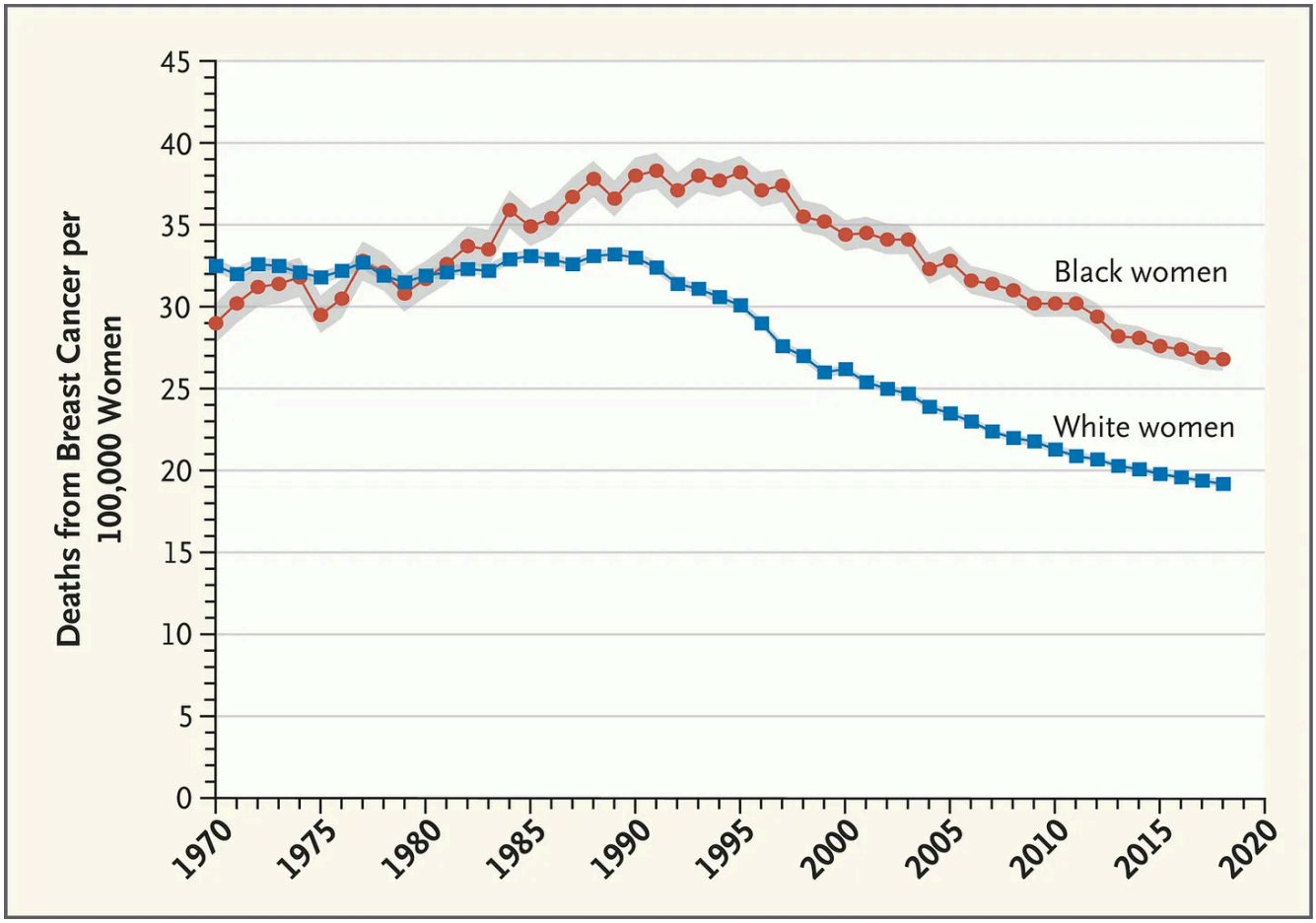
Our initial essays on how cancer arises, summarized here, focused on 4 subspecialties (neuropathology, dermatopathology, bone, joints & soft tissue and hematopathology) in which malignancies rarely have precursors (17 precursors for 540 malignancies or 3.1%). We now focus on epithelial malignancies that commonly have precursors, beginning with breast cancer in women.

Breast cancer mortality

Breast cancer is the fourth leading cause of U.S. cancer death after lung, colorectal and pancreatic cancer, with 42,780 deaths projected in 2024 (42,250 in women, 530 in men). In women, it is the second leading cause of U.S. cancer death after lung cancer. Breast cancer is by far the most common cause of new U.S. cancer cases in women, excluding skin cancer, with 310,720 new cases of invasive breast cancer and an additional 56,500 cases of DCIS (ductal carcinoma in situ) projected in 2024.

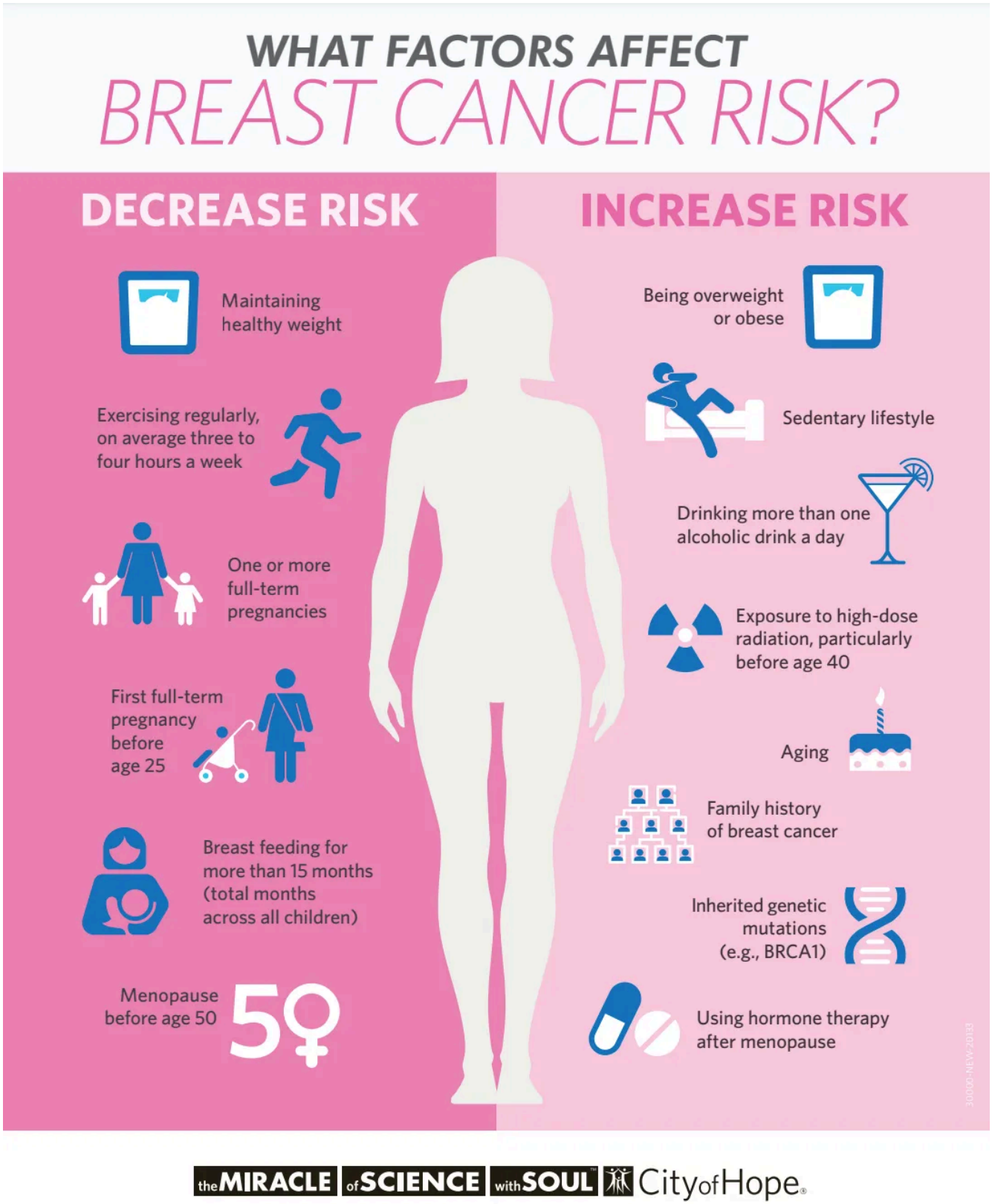


New England Journal of Medicine

U.S. breast cancer mortality has declined substantially, from 33.2 deaths per 100,000 in 1989 to 18.8 deaths per 100,000 in 2022. This decline is attributed to earlier detection, increased awareness and improved treatment (see also here).

Treatment is usually effective with high 5 year (91%) and 10 year (85%) relative survival rates for invasive breast cancer. The survival rate is 10% lower for Black women than White women due in part to more advanced disease at presentation. Survival for all women differs by the extent of disease: the 5 year survival is 99% (Table 8) when the tumor is localized (67% of White women) compared to 86% for regional and 31% for distant stage disease.

Breast cancer risk factors


WHAT FACTORS AFFECT
BREAST CANCER RISK?
DECREASE RISK
Maintaining healthy weight
Exercising regularly, on average three to four hours a week
One or more full-term pregnancies
First full-term pregnancy before age 25
Breast feeding for more than 15 months (total months across all children)
Menopause before age 50
50
INCREASE RISK
Being overweight or obese
Sedentary lifestyle
Drinking more than one alcoholic drink a day
Exposure to high-dose radiation, particularly before age 40
Aging
Family history of breast cancer
Inherited genetic mutations (e.g., BRCA1)
Using hormone therapy after menopause
the MIRACLE of SCIENCE with SOUL
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CityofHope.org/breast-cancer-environment

City of Hope

The most important breast cancer risk factors are being born biologically female (women have 100 times the risk compared to men) and increasing age.

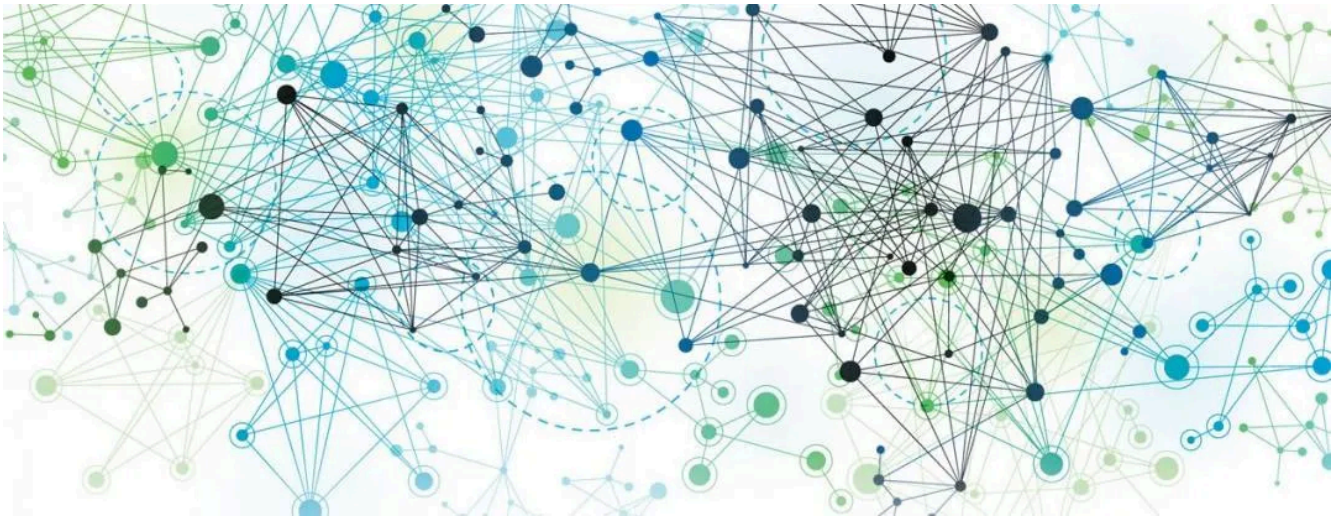
Reproductive and hormonal risk factors are related to increased estrogen exposure: early onset of menstruation, late menopause, not having children or having a child after age 30, obesity for post-menopausal breast cancer (promotes estrogen production) and hormone replacement therapy. Breastfeeding, which reduces estrogen levels, lowers the risk.

Genetic risk factors are not common but having one first degree relative (mother, sister, daughter) increases the risk by 2 - 3 times, higher if the relative is affected before age 50 or had bilateral disease; the increased risk with two first degree relatives is 4 - 6 times. Mutations of the *BRCA1* and *BRCA2* genes are associated with familial breast cancer at an early age; they account for 20 - 60% of familial breast cancer cases but only 5% of all cases. Other genetic changes that increase the risk are less common.

Medical risk factors include the presence of DCIS (ductal carcinoma in situ), some proliferative breast diseases (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ), cancer in the endometrium (uterus) or opposite breast, radiation exposure in young women and dense breast tissue.

Behavioral risk factors include a high fat diet, obesity, heavy alcohol use and failure to get screening mammograms. Eating soy and carotenoids and engaging in physical activity reduces the risk.

How breast cancer arises



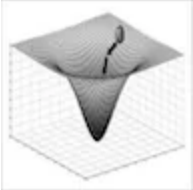
In contrast to machines, which can be understood by reductionist principles (i.e., "the behavior of the whole equals the behavior of the sum of the parts"), human life is a complex system composed of thousands of biological networks that interact in a nonintuitive way and are influenced by their prior history. These networks consist of 20,000 protein-coding genes that regulate each other by switching each other on and off, along with proteins that interact with these genes. These networks create and alter the biomolecules that transform a fertilized egg into an embryo, fetus, infant, child, teenager and adult. These networks must also respond to environmental dangers (infections, infestations, trauma, heat and cold) and enable human reproduction and evolution.

The network proteins and genes have a chemical structure that promotes their interaction with each other in numerous ways, some disruptive to their preferred function. Yet these networks must remain "on track" because inappropriate activation can cause untoward consequences, such as cancer. Human evolution has minimized disease by developing redundant control systems that limit the inappropriate activity of biomolecules and networks. However, evolution, which may require up to 1 million years to occur, is not effective against the recent onset of cancer risk factors. Evolution also does not primarily affect factors that help us live beyond the reproductive years.

Human life begins with a fertilized egg that uses preexisting proteins and transcripts in the egg to rapidly multiply and develop into an embryo. Cells then secrete morphogens that diffuse across the embryo and interact with each other, creating three dimensional concentration gradients that cause the activation of specific genes, leading to cell

differentiation. This unidirectional process creates different genetic activity in neighboring cells, which explains how cells differ despite having the same DNA. The principles of self-organization guide further development, similar to how proteins "know" how to fold.

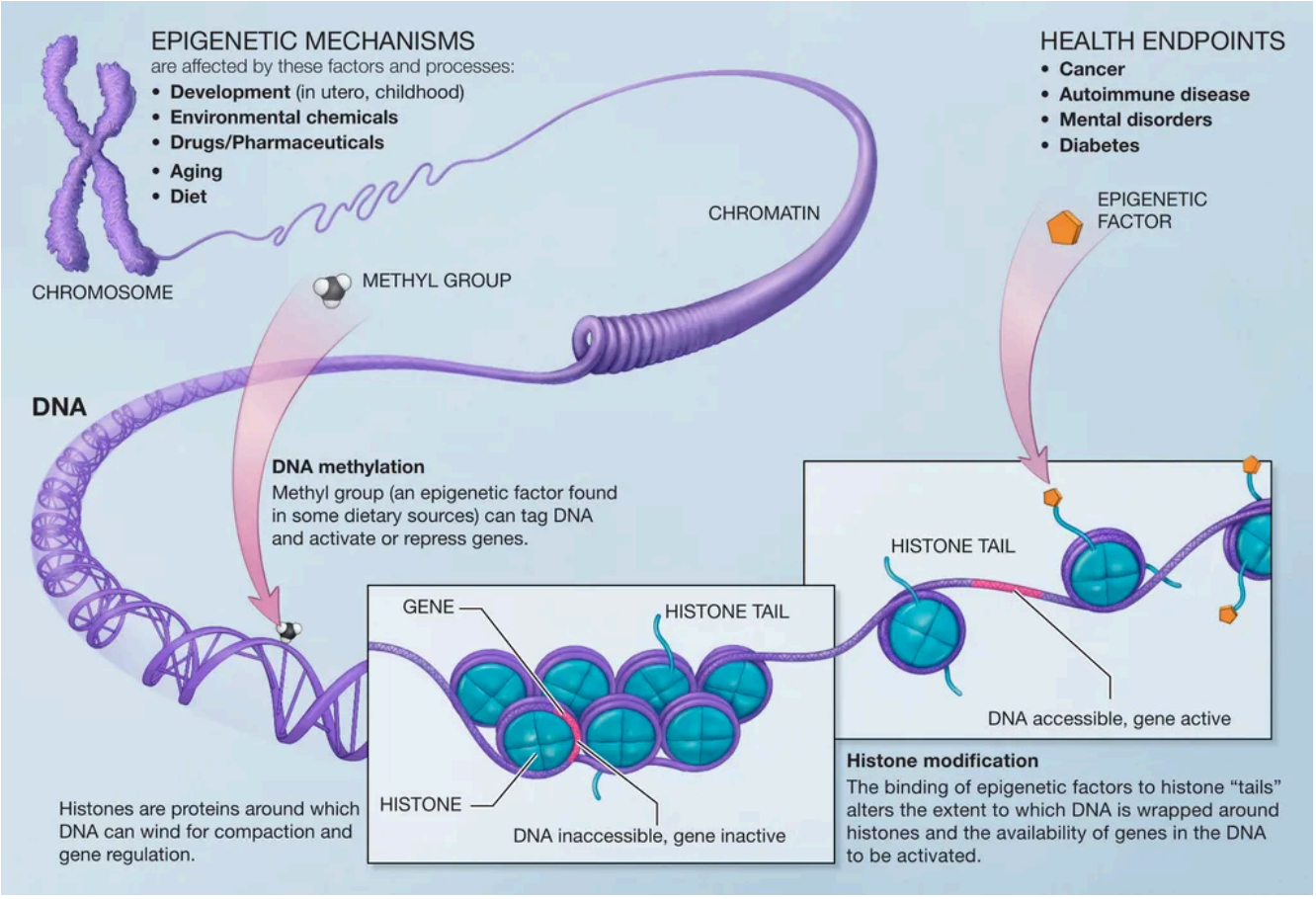
DNA may be organized into cascades so that activation of one gene may lead to the activation of other genes. For example, in embryogenesis, activation of homeobox genes, which function as transcription factors, leads to the direct formation of body axes and structures through cascades of coregulated genes.



Cell attractors pull breast epithelial cells into a common configuration.

The attractor concept explains how our estimated 30 trillion cells, many with small differences in network activity, are pulled into only 200 cell types with similar functions and microscopic appearances. Attractors have been analogized to a low-energy state or valley on a topographic diagram that tends to maintain cellular network stability against common disruptions.

Adult biological networks typically are relatively stable due to interactions with numerous other networks, which constrains rapid change. Networks may become poised at "tipping points" to facilitate changes to cellular physiology, including the inflammatory response to trauma and infection. These tipping points are a component of self-organized criticality, a property of complex systems in which stresses to networks typically cause minimal changes but rarely cause catastrophic failures, such as cancer. Thus, cancer is inevitable in humans, although not necessarily in each individual. We can reduce its incidence, we can detect it earlier and we can treat it more effectively but attaining a world without cancer is not possible.



Cells function based not just on their DNA but on organic codes and cellular memory. Organic codes are signals from the environment, including physical forces and mechanical stress, that are "decoded" or responded to by the cell based on its own rules. For example, proteins fold in specific ways based on organic codes to maximize their functionality and minimize untoward reactions, but this is not hard coded in the DNA. Cellular memory includes histone modifications and other epigenetic modifications that survive mitosis and affect cell function.

Cancer arises from the disruption of our biological networks, often initiated by cancer risk factors. Risk factors undermine the redundant control systems, although it typically takes decades to pierce the multiple levels of controls that prevent cancer development. Cancer risk factors appear to activate these four superpromoters of malignant transformation:

- Chronic inflammation destabilizes many biological networks and is difficult to inactivate when triggered by risk factors. Physiologic initiators of inflammation typically simultaneously trigger resolution mechanisms to turn these networks off

so they don't cause untoward damage to the individual. However, cancer risk factors activate inflammatory networks without triggering resolution pathways. This causes constant activation of these networks that may overcome the redundant control systems and ultimately trigger the malignant process through pathways that are difficult to restore to normal. Chronic inflammation promotes cancer by (a) producing reactive oxygen and nitrogen species that damage DNA, (b) producing cytokines and other growth factors that promote cell proliferation, (c) creating a microenvironment that nurtures the malignant process and (d) through damage to the immune system.

    - Chronic inflammation related to breast cancer is primarily due to excess weight, the Western diet (high fat, low fiber, low consumption of fruits and vegetables), alcohol consumption and aging (which produces a low grade chronic inflammatory state).

- DNA alterations change network structure so they don't function as intended. They may be germline (before birth), somatic (after birth), random or due to other "network rewiring", such as epigenetics or changes to mRNA. These network changes may have a minimal impact initially because there are enough other controls to keep the networks on track. However, as other networks change and control systems are rendered less effective, they have a larger effect on promoting malignant transformation.
    - For breast cancer, DNA changes may be due to chronic inflammation (see above), chronic estrogen exposure, alcohol use and the genetic risk factors described above.
    - These network changes may also occur in the microenvironment (neighboring area) of breast epithelial cells, which act independently to promote and sustain the malignant transformation of these epithelial cells.
- Immune system dysfunction hinders the usual immune system killing of damaged cells.
    - Chronic inflammation appears to be the most important risk factor causing immune system dysfunction in breast cancer. Immune system function also declines with age (immunosenescence).

    - We also consider public health failures, such as inadequate governmental programs to promote regular mammograms or physical exams, to be a "societal immune system failure" that leads to many clinical breast cancer cases that would otherwise have been avoided.

- Prolonged hormonal exposure (estrogen for breast cancer) promotes the continuous reproduction of breast epithelial cells, including the transmission of DNA alterations to daughter cells. Estrogen may also directly alter how cells repair DNA.
    - When estrogen exposure is shortened (through the late onset of menstruation or early menopause), interrupted (by having children, particularly by age 30) or reduced (by breastfeeding children, maintaining a normal weight and avoiding hormone replacement therapy), breast cancer risk is reduced.

These network changes interact with each other to further destabilize themselves and other networks. Variations in germline DNA may make biological networks more or less sensitive to the changes induced by risk factors or may be a risk factor themselves, such as BRCA mutations. Changes to biological networks seemingly unrelated to cancer, such as oxygen sensing, may also have an impact because of the interactions between networks.

These risk factors act on large numbers of cells but often in different ways, resulting in breast cancer cells that frequently have varied properties even if they look similar microscopically.

The next essay will discuss breast anatomy and histology as well as cancer precursors; it then will begin the discussion of all breast cancers with known precursors, starting with infiltrating duct carcinoma of no special type, lobular carcinoma and pleomorphic lobular carcinoma.

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- Strategic plan to substantially reduce cancer deaths
- American Code Against Cancer (how you can prevent cancer)
- Cancer Precursor Project spreadsheet and General Overview

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