The Ecology of Breast Cancer

The promise of prevention and the hope for healing

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Toward a systems perspective of breast cancer

Breast cancer is an ancient disease. Its recorded history dates back to ancient Egypt (3000-2500 BCE). Early documents describe what tumors looked like as they surfaced and progressed.[1,2] Recorded speculations about their origins appear much later. Hippocrates and others espoused a humoral theory, thinking that imbalances among four bodily fluids—blood, yellow bile, black bile, and phlegm—caused this to happen. Galen (130-c.200 CE) subscribed to Hippocrates' bodily humors theory, persuaded that he saw breast cancer more often in melancholy (literally, "black bile") women who were creative, kind, and considerate. Some thought they saw cancer more generally in women who were anxious, depressed, or grieving.[3] For Galen and many who followed, breast cancer was a systemic disorder and not confined to a single part of the body.

In the 17th century, Italian physician Ramazzini saw that "tumors of this sort [breast cancer] are found more often in nuns than in any other women. In my opinion, these tumors are not due to amenorrhea, but rather to the celibate life led by these nuns."[4,5] Some theories proposed that trauma or lymphatic or milk duct blockage was involved. But with the invention of the microscope and emerging understanding of a cellular basis of anatomical structures, cancer cells became visible, and breast cancer began to be seen as a more localized disease. New anesthetic techniques aided a dramatic increase in surgery and, for decades, the radical mastectomy, pioneered by William Halstead, dominated breast cancer treatment. Halstead believed that removing enough tissue and precision to avoid spreading cancer cells during surgery led to the best chances of cure.

In the late 19th century Scottish surgeon George Beatson reported that removal of the ovaries in several of his patients caused remission of inoperable breast cancer.[6,7] Hormones had not yet been characterized, but Beatson saw lactation prolonged in farm animals after their ovaries were removed. "Lactation is at one point perilously near becoming a cancerous process if it is at all arrested," he said.[8]

During ensuing years, scientists identified estrogen and other hormones.[9] Surgeons sometimes added removal of the ovaries, adrenals, and pituitary glands to breast cancer treatment. Thus, the emphasis on the cellular basis of cancer began to include consideration of the general hormonal environment influencing tumor growth.

In his 1966 Nobel acceptance speech, Charles Huggins, a cancer biologist who studied the hormone dependency of various cancers, observed, "The net increment of mass of a cancer is a function of the interaction of the tumor and its soil. Self-control of cancers results from a highly advantageous competition of host with his tumor. There are multiple factors which restrain cancer - enzymatic, nutritional, immunologic, the genotype, and others. Prominent among them is the endocrine status, both of tumor and host."[10] Huggins saw cancer not just as a disease of aberrant cells but as one that requires a host environment favoring tumor growth. Despite this understanding, with the development of techniques of molecular biology that have enabled more detailed study of cells and sub-cellular parts, many cancer biologists continued to focus their attention on the cancerous cell.

Cancer: A disease of cells or tissues?

Scientists have long been aware that cancer development is a multi-stage, multi-factorial phenomenon. The models they use generally describe tumor initiation, promotion, progression, and metastasis. In a widely-cited paper, Hanahan and Weinberg listed six hallmarks of cancer generally having to do with cancer cells—their response to various signals, evading growth suppressors, activating invasion and metastasis, resisting cell death, and so on.[11] Recently, they added tumor promoting inflammation to their framework,[12] but basically they privilege the original mutated cancer cell as most important, with secondary contributions from the nearby tissue microenvironment. This is the somatic mutation theory of carcinogenesis.

Another view holds that cancer is a tissue-based disease.[13,14] It proposes that changes in the tissue environment that normally keep cellular proliferation in check are central to the origins of cancer. Advocates of this view point out that cellular proliferation is the default state of most cells and gene mutations and changes in gene expression are common even within cells that do not develop into cancer. Interactions with the surrounding tissue are essential for modulating these activities and their effects. Experimental evidence in laboratory ani-

mals, for example, shows that tumors developing in the ductal epithelial cells of mammary glands depend on exposure of the surrounding stroma to a carcinogen and not just epithelial cell exposure.[15] Moreover, using the same animal model, these authors showed that epithelial cancer cells introduced into normal stroma could form normal, non-cancerous mammary ducts.[16] That is, the cancer cells could revert to normal. Thus, this theory holds, stromal-epithelial interactions in the tissue environment are more important than events in a mutated cell in the development and progression of cancer. From this it follows that an integrated approach, whereby cancer causation occurs in all directions, namely bottom-up, top-down, and reciprocally, will best illuminate the complexity of cancer and opportunities for prevention.

These contrasting views differ with respect to the level of organization most appropriate for understanding the origins of cancer. One emphasizes the primary role of aberrant cells, while the other features an altered tissue environment and the importance of multi-level interactions.

Breast cancer and the more general environment

The importance of the more general environment in the origins and progression of breast cancer becomes clear after looking at evidence discussed in later chapters. We know that latent, undiagnosed breast cancer develops over many years—in some cases over decades—and may be undetected during life. A review of seven autopsy studies reported invasive breast cancer in an average of 1.3 percent of 852 women ages 40-70 who had died from other causes and were not known to have breast cancer while alive.[17] The number of tissue sections examined ranged from 9-275 per breast in five of the seven studies and was not described in two. Carcinoma *in situ* (CIS)* was reported in 8.9 percent on average. Highest percentages were reported in studies where the breasts of the deceased were examined more thoroughly. One of the studies included 110 consecutive autopsies of young and middle-aged women (ages 20-54), finding invasive breast cancer in two (1.8 percent) and CIS in twenty (18 percent).[18]

* There are two kinds of carcinoma in situ, ductal and lobular. Ductal carcinoma in situ (DCIS) refers to breast duct epithelial cells that have become "cancerous," but still reside in their normal place. Lobular CIS (LCIS) refers to cells in the lobules that have undergone similar changes. In this setting cancerous means that there is an abnormal increase in the growth of the cells. CIS is nonlethal because it stays in place, but is important because it may progress to invasive breast cancer. However, some cases of CIS do not progress to invasive disease and predicting which ones will and when that may happen is difficult. DCIS is commonly first identified by mammography since it frequently contains calcium deposits that show up on the image. See also http://www.ncbi.nlm.nih.gov/pubmed/20956817 for access to a more complete discussion.

Although CIS is considered a precursor of breast cancer, some cases do not progress to invasive disease. Recently, some medical professionals have argued that the term "carcinoma" should not even be used in the name of this lesion since it contributes to over-diagnosis and over-treatment.[19] Predicting which ones will progress is an unsolved important problem. For those that do progress to invasive breast cancer, whether some may actually spontaneously regress and disappear is unclear but of intense interest.

To help to address this question, scientists in Denmark compared breast cancer incidence in women of comparable ages before and after breast cancer screening by mammography was introduced.[20] They reasoned that if mammography was simply going to enable a diagnosis of breast cancer earlier, one would expect to see a drop in age-adjusted incidence in screened women sometime after screening was initiated. They found that the increase in incidence of breast cancer was closely related to the introduction of screening, but that little of this increase was compensated for by a drop in incidence in previously screened women. They concluded that one in three invasive breast cancers detected in a population offered screening mammography will not lead to symptoms or death. The percentage was considerably higher (52 percent) when CIS was included.

This report sparked debate, and critics suggested that the findings could be explained by the discontinuation of hormone replacement therapy that coincided with the study period. In response, the study was repeated using data from an earlier period, when few women were using hormone therapy.[21] The study compared breast cancer incidence in two groups of women aged 40-69 years. One group was screened repetitively during a six-year period and a matched control group was screened only once, at six years. The research team hypothesized that cumulative breast cancer incidence should be similar in the two groups after the follow up period if no tumor regression occurred. They found 14 percent higher incidence in the repetitively screened group, suggesting that some invasive breast cancers would regress spontaneously if not diagnosed at screening.*

What are we to make of this? What does it tell us about the natural history of breast cancer? Here are some things we know. CIS is relatively common. Some CIS progresses to invasive breast cancer but some does not. CIS and invasive breast cancer can begin at a relatively early age. The time that elapses between the initiation of breast cancer and when it becomes clinically apparent—the latency period—varies considerably but can be spread out over decades.[22] Screening studies conclude that some breast cancers will spontaneously regress.

* Another explanation could be that repetitive screening actually caused the increased breast cancer in that group. It's unlikely because a six year follow up is generally too short to see cancer as a result of radiation exposure, although it's not out of the question. But this raises an important question about the relative safety of using a known carcinogen (ionizing radiation) to diagnose breast cancer. New diagnostic methods are urgently needed.

The general physiologic environment also influences the course of breast cancer after diagnosis. The internal environment is shaped by diet, activity levels, exposure to environmental chemicals, stress, sleep, and other variables. They influence immune system function, levels of inflammation, hormones, and various growth factors that promote tumor cell growth or death. They establish a *milieu intérieur* (the environment within), a phrase coined by physiologist Claude Bernard. It is the context—Huggins' "soil"—that favors or discourages cancer development and growth.

As we will see, community and societal characteristics can also strongly influence this internal environment. Breast cancer is not only a disease of individuals, but also of communities. Breast cancer patterns arise out of the societies that we design. In that way, breast cancer is profoundly a public health concern requiring a public health response (see Box 1.1). A larger framework that includes multiple levels of organization—the individual, family, community, ecosystem, and society—and reciprocal interactions among them, is arguably essential for better understanding the origins and prevention of breast cancer.

Breast cancer as an ecologic disorder

Ecologists often use a nested hierarchy of levels of organization to construct models and design studies (see Figure 1.1).[23] Here, hierarchy does not refer to importance or power but is a way of describing relationships within a complex system. In that tradition, some epidemiologists advocate an eco-social framework to help design investigations into the origins of diseases as well as medical and public health interventions to prevent or treat them.[24,25,26,27]

An eco-social* framework recognizes that context matters. It acknowledges the ways that family, community, and societal experiences shape the health of individuals and populations. What I eat may seem to be mostly a personal choice, but it's not entirely. What the food system produces, the price and availability of various kinds of food, opportunities I may or may not have to grow my own food, and the impact of media and advertising will also strongly influence my diet.

Similarly, my internal physiologic response to walking alone at night in an unlit urban neighborhood or forest will be conditioned by how safe I think it is. If I live in a neighborhood that I think is unsafe, I will most likely live in a state of constant vigilance that chronically raises

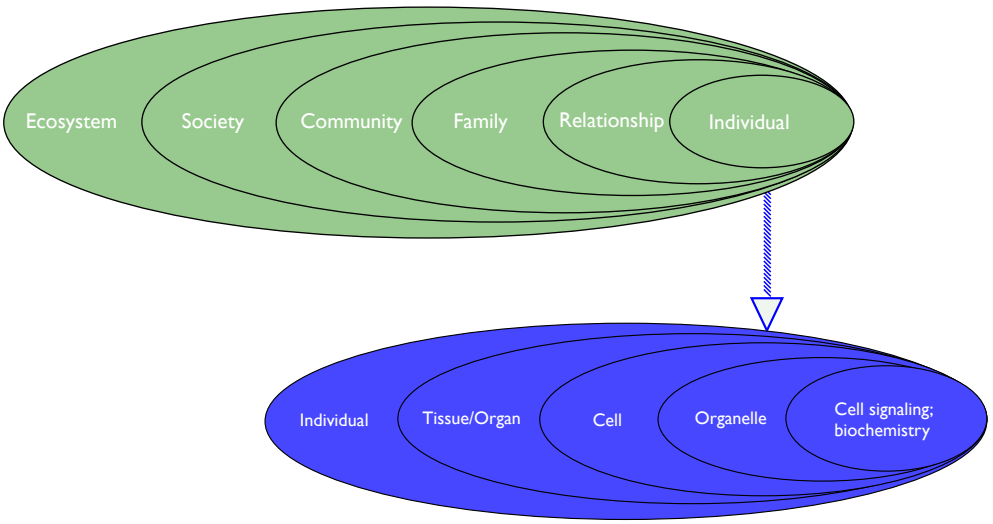
* This is sometimes called an ecologic or complexity framework. Terminology varies to some extent because of the variables included in the model and also because of connotations associated with various words. But the important commonality is the attempt to incorporate multiple level variables in a richly interactive system undergoing change over time.

markers of stress measureable in my blood that increase my risk of various diseases. If I can sometimes walk amongst trees and listen to bird songs that impact is diminished.[28]

The point is that societal and community level variables intimately influence the biology of individuals, even at the sub-cellular level. Thus, within an eco-social framework, when investigating the origins of breast cancer or other complex diseases, it is essential to consider the social, cultural, economic, and political environments within which cells, tissues, individuals, and families live.

Long ago, microbiologist René Dubos pointed out that every civilization creates its own diseases. In recent decades, population growth, technological achievements, and industrialization have dramatically altered energy production and use, transportation, buildings, the nature and availability of consumer products, food and agriculture, and social, political, and economic structures. No place on earth or in the atmosphere surrounding the planet is untouched by human activities. The nature of work and leisure activities is profoundly changed. Within this context the patterns and distribution of breast cancer and other common diseases have arisen. It is increasingly clear that a multi-level framework is essential to study and address them.

Figure 1.1: Ecological (eco-social) model of nested relationships from sub-cellular to ecosystem



Box 1.1: Ecology, ecosystems, and regime shifts

Ecologists have long grappled with complex models to describe and study ecosystems. Their models feature interactions among multi-level variables—microbes, soil, trees, forests, grasses, water, region, climate, diverse wildlife, people, farms, cities, and so on. In these models, interactions and feedback loops are primary phenomena—not secondary. Impacts cascade through parts and subparts of this complexity over varying timeframes. Interactions among mixtures of variables determine system structure and function—resilience or vulnerability. These are science-based models that attempt to represent current understanding of ecosystem dynamics.

Ecosystem disturbances can come from various levels—from changes somewhere in the internal food web or a hurricane. A resilient ecological system is able to absorb and adapt to disturbances while maintaining essential functions, structures, and feedback loops. A vulnerable system is operating close to a threshold, where even small disturbances can push it beyond a tipping point so that structures and functions change fundamentally. When that happens, a new relatively stable set of operating conditions makes it difficult, if not impossible, for the system to revert to its previous state, even if a triggering event is removed.

There are many examples of this phenomenon. After a long period of fluctuating but slowly declining vegetation the Sahara region collapsed suddenly into a desert.[29] A lake gradually but inexorably receiving excessive nutrient loading from fertilizer runoff suddenly transforms from being fish-rich to fish-poor. Algal blooms and plant growth accelerate, oxygen levels crash, a threshold is crossed, and the entire food web changes, resulting in massive fish kills. This is a regime shift—the operating conditions of the lake have fundamentally changed; its structure and function are different. New conditions in the lake are exceedingly stable and simply stopping the flow of nutrients will not re-establish previous conditions in the short term. This kind of abrupt and irreversible change can happen in vulnerable communities and people who are burdened with one or more stressors.

Ecological scientists note that regime shifts can also occur as a result of crossing several smaller-scale thresholds within a complex system.[30] For example, small-scale social, economic, and ecologic changes in an agricultural region can cause threshold interactions that result in major system transformation—the regional ecosystem, including its human communities, fundamentally changes.[31] For most people living and working in the region it's a collapse.

Here are a few lessons from extensive information about ecosystem structure, function, and behavior:

- Complex system characteristics differ from those in simpler systems in many important ways (see Table 1.1);
- Resilience or vulnerability are characteristics of system operating conditions; vulnerable ecosystems are less able to absorb and adapt to disturbances than resilient ecosystems;
- System operating conditions are largely determined by interactions among multi-level variables, acting over varying timeframes; not by single variables in a constrained timeframe;

- Slow-acting variables, over time, can set the stage for vulnerability to a fast-acting variable;
- Fundamental changes in ecosystem structure and function can be caused by large single or multiple small disturbances coming from the outside or from within;
- Studying this complexity requires models and techniques designed for the task rather than simplifying the complexity to accommodate models suited for simpler systems.

Table 1.1 System characteristics: simple vs. complex

Simple	Complex
• Homogeneous • Linear Behavior • Deterministic • Static • Lack feedback loops	• Heterogeneous • Interactions; feedback loops • Non-linear behavior • Causal cascades • Dynamic, adaptive, self-organizing • Tipping points (system behavior change) • Emergent properties not predictable from individual parts • Resilience, vulnerability

What does this have to do with breast cancer? It's a way of gaining further insight into the patterns that we see. In the ecological sciences, single variables rarely explain system behavior—interactions and relationships are of primary importance. Vulnerability can develop over time, making a system much more susceptible to a later disturbance. Resilience varies.

Breast cancer fits well within this framework. Many, multi-level environmental factors interact with human breast biology, beginning with early development and continuing throughout life. Breast cancer is an ecological disease as much as it is a disease of abnormal cellular growth. It arises from system conditions. Early life nutrition influences the vulnerability of the breast to exposure to a chemical carcinogen later in life. Stress alters BRCA gene expression. Nutrition, exercise, and stress levels collectively influence response to breast cancer treatment and likelihood of recurrence. And, so on. Failures to account for dynamic interactions among multi-level variables limit the utility of many epidemiologic studies that were painstakingly carried out over many years.

In large part, this is a design problem—an ongoing commitment to a familiar reductionist approach rather than turning to alternative ecological models. The reductionist approach makes something complex into something simpler by taking it apart into constituent pieces. That's how science is often done, and it has yielded enormous, valuable insights. But it comes up against its limits when it fails also to examine the reassembled pieces. It lacks insights from geometry, topology, and ecosystem dynamics. This is now beginning to change. New complex-system models will hopefully shed additional light not only on the functioning of ecosystems, but also on the origins of complex diseases like breast cancer.

Breast cancer: An ecologic perspective

Breast cancer is a diverse group of diseases of different sub-types. Their biology differs with respect to hormone-receptor features, menopausal status, and invasiveness. The origins of breast cancer are multi-factorial, and risk factors among sub-types differ. Opportunities for prevention and response to treatment vary.

One way to think about this is that different combinations of multi-level variables over time create the conditions in which breast cancer can develop and progress. In many ways, this is like a complex ecosystem and scientists are continuing to develop new models for studying the disease that reflect this complexity (see Box 1.1).

One example moving in this direction is an evidence-based complex model of postmenopausal breast cancer causation developed by scientists at the University of California San Francisco. It includes biologic, societal/cultural, behavioral, and physical/chemical dimensions.[32] It also includes estimates of the strength of the associations and quality of evidence that link these many variables together in a complex, interactive network.

This model is a step forward. The complexity becomes clear, and immediately we begin to imagine new and different study designs and interventions. It's not truly multi-level in that it generally addresses variables at the individual- but not community- or societal-levels. Assessments of neighborhood safety, for example, will influence activity levels and stress. Federal farm crop subsidies can alter cancer risk through their influence on food prices and availability. These additional levels could be included in system models.[33] They highlight additional opportunities not only for understanding the origins of diseases but also for intervening in system dynamics.

Complex system models often look like a tangle of arrows with everything so interconnected that at first glance it seems impossible to sort out. But, these models serve a number of different purposes. They acknowledge and communicate complexity, confirming the inescapably messy, systemic nature of the problem. Complex system models also provide a basic architecture for organizing facts and categories. Once the top-level architecture is grasped, it becomes easier to identify relevant variables and plan an approach for further study or intervention.

These models also make clear that complex systems cannot be tightly micro-managed. Quantitative impacts of changes in single variables will often be difficult to predict and even to identify. Moreover, in order to prevent the development of cancer or improve outcomes after diagnosis, broad and diversified strategies will be necessary to change the dynamics of the system. Closer study of a complex model reveals features that help in deciding how and where to intervene most effectively in the system—at multiple levels, leverage points, feed-

back loops, and causal cascades. Combinations of multi-level interventions are more likely to bring about outcomes as close to what we want as possible (See Box 1.2).

Box 1.2: Individual Health—Public Health: The North Karelia Project

Public health practitioners have long recognized the benefits—or risks—associated with small shifts in determinants of health within populations. In 1985, epidemiologist Geoffrey Rose observed that a large number of people at a small risk will give rise to more cases of a disease than a small number of people at a large risk.[34] The causes of cases of a disease in individuals, he said, differ from the causes of incidence of that disease in a population. Why some individuals have hypertension is a different question from why some populations have much hypertension, while in others it is rare.

Rose was interested in strategies for disease prevention. He recognized that small downward population-wide shifts in blood pressure where hypertension was common could have large public health benefits. Community-level interventions differed from what individuals could do to accomplish the same goal.

The North Karelia project in Finland put these ideas to work about 25 years after demographer, Vaino Kannisto, published his doctoral thesis pointing out that eastern Finland had the highest heart disease mortality in the world.[35] By this time, the Framingham Heart Study, started in 1948, had begun to identify risk factors that contribute to cardiovascular disease by following its development over a long period of time in a large group of participants. Based on Framingham findings, population-wide efforts to reduce smoking, cholesterol, and blood pressure were undertaken in N. Karelia. Efforts involved not only individual education and treatment but also work with the media, supermarkets, and agriculture. The results were dramatic. In 35 years the annual age-adjusted coronary heart disease mortality rate among 35-64 year-old men declined 85 percent. Cancer-related mortality was also reduced, and all-cause mortality reduced for men and women.

One early commentary on the North Karelia project critically called it "shot-gun prevention."[36] But, it worked. It showed the value of multi-level interventions in a population rather than focusing on individuals at highest risk. Data from five different surveys showed that an estimated 20 percent of the coronary heart disease mortality could be prevented by reducing cholesterol levels in the entire population by 10 percent, while a 25 percent cholesterol reduction in only those with the highest levels would reduce morality by only five percent. Lifestyle changes, they concluded, are not just responsibilities of individuals but also of communities.

We often debate which public health interventions should be directed at entire populations or focused more on individuals at risk to address disorders such as cancer, diabetes, cardiovascular disease, obesity, and dementia, among others. But it's undeniably clear that prevention of complex diseases cannot be achieved by individuals alone. Community- and societal-level interventions are also essential.

Historically, epidemiologic studies investigating the causes of breast cancer have typically controlled for various confounders and other factors known to independently influence risk while attempting to isolate the impact of a particular variable of interest. They have tended, for example, to focus on particular aspects of diet, a specific chemical or physical exposure, or exercise. They have contributed valuable information. Most basically, we have learned that, for breast cancer, there is no smoking gun like the tobacco-lung cancer connection. It's truly a systemic problem. New study designs and interventions are urgently needed.

In 2008, Congress passed the Breast Cancer and Environmental Research Act, which required, among other provisions, the establishment of an interagency committee comprised of scientists from Federal agencies, universities, and other non-Federal organizations to examine the status of breast cancer research in the United States and make recommendations for improving it. This committee, known as the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC), issued its final report in 2013, with a clear call for prioritizing the prevention of breast cancer.[37] They said:

- The complexity of breast cancer necessitates increased investment in research to explore mechanisms underlying breast cancer over a person's life span. Exploration of the impact of environmental factors on breast development is needed, as altered development may influence breast cancer risk. Gene-environment interactions and epigenetic alterations — heritable changes that do not involve changes in DNA sequence — that occur over the lifespan deserve more attention.

- Research must evaluate the impact of multiple risk factors and periods when the breast may be most susceptible to exposures, and investigate how certain populations, such as underrepresented minorities, have disproportionate exposures and different levels of breast cancer risk. By engaging researchers from many disciplines, new ways of thinking about breast cancer prevention can be developed.

- Research must include investigations into the effects of chemical and physical factors that potentially influence the risk of developing, and likelihood of surviving, breast cancer. Characterizing the myriad of exposures in our environment in diverse population groups is part of this important challenge.

The committee called for:

- Trans-disciplinary coordination; and
- Transparency and inclusion of representatives of the general public and health affected groups in planning, implementation, and translation of research findings, built from the start into every funded program that focuses on breast cancer and the environment.

This committee is promoting new models for understanding the origins and treatment of breast cancer. They emphasize the importance of a life-course approach, the timing of exposures, and exposure to mixtures of risk factors. Multi-level, ecological frameworks are best suited to this complex task.

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