The Ecology of Breast Cancer

The promise of prevention and the hope for healing

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By Ted Schettler MD, MPH

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Foreword

The Ecology of Breast Cancer is a necessary book. It is fundamentally necessary to not only understand but also embrace the complexity of the causes of this tragic epidemic disease.

Ted Schettler persuasively argues that breast cancer is ultimately a design problem. He situates the breast cancer epidemic among the other epidemic diseases of our time. He presents breast cancer as a model for understanding the epidemics of learning disabilities, autistic spectrum disorders, infertility, obesity, diabetes, Parkinson's disease, Alzheimers, asthma, other cancers, and many other conditions.

Schettler has been a leading voice in the international dialogue that has promoted an ecological paradigm of health. The objectivity of his science and the breadth and depth of his vision are widely recognized.

What is the ecological paradigm of health? It is a way of understanding biological systems as they interact with their environmental contexts. We may equally speak of multi-causal paradigms of disease – a familiar term in medicine. We may also speak of environmental public health – a recognized term in the public health community.

In the environmental justice community the accepted term is cumulative impact – the totality of the impact of the environment on health. Complexity theory is another language that fits well with the ecological paradigm of health. What we are doing is pointing to the infinite complexity of interactions in nested biological systems.

If ending the epidemic of breast cancer seems utopian, Schettler's paradigm actually suggests many personal lifestyle and community design strategies that are likely to reduce the incidence of breast cancer, increase resilience, and improve outcomes for those already diagnosed.

The bad news about the complexity of breast cancer is that the causes are complex. The good news is that a wide range of interventions can be beneficial—more so when they are combined. Even better, the benefits redound to a wide range of health concerns – not just breast cancer.

The Ecology of Breast Cancer is an heroic summary of an extremely complex body of science. We must follow the science, embrace the complexity of breast cancer, and recognize the promising insights that the ecological paradigm of breast cancer offers.

If we progress toward the personal, community, and global design changes that will reverse the breast cancer epidemic, we will also reverse many of the other disease epidemics of our time. That is a vision to live by.

Michael Lerner
Commonweal
Fall, 2013

Michael Lerner is president of Commonweal, a nonprofit center in Bolinas, California that works in health, education, environment and justice. He is co-founder of the Commonweal Cancer Help Program, the Collaborative on Health and the Environment, and The New School at Commonweal. He has co-led Cancer Help Program retreats for 28 years. Most of the participants in the Cancer Help Program are women with breast cancer.

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I am also extraordinarily grateful to those who agreed to take time from their busy lives to review various portions of this manuscript, including Susan Braun, Suzanne Fenton, Melinda Irwin, Michael Lerner, Nancy Myers, Carolyn Raffensperger, Cheryl Rock, Julia Rowland, Ruthann Rudel, Louis Slesin, and Patrice Sutton. Their comments and suggestions were extremely valuable and improved the manuscript considerably. Any errors that remain are entirely my responsibility. Many, many thanks also to Danielle Nierenberg for her invaluable editing assistance. I am also grateful to Heather Sarantis, who devoted considerable time and effort to layout and design. I hope that we have succeeded in making an extensive amount of information accessible and useful.

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Introduction

The diagnosis of breast cancer profoundly changes the lives of women, men, and their families. At the same time that people struggle with making difficult treatment-related decisions, they also commonly ask, why me? Why did this happen? The search for answers usually raises more questions.

In important ways, like other complex diseases, breast cancer is a design problem. By that I mean two things. First, although breast cancer is an ancient disease, it becomes much more common in countries where people adopt industrialized, Western-styles of eating, moving around, making and using consumer products, and general living. This strongly suggests that as we collectively make choices about the way we live, we can actually design disturbing breast cancer patterns into the complex fabric of society. This is not unique to breast cancer. It also applies to diabetes, cardiovascular disease, cognitive decline, dementia, other kinds of cancer, and asthma, among others.

Second, understanding, preventing, and treating breast cancer pose significant challenges for designing research and interventions. To be effective, proposed solutions must confront considerable complexity. Ideally they will connect and integrate knowledge from different disciplines and perspectives. Science, art, health, and healing must converge in the process of re-design.

Breast cancer is the most common invasive cancer among women in the United States, and rates are rapidly increasing in many other countries throughout the world. After increasing

for several decades, female breast cancer incidence in the U.S. began decreasing somewhat in 2000 and has been relatively stable in recent years. In the U.S., about one in eight women will develop breast cancer during their lives. The disease is about 100 times less common among men. Fortunately, death rates from breast cancer have been declining over the past 25 years, with larger decreases in women younger than 50. These decreases are probably due to a combination of more effective treatments and earlier detection. New therapies for some sub-types of breast cancer have especially improved.

Women and men who undertake combinations of surgical, pharmaceutical, and radiation therapies for breast cancer often wonder what else they might do to improve their long-term outcomes. This project began with a goal of addressing that question. A number of studies have examined the extent to which diet, exercise, weight control, stress reduction, and other factors are associated with recurrence and survival following diagnosis and initial treatment. My original intent was to summarize their findings, but for several reasons that goal soon began to seem too narrow.

Even though I have spent many years treating illnesses and injuries in medical practice, I have long been interested in the causes and primary prevention of diseases like breast cancer that are related in complex ways to environmental conditions. Here, by "environment" I mean the totality of the biologic, physical, chemical, built, nutritional, and social environments that humans have participated in creating throughout the world. In addition to its effects on breast cancer prognosis, I wanted to look more extensively into the role this complex environment might play in contributing to or preventing the disease in the first place.

Beyond that, since the latency period of breast cancer—the time between earliest tumor initiation and clinical diagnosis—is often decades long, an unknown number of people harbor early stages of the disease for a number of years without knowing it. In fact, some very early life experiences are clearly associated with breast cancer risk. For example, fetal diethylstilbestrol (DES) exposure or early onset of menarche increases breast cancer risk decades later. Some studies also show that certain kinds of diets and exercise patterns, beginning even in childhood, are linked to reduced risk or improved outcomes in people who develop breast cancer much later. It is, therefore, increasingly clear that efforts to prevent breast cancer and improve outcomes after diagnosis and treatment must begin in the earliest days of fetal development, if not before. In short, there is no bright line between interventions intended to make breast cancer less likely, slow its progression, perhaps even reverse its course, and improving outcomes. As a result, the scope of this project expanded to include breast cancer prevention.

Simply creating a list of known, probable, and plausible risk factors for breast cancer makes it apparent that they encompass many aspects of our individual and collective lives. At the population level, one or two variables do not stand out as overwhelmingly responsible for

changes in breast cancer incidence, although some individuals are at higher risk because of certain susceptibility genes. Rather, breast cancer patterns are largely determined by a complex mix of interacting, multi-level variables strongly pointing toward a more systemic problem.

We will undoubtedly be more successful at preventing the disease and promoting healing if we approach it through multi-level interventions. Individuals cannot do this alone. Opportunities and responsibilities lie within the range of activities of a large number of social, political, and professional organizations and institutions. All health care practitioners, including obstetricians and pediatricians, have important roles to play. Many public health professionals who do not typically see their work as related to breast cancer will inevitably see the connections if they step back and look at a bigger picture. Even more broadly, because of the complexity of breast cancer, decision-makers in all sectors whose activities help to shape the conditions out of which breast cancer is more or less likely to arise can make important contributions. They include teachers, city planners, farmers, legislators, and business leaders whose decisions and priorities strongly influence breast cancer-related features of the world we live in.

How this book is organized

This book is divided into three sections. Section I (chapters 1 and 2) briefly reviews the history of breast cancer and the evolution of ideas about its origins. It concludes that an ecological or eco-social framework is best suited to acknowledge and help clarify the complexity of the disease as well as helping to design research and interventions. This section includes a brief summary of breast cancer demographics, trends, and known risk factors.

Section II is comprised of five chapters addressing diet (chapter 3), exercise (chapter 4), environmental chemicals (chapter 5), features of the electromagnetic spectrum including vitamin D, light at night, and non-ionizing radiation (chapter 6), and stress (chapter 7). Each of these reviews an extensive literature and because of that, begins with a summary of the more detailed material that follows. In some instances, I found it particularly instructive to review the history of research into these categories of risk factors and have occasionally included discussions of older studies that influenced the direction and design of subsequent investigations.

Section III (chapter 8) summarizes and begins to reassemble the various risk factors into a more integrated whole. It explores implications for individuals, families, and communities as well as health care providers, public health officials, and others who can make a difference.

Most of the material reviewed in this book is drawn from epidemiologic and laboratory animal studies. I do not intend for it to be construed as medical advice. Nor, have I made any attempt to review or comment on a range of conventional medical therapies or their alternatives. But I do hope that people interested in a comprehensive approach to breast cancer prevention or treatment will find this material useful as they explore options.

Almost daily, medical journals and the press report new breast cancer research findings. Undoubtedly, some of the conclusions I reach here will need to be modified as new information becomes available. But, no matter how some of the details may change, it is my hope that we will increasingly address breast cancer—its origins and treatment—as a systems challenge, requiring an integrated, multi-level response.

Section 1

An Ecological Framework

Chapter 1

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 Halsted, dominated breast cancer treatment. Halsted 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

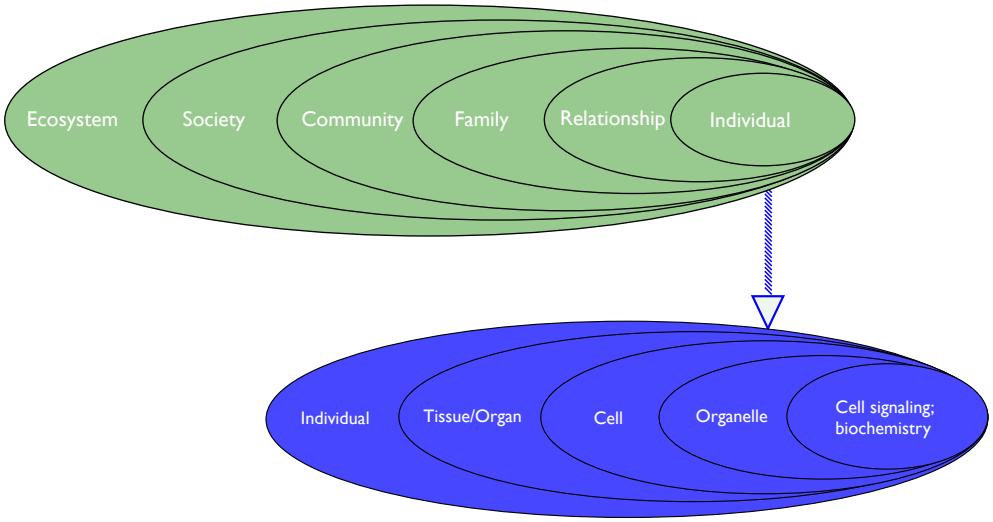
* This is sometimes called an ecologic or complexity framework. Terminology varies to some extent because of the variables included in the model and also because of connotations associated with various words. But the important commonality is the attempt to incorporate multiple level variables in a richly 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 mortality 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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Chapter 2

Breast cancer trends and risk factors

Breast cancer is the most common cancer in women and the second leading cause of cancer death in women after lung cancer in the United States.[1] It is the leading cause of cancer death in women worldwide.[2] Breast cancer also occurs in men, though it is rare, accounting for less than one percent of all breast cancer in the U.S.

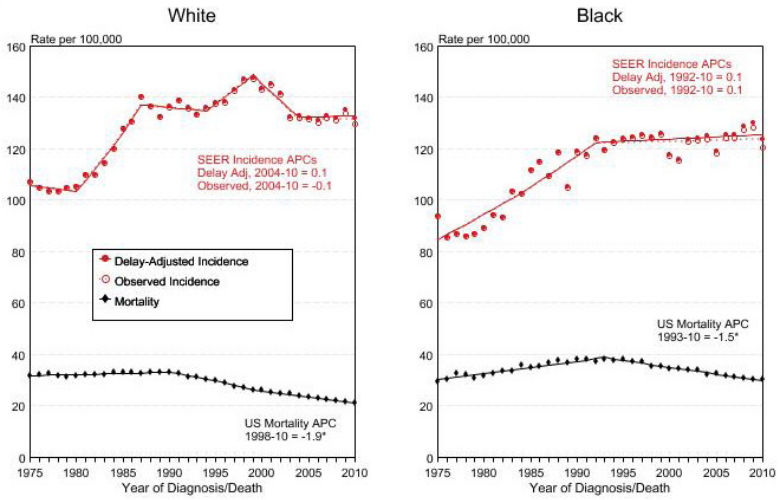
The National Cancer Institute and the Center for Disease Control's National Program of Cancer Registries regularly collect information to produce estimates of cancer incidence and mortality. Data collected by these surveillance systems indicated that approximately 227,000 new cases of invasive breast cancer and 63,000 new *in situ* cases would be diagnosed in U.S women in 2012, with 2,200 new cases of breast cancer in men.[3] Forty thousand women and 400 men were expected to die from breast cancer – 14 percent of all cancer deaths.

The risk of breast cancer increases with age, and the majority of women are diagnosed after menopause. About half of all female breast cancer patients are diagnosed by age 61, and approximately 12 percent are diagnosed at ages younger than 45.[4]

Data from the National Cancer Institute show breast cancer trends in the U.S. since 1975 and age-related incidence rates (See Figures 2.1 and 2.2). They show an increase in breast cancer in individuals ages 50 and older until about 2003 when incidence rates began to decline, most notably in white women. This was shortly after the Women's Health Initiative randomized study identified combined (estrogen plus progestin) hormone replacement therapy as a risk factor for breast cancer and many women discontinued its use.[5] Most ana-

lysts believe that this helps explain the observed decline shortly thereafter. These data also show that invasive breast cancer incidence rates have been almost unchanged since 1975 in women ages 20–49. However, the incidence rate of breast cancer in situ (CIS) has been rising since the introduction of mammography screening in the 1980s.[6] Since CIS is a precursor of invasive breast cancer, but not all CIS will progress to invasive breast cancer, individuals and their medical providers face difficult treatment decisions when CIS is diagnosed.

Figure 2.1:[7] SEER Observed Incidence, SEER Delay Adjusted Incidences and U.S. Death Rates* Cancer of the Female Breast by Age and Race

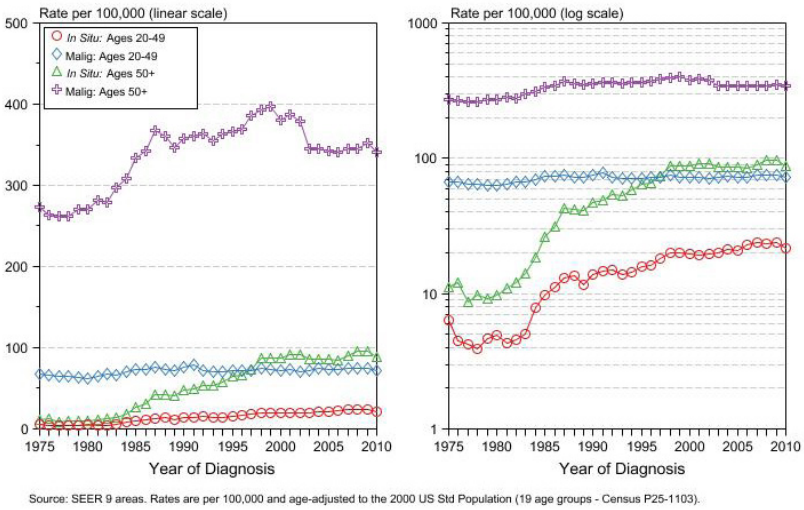


[a] Source: SEER * areas and US Mortality Files (National Center for Health Statistics, CDC).
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines and APCs are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute.
The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.
* The APC is significantly different from zero ($p < 0.05$).

Breast cancer trends before 1975 are somewhat less certain because of a lack of systematic record keeping prior to the establishment of cancer registries. In Connecticut—which has the oldest cancer registry in continuous operation in the United States—age-adjusted incidence rates of breast cancer rose by about 1.2 percent per year from 1940 to the early 1980s.[8]

Breast cancer risk and mortality varies significantly by race and ethnicity. Incidence rates are highest for white women, next highest for black women, followed by Hispanic, Asian and Pacific Islander, and American Indian and Alaskan Native women.[9] Black women experience the highest death rate from breast cancer despite lower incidence than white women. The reasons for this disparity are not fully understood but likely include combinations of more aggressive tumor types in many black women, later stage at diagnosis, and factors related to access to care and optimal treatment.[10, 11]

Figure 2.2:[12] Cancer of Female Breast, Incidence Rates, 1975-2010, *In situ* vs Malignant, by Age, All Races, Females



Breast cancer risk factors

In addition to female gender and aging, other established risk factors include:

Family history

According to the American Cancer Society, having one first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles a woman's risk. Having two first-degree relatives increases her risk about 3-fold.[13] However, fewer than 15 percent of women with breast cancer have a family member with the disease.

Genetic factors

About five to 10 percent of breast cancer cases are thought to be the result of inherited genetic susceptibility. The most common genetic mutations known to increase breast cancer risk are in the BRCA 1 and BRCA 2 genes. Normally, these genes have tumor suppressor functions, but when mutated, that function is reduced and breast cancer risk sharply increases. In the U.S., BRCA mutations are more common in Jewish women of Ashkenazi origin but they occur in individuals of all racial and ethnic groups. A recent study of African-American women with breast cancer revealed a higher frequency of mutations in breast cancer-related susceptibility genes than expected or previously reported.[14]

Personal history of breast cancer

Having cancer in one breast increases the risk of developing a new cancer in the same or other breast.

Dense breast tissue

Dense breast tissue, as seen on a mammogram, contains more glandular and fibrous tissue and less fatty tissue. Dense breast tissue is associated with a higher risk of breast cancer. Other than age, pregnancy, menopausal status, and genetics, the reasons for dense breast tissue are not fully understood.

Late age of first pregnancy or having no children (nulliparity)

Women who have had no children or who had their first child after age 30 have a slightly higher breast cancer risk. Having many pregnancies and becoming pregnant at a younger age reduces breast cancer risk. Maturational changes in the breast associated with pregnancy and lactation are thought to reduce the susceptibility of breast tissue to cancer. Reduced number of menstrual cycles may also play a role.

Early age of puberty

Earlier onset of menarche (menses) increases the risk of breast cancer. In the U.S. and many other countries, the age of puberty in girls has been significantly declining, although the reasons for this are not well understood.[15] Most of the acceleration in the timing of puberty is associated with earlier breast development (thelarche) while the timing of the onset of menses has not declined as much.

Later age of menopause

Menopause after age 55 also slightly increases breast cancer risk. One plausible explanation holds that earlier menarche and later menopause results in higher lifetime estrogen and progesterone exposures.

Chest radiation

Ionizing radiation (e.g., X-rays) is known to increase the risk of breast cancer. According to *Breast Cancer and the Environment,*[16] a report from a committee convened by the Institute of Medicine (IOM), some of the strongest evidence supports a causal association between breast cancer and exposure to ionizing radiation. The committee also noted that population exposures to ionizing radiation in medical imaging are increasing. Standards intended to

minimize exposures from mammography exist and new imaging technologies could reduce or eliminate that source. In addition, more needs to be done to minimize radiation exposures from other medical procedures. Breast cancer risk is higher if radiation exposure occurs during adolescence as the breasts are developing. This is particularly a concern when chest radiation is used to treat another cancer during that time. Age-related windows of vulnerability to radiation and other environmental exposures are a recurrent theme explored more fully in later chapters.

Recent oral contraceptive use

According to the IOM committee report, oral contraceptives modestly increase the risk of breast cancer among current users—but this increased risk disappears within four years following cessation. However, the committee also notes that oral contraceptives are associated with a long-term reduced risk of endometrial (uterine) and ovarian cancers.

Combination hormone therapy

The IOM committee concurred with the prevailing opinion that combination estrogen-progestin hormone replacement therapy increases the risk of breast cancer. This increased risk was identified in the Women's Health Initiative study.

Cigarette smoking

Some major studies and reviews have concluded that active smoking increases breast cancer risk. Evidence is also growing that being exposed to secondhand tobacco smoke (passive smoking) increases the risk of breast cancer.[17]

Other factors reviewed by the IOM committee

Among other factors reviewed by the IOM committee,* those most clearly associated with increased breast cancer risk in epidemiologic studies are overweight and obesity among post-menopausal women and alcohol consumption. Greater physical activity is associated with decreased risk. These and other potential risk factors are more fully discussed in later chapters.

With this as background, the following chapters address additional risk factors in more detail. Evidence is often limited and sometimes conflicting. Keeping in mind the ecological

* The committee limited their review to a select group of potential risk factors. It was not intended to be a comprehensive review.

framework discussed in chapter 1, we are learning that much of the available epidemiologic research is limited to some extent by various features of study design that did not (and often, could not) account for the complexity. For example, as noted in chapter 3, after decades of research on diet and breast cancer, it became clear that much of that work was limited by its failure to account for confounding or effect modification by exercise.[18] That is, exercise can independently influence both diet and breast cancer risk. Thus, it can be a confounder of the relationship. Exercise can also influence biologic pathways that do link diet to breast cancer—for example, inflammation and oxidative stress. Thus, exercise is a potential effect modifier of any relationship between diet and breast cancer. This has practical importance beyond complicating epidemiologic study design. It means that well-designed interventions can be mutually reinforcing and have benefits that may exceed what would be predicted by considering them individually.

As noted by the IOM committee report, more complex models "which attempt to depict the multiplicity of factors that seem to have a role in breast cancer, help underline the biological complexity of the pathways along which those factors may be acting, the difficulty of distinguishing truly causal effects from associations with intermediate factors, and the challenges of designing, conducting, and interpreting studies that try to evaluate risk factors for the various forms of this disease.[19] Although these challenges share similarities across the spectrum of risk factors evaluated in this report, they may be particularly acute for evaluating risk relationships from exposures to environmental chemicals."

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Section 2

Looking Within the Complexity

Chapter 3

Diet, nutrition, and breast cancer

Chapter Summary

For many years, the relationship between diet and breast cancer has been of great interest. Scientists have studied this connection particularly intensively over the past 30 years. Initial case-control studies were followed by the addition of large prospective cohort observational studies and occasional intervention trials. Inconsistency in findings is a recurrent theme. Perhaps this is inevitable for at least two reasons. Breast cancer is not a single disease. It is comprised of different subtypes—classified according to menopausal status, hormone receptor status, or other markers—with differing and complex biology. Many studies attempting to shed light on their origins make no distinction. Beyond that, studies with a singular focus on diet, by their design, often prevent understanding the ways diet can interact with other risk factors such as exercise or exposure to environmental chemicals. The research agenda has largely featured a reductionist approach—but that is slowly beginning to change.

At the outset, studies largely examined the influence of single dietary variables or macronutrients on breast cancer risk and prognosis. Initial enthusiasm surrounding the role of dietary fat waned as results from prospective cohort and intervention studies did not confirm findings from case-control studies showing an association between higher dietary fat and breast cancer risk. Subsequent studies examined the role of fruits, vegetables, soy, carbohydrates, dairy, and fiber. Occasional more recent studies examine dietary patterns.

Most analyses have assumed that if a nutrient group is related to breast cancer, the relationship will be in the same direction—that is, if some particular food is beneficial, more will be more beneficial; or if some is harmful, more will be more harmful. But that assumption may be incorrect. There may be optimal amounts of nutrient groups or micronutrients, above and below, which breast cancer risk increases or prognosis is poorer. This gives a J-shaped dose response curve that most existing epidemiologic studies do not consider in data analyses.[1]

With a few exceptions, almost all early epidemiologic studies examined the influence of adult diet on breast cancer risk. Most concentrate on current or fairly recent diet. But if most breast cancer has a latency of 15-20 years or even longer, as experts generally agree, recent dietary information tells us more about associations with cancer progression than initiation. Laboratory animal and more recent human epidemiologic studies now show that diet in childhood and adolescence has a stronger link to breast cancer risk—perhaps more than diet in adulthood. This has striking implications for breast cancer prevention, as well as posing challenges for the design of future research.

Recent studies also show that exercise, which is often ignored in dietary studies, is a significant confounder and may modify the effect of dietary variables on breast cancer risk. Exercise influences what and how much individuals eat and is also independently associated with breast cancer risk. Exercise influences some of the same biologic pathways through which dietary variables may act. The few studies that consider diet and exercise together show the magnified value of eating well and exercising. These reinforce the idea that breast cancer is a disease arising out of system conditions—the result of interacting multi-level variables that begin early and extend throughout life. More complex analyses hold the most promise for better understanding and designing interventions that help to prevent the disease and improve outcomes.

Overweight and obesity are associated with an increased risk of post-menopausal breast cancer and less favorable prognosis after diagnosis and initial treatment. Excess body weight typically has multiple contributing causes, but dietary interventions, along with exercise, can help maintain a healthy body weight and reduce risk. For premenopausal breast cancer, however, overweight and obesity are associated with a slightly decreased risk.[2]

Dietary fat

Independent of weight gain, most analysts conclude that total dietary fat, within the range common in the Western diet, has a weak, if any, association with breast cancer risk in general.[3] Evidence linking higher total dietary fat to breast cancer is stronger in post-menopausal women. Some evidence shows that reducing total dietary fat to 20 percent or less of total calories, an uncommonly low level in the United States, is likely to lower breast cancer risk.[4] Higher amounts of saturated fat and trans-fats modestly increase breast cancer risk. Trans-fats are, to a large extent, the result of partial hydrogenation

of vegetable oils used in processed foods although some are present in trace amounts in meat and dairy. In addition, trans-fats are clearly linked to cardiovascular disease risk and should be avoided.

Diets high in omega 6 fatty acids (FAs) (e.g., from corn, safflower, and soy oils; processed foods) that do not also contain adequate amounts of omega 3 FAs (e.g., from wild fish, fish oil, flax, walnuts) are likely to increase breast cancer risk. Laboratory animal studies clearly show this to be true, but epidemiologic studies are somewhat inconsistent. Ideally, some omega 6s should be replaced with omega 3s and mono-unsaturated FAs, like oleic acid in olive oil, which is prominent in the Mediterranean diet.* Excessive dietary levels of omega 6 FAs may be particularly problematic in individuals who disproportionately metabolize them into higher levels of pro-inflammatory substances, based on genetic variability.

Meat

Results of studies of dietary meat in adulthood and breast cancer risk have been inconsistent and largely negative. However, the Nurses' Health Study (NHS) II found a strong association of higher meat consumption during adolescence with increased premenopausal breast cancer risk. This is consistent with additional findings described in this and other chapters suggesting that early-life experiences help shape susceptibility to breast cancer. They provide strong support for beginning efforts to prevent breast cancer early in life and continuing through adolescence and adulthood.

Fruits and vegetables

Despite inconsistent evidence in early studies, more recent analyses show that higher dietary levels of fruits and vegetables significantly reduce the risk of developing breast cancer. Inconsistencies in the evidence may be due to different ways of estimating consumption. Studies using serum measures of carotenoids as a marker for fruit and vegetable consumption, rather than food-frequency questionnaires, find a significant protective association with higher levels. The Women's Healthy Eating and Living (WHEL) intervention study and others also showed improved prognosis after breast cancer diagnosis in individuals with the highest baseline levels of carotenoids.

Dietary pattern studies fairly consistently show modest risk reduction with a diet featuring plant-based foods. And, a WHEL analysis of postmenopausal women with breast cancer found that a diet with more than five servings of fruits and vegetables daily, combined with a level of exercise equivalent to brisk walking 30 minutes daily, six days/week, reduced mortality risk by half over a 10 year period.[5]

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* It should be emphasized that omega 6s and 3s are both essential fatty acids (FAs). But based on a large number of animal studies and less consistent human data, high omega 6 FA intake in the setting of low omega 3 FA intake is likely to increase the risk of breast cancer.

It is increasingly clear that higher soy consumption decreases the risk of breast cancer, although the level at which risk reduction becomes significant is uncertain, and the kind of soy-derived food is an important consideration (Although not reviewed here, an expert panel concluded that higher soy consumption also reduces the risk of uterine cancer.[6]). Higher soy consumption more persuasively lowers breast cancer risk in Asians than in Westerners, perhaps because Asians traditionally eat whole soy foods and consume 10-100 times more soy-derived isoflavones than Westerners. In many studies these larger amounts appear to confer more significant protection. The traditional Asian diet includes tofu and fermented soy products, such as miso and tempeh made from the whole bean. Soy oil and soy protein isolates are more common in the United States, particularly in processed foods. Health benefits from this heavily processed soy should not be inferred from the results of studies of more traditional soy-based food.

Available studies consistently show that higher soy consumption during childhood and adolescence is associated with lower breast cancer risk than higher dietary levels in adulthood. The findings are striking. Multiple mechanisms are likely to be involved. Here again, it looks as if early life experience may influence breast cancer risk years later. This has profound implications for breast cancer research and public policy.

Despite evidence in laboratory studies that genistein can cause breast cancer cells to proliferate,[7] three well designed, prospective studies with follow up periods of up to six years conclude that higher soy consumption post-diagnosis and treatment is associated with improved survival and lower risk of recurrence. The association is strongest in Asians, who may have been consuming traditional soy products throughout life. These findings cannot, however, be generalized to include soy supplements or purified isoflavones that may be added to processed, non-traditional soy food products. There is no evidence that soy consumption at current levels in Westerners or Asians post-diagnosis interferes with tamoxifen therapy and efficacy.

Other foods

Consistent, but limited, evidence from laboratory animal and epidemiologic studies points to a beneficial role of dietary seaweed in breast cancer prevention—even more in combination with soy, fish, fruits, and vegetables. Data also show a protective effect of mushrooms, which are commonly included in traditional Asian diets in countries where breast cancer is less common.

The role of carbohydrates, glycemic index, and glycemic load in the origins or prognosis after treatment of breast cancer is unclear. To the extent that refined carbohydrates, independently or along with other dietary features, promote elevated blood sugar, insulin resistance, metabolic syndrome, or overt diabetes, breast cancer risk will increase and prognosis after diagnosis will be less favorable. Comprehensive efforts to normalize blood sugar, improve insulin sensitivity, and reduce insulin levels are likely to be protective and beneficial.

Dietary patterns

Some epidemiologic studies have addressed the association of breast cancer with dietary patterns rather than single nutrient groups. In general, diets featuring higher amounts of fruits and vegetables, particularly those that are darkly colored, traditional soy products, whole grains and less refined carbohydrates, low-fat dairy, with poultry and fish and less red meat are associated with lower breast cancer risk. In some studies, where tumor subtypes are considered, this relationship is stronger for estrogen-receptor negative (ER-) breast cancer.

A number of observational and two large intervention studies provide varying levels of evidence that lower levels of dietary saturated fat and higher amounts of fruits and vegetables may reduce or delay cancer recurrence and improve survival. Higher amounts of dietary soy pre- and post-diagnosis are associated with decreased mortality and may be associated with decreased likelihood of recurrence.

When combined with weight loss in people who are overweight and regular exercise, benefits of this dietary pattern increase (See Appendix A).

Conclusions

Efforts to prevent breast cancer should begin in utero and continue throughout infancy, childhood, adolescence, and adulthood. Significant opportunities to reduce breast cancer risk through dietary interventions begin early in life and may be even more effective than steps taken later. That said, dietary interventions in adulthood can also reduce risk and importantly, improve prognosis after the diagnosis of breast cancer. Strong evidence shows that obesity is a significant risk factor for developing post-menopausal breast cancer and for progression of pre- and post-menopausal breast cancer. Dietary changes can be combined with other efforts aimed at weight control.

Breast cancer is less common in countries where people consume less meat and fat. But many aspects of lifestyle are also markedly different in these countries than in affluent Western countries, including physical activity, body composition, diet other than meat and fat consumption, and exposures to other environmental agents. Thus, cross-country comparisons are useful for generating hypotheses, but they are subject to considerable confounding and more detailed studies are needed.

Studying the impact of diet on breast cancer risk is complicated. Data are difficult to gather and their quality varies significantly. Unlike laboratory animal studies, where careful dietary control allows close monitoring of impacts, human studies are less precise. They often rely on food frequency questionnaires to reconstruct dietary histories, even from the distant past. Prospective studies can use food diaries since current eating patterns can be recorded more accurately than past practices can be recalled, but these too are often inaccurate. Moreover, in a population where the differences in dietary fat or food groups may not vary dramatically between the highest and lowest consumers, influences on cancer risk may be difficult to identify, even when they exist.

In recent years it has become increasingly apparent that nutrition, along with other environmental exposures, during fetal development, infancy, childhood, and adolescence influences subsequent breast cancer risk—perhaps even more than adult diet. This conclusion is based on diverse threads of evidence. Animal studies show that maternal diet during pregnancy significantly alters mammary cancer risk in female offspring—including susceptibility to mammary carcinogens before or after a first pregnancy.[8,9]

A prospective cohort study of 3,834 people who took part in a family diet and health survey between 1937 and 1939 reported increased cancer mortality, including breast-cancer related deaths, associated with higher levels of total childhood energy intake.[10] An ecologic study found that during World War II in Norway, peri-pubertal women whose diets were calorie-restricted but otherwise adequate had decreased risk of subsequent breast cancer compared with women exposed to both severe calorie restriction and poor food quality.[11]

A retrospective analysis from Nurses' Health Study (NHS) II found decreased risk of breast cancer with higher intakes of vegetable fats (RR=0.58) and vitamin E (RR=0.61) in adolescence and increased risk with a high glycemic diet (RR=1.47).[12] Another analysis from NHS II found that a higher level of meat consumption in adolescence increases the risk of breast cancer (RR=1.34). Several studies show that increased soy consumption in childhood decreases risk (see below).

These findings are among the increasingly persuasive evidence pointing to the developmental origins of adult diseases. They are consistent with studies of survivors of the atomic bombing of Japan in WWII showing that radiation exposure during childhood and adolescence most strongly increased breast cancer risk while exposure after age 40 had a much smaller effect.[13]

Migration studies show that breast cancer risk remains low in first generation immigrants who have spent their early life in a country with low risk of breast cancer, but increases among second generation immigrants who spend their childhood in a country with higher risk.[14] And, in a study that was able to determine the age of participants at the time of ex-

posure to the insecticide DDT, higher exposures before age 14 were associated with much higher breast cancer risk but not in women who were older when exposed (see chapter 5).[15] These findings are biologically plausible inasmuch as puberty and adolescence are times of unique susceptibility to environmental exposures because of rapid cellular proliferation and development of tissue architecture in the breast prior to pregnancy. Unique events during fetal development are also likely to contribute. But as important as it may be, accurate information about maternal, childhood, and adolescent nutrition can be extremely challenging to acquire decades later.

In general, nutritional studies tend to control for other variables that influence breast cancer risk, such as age at menarche and menopause, history of pregnancies, and alcohol and tobacco use, but some do that more rigorously than others. To add to the complexity, diet probably has different influences on pre- and post-menopausal cancer risk, but many studies do not report data by menopausal status, making interpretation difficult.

Case-control epidemiologic studies dominated early investigations. These compare diets of people with breast cancer to a control group without cancer. They depend on dietary recall. Prospective cohort studies, which assemble a group of participants without cancer, gather dietary and other relevant information, and periodically check on health status, soon followed. In general, case-control studies are subject to more dietary recall bias than cohort studies, which may explain at least some of the differences in their findings. Population-based, nested case-control studies are also fairly common in breast cancer research. Even though they are of case-control design, they have the advantage of being drawn from a fairly large, previously defined population being followed prospectively. They minimize some of the difficulties associated with matching cases with controls and controlling for recall bias.

The following sections summarize the results of many studies, most of which examined the independent influence of dietary fat, meat, soy, or fruits and vegetables on breast cancer risk or outcomes. Dietary pattern analysis shows up in more recent studies. This approach may add value since people eat complex diets with important interactions among nutrients that are likely to be missed when concentrating on single nutrient groups. Information from studies looking at dietary influences on breast cancer outcomes following diagnosis is also included.

The emphasis here is on prospective observational cohort studies and intervention trials, although occasional case-control studies are included, along with some laboratory animal data. Inconsistencies in findings are common, some of which are undoubtedly due to differences in study design. Moreover, virtually none of these studies considered exercise or activity levels as a potential confounder or modifier of the effect of diet on breast cancer risk. This is a regrettable shortcoming since the intertwined biologic effects of diet, exercise, and

body weight can strongly influence breast cancer risk. Analyzing dietary data independently, without accounting for interactions with exercise or other relevant variables, can obscure its relevance.

Dietary fat and breast cancer

Initial enthusiasm for the idea that higher amounts of dietary fat would explain most of the elevated incidence of breast cancer in some countries has waned to a large degree, based on inconsistent results from a number of prospective studies. Until recently, however, these studies almost always evaluated diets in adults rather than childhood or adolescence. Despite inconsistent results, some conclusions can be drawn:

- Reduced dietary saturated fat and total fat may modestly reduce breast cancer risk, particularly in post-menopausal women. In the Women's Health Initiative intervention study of post-menopausal women, reduced fat consumption was associated with most risk reduction in women who had higher baseline levels of dietary fat. Increasing trans fat consumption is associated with increased risk.[16]

- The NHS II found a significantly increased risk of premenopausal breast cancer with higher dietary levels of animal fat. Premenopausal breast cancer risk was also higher in women who had higher dietary levels of fat or red meat consumption during adolescence. This will be important to keep in mind, along with other adolescent dietary patterns discussed below, because childhood and adolescent diets may have a greater influence on breast cancer risk than diets later in life.

- Studies examining the effect of total polyunsaturated FAs (PUFAs) on breast cancer risk are inconsistent, but some studies with PUFA subtype analyses show that high intake of omega 6 FAs combined with low levels of dietary omega 3s increase risk. Relatively new evidence of individual differences in metabolism of omega 6 FAs suggests the possibility that high dietary levels of omega 6 FAs may increase risk more in people who, because of genetic variability, metabolize them more completely into pro-inflammatory compounds associated with a number of chronic diseases, including cancer. In order to address this, reducing dietary omega 6 FAs and adding long chain omega 3 FAs from fish or monounsaturated fats from, for example, olive oil are likely to be most helpful, not only to reduce breast cancer risk but also other chronic diseases in which inflammation plays a role.

Study descriptions: Dietary fat and breast cancer

Many studies have examined the relationship between dietary fat and breast cancer risk because the two are highly correlated at the national level, particularly for animal fat consumption.[17] Considerable laboratory animal data show that dietary fat can significantly enhance mammary tumor growth, apart from total calories consumed. In fact, a relationship between dietary fat and breast cancer risk may begin as early as fetal development, and changes in hormone levels may play a role.

In rodents, high levels of maternal dietary omega 6 FAs during pregnancy and lactation alters breast development in offspring, increasing susceptibility to cancer later in life.[18,19] High levels of maternal dietary omega 6 FAs are also associated with higher estrogen levels in pregnancy. A meta-analysis of animal studies concluded that omega 6 FAs had the strongest mammary gland tumor promoting properties, while the effect of saturated fat was somewhat less, and omega 3 FAs seemed slightly protective.[20]

One study of 189 women who gave birth to single female babies showed that higher intake of omega 6 FAs was associated with significantly higher umbilical cord blood levels of estriol and testosterone.[21] Higher dietary omega 3 FAs were linked to lower levels. A meta-analysis of ten intervention studies found that a low-fat, high-fiber diet had an estrogen-lowering effect in premenopausal women.[22] This occurred both in studies in which women lost weight and when they did not. A recent study in Japan found higher dietary saturated fat intake associated with higher estrogen levels in premenopausal adult women.[23]

Initial epidemiologic studies supported a link between dietary fat and breast cancer risk. A large 2003 meta-analysis of 45 case-control and cohort studies concluded that higher amounts of dietary fat during adulthood increased the risk of breast cancer by about 13 percent, largely attributable to saturated fat.[24] But findings from several large, prospective cohort studies have not been entirely consistent, and differences in study design make interpretation more uncertain.

Prospective cohort studies

Nurse's Health Studies: The NHS, established in 1976, is a prospective cohort study consisting of 121,701 U.S. registered nurses aged 30–55 years at baseline. At enrollment, women completed a mailed questionnaire regarding their medical histories and lifestyles. Follow-up questionnaires are mailed every two years in order to update information on health and lifestyle. In 1980, a food frequency questionnaire was added. A second Nurse's Health Study (NHS II) consisting of 116,671 female nurses 25-42 years old was begun in 1989. The NHS II racial/ethnic distribution is about 96 percent white with the remainder being roughly similar numbers of African-Americans, Asians, and Hispanics.

- ***NHS: dietary fat and breast cancer:*** NHS: 89,494 women 34-59 yrs old; eight year follow up; 1,439 cases of breast cancer, including 774 post-menopausal; adjusted for age, established risk factors; no positive association between total fat intake and breast cancer incidence in the entire group or among just post-menopausal women; no evidence of protective effect of dietary fiber.[25]

- ***NHS: Dietary fat and post-menopausal breast cancer:*** NHS; Over 80,000 participants; average 20 years follow-up; no relationship between mid- to later life dietary fat and postmenopausal breast cancer risk. This was also true for specific kinds of fat with the exception of trans fat intake where the risk of breast cancer increased by 8 percent for every 1 percent increase of trans fats as a percentage of total calories.[26]

- ***NHS II: Dietary fat and premenopausal breast cancer:*** NHS II; 90,655 premenopausal women ages 26-46 years; >90 percent Caucasian; fat intake was assessed with food-frequency questionnaires; eight years of follow-up; 714 cases of pre-menopausal breast cancer; 25 percent increased risk of breast cancer with total dietary fat although this was not statistically significant (RR 1.25; 95 percent CI 0.98-1.59); 33 percent increased risk associated with higher intake of animal fat. Higher intake of red meat and high-fat dairy each associated with increased risk of breast cancer, but this was largely attributable to higher amounts of animal fat in general.[27] The association between dietary animal fat and breast cancer was stronger in women who were using or who had ever used oral contraceptives and in women whose tumors were ER+ or PR+.

- ***NHS II: Adolescent diet and premenopausal breast cancer:*** NHS II; 39,268 premenopausal women completed a 124-food item questionnaire about their diets during high school; 7.5 yrs follow up; 455 cases of breast cancer occurred; 35 percent increased risk of breast cancer in the group with the highest total fat consumption in adolescence compared to the lowest.[28] The risk was higher for hormone-receptor negative tumors than hormone-receptor positive tumors. Risk also increased (34 percent) with highest red meat consumption during adolescence.[29] In this case, the increased risk associated with higher amounts of meat consumption was not explained by higher amounts of animal fat alone—red meat independently was associated with higher risk. Adolescent dietary milk, dairy, total carbohydrate, glycemic index, dietary fiber were not associated with breast cancer risk.

Canadian National Breast Screening Study: 56,837 women;[30] 40-59 yrs. old at enrollment; dietary information obtained by questionnaire at the time of enrollment; over five years of follow-up, 519 cases of breast cancer diagnosed; menopausal status of cases was not specified, but most were post-menopausal at diagnosis. When dietary fat was treated as a continuous variable in the statistical model, there was a 35 percent increased risk of

breast cancer per 77 gm of dietary fat, (which represented the differences in dietary fat between the highest and lowest quartiles; 47 percent vs. 31 percent of total calories from fat), independent of total calories consumed; no evidence of an association with protein or carbohydrate intake.

Swedish Women's Lifestyle and Health Cohort:[31] 49,261 women enrolled; 30-49 yrs. old; 9 percent post-menopausal at enrollment; dietary history over the past six months obtained by questionnaire; average follow up 13 years; 974 cases of breast cancer; 432 occurred before the age of 50. Total fat was not associated with breast cancer risk before or after age 50; compared to the lowest intakes, highest intake of monounsaturated fat was associated with a significant 55 percent decreased risk of breast cancer after age 50; higher polyunsaturated fat also associated with decreased risk while higher amounts of saturated fat associated with increased risk after age 50; the decreased risk with PUFAs most marked in ER + and PR + tumors.

Swedish Mammography Screening Cohort study:[32] 61,471 women enrolled; 40-76 yrs old; 4.2 years average follow up; 674 cases of breast cancer diagnosed; dietary history over past six months obtained by questionnaire. There was no association of breast cancer risk with total dietary fat, adjusted for total calories. However, when treated as continuous variables, increasing amounts of monounsaturated fat was associated with decreased risk of breast cancer whereas increasing amounts of PUFAs was associated with increased risk. Results based on quartiles were in the same direction but not significant.

The European Prospective Investigation into Cancer and Nutrition (EPIC): EPIC is a large prospective study in ten countries in the EU; 319,826 participants; average 8.8 years follow up; diet assessment through food frequency questionnaires and 24 hr. food recall interviews in a subset. The study found a 13 percent increase in breast cancer risk for the highest consumers of saturated fat.[33] This association did not vary with BMI or menopausal status although in post-menopausal women, it was stronger among those who never used hormone replacement therapy. No association with total fat, monounsaturated, or polyunsaturated fat was found. Higher BMI[34] and lower amounts of exercise[35] were associated with increased risk. No consistent findings with meat, dairy, egg consumption.[36] In subgroup analyses, higher processed meat consumption associated with 13 percent increased risk of BC in post-menopausal women; no association with red meat consumption over all, but in countries where red meat is typically cooked at higher temperatures, consumption associated with higher risk of breast cancer. This suggests that carcinogens, such as heterocyclic amines and polyaromatic hydrocarbons, produced by high temperature cooking, may play a role. In this study higher butter consumption was also associated with increased risk of breast cancer in premenopausal women. EPIC did not identify or analyze data by hormone receptor status of breast tumors.

National Institutes of Health-AARP Diet and Health Study: dietary fat and postmenopausal breast cancer: A U.S. study of 188,736 postmenopausal women who completed a 124-item food-frequency questionnaire in 1995-1996; approximately 88 percent white, 6 percent African-American, 2 percent Hispanic; average follow up 4.4 years; 11 percent higher incidence of BC in women in highest quintile of total fat compared to lowest; this association was also observed for all fat subtypes.[37] There was no association of meat intake or meat cooking methods with breast cancer after 8 years follow up.[38]

Women's Health Initiative Dietary Modification Trial (an intervention study): The Women's Health Initiative (WHI) trial is a prospective, randomized, intervention study of 48,835 postmenopausal women, aged 50-79 years;[39] 81 percent white, 11 percent African-American, 4 percent Hispanic; 4 percent Asian/Pacific, American Indian. Intervention group: reduction of dietary fat to 20 percent of total energy, increased consumption of fruits, vegetables, whole grains. Control group: given health related printed materials but not advised to make any dietary changes; average follow up 8.1 years. Results: 9 percent lower risk of breast cancer in intervention group although this was not statistically significant; however, in subgroup analyses, women who had higher baseline percentages of total energy from dietary fat experienced 22 percent reduction of risk of breast cancer from the intervention; risk reduction from intervention much greater in ER+/PR- tumors. Only 14 percent of women met the dietary target of 20 percent of energy from fat. Fat mass reduction was greater in women in the intervention group than in controls.[40]

In the WHI prospective intervention study, breast cancer incidence was more dramatically reduced by a low-fat diet in women who had experienced hot flashes compared to women who had not (73 percent vs. 58 percent reduction).[41] This finding was specific for ER+/PR+ tumors and suggests that some post-menopausal women may particularly benefit from low-fat dietary intervention.

Pooled analyses of prospective studies of dietary fat and breast cancer

A pooled analysis of 8 prospective cohort studies including 7,329 cases of breast cancer among over 350,000 women concluded that the risk of breast cancer increased modestly with increased saturated fat consumption (9 percent for every 5 percent increase in saturated fat as a percentage of total caloric intake).[42] Menopausal status did not alter this association.

A recent pooled analysis of data from 52 cohort and case control studies examining the relationship between dietary fat and breast cancer, published over the past 20 years concluded:[43]

- In studies that did not distinguish by menopausal status, there is a small but significant increased risk of breast cancer with increased amounts of dietary PUFA and total fat;

- Among post-menopausal studies only, breast cancer risk increases with higher dietary PUFA and total fat;
- Among pre-menopausal studies only, no increased risk of breast cancer with total dietary fat or any subtypes.

Polyunsaturated fatty acids and breast cancer risk

A 2006 review of omega 3 FAs and cancer risk included analysis of 8 prospective studies of breast cancer.[44] Two of four using fish consumption as a marker for omega 3s found no association with breast cancer risk, one found an increased risk, and one a decreased risk. Studies that included omega 3s from all sources found no association.

A 2013 meta-analysis of 21 prospective cohort studies including 20,905 cases of breast cancer among 883,585 participants found the highest level of dietary marine omega 3 FA was associated with a 14 percent reduction in breast cancer risk, whether measured as dietary intake or as tissue biomarkers.[45] This association was stronger in studies that did not adjust for BMI. No significant association was observed for dietary fish or exposure to alpha linolenic acid (a somewhat shorter-chain omega 3 FAs compared to marine omega 3 FAs).

Occasional studies examine breast cancer risk associated with varying combinations of omega 3 and omega 6 FAs. The large prospective Singapore Chinese Health Study of over 35,000 women 45-74 yrs of age found that higher intakes of omega 3 FA, primarily from fish/shellfish was associated with a 24 percent lower risk of developing breast cancer. Moreover, among women whose omega 3 FA intake was low, high levels of dietary omega 6 FAs was associated with a near doubling of breast cancer risk.[46] This was also reported in another large prospective study in France.[47]

Several things could explain inconsistent outcomes of studies of the impacts of omega 6 and omega 3 FAs. In Asian populations with low breast cancer incidence, marine fish are a major source of long chain omega 3 FAs. In laboratory and some epidemiologic studies these have the most protective effect with respect to breast cancer risk. In the typical Western diet, alpha-linolenic acid, a shorter chain omega 3 FA, is dominant. Humans do not biochemically convert this FA to the longer chain omega 3 very efficiently. As a result, the omega 3 FAs in diets that do not contain marine fish may not be as protective. Traditional Asian diets also often contain soy products and seaweed, which seem to confer additional protection, as discussed below.

In addition to being incorporated into cell membranes throughout the body, omega 6 and omega 3 FAs are enzymatically converted into a family of chemicals called eicosanoids, which are signaling molecules that influence a number of biologic processes, including inflammation and immune system function. Omega 6 FAs are converted largely, although

not entirely, into eicosanoids that promote inflammation. Omega 3 FAs, however, are converted almost exclusively into anti-inflammatory compounds. Thus, a diet featuring higher amounts of omega 6s and low amounts of omega 3s would generally be pro-inflammatory. It is increasingly clear that chronic inflammation plays an important contextual role in carcinogenesis and cancer progression, as well as a number of other chronic diseases, including cardiovascular disease, diabetes, metabolic syndrome, arthritis, asthma, Alzheimer's disease, and other neurodegenerative disorders.[48,49,50]

The dominant dietary omega 6 FA, linoleic acid, obtained from some vegetable oils, margarine, and processed foods, is partially converted enzymatically into arachadonic acid, an essential but inflammation-promoting eicosanoid. Early studies generally concluded that only a small portion of dietary linoleic acid was converted into arachadonic acid, but now it appears that enzyme levels influencing this conversion (FA desaturase) vary with genetic inheritance. A recent study showed that the genetic variations responsible for higher enzyme levels leading to higher levels of arachadonic acid production are much more common in people of African than of European ancestry.[51] The implications could be profound, since African and African-American women are at higher risk of more aggressive and hormone-receptor-negative tumors than white American women.[52]

5-lipoxygenase is an additional enzyme that converts arachadonic acid to various inflammatory mediators called leukotrienes. The 5-lipoxygenase pathway has been implicated in carcinogenesis and tumor progression in several different tissues.[53] A case-control study of White, Latina, and African-American women with breast cancer in the San Francisco area found that women with a particular polymorphism of genes responsible for levels of this enzyme and its activating protein were at an 80 percent increased risk of breast cancer only if their diet contained high levels of linoleic acid, the most prominent omega 6 polyunsaturated FA.[54] In this study, the polymorphism associated with increased risk was rare in African-American women and much more common in White and Latina participants.

Thus, health risks associated with high dietary levels of omega 6 FAs may be most marked in people who more readily metabolize them into arachadonic acid and other pro-inflammatory compounds. Since linoleic-to-arachadonic acid conversion appears to be more pronounced, on average, in African-Americans, this could help to explain black-white health disparities for a number of diseases, including various kinds of cancer, where those differences cannot otherwise be fully accounted for. Gene-related differences in FA metabolism may also help explain some of the inconsistency in the studies examining the relationship between omega 6 FAs and breast cancer risk.

Dietary meat and breast cancer

Among many case-control and cohort studies, evidence linking meat consumption to breast cancer risk is inconsistent. Prospective studies generally find little or no relationship between meat consumption in mid- or later-life and breast cancer risk. But these studies usually determine meat consumption at baseline and perhaps one time thereafter in relatively short periods of follow up and cannot shed light on the extent to which earlier life meat consumption influences breast cancer risk. .

The NHS II found a significantly increased risk of pre-menopausal breast cancer with increased meat consumption during adolescence. Moreover, several studies find that higher amounts of dietary meat in childhood are associated with earlier age at menarche—a well-recognized risk factor for breast cancer (See Box 3.1).

Increased breast density is strongly associated with increased breast cancer risk. Data linking meat consumption with increased breast density are mixed (See Box 3.2). Inconsistent findings may be due to differences in study design, including the potential for "over controlling" for age of menarche when analyzing data.

Thus, higher levels of meat consumption in childhood and adolescence may increase the risk of premenopausal breast cancer significantly while meat consumption in mid-life and later is probably not independently associated with breast cancer risk much, if at all. That said, other reasons for keeping red meat consumption low, even in adulthood, include a reduced risk of diabetes and cardiovascular disease[55,56] as well as environmental benefits.[57]

It should also be noted that the nutritional profile of beef varies with production methods. The omega 3 FA content is higher in grass-fed animals than in those fed corn.[58,59] To my knowledge, no study has examined the influence of variable kinds of animal feed or the use of hormones during meat production on breast cancer risk.

Dietary meat and breast cancer study descriptions

The NHS II (see above) found an increased risk of premenopausal breast cancer with higher levels of red meat consumption during adolescence.

A 2002 pooled analysis of data from eight prospective studies found no significant relationship between mid- or later life dietary meat and risk of pre- or post-menopausal breast cancer.[60] None of these eight studies attempted to estimate meat consumption earlier in life.

Box 3.1: Should studies of diet and breast cancer always control for age at menarche?

Most investigations into impacts of environmental factors on breast cancer risk use statistical methods to control for known risk factors, such as age at menarche, age at first pregnancy, number of pregnancies, use of oral contraceptives, and so on. This is intended to isolate the influence of the variable of interest, by mathematically holding the other risk factors "constant." In some circumstances, however, this might be an example of inappropriate "over-controlling." Here's why.

Although in NHS II, information was gathered about diet during high school, when presumably most participants had already undergone menarche, a study examining childhood dietary influences on breast cancer risk that controlled for age at menarche would tend to miss the impacts of diet on both age of menarche and breast cancer risk. For example, if higher childhood meat consumption advances the age of menarche and thereby, the subsequent risk of breast cancer, controlling for age of menarche in statistical data analyses will tend to obscure the influence of childhood dietary meat on cancer risk.

This is not just a theoretical concern. A prospective study of more than 3,000 girls in the United Kingdom, followed since birth, found that earlier menarche was strongly associated with higher consumption of red meat, total protein, animal protein and total energy measured at ages three and seven.[61] There was no impact of total dietary fat or fruit and vegetable consumption on age at menarche in this group.

A similarly designed study of 67 white girls born in Boston in the 1930s and 1940s found that age at menarche was earlier with higher amounts of dietary animal protein at ages three-five and five-eight years and delayed with higher vegetable protein intakes at three-five years.[62] There was no association with total energy or fat intake.

A cross-sectional study in the UK found no difference in age at menarche among women who were life-long vegetarians vs. those who became vegetarian as adults. However, age at menarche was later in those who became vegetarian at age 10-14 years.[63]

Studies that measure protein intake around the time of menarche rather than earlier in childhood generally do not find an association with the onset of menses.[64,65]

A second example arises from concerns that low levels of vitamin D may increase breast cancer risk (see chapter 6). Considerable evidence supports this relationship although epidemiologic studies are somewhat inconsistent. However, a recent prospective study of 242 girls in Bogota, Columbia found that lower serum levels of vitamin D were associated with significantly earlier menarche.[66] This association remained after controlling for BMI. If follow-up studies confirm this relationship, controlling for age of menarche when examining the link between vitamin D and breast cancer would be inappropriate.

As more studies begin to look at the influence of early life diet or other environmental factors on breast cancer risk, it will be important to avoid "over-controlling" for risk factors, like early onset of menses, which may actually be driven by the exposures of interest.

A more recent meta-analysis of 10 studies found a significant 24 percent increased risk of premenopausal breast cancer with increased meat consumption.[67] This finding was largely driven by case-control rather than cohort studies, which generally find no association when meat consumption at study baseline is used as an estimate. One population-based case-control study that found an increased risk concluded that the association was particularly strong with a high intake of well-done meat.[68] This is consistent with the EPIC study, discussed above.

The large, prospective NIH-AARP study of 120,755 post-menopausal women identified 3,818 cases of breast cancer in eight years of follow-up.[69] Information on diet at baseline was obtained by questionnaire, with follow-up at six months, including questions about meat preparation and degree of "doneness." Age-adjusted or fully-adjusted data analysis showed no significant associations between meat consumption or methods of meat preparation and breast cancer risk. Fully adjusted models controlled for age, BMI, height, age at first men-

Box 3.2: Diet and breast density

Increased breast density is strongly associated with increased risk of breast cancer[70] and investigators have wondered if childhood diets can influence breast cancer density in adulthood. Study results are inconsistent.

A study of 250 women of Chinese ancestry who had migrated to the U.S. in adulthood found that increased breast density after age 40, as determined by mammography, was strongly associated with higher meat intake during adolescence.[71] Interestingly, age at menarche was not associated with breast density and was not adjusted for in the models examining the relationship between dietary meat and breast density.

The Minnesota Breast Cancer Family study found no association between diet at age 12 and later breast density.[72] This study did adjust for age at menarche in the final analysis. Was that appropriate or is it an example of over-controlling in data analysis? Neither of these studies had information about diet in earlier childhood.

A prospective study of 1,161 women in the UK collected data on dietary habits at age 4 and again at several times during adulthood.[73] The authors found no association between diet at age 4 and breast density on mammography in adulthood. However, dietary patterns at age 4 were classified as breads and fats, fried potatoes and fish, and milk, fruit, biscuits, with no attempt to examine the impact of meat independently. Moreover, data analyses were adjusted for age at menarche, potentially obscuring the effect of childhood meat consumption on age at menarche. In this study, higher total energy in mid-adulthood was associated with higher breast density 15 years later.

strual period, age at first live birth, age at menopause, number of breast biopsies, family history of breast cancer, menopausal hormone therapy, education, race, total energy intake, saturated fat, alcohol, physical activity, and smoking.

In the prospective study of over 60,000 women in the Swedish Mammography Cohort over an average of 17 years of follow up, no association was found between risk of breast cancer and red meat consumption.[74] However, higher consumption of pan-fried meat was association with a 45 percent increased risk of breast cancer for ER+/PR- tumors.

Dairy product consumption and breast cancer risk

A relationship between breast cancer risk and milk and dairy consumption has been proposed for many years and is biologically plausible. In addition to its nutritional composition, milk contains various hormones and growth factors that are potentially associated with increased breast cancer risk, including estrogens, progesterone, and insulin-like growth factors (IGFs). Earlier age of menarche, a risk factor for breast cancer, is weakly associated with higher total dairy consumption.[75] In adolescent girls, milk consumption results in higher IGF-1 levels.[76] IGF-1 promotes cellular proliferation and impedes apoptosis and higher levels may be associated with increased risk of breast cancer, although study results are inconsistent. In a prospective study of pre-menarchal girls, higher levels of dairy consumption were associated with more rapid height growth,[77] which in turn is related to increased breast cancer risk.

But, epidemiologic studies have yielded inconsistent results regarding dairy consumption and breast cancer, ranging from increased risk to reduced risk.[78,79,80] Childhood or adolescent milk consumption is associated with decreased risk in several studies.[81,82,83]

In laboratory studies, dietary milk in adulthood inhibits the regression of chemically induced mammary gland tumors in rodents.[84] On the other hand, dietary milk administered to rodents before puberty reduced susceptibility to tumor development after administration of a carcinogen (DMBA) in adulthood.[85] Similarly, diethylstilbestrol, a synthetic estrogen, administered in the neonatal period reduces susceptibility to a mammary gland carcinogen (DMBA) administered in adulthood,[86] whereas prenatal exposure increases mammary gland cancer risk. This suggests that the impact of dietary cow's milk on breast cancer risk, as with other hormonally-active substances, may depend on life-stage and the relative timing of other exposures. Dietary dairy products containing hormones and other growth factors could promote tumors that have already been initiated, for example. The nature and timing of co-exposures may underlie the inconsistencies of epidemiologic studies looking at dairy products and breast cancer risk.

Fruits and vegetables and breast cancer risk

Higher amounts of fruit and vegetable consumption appear to reduce breast cancer risk, along with many other well-established benefits. Carotenoids are pigmented compounds in many fruits and vegetables—particularly yellow and orange fruits and vegetables and green, leafy vegetables. They are antioxidants; some inhibit cellular proliferation, induce apoptosis (programmed cell death), and have other beneficial effects on physiology and metabolism.[87] Beta-carotene, one of the major carotenoids, may be particularly important because it is converted to vitamin A. Vitamin A is in turn converted to retinoic acid, which tends to reduce cellular proliferation and encourage cellular differentiation. Thus, dietary carotenoids may not only reduce breast cancer risk but also be beneficial after breast cancer diagnosis.* Carotenoid absorption from the intestine and the extent to which it is converted to vitamin A is highly variable and can be affected by the food matrix, food-processing, and amounts of dietary fat and fiber, as well as genetic differences in carotenoid metabolism.[88]

Enterolactone and enterodiol are two dietary lignans formed in the intestine from precursors in whole grains, vegetables, fruits, and berries. Some data show that higher serum levels of enterolactone are associated with reduced risk of post-menopausal breast cancer[89] and improved survival after diagnosis.[90]

Studies show that women eating a vegetarian diet excrete higher levels of estrogen in their feces than do omnivores, reducing circulating levels.[91] Lower levels of estrogen are likely to contribute to lower breast cancer risk.

A meta-analysis of 26 studies looked at the role of dietary vegetables, fruit, carotene, or vitamin C.[92] It included more case-control than cohort studies of both pre- and post-menopausal breast cancer. Study designs varied considerably, including dietary assessment ranging from current diet to one, two, and five years prior to interview. All studies used a food-frequency questionnaire to obtain information on diet, although there were large differences in the number of food items listed. Data were analyzed in a number of ways and subject to sensitivity analysis. The results showed a moderately protective role, particularly for higher intake of vegetables, which showed a 25 percent reduction in breast cancer risk.

An analysis of eight prospective cohort studies from North American and Europe observed only a weak, non-significant protective effect of fruits and vegetables in the adult diet, with follow up ranging from five-10 years.[93] Similarly, a large prospective study in the EU in which most participants were 35-70 yrs old when entered, found no protective effect of

* The effects of dietary carotenoids may be quite different from effects of supplements, which may not be beneficial.

higher dietary fruits and vegetables after a relatively short average follow up period of 5.4 years.[94]

A number of studies have investigated associations of dietary carotenoids with breast cancer risk. Two meta-analyses have been reported. The first pooled the results of seven case-control and four cohort studies and found that higher dietary levels of beta-carotene were associated with a 20 percent reduced risk of breast cancer.[95] The second meta-analysis considered data from 33 studies—a mixture of case-control, nested case-control, and cohort designs—and found a six percent reduced risk with the highest amounts of dietary beta-carotene and nine percent reduced risk with highest amounts of alpha-carotene. These studies generally obtained dietary information in adulthood from food-frequency questionnaires.
In some cases, scientists have measured blood levels of carotenoids at the beginning of a study and then followed participants over a period of time to see if there is an association with subsequent development of breast cancer. A recent study analyzed data from eight prospective studies using that approach.[96] The time between blood collection and breast cancer diagnosis ranged from 0.8 to 13.7 years, with an average of 4.3 years. The analysis included 3055 cases of breast cancer and 3,956 controls. Mean age at blood collection for cases was 51.3-66.0 in the eight studies, and 67 percent of all participants were postmenopausal. The authors reported statistically significant decreased risk of breast cancer in women with higher baseline levels of alpha-carotene (RR=0.87), beta-carotene (RR=0.83), lutein + zeaxanthin (RR=0.84), lycopene (RR=0.78), and total carotenoids (RR=0.81).

Among the limitations of these studies is the lack of information about diet during childhood and adolescence. Studying adult dietary habits will not help to clarify potential benefits (or risks) associated with fruit and vegetable consumption during vulnerable periods of breast development earlier in life.

Dietary soy and breast cancer risk

The effect of dietary soy on breast cancer risk has long been of interest primarily because Asian women, living in their ancestral countries, whose diets traditionally include a variety of soy products, are much less likely to develop breast cancer than women consuming a more Western diet. The studies summarized below show that dietary soy appears to have a protective effect against breast cancer and higher amounts in childhood and adolescence seem to be particularly beneficial. That conclusion does not extend to soy formula in infancy and subsequent breast cancer risk, which has not been investigated. It also does not extend to highly processed soy components, common in processed food in the U.S., or to soy supplements.[97]

The biologic effects of soy isoflavones

Although the mechanisms by which dietary soy may be protective are not completely understood, animal studies show that pre-pubertal exposures to soy isoflavones, a family of compounds in soy products, promote cellular differentiation so that the resulting tissue structure is more mature and less likely to develop cancer. Pre-pubertal exposures also alter the expression of a number of different genes, thereby influencing hormone receptor levels and various other chemical signaling molecules and pathways in ways that would be expected to inhibit tumor development and progression (also reviewed in Warri, 2008).[98]

Soy isoflavones are sometimes called phytoestrogens because they have structural similarities to the hormone estrogen and have some estrogenic activity, although it differs in important ways from endogenous hormones. The impact of isoflavones on breast cancer risk deserves a close look because of concerns that estrogenic stimulation may actually promote cancer growth. But studies show that soy isoflavones have a diverse array of biologic activities, including blocking cell signaling mechanisms important in cancer development, reducing cellular proliferation, inducing apoptosis, altering hormone metabolism, and anti-oxidant effects, among others.[99,100]

Estrogen-like compounds influence gene expression through multiple mechanisms. Estrogen receptor (ER)-alpha and ER-beta activation are among several receptor-mediated pathways—others include cell membrane bound receptors and estrogen-related receptors. Each of these has different biologic activity when activated. (Chapter 5 discusses the influence of bisphenol A, an environmental chemical, on these receptors and how it might influence breast cancer risk by mechanisms independent of its activation of the classic estrogen receptor).

Genistein and daidzein are two isoflavones at relatively high concentrations in soybeans and soy products, particularly miso and tempeh. Several others, including glycitein, are present in lower amounts. Intestinal bacteria can metabolize daidzein into another isoflavone called equol. Equol has a particular affinity for the ER-beta receptor. This may be important because, in many studies, ER-beta activation inhibits breast cancer cell proliferation in tissue cultures, while ER-alpha activation promotes proliferation.[101] Equol also has anti-androgenic activity.

Studies show that only 20-30 percent of Western adults harbor intestinal bacteria that metabolize daidzein to equol, compared to 50-60 percent of Asian adults.[102] Among Western adults, vegetarians are more common equol-producers. This suggests that regular consumption of larger amounts of soy products can modify intestinal bacterial composition, which may help to explain discrepancies in the relationship between diet and health outcomes in populations with different amounts of soy in their daily diets.

Study summaries: Dietary soy and breast cancer risk

Individual and grouped epidemiologic studies, including some looking at differences in Asian and Western populations, have produced different results. A 2006 meta-analysis of 18 studies (12 case- control, 6 cohort or nested case-control) found a 14 percent reduction of breast cancer risk associated with higher dietary soy intake.[103] The magnitude of the risk reduction was similar in Asian and Western populations and was slightly stronger for pre-menopausal breast cancer. In this study, the Western category included Asian Americans.

A 2008 meta-analysis looked at 8 studies conducted in Asia and in Asian Americans (1 cohort; 7 case-control) and separately, at 11 studies (4 cohort, 7 case-control) in Western populations. Studies of Asians, including women living in Asia and Asian Americans, showed a significant 29 percent reduction in both pre- and post-menopausal breast cancer risk in women with highest soy consumption compared to those with the lowest.[104] The meta-analysis of studies of Western populations, which did not include Asian Americans, found no significant relationship between dietary soy and breast cancer risk.[105]

A 2011 meta-analysis of 14 prospective studies (cohort or nested case-control; average follow-up 2-13 years) of dietary soy and breast cancer found higher isoflavone intake associated with a 24 percent risk reduction in Asian but not Western populations.[106] Risk reduction was greater among post-menopausal women.

These apparently inconsistent results may be reconcilable. Soy consumption was dramatically different in the two different populations in the 2008 meta-analysis. In the Asian studies, 20 mg. or more daily isoflavones in the highest vs. 5 mg. or less in the lowest subgroup compared to 0.8 mg. or more vs. 0.15 mg. or less in the Western population studies—a 25-fold difference. Moreover, participants in the Western studies were more likely to obtain their dietary isoflavones from soy fillers in baked goods and canned products, whereas Asians were more likely to be consuming tofu and other traditional Asian products. The amount and ratios of isoflavones in soy-containing food can vary considerably depending on whether or not the whole bean or just the protein isolate is used.[107]

These findings are consistent with a protective effect in Asian and Asian American women who consume soy on a daily basis and who may well have been regularly consuming soy products throughout their lives. It is entirely plausible that a protective effect is also realized by Western women under similar circumstances.

Dietary soy in childhood and adolescence and subsequent breast cancer risk

A number of laboratory animal studies show that early life exposure to soy isoflavones can influence mammary gland development and in some instances protect the mammary glands, reducing the risk of cancer after later exposure to known mammary carcinogens.[108] In rodent studies, however, the effects of genistein on growth and development depend on the dose, timing, and route of exposure. This is particularly important because many infants in the U.S. consume soy formula soon after birth.

In mice treated with genistein soon after birth, a high dose caused a decrease in the number of terminal end buds (TEBs) and decreased branching in the mammary gland at puberty, while a low dose caused increased branching and ductal elongation.[109] The high-dose changes persisted into adulthood.

In rats, pre-pubertal genistein exposure decreased the number of TEBs in the mammary glands of adults and increased the number of more mature lobules.[110] Animals treated with genistein pre-pubertally also had reduced numbers of mammary gland tumors after treatment with DMBA, a mammary carcinogen. Another rodent study showed that higher exposures to an isoflavone-rich or genistein-rich diet *in utero* and up to young adulthood reduced mammary gland responsiveness to estrogen.[111]

These findings are all consistent with the hypothesis that dietary soy during childhood may contribute to earlier breast tissue differentiation and reduced susceptibility to cancer. They are also consistent with results of several epidemiologic studies published within the past 10 years.

A population-based case-control study of women of Chinese, Japanese, or Filipino descent living in California or Hawaii examined the impact of dietary soy during childhood and adolescence on subsequent breast cancer risk.[112] The study included 597 cases and 966 controls all of whom were 22-55 yrs old. Seventy-three percent of cases were premenopausal at diagnosis. Dietary histories were obtained from participants and when possible, from their mothers. Comparing highest soy intake with the lowest in childhood, adolescence, and adulthood, breast cancer risk was reduced by 60 percent, 20 percent, and 24 percent respectively. The risk reduction associated with higher soy intake in childhood was highly significant, seen in women from all three countries, in all study sites, and women born in Asia and the U.S.

Two studies of Asian or Asian American women in the 2008 meta-analysis mentioned above had asked and found that higher soy consumption during adolescence had a more protective association than high consumption in adulthood.[113,114]

The Shanghai Women's Health Study was included in the 2011 meta-analysis.[115] This is a prospective study of more than 70,000 women, 40-70 years old, with an average follow-up of 7.4 years. Higher intake of soy protein and isoflavones was associated with a lower risk of breast cancer, and this association was particularly strong for pre-menopausal women. Information about the adolescent diet of participants had also been collected. Higher soy intake during adolescence was highly significantly associated with lower breast cancer risk in adulthood, independent of adult soy intake. Women with the highest adolescent and adult soy intake showed the most dramatic reduction in breast cancer risk—60 percent lower than women in the lower intake categories.

Similarly, in a population-based case control study of non-Asians in Canada, higher intake of isoflavones, lignans, and total phytoestrogens in adolescence were each associated with lower risk of breast cancer.[116] Lignans are the principal phytoestrogen in typical Western diets—present in grains, nuts, fruits, vegetables, tea, and coffee.

Thus, each study that examines the relationship between dietary soy in childhood and subsequent breast cancer risk finds a protective association—higher intake is associated with lower risk. Evidence consistently shows that higher soy intake in childhood and adolescence is associated with even greater reduction of risk than higher amounts in adulthood. Most laboratory animal studies also show a preventive effect of early-life soy isoflavone exposure on mammary tumor development.[117]

Whether or not soy formula in infancy has an influence on breast cancer risk is an important question that is largely unexplored. In addition, it is important to note that the findings in these epidemiologic studies do not mean that soy supplements will be beneficial and protect against breast cancer. Dietary soy is consumed as part of a complex meal pattern. In one study of soy supplements for six months in women at risk for breast cancer, aspirates of breast epithelial cells showed a small increase in cellular proliferation in premenopausal women using the supplements, suggesting an estrogenic effect.[118] Whether or not this will increase breast cancer risk is unknown.

Seaweed, mushrooms

Soy content is not the only difference between traditional Asian and Western diets. In Japan, where breast cancer incidence has historically been quite low, although increasing in recent years, diets regularly contain fish, seaweed, mushrooms, rice, and fruit as well as soy products.[119] Sushi wrappings, seasonings, condiments, and other dishes contain seaweed, and it can be a significant part of the daily diet.

Brown, green, and red seaweeds are rich in unique polysaccharides (fucans), iodine, minerals, vitamins, and dietary fiber.[120,121] Thirty years ago, cancer researcher Jane Teas wondered if seaweed in the Japanese diet might help explain the low incidence of breast cancer in that country compared to others.[122] She proposed that alteration of cholesterol and hormone metabolism, alteration of intestinal flora, increased consumption of iodine and other trace minerals, and anti-oxidant properties might explain a protective effect. Anti-oxidant and anti-tumor effects of seaweeds have been reported in studies *in vitro* and *in vivo* since then.[123,124] For example, extracts from two different kinds of seaweed, wakame and mekabu, administered in drinking water dramatically reduced carcinogen-induced mammary tumors in rodents.[125]

A case-control study in Korea found that increasing amounts of dietary seaweed (gim) were associated with decreased breast cancer risk in both premenopausal and postmenopausal women.[126] This association was less robust when dietary soy, mushrooms, and vitamins were taken into account—suggesting that dietary patterns are important.

Studies of Japanese postmenopausal breast cancer survivors report serum estrogen levels far lower than in postmenopausal breast cancer survivors in the U.S.[127,128] A double blind cross-over study of 15 healthy non-Asian post-menopausal U.S. women showed that seaweed-soy supplements caused significantly lower serum estrogen levels with a sharp increase in estrogen excretion.[129] The amounts of seaweed associated with this effect are about four to seven gm. daily, depending on body weight—well within the typical range of seaweed consumption in Japan. Since higher estrogen levels drive cellular proliferation in ER+ breast cancer, diets regularly containing soy and seaweed that reduce estrogen levels may therefore be beneficial not only for breast cancer prevention but also after diagnosis.

Mushrooms are also more common in the Asian than American diet. A case-control study in Korea found that post-menopausal women who ate mushrooms at least three times a week had a sharply reduced breast cancer risk compared to women who ate few or no mushrooms.[130] A subsequent study found reduced risk in both pre-menopausal and post-menopausal Korean women.[131] Risk reduction was highest for ER+/PR+ tumors in pre-menopausal women. A protective effect of dietary mushrooms is plausible since studies show that mushroom extracts reduce oxidative stress, inhibit cell proliferation, and reduce aromatase activity, an enzyme essential for estrogen production. Aromatase inhibitors are now used to treat some kinds of breast cancer.[132]

Carbohydrates and breast cancer

Studies investigating dietary carbohydrates and breast cancer risk have inconsistent results but generally find no significant relationship.[133,134] Occasional studies find an increased risk

associated with higher consumption of sucrose-containing foods, including desserts. For example, the Long Island Breast Cancer study found a 27 percent increased risk with higher consumption of desserts, sweetened beverages, and added sugars.[135] The risk was about 50 percent higher when just desserts were considered and was higher for pre-menopausal than post-menopausal breast cancer. Other case-control studies have also found a modestly increased risk of premenopausal breast cancer with higher intake of sweet foods and beverages.[136,137,138] However, some studies find no relationship.[139,140]

Dietary patterns

In recent years studies have begun to evaluate dietary patterns rather than concentrating almost exclusively on individual nutrients.[141] Intuitively, this makes sense. People eat food and meals—not individual nutrients. Complex combinations of nutrients and food groups have biologic effects that are independent of the contribution of individual nutrients in isolation and cannot be predicted easily. One nutrient may influence the intestinal absorption of another. Or, one may increase cancer risk while others are protective, and their impacts in the aggregate will matter most. Dietary patterns also influence the composition of the microbial inhabitants of the intestine (the intestinal microbiome), which in turn influences systemic hormone levels.[142]

From a research perspective, the high degree of correlation of some nutrients also makes it difficult to study their effects independently. The effect of a single nutrient may be too small to detect, but combinations of nutrients may have a larger effect easier to see. These are among the reasons that dietary pattern analysis has entered into breast cancer research.

But, dietary pattern analysis also presents new research challenges. How is a pattern defined? Researchers often group dietary components together in various ways and name them—for example, the "prudent healthy diet," the "Mediterranean diet," the "recommended food score," among others—with the hope that useful groupings will become apparent and move our understanding forward.

With few exceptions, dietary pattern analyses show reductions in breast cancer risk in women whose diets feature more plant based foods and seafood and less meat. The reduced risk in some studies is small but in others quite dramatic. Overall the findings are quite consistent. No research has yet addressed patterns of childhood and adolescent diets and breast cancer risk.

Study summaries: Dietary pattern analysis and breast cancer risk

In 2010, a meta-analysis of 39 case-control and cohort studies reported on dietary patterns and breast cancer risk, using the prudent healthy, Western/unhealthy, and drinker dietary patterns for analysis.[143] The prudent/healthy pattern tended to have higher amounts of fruit, vegetables, poultry, fish, low-fat dairy, and whole grains. Western/unhealthy dietary patterns had higher amounts of red and/or processed meat, refined grains, potatoes, sweets, and high-fat dairy. Drinker dietary patterns had higher amounts of wine, beer, and spirits. In general the dietary information obtained in these studies was restricted to current or fairly recent dietary habits. The analysis found a significant 10 percent decreased risk of breast cancer among women in the highest compared with the lowest categories of intake of the prudent/healthy diet. Higher intake of an unhealthy/Western diet was associated with a slight increase in risk that was not statistically significant. The four studies identifying a drinker dietary pattern collectively showed a 20 percent increased risk.

The analysis included a long-term follow up of participants in the NHS. It found a reduced risk of ER-postmenopausal breast cancer with stronger adherence to the alternative Mediterranean Diet,* Alternative Healthy Eating Index,† and Recommended Food Score.‡[144]

The reduced risk was mostly explained by the vegetable component and higher polyunsaturated:saturated fat ratio of the Alternative Healthy Eating Index. The higher monounsaturated:saturated fat ratio in the Alternative Mediterranean Diet Score explained most of its reduced risk. No association was observed with the nuts and soy component, cereal fiber, white: red meat ratio, trans-fats, multivitamin use, or the alcohol component of that dietary pattern. The vegetable component explained most of the reduced risk associated with the Recommended Food Score.

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* The Mediterranean diet scale is based on the intake of vegetables, legumes, fruits and nuts, dairy, cereals, meat and meat products, fish, alcohol, and the monounsaturated:saturated fat ratio. Lower intake of meat and dairy scores higher. The alternative Med diet excludes potato products from the vegetable group, separates fruits and nuts into 2 groups, eliminates the dairy group, includes whole-grain products only, includes only red and processed meats for the meat group, and assigns 1 point for alcohol intake between 5 and 15 g/day

† The Healthy Eating Index contains 10 components consisting of grains, vegetables, fruit, milk, meat, total fat, saturated fat, cholesterol, sodium, and diet variety. It reflect recommendations based on the USDA Food Guide Pyramid and the 1995 Dietary Guidelines for Americans. The AHEI differs by removing potatoes from vegetables, and including fruit, nuts and soy, white/red
meat ratio, trans fat and the polyunsaturated:saturated fat ratio, cereal fiber, and adding long-term multivitamin use, and alcohol intake.

‡ The RFS features fruits, vegetables, whole grains, lean meats or meat alternates, and low-fat dairy products

A more recent analysis of dietary data from 86,620 participants in the NHS examined whether a low carbohydrate or the DASH (Dietary Approaches to Stop Hypertension) diet was associated with postmenopausal breast cancer risk.[145] The DASH diet features plant proteins, fruits and vegetables, moderate amounts of low-fat dairy, and limited sugary foods and salt. In up to 26 years of follow up, neither low-carbohydrate diets nor the DASH diet were associated with overall incidence of breast cancer or ER+ breast cancer. But both the vegetable/low-carbohydrate diet and the DASH diet were associated with decreased ER- breast cancer risk.

A recent large prospective study of women 35-79 years of age in the UK found that stronger adherence to a Mediterranean Diet was associated with a 35 percent reduced risk of developing breast cancer in pre-menopausal women over an average follow up period of nine years, although the result did not quite reach statistical significance.[146] The Mediterranean Diet includes higher intakes of vegetables, fruits, legumes, whole grains, fish, and moderate amounts of red wine during meals.

A prospective study of 20,967 women in the Melbourne (Australia) Collaborative Cohort Study[147]; 27-76 years old at baseline; average follow-up 14.1 years; dietary habits ascertained through food frequency questionnaire and 121 food items analyzed using principal factor analysis, a technique for identifying groups of variables that explain most of the variability in the diets of participants. For example, some groups of variables correlate well with high vegetable intake, while others correlate with high intakes of fruits, cereals, or meat. These were called the vegetable, fruit and salad, traditional Australian, and meat diets. Results: The fruit and salad pattern correlated with reduced risk of breast cancer. The correlation was much stronger for hormone receptor negative tumors.

Two recent studies are available from China, where breast cancer incidence is about 5-fold lower than in the U.S. but recently increasing. In the Singapore Chinese Health Study; (a prospective study of 34,028 women without cancer at baseline, 72 percent post-menopausal; average 10.7 yrs follow-up); meat-dim sum vs. fruit-vegetable-soy dietary patterns; 30 percent decreased risk of post-menopausal breast cancer in women who highest adherence to fruit-vegetable-soy dietary pattern compared to lowest adherence to that pattern.[148]

The second is a case-control study of 438 Chinese women with breast cancer and 438 controls.[149] Dietary history over the previous year was obtained with food frequency questionnaires. After adjustment for confounders, women in the highest quartile of vegetable-fruit-soy-milk-poultry-fish dietary pattern had a 74 percent decreased risk of breast cancer compared to the lowest quartile. The refined grain-meat-pickle pattern was associated with 2.6-fold increased risk.

Similarly, a case-control study in Korea showed an 86 percent decreased risk of breast cancer in women with the highest intake of the vegetable-seafood pattern compared to the lowest.[150] This association was not affected by menopausal status. No significant differences in risk were seen across the quartiles of the meat-starch pattern.

Diet and breast cancer outcomes following diagnosis

Interpreting available data addressing the relationship between diet and breast cancer prognosis and survival is complex for a number of reasons. Pre-diagnosis as well as post-diagnosis diets can influence breast cancer outcomes, and each introduces its own measurement challenges. Moreover, after the diagnosis of breast cancer, stress levels increase and individuals often change their daily routines in various ways, including physical activity levels, diet, and use of nutritional supplements.[151] Individually and collectively these may influence outcomes. Thus, isolating and evaluating the impacts of dietary variables is difficult.

Despite these challenges, a number of observational and two large intervention studies provide varying levels of evidence that lower levels of dietary saturated fat and higher amounts of fruits and vegetables, combined with regular exercise and weight loss in people who are overweight, reduces mortality following breast cancer diagnosis and treatment and may also reduce or delay recurrence. Higher amounts of dietary soy pre- and post-diagnosis are associated with decreased mortality and may be associated with decreased likelihood of recurrence.

Study summaries: Dietary associations with breast cancer outcomes after diagnosis and treatment

Conclusions from observational studies of the association between dietary fat and breast cancer outcomes are mixed. In general, they find that higher levels of fat weakly increase the risk of recurrence or death or that dietary fat has no discernible effect on outcomes.[152,153,154,155,156,158,159] Obesity, however, is associated with increased risk of all-cause and breast cancer specific mortality after diagnosis in both pre- and post-menopausal cases.[160] Diet, of course, is not the only determinant of body weight, but it plays a substantial role, and dietary changes can contribute significantly to weight loss in overweight or obese individuals diagnosed with breast cancer.

Some evidence suggests an influence of dietary fat prior to diagnosis on breast cancer outcomes. A 1994 Canadian study of 678 women with breast cancer found that lower levels of pre-diagnosis dietary saturated fat and higher levels of beta-carotene and vitamin C were associated with increased survival.[161] The association with saturated fat was most marked in post-menopausal women.

A Swedish study examined the dietary patterns of 240 women recently diagnosed with breast cancer (209 post-menopausal) and found that higher amounts of total and saturated fat around the time of diagnosis were associated with shorter period of disease-free survival over four years of follow-up in those with ER+ tumors.[162]

Initial analyses of data from the NHS showed that higher amounts of dietary fat were associated with a modestly increased risk of death from any cause after the diagnosis of breast cancer.[163] The NHS also found that a prudent diet, high in fruit, vegetables, whole grains, and low-fat dairy products was associated with lower overall mortality but not breast-cancer specific mortality.[164] Conversely, a diet high in refined grains, processed meat, high fat dairy, and desserts was associated with higher mortality from non-breast cancer related causes. Subsequently, however, when data were reanalyzed and included more breast cancer cases, it became clear that the relationship between dietary fat and all-cause mortality was strongly influenced by exercise levels.[165] Higher levels of physical activity attenuated the relationship. As it turned out, women who exercised more tended to have healthier diets with lower amounts of fat, and more exercise, rather than lower dietary fat, largely explained the lower mortality. In a subsequent analysis, greater adherence to the Mediterranean diet was associated with lower overall but not breast-cancer specific mortality in women who were less physically active.[166]

A 1992 study of 103 women in the UK with breast cancer (menopausal status not specified) showed that higher levels of vegetable, fruit, beta-carotene, and fiber consumption was associated with more favorable characteristics in tumors at diagnosis—smaller size, more highly differentiated cells, and less blood vessel invasion.[167] Over six years of follow up, higher intake of beta-carotene in this group, as estimated by questionnaire responses shortly after diagnosis, was associated with improved survival.[168] Beta-carotene is a marker for fruit and vegetable consumption and other nutrients in those foods may also be responsible for these findings.

The Health, Eating, Activity, and Lifestyle (HEAL) study is a multicenter, multiethnic (58 percent white, 28 percent African American, 12 percent Hispanic, two percent Asian or mixed ethnicity) cohort study of 1,183 breast cancer patients designed to examine whether weight, physical activity levels, diet, and hormones influence breast cancer prognosis and survival.[169] A study of 688 members of the HEAL cohort (60 percent post-menopausal at baseline), with an average follow up of 6.7 years, found no relationship between dietary carbohydrates, glycemic load, and risk of death from any cause. However, higher levels of dietary fiber (8.8 gm/day or more) were associated with decreased risk of death and breast cancer recurrence, although this became statistically insignificant when adjusted for total caloric intake. Higher dietary fiber in this study was associated with lower levels of a marker of inflammation (C-reactive protein) in the blood, which may help to explain benefits of fiber.[170]

Another study of 516 post-menopausal women with breast cancer found that higher levels of dietary fiber, fruits, and vegetables, and lower levels of dietary fat in the year prior to diagnosis was associated with significantly lower risk of death from any cause over 7 years of follow up.[171]

The Collaborative Women's Longevity Study[172] examined the relation between post-diagnosis dietary factors and survival in 4,441 women with invasive breast cancer. They were 20-79 years old at diagnosis and followed over a period of 7 years. The study used food-frequency questionnaires and adjusted data for age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, and history of hormone replacement therapy. Women in the highest compared to lowest levels of dietary saturated fat and trans fat had a significantly higher risk of dying from any cause [for saturated fat (HR =1.41, 95 percent CI = 1.06-1.87); for trans fat (HR = 1.78, 95 percent CI = 1.35-2.32]. Associations were similar, though did not achieve statistical significance, for breast cancer-specific death.

Dietary soy prior to diagnosis and breast cancer prognosis

Two fairly large studies have looked at relationships between dietary soy prior to diagnosis and course of the disease after diagnosis. In the population-based case control Long Island Breast Cancer study, 1,508 women with breast cancer completed food frequency questionnaires reporting on their diets for the year prior to diagnosis.[173] Over 6 years of follow up, women with the highest intake of flavones, isoflavones, and anthocyanidins (in darkly pigmented berries, red cabbage, eggplant) had reduced risk of death from any cause (37 percent, 48 percent, and 36 percent reduction respectively) compared to those with the lowest intake. Reductions in mortality were most marked among post-menopausal women. Breast cancer specific mortality data were similar. Isoflavone intakes in this study ranged from very low to 7.5 mg or more daily in the upper quintile. As previously noted, daily isoflavone intakes of 20 mg or more from traditional soy products are common among Asians.

In the Shanghai breast cancer study[174] of 1,459 breast cancer patients, soy food intake was assessed using a validated food frequency questionnaire at baseline. In an average follow-up of 5.2 years, soy intake pre-diagnosis was unrelated to disease-free breast cancer survival and this did not differ according to ER/PR status, tumor stage, age at diagnosis, body mass index (BMI), or menopausal status. No information on tamoxifen use was provided.

These two studies are not comparable in that the Long Island study looked at risk of death from breast cancer or other causes, whereas the Shanghai study used disease-free survival as the outcome of interest.

Dietary soy after breast cancer diagnosis

Because of concerns that phytoestrogens in soy products could stimulate breast cancer cell growth and proliferation, many patients and health care providers have understandably been cautious about consumption after diagnosis. Three prospective epidemiologic studies have now addressed this concern.

The Shanghai Breast Cancer Survival Study:[175] population-based, prospective study; 5033 participants with diagnosis of breast cancer; all had undergone surgical therapy and combinations of radiation, chemotherapy, immunotherapy, hormone therapy; 20-75 years old; dietary and other information collected at 6, 18, 36, and 60 months; average follow up 3.9 years (range 0.5-6.2); women with the highest soy protein or soy isoflavone consumption were 20-30 percent less likely to die or experience recurrence than women with the lowest consumption. The associations of soy protein and isoflavones with mortality and recurrence followed a linear dose-response pattern until soy protein intake reached 11 gm/day or soy isoflavone intake reached 40 mg/day, where it leveled off. The adjusted four-year mortality rates were 10.3 percent and 7.4 percent and 4-year recurrence rates were 11.2 percent and 8.9 percent respectively for women in the lowest and highest quartiles of soy protein intake. These reductions were seen in women with either ER+ or ER- tumors and were independent of menopausal status. Benefits of tamoxifen were seen in the low and moderate soy consumption groups. In women consuming highest amounts of soy, tamoxifen did not confer additional benefits. And, women who had the highest level of soy food intake and who did not take tamoxifen had a lower risk of mortality and a lower recurrence rate than women who had the lowest level of soy food intake and used tamoxifen, suggesting that high soy food intake and tamoxifen use may have a comparable effect on breast cancer outcomes.

Life After Cancer Epidemiology study:[176] 1,954 women from the U.S.; included white, black, Hispanic, and Asians; criteria for enrollment included breast cancer diagnosis within 39 months; no other cancers within 5 yrs. of enrollment. Participants were 18-79 years old, had completed cancer treatment aside from adjuvant hormone therapy, and were free of recurrence. Soy use since diagnosis was determined by detailed questionnaire. Over an average 6.3 yrs follow up, there was a borderline significant decreased risk of recurrent breast cancer with increasing intake of daidzein and glycetin. Women with the highest intake of these isoflavones had a 50 percent lower likelihood of recurrence. In post-menopausal women who had ever used tamoxifen, higher intake of daidzein was associated with a significant 60 percent decreased likelihood of recurrence. When examined by hormone receptor status, the reduced risk of recurrence with isoflavone intake was limited to those with ER+ or PR+ tumors.

A recent analysis of the association of dietary soy with breast cancer prognosis in the previously mentioned WHEL study also showed that higher soy isoflavone intakes were associated

with decreased risk of death, with a 54 percent risk reduction at the highest intake.[177] No association with cancer recurrence or metastasis was found.

Thus, three studies which vary in ethnic composition, find no adverse effects of soy foods on breast cancer prognosis and considerable evidence of a beneficial role.

Dietary intervention studies

Beginning in the late 1980s, two large prospective studies examined the effects of particular dietary interventions on breast cancer outcomes, supplementing results of the observational studies described above. In the Women's Healthy Eating and Living (WHEL) study, over 3,000 women with breast cancer were followed for an average of 7.3 years.[178] About 85 percent of participants were white, 4 percent African American, 11 percent Hispanic, Asian, or other. Eligibility criteria included diagnosis of a primary operable stage I, II, or IIIA breast cancer within the past 4 years; age at diagnosis was between 18 and 70 years; treatment with axillary dissection and total mastectomy or lumpectomy followed by primary breast radiation; no current or planned chemotherapy; no evidence of recurrent disease or new breast cancer since completion of initial local treatment; and no other cancer in the past 10 years.

Women in the intervention group were encouraged to adopt a daily diet including 5 vegetable servings, 16 oz. of vegetable juice, 3 fruit servings, 30 gm. of fiber and 20 percent energy from fat. They received newsletters and were invited to cooking classes during the first year. Women in the comparison group were advised to consume 5 servings of vegetables and fruit daily, more than 20 gm fiber, and less than 30 percent of calories from fat. They were also offered cooking classes and newsletters. At the beginning of the study, women randomly assigned to both groups were already consuming about seven servings of vegetables and fruits daily.

The intervention group increased their vegetable and fruit consumption, and their plasma carotenoid concentrations were 73 percent higher than the comparison group at one year and 43 percent higher at four years. But there were no differences in any breast cancer event (local, regional, or distant recurrence, or new primary tumor) or overall mortality between the intervention and comparison groups. However, higher blood levels of carotenoids were associated with a significant delay in tumor recurrence, regardless of the study group.[179] In subgroup analyses, peri-menopausal and post-menopausal women who had higher levels of estrogen at baseline were at higher risk of recurrence of disease. And women who had not experienced hot flashes, presumably because of higher estrogen levels, were also at higher risk of recurrence of disease.[180] In an analysis of hormone levels at one year of follow up, higher levels of dietary fiber and lower levels of fat had significantly lowered circulating estrogen levels in the intervention group, compared to baseline.[181]

Another large study, the Women's Intervention Nutrition Study (WINS), was launched in 1987.[182, 183] This was a randomized clinical trial involving 2,437 participants examining whether dietary fat reduction would increase relapse-free survival in women between the ages of 48 and 79 years with early-stage breast cancer. Eligibility criteria included completely resected unilateral invasive breast cancer, baseline caloric intake from fat of >20 percent, and additional therapy appropriate to their condition (e.g., women with estrogen-receptor-positive tumors must have daily tamoxifen, other chemotherapy optional; women with estrogen-receptor-negative tumors must have chemotherapy). Eighty-five percent of participants were white, 5 percent Black, and the remainder Hispanic or Asian-Pacific Islanders.

At baseline, both the intervention and comparison groups obtained about 30 percent of their calories from fat. During the trial, the intervention group succeeded in reducing fat intake to an average of about 20 percent of calories. Although weight loss was not the goal, the intervention group did experience significant weight reduction. After an average follow-up of five years, relapse-free survival (lack of breast cancer recurrence at any site) was 24 percent higher in the intervention group. In subgroup analyses, the intervention effect on relapse-free survival was greater in women with hormone-receptor negative disease than in women with receptor-positive disease. This suggests that factors other than modified estrogen levels are involved and may include reduced insulin levels or improved insulin sensitivity.

WHEL / WINS interventions; summary

WHEL focused on a plant-based dietary pattern that also included reduction in fat. WINS focused exclusively on dietary fat reduction. WHEL included women with pre- and post-menopausal breast cancer, while WINS participants were exclusively post-menopausal. WHEL found no effect of that dietary intervention on prognosis although higher levels of carotenoids, a marker for fruit and vegetable consumption, was associated with delayed recurrence, regardless of the study group. WINS found a beneficial effect from dietary fat reduction.

A subsequent analysis of data from the WHEL study found that the combination of higher levels of dietary fruit and vegetables along with high levels of physical activity reduced the risk of death over 10 years of follow up by half[184] (93 percent survival in the high vegetable/fruit; high physical activity group vs. 86-87 percent survival in the other groups). This effect was most marked in women with hormone receptor positive tumors. Once again, this highlights the difficulty interpreting dietary observational or interventional studies that have not accounted for exercise levels among participants. Looked at another way, combinations of dietary modifications and exercise are likely to be more beneficial than either alone.

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Exercise, physical activity, and breast cancer

Chapter summary

Humans evolved in the context of physical activity levels very different from today.* Sedentary living, more common now than ever before, is unhealthy and increases the risk of many diseases and earlier death. In fact, prolonged sitting itself is unhealthy, regardless of physical activity levels at other times.[1,2]

Physical activity benefits health across the entire lifespan. Stretching, resistance, and other aerobic fitness exercises influence immune and endocrine function, cardiovascular, pulmonary, and muscular health, body composition, and quality of life, including psychological well-being.

The American College of Sports Medicine recommends healthy adults and cancer survivors perform a minimum of 30-minutes of moderate-intensity exercise five days a week to promote health.[3,4] The American Institute for Cancer Research (AICR) and the World Cancer Research Fund recommend even more–60 minutes of moderate-intensity or 30 minutes of vigorous-intensity exercise daily to reduce cancer risk.[5]

In 1989, scientists from the National Cancer Institute examined the relationship between self-reported physical activity and cancer in the first NHANES cohort, originally assembled from 1971 to 1975, designed to represent

* Exercise is a form of physical activity that is usually planned, structured, and done to improve some aspect of fitness such as strength, flexibility, or aerobic endurance. Exercise also improves general health, well-being, and overall quality of life. Physical activity includes activity that is part of daily life. Household, workplace, and lifestyle physical activity are most common.

the general population, and followed for about 10 years.[6] They reported an increased risk of various kinds of cancer among inactive individuals compared to very active people (80 percent increased risk for men and 30 percent increased risk for women), even after correcting for smoking and BMI. The association was strongest for colorectal and lung cancer in men, and post-menopausal breast and cervical cancer in women.

Exercise, physical activity: breast cancer prevention

Strong evidence continues to show that increased physical activity helps to prevent post-menopausal breast, colorectal, and endometrial cancer.[7] Risk reduction ranges from 20 to 80 percent for post-menopausal breast cancer with increasing physical activity.[8] Evidence for prevention of pre-menopausal breast cancer is not as strong.

Most studies show that increasing levels and duration of physical activity increase the benefit. One review finds that moderate-to-vigorous intensity physical activity two to three hours/week is associated with an average breast cancer risk reduction of nine percent compared to 30 percent decreased risk with 6.5 hours/week or more.[9]

Studies that distinguish among kinds of physical activity find the greatest risk reductions for recreational activity (average 20 percent decrease), followed by walking/cycling for transportation (14 percent), household work (14 percent), and occupational activity (13 percent).[10]

Increased physical activity is beneficial at all life stages. A 15-year follow-up of 3940 former college athletes and their non-athlete classmates confirmed a significantly lower risk of breast cancer in the athletes. Among the entire group of former athletes, breast cancer risk was 40 percent lower than among the non-athletes. For women under age 45, former athletes experienced a striking 84 percent risk reduction.[11]

A prospective analysis of over 40,000 women participating in the Nurses' Health Study II found that increased amounts of physical activity in childhood, adolescence, and adulthood was associated with a decreased risk of developing proliferative benign breast disease—a condition generally considered an early stage in the development of breast cancer.[12] Women engaged in 39–50 MET-hrs/week of physical activity seemed to be at lowest risk. Thirty-nine MET-hrs/week is roughly equivalent to 13 hours/week of walking or 3.25 hours/week of running.

In general, higher lifetime levels are more consistently associated with decreased breast cancer risk than more recent measures. Nonetheless, increased physical activity after age 50 appears to reduce risks more than levels earlier in life. In studies that have examined the effects of exercise on breast cancer risk in various ethnic/racial groups, the largest risk reduction was observed in African-American and Asian women.

Exercise, physical activity: benefits after initial breast cancer treatment

Strong evidence, including results from randomized controlled trials, shows that regular exercise improves numerous measures of health, well-being, and quality of life from the time of a diagnosis of cancer throughout the pre-treatment and treatment periods and beyond. Most but not all studies show that women who regularly exercise after breast cancer treatment experience reduced all-cause and breast-cancer specific mortality compared to sedentary women over follow-up periods averaging four to eight years. In many studies, higher levels of physical activity or exercise before diagnosis are also associated with improved survival after diagnosis and treatment.

Biologic mechanisms linking physical activity and exercise to breast cancer risk

Multiple, inter-related biologic mechanisms probably explain how increasing physical activity levels help to reduce breast cancer risk and improve prognosis following diagnosis and treatment. They include:

- reduced adipose tissue,
- changes in metabolism,
- altered levels of various growth factors, hormones, and their metabolism,
- improved immune function,
- reduced chronic inflammation,
- altered gene expression.

Most but not all studies that examine whether BMI has an influence on the effect of physical activity levels find that increasing levels of exercise reduce breast cancer risk more in women with lower compared to higher BMI. But this is not a consistent finding. It is likely that increased levels of physical activity have benefits that are independent of BMI status.

A number of observational studies conclude that obesity is a risk factor for breast (post-menopausal only), colorectal, endometrial, esophageal, pancreatic, and kidney cancer. Only a few, however, examine whether weight loss lowers cancer risk. In patients who have undergone bariatric surgery, early evidence suggests that to be true. After nearly 11 years of follow-up, a Swedish study found that women undergoing the surgery had a 42 percent lower overall cancer risk and a 32 percent lower weight than those of controls.[13] Interestingly, men who underwent the surgery had no reduction of cancer risk during the same period. Another study reported that over an average of 12 years after surgery, women had a 27 percent lower total cancer incidence after a 31 percent reduction in weight compared with control subjects.[14] However, breast cancer incidence was not different between the groups. Again, men did not experience cancer risk reduction with the surgery.

Since elevated BMI is itself a risk factor for post-menopausal breast cancer, exercise should be combined with dietary modifications and other efforts to reduce overweight or obesity, particularly in post-menopausal women. After diagnosis and treatment of breast cancer, reducing overweight or obesity is beneficial in all women, regardless of menopausal status.

Interest in the influence of exercise on breast cancer risk began to rapidly grow in the 1980s after studies showed that increased physical activity was associated with fewer ovulatory menstrual cycles, particularly in adolescent girls.[15] A 1987 study monitored 169 high school girls for six months.[16] Increasing amounts of physical activity, including moderate levels of aerobic exercise about two hours weekly, was associated with higher likelihood of anovulatory menstrual cycles. The authors wondered if this might reduce breast cancer risk.

Numerous studies of differing design have examined the relationship of exercise or physical activity to breast cancer in detail. Some use comprehensive assessments of lifetime physical activity, while others use shorter-term measures. They also classify the intensity of physical activity in various ways. Many use metabolic equivalents (METs) as a measure. Metabolic equivalents describe activity intensity relative to a person's resting metabolic state, taking into account basal energy expenditure, age, size, and level of fitness (See Table 4.1).

Alternatively, physical activity intensity may be stratified by heart and breathing rates: vigorous (increases heart and breathing rates up to 80 percent or more of maximum), moderate (increases heart rate to 60-70 percent of maximum), and light (minor effects on heart and breathing rates).

Table 4.1: Intensity of physical activity expressed as metabolic equivalents

Physical Activity	MET
Light Intensity Activities	<3
sleeping	0.9
watching television	1.0
writing, desk work, typing	1.8
walking 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3
walking 2.5 mph (4 km/h)	2.9
Moderate Intensity Activities	3 to 6
bicycling, stationary, 50 watts, very light effort	3.0
walking 3.0 mph (4.8 km/h)	3.3
calisthenics, home exercise, light or moderate effort, general	3.5
walking 3.4 mph (5.5 km/h)	3.6
bicycling <10 mph (16 km/h), leisure, to work or for pleasure	4.0
bicycling, stationary, 100 watts, light effort	5.5
Vigorous Instensity Activities	>6
jogging, general	7.0
calisthenics (e.g. pushups, situps, pullups, jumping jacks), heavy, vigorous effort	8.0
running jogging, in place	8.0
rope jumping	10.0

Individual studies of exercise and breast cancer risk

More than 70 cohort and case-control studies have examined the relationship between physical activity, exercise and breast cancer risk. Others have studied the relationship between physical activity levels and breast cancer prognosis after diagnosis and treatment. Most studies are done in countries with low average levels of occupational, household, and transport physical activity—thus, generally sedentary ways of life. Table 4.2 summarizes results of 17 large prospective cohort studies.

Summaries of published literature reviews

The most recent reviews have concluded that the evidence supporting a relationship between increased physical activity and decreased risk of breast cancer is convincing.[17,18,19]

Monninkhof, et al. reviewed 19 cohort studies and 29 case control studies and found strong evidence for post-menopausal breast cancer risk reductions ranging from 20-80 percent with increasing physical activity. The evidence for pre-menopausal breast cancer prevention was weaker.[20]

Friedenreich and Cust reviewed 34 case-control and 28 cohort studies finding reduced breast cancer risk with increased physical activity in three-quarters with greater risk reduction with more intense exercise.[21] Studies that distinguished among kinds of physical activity found the greatest risk reductions for recreational activity (average 20 percent decrease), followed by walking/cycling for transportation (14 percent), household work (14 percent), and occupational physical activity (13 percent). Increased physical activity seemed to be beneficial at all life stages, but higher lifetime amounts were more consistently associated with decreased risk than more recent measures. There was, however, a tendency for activity after age 50 to have a stronger risk reduction effect than activity earlier in life. Among the studies that distinguished results according to menopausal status, both pre- and post-menopausal women appeared to experience decreased risk with increased activity, but the decrease was larger and most consistent for post-menopausal women. Sixteen of the studies reviewed examined whether BMI had an influence on the effect of activity levels on breast cancer risk. Increasing physical activity reduced cancer risk more in women with low or normal BMI. This suggests that increased physical activity should be coupled with other efforts to reduce overweight or obesity, particularly in post-menopausal women in whom overweight is a risk factor for breast cancer. In studies that examined the effects of exercise in various ethnic/racial groups, the largest risk reduction was observed in African-American and Asian women.

Table 4.2: Individual prospective cohort studies

Study	Study Population (number of cases)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk (or Hazard Ratio) of Breast Cancer in Physically Active Women Compared with Inactive Women, RR or hazard ratio HR (95 percent CI)		
				Pre-menopausal	Post-menopausal	Pre- and post-menopausal combined
NIH-AARP Diet and Health Study[22, 23]	182,862 (6,609 cases)	7	At least 20 min. physical activity at least 5 times/ wk that caused increased breathing, heart rate, or sweating vs. inactive		0.92 (0.85-1.00)*	
Nurses' Health Study [24]	95,396 (4,782 cases)	20	27 or more vs. less than 3 MET hr/wk		0.88 (0.79-0.98)	
French E3N cohort [25]	90,509 (3,424 cases)	11.4	22.3-33.8 MET hrs/wk recreational activity vs. inactive			0.88 (0.79-0.98) [protective effect persisted regardless of family history, nulliparity, HRT use, BMI]
French E3N cohor	90,509 (3,424 cases)	11.4	33.8 or more MET hrs/wk recreational activity vs. inactive			0.81 (0.72-0.92)
EPIC [26]	218,169 (3,423 cases)	6.4	Recreation: At least 42 vs. less than 14 MET hrs/wk of recreational activity Household activity: > 90 vs < 23 Met hrs/wk	0.94 (0.76-1.15) 0.71 (0.55-0.90)	0.96 (0.85-1.08) 0.81 (0.70-0.93)	
California Teachers Study[27]	110,599 (2,649 cases)	6.6	5 or more hrs/wk moderate physical activity vs. inactive			ER- tumors 0.53 (0.33-0.85); ER+ tumors 0.98 (0.82-1.16)
Iowa Women's Health Study[28]	36,363 (2,548 cases)	15.3	High vs. low level of physical activity		0.91 (0.82-1.01) 0.66 (0.46-0.94) for ER+/PR- tumors	
National Breast Cancer Screening Study-Canada[29 ##]	40,318 (2,545 cases)	16.4	At least 1 hr/day vigorous physical activity vs. inactive	0.87 (0.68-1.09)	1.00 (0.78-1.29)	0.93 (0.78-1.10)
Cancer Prevention Study II (CPS II)[30]	72,608 (1,520 cases)	5	At least 42 vs. less than 7 MET hrs/wk physical activity		0.71 (0.49-1.02) Non-recreational activity not associated with BC risk	

Study	Study Population (number of cases)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk (or Hazard Ratio) of Breast Cancer in Physically Active Women Compared with Inactive Women, RR or hazard ratio HR (95 percent CI)		
				Pre-menopausal	Post-menopausal	Pre- and post-menopausal combined
Norwegian-Swedish Women's Lifestyle and Health Cohort Study[31]	99,504 (1,166 cases)	9.1	Vigorous physical activity vs. no physical activity	1.24 (0.85-1.82)‡ (7 percent of cohort post-menopausal at enrollment) A change from being inactive to active at age 30; RR 0.66 (0.44-0.96)		
Women's Health Initiative[32]	74,171 (1,780 cases)	4.7	Strenuous physical activity 3X/wk; (enough to sweat, make heart beat fast); at ages 35 and at 50		0.82 (0.68-0.97); similar risk reduction for exercise at age 35 and 50; less effect with exercise at age 18	
Breast Cancer Detection Demonstration Project Follow-up Study[33]	32,269 (1,506 cases)	8.4	Most vigorous vs. lower level of physical activity		0.87 (0.74-1.02); effect largest in normal weight women	
Netherlands Cohort Study[34]	62,537 (1,208 cases)	7.3	More than 90 minutes/day of physical activity vs. less than 30 minutes/day		0.76 (0.58-0.99); more marked risk reduction in women with higher BMI	
U.S. Radiologic Technologies cohort[35]	45,631 (864 cases)	8.9	At least 97 vs. less than 9.5 MET hrs/wk physical activity			0.91 (0.74-1.13)
U.S. Radiologic Technologies cohort	45,631 (864 cases)	8.9	Walking/hiking at least 10 hrs/wk vs. never walking/hiking	0.37 (0.16-0.84)		0.57 (0.34-0.95)
Nurses' Health Study II[36]	110,468 (849 cases)	10	27 or more vs. less than 3 MET hrs/wk; running or jogging > 2 hrs/wk; lifetime physical activity > 39 MET hrs/wk	1.04 (0.82-1.33)§ 0.71 (0.45 – 1.12) 0.77 (0.64-0.93)		
PLCO Cancer Screening Trial[37] #	27,541 (764 cases)	4.9	3 hrs/wk recreational activity vs. inactive		1.02 (0.79-1.30)	

Study	Study Population (number of cases)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk (or Hazard Ratio) of Breast Cancer in Physically Active Women Compared with Inactive Women, RR or hazard ratio HR (95 percent CI)		
				Pre-menopausal	Post-menopausal	Pre- and post-menopausal combined
PLCO Cancer Screening Trial	27,541 (764 cases)	4.9	4 or more hrs/wk recreational activity vs. inactive		0.78 (0.61-0.99)	
Japan Public Health Center-based Prospective Study; case-control design[38]	53,578 (652 cases)	14.5	Leisure-time physical activity at least 3 days/wk vs. 3 or fewer days/month[###]	0.66 (0.40-1.09)	0.78 (0.52-1.17)	0.73 (0.54-1.00)
Swedish Twins Cohort[39]	9,539 (506 cases)	20	Regular vs. very little physical activity		0.6 (0.4-1.0) regular leisure physical activity	
Shanghai Women's Health Study[40]	73.049 (717 cases)	9	Non-occupational and occupational physical activity levels	HR 1.25, (0.77-2.01) for women exercising more than 8 MET h/wk/yr in past 5 yrs	HR 0.73, (0.57-0.92) for women exercising more than 8 MET h/wk/yr; effect greater in women with BMI > 24	

[*] Additional analyses of 97,039 postmenopausal women (2,866 cases) found that women whose daily routines included activities such as walking or heavy lifting/carrying had a lower risk of breast cancer compared to women who sat all day.

[‡] This study also found no link between physical activity at age 30 and breast cancer risk (vigorous activity vs. no activity 1.20 (0.77-1.95), nor between physical activity at age 14 and breast cancer risk (vigorous activity vs. no activity, RR was 1.05 (0.72-1.54).

[§] Among 64,777 premenopausal women in this study, average lifetime physical activity was found to decrease risk of breast cancer. Women who averaged at least 39 MET hours of physical activity a week during their lifetime had lower risk of breast cancer compared to inactive women, RR was 0.77 (0.64-0.93).

[#] This study also examined post-menopausal breast cancer risk associated with total energy intake (as estimated by food frequency questionnaire), BMI in combination with various levels of exercise. Women with highest quartile of total energy intake, BMI >30, and less than 4 hrs/wk of exercise had a 2.2-fold increased risk of breast cancer (RR 2.1; 1.27-3.45) compared to women in the lowest quartile of energy intake, with BMI <30, and who exercised >4 hrs/wk. The relationship of energy intake to breast cancer risk was not dependent on BMI or activity level.

[##] This study found increased cancer risk in premenopausal women with highest energy intake, independent of BMI (for BMI <25, RR 1.44 (1.13–1.82); for BMI >25, RR 1.49 (1.12–1.99)). This increased risk was identified across exercise levels. This suggests that energy intake and BMI may have different effects on pre-menopausal breast cancer risk, and BMI is not necessarily a good surrogate for energy intake.

[###] In this study, most marked risk reduction for pre- and post-menopausal breast cancer seen with strenuous activity at age 12 and moderate activity at age 20 and within the past 5 years.

Lynch, et al. reviewed 33 cohort and 40 case-control studies.[41] Forty percent of the studies found a statistically significant decrease in breast cancer risk when comparing the highest with the lowest physical activity levels. An additional 11 percent had a borderline statistically significant risk reduction. Across all studies, there was a 25 percent risk reduction with higher amounts of physical activity. Thirty-three of 41 studies that looked found increasing risk reduction with increased amounts of exercise. In studies that distinguished menopausal status, risk reduction was slightly greater for post-menopausal than pre-menopausal breast cancer. Duration seemed to have a greater effect than intensity of physical activity. Moderate-to-vigorous intensity activity two to three hours/week was associated with an average risk reduction of nine percent, compared to 30 percent decreased risk with 6.5 hours/week or more.

Chandran, et al. reviewed the role of diet, exercise, and BMI in breast cancer risk in African-American women.[42] In four case-control studies increasing physical activity tended toward being protective against pre- and post-menopausal breast cancer. Studies including African-American and white women suggested an even stronger protective effect of exercise in African-American women.

Physical activity or exercise before and after diagnosis of breast cancer: quality of life, recurrence, and survival

Strong evidence, including results from randomized controlled trials, also shows that regular exercise improves numerous measures of health and well-being from the time of a diagnosis of cancer throughout the pre-treatment and treatment periods and beyond.[43,44,45] Most but not all studies show that regular exercise improves quality of life and reduces all-cause and breast- cancer specific mortality over an average follow-up of four to eight years.

Physical activity/exercise at the time of diagnosis and initial treatment

For breast cancer specifically, physical activity levels, both before and after diagnosis and treatment, can influence the likelihood of recurrence and the risk of death—from breast cancer or any cause. Even short-term (12-week) involvement in a supervised exercise program during and after treatment can improve quality of life and outcomes over the long term.[46]

Many controlled and uncontrolled studies of the effects of exercise soon after the diagnosis and during the treatment of breast cancer have been published.[47,48] In a recent meta-analysis of 82 controlled trials of exercise in people recently diagnosed with cancer, 66 were considered of high quality and 83 percent were conducted in breast cancer survivors.[49] The majority found significant benefits from exercise interventions. Early on, upper and lower body

strength and self-esteem improved. Following initial treatment, participants experienced significant benefits in aerobic fitness, upper and lower body strength, flexibility, lean body mass, overall quality of life, vigor, fatigue reduction, and measures of hormone and immune parameters (insulin-like growth factor 1 (IGF-1), IGF binding protein-3, cellular immunity, and inflammatory markers).

The majority of exercise interventions were longer than five weeks—about half were more than three months. Aerobic or combined activity interventions were the most common and typically moderately or vigorously intense, three-five times per week, for 30 – 45 minutes per session, both during and after initial cancer treatment.

Many participants were fearful of harm from exercise, particularly related to anemia, weight loss, and lymphedema in their arms. With few exceptions, aerobic and upper body resistance exercises were well tolerated with no evidence of adverse effects on the development or worsening of lymphedema. One study did not exclude participants with anemia and found no adverse effects of vigorous aerobic exercise even after recent hospital discharge following high dose chemotherapy and stem cell transplantation.[50] However, a number of authors caution against prolonged, repetitive high-intensity exercise in cancer survivors near the end of treatment when immune function may be compromised because of the potential for added adverse immune system impacts, as have been noted even in healthy people who exercise excessively.[51]

Exercise also helps to diminish depression associated with the diagnosis and treatment of cancer.[52] Depression is not only important psychologically but also can increase inflammation and alter some immune system functions.[53] This can promote conditions for tumor growth, invasion, and metastasis.

One systematic review examined evidence that tai chi may be beneficial for BC survivors.[54] Tai chi combines physical exercise with mindful meditation and breathing control and is claimed to have positive effects on psychological health, quality of life, mood, flexibility, and balance. The review included three randomized clinical trials in the U.S. and four controlled clinical trials in Korea involving a total of 201 participants. Duration of treatment varied from six to twelve weeks, with one to three supervised sessions weekly. None of the trials found that tai chi improved quality of life or mood compared to controls. One trial found improved range of motion of the shoulder joint, upper limb function, and daily life activity. Three found favorable effects on pain and range of motion of the shoulder, but not on hand grip strength, flexibility, and upper limb function compared with no treatment. No adverse effects were reported.

Physical activity/exercise after the initial treatment period

Beyond the initial treatment period, increased exercise also appears to reduce both breast cancer – specific and overall mortality over the longer term.[55] The evidence is particularly strong for post-menopausal breast cancer. Some evidence shows increased risk reduction with increasing exercise levels. In general, highly significant reduction in risk of mortality over the follow-up period of a number of studies is associated with exercise levels equivalent to about two-three hours of brisk walking weekly (roughly nine MET hours/week). Evidence that exercise reduces the risk of breast-cancer recurrence or that increased activity is more or less beneficial for certain sub-groups of individuals—for example, women with higher (or lower) BMI, hormone receptor status of tumors, stage of disease—is inconsistent.

Table 4.3 summarizes the results from a number of large cohort and population-based case control studies examining the relationship between pre-diagnosis physical activity levels and outcomes following diagnosis and treatment. Table 4.4 summarizes results of studies looking at outcomes associated with varying levels of physical activity post-diagnosis and treatment.

Literature reviews of pre- and post-diagnosis exercise levels and breast cancer outcomes

Ballard-Barbash, et al. systematically reviewed available observational studies and randomized trials of physical activity and cancer-specific and all-cause mortality and relevant biomarkers in cancer survivors.[56] None of the studies reported that higher levels of physical activity were associated with an increased risk of death from breast cancer or any cause. For breast cancer–specific mortality, four studies reported no association with physical activity, seven studies observed non – statistically significant decreased risk of death that ranged from 13 to 51 percent when comparing the highest with the lowest physical activity categories, and six studies observed statistically significant decreased risks of breast cancer-specific mortality that ranged from 41 to 51 percent. With regard to the association between physical activity and mortality from any cause, two studies reported no effect, five studies reported non – statistically significant reduced risks, and seven studies reported statistically significant reduced risks.

Several possible reasons may explain inconsistencies in study results. Study participants may not be comparable. For example, women in the Nurse's Health Study were generally leaner than those in LACE. Measures of physical activity levels are not the same among studies. There may also be unaccounted for differences in the severity of disease, tumor types, or other interventions, such as dietary changes.

Table 4.3: Association of pre-diagnosis exercise on post-diagnosis outcomes

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	All-cause mortality	Breast-cancer specific mortality
Population-based case control study; Alberta, CA[57]	1231; 60 percent post-menopausal	minimum of 8.3 years for any cancer progressions, recurrences, new primaries; minimum of 10.3 years for deaths	Lifetime level of physical activity; highest vs lowest quartile	Moderate intensity recreational activity decreased the risk of recurrence, progression or new primary cancer RR 0.66; (0.48–0.91)	No association with total physical activity; Highest vs lowest recreational activity HR 0.54, (0.36–0.79)	No association with total physical activity; Moderate recreational activity: HR 0.56, (0.38–0.82) Vigorous recreational activity: HR 0.74 (0.56–0.98)
WHI[58]	4,643 post-menopausal	Physical activity assessment pre-diagnosis average 4.3 yrs. Physical activity assessment post-diagnosis 1.8 yrs Follow-up average 3.3 yrs.	>9 MET-h/week compared to inactive same		HR 0.61; (0.44–0.87) HR 0.54; (0.38–0.79)	HR 0.61; (0.35–0.99)
Population-based case control study; NJ or Atlanta[59]	1264; age 20-54; 85 percent per-menopausal	Follow-up average 8.5 yrs.	Physical activity estimates at age 13, 20, and the year prior to diagnosis		Reduced mortality associated with high physical activity during the previous year in women with BMI >25; HR 0.70 (0.49–0.99)	
Population-based case control study; Australia[60]	451 cases; age 20-74	Average follow-up 5.5 yrs.	Assessed association of physical activity in the year before diagnosis			No significant association with physical activity: pre- or post-menopausal cases
CA teachers study[61]	3,539 cases; age 26-94 yrs; average 59 yrs	Median follow-up of women who died 38.5 mos; medium follow-up of women who survived 64 mos.	Long-term (high-school-age to age 54) and recent exercise (last 3 yrs); Strenuous and moderate exercise; moderate exercise by quartile		Higher long-term exercise RR 0.73 (0.55-0.96); association mostly in women with BMI>25; other levels no effect	Intermediate long-term exercise RR 0.65 (0.45-0.93); high long-term exercise RR 0.53 (0.35-0.80). Recent exercise-no association

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	All-cause mortality	Breast-cancer specific mortality
Breast cancer family registry[62]	4,153 cases; ages < 35 - >60 yrs.	Median follow-up 7.8 yrs.			HR 0.77 (0.60-1.00) for recreational physical activity of >38.2 vs 0 MET-h/wk within last 3 yrs.; effect mostly in ER+ tumors; beneficial effects also at < 9 MET hrs/wk; No significant effect of earlier physical activity levels	
Population-based survival study; Norwegian Counties Study [63]	1,364 cases; ages 27-79 yrs. at diagnosis	Mean follow-up 8.2 yrs.	Level of leisure physical activity in the year prior to study entry		HR 1.47, (1.08–1.99) for pre-diagnostic BMI > 30 compared to BMI 18.5-25*; Active compared to inactive women: HR 0.60, (0.36–0.99)	
Population-based case control study; So. CA[64]	717 cases; all pre-menopausal	10.4 yrs.	Lifetime recreational exercise history; from menarche to one yr. before diagnosis			No association of exercise with breast cancer survival

*effect stronger in pre/perimenopausal women. Women with BMI < 25 kg/m2 and age of diagnosis > 55 years had a 66 percent reduction in overall mortality if they regularly exercised before diagnosis compared with sedentary women; HR = 0.34 (0.16–0.71). Women with the highest total cholesterol had a 29 percent increase in mortality compared to women with the lowest cholesterol (HR = 1.29, [1.01–1.64]). Women with the highest blood pressure had a 41 percent increase in mortality compared to women with the lowest BP. (HR = 1.41, [1.09–1.83]).

Table 4.4: Association of post-diagnosis exercise on outcomes

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	All-cause mortality	Breast-cancer specific mortality
Nurse's health study[65]	3,846 cases; average age at diagnosis 58 yrs.	Median length of follow-up 83 months, and maximum length of follow-up 321 months.	Level of physical activity after diagnosis			Decreasing risk associated with increasing amounts of physical activity (by quintile) RR 0.53 (0.39-0.71); 0.36 (0.26- 0.51); 0.28 (0.19- 0.41); 0.17 (0.11-0.27)

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	All-cause mortality	Breast-cancer specific mortality
WHI	4,643 post-menopausal; average follow-up 3.3 yrs.		Physical activity assessment post-diagnosis 1.8 yrs		Activity > 9 MET hr/wk; HR 0.54; (0.38–0.79)	Activity > 9 MET hr/wk; HR 0.61; (0.35–0.99)
China; Shanghai Breast Cancer Survival Study[66]	4826 cases, mean age 53.5 yr; mostly Asian; pre- and postmenopausal; interviewed 6, 18, 36 mos. after diagnosis	Median median follow-up 4.3 yrs.	Exercise determined at interview 6, 18, 36 mos. after diagnosis		HR 0.65 (0.51-0.84) for exercise ≥ 8.3 MET-h/wk vs. no exercise	HR 0.59 (0.45-0.76) at 36 mo. after diagnosis with exercise of ≥ 8.3 MET-h/wk vs. no exercise
Life After Cancer Epidemiology Study, U.S. [67] (LACE)	Cohort study of cancer survivors; 1970 cases, ages 18–79 yrs; mostly white	Median follow-up 7.25 yrs.	Interviewed at study entry; mean 1.9 yrs. post-diagnosis; occupational, household care giving, leisure-time, transportation-related physical activity, in MET-hr/wk, during the preceding 6 mo	HR 0.91 (0.61-1.36) for recurrence for physical activity of ≥ 62 vs <29 MET-h/wk =	HR 0.76 (0.48-1.19) for death from any cause for physical activity of ≥ 62 vs <29 MET-h/wk	HR 0.87 (0.48-1.59) for death from breast cancer for physical activity of ≥ 62 vs <29 MET-h/wk
Health, Eating, Activity, and Lifestyle (HEAL) Study; U.S.[68]	Cohort study of cancer survivors; 933 cases; mean age 55 yrs; multiethnic; pre- and post-menopausal cases	Mean follow-up 7.25 yrs.	frequency and duration of leisure, occupational, household, physical activity; in MET hr/wk		HR 0.33 (0.15 to 0.73) for leisure activity ≥ 9 vs 0 MET-h/wk	HR 0.65 (0.23-1.8) for leisure activity > 9 vs 0 MET-h/wk
Women's Healthy Eating and Living Study (WHEL) [69]	A dietary RCT in which physical activity also assessed; 2361 cases; mean age 54 yrs; multiethnic; pre- and post-menopausal;	Mean follow-up 5.6 yrs.	frequency, duration, and intensity of physical activity, in MET-h/wk, interviewed after treatment at baseline and 1 yr later	HR 0.74 (0.50 to 1.10) for 24–107 vs 0–2.5 MET-hr/wk	HR 0.47 (0.26-0.84) for 24–107 vs 0–2.5 MET-hr/wk =	
Collaborative Women's Longevity Study; U.S. [70]	4482 cases; mean age 61.7 yrs; mostly white; pre- and post-menopausal 88 – 2001; pre- and postmenopausal; interviewed 2 y after diagnosis		Frequency and duration of weekly leisure physical activity		HR 0.44 (0.32-0.61) for physical activity of ≥ 21 vs <2.8 MET-h/wk	HR 0.49 (0.27-0.89) for physical activity ≥ 21 vs <2.8 MET-h/wk

In summary, the authors concluded that there is fairly consistent evidence that increased physical activity either before or after breast cancer diagnosis is associated with a reduction in both breast cancer – specific mortality and overall mortality, with some evidence suggesting increased risk reduction with increasing activity levels.

Mechanisms by which physical exercise may reduce breast cancer risk and improve prognosis following diagnosis

Multiple, inter-related biologic mechanisms probably explain how increasing activity levels help to reduce breast cancer risk and improve prognosis following diagnosis and treatment. They include:

- reduced adipose tissue accumulation,
- changes in metabolism,
- altered levels of various growth factors, hormones, and their metabolism,
- improved immune function,
- reduced chronic inflammation,
- altered gene expression. A recent randomized exercise intervention study reported that 6 months of moderately vigorous regular exercise modified methylation patterns on a number of genes, including reducing methylation of a tumor suppressor gene, allowing it to be more strongly expressed.[71]

In addition to estrogen and insulin, two additional hormones, leptin and adiponectin have attracted considerable attention with respect to their role in post-menopausal breast cancer. Leptin is a protein hormone manufactured primarily in adipose tissue. It is a key regulator of appetite, food intake, and body weight and plays a role in energy balance and metabolism. Elevated leptin levels are associated with overweight, obesity, and inflammation-related diseases. A reduction in elevated leptin concentrations can lead to an improvement in blood lipid levels, blood pressure, and insulin sensitivity.[72] Adiponectin is an insulin-sensitizing, anti-inflammatory hormone, also produced primarily in adipose tissue. It plays a central role in energy homeostasis, as well as lipid and glucose metabolism. The Nurses' Health Study reported that higher levels of adiponectin were associated with lower postmenopausal breast cancer risk.[73] A systematic review concluded that measurement of adiponectin might serve as a means for predicting risk of obesity-related cancers.[74]

Pre-menopause

The effects of exercise on levels of hormones and related growth factors in pre-menopausal women are not entirely clear. Most studies show little or no relationship between exercise and IGF-1 or IGFBP-3 levels in pre-menopausal women.[75,76,77,78]

With regard to sex hormones, it is important to note that, unlike hormone-receptor-positive, post-menopausal breast cancer, the relationship between endogenous estrogen levels, estrogen metabolites, and premenopausal breast cancer risk is less certain.[79] Nonetheless, the effect of exercise on estrogen levels in premenopausal women is at least plausibly related to breast cancer risk. However, results of studies of this relationship in premenopausal women have been inconsistent.

A recent study of 318 women (165 exercisers, 153 controls), using 24-hour urine collections at the mid-follicular phase of the menstrual cycle, found that the ratio of 2-hydroxyestrone:16α-hydroxyestrone was significantly increased in women who engaged in 30 minutes of aerobic exercise five days a week for 16 weeks.[80] This estrogen metabolic profile may reduce breast cancer risk since the 2-hydroxy metabolite of estrogen is less genotoxic than the 16α-hydroxy metabolite.[81] However, a smaller study of 32 women found no difference in estrogen metabolites between participants who engaged in aerobic exercise 30-40 min. four days/week for 12 weeks and controls.[82] In this study, estrogen metabolites were measured in a morning urine specimen once during the luteal phase of each menstrual cycle during the trial.

Inconsistent findings may be due in part to the wide variability of estrogen levels during the menstrual cycle, making it difficult to estimate total exposure to endogenous estrogen from single or even a few measures during monthly cycles. A recent small study addressed this problem by measuring hormone levels of seven healthy women 25-35 years old before and after an exercise program intervention.[83] Participants were healthy but believed to be at high risk of breast cancer because of BRCA-status or family history. Urinary estrogen and progesterone metabolite levels were monitored daily at baseline during two menstrual cycles and after the introduction of an exercise program to a maintenance level of 300 minute/week to 80-85 percent of aerobic capacity. This approach provided a more accurate estimate of hormone levels throughout the menstrual cycles. Average total estrogen exposure declined by 18.9 percent and total progesterone exposure by 23.7 percent after the maintenance level of exercise was achieved. The declines were mostly due to decreased luteal phase (post-ovulation) levels.

Post-menopause

After menopause, when the ovaries are no longer producing estrogen, the enzyme aromatase continues to facilitate estrogen synthesis in adipose tissue. This is likely to contribute to increased post-menopausal hormone-receptor-positive breast cancer risk. It also helps to explain why reduced adipose tissue lowers the risk of post-menopausal breast cancer. Although exercise will help with weight loss, other mechanisms are also probably involved.

The NIH-AARP Diet and Health study (90 percent Caucasian) found that post-menopausal breast cancer risk was reduced by about 13 percent in women who reported the highest levels of relatively recent physical activity at baseline after 7 years of follow up.[84] The risk reduction was not entirely explained by BMI and was somewhat more pronounced for ER-negative tumors. This has also been reported in some but not all other studies that distinguished tumor hormone-receptor status.[85] Thus exercise may also reduce post-menopausal breast cancer risk through non-estrogenic mechanisms.

In a study of over 1,000 post-menopausal women from the National Health and Nutrition Examination Survey, increased activity was associated with reduced insulin resistance and lower levels of markers of chronic inflammation.[86] Even light-intensity activity reduced markers of inflammation, while increased sedentary time increased levels, independent of levels of exercise at other times. Chronic inflammation is increasingly well-established as a promoter of carcinogenic processes.[87]

Three prospective, randomized, controlled trials examined biologic pathways that might connect physical activity with post-menopausal breast cancer risk. A study of 173 post-menopausal women from the Seattle area (87 intervention, 86 control) assessed the effect of at least 45 minutes of moderate-intensity exercise, 5 days/week for 12 months on serum hormone levels and other markers.[88] It showed that exercise can lower levels of circulating estrogens and increase levels of sex hormone binding globulin in previously sedentary, overweight/obese postmenopausal women. Loss of adipose tissue in addition to exercise was necessary to see the changes.

The Sex Hormones and Physical Exercise (SHAPE) study randomly prescribed a 12-month strength and aerobic training program of approximately 150 minutes per week to 189 sedentary post-menopausal women from the Netherlands. (96 intervention, 93 controls) At the end of the year, estrogen levels were reduced an average of 17 percent in participants who lost at least two percent of their body weight, whether or not they were in the exercise-intervention group.[89] Androgen levels (testosterone, androstenedione) also declined in that group.

The Alberta Physical Activity and Breast Cancer Prevention (ALPHA) trial (320 participants; 160 exercise, 160 controls) involved a moderate- to vigorous-intensity physical activity intervention of approximately 225 min per week over 12 months. After one year, C-reactive protein (CRP) levels—a marker of inflammation—were significantly lower in the exercise-intervention group, though the effect seemed to be primarily mediated by weight loss and higher levels of dietary fiber. Two other markers of inflammation (IL-6, TNF-alpha) were unchanged. Other studies have not observed the same effect on CRP but this may be attributable to lower intensity and amounts of exercise in those trials.[90,91]

The HEAL study of pre- and post-menopausal women with breast cancer (see table 4.4) reported statistically significantly lower levels of leptin, IGF-1, and CRP with increasing levels of physical activity.[92] The study found no association between activity levels and mammographic breast density (mammograms taken one year before or 1-2 years after diagnosis), insulin-like growth factor binding protein-3 (IGFBP-3), or the ratio of IGF-1 to IGFBP-3.

A recent study of 439 overweight/obese healthy 50-75 year old post-menopausal women examined the effect of a 12-month intervention of a reduced calorie, weight loss diet, exercise, or diet + exercise on levels of leptin and adiponectin.[93] Eighty-five percent of the women were non-Hispanic white, seven percent African-American, and the remainder Asian and Hispanic. The diet had a total energy intake goal of 1200-2000 kcal/day and <30 percent daily energy intake from fat. The weight loss goal was 10 percent by 6 months, with maintenance thereafter. The exercise intervention goal was 45 minutes of moderate-to-vigorous intensity exercise five days/week for 12 months. Adiponectin increased by 9.5 percent in the diet group and 6.6 percent in the diet + exercise group, both significantly greater than in a control group. Compared with controls, leptin significantly decreased with all interventions (diet + exercise, -40.1 percent; diet, -27.1 percent; exercise, -12.7 percent). The results were not influenced by the baseline BMI. Thus combinations of diet, exercise, and weight loss may be particularly effective at beneficially altering concentrations of these hormones, at least in this population of women.

A recent review[94] of four primary prevention and five tertiary prevention (exercise intervention following diagnosis and treatment) trials found:

- Primary prevention: All trials showed weight loss; three of 4 showed reduction in estradiol levels; one showed reduction in insulin levels, insulin resistance, and leptin in inactive, overweight, post-menopausal women. All of these trials were 12 months long and met the ACSM recommendations for intensity and duration of exercise. None met AICR recommendations.

- Tertiary prevention: Trials involved combinations of aerobic and resistance exercises. Two did not meet ACSM guidelines for cancer survivors. Most participants were post-menopausal cancer survivors. The two trials that met ACSM guidelines showed reduction in insulin levels. Two trials showed decreased IGF levels. The two studies that examine immune function showed significant improvements, including increased natural killer cell (NKC) activity. C-reactive protein, a marker of inflammation, also moderately decreased.

In summary, multiple biologic mechanisms probably explain how exercise helps to reduce pre-menopausal and post-menopausal breast cancer risk and improve prognosis following diagnosis. They include mechanisms that may influence the likelihood of malignant trans-

formation of cells as well as mechanisms involved in tumor growth and progression. These findings support a conceptual model of breast cancer in which the *milieu intérieur* (the environment within) plays an important role in the origins and progression or remission of breast cancer.

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Chapter 5

Environmental chemicals, contaminants, and breast cancer

Chapter Summary

More than 75 years ago, scientists began using coal tar derivatives to induce mammary gland cancer in laboratory rodents in order to investigate the process of carcinogenesis and hormone dependency of certain tumors. This animal model has been in widespread use ever since, but more general research into the role of environmental chemicals in the origins of breast cancer has been slow to develop.

Early studies of environmental chemicals and breast cancer in humans dealt exclusively with exposures in adults. But, recent developments have firmly established the importance of adopting a life-course perspective when looking for the origins of breast cancer, including those related to chemical exposures. For example, combination hormone replacement therapy after menopause is associated with increased breast cancer risk within a few years, while diethylstilbestrol exposure *in utero* increases breast cancer risk decades later. A life-course perspective makes epidemiologic studies of environmental chemicals particularly challenging because of difficulty establishing an exposure history and variable latency periods between relevant exposures and breast cancer diagnosis.

A variety of mechanisms are probably involved in chemical carcinogenesis in the breast. Endocrine disrupting chemicals can alter breast development, tissue structure, and hormone responsiveness, increasing susceptibility to cancer years later.[1] They may promote early stages of cancer, long before it is clinically apparent. Environmental chemicals or their metabolites can directly damage DNA, alter gene expression, influence the cell cycle, cellular proliferation, and programmed cell death. They can also modify the immune response to cancer.

Studies of workplace-related chemical exposures and breast cancer risk are inadequate and historically relatively uncommon. Now it appears increasingly likely that workplace exposures to known or suspected carcinogens and endocrine disrupting chemicals can increase the risk of breast cancer. Specific occupations, including chemical, rubber, plastics, and textile manufacturing, agriculture, and nursing deserve urgent attention.

Rodent studies are relevant for evaluating risks to humans because the biological processes involved in mammary gland growth, differentiation, development, and response to environmental stimuli are similar. By enabling better understanding of risk factors for breast cancer and their mechanisms of action, rodent studies can help to identify opportunities for breast cancer prevention. A recent literature review using data from the National Toxicology Program, the International Agency for Research on Cancer (IARC), the Carcinogenic Potency Database, and the Carcinogenesis Research Information System identified 216 chemicals associated with increases in mammary gland tumors in at least one well-conducted animal study.[2] They include industrial chemicals, products of combustion, pesticides, dyes, drinking water disinfection byproducts, pharmaceuticals, hormones, and research chemicals. Most of these have been classified by IARC as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans. Unfortunately, human epidemiologic studies of these chemicals, some of which are commonly encountered in food, air, water, or consumer products, are extremely limited or non-existent.

According to a report from the Institute of Medicine, the strongest evidence of chemically-related increased breast cancer risk in humans comes from studies of combination hormone therapy products, current use of oral contraceptives, alcohol consumption, and tobacco smoking.[3] Evidence linking passive smoking, other organic solvents, ethylene oxide, polycyclic aromatic hydrocarbons (PAHs), 1,3 butadiene, and some agricultural chemicals to breast cancer is not as strong but increasingly persuasive (see box 5.2).

Other chemicals that alter mammary gland development and are associated with evidence of increased cancer risk in animal studies include bisphenol A, cadmium, perfluorinated compounds, dioxins, and atrazine.

In a 2011 paper from IARC, "Preventable Exposures Associated with Human Cancers," the authors note that every agent known now to be carcinogenic to humans "can be considered to represent cancers that might have been prevented had scientists been able to predict cancer hazards earlier or had public health authorities been willing to act more quickly when scientific information became available." [4]

Therein lies a challenge. When do we know enough to act and who should decide? Randomized controlled trials of the effects of non-pharmaceutical chemicals on breast cancer risk will never be available. Even well-designed prospective epidemiologic studies with accurate exposure assessment and long-term follow up cannot provide meaningful data for decades. Moreover, it is exceedingly difficult to tease out

the effect of chemicals within the noisy variability of hormones, other environmental exposures, diet, exercise, stress, and other biologic and social factors.

Although understanding the role of environmental chemicals in the origin of breast cancer will always be limited by research challenges, that need not keep us from taking action to minimize risk, based on what we know. Despite uncertainties and data gaps, individuals, health care providers, public health officials, and policy makers have multiple opportunities to intervene throughout the life course, based on sound, early warnings and firmly established evidence, to reduce exposures to hazardous chemicals with the goal of preventing breast cancer.

A brief history of environmental chemicals and breast cancer

More than 200 years ago Percival Pott, a London surgeon, recognized that chimney sweeps can develop scrotal cancer from exposure to soot laden with polycyclic aromatic hydrocarbons (PAHs). This was the first time that an environmental chemical cause of cancer was identified. It raised new questions about the origins of cancers in other organs. Many years later, in the 1930s, studies showed PAHs could also cause mammary gland cancer in laboratory animals.

PAHs occur naturally in coal and crude oil. They are common environmental pollutants formed by the incomplete combustion of fossil fuels and wood. Coal tar sealants, creosote, and asphalt have high concentrations of PAHs. Traffic-related air pollution and cosmetics made of coal tar contain PAHs. Barbecuing, smoking, or charring food over a fire produces PAHs.

Among the PAHs, 3,4-benzopyrene (BP); 3-methylcholanthrene (MCA); 2-acetylaminofluorene (2-AAF); and 7,12 dimethylbenzanthracene (DMBA) are most widely studied. DMBA is more efficient than the others in inducing mammary cancer in susceptible strains of animals, and the DMBA model is still widely used in research after more than 75 years. It is sometimes called the Huggins model, named after Nobel prize-winning cancer biologist Charles Huggins, who used it to investigate the hormone-dependency of various cancers, including in the breast.[5]

Huggins realized that the chemical acted within a context that influenced its ability to cause cancer. He sometimes called this context "the soil," metaphorically comparing soil nutrient requirements for seed germination and plant growth to a susceptible host environment for cancer initiation and growth. Huggins and many others since have shown that the hormonal

environment, along with dietary manipulations at various times, can strongly influence the capacity of DMBA to cause mammary tumors and their progression.[6]

Among the features of DMBA-induced mammary tumors:[7]

- The timing of exposure to DMBA strongly influences its potency; a single oral dose at 50 days of age can induce mammary tumors in nearly 100 percent of susceptible rodents, whereas earlier or later exposures are less effective.
- Sprague Dawley rats fed a diet consisting of 20 percent corn oil (high omega 6:3 fatty acid ratio) from weaning are much more susceptible to developing mammary gland cancer after exposure to the carcinogen DMBA than animals fed a low fat diet exposed to the same carcinogen.[8]
- Pre-pubertal dietary omega 3 fatty acids can help to protect against DMBA-induced mammary tumors in laboratory rodents, but exceptionally high levels of this kind of fat (39% of total calories) can actually promote mammary cancer development.[9]
- DMBA tumors are hormonally responsive. Reducing prolactin levels, removing the ovaries, or treating with testosterone causes the tumors to regress. Moderate doses of estrogen or progesterone treatments stimulate their growth, as does insulin. High doses of estrogen can cause DMBA-induced tumors to regress

Although rodent strains differ in their susceptibility, most scientists agree that the DMBA model is relevant for studying the origins of human breast cancer[10] (see box 5.1). But, despite decades of experience using this chemical to cause mammary cancer in laboratory animals, the notion that other environmental chemicals could increase breast cancer risk in humans has been slow to gain traction—probably for several inter-related reasons.

First, breast cancer has always been predominantly seen as a quintessential hormone-related malignancy. In the late 19th century, Scottish surgeon George Beatson reported that removal of the ovaries in several of his patients caused the remission of inoperable breast cancer.[11,12] Then various hormones, including estrogen, were isolated and characterized.[13] In 1932, Lacassagne induced mammary cancer in male rodents with estrone, stimulating more research into endocrine carcinogenesis.[14] Many studies show that higher lifetime exposure to estrogen is a predictor of breast cancer risk.

Thus, from the beginning, breast cancer research has been dominated by investigating the roles of endogenous estrogen and other hormones. Relatively recently, however, a long and growing list of chemicals present in the ambient environment or in consumer products have been shown to have hormone-like activity or otherwise disrupt hormone function. The role of these endocrine disruptors in the development of breast cancer is now gaining increased attention.

Second, an appreciation of the importance of a life course perspective for understanding the origins of breast cancer is relatively new. In the 1970s, the recognition that fetal exposure to diethylstilbestrol (DES) could cause reproductive tract malignancies in humans decades later stimulated entirely new avenues of research.[15] Animal studies show that developmental exposures to endocrine disrupting compounds can alter tissue architecture, hormone recep-

Box 5.1: Evolution of animal testing

Scientists have used laboratory animals to study the cancer-causing properties of chemicals since early in the 20th century. In the U.S., the process became more standardized at the National Cancer Institute in the 1960s and further developed at the National Toxicology Program beginning in 1978. Carcinogenic assays generally utilize two or three dosage levels of the test chemical over two years in adult rats and mice. Along with PAHs, ethylene oxide, methylnitrosourea, butylnitrosourea, ethylnitrosourea, and urethan were among the first chemicals identified as mammary carcinogens in laboratory mice.[16,17] By 1991, the National Toxicology Program had reported that 198 of 379 chemicals were carcinogenic in at least one of four long-term experiments. Among them, 27 chemicals were positive and seven chemicals equivocal for causing mammary gland cancer.[18] These findings added to the growing concern that exogenous chemicals might be contributing to the rising incidence of breast cancer in the general population.

A recent literature review using data from the National Toxicology Program, the International Agency for Research on Cancer, the Carcinogenic Potency Database, and the Carcinogenesis Research Information System identified 216 chemicals associated with increases in mammary gland tumors in at least one well-conducted animal study.[19] They include industrial chemicals, products of combustion, pesticides, dyes, drinking water disinfection byproducts, pharmaceuticals, hormones, natural products, and research chemicals. Of these, 73 have been present in consumer products or as contaminants of food, 35 are air pollutants, 29 are produced at more than one million pounds per year in the United States, 35 are air pollutants, and 25 have involved occupational exposures to more than 5000 women. Nearly all of the chemicals can cause DNA mutations and most caused tumors in multiple organs and species. These features mean that they are also likely to cause cancer in humans. Unfortunately, few of these chemicals have been studied as causes of breast cancer in epidemiologic studies.

Rodents continue to be used because the biological processes involved in mammary gland growth and differentiation are similar to humans. Scientists are now more systematically investigating the effects of environmental chemicals on mammary gland development and subsequent cancer risk in laboratory animals, but new protocols have not yet been incorporated into assessments used for regulatory purposes.[20] Nonetheless, it is increasingly clear that critical windows of vulnerability to chemical and other environmental exposures occur prenatally and in infancy, puberty, and pregnancy, influencing the risk of mammary gland cancer.[21]

tors, hormone responsiveness, gene expression, and various biologic set points, increasing cancer susceptibility in adulthood.[22] Now we know that developmental exposure to DES and probably the pesticide DDT increase breast cancer risk in humans as well.[23,24] Widespread early-life exposures to other endocrine disrupting chemicals are a growing concern.

Third, with few exceptions, human evidence for chemical carcinogens identified by the International Agency for Research on Cancer (IARC) or the EPA comes primarily from occupational studies. The large majority of these were conducted when most employees in industry were men. Thus, the likelihood of identifying breast carcinogens in the workplace, should they exist, was initially extremely low. A few early occupational studies reported no excess of breast cancer-related deaths in workers exposed to various industrial chemicals. As a result, for a long time scientists and public health officials interested in breast cancer saw little reason to look more closely at environmental chemicals.[25,26,27]

Finally, studying the potential role of environmental chemicals in breast cancer causation poses many challenges:

- Breast cancer is not a single disease but rather a collection of different diseases with different etiologies. Environmental chemicals are likely to play a more important role in some than in others.

- The biologic effects of chemicals depend on timing, duration, and magnitude of exposure, and establishing an exposure history is often very difficult. Individuals usually do not know and cannot report their exposure to environmental chemicals in the ambient environment. Exposures in the workplace and from consumer products are usually poorly characterized. Job histories, residential location, and biomonitoring can add useful information, but each has limits. The long latency of breast cancer makes it particularly difficult to overcome these challenges.

- Epidemiologic studies must deal with various kinds of bias and confounding. Interactions among chemicals, nutrition, other behavioral factors, genetic background and social circumstances create a complexity that is difficult to disentangle and understand. Individual differences in metabolism of environmental chemicals and differences in susceptibility due to underlying contextual features are likely to be important in various subgroups, but these will be obscured in analyses of larger populations.

Early Occupational studies

Studies of breast cancer risk associated with occupational chemical exposures did not begin to appear in the medical literature until the 1970s. A report from the UK found that sin-

gle women hair-dressers had higher than expected deaths from breast cancer during 1959-1963.[28] Data related to married hair-dressers were lacking because they were classified according to their husbands' occupations, leaving many women out of the analysis. These findings led to a number of cohort and case-control studies of varying design and length of follow up that attempted to determine if regular exposure to hair dyes increased the risk of breast cancer.

Laboratory studies (the Ames test) had shown that many hair dyes were mutagenic. They contained aromatic amines or aromatic nitroso compounds that might be implicated in increased breast cancer risk. Moreover, many hair sprays were aerosolized initially with vinyl chloride[29] and then methylene chloride, until banned from this use by the FDA in 1989.[30] Both vinyl chloride and methylene chloride are mammary gland carcinogens in rodents.[31]

A recent evaluation of the literature by the IARC found that hair dyes are probably carcinogenic in hairdressers and barbers. Most, although not all, studies of breast cancer specifically found no association.[32] A 2005 meta-analysis of studies from 1966-2005 found no increased risk of breast cancer with the personal use of hair dyes, although the risk of blood-related malignancies was slightly increased.[33]

This issue is complicated by changes in the formulations of hair dyes beginning in the 1980s as some manufacturers moved away from more obviously carcinogenic chemicals after concerns became public. Nonetheless, a recent study reports more evidence of DNA damage in breast ductal epithelial cells in breast milk of women who use hair dyes compared to those who do not.[34] A report from a committee convened by the Institute of Medicine concluded "current personal use of hair dyes is unlikely to be an important risk factor for breast cancer."[35]

After the initial report related to hair dyes, additional occupational studies of other chemical exposures and breast cancer risk occasionally began to appear. One found excess breast and urinary tract cancer mortality among white women working in seventeen companies engaged in polyvinyl chloride (PVC) fabrication.[36] Soon after, a cluster of cancer in women was reported in a Swedish factory where workers wrapped bearing rings that were covered with anti-rust oil. Findings included excess mortality from cancer of the uterus, ovary, breast, thyroid, brain, colon, and bladder.[37] The authors suspected that N-phenyl-1-naphthylamine, an anti-oxidant in the oil, or one of its derivatives was likely to be responsible.

An apparent cluster of breast cancer in women working in a coiling and wire-drawing area of a lamp manufacturing department of Canadian General Electric prompted a study of all women who had worked there for at least six months and long enough before to account for the latency of cancer development.[38] They found a significantly increased risk of breast and

other gynecological cancers in women who worked in the area where they had been exposed to the solvents methylene chloride and trichloroethylene.

Beyond the workplace: The evolution of epidemiologic studies in women

Support for a closer look at the role of exogenous carcinogens in the origins of breast cancer in the general population grew with reports of chemicals regularly detected in breast milk. Although the pesticide DDT and its residues had been detected in breast milk as early as the 1950s, newer studies showed additional fat-soluble chemical contaminants, including polychlorinated biphenyls (PCBs) and the pesticides dieldrin, chlordane, and heptachlor. Some of these chemicals were carcinogenic in animal testing, and they were known to concentrate in fat tissue.[39] DDT was reported to promote PAH-induced mammary gland cancer in male rats.[40]

New technologies also enabled scientists to measure metals in breast tissue and breast milk.[41] Despite the prevailing view that endogenous hormones were largely responsible for breast cancer patterns, some scientists and public health advocates were increasingly concerned that exposures to exogenous environmental agents were wrongly being ignored.

Results of initial studies of organochlorine chemicals residues in fat tissue or blood from women with and without breast cancer were inconsistent. One showed no difference in levels of these chemicals[42] while others showed higher levels of PCBs, DDT, and DDE[43,44] and beta-hexachlorocyclohexane (HCH)[45] in women with breast cancer.

A report from Israel found decreasing population-wide exposures to organochlorines in milk associated with a reduction in breast cancer mortality, adding support to the hypothesis that they might be causally related.[46] Participants in a workshop convened at the International Society for Environmental Epidemiology discussed whether organochlorine compounds might contribute to breast cancer risk by altering estrogen production or metabolism.[47] A 1992 review and commentary summarized experimental and epidemiologic evidence that some organochlorines have estrogenic properties and are often, though not always, present at higher levels in women with breast cancer.[48]

The emergence of a life-course perspective

In the late 1980s, new evidence showed that higher exposure to estrogens in the prenatal period was associated with increased breast cancer risk.[49,50] This suggested that prenatal imprinting could alter the trajectory of breast development and create vulnerability, perhaps through priming estrogen receptor responses later in life. Although the initial focus was on estrogen levels, the possibility that early life exposures to other agents could also influence

breast cancer risk decades later began to get attention.[51] After all, it was already known that prenatal exposure to radiation increased the risk of leukemia in children, and intrauterine exposure to diethylstilbestrol (DES) could cause vaginal adenocarcinoma in young girls and women. More recent studies show that fetal exposure to DES also increases the risk of breast cancer in women.[52,53,54]

Epidemiologist Nancy Krieger pointed out that after decades of research, known risk factors accounted for only about one-third of breast cancer cases in the U.S.[55] Krieger and others proposed combinations of exposure to exogenous carcinogens and biologic susceptibility—both of which are influenced by social conditions—as a way of explaining breast cancer patterns and its social gradients.[56] This might help explain why African-American women are at higher risk of breast cancer than white women before age 40 but at lower risk after that.

A life-course perspective proposes that determinants of breast cancer risk begin early in life when rapidly dividing ductal cells are more vulnerable to DNA damage than cells at rest. After puberty, monthly fluctuations in breast cell growth related to the menstrual cycle would sustain susceptibility to various exposures, including endogenous hormones that could promote the growth of cells or tissues that had been initiated on pathways toward cancer by exogenous agents. An early full term pregnancy would result in more complete differentiation of breast tissue, making it ultimately less vulnerable to malignant transformation. This, Krieger said, "implies that the presumed joint determinants of breast cancer incidence—exposure and susceptibility—cannot be examined statically, but instead must be considered in relation to each other at every stage in a woman's life."

Several lines of evidence support the idea that early-life chemical exposures can increase breast cancer risk. A 2001 review of epidemiologic studies concluded that most well conducted, well controlled epidemiologic studies looking at exposures in adults did not find a significant correlation between body burdens of DDT or DDE and breast cancer risk.[57] Similarly, results of studies of body burdens of dieldrin and breast cancer risk were inconsistent. In 2007, however, scientists gained access to blood samples that had been collected from a group of women much earlier in their lives and stored for later analysis. They averaged 26 years of age when blood was collected. In this group, high levels of serum DDT were associated with a significant 5-fold increased risk of breast cancer among women who were born after 1931.[58] These women were under 14 years of age in 1945, when DDT came into widespread use, and mostly less than 20 years old as DDT use peaked. This study clearly supported the hypothesis that early life chemical exposures may influence breast cancer risk even more than adult exposures. This finding is similar to evidence that breast cancer risk is higher with radiation exposures earlier in life compared to later in adulthood.

More recently, a study using stored serum identified a six-fold increased risk of breast cancer before age 50 in women with higher levels of a certain kind of polychlorinated biphenyl

(PCB 203) measured shortly after giving birth.[59] Because PCBs are persistent, it can be assumed that the levels were similar during pregnancy and probably during puberty.

Another intriguing observation comes from studies of the influence of birth order on breast cancer risk. When the *in utero* origin of breast cancer was first proposed, most attention focused on the hormonal environment within the uterus. Studies showed that estrogen levels were higher in first pregnancies than in those that followed, leading to speculation that breast cancer risk might differ by birth order and be higher women who had been first-born.[60] A 1991 study using data collected in the 1960s from three countries with high, medium, and low breast cancer incidence found reduced risk of pre-menopausal breast cancer in women who were not first-born but statistically significant only for those second-born. (RR= 0.71)[61] Since then, the results of other studies have been inconsistent.

A recent report finds that birth order is more strongly associated with breast cancer risk when breastfeeding was taken into account. In this population-based case-control study, being born later was associated with much lower breast cancer risk among breastfed women (OR=0.58) who have three or more older siblings compared to first-born women.[62] But, this was not the case among non-breastfed women, suggesting that something in addition to higher estrogen levels in first pregnancies may influence breast cancer risk.

Breast feeding lowers maternal levels of persistent, fat soluble chemicals that build up over time by off-loading them to a nursing infant. Thus, fetuses and infants borne in subsequent pregnancies will be exposed to lower levels. Breast fed first-born children will not only be exposed to higher estrogen levels but also to higher levels of contaminants *in utero* and during breast feeding, which may help explain a higher breast cancer risk than in siblings born later.

In their recent report "Breast Cancer and the Environment: A Life Course Approach" a committee convened by the Institute of Medicine has fully endorsed the importance of adopting a life-course perspective for understanding the origins of breast cancer and breast cancer risk.[63] Endocrine disrupting chemicals are particularly of rapidly growing interest. Hormones and other signaling molecules are critically important mediators of development in cells, tissues, organs, and whole biologic systems. Small changes in hormone levels or function during development can alter tissue architecture, gene expression, and biochemical set points, with consequences for disease risk many years later.

Animal studies showing the influence of early-life exposures to environmental chemicals on mammary gland development and subsequent cancer risk make clear the challenges facing epidemiologists who seek to study the impacts of chemicals on breast cancer risk in humans. In general, estimating developmental exposures to non-persistent chemicals and following a cohort of women for decades in order to assess breast cancer risk is difficult

and expensive. Some large cohort studies have assessed certain early life variables, such as birth weight, height, breast feeding, and childhood nutrition, but none has been designed to measure or estimate exposure to non-persistent environmental chemicals, with the exception of DES, intentionally administered as a pharmacologic agent to pregnant women. The increased breast cancer risk associated with fetal exposure to DES and higher exposure to DDT before age 14 show that developmental exposures are important in humans, as they are in laboratory animals.

Recent epidemiologic studies of environmental chemicals and breast cancer

In 2007, scientists from the Silent Spring Institute published a review of epidemiologic studies of chemicals and breast cancer, with an emphasis on those published within the previous five years.[64] Based on a relatively small number of studies, they concluded that evidence supported an association between breast cancer and PAHs as well as polychlorinated biphenyls (PCBs) in conjunction with certain genetic profiles that influence hormone metabolism and carcinogen activation. Some but not all studies show an increased risk of breast cancer with higher levels of exposure to pesticides.

A recent population-based case control study in France[65] found modest increases in breast cancer risk that may be related to exposure to occupational carcinogens among nurses, textile workers, rubber and plastics product makers, and in women employed in the manufacture of chemicals and non-metallic mineral products.

This study in France found a decreased incidence of breast cancer among women in agriculture, as has also been reported in other European studies.[66,67] In some countries, however, including the U.S. and Canada, increased breast cancer risk is reported in female farmers associated with some pesticide exposures.[68,69] These discrepancies may be explained by differing agricultural practices and pesticide use in various countries.

A recent population-based case-control study in Canada found a greater than four-fold increased risk of pre-menopausal breast cancer in women employed in the automotive plastics industry.[70] Metal working, food canning, and agricultural work were also associated with significantly increased risk. The authors of this study noted that women are often exposed to a "toxic soup" of chemicals in these occupations, including known or probable carcinogens and endocrine disruptors, such as phthalates, bisphenol A, and flame retardants.

Nurses are at increased risk of breast cancer as well.[71,72,73] They may be exposed to ionizing radiation, chemotherapeutic agents, and ethylene oxide. They may also have worked rotating night shifts and been exposed to excessive light at night, which increases breast cancer risk (see chapter 6).[74,75,76]

Specific chemicals and breast cancer

Endocrine disrupting compounds

Endocrine disrupting compounds (EDCs) interfere with hormone functions through a variety of mechanisms. They may mimic or block the action of hormones, interfere with hormone synthesis, metabolism, or excretion, alter the concentration of hormone receptors, or interfere with gene transcription after a hormone-receptor complex has attached to response elements on DNA. Early-life exposures to EDCs are of particular concern because they can alter the trajectory of developmental processes with long-term consequences.[77,78]

In animal studies, prenatal or early postnatal exposure to some endocrine disrupting chemicals causes permanent changes in mammary gland development, altering their susceptibility to cancer-causing environmental agents later in life. Recently, Fenton et al. reviewed much of this research.[79] Examples of chemicals that can modify mammary gland development and influence subsequent breast cancer risk in laboratory animals and in humans, if data are available, include:

Diethylstilbestrol (DES)

Diethylstilbestrol is a synthetic estrogen given to some women during pregnancy in the 1950s through the early 1970s. Its purpose was to minimize the risk of miscarriage, despite the lack of evidence that it was effective. *In utero* exposures were first shown to be associated with increased risk of cancer of the female reproductive tract and more recently, breast cancer.[80] Laboratory rats exposed around the time of birth to 1-2 µg of DES have an increased susceptibility to mammary gland cancer after later treatment with DMBA.[81] *In utero* DES exposure probably increases cancer susceptibility by slowing mammary gland maturation.[82] The most mature structures of the mammary gland, lobules, are most resistant to developing cancer after exposure to chemical carcinogens, while terminal end buds are more susceptible. Prenatal DES exposure increases the number of terminal end buds. Permanent re-programming of gene expression, through epigenetic mechanisms, is likely to be involved.

Bisphenol A

Bisphenol A (BPA) is a chemical that can be polymerized to make polycarbonate plastic. Unpolymerized BPA can leach from polycarbonate food or beverage containers contaminating what people eat and drink. Bisphenol A is also a component of epoxy resins lining most food and beverage cans. Food and beverages contaminated with BPA are a major source of human exposures. A more-recently discovered route of exposure comes from handling printed receipt papers that are coated with BPA.[83] In fact, many paper products contain BPA and are

likely to result in exposure through the skin.[84] According to the Centers for Disease Control and Prevention, over 90 percent of Americans have measureable BPA and its metabolites in their urine.

Considerable scientific debate centers on the extent to which BPA exposures are rapidly metabolized into an inactive form and excreted.[85,86] This is an exceedingly important issue because human exposures to BPA are ubiquitous. A large and rapidly growing body of experimental evidence shows diverse adverse effects of BPA, often after exposures similar to those experienced in the general population.[87] This is not a circumstance in which professionals charged with protecting the public's health want to be wrong.

Most efforts to restrict BPA in consumer products have focused on exposures in infants and children. Recently, the Food and Drug Administration withdrew authorization to use BPA in infant formula packaging, based on packaging manufacturers' earlier decision to voluntarily stop using it for that purpose rather than an agency determination that the use is unsafe.[88]

Evidence that free, active bisphenol A has been measured in amniotic fluid, umbilical cord blood, and the livers of human fetuses is unaddressed by this decision.[89,90,91,92,93] Efforts to protect infants and children from exposure to BPA are laudable, but the developing human fetus is also directly exposed to the active compound. Reducing or eliminating exposures in adults as well is the only way to address that critical time window of vulnerability.

Bisphenol A is a relatively weak estrogenic agent as measured by its affinity for the classic estrogen receptor. But, BPA has a number of other biologic activities, including interacting with at least three other non-classic estrogen receptors with even higher affinity than endogenous estrogen.[94] It can also act as an androgen receptor antagonist and interact with the thyroid hormone receptor.

Studies linking Bisphenol A and breast cancer include:

- In mice, maternal exposure to low levels of BPA administered beneath the skin during the second half of pregnancy and for several days after birth caused an increased number of terminal end buds (TEBs) in the mammary glands, a decreased rate of apoptosis in the TEBs, an increased percentage of cells expressing the progesterone receptor (PR) in the mammary gland, increased lateral branching, and pre-cancerous changes.[95,96] These changes increase the risk of mammary gland cancer in adult female animals.

- In Wistar rats, with gestational exposure alone, BPA increases the number of terminal ducts, TEBs, alveolar buds, and pre-cancerous lesions in the mammary gland.[97] Prenatal exposure to BPA (via maternal subcutaneous dosing), coupled

to a sub-carcinogenic dose of N-nitroso-N methylurea (NMU), resulted in an increased percentage of cancers in the mammary gland.[98]

- In Wistar rats, maternal exposure to low levels of BPA administered beneath the skin during pregnancy induces excessive cellular growth in mammary gland ducts and pre-cancerous lesions in female offspring.[99]

- In Sprague-Dawley rats, subcutaneous maternal exposure to BPA at 250 microgms/kg/day resulted in serum levels of active and inactive BPA similar to what has been measured in humans.[100] Occasional female offspring exposed at this level during gestation and lactation developed mammary gland cancer beginning at post-natal day 90 in the absence of any additional carcinogen exposure although the incidence was not statistically significant. The authors concluded that BPA may act as a complete mammary gland carcinogen.

These studies are sometimes criticized because the BPA was administered by injection rather than via the gastrointestinal tract. Oral administration, some people argue, would more closely mimic human dietary exposures and allow more rapid metabolism of BPA into the inactive compound in the liver after intestinal absorption. Administration of the chemical by injection bypasses the detoxifying liver allowing longer exposure to the active compound—a scenario many conclude is irrelevant for assessing human risks.

While the argument has some merit, numerous human studies document significant blood levels of free, active BPA.[101] These studies challenge the model of rapid BPA metabolism and excretion. Significant human exposures to BPA may also occur through the skin or through the mucous membranes of the mouth—pathways that also bypass rapid liver metabolism. Nonetheless, a number of experimental studies have used oral dosing as the exposure route.

- In Sprague-Dawley rats, early postnatal oral maternal exposures to a low (25 microgm/kg) and high (250 microgm/kg) daily dose of BPA from day two postpartum until weaning caused a dose-dependent increase in mammary gland cancer in offspring subsequently treated with DMBA.[102,103] Maternal gestational and lactational exposures to orally administered BPA also shift the window of susceptibility to DMBA carcinogenesis and alter levels of proteins related to cell proliferation, including estrogen and progesterone receptors, in the mammary glands of offspring.[104]

- In mice, oral maternal exposure to BPA at 25 microgm/kg/day and 250 microgm/kg/day during gestation resulted in increased susceptibility to DMBA-induced

mammary gland cancer in female offspring.[105] There was no effect of the lower dose on mammary gland morphology, despite increased cancer risk.

- In rhesus monkeys, BPA administered orally (400 microgm/kg/gestational day 100-165 of pregnancy) advanced development of the mammary glands in female offspring and resulted in more buds per ductal unit compared to controls.[106] The dose resulted in serum levels of unconjugated, active BPA similar to levels measured in humans.

Taken together, these findings show that environmentally-relevant exposures to BPA alter development of the mammary gland in mice, rats, and monkeys. Whether administered by injection or orally, the chemical increases susceptibility to and the risk of mammary gland cancer in later life. No epidemiologic studies have explored the impacts of fetal, infant, or childhood BPA exposures on breast development and breast cancer risk in humans.

Parabens

Parabens are a family of related compounds that includes esters of p-hydroxybenzoic acid. They were first introduced as preservatives in pharmaceutical products in the 1920s, but are now used in other applications.[107] Various forms of parabens — methyl-, ethyl-, propyl-, butyl-, and isobutyl-paraben — serve as preservatives in an array of foods, cosmetics, and pharmaceuticals.[108]

Parabens have estrogen-like properties in cell cultures, causing proliferation of estrogen-responsive cells, although they are thousands of times less potent than naturally-occurring estrogen in this regard.[109,110] However, studies also show that parabens alter gene expression in estrogen responsive cells in patterns that differ from naturally-occurring estrogen.[111] Thus, parabens could plausibly have biologic effects not predicted solely by the potency of their ability to activate the estrogen receptor and cause cell proliferation.[112] Some parabens also have anti-androgenic properties.[113]

In 2003, scientists proposed that parabens in underarm deodorants and antiperspirants could be absorbed through the skin and might be related to increased risk of breast cancer, particularly since tumors disproportionately occur in the upper outer quadrant of the breast.[114] Parabens have also been detected in breast cancer tissue after surgery, at concentrations sufficient to stimulate proliferation of MCF-7 breast cancer cells in cell cultures.[115,116]

Two epidemiological studies of associations between cosmetic use and breast cancer in the general population have been published. In a population-based case-control study of 813 case subjects and 793 controls, self-reported underarm antiperspirant/deodorant use was not associated with an increased risk of breast cancer.[117] This study is limited by the potential

for exposure misclassification inasmuch as paraben exposures were not actually measured and the study was unable to take into account other potential sources of parabens in cases or controls.

In a retrospective study of 437 women diagnosed with breast cancer, frequency of use and early onset use of deodorants/antiperspirants were associated with an earlier age of breast cancer diagnosis.[118] This study lacked age adjustment and controls. It was also undertaken when deodorant use and breast cancer rates were both increasing, but the two could be totally unrelated.

Whether or not parabens have any relationship to breast cancer risk remains unresolved. But human exposures to parabens from various sources are nearly ubiquitous.[119] This is, therefore, an important public health concern and highlights the need for controlled and detailed evaluation of breast cancer risk from personal care products, taking into account product ingredients, effect of formulations, and total quantities applied, especially in potentially highly sensitive subgroups such as babies and children.[120]

Cadmium

Human exposures to cadmium come from breathing cigarette smoke and polluted air from fossil fuel and municipal waste combustion. Workers can be exposed by breathing air from the smelting or refining of metals or in factories manufacturing batteries, coatings, or plastics. Cadmium is also in pigments and plastics in many consumer products, including children's toys. Food grown in contaminated soil can contain cadmium. Exposures are widespread in the general population.[121] Cadmium is toxic to the lungs, kidneys, testes, and placenta.[122] It causes cancer in multiple organs in experimental animal studies, probably through multiple mechanisms including genotoxicity, altered gene expression, disruption of gene repair, and production of reactive oxygen species.[123] It is also estrogenic. The EPA classifies cadmium as a probable human carcinogen.

- Prenatal exposure to low levels of cadmium alters mammary development in mice and rats, mimicking the effects of estrogen. *In utero* exposure to cadmium at levels similar to those in the humans cause increased numbers of terminal end buds and reduced alveolar buds in the mammary glands in adulthood.[124]

- A case–control study of urinary cadmium levels in 246 women with breast cancer in Wisconsin found a two-fold higher risk in women with the highest levels of urinary cadmium compared to the lowest, after adjustment for other risk factors, including smoking.[125]

- A case-control study of 153 women with breast cancer and 431 controls found a six-fold higher risk in women with the highest levels of urinary cadmium compared to those with the lowest levels.[126] Cadmium levels in the most highly exposed women were higher than in the Wisconsin women in the previous study.

- A case-control study of 100 women with breast cancer in New York and 98 controls found that women in the highest quartile of urinary cadmium had more than twice the risk (OR=2.69) compared to women in the lowest quartile.[127] The same authors found a similar increased risk in 92 women with breast cancer and 2,884 without from the 1999-2008 NHANES cohort.

Atrazine

Atrazine is a widely-used agricultural herbicide, and it is a common surface and groundwater contaminant to which many people are exposed.[128,129]

- In some rodent studies, atrazine and its metabolites cause abnormal and delayed mammary gland development, resulting in less ductal branching and fewer but more persistent TEBs[130] while others find no long term effects on mammary gland development.[131] However, since different rat strains were used in these conflicting studies and experimental procedures differed as well (researchers discarded some mammary gland specimens that did not contain the entire ductal network in the study finding no effect), it's difficult to draw firm conclusions. Atrazine can also alter puberty timing in various rodent strains, although the doses at which this occurs are unlikely to be encountered by people.[132]

- Lifetime dietary exposure to atrazine in Sprague-Dawley rats causes increases in mammary gland cancer. However, there is considerable debate about whether atrazine should be considered a human carcinogen. In these rats, atrazine suppresses luteinizing hormone secretion resulting in a state of persistent estrus. It is hypothesized that this results in prolonged exposure to elevated levels of estrogen and prolactin, which may foster the development of mammary gland cancer in older animals.[133] If true, this mechanism of action may not be relevant to humans.[134] However, since atrazine can also alter puberty timing in various rodent strains and alter mammary gland development and milk production, other mechanisms that are relevant to humans may influence breast cancer risk. This debate remains unresolved.

Perfluorinated compounds (PFCs)

Perfluorinated compounds are a family of chemicals long used as surfactants, to impart stain resistance and as water repellants on materials and fabrics, and for non-stick properties

on cooking utensils. They are environmentally persistent and many are bioaccumulative. Human exposures are widespread, mostly from diet and contaminated drinking water and dust.[135] Perfluorooctanoic acid (PFOA) is a breakdown product of members of this family of chemicals containing eight carbon atoms in the molecular backbone. Studies in mice show altered mammary gland development after gestational exposure to PFOA at levels similar to some more highly exposed people.[136,137]

Few human studies have attempted to examine the relationship between PFCs and breast cancer risk. A case-control study of Inuit women in Greenland found significantly higher levels of PFCs in the serum of cases compared to controls.[138] Women with breast cancer were more likely to be pre-menopausal than controls. The women with breast cancer also had higher levels of PCBs. This study is limited by incomplete pregnancy information for a number of participants.

A study of cancer incidence in an area contaminated with PFCs from a nearby Dupont Teflon manufacturing plant used drinking water levels of PFOA to estimate serum levels among residents.[139] Investigators found increases in testicular, kidney, prostate, and ovarian cancers and non-Hodgkin lymphoma—but not breast cancer—associated with higher estimated serum levels of PFOA.

Dioxins

Dioxins are a family of chlorine-containing chemicals formed by waste incineration, metal smelting, coal fired boilers and cement kilns burning hazardous waste.[140] Burning waste containing polyvinylchloride (PVC), which contains large amounts of chlorine, can produce significant amounts of various dioxins, depending on temperature and operating conditions of the incinerator. Back yard burn barrels are notorious sources of dioxin emissions.

The toxicity of dioxins varies with number of chlorine atoms attached to the basic molecular structure. In general, dioxins are persistent and bioaccumulative. Half-lives of dioxins in humans range from seven to eleven years.[141] Human exposures to dioxin are largely from consuming contaminated food. Fortunately, dioxin levels in humans are decreasing as a result of more stringent controls on environmental releases.

The toxicity of dioxin is mediated through attachment to the aryl hydrocarbon receptor (AhR), a nuclear receptor involved in metabolism of environmental chemicals, among other functions. Activated AhR also interacts with the estrogen receptor, resulting in what sometimes appears to be an anti-estrogenic effect.[142]

The International Agency for Research on Cancer (IARC) and the National Toxicology Program list the most potent dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), as a known

human carcinogen. This is based on occupational studies showing increased cancer mortality in more highly exposed individuals. With regard to breast cancer, dioxins do not induce mammary tumors in adult rats, but rats with pre-natal exposure to TCDD undergo altered mammary gland development and are more susceptible to DMBA-induced mammary tumors.[143] This does not, however, occur in mice, in which prenatal exposure to TCDD delays and reduces DMBA-induced mammary tumors.[144]

A 1991 study of workers exposed to dioxin in a German herbicide-production facility reported excess deaths from breast cancer among women.[145] An industrial explosion in Seveso, Italy in 1976 exposed a large population of people to substantial amounts of TCDD. Blood levels of TCDD in residents were measured and ongoing studies continue to look for evidence of excess cancer and other health outcomes. After twenty years of follow up, women in the zone most highly contaminated with TCDD experienced a significant 2.5-fold increased risk of breast cancer.[146] Women who were young girls at the time of the incident are just reaching the age when breast cancer is more likely, and future studies are forthcoming.

Additional chemical agents

Alcohol and other solvents

Many studies conclude that alcohol ingestion is a risk factor for breast cancer, and the effects of alcohol may begin early in life. In laboratory animals, pre-pubertal exposure to moderate levels of alcohol alters development of the mammary gland, resulting in increased numbers of TEBs and fewer more mature structures after puberty.[147]

Beginning in the 1980s, case-control studies reported 2-2.5 fold increased risk of breast cancer in women who ingested any alcohol compared to women who did not drink.[148,149,150] Since then, more than 100 epidemiologic studies have been conducted, confirming an increased risk, and the IARC has concluded that alcohol consumption is causally related to breast cancer.[151] A recent review of studies examining risks associated with low levels of alcohol consumption finds about a four percent increased risk of breast cancer at intakes of up to one alcoholic drink/day and 40-50 percent increased risk associated with three or more drinks/day.[152] It should be noted, however, that the slight increased risk associated with one alcoholic drink daily represents a very small increased individual risk and should be considered alongside the cardiovascular benefits associated with a similar level of alcohol ingestion. Coronary artery disease is a more common cause of death in post-menopausal women than breast cancer.[153]

The mechanisms by which alcohol may increase breast cancer risk are not well understood. They may include increased estrogen levels associated with alcohol ingestion (unlikely in

post-menopausal women), exposure to toxic metabolites, and increased oxidative stress that can damage DNA.[154]

Although a number of animal studies show increases in mammary gland cancer with exposures to other organic solvents, studies in humans are few and generally inadequate. Exposure assessments are often poor, follow up periods too short for a disease with long latency like breast cancer, and most occupational studies have historically focused on men. An exception is the previously mentioned study of a breast cancer cluster at Canadian General Electric implicating methylene chloride and trichloroethylene.

One population-based study in which the investigators undertook extensive efforts to estimate exposure levels found a 50-100 percent increased risk of breast cancer in women in a community exposed to higher amounts of perchlorethylene that had leached into their drinking water from the polyvinylchloride pipes in the water distribution system.[155,156]

A retrospective cohort study of over 270,000 women in the military found a 48 percent increased risk of breast cancer in women less than 35 years of age with moderate to high exposure potential to one or more volatile organic compounds, many of which are solvents.[157] Several other studies also show an increased risk of breast cancer with occupational exposure to solvents.[158,159,160,161]

A recently identified cluster of breast cancer in men who lived for varying periods of time at the U.S. Marine base at Camp Lejeune in North Carolina where drinking water was contaminated with trichloroethylene and other organic solvents is actively being investigated by the Centers for Disease Control and Prevention.[162]

Polycyclic aromatic hydrocarbons (PAHs)

Evaluation of the cancer causing potential of PAHs in humans is complicated by the hundreds of forms of PAHs with differing compositions and properties. The IARC reviewed sixty PAHs, with separate classifications for individual compounds.[163] They concluded that benzo(a)pyrene (BaP) was carcinogenic to humans (Group 1) "based on sufficient evidence in animals and strong evidence that the mechanisms of carcinogenesis in animals also operate in exposed human beings."[164] Several other PAHs were classified as probably carcinogenic in humans.

The results of studies of the effects of estimated dietary PAHs on breast cancer risk in people are inconsistent. A few studies have attempted to assess risks associated with certain periods of exposure. A case-control study in New York examined exposure to traffic emissions at specific times on the basis of residence.[165] Higher exposure at the time of menarche was associated with increased risk for premenopausal breast cancer (OR = 2.05; 95% CI 0.92–

4.54) Higher exposures at the time a woman had her first birth were associated with a significantly increased risk for postmenopausal breast cancer (OR = 2.57, 95% CI, 1.16–5.69)

Studies looking at biomarkers of PAH exposures after diagnosis of breast cancer are also inconsistent. In the population-based, case-control Long Island Breast Cancer Study, the presence of PAH-DNA adducts, which form after exposure to PAHs and are measured in white blood cells, were associated with a 29 to 35 percent increase in the risk of breast cancer.[166] In contrast, results from the case-control Shanghai Women's Health Study found no association between PAH metabolites and oxidative stress markers and breast cancer.[167]

Some of the inconsistencies in findings in different studies may be due to genetic differences in DNA-repair mechanisms. For example, in the Long Island breast cancer study, variations in genetic profiles associated with DNA repair influenced the breast cancer risk associated with PAH exposures.[168]

The IOM committee report concluded that epidemiologic studies of PAHs provide modest support for their ability to cause human breast cancer (See Box 5.2).

Ethylene oxide

Ethylene oxide is a highly reactive gas used mainly as a chemical intermediate in the manufacture of textiles, detergents, polyurethane foam, antifreeze, solvents, pharmaceuticals, adhesives, and other products. Smaller amounts are used as a fumigant, a sterilant for food (spices) and cosmetics, and in hospital sterilization of surgical equipment and plastic devices that cannot be sterilized by steam.[169]

Exposure to ethylene oxide occurs mainly in the workplace, including hospitals. It is classified as a human carcinogen by both IARC and NTP on the basis of evidence from epidemiologic and animal studies. Some studies find an increased risk of breast cancer in women exposed to the sterilant ethylene oxide in health care facilities or manufacturing plants in which the chemical is used.[170,171] The IOM committee report concluded that ethylene oxide is plausibly related to breast cancer risk after adult exposures.

BOX 5.2: The Institute of Medicine report

In their 2012 report "Breast Cancer and the Environment: A life course approach," a committee convened by the Institute of Medicine reviewed the evidence linking select environmental variables to breast cancer incidence.[172] It was not a comprehensive review. The committee selected a limited set of factors from an extensive list in order to illustrate a variety of environmental exposures, and to emphasize the need for new approaches to research into environmental risks for breast cancer. The committee did not review dietary variables.

For this review, the chemicals the committee selected included:

- Exogenous hormones: hormone replacement therapy (HRT), oral contraceptives (OCs)
- Consumer products and constituents: alkylphenols, bisphenol A, nail products, hair dyes, parabens, perfluorinated compounds, phthalates, polybrominated diphenyl ethers (a family of flame retardants)
- Industrial chemicals: benzene, 1,3 butadiene, PCBs, ethylene oxide, vinyl chloride
- Pesticides: DDT/DDE, aldrin, dieldrin, atrazine
- PAHs
- Dioxins
- Metals: Cadmium, arsenic, aluminum, lead, iron, mercury

The committee concluded that:

- The clearest evidence from epidemiologic studies of increased risk of breast cancer were: combination (estrogen-progestin) hormone therapy products, current use of oral contraceptives, alcohol consumption, and exposure to ionizing radiation.
- Some but not all reviews find active tobacco smoking causally related to increased risk of breast cancer.
- The evidence linking passive smoking, shift work involving night work, benzene, 1,3-butadiene, and ethylene oxide to increased risk is less strong but suggestive. For bisphenol A, zearalenone*, vinyl chloride, and alkylphenols†, human epidemiologic evidence regarding breast cancer is not available or inconclusive, but laboratory studies provide a biologic basis for concern that they may increase risk.

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* Zearalenone is a potent estrogenic compound produced by some species of fungi. It can contaminate some kinds of food, particularly corn.

† Alkylphenols are chemicals used in the production of detergents and other cleaning products, and as antioxidants in products made from plastics and rubber. They are also found in personal care products, especially hair products, and as an active component in many spermicides. Some alkylphenols or their breakdown products are estrogenic.

- Non-ionizing radiation and personal use of hair dyes, have not been associated with breast cancer risk in multiple, well-designed human studies.
- For several other factors, evidence was too limited or inconsistent to reach a conclusion (e.g., nail products, phthalates).
- For most of the factors examined, information on the potential for exposure at different life stages to affect risk is limited or nonexistent.
- There is a need for future research "to better reflect the growing understanding of a life course perspective whereby the potential for influencing breast cancer risk may depend exquisitely on the timing of exposure, and an appreciation of the potential for different factors to play a role in specific, etiologically distinct varieties of breast cancer based on histologic or molecular subtype."

Among their high priority research recommendations, the committee called for more systematic and urgent investigation of:

- Chemicals with endocrine activity,
- Interactions between chemicals, such as BPA, polybrominated diphenyl ethers (PBDEs), zearalenone, and certain dioxins and dioxin-like compounds,
- The importance of timing of exposure, diet, and other factors that may influence the relationship of these types of compounds to breast cancer risk.

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Chapter 6

The electromagnetic spectrum and breast cancer: Sunlight and vitamin D; shift work, artificial light, and sleep; electromagnetic fields

Electromagnetic radiation is a form of energy emitted and absorbed by charged particles. It has wave-like characteristics as it moves through space. The electromagnetic spectrum is the range of wave-lengths and frequencies of electromagnetic radiation (see figure 6.1). Visible light occupies a small portion of this spectrum, bounded on the lower frequency side by infrared and above by ultraviolet. X-rays and gamma rays lie beyond ultraviolet at much higher frequencies. Microwaves, radio frequency (RF) and extremely low frequency (ELF) radiation lie below infrared. The entire spectrum frequency distribution covers many orders of magnitude.

Sunlight includes ultraviolet light, which is responsible for initiating the conversion of vitamin D precursors into the active hormone in most animals and some plants. ELF electromagnetic fields are generated by electrical and electronic appliances and power lines. Radiation in the RF spectrum is generated by wireless devices such as cell phones and cordless phones, cellular antennas and towers, and broadcast transmission towers. This chapter discusses the relationship of these diverse frequencies of electromagnetic radiation to breast cancer.

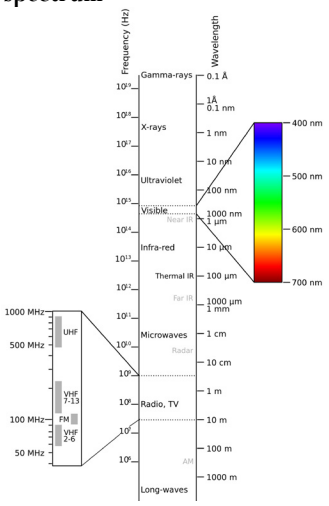
6.1 Vitamin D and breast cancer

Summary

Studies addressing the relationship between dietary vitamin D, vitamin D serum levels, and breast cancer are somewhat inconsistent, but most find higher vitamin D levels associated with lower risk. Insufficient levels of vitamin D are exceedingly common in the U.S. population. Vitamin D insufficiency may be particularly important during fetal development, childhood, and adolescence when cells are rapidly proliferating, tissues are developing, and their hormone responsiveness is established.

Based on estimated current vitamin D intake levels, measured serum levels, the benefits and safety of higher levels, and the available evidence that points toward lower breast cancer risk with higher levels of vitamin D, achieving and maintaining serum levels of 25(OH)D in the range of 30-40 ng/mL is supportable and highly unlikely to be associated with adverse consequences. This serum level is entirely consistent with conclusions of the IOM and the Endocrine Society. For most people, achieving this serum level will probably require some vitamin D supplementation, beginning in pregnancy and continuing in infancy and throughout life, as necessary.[1,2] It is important to recognize, however, that at some point, more is not better. Excessive vitamin D intake carries its own risks. Nonetheless, the margin of safety between current intake levels and safe upper limits is sufficiently large to justify supplementation, guided by laboratory testing of serum levels of 25(OH)D.

Figure 6.1: The electromagnetic spectrum*



* From Wikipedia http://en.wikipedia.org/wiki/File:Electromagnetic-Spectrum.svg

Vitamin D: Biologic activity and breast cancer risk

Vitamin D is an ancient hormone. It is not a vitamin in the sense that it must be supplied from dietary sources. Plants and animals have produced vitamin D as far back in evolutionary time as is traceable.[3] Phytoplankton, zooplankton, almost all animals, and some fungi

and plants exposed to ultraviolet rays from sunlight make forms of vitamin D from existing precursors.* It has diverse, essential biologic functions.[4]

Vitamin D deficiency causing abnormal calcium metabolism and rickets became a major public health problem at the beginning of the industrial revolution when children began to spend increasing amounts of time in sunless environments. The importance of sunlight and consequences of its absence was confirmed. A search for food that would help prevent rickets identified cod liver oil, the flesh of some fatty fish, and to a lesser extent, some mushrooms and eggs that contain naturally-occurring vitamin D. In the United States many dairy products and cereals are now fortified with vitamin D. It is also available as a dietary supplement.

Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo metabolic transformation to the active form. The liver converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. A second step yields the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], known as calcitriol. This conversion occurs primarily in the kidney and to a lesser extent in other tissues, including the breast. Calcitriol binds to vitamin D receptors (VDRs) and initiates biologic effects. Some VDRs are present in the cell nucleus and, when occupied by vitamin D, interact with DNA to modulate gene expression. Other VDRs are present in cell membranes and when activated, initiate a different cascade of events. Vitamin D receptors are present in most body cells, including the small intestine, colon, brain, heart, skin, prostate, gonads, breast, lymphocytes, osteoblasts, and β-islet pancreatic cells.

Historically, the role of vitamin D in calcium metabolism and bone health has received most attention, but in recent years it has become clear that vitamin D has multiple functions in the regulation of cellular growth and differentiation more generally. Inadequate vitamin D levels have been linked to a range of acute and chronic illnesses, including some cancers, immune disorders, infectious diseases, diabetes, neurocognitive disorders, and overall mortality.[5]

In support of the idea that inadequate levels of vitamin D might be linked to cancer, the authors of a paper published in 1980 proposed that lower levels of vitamin D at higher lat-

* Here the term vitamin D refers to vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) Both are produced by photolysis from naturally occurring precursors with light in the UVB spectrum (280–320 nm). Vitamin D2 is produced from ergosterol, a compound found only in plants and fungi. Vitamin D3 is produced from 7-dehydrocholesterol (7-DHC), found in high concentration in the skin of animals, including humans, and some plants.

itudes, where sun exposure is significantly less than at lower latitudes, might help explain geographic differences in colon cancer patterns.[6] More recent ecologic studies also show higher breast cancer incidence or mortality at higher latitudes.[7,8,9]

In vitro laboratory studies show that 1,25(OH)2D can inhibit cellular proliferation and promote programmed cell death (apoptosis) and cellular differentiation in breast tissue.[10,11] The mammary glands of laboratory rodents lacking the vitamin D receptor show altered mammary gland development with enhanced ductal proliferation and responsiveness to estrogen and progesterone stimulation.[12]

A prospective study of 242 pre-puberal girls in Bogota, Columbia also found that lower levels of plasma 25(OH)D were associated with earlier onset menarche.[13]

Laboratory studies show that rodents fed low levels of dietary vitamin D develop more mammary tumors when exposed to a carcinogen than animals fed adequate amounts of vitamin D.[14] The effect is most marked in animals that were also fed a high fat diet, showing that the combination of high fat diet and low levels of vitamin D created increased susceptibility to tumor development after exposure to a carcinogen. Animal studies also show that vitamin D can inhibit both early and later events in mammary tumor development.[15] *In vitro* studies of breast cancer cells show that vitamin D reduces aromatase levels.[16,17] Aromatase is an enzyme that aids in the conversion of androgens to estrogens, and aromatase inhibitors are among the pharmaceutical agents used to treat ER+ breast cancer. Thus, based on extensive laboratory data, a role for vitamin D in breast cancer prevention and treatment is plausible.

A number of epidemiologic studies have examined vitamin D status as a risk factor for breast cancer. Challenges in study design include determining the optimal time for measuring vitamin D status, using food frequency questionnaires to estimate dietary levels, accounting for correlations between calcium and vitamin D status (each may influence breast cancer risk independently), and estimating the primary source of vitamin D from exposure to sunlight.

Prospective observational studies

Some prospective observational studies attempt to examine breast cancer risk related to estimates of vitamin D intake from food or supplements.

The Nurses' Health Study included 88,691 pre- and post-menopausal women and estimated vitamin D intake from repeated food frequency questionnaires and assessment of supplement use.[18] After 16 years of follow-up, the highest vs. lowest estimated total vitamin D intake was associated with 28 percent lower risk of premenopausal breast cancer. There was no association with post-menopausal breast cancer risk and no effect of supplemental calcium. Among premenopausal women, high intake of low fat dairy foods was associated

with about 30 percent decreased risk of breast cancer. But, vitamin D appeared to have a protective effect independent of the "milk effect." This effect was apparent when vitamin D intake of > 500 IU daily was compared to <150 IU daily.

A recent analysis of data from the Nurses' Health Study II (NHS) reports that women with the highest levels of vitamin D intake during adolescence had a 21 percent reduced risk of developing proliferative benign breast disease.[19] This condition is associated with an increased risk of breast cancer subsequently.[20]

The NHANES I epidemiologic 1971-1975 to 1992 follow-up study[21] involved 4,747 white women including 179 breast cancer cases. Non-white women were excluded because there were too few breast cancer cases for a separate analysis. Participants were 25-74 yrs old and baseline vitamin D levels were estimated from sunlight exposure, diet, and dietary supplements. Sunlight vitamin D was classified as considerable, moderate, or low by dermatological skin exam and self-report of time spent in the sun. Several measures of sunlight exposure were associated with an approximately 30 percent decreased risk of breast cancer when comparing highest to lowest. Intake of at least 200 IU vitamin D was associated with 20 percent decreased risk of breast cancer. Higher sun exposure and higher dietary vitamin D intake in women who lived in an area of high solar radiation was associated with 64 percent risk reduction.

The Cancer Prevention Study II nutrition cohort followed 68,567 post-menopausal, mostly white women, using a baseline food frequency questionnaire and information about vitamin D supplement use for past year.[22] Over 9 years of follow-up there were 2855 incident cases of breast cancer. Women with highest level of dietary calcium intake had 20 percent lower risk of breast cancer. There was no association with supplemental calcium or vitamin D intake. Two or more dairy servings a day was associated with 20 percent decreased risk. For estrogen receptor positive tumors, higher levels of dietary calcium, vitamin D, and dairy were each associated with 20-30 percent decreased risk of breast cancer. This study did not inquire about sun exposure or measure serum levels of vitamin D.

Serum levels of 25(OH)D and breast cancer risk

Some studies have examined the relationship between vitamin D status and breast cancer risk by actually measuring serum levels of 25(OH)D rather than estimates of dietary sources or sun exposure. A pooled analysis from the NHS and a British case-control study concluded that women with 25(OH)D serum concentrations* of >52 ng/mL had a 50 percent lower

* Serum levels of 25(OH)D can be expressed as ng/mL or nmol/L. Multiply levels expressed as ng/mL by 2.5 to convert to equivalent levels expressed as nmol/L. For example, 20 ng 25(OH)D/mL is equivalent to 50 nmol 25(OH)D/L.

risk of breast cancer than those with levels < 13 ng/mL.[23] The authors estimated that a serum level of 50 ng/mL can be achieved by consuming about 4000 IU vitamin D daily or alternatively, consuming 2000 IU vitamin D daily and spending about 12 minutes/day in the noon time sun with 50 percent of skin exposed.

A recent meta-analysis of 9 studies (5 case-control; 4 nested case-control) reported that seven of the nine studies showed a lower incidence of breast cancer with higher serum levels of vitamin D.[24] This association was significant in five studies. This association was stronger in case-control (serum 25(OH)D levels measured after diagnosis; higher levels were associated with 40 percent decreased risk) than nested case-control studies (serum levels measured prior to diagnosis; higher levels were associated with 8 percent decreased risk). Thus, the findings are ambiguous.

Recognizing that differences in study populations, including menopausal status and a wide range of circulating levels of 25(OH)D, might explain these inconsistencies, the authors of a recent meta-analysis examined prospective studies using a non-linear dose-response evaluation and looking at pre-and post-menopausal breast cancer risk separately.[25] They found steadily decreasing risk of post-menopausal breast cancer associated with serum levels of 25 (OH)D beginning at 27 ng/mL and continuing up to 35 ng/mL, where the risk decline leveled off. There was no apparent association with risk of pre-menopausal breast cancer. This finding supports the hypothesis that there is a threshold effect of vitamin D on breast cancer risk and that intervention trials should be designed to use enough vitamin D to raise serum levels at least into the 30-35 ng/mL range.

Another meta-analysis examined the impact of individually estimated vitamin D intake, serum 25(OH)D levels, and calcium intake on breast cancer risk.[26] The authors also found decreased risk associated with higher levels of 25(OH)D, as well as with higher intake of vitamin D and calcium.

A more recent nested case-control study in France found that higher levels of serum 25(OH) D at baseline were associated with a 27 percent lower risk of breast cancer during 10 years of follow up.[27] In this study, the decreased risk was more pronounced in premenopausal women.

A case–control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and consisting of 1,391 breast cancer cases and 1,391 controls did not find a significant association between serum 25(OH)D levels and the risk of breast cancer.[28] However, higher levels of 25(OH)D were associated with lower risk in women who had taken hormone replacement therapy.

A case-control study found that African Americans were at much higher risk of vitamin D deficiency than European Americans. Low levels of vitamin D coupled with genetic variations in vitamin D metabolism were associated with much higher risk of ER- breast cancer in African Americans, whereas those same genetic variations did not affect the risk of breast cancer in European Americans.[29,30] This suggests that baseline low levels of vitamin D in African American women may increase the risk of aggressive breast cancer, particularly in a subset of women who metabolize vitamin D in a certain way, and adds support to the call for more vigorous vitamin D biomonitoring and supplementation when indicated.

Randomized controlled trials

The Women's Health Initiative included 36,282 post-menopausal women aged 59-70 years in a randomized, double blind study.[31] Half were given vitamin D (400 IU daily) and calcium (1000 mg daily) supplements; half were given a placebo. After an average follow up of 7 years, there was no difference in breast cancer incidence in the two groups. However, further analysis of data showed that women who were not taking vitamin D or calcium supplements at the time the study began and who were assigned to the vitamin D-calcium supplement intervention group had 14-20 percent decreased risk of all cancer, breast cancer, and invasive breast cancer over seven years of follow up.[32]

Another population based, double blind, randomized controlled trial in 1179 postmenopausal women followed for four years compared outcomes using vitamin D (1100 IU daily) plus calcium (1400-1500 mg. daily), calcium alone, or placebo.[33] The study was primarily designed to study bone fracture incidence but the data were secondarily analyzed for cancer incidence. Compared to women taking placebo, the risk of any cancer was 60 percent lower in the vitamin D plus calcium group and 47 percent lower in the calcium-only group. Both treatment and serum 25(OH)D concentrations were significant predictors of cancer risk, including breast cancer.

Studies that assess relationship of time outdoors with breast cancer risk

The Ontario Women's Diet and Health Study is a population based case control study of 3,101 women with breast cancer and 3,420 controls, ages 25-74 with an average age of 56 years.[34] Sixty-eight percent were post-menopausal and most Caucasian. Detailed information was collected about the amount of time spent out of doors at various ages. A decreased risk of breast cancer was associated with increasing time spent outdoors (>21 vs < 6 hrs/week) during the teenage years (29 percent lower risk), 20s-30s (36 percent lower risk), 40s-50s (26 percent lower risk), and 60s-75 years (50 percent lower risk), all statistically significant. In this same study, vitamin D supplement use of 400 IU or more daily was associated with a decreased risk of breast cancer.[35]

Another population based case-control study in Ontario found a sharply reduced risk of breast cancer in women who had spent more time outdoors during adolescence, but weaker evidence of reduced risk with time spent outdoors from ages 20-29, and no evidence for ages 45-54.[36] Reduced risk was also associated with adolescent cod liver oil use and increasing milk consumption. Cod liver oil is a rich source of vitamin D and milk a source of both vitamin D and calcium.

Vitamin D post-diagnosis and recurrence

A study of 12,019 breast cancer survivors from four different cohorts in the U.S. and China found that vitamin D supplement use after initial diagnosis and treatment was associated with a 36 percent lower risk of recurrence in women with ER+ tumors but not ER- tumors.[37] This finding could be explained at least in part by reductions in levels of aromatase.

Vitamin D status of people in the United States: What level is healthy?

In 2011 an Institute of Medicine (IOM) expert panel concluded that most Americans had adequate levels of vitamin D, based on their assessment that a serum level of 25(OH)D of 20 ng/mL (50 nmol/L) or greater was sufficient.[38] A 2001-2004 NHANES survey had reported the average 25(OH)D level was over 20 ng/mL in the study population. However, people of color, particularly African-Americans, and older people are among those with significantly lower levels.[39] Children who are overweight or obese are also much more likely to have serum 25OH-D levels less than 20 ng/mL.[40]

In contrast, the Endocrine Society Clinical Practice Guidelines recommend a target level of serum 25(OH)D of at least 30 ng/mL, based on their assessment that levels at 20 ng/mL are not adequate.[41] Using the Endocrine Society guideline, over 50 percent of the U.S. population has insufficient levels of vitamin D.

The IOM committee had been charged with determining whether dietary reference intakes (DRIs) for calcium and vitamin D should be changed, based on new scientific information. Dietary reference intakes are intended to improve public health in the general population and provide recommendations for adequate and safe daily intakes of nutrients consumed over many years, possibly a lifetime. Thus, the committee said, the need for sound, causal evidence to make recommendations is essential. The IOM committee prioritized randomized clinical trials (RCTs) as providing the most persuasive evidence, although they supplemented their analysis with observational epidemiologic evidence but gave it lower standing.

After reviewing the available data addressing breast cancer, the IOM report says: "In summary, although experimental studies are suggestive of a role for vitamin D in breast biology, a review of the available evidence from both randomized controlled trials and observational

studies of associations between vitamin D and calcium and risk of breast cancer shows a lack of consistency between study outcomes and insufficiently strong evidence to support DRI development. Both retrospective and prospective studies do not show consistent associations between estimated vitamin D intake or 25 (OH)D status and breast cancer risk. A paucity of RCTs of vitamin D, calcium, or both with breast cancer as a primary outcome further limited the strength of the evidence."

The IOM committee found similar incomplete or inconsistent data for most other health endpoints and based their final recommendations on the relationship between vitamin D, calcium, and bone health alone, for which the data met their criteria for sufficiency.

The IOM report estimates that the average vitamin D intake for males in the U.S. is 300-400 IU daily; for females 200-400 IU daily. The estimates vary with age and do not account for vitamin D from sun exposure. Thus, on average, vitamin D intake in the U.S. is below the recommended daily intake (RDA) of 600 IU vitamin D daily and well below the estimated safe upper limit.

The committee affirmed a RDA of 600 IU daily, except 800 IU daily for men and women > 70 yrs of age, based only on requirements for bone health. But the committee acknowledged a safe upper limit of 1000-1500 IU in infants, 2500-3000 IU in children, and 4000 IU in adolescents and adults

Vitamin D status during pregnancy

The American College of Obstetricians and Gynecologists (ACOG) recommends testing only pregnant women who are at increased risk of vitamin D deficiency (e.g., women with limited sun exposure, women with darker skin that limits absorption of vitamin D). If a woman's vitamin D levels are 20 ng/mL (50 nmol/ L) or less, ACOG recommends vitamin D supplementation in a dosage of 1,000 to 2,000 IU daily.[42]

Vitamin D status in infancy

The American Academy of Pediatrics recommends that all infants, whether breast fed or formula fed, receive a vitamin D supplement, based on widespread inadequate serum levels.[43]

6.2 Shift work and breast cancer

In 2010, the International Agency for Research on Cancer (IARC) concluded that shift work that involves circadian rhythm disruption is "probably carcinogenic to humans."[44] Exposure to light at night may help explain the relationship between shift work and cancer risk.

The major hypothesized mechanism by which shift work and disrupted circadian rhythm might influence breast cancer risk is through alteration in melatonin levels. Melatonin is a hormone secreted by the pineal gland, located in the middle of the brain. Circulating melatonin levels are lowest in daytime light and highest at night. Light at night depresses melatonin levels and disrupts its rhythmic cycle.

Melatonin is a powerful anti-oxidant. It exerts this effect not only by scavenging DNA-damaging free radicals but also by up-regulating antioxidant enzymes.[45] Melatonin also regulates the activity of other hormones and growth factors. It suppresses cell proliferation by delaying the progression of the cell cycle.[46] In breast cancer cells, this is most marked in those that are ER+.[47] Melatonin modulates gene transcription activity of the estrogen receptor and other nuclear receptors. It reduces aromatase activity, thereby reducing estrogen levels, promotes apoptosis in breast cancer cells, and may enhance DNA repair.[48] Laboratory animal studies show that melatonin significantly reduces the incidence and tumor size of rat mammary cancers induced by DMBA or N-nitrosomethylurea (NMU).[49]

Additional evidence supporting the influence of melatonin comes from the observation that blind women have a significantly lower breast cancer risk than women who are not, even after controlling for known risk factors.[50] The risk is more sharply reduced in women who have no light perception at all. People who are blind tend to have reduced spikes of melatonin, but higher baseline levels that vary considerably among individuals. It is unclear, however, whether this fully explains their reduced risk.[51,52]

Other factors at play in shift work may also influence breast cancer risk. People who work at night may spend less time outdoors in sunlight during the day and thereby have lower vitamin D levels. One study in the UK found that women working at night had an average 8 percent lower vitamin D level than others after controlling for social class, BMI, and season.[53] Surprisingly few studies have examined this relationship, however.

Most studies have examined breast cancer risk as it relates to shift work although some have also investigated prostate, colon, and uterine cancer risks. The IARC identified eight studies that examined the relationship between breast cancer and shift work that involved working at night. Six of those studies, including two prospective cohort studies in nurses, showed a modestly increased risk of breast cancer in long-term employees who worked night shifts. The two studies not showing an increased risk had limitations in study design, according to IARC.

A more recent systematic review and meta-analysis identified 12 case-control and four cohort studies examining night shift work as a risk factor for breast cancer.[54] Many of the studies analyzed focused on nurses and most were comprised of relatively high-income, white participants. This analysis excluded studies of airline crews because of other potentially com-

plicating exposures such as cosmic radiation and time-zone changes. The authors reported a nine percent increased risk per five years of night-shift work in case control studies but no increased risk in cohort studies.

6.3 Sleep and breast cancer

In addition to shift work and light at night, epidemiologic studies have also investigated links between sleep and breast cancer risk. Of six studies that have investigated sleep duration and breast cancer, three found no association,[55,56,57] one reported an increased risk with increased sleep duration[58], one found an increased risk with short sleep duration (<6 hrs/day),[59] and one reported a decreased risk with increasing sleep duration and no association with sleep quality.[60]

The metrics associated with the epidemiology of sleep are not yet standardized and this may help explain disparate findings.[61] Sleep duration, quality, and disturbance may be collectively or independently related to disease risk. Erren proposed a "sleep-years" index to assess cumulative sleep over decades as a possible approach.[62]

6.4 Radiation, electromagnetic fields and breast cancer

In general, electromagnetic radiation with frequencies higher than the visible spectrum has sufficient energy to break chemical bonds, creating charged particles (ions) that can cause DNA mutations, various other kinds of cellular damage, and cell death.[63] This is ionizing radiation. Lower-frequency radiation from ELF-EMFs and RF-EMFs does not have sufficient energy to break chemical bonds and create highly reactive ions. Thus, it is called non-ionizing.

In the 20th century it became clear that ionizing radiation could cause mammary gland tumors in laboratory animals and breast cancer in women who had undergone chest fluoroscopy for tuberculosis or X-irradiation for mastitis and in survivors of the atomic bombing in Japan.[64,65,66,67] According to the 2008-2009 Annual Report of the President's Cancer Panel, while ionizing radiation exposures from radon, occupational, and other sources have remained essentially stable over the past 30 years, Americans now are estimated to receive nearly half of their total radiation exposure from medical imaging and other medical sources, compared with only 15 percent in the early 1980s.[68] This panel and others have concluded that reducing exposure to ionizing radiation, including from unnecessary medical procedures, is an obvious and important way to reduce breast cancer risk.[69]

Two kinds of non-ionizing radiation from EMFs are 1) extremely low frequency electromagnetic fields (ELF) from electrical and electronic appliances and power lines and 2) radiofrequency radiation (RF) from wireless devices such as cell phones and cordless phones, cellular antennas and towers, and broadcast transmission towers.[70]

Regulation of the non-ionizing electromagnetic spectrum is muddled. No agency routinely monitors and responds to health concerns arising from exposure to ELF-EMF. The Food and Drug Administration (FDA) has the regulatory authority to take action if a cell phone is found to emit RF-EMFs of sufficient energy to pose a risk of harm. However, to a large extent the FDA allows the Federal Communications Commission (FCC) to set regulatory guidelines for emissions from cell phones, transmission antennas, and towers. The FCC certifies wireless devices, and all phones that are sold in the United States must comply with FCC guidelines on RF exposure.

Some people believe that current regulations, promulgated in 1996 with minor updates in 2003, are out-of-date and not based on more current information that looks beyond thermal effects of exposure.[71] Indeed, there is evidence that the FCC has even failed to enforce certain existing standards.[72] After urging by the Government Accounting Office, the FCC has recently agreed to undertake a review of cell phone exposure standards and the way the phones are tested for compliance with that limit.[73]

Historically, scientists and concerned citizens have considered health effects associated with exposure to EMFs against a backdrop of a commonly-held belief that non-ionizing EMFs that do not generate heat could not plausibly have any adverse biologic effects. The field abounds with skeptics convinced that radiation of insufficient energy to break chemical bonds, ionize atoms, and at least produce heat cannot possibly be harmful. Data tell a different story. They support often-ignored concerns that this is an important public health issue, particularly since virtually everyone in today's world is exposed to ELF-EMFs and RF-EMFs. This means that even relatively small increases in disease risks can have large public health consequences.

This topic is mired in controversy. The BioInitiative 2012 report extensively reviews mechanisms by which ELF- and RF-EMFs can have diverse non-thermal adverse biologic effects and a range of health effects linked to these exposures, including cancer.[74] Potential mechanisms for which there are varying levels of support include genotoxic effects, alterations in gene expression, oxidative stress, up-regulation of stress responses, changes in permeability of membranes and the blood brain barrier, reduced melatonin levels, and altered immune function, among others. Another summary of "expert group reports" finds no "demonstrated health risk" from RF-EMF exposure from cell phones or other wireless technologies.[75] This is a long-standing debate that is unlikely to be resolved anytime soon.

With regard specifically to cancer, in 2001 the International Agency for Research on Cancer (IARC) classified ELF-EMF as possibly carcinogenic to humans, based on an association between higher levels of exposure to EMFs from proximity to high voltage power lines and increased risk of childhood leukemia. In 2011, IARC classified RF-EMFs (cell phones and related technology) as possibly carcinogenic to humans, based on an increased risk of glioma, a malignant brain tumor, associated with wireless phone use.[76] Investigators have also examined the possibility that exposure to ELF-EMF might be associated with an increased risk of breast cancer.

Studying the health impacts of ELF-EMF exposure is challenging. Most importantly, exposure assessments are difficult. At a basic level, it is not always obvious which aspect of the EMF is most biologically important. ELF-EMF exposures have both electric field and magnetic field components. Most epidemiologic studies of ELF and breast cancer have focused on associated magnetic fields. But it may be that electric field exposures also matter.[77] Moreover, investigators often use estimates of average exposures, but peak exposures or even rate of change may be equally or more important. And, since ELF-EMFs are not perceptible and vary substantially with everyday circumstances, they must either be directly measured or estimated using proxies based on conditions that influence exposure—e.g. occupation or electric blanket use. Thus, epidemiologic studies are often limited by imprecise exposure assessments, subject to exposure misclassification, and are likely to be biased toward finding no association, even if one truly exists.

Decreased melatonin production associated with higher exposures is one proposed mechanism by which ELF-EMF could influence breast cancer risk. As previously noted melatonin is a powerful anti-oxidant and has various other properties that are likely to reduce breast cancer risk. Laboratory studies show that melatonin can inhibit proliferation of ER+ breast cancer cells. Studies in cell cultures show that ELF-EMFs can interfere with this effect.[78,79] Other cell culture studies show that the magnetic field associated with ELF-EMF at typical environmental levels can not only interfere with the suppressive action of melatonin but also tamoxifen, a pharmaceutical estrogen antagonist commonly used in the treatment of ER+ breast cancer.[80,81] Thus, ELF-EMFs could plausibly promote ER+ breast cancer.

Results from melatonin studies in various laboratory animal species and humans are inconsistent. Some show that ELF-EMFs reduce melatonin production and activity while others do not.[82] The reasons for these inconsistencies are not entirely clear but differences in study design, including variable exposure patterns and timing of melatonin measurements, are likely to be at least partly responsible.

A 2001 meta-analysis of 15 case-control and 21 cohort studies found a 12 percent increased risk of breast cancer associated with higher ELF-EMF exposures in women [relative risk 1.12 (95 percent CI: 1.09, 1.15)] and a 37 percent increased risk in men [relative risk of

1.37 (95 percent CI: 1.11, 1.71)].[83] The findings in men may be particularly instructive since men do not have many other known risk factors and breast cancer in men is much less common than in women. In the 19 studies of men included in this meta-analysis (5 case-control; 14 cohort), nine used job title or job-exposure matrix to estimate ELF-EMF exposure while the remainder used job title and various other estimates of exposure. Some degree of exposure misclassification is almost inevitable, potentially biasing the results toward finding no association, even if one exists. Thus, the 37 percent increase in relative risk may actually be an under-estimate.

A more recent meta-analysis of 15 studies published between 2000 and 2009 found no significant association between ELF-EMF exposure and female breast cancer risk (OR =0.988, 95 percent CI: 0.898–1.088), including subgroup analyses by exposure modes, menopausal status, or estrogen receptor status.[84] Subgroup exposure modes included occupational vs. residential exposures and electric blanket exposures specifically.

No studies of RF-EMF and breast cancer have been published. However, IARC's recognition of the possible link of RF-EMF to brain cancer has raised concerns about other cancer risks associated with widespread cell phone use and its accompanying infrastructure. Even though RF-EMF is not ionizing radiation, some studies show evidence of genotoxicity associated with experimental RF exposures similar to those from cell phones while others do not.[85,86,87] This has sparked considerable debate inasmuch as exposure to RF-EMF is widespread. According to a UN report, about six billion people throughout the world now have access to cell phones.[88,89]

Anecdotal reports of breast cancer in young women who carried their cell phones in their bras have helped to reveal just how widespread the practice is today.[90] Inasmuch as solid tumors like breast and brain cancer have long latency periods, it will be many years before definitive studies resolve uncertainties about the safety of cell phones and related technologies. To the extent that RF-EMF exposures raise cancer risks even modestly, the public health consequences will be large because of such widespread exposures.

The best ways to reduce RF-EMF exposures from cell phones include:

- keep conversations on cell phones as short and infrequent as possible; use a land line or send texts instead;
- do not put it against your body. Put it in your purse, your backpack, or your case;
- do not keep your cell phone in your bra or pocket;
- always try to keep it a few inches away from your body. The strength of the antenna signal decreases quickly with increasing distance from the source;
- do not call in vehicles (car, bus, train). If your mobile does not have an external antenna, the radiation levels go up in moving vehicles. This is because each time the

cell phone connects to a new tower (the "handshake") an increase in power follows until an optimal level is established;

- avoid placing mobile calls in places with poor reception such as cellars or elevators. The cell phone will increase its power (and thus the radiation) in such situations;
- use the speaker phone feature;
- plug in earphones while talking;
- use the hands-free device;
- keep the phone away from your head;
- do not sleep with it under your pillow;
- put your cell phone in airplane mode.

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Chapter 7

Stress, social support, and breast cancer

Chapter summary

Stress depends on our surroundings, how we perceive them, and how we respond. The stress response is non-specific. It involves the brain, endocrine, reproductive, and immune systems. The nature of the response can be highly dependent on individual coping skills, personal history, age, health status, and socio-cultural circumstances. Recent studies of stress have made considerable progress in demonstrating mechanisms by which stress can influence health status as well as showing that reducing stress can improve health and modify the course of diseases in beneficial ways.

Although many people feel strongly that stress can cause or increase the risk of developing cancer, evidence is inconsistent. However, animal and human studies show that stress can promote tumor growth through a variety of mechanisms. Thus, at least in some instances, stress may advance the time at which a slowly-developing latent tumor becomes clinically apparent.

A variety of psychotherapeutic interventions can reduce stress and beneficially modify associated biologic markers. Techniques that have undergone fairly rigorous scrutiny in epidemiologic studies and clinical trials often involve variations on mind-body-spirit interventions. These include meditation, yoga, mindfulness exercises, guided imagery, music, and cognitive behavioral therapy, among others. But, in addition to psychotherapeutic interventions, establishing and taking advantage of existing social support networks can markedly reduce stress and improve outcomes through many pathways, including providing services and needed resources as well as a sense of being valued, loved, and cared for by others.

Improved quality of life

Rigorously conducted studies show that stress reduction can significantly improve quality of life in people with breast cancer. In general, group therapy, education, structured and unstructured counseling, and cognitive behavioral therapy help significantly to reduce anxiety, depression, and fatigue and generally improve functional ability and quality of life. For many people, guided imagery, music therapy, meditation, and relaxation training are highly beneficial. A number of these interventions also improve indicators of immune function.

Improved survival/delayed recurrence

Observational studies show the most significant associations of lower stress levels with improved outcomes in groups of women who do not have metastatic disease at the time of initial diagnosis and treatment. In groups of women with metastatic disease, reduced stress is not clearly associated with delayed recurrence and improved survival, but within those groups some individuals appear to benefit. Stress reduction is clearly associated with improved quality of life in women with all stages of the disease. It is increasingly clear that outcomes improve most when conventional therapy is combined with more comprehensive interventions that not only reduce stress but also improve diet, exercise, sleep, and social support.

Stress is a subjective, highly individualized experience. Within large groups of study participants there will always be individuals who will benefit more or less from a particular intervention. The results of the studies described here may serve as a guide for developing general policies and recommendations. But they should not be interpreted as being a definitive guide for all individuals and families making complex treatment-related decisions. Some individuals are likely to benefit from psychological interventions and practices more than others. This is a highly personal decision. However, considerable evidence supports a choice to pursue psychological practices in response to a diagnosis of breast cancer. For breast cancer prevention, the data are less clear. It is also important to keep in mind that stress reduction and the development and maintenance of social support have proven benefits for a variety of other diseases and disorders as well.

Many aspects of our social, political, physical, chemical, and biologic environments shape conditions that foster health and promote disease. How we perceive and ultimately experience what happens to us also plays a role. Stressors and our bio-psychosocial responses to them involve the brain, endocrine, reproductive, and immune systems, with behavioral and health consequences over the short- and long-term. This chapter reflects on a long his-

tory of evolving theories of stress. It summarizes findings of epidemiologic studies addressing the role of stress and stress reduction related to breast cancer. It makes no attempt to describe extensive studies in laboratory animals that add richer insight.

An immediate fight-or-flight stress reaction to an imminent danger can, of course, be life-saving. Learning to cope with ordinary stressors of daily life so that they are not too disruptive is also healthy. But, unusual or prolonged stress, particularly when combined with limited coping skills and resources needed to respond, can be detrimental to health. The consequences of stress are not only deeply related to what happens to us but also who we are, our interpretation of events, and where we live.

Long before current understanding of stress and stress-related diseases developed, theories related to the role of personality and psychological variables in the origins of disease were formulated. Michael Lerner reviews this history as it relates to cancer, including whether there may be a "cancer-prone personality," in *Choices in Healing: Integrating the best of conventional and complementary approaches to cancer.*[1]

Briefly, Galen (c.130–c.210 A.D.) subscribed to Hippocrates' bodily humors theory, which held that differences in human moods are a consequence of imbalances in one of four bodily fluids: blood, yellow bile, black bile, and phlegm. Galen saw breast cancer more often in melancholy (literally, "black bile") women. Outwardly, they were creative, kind, and considerate. Some saw more cancer in women who were anxious, depressed, or grieving.[2]

Much later LaShan, Bahnson, and others proposed a role for "psychophysiological complementarity"—or mind-body connections—in the origins and treatment of cancer.[3,4] Their experiences began to convince them that "malignant processes are related to certain psychosocial conditions and psychodynamic states," although the mechanisms explaining those relationships were unclear.

LeShan reported a statistically-significant relationship between cancer and 1) a lost relationship prior to the diagnosis; 2) an inability to express hostility in one's own defense; 3) feelings of unworthiness and self-dislike; and 4) tension in the relationship with one or both parents, when compared to a control group. Bahnson thought "the phenomenological experience of loss, despair, and strain is the significant variable, since individuals react quite differently to conditions of 'external' stress."

Much of this work was happening during a time of emerging interest in the physiology of stress. Hans Selye, an endocrinologist and pioneer of research in this field, developed a framework in many ways similar to Bahnson's.[5,6] Selye described what he called "the general-adaptation syndrome" as having three chronologic stages: 1) the alarm reaction; 2) the stage of resistance; and 3) the stage of exhaustion. He believed prolonged stress would even-

tually exhaust an individual's response capacity and result in "diseases of adaptation." He saw stress as the combination of external events and the way they are experienced, including resultant changes in various neuroendocrine pathways, including cortisol, frequently called the "stress hormone." For Selye, stress was both the stimulus and response.

Selye's study of stress took place within an evolving concept of homeostasis—an idea that can also be traced to antiquity, where harmony and balance were associated with health, while disharmony and imbalance led to disease. Selye's work was influenced by 19th- century experimental physiologist Claude Bernard, who spoke of the "*milieu interieur*", and later by Walter B. Cannon, both of whose work was rich with empirical measurements of physiologic responses to various stressors.

Homeostasis refers to maintenance of an internal physiologic balance. Feedback loops responding to changing conditions are fundamental to homeostatic processes. Physiologists used terms like *stresses* and *strains*, but they were generally referring to specific stressors and a specific adaptive response, rather than what Selye saw as a less specific stress-response paradigm that could be triggered and maintained by a number of different stressors.

Levels of hormones, neurotransmitters, and various markers of immune function normally fluctuate in a pattern over the short- or medium-term timeframe. Various events—an infection, imminent danger, acute hunger—perturb them in useful, adaptive ways. As events resolve, homeostatic equilibrium is re-established. But some events—e.g., loss of a loved one, prolonged hunger, financial hardship, job stress, chronic danger—along with the patterns of arousal or emotion that they evoke in an individual, result in long term changes in these same physiologic measures that can ultimately be mal-adaptive.[7]

It is now apparent that ongoing stress continues to alter a variety of neuroendocrine pathways, and this response can itself become damaging to health. Allostasis, a more recent concept that builds on a homeostatic framework, refers to maintaining relative stability through change.[8,9,10,11] Allostasis incorporates the realization that the response to predictable and unpredictable events often involves re-tuning of various physiologic processes because of the way these events are experienced. Over the long-term, the response may turn out to be mal-adaptive. Allostatic load refers to the cumulative cost of maintaining a semblance of stability in the context of multiple stressors. Chronically stressful conditions can result in long-term changes in stress hormones, neurotransmitters, markers of inflammation, and other variables. Excessive allostatic load can increase the risk of a variety of illnesses, including cardiovascular disorders, diabetes, asthma, and cancer.[12,13,14]

Stress and breast cancer

The relationship of psychosocial stress to breast cancer onset or prognosis covers a range of topics and is difficult to study. Personality, age, defense mechanisms, coping strategies, history of psychological stress, socioeconomic status, and cultural history create a baseline context. Within that diverse mix, stressful events happen—e.g., the loss of a partner, illnesses, job loss, or financial difficulty—that can alter lifestyle, behavior, and outlook, triggering changes in empirical measures of physiologic function in the brain, endocrine, and immune systems.

Physiologic changes associated with stress depend to some extent on one's capacity to cope. Without coping mechanisms, an individual may react with feelings of helplessness or hopelessness. But coping mechanisms themselves may be of low- or high-cost. Facing a challenge and fears, participation in problem-solving, and seeking social support can improve resilience and help restore health. In contrast, denial, avoidance of conflicts, suppression of emotions, and disengagement may provide short-term benefits but are often ultimately detrimental.[15] Within this context, individual differences in other known risk factors for breast cancer increase the complexity, making it extremely challenging to identify the contribution of stress to the onset or prognosis of the disease.

Mechanisms

Numerous independent and interconnected mechanisms can link stress to cancer initiation and progression. The hypothalamic-pituitary-adrenal axis (HPA axis), involving the hormones adrenalin (epinephrine), norepinephrine, and cortisol, among others, is deeply involved in stress resilience and vulnerability. Mental processing of various stressors influences systemic levels of hormones and neurotransmitters.[16] Independently and collectively, components of this interactive system can alter and impair functions of the brain, endocrine, reproductive, and immune systems, including antigen presentation, T cell proliferation, and antibody- and cell-mediated immunity.[17,18,19,20,21,22,23] Inasmuch as the immune system plays a vital role in ongoing surveillance and elimination of cancer cells, functional impairments may lead to increased risk of cancer or cancer progression. Stress-related hormones can increase blood vessel growth in tumors, enhancing their viability.[24] Stress can also increase the levels of inflammatory mediators in the blood, enriching the tumor microenvironment.[25]

Stress can promote DNA damage as well as reduce tumor-suppressing gene function.[26,27,28] One link is likely to be through cortisol. A study of 220 men and women 65-83 years old found a strong correlation between higher 24-hour urinary levels of cortisol and oxidative DNA damage.[29] Another recent report found that expression of the normal, non-mutated BRCA1 gene—which serves important breast tumor suppressor functions and when mutated, sharply increases breast cancer risk—is enhanced by connecting with the unoccupied

cortisol receptor. As cortisol levels rise, causing increased binding of cortisol receptors, BRCA1 activity is reduced.[30,31,32] Elevated cortisol levels may also influence breast cancer outcome. Cortisol levels normally vary diurnally, with higher levels in the morning and lower levels in the afternoon and evening. A study of 104 women with metastatic breast cancer showed that, compared to those whose cortisol levels dipped normally later in the day, women whose cortisol levels remained relatively constant were at risk of earlier death.[33]

Studies of stress as a risk factor for developing breast cancer

Many laboratory animal studies show stress-related changes in immune system function and various aspects of the tumor environment that are associated with increased tumor development and metastasis, as well as decreased response to chemotherapy and survival.[34] Studies of stress in humans find differing effects on markers of immune system function, depending on study design, age of participants, coping mechanisms, and the nature of the stress being investigated. Human studies generally distinguish between stress as a potential contributor to the onset of breast cancer or as an influence on breast cancer progression and prognosis.

Many people believe that stress can increase the risk of cancer generally and breast cancer specifically.[35] In epidemiologic studies, the hypotheses most commonly studied are that breast cancer risk increases with 1) major stressful life events (e.g. death of a loved one); 2) larger cumulative number of major life events; and 3) amount of self-perceived stress due to major life events. Many studies attempt to examine one or more of these connections, and their findings are inconsistent.

Several systematic reviews of the literature addressing stress as a causal contributor to the onset of breast cancer have been published.

- In 1999, Petticrew, et al. reviewed 29 studies of sufficient quality to meet a minimal set of criteria.[36] Fifteen were prospective studies, 14 of which were "limited prospective," meaning that stress exposure was assessed while participants were waiting for but did not yet know the results of a breast biopsy. Fourteen studies were case-control design. Combined analysis of twelve studies of bereavement as a source of stress found no association with breast cancer risk (Three of the studies identified a positive association, while nine did not.) Combined analysis of 15 studies examining other kinds of stress found that participants with breast cancer were more than twice as likely (OR 2.63; 95 percent CI 2.34-2.96) to report significant adverse life events. They included divorce or separation, job loss, financial problems, and interpersonal conflicts. When the analysis was limited just to studies of high quality, based on author criteria, no apparent relationship was found.

- A later meta-analysis used qualitative and quantitative data from 27 studies (10 retrospective case-control, 4 prospective case-control, 9 limited prospective cohort [participants waiting for biopsy results], and 4 prospective cohort studies).[37] The categories of stressful life events generally (OR 1.77, 95 percent CI 1.31–2.40), death of spouse (OR 1.37, 95 percent CI 1.10–1.71) and death of relative or friend (OR 1.35, 95 percent CI 1.09–1.68) were associated with a modestly increased risk of breast cancer. But after controlling for publication bias, death of a spouse was the only stressful event that remained significantly associated with increased risk.

At least some of the inconsistency in findings is likely to be due to differences in study design and variability in the measures of stress. For example, marital separation and divorce may be more stressful than bereavement after the death of a spouse.[38] Stress may have more marked effects on immune function when it is associated with depression.[39] Incorporating these and other more precise details into study design can be challenging.

Another limit of many studies follows from the latency period, perhaps as long as 15-20 years, between breast tumor initiation and when it becomes clinically apparent. Thus, studies that examine the influence of stressful events within the five years immediately before diagnosis are more likely measuring their impacts on tumor promotion than as an initial contributing cause.

Many studies also fail to consider the context in which major stressful events occur—an important component of the maladaptive stress model. For example, a limited prospective study of 514 women requiring follow up after a suspicious finding on mammography found no relationship between a major stressful event within the past two years and the likelihood of having breast cancer.[40] However, further analysis showed that a major stressful event in combination with lack of intimate emotional support was strongly associated with increased risk. Models that integrate stressful events with the capacity and resources to respond better accommodate the biology of stress than those addressing single variables independently.

The timing and duration of stress also appear to be important. A prospective study of 1213 women, averaging 43 years old at baseline, followed up14-16 years later, found that maternal death in childhood or lifelong depression with periods of severe exacerbation were independently strongly associated with increased risk of breast cancer.[41] In this study, recent stressful events were not associated with increased risk.

Another limited prospective study in Finland found that women with breast cancer were somewhat more likely to have reported more severe losses and cumulative stresses in childhood and adolescence than women with benign breast disease.[42]

Stress reduction and quality of life in people with breast cancer

Many investigators have explored stress reduction as a way to help improve the lives and survival of people with breast cancer. Adding to pre-existing sources of stress, a diagnosis of cancer and various aspects of treatment are themselves, of course, highly stressful. Cancer patients' ability to carry out daily activities decreases, distress and depression may increase, which depletes energy, disrupts sleep, and adds to fatigue. Survivors face fear of recurrence, managing treatment-related physical and emotional effects, maintaining or resuming an intimate relationship with a partner, maintaining or establishing a social support network, and reconsidering life's meanings. Documented links among psychological factors and immune system function, inflammation, blood vessel growth, and tumor promotion have led many investigators to wonder if psychotherapeutic interventions might help to reduce symptoms, delay recurrence, and increase survival.

Early trials of group therapy, self-hypnosis, and education reported improvements in mood, pain, anxiety, self-perception, and adjustment in people dealing with cancer.[43,44,45] Since then, many additional studies of varying quality have attempted to assess the value of adding psychotherapeutic interventions to the care of people with cancer.

A 1995 critical review by Fawzy and colleagues assessed the published literature examining the value of education, behavioral training, individual psychotherapy, and group interventions in the care of people with cancer.[46] They concluded that a variety of psychological therapies can help cancer patients in a variety of ways, saying,

> "A short-term, structured, psycho-educational group intervention is the model that we propose to be used for newly diagnosed patients and/or patients with good prognoses. The focus is on learning how to live with cancer. We also encourage the development of ongoing weekly group support programs for patients with advanced metastatic disease, based on the studies of Spiegel et al., that focus on daily coping, pain management, and dealing with the existential issues related to death and dying. Psychiatric interventions should be used as an integral part of competent, comprehensive medical care and not as an independent treatment modality for cancer."

A 2002 systematic review of the benefits of various forms of psychotherapy in cancer therapy began by noting a strong existing view that psychotherapies may help in the care of people with cancer by increasing their knowledge about their disease and treatment, improving emotional adjustment, quality of life, coping skills, satisfaction with care, physical health and functional adjustment; by reducing treatment-related and disease-related symptoms;

by increasing patients' compliance with traditional treatments; by improving indicators of immune system function; and by increasing the length of survival or time to recurrence.[47]

The authors identified hundreds of studies and, based on rigorous pre-established quality criteria, narrowed the final assessment to 34 trials with psychosocial outcomes, 38 trials with side effect outcomes, and 10 trials with survival or immune system outcomes. Based on their analysis, the authors made tentative recommendations for routinely incorporating psychological therapies in treatment to improve cancer patients' outcomes. They concluded that:

- In general, group therapy, education, structured and unstructured counseling, and cognitive behavioral therapy offer the most promise for their medium- and long-term (up to five-six years) benefits for many psychosocial outcomes.
- For anxiety reduction, structured or unstructured counseling, including music therapy, provides long-term benefits. Individual therapy, cognitive behavioral therapy, communication skills training, guided imagery, and self-practice of chosen interventions hold promise and warrant further exploration.
- Of all the strategies investigated, relaxation training, and guided imagery appeared to be most beneficial for reducing treatment-related side effects.
- Interventions involving structured or unstructured counseling and guided imagery improve patients' general functional ability and quality of life.
- Group therapy improves patients' coping or control skills and interventions involving relaxation training, cognitive behavioral therapy, and communication skills training warrant further exploration.
- Group therapy and cognitive behavioral therapy are beneficial for fatigue reduction.
- Although no intervention strategies clearly improved patients' length of survival, a number of interventions improved indicators of immune system function.

A more recent Cochrane review of individual psychosocial interventions intended to improve quality of life and reduce general psychological distress in the first 12 months after cancer diagnosis found modest but significant benefits.[48] Cochrane reviews use strict evidentiary criteria, and studies not meeting those criteria are not considered. In this review, only randomized controlled trials of psychosocial interventions involving interpersonal dialogue between a "trained helper" and individual newly diagnosed cancer patients were selected. Only trials measuring quality of life and general psychological distress were included. Trials involving a combination of pharmacological therapy and interpersonal dialogue were excluded, as were trials involving couples, family members or group formats. In the end, the review was based on 1249 people who took part in clinical trials to test psychosocial interventions.

The reviewers noted considerable variation in the style and delivery of psychosocial interventions—e.g. one or two discussions vs. ongoing contact; telephone vs. face-to-face interventions, etc. They said that the statistically combined results may be limited and susceptible to criticism because of this. They also concluded that risk screening would help to identify and target patients who are at most risk of emotional difficulties and, therefore, most in need of support, along with consideration of a range of possible intervention types to suit identified needs.

Stress reduction: influences on breast cancer recurrence and survival

In that chronic stress can impair immune system function, alter cellular signaling, promote inflammation, and stimulate blood vessel growth, it seems plausible that pre-existing and newly-added stress can enrich the tumor microenvironment and help to foster tumor recurrence, growth, and metastasis.[49]

An early prospective study of 208 white women with breast cancer, diagnosed 1958-1960, asked participants about objective and subjective stress and social support in the five years prior to diagnosis. The group was followed over 20 years. The relationships between stress and survival were examined for three age groups: 15-45, 46-60, and 61 and older. Objective stress was related to survival in the older group while subjective stress was related to survival in the youngest group. Neither was related to survival in women aged 46-60. When women aged 46-60 were eliminated from the analysis, stress and social involvement accounted for twice as much variance in survival as the stage of cancer at the time of diagnosis.[50]

A case-control study of 50 women with recurrent breast cancer reported that women with recurrent disease were nearly six times as likely to have experienced severe, stressful life events—including death of a spouse or child, divorce, or otherwise severe breakdown in family relationships—since their initial treatment, compared with 50 women whose breast cancer was in remission.[51] Less severe stressful events were associated with a two-fold increased risk of recurrence.

Many clinicians and investigators have wondered if stress reduction might not only improve the quality of life for breast cancer survivors but also reduce the risk of recurrence and lengthen time of survival. In 1984, Morgenstern and colleagues published one of the first studies that statistically evaluated the impacts of psychotherapeutic interventions on breast cancer survival.[52] It was a small retrospective study of 34 women with breast cancer and matched controls. The intervention consisted of group discussions, meditation, and mental imagery using drawings. Analysis showed a modest, statistically-insignificant survival benefit. In 1993 this group published a larger study finding no survival benefit of a weekly program of individual counseling, patient peer support, family therapy, and direction in relaxation, positive mental imagery, and meditation.[53]

Investigators have also prospectively examined the effect of supportive group therapy on survival in women with metastatic breast cancer.

- In 1989 Spiegel and colleagues reported the results of a prospective study of patients with metastatic breast cancer, showing that 50 women who had received weekly group therapy and who used self-hypnosis for pain management in addition to routine care survived an average of 18 months longer than 36 women who received routine care.[54] It was a small study, and when the same group attempted to replicate their findings with a larger number of participants, they found no added survival benefit with supportive-expressive psychotherapeutic interventions in the group analysis. However, a subgroup of women with ER negative tumors who participated in the intervention survived significantly longer than their counterparts who did not.[55] It's important to recognize that conventional breast cancer therapy was rapidly improving during this time period so that any benefits of psychotherapeutic interventions were likely to be more difficult to see and may well have been most beneficial in women with the most treatment-resistant disease.

- A recent randomized controlled trial of supportive-expressive group therapy, added to three classes in relaxation therapy in both the intervention and control groups, among 485 women with metastatic breast cancer at baseline, found that the intervention reduced and prevented depression, reduced hopeless-helplessness and trauma symptoms, and improved social functioning. It did not improve survival.[56]

- In another randomized controlled trial of 235 women with metastatic breast cancer, designed to replicate the work of Spiegel, et al., 158 participated in weekly supportive-expressive group therapy, while 77 did not.[57] All women received educational material and otherwise appropriate medical and psychosocial care. The group therapy intervention did not prolong survival but significantly improved mood and reduced pain perception, particularly in women who were more distressed at the outset of treatment.

- One long-term prospective study has examined the effects of a group psychosocial intervention on survival and recurrence in 227 women with non-metastatic breast cancer.[58] Women were randomized to standard care or 4 months of weekly group-based intervention and 8 months of monthly sessions. The intervention included relaxation and stress reduction exercises, coping skills training, and health behavior change related to diet and exercise. Intervention participants showed a significant reduction in overall and breast cancer-specific mortality as well as 45 percent reduced risk of cancer recurrence at an average of 11 years follow-up. Those who did experience recurrence were cancer free for an average of six months longer, after controlling for multiple variables. Among those who died from breast cancer, me-

dian survival time in the intervention group was 1.3 years longer. The psychosocial intervention caused alterations in some stress-related immune processes that could help to explain improved general health and altered disease course.[59] This study also shows the value of more comprehensive interventions, which not only help to reduce stress but also improve diet, exercise, sleep, and social support.[60] These will be further discussed in chapter 8.

Adding psycho-social interventions to routine cancer care increasingly shows a variety of benefits. Improved quality of life and reduced stress- and treatment-related symptoms are well documented in women with metastatic and non-metastatic breast cancer. Psycho-social interventions may independently contribute to delayed recurrence and improved survival for at least some people, particularly those with non-metastatic disease at the outset and perhaps for those with most treatment-resistant disease. The most beneficial designs of interventions, their timing, and identification of subgroups of individuals who will benefit most continue to be clarified.[61]

Body-mind-spirit; mindfulness-based stress reduction

Variations on body-mind-spirit interventions are increasingly employed as a component of conventional breast cancer therapy. Mindfulness is a way of paying attention—of consciously being aware of our experience, in the present moment, without judgments.[62] Mindfulness exercises use techniques like walking and breathing meditation, yoga, mindful movement, and psychological education. The intent is to help individuals become more aware of their thoughts and feelings so that instead of being overwhelmed by them, they manage them better.

Mindfulness-based stress reduction (MBSR) is a psycho-educational training initially developed by Kabat-Zinn for chronic pain patients and stress-related conditions.[63] It is a group program that can be conducted varying amounts of time—often for 8 weeks, with weekly 2.5-hours sessions and one full retreat day. The participants are given instructions for home practice.

A meta-analysis of nine studies examined the impact of using MBSR on perceived stress, depression, and anxiety in women with breast cancer.[64] Participants in the studies were 45-61 years old and more than 90 percent were Caucasian. Twenty-four studies were left out of the analysis because of inadequate data or other design flaws. The meta-analysis found that the use of MBSR significantly improved participants' mental health by reducing perceived stress, depression and anxiety. The effect was graded as moderate to large based on a scale (the Cohen scale) calculated from the difference of means in two populations, accounting for the standard deviation of the data. Another systematic review and meta-analysis limited to randomized controlled trials and using Cochrane review criteria for study inclusion also

found that the addition of MBSR to standard care significantly reduced depression and anxiety in women with breast cancer compared to standard care.[65]

Several studies examining physiologic changes in breast cancer patients who have participated in MBSR interventions report lower afternoon cortisol levels, a steeper diurnal cortisol pattern compared to controls, improvements in measures of the immune function, and/or reduced pro-inflammatory gene expression.[66,67,68,69]

Social support and stress reduction

Along with other interventions, strong social support can substantially help ameliorate the stress response and improve outcomes in women with breast cancer. Social support has both structural and functional dimensions.[70,71] Structural support refers to the size and complexity of the network of reciprocal relationships that an individual has with friends, relatives, and co-workers. The functional component has to do with what the network actually provides, such as information, tangible contributions and services, and emotional support. It may include information regarding medical care options, financial assistance, transportation, and childcare, along with the perception of being loved, valued, and cared for.

Studies of the impact of social support on cancer survival often distinguish between network size and how it is actually experienced by an individual with cancer. The association with marital status is sometimes examined separately. These studies are challenging because the size and perception of social support can be influenced by age, presence or absence of depression, and socioeconomic status, each of which can independently influence disease outcomes.

A 2010 meta-analysis of 87 studies addressing the association between social networks and cancer survival includes an excellent discussion of some of these challenges.[72] The authors found that having high levels of perceived social support, larger social networks, and being married were associated with decreases in the risk of mortality of 25 percent, 20 percent, and 12 percent, respectively. In subgroup analyses, they reported a stronger association with increased survival for larger network size (number of social contacts) in studies of breast cancer and increased perceived support in studies of lymphoma and leukemia.

Several additional studies are also available:

- In a population-based study of younger women with breast cancer, 584 were followed for up to 12.5 years.[73] The mean age at diagnosis was 44 years, 81 percent were married, and 29 percent were racial/ethnic minorities. They were participants in a psycho-educational intervention project addressing the needs of younger women soon after diagnosis, with evaluation of the association between social

support and disease progression. Although the size of their social network did not make a difference, women who reported increased contact with their social support network post-diagnosis experienced a 69 percent increased survival at up to 12.5 years, compared with those who maintained the same level of contact with relatives and friends. The authors concluded that increasing social contact and support may increase the likelihood of survival by enhancing coping skills, providing emotional support, and expanding opportunities for information-sharing.

- In an evaluation of 2,835 women 46-71 years old from the Nurses' Health Study who were diagnosed with stages one to four breast cancer, social networks were evaluated on three occasions over ten years.[74] Women who were socially isolated before diagnosis had a 66 percent increased risk of all-cause mortality and a two-fold increased risk of breast cancer mortality compared with women who were socially integrated. Women without close relatives, friends, or living children had elevated risks of breast cancer mortality and of all-cause mortality. Participation in religious or community activities or having a close confidant was not related to outcomes. The authors concluded that socially isolated women were likely to have an elevated risk of mortality because of a lack of access to beneficial care-giving from friends, relatives, and adult children.

- A group of 2,264 women, average 58 years old, from the Life After Cancer Epidemiology study who were diagnosed with early-stage, invasive breast cancer between 1997 and 2000, were evaluated for associations between social network size and function and disease progression over an average of 10.8 years of follow up.[75] Socially isolated women did not have an increased risk of recurrence or breast-cancer specific mortality but did experience higher all-cause mortality. Among those with low levels of social support from friends and family, lack of religious/social participation and lack of volunteering were associated with higher all-cause mortality. Small networks and high levels of support were not associated with higher mortality, consistent with other studies showing that the quality of support, independent of network size, has value.

- A population-based, multi-center, case-control study of 4,589 women with invasive breast cancer found that higher scores on a composite measure of social connectedness as determined by the frequency of contacts with family and friends, attendance of religious services, and participation in community activities was associated with a 15–28 percent reduced risk of death from any cause over an average of 5.6 years of follow up.[76] No significant associations were found between social networks and breast cancer-specific mortality. The average age of study participants was 59 years; about 75 percent were post-menopausal.

- An analysis of the association of social networks and survival in 4,530 women, average 64 years old, who were participants in the Women's Health Initiative study, found that in those with high levels of social support, being married was related to lower all-cause mortality.[77] In contrast, among women with high social burdens, those with a higher number of first-degree relatives, including siblings, parents, and children, had higher all-cause and breast cancer-specific mortality. The authors concluded that social relationships may have both beneficial and adverse influences on breast cancer survival, depending on the context of women's relationships.

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Section 3

Re-designing for Prevention and Healing

Chapter 8

Designing for breast cancer prevention and improved outcomes

Breast cancer has long been described as a malignant disease of cells related to hormones, in which an individual's maturation, reproductive history, and behavior play dominant roles. But this narrative is woven into a far more general, complex fabric of communities and society. Breast cancer increases when people in countries with low rates adopt U.S.-Western styles of eating, working, moving around, communicating, making and using consumer products, and general living. This is apparent, for example in Japan, China, and Greenland, where recent breast cancer rates have increased sharply compared to historic patterns.[1,2,3] Breast cancer risk increases in people who migrate from low-incidence to high-incidence countries—particularly when they migrate at a younger age. Within two generations, immigrants are generally as likely to develop breast cancer as people who are native-born. One, two, or even several variables do not explain these realities.

To a large extent breast cancer, like other common complex diseases, arises out of intertwined societal conditions largely of our own making. This chapter looks at steps that people might take in their personal lives as well as other opportunities to re-design community and societal conditions in ways less likely give rise to breast cancer and improve outcomes after diagnosis and treatment.

Generally accepted individual risk factors, briefly discussed in Chapter 2, are simply insufficient to explain differences in breast cancer patterns around the world. An ecological framework is better suited—one in which multiple, multi-level variables collectively inter-

act to create a context in which breast cancer is more or less likely to occur. Appropriate interventions and a more informed research agenda can follow.

Additional breast cancer risk factors for which the strength of evidence varies from strong to probable to plausible—certain kinds of diets, inadequate physical activity, exposures to certain environmental chemicals or contaminants, non-ionizing radiation, inadequate vitamin D status, shift work, light at night, and stress, and their societal determinants, also help shape conditions that foster vulnerability to the disease and less favorable outcomes. Many of these can only partially be addressed by changes in individual behavior. Multi-level public health and policy interventions at the population level are also necessary in order to re-design system conditions in more favorable ways. To illustrate:

- People are often exposed to chemicals that are mammary gland carcinogens in animal studies. These exposures can occur during fetal development, in the workplace, and in the everyday life of children and adults. With virtually no requirement for pre-market safety testing of most chemicals in commerce*, it's difficult to see this as anything but societal failure to protect the general public from exposure to hazardous chemicals almost certain to increase breast cancer risk.

- Over many years, federal subsidies and insurance programs for commodity crops like wheat, corn, and soy beans, but not for fruits and vegetables, have handicapped produce growers and promoted crops used disproportionately in cheaper, processed, unhealthy junk food. The resulting food environment increases the risk of cancer, obesity, diabetes, cardiovascular disease, cognitive decline, and dementia. This is a predictable result of the way we have designed today's dominant food system.

- Lack of safe sidewalks and nearby parks and recreation areas result in reduced physical activity levels of neighborhood residents.[4] Physical activity breaks in school not only improve student fitness but also improve school performance, yet they are increasingly absent because of budget cuts or different priorities.[5,6] Their benefits are lost, and the message to children is that exercise doesn't really matter much.

* Pharmaceuticals and pesticides undergo required safety testing before being allowed onto the market. Even among these chemicals, however, their impacts on the mammary glands of laboratory animals or breasts of humans are poorly evaluated pre-market. Other industrial chemicals, including those produced and used in high volumes in various consumer products, are not required to undergo any pre-market safety testing. The problem is particularly acute for thousands of chemicals that have been on the market for decades without adequate evaluation. Current Federal regulatory authority to address the concern is extremely limited. New legislation, recently introduced in the Senate, is under consideration.

Opportunities to prevent breast cancer and to improve outcomes in breast cancer survivors are readily available. Future research will no doubt help clarify which combinations are most effective, but it's clear that more than individual behavioral change is necessary. Communities and society as a whole must also be involved.

Making sense of complexity

The biology of breast cancers includes differences as well as similarities. Pre- and post-menopausal breast cancers share many but not all risk factors. The distribution of sub-types of breast cancer differs among racial and ethnic groups. Some tumors are more aggressive than others. Treatment varies. Despite this variability we're learned some important general lessons:

- Preventing breast cancer requires an historical, life-course perspective, certainly beginning with fetal development and, in all likelihood, including aspects of the health of parents and grandparents.

- With few exceptions, one, two, or several individual-level risk factors are relatively poor at predicting whether or not a person will develop breast cancer or explaining population trends and variability among populations. This disease is unlike cancer of the lung where a high-impact exposure like cigarette smoking can be a major focus for prevention. When multi-level, interacting variables contribute somewhat similarly to risk, it's a more systemic problem that must be approached differently.

- Multi-level, ecologic models are best suited for understanding the origins of breast cancer and for designing strategies to prevent it and improve outcomes after diagnosis. This is precisely the kind of problem those models are intended to address. Individuals, families, and communities can use an ecological framework to help them decide what to do. Multiple, multi-level interventions, based on a general understanding of system dynamics, are more likely to shift those dynamics in favorable ways, making breast cancer less likely and improve outcomes after diagnosis—in an individual or across an entire population.

- This complexity also means that understanding cause-and-effect relationships in breast cancer development and response to treatment interventions will always be clouded by some degree of uncertainty. It does not yield to precise, granular analysis. That need not be nor should it be a reason for failing to act, based on available information.

Thinking of breast cancer as a disease arising from complex system conditions seems overwhelming at first. Models of interactions among many, multi-level variables related to breast cancer are messy. Graphic representations are usually a tangle of arrows pointing here and there with everything interconnected. They are difficult to interpret and it's worth asking, why even do this?

First, it helps to acknowledge and communicate complexity. It confirms the multi-level, systemic nature of the problem. This highlights the need for broad, diversified efforts to study and change the dynamics of the system. Individuals cannot do this alone.

Second, it helps in making sense of the complexity. Once a general, top-level architecture becomes clear, it can be a screen for sifting through relevant variables in order to plan further study and interventions.

Third, seeing the origins of breast cancer as a problem entailing complex systems dynamics helps to shape thinking about ways and places to intervene most effectively. Systems science highlights leverage points, feedback loops, and causal cascades as particularly influential targets.[7] That is not to say that single, proximate variables are unimportant. We should do what we can, for example, to reduce unnecessary ionizing radiation exposure, particularly in children, adolescents, and young adults when they are more vulnerable to radiation-induced cancer, as a matter of personal choice and medical and public policy. But we can also look upstream at the beginning of causal cascades with multiple downstream impacts—the food system and individual diets, the built environment and physical activity, the material economy and environmental chemical exposures, and so on. Then we can better design interventions with the intention of reaping multiple downstream benefits.

Re-designing the terrain

All levels, individual to societal, contribute to the shape of system conditions—the terrain—that increase or decrease the likelihood of breast cancer, its recurrence, or progression. (see Box 8.1). Opportunities to re-design the topography of that terrain begin with fetal development and continue through childhood, adolescence, and well into adulthood. They feature time-windows of vulnerability, when many influences, independently and collectively, can push breast biology toward malignant transformation and tumor growth or conversely, toward resilience and decreased risk. Efforts to change the design of that terrain can continue throughout life, so that breast cancer or its recurrence after initial treatment is less likely. Well-designed interventions can have the added benefit of helping to reduce the risk of other diseases as well. But they cannot be accomplished by individuals alone. Public health strategies to re-shape the terrain are essential and must include community organiza-

BOX 8.1: The biologic terrain

"Biologic terrain" is a concept that comes from Antoine Béchamp, Claude Bernard, and Louis Pasteur. Bernard described the *milieu intérieur*—the internal physiologic environment and its relevance to health and disease. Pasteur formulated the germ theory of disease and emphasized the invasion of the body by external "germs" as an explanation for illnesses. Béchamp argued that germs could not invade a host and create disease without internal host susceptibility.

It is widely claimed that, on his death bed, Pasteur said, "Bernard [or Béchamp] was right. The pathogen is nothing. The terrain is everything" ("*Le microbe n'est rien, le terrain est tout*"). Pasteur had come to realize how critical the internal terrain is to the susceptibility to infectious diseases. This concept can be broadened beyond the biologic terrain of individuals to include the eco-social terrain in which people live. That, too, helps shape the *milieu intérieur*. It is also applicable to most non-infectious as well as infectious diseases. The eco-social terrain is a major determinant of who gets sick or remains healthy.

tions, governments, businesses, schools, and health care institutions in more comprehensive, multi-level approaches.

These summaries of specific risk factors are based on more detailed material from previous chapters. Supporting references are not repeated here. This is not intended to be medical advice since individuals' needs, health status, and circumstances vary. But, these summaries can offer general guidance, based on what is known about the associations of each variable with breast cancer onset and prognosis after diagnosis and initial treatment.

Diet, nutrition, and the food environment (Chapter 3)

These conclusions are based on the findings of many studies examining links between diet and breast cancer reviewed in Chapter 3. In addition to serving as a guide for individuals and families, health care professionals, food-service providers, local, state, and federal government officials, and other policy makers should be able to identify opportunities they have to use this information to help improve diets and nutritional status in people of all ages. In general, following these guidelines is likely to improve health in other ways as well, although some individuals may have health conditions for which they are not appropriate.

- Beginning in childhood, emphasize consumption of fruits and vegetables. Yellow and orange fruits and vegetables and leafy greens are particularly beneficial as they contain higher levels of carotenoids. Many studies show foods containing higher levels of carotenoids and associated substances to be beneficial for health general-

ly. Studies also find a lower breast cancer risk and improved outcomes following diagnosis and initial treatment with higher baseline carotenoid levels. Whether the observed association between higher levels and reduced breast cancer risk is causal is still somewhat uncertain since the data are largely from observational studies, and carotenoids could also be a marker for other dietary factors associated with decreased risk.[8] But the data are quite consistent, and even in women diagnosed with breast cancer higher baseline serum levels of carotenoids are associated with improved prognosis following initial treatment. This does not mean that carotenoid supplements should be used as a replacement for regular dietary sources since foods containing high levels of carotenoids have other beneficial nutrients as well. Fruits, including berries, also contain a variety of highly beneficial nutrients.

- Total fat should be limited to 20-35 percent of dietary calories. Total dietary fat, at least in adulthood, is only weakly linked to breast cancer risk, but various sub-types of dietary fat have very different health consequences.

  - » Trans fats should be limited as much as possible. They are clearly associated with increased risk of breast cancer and coronary heart disease.

  - » Polyunsaturated fatty acids (FAs) are necessary and beneficial but excessive intake of omega 6 FAs compared to omega 3 FAs may actually increase breast cancer risk. This is clearly true in animal studies, although the evidence from epidemiologic studies is somewhat inconsistent but quite suggestive. Since the diet of most people contains a large excess of omega 6 FAs compared to omega 3s, ingestion of food containing omega 3 FAs should be increased while omega 6 FA consumption is reduced. Certain cold-water fish, like wild salmon and sardines, are a rich source of beneficial long chain omega 3 FAs.* Walnuts also contain beneficial omega 3 FAs. Of the common vegetable oils, soy oil contains only about seven percent omega 3 FAs and canola oil slightly more at 10 percent. Corn, safflower, and sunflower oils generally contain less than one percent omega 3 FAs. Reducing consumption of processed and fast foods and some polyunsaturated vegetable oils—corn, sunflower, safflower, soy, and cottonseed, for example—will help reduce omega 6 FA intake to healthier levels.

* Some marine and freshwater fish are contaminated with hazardous environmental chemicals such as methylmercury, polychlorinated biphenyls, and flame retardants that should be avoided. Consumers should check state fish advisories and information on the Food and Drug Administration website for information about fish species to avoid.

» Monounsaturated fatty acids, such as oleic in extra virgin olive oil, are beneficial and should also be emphasized as a replacement for oils high in omega 6 FAs. Olive oil is prominent in the Mediterranean diet, which is fairly consistently associated with lower breast cancer risk.

» Low-fat dairy is a good option for reducing total energy intake. Some studies show that higher levels of animal fat from dairy and red meat in adolescence and young adulthood are associated with increased risk of premenopausal breast cancer.

- Limit red meat and avoid processed meat consumption, beginning in childhood, as this is likely to reduce breast cancer risk and will have multiple additional benefits throughout life, including reducing the risk of colon cancer and cardiovascular disease.[9,10] Some experts recommend that red meat should be consumed only occasionally, if at all.[11] In addition to saturated fat content, other properties of meat could explain its associations with health effects demonstrated in epidemiologic studies. Some people are concerned about steroid hormone residues present in meat from these animals, even when good veterinary practices are followed.[12] Whether or not these residues are biologically significant to meat eaters is unresolved. Most but not all beef production in the United States utilizes growth promoting hormones. When cooking meat, avoid charring since this creates known carcinogens. Nuts, fish, poultry, and legumes are good protein replacement sources.

- Include consumption of traditional soy products including tofu and fermented miso and tempeh, beginning in childhood, based on evidence of reduced breast cancer risk associated with higher dietary levels. Several studies show that childhood dietary soy is associated with even lower breast cancer risk than soy in adulthood. This does not, however, pertain to infant soy formula, where the impacts on cancer risk are largely unexplored. Nor does it pertain to heavily-transformed soy product additives in processed foods. Processed foods often contain soy oil or soy protein isolates, which don't resemble traditional soy products consumed for centuries in countries with historically low rates of breast cancer. Organic soy products are available for people who want to avoid genetically-modified food and pesticide residues.

- Consider adding seaweed and mushrooms to diets on a regular basis as the few available studies consistently show an association with lower breast cancer risk.

- Dietary carbohydrates are not directly linked to breast cancer risk, but a diet with excessive refined carbohydrates can cause repetitive, exaggerated spikes in insulin secretion and increase the risk of diabetes.[13] Diabetes increases the risk of breast

cancer. Elevated insulin levels can also promote breast cancer. Moreover, in the context of insulin resistance and overweight, a high-carbohydrate diet can also increase triglycerides and reduce high-density lipoprotein (HDL) cholesterol ("good" cholesterol), increasing the risk of coronary heart disease. Compared to refined sugar and carbohydrates common in processed food and beverages, whole grains are healthier as they are a source of fiber and other micronutrients, less likely to cause spikes in insulin secretion, and are associated with lower risk of heart disease and diabetes.

- In individuals with insulin resistance or elevated fasting blood sugar (type 2 diabetes or pre-diabetes), efforts to improve insulin sensitivity may be particularly helpful, including after diagnosis and initial treatment of breast cancer. A heart-healthy or Mediterranean-like diet with emphasis on fruits, vegetables, nuts, whole grains, olive oil, low-fat dairy, and fish, with minimal red meat and refined carbohydrates helps to improve insulin sensitivity and reduce diabetes onset, even in people at risk.[14,15,16] In addition to dietary changes, exercise, and weight loss, clinical trials using metformin, a pharmaceutical for treating type 2 diabetes, for prevention or as part of the treatment of breast cancer are currently underway. Metformin improves insulin sensitivity and lowers blood glucose levels. Some clinicians already use metformin as one component of a more comprehensive approach to prevent or treat various kinds of cancer.

- Breast feeding infants for at least six months is not only beneficial for the long-term health of the child but is also associated with multiple maternal benefits, including a reduced risk of breast cancer.[17,18]

- Limit alcohol intake. Alcohol consumption is generally accepted as a risk factor for developing breast cancer. However, the risk of alcohol consumption after diagnosis and treatment is much less clear. Some studies show that the risk of consuming more than three-four drinks/week after breast cancer diagnosis may increase the risk of recurrence[19] while others do not and actually show reduced risk of cardiovascular and all-cause mortality with limited alcohol consumption.[20]

For recipes and further information see *The Cancer Fighting Kitchen: Nourishing big-flavor recipes for cancer treatment and recovery*[21] and cookbooks available through the American Cancer Society.[22]

How well are we doing?

General consensus from virtually every profession finds that today's typical U.S. diet features too many calories and unhealthy and often excessive dietary fats, salt, sugar and other

refined carbohydrates, combined with inadequate fruits and vegetables, healthy fats, whole grains, and micronutrients (see Box 8.2). This dietary pattern contributes substantially to a range of costly diseases and disorders—including obesity, diabetes, cardiovascular disease, cognitive decline, dementia, other neurodegenerative disorders, and various kinds of cancer.[23,24,25,26]

BOX 8.2: A brief summary of current U.S. dietary patterns and trends

- In 2000, on average, individuals in the US consumed roughly 300 more calories every day than in 1985.[27] Since 1970, average daily intake of calories from added fats and oils has increased by 69 percent, driven primarily by increases in salad and cooking oil consumption. Soy oil, in salad dressings, processed food, and for cooking comprises 68 percent of the fats and oils that Americans eat.[28]

- According to the Center for Disease Control and Prevention, fewer than 25 percent of people in the U.S. consume at least five servings of fruits and vegetables daily. This has been relatively constant over the past fifteen years.[29] There is, however, significant variability among states and the CDC encourages states to adopt policies that will promote fruit and vegetable consumption and make them more accessible.[30]

- Total per capita meat consumption in the U.S. is among the highest in the world and steadily rose from 1960 to 2007. It has fallen about 12 percent in the last five years.[31] Declines in beef and increases in poultry consumption are most notable. Twenty-two percent of the meat consumed in the U.S. is processed.

- Per capita consumption of refined sugars and sweeteners has steadily increased. According to the USDA, sugar and sweeteners continue to represent about 36-40 percent of the steadily growing U.S. per capita consumption of carbohydrates.[32]

What people eat is decided by a mix of availability, cost, convenience, taste, and preferences, shaped by agricultural policy, media, advertising, and culture. For decades, agricultural policy has made relatively inexpensive, calorie-rich, nutrient-poor food more readily available to people across the country.[33] Farm policies have favored large commodity crops like soybeans, corn, and wheat, while lacking incentives for growers to increase fruit and vegetable production. A 2008 report from the U.S. Federal Trade Commission concluded that the food industry spent nearly two billion dollars annually marketing food to children and adolescents.[34] The majority of these ads (72 percent) promote foods of low nutritional quality, even though 53 percent include a health-benefit claim.[35]

Individuals can of course be encouraged to make healthier food choices, but clearly there are unrealized opportunities for shaping food and agricultural policy in ways that make healthy choices more affordable, accessible, and desirable. These efforts must address the entire life course—beginning with fetal development. In addition to agricultural policy reforms, state and local governments, individuals and organizations in health care delivery, childcare, schools, and communities more generally have critical roles to play to encourage and enable healthier food consumption.

Physical activity and exercise (Chapter 4)

Strong evidence shows risk reductions of 20-80 percent for post-menopausal breast cancer with increasing physical activity. Evidence for exercise-related prevention of pre-menopausal breast cancer is not as strong. Most studies show that increasing levels and duration of physical activity increase the benefit. For example, one review finds that moderate-to-vigorous intensity physical activity two-three hours/week is associated with an average breast cancer risk reduction of nine percent, compared to 30 percent decreased risk with 6.5 hours/week or more.[36]

Strong evidence, including results from randomized controlled trials, shows that regular exercise also improves numerous measures of health and well-being from the time of a diagnosis of cancer throughout the pre-treatment and treatment periods and beyond. In short, regular exercise not only helps to prevent cancer but also improves health and well-being after the diagnosis and initial cancer treatment.

The American Institute for Cancer Research (AICR) and the World Cancer Research Fund recommend 60 minutes of moderate-intensity or 30 minutes of vigorous-intensity exercise daily to reduce cancer risk.[37] The American College of Sports Medicine recommends healthy adults and cancer survivors perform a minimum of 30 minutes of moderate-intensity exercise five days a week to promote health.[38,39]

Here are some ways people can meet exercise recommendations in a week, according to the Physical Activity Guidelines for Americans:

- Take a brisk walk for 30 minutes on five days (moderate intensity); exercise with resistance bands two days (muscle strengthening).
- Run for 25 minutes three days (vigorous intensity); lift weights on two days.
- Take a brisk walk for 30 minutes two days (moderate); go dancing for an hour one evening (moderate); mow the law for 30 minutes (moderate); do heavy gardening two days (muscle strengthening).

- Do 30 minutes of an aerobic dance class (vigorous); do 30 minutes of running one day (vigorous); take a brisk walk for 30 minutes one day (moderate); do calisthenics (sit-ups, push-ups) on three days.
- Bike to and from work for 30 minutes on three days (moderate); play softball for 60 minutes one day (moderate); use weight machines two days.

How well are we doing?

Unfortunately, most children, adolescents, and adults are not regularly physically active. According to the Centers for Disease Control and Prevention, most children and adolescents aged nine-13 years do not participate in any organized physical activity during nonschool hours.[40] A 2009 survey indicated that only 18 percent of high school students had been physically active for 60 minutes every day in the previous week. Only 33 percent of high school students nationwide attended physical education classes 5 days/week compared to 43 percent of students in 1991. In 2005, fewer than 15 percent of children and adolescents walked or bicycled to and from school.

A 2011 survey relying on self-reports found that only about 20 percent of U.S. adults met the 2008 guidelines for both aerobic and muscle-strengthening physical activity. Nationwide, about half of U.S. adults met the aerobic activity guideline—at least 150 minutes per week of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity. About 30 percent of adults met the guideline of muscle-strengthening activities at least two times per week.[41] Based on actual measurements of physical activity rather than self reports, only about 10 percent of adults engage in 150 minutes or more of moderate physical activity weekly.[42]

Clearly we have a long way to go to meet generally accepted physical activity guidelines that will not only reduce cancer risk but also the risk of many other chronic conditions, including cardiovascular disease, diabetes, cognitive decline, and dementia. And, it's not just an issue for adults. Increased physical activity improves academic performance among children and is central to efforts to reduce childhood obesity.[43,44]

Physical activity levels are not just a matter of personal choice and behavior; policies at all levels influence them (see Box 8.3). Partnerships are often necessary to improve conditions, services, and environments that enable physical activity. They can establish bike paths, parks, recreation programs, and infrastructure design and maintenance standards. Most studies find that cycling infrastructure, trails, and park upgrades lead to increased physical activity.[45]

According to the Institute of Medicine and the Centers for Disease Control, given the implications for the overall health, development, and academic success of children, schools should also play a primary role in ensuring that all students have opportunities to engage in

vigorous or moderate-intensity physical activity at least 60 minutes daily.[46,47] Churches can also become involved in promoting healthy levels of physical activity for all ages.[48,49]

BOX 8.3: What influences physical activity levels?

Total physical activity levels are a composite of activity at home, in the workplace, in transport, and during leisure time. Most research into influences on physical activity levels has focused on leisure activity and transport. Variables from all levels seem to matter—individual, interpersonal, the social, natural, and built environments, policies, social and cultural norms, global media, and marketing.

At the personal level

- In adolescents, increased physical activity levels correlate with male sex, higher previous physical activity levels, self-efficacy, and family and social support.[50,51] Self-efficacy—confidence in the ability to be physically active in specific situations—seems to be a particularly strong influence in children and adolescents.

- In adults, health status and self-efficacy are the strongest associations with physical activity levels, followed by personal history of physical activity during adulthood and intention to exercise. Male sex, higher education level, and social support are also associated with higher physical activity levels. Self-efficacy is linked to motives related to mastery, physical fitness, social aspects of physical activity, psychological state, enjoyment, and willingness to be fitter and look better than others.[52] Being overweight, perceived effort, job strain, long working hours, and stress are associated with lower exercise levels.

Environmental attributes also influence leisure time physical activity levels

- For children, neighborhood walkability, traffic speed and volume, land-use mix (proximity of homes to destinations such as shops), residential density, and access to recreation facilities are the strongest associations.[53]
- For young people, neighborhood design, availability of recreation facilities, and the transportation environment are the strongest associations.
- For adults, availability and location of recreation facilities, the transportation environment, and aesthetics are most strongly associated with physical activity levels.

Studies have not clearly identified environmental features consistently associated with physical activity levels among older adults. But this is an area of intense interest as part of rapidly growing efforts to develop and implement a national agenda related to the public health aspects of healthy aging.[54] Efforts are underway in cities around the country. There also appear to be cultural differences. Physical activity increases with age as people retire in some Asian nations.[55]

Environmental chemicals and contaminants (Chapter 5)

Historically, interest in exploring connections between environmental chemicals and breast cancer has been slow to develop, even though a chemical, dimethylbenz(a)anthracene, was used to create the first animal model of breast cancer more than 75 years ago. Most laboratory animal and epidemiologic studies have focused on exposures in adults. According to a report from the Institute of Medicine, the strongest existing epidemiologic evidence related to chemical exposures shows increased breast cancer risk from combination hormone therapy products, current use of oral contraceptives, alcohol consumption, and tobacco smoking.[56] Evidence linking passive smoking, other organic solvents, ethylene oxide, polycyclic aromatic hydrocarbons (PAHs), 1,3 butadiene, and some agricultural chemicals to breast cancer is increasingly persuasive. Over 200 chemicals have been identified as mammary gland carcinogens in at least one well-conducted laboratory animal study, but few of these have been examined in epidemiologic studies in people.[57]

Adult exposures are of course important, but a life-course perspective, beginning with *in utero* fetal development, is essential for identifying the connections between chemicals and breast cancer more completely. Laboratory animal studies show that early-life chemical exposures can alter mammary gland development, increasing the risk of cancer in adulthood. Bisphenol A, cadmium, perfluorinated compounds, dioxins, and diethylstilbestrol are examples of this. Human studies are limited, but data show that fetal exposure to diethylstilbestrol (DES) and, in all likelihood, early life exposures to DDT increase breast cancer risk. These examples show that a comprehensive breast cancer prevention agenda must include attention to chemical exposures beginning with fetal development and continuing through childhood, adolescence, and adulthood. This perspective has gained broad support and is slowly leading to fundamental changes in breast cancer research.

Chemicals identified as mammary gland carcinogens as well as those that can modify breast development and increase cancer risk are encountered in consumer products, food, water, various workplace settings, and the general environment. Unfortunately, it is virtually impossible for people to know the identity of or keep records of their exposures to potentially hazardous chemicals in daily life. Bio-monitoring studies of blood, urine, breast milk, or other tissues can identify specific chemicals and levels of exposure in workers or the general population, but with the exception of persistent compounds, they give only a snapshot of what's present at the time of testing and no information about earlier exposures.

Except for substances like alcohol or tobacco smoke, the names of substances linked to cancer in animal or human studies are likely to be unfamiliar to many people. Moreover, manufacturers are not required to disclose the chemical makeup of many consumer products, claiming it to be "confidential business information." And, with the exception of pharmaceuticals, pesticides, and some food additives, no premarket safety testing of chemicals

in consumer products is required, making it difficult for people to make more informed decisions about what they are purchasing.

There are some differences in the workplace. Under the Hazard Communication requirements of the Occupational Safety and Health Administration regulations, workers are entitled to access to Material Safety Data Sheets (MSDS) that will help them identify the chemicals they may be exposed to at work.[58] Although MSDS are often incomplete with regard to health effects, they do enable workers to identify the name(s) of chemicals produced or used in their workplace. They can then further investigate toxicity concerns in various databases or discuss them with an informed health care provider.[59]

Some states have undertaken efforts to identify and reduce exposure to hazardous chemicals, including carcinogens. For example, California's Office of Environmental Health Hazard Assessment maintains a list of chemicals known by the state to cause cancer or reproductive harm.[60] The Washington state Department of Ecology has generated a list of persistent, bioaccumulative, toxic chemicals (PBTs) with the intent of phasing out their use, release, and exposures in order to reduce and eliminate threats to human health and the environment.[61] Some of the listed PBTs are carcinogens. The Maine Department of Environmental Protection and the Minnesota Department of Health have also generated lists of chemicals of concern.[62,63]

In Massachusetts, the Toxics Use Reduction Act (TURA) program is an effort to reduce the use of toxic chemicals in companies and communities. Under TURA, Massachusetts companies that use or manufacture large quantities of any one of nearly 1,500 listed chemicals are required to: (1) report their use and release of these chemicals every year; (2) prepare a Toxics Use Reduction Plan every two years describing how they can reduce their use of them. A recent report identifies uses and trends of chemicals reported to the TURA program that may cause cancer.[64,65] Those linked specifically to breast/mammary gland cancer in at least one laboratory animal or epidemiologic study include:

1. 1,2-dibromo-3-chloropropane
2. 1,3-butadiene
3. 1,4-dioxane
4. 2-methylaziridine
5. 3.3'-dichlorobenzidine dihydrochloride
6. 4.4'-methylene bis(2-chloroaniline)
7. Acrylonitrile
8. Benzene
9. Carbon tetrachloride
10. Methylene chloride
11. Dioxins
12. Ethylene dichloride
13. Ethylene oxide
14. Hexachlorobenzene
15. Hydrazine
16. Nitrobenzene
17. o-aminoazotoluene
18. Polychlorinated biphenyls
19. Styrene monomer
20. Toluene diisocyanate

Consequently, Massachusetts workers and communities have access to more locally relevant chemical information and can take steps to reduce exposures. State efforts to identify chemicals of concern will hopefully lead to their replacement with safer alternatives.

Recognizing the importance of protecting the developing fetus from chemical exposures, the Royal College of Obstetricians and Gynecologists in the United Kingdom recently published a position paper addressing concerns of expectant parents who want to do what they can.[66] They say:

> "Epidemiological research has linked exposure to some of these chemicals in pregnancy with adverse birth outcomes; pregnancy loss, preterm birth, low birth weight, congenital defects, childhood morbidity, obesity, cognitive dysfunction, impaired immune system development, asthma, early puberty, adult disease and mortality (cardiovascular effects and cancer)."
>
> "Under normal lifestyle and dietary conditions, the level of exposure of most women to individual environmental chemicals will probably pose minimal risk to the developing fetus/baby. However, women who are pregnant are exposed to hundreds of chemicals at a low level. Potentially, this exposure could operate additively or interactively and raises the possibility of 'mixtures' effects. On present evidence, it is impossible to assess the risk, if any, of such exposures. Obtaining more definitive guidance is likely to take many years; there is considerable uncertainty about the risks of chemical exposure. The following steps would however reduce overall chemical exposure:
>
> - use fresh food rather than processed foods whenever possible;
> - reduce use of foods/beverages in cans/plastic containers, including their use for food storage.* (Comment: This will help reduce exposure to bisphenol A and other additives that can leach into food or liquids resulting in direct human exposure);

* Most food and beverage cans are lined with a resin that can leach bisphenol A (BPA) into the container contents, which is then directly ingested. Recently, the Food and Drug Administration has banned BPA from infant formula packaging but this does not address the problem of fetal exposure resulting from maternal ingestion of BPA-contaminated food or beverages. Free, biologically active BPA has been repeatedly measured in umbilical cord blood and amniotic fluid, showing that the chemical crosses the placenta, exposing the developing fetus. Animal studies show that in utero exposure to BPA alters mammary gland development, thereby increasing cancer risk later in life. (chapter 5)

- minimize the use of personal care products such as moisturizers, cosmetics, shower gels and fragrances (Comment: This will help reduce exposure to chemicals that have been linked to developmental abnormalities, primarily in animal tests. However, some manufacturers have reformulated their products in response to concerns. See the Skin Deep data base referenced below);
- minimize the purchase of newly produced household furniture, fabrics, non–stick frying pans, and cars whilst pregnant/nursing;
- avoid the use of garden/household/pet pesticides or fungicides (such as fly sprays or strips, rose sprays, flea powders);
- avoid paint fumes;
- only take over–the–counter analgesics or painkillers when necessary; and
- do not assume safety of products based on the absence of 'harmful' chemicals in theiringredients list, or the tag 'natural' (herbal or otherwise).

Despite uncertainty surrounding the effects of common environmental chemicals, mothers should be made aware of the sources and routes of exposure, the potential risks to the fetus/baby and the important role that the mother can play in minimizing her baby's chemical exposure. Such information should be conveyed routinely at infertility, antenatal and well woman clinics as well as via the media. In this way, women will be made aware of the uncertainties which will enable them to make informed choices regarding lifestyle changes which can be made to minimize environmental chemical exposure to their unborn child."

This position paper from a large, international medical organization gives good general guidance to people who want to reduce exposures to potentially hazardous chemicals in their daily lives. It could be supplemented with advice to make certain that drinking water is free of dangerous contaminants, particularly for people who have private wells. And, reduction in workplace exposures to potentially hazardous chemicals could also be added to this list. Unfortunately, many women and men who are exposed to known, probable, or possible carcinogens in their workplace are fearful of losing their jobs if they push too hard for exposure reduction or elimination.

This discussion also implicitly acknowledges important chemical safety data gaps and shortcomings in regulatory systems in the U.S. and abroad: fetuses, infants, children, adolescents, and adults are routinely exposed to environmental chemicals of concern and many that have not undergone adequate safety testing before entering the market. In the U.S., Federal regulations are outdated and ineffective for most industrial chemicals.[67]

Recently, interest in regulatory reform in the U.S. has gained some momentum at the state and Federal levels. But, truly protective measures are broadly opposed by many chemical and product manufacturers who are concerned about economic competitiveness and maintaining trade secrets. They argue that requirements for pre-market safety testing and disclosure of results would put them at a competitive disadvantage. Now, consumers make purchasing decisions in the context of considerable ignorance and uncertainty about the safety of what they are buying, and that seems likely to continue.

A number of other organizations concerned about environmental chemicals and their relationship to breast cancer risk have made available resources that will help individuals make more informed personal decisions with respect to purchases and use of consumer products. They include, but are not limited to:

- **The Silent Spring Institute** (http://www.silentspring.org/): This organization has an extensive catalog of resources at http://www.silentspring.org/our-publications.
- **The Breast Cancer Fund** (http://www.breastcancerfund.org/): Among an array of resources, this organization publishes "State of the Evidence: The connection between breast cancer and the environment", which is newly updated and available at http://www.breastcancerfund.org/media/publications/state-of-the-evidence/. Its user-friendly web-based format includes an extensive summary of current science and recommendations addressing chemical exposures.
- **Breast Cancer Action** (http://www.bcaction.org/): This organization makes available a number of resources addressing environmental links to breast cancer and the failure of corporations and governmental agencies to evaluate chemicals for their safety before they are marketed.
- **Environmental Working Group** (www.ewg.org): This organization has assembled a searchable database, Skin Deep, which enables users to identify hazardous chemicals, including carcinogens, in specific personal care products, see http://www.ewg.org/skindeep/. Information about healthy fish consumption and unhealthy fish contaminants associated with adverse health effects is also available on their website.

Vitamin D (Chapter 6)

Studies addressing the relationship between vitamin D and breast cancer risk are inconsistent, but most using serum levels as a marker of vitamin D status find higher levels associated with lower risk. In 2011 an Institute of Medicine (IOM) expert panel concluded that most Americans had adequate levels of vitamin D, based on their judgment that a serum level of 25OH-D of 20 ng/mL (50 nmol/L) or greater is sufficient. Average levels in the population

sample they studied were slightly greater, although one-third of adults had 25OH-D levels less than 20 ng/mL.[68] Their conclusion was based only on a consideration of vitamin D and bone health. The committee privileged randomized controlled trials as the gold standard, finding the available evidence of insufficiently high quality to make population-wide recommendations for dietary intake of vitamin D based on any other health endpoint.

The Endocrine Society Clinical Practice Guidelines recommend a target level 25OH-D of at least 30ng/mL.[69] They conclude that lower levels are inadequate. Using the Endocrine Society guideline, over 50 percent of the U.S. population has insufficient levels of vitamin D.

People of color, particularly African-Americans, have significantly lower levels than people with lighter skin because skin pigmentation tends to block UV light absorption and vitamin D synthesis. Older peoples' vitamin D levels also tend to be lower.[70] But, compared to normal weight children, those who are overweight or obese are much more likely to have serum 25OH-D levels less than 20 ng/mL.[71]

Vitamin D sufficiency is important throughout life—beginning with fetal development, childhood, and adolescence when cells are rapidly proliferating. The effects of vitamin D are far more widespread than bone health. Vitamin D is a hormone with receptors in many organs.

With regard to breast development, laboratory animal studies show that lack of a vitamin D receptor results in enhanced mammary gland ductal elongation and branching and increased responsiveness to hormonal stimulation.[72] These are precisely the kinds of changes that increase cancer risk. A prospective study also found earlier onset of menarche in girls with low 25OH-D levels. If this finding is confirmed it adds to the evidence for a link between vitamin D and breast cancer and has broader implications for breast cancer research.

Given what we know about current population vitamin D status, the safety of higher levels, and evidence that generally although inconsistently points toward lower breast cancer risk with higher levels of vitamin D, achieving and maintaining serum levels of 25OH-D in the range of 30-40 ng/mL is supportable and highly unlikely to be associated with adverse consequences. This serum level is consistent with conclusions of both the IOM and the Endocrine Society.

For most people, achieving this serum level will probably require vitamin D supplementation, beginning in pregnancy. The modest levels of vitamin D in many prenatal vitamins are insufficient for achieving optimal serum levels.[73,74] The American Congress of Obstetricians and Gynecologists (ACOG) recommends testing pregnant women who are at increased risk of vitamin D deficiency (e.g., women with limited sun exposure, women with darker skin that limits absorption of vitamin D). If a woman's vitamin D levels is 20 ng/mL (50 nmol/

L) or less, ACOG recommends vitamin D supplementation in a dosage of 1,000 to 2,000 IU daily.[75]

The Centers for Disease Control and Prevention and the American Academy of Pediatrics (AAP) also find that most U.S. infants and children are not consuming enough vitamin D according to 2008 recommendations.[76] The AAP recommends that all infants, whether being breast fed or formula fed, receive a vitamin D supplement.

The IOM committee affirmed a recommended daily allowance (RDA) of 600 IU vitamin D daily, except 800 IU daily for men and women > 70 yrs of age, based only on requirements for bone health. The committee also acknowledged that many people are not receiving that amount and recognized a safe upper limit of 1000-1500 IU in infants, 2500-3000 IU in children, and 4000 IU in adolescents and adults

For many people, supplementation will need to continue through adolescence and adulthood. A supplement of 1000 IU- 2000 IU vitamin D daily will bring most people into the range of 30-40 ng/mL, although some people may need more to achieve that level.[77] However, excessive vitamin D intake can have adverse consequences and levels of supplementation beyond recognized safe upper limits should be guided by testing serum levels.

Night work; light at night (Chapter 6)

The International Agency for Research on Cancer (IARC) decision classifying shift work with circadian rhythm disruption as probably carcinogenic to humans led to efforts to identify interventions to mitigate risk, especially related to breast cancer. For studies looking specifically at breast cancer and duration of shift work, significantly increased risk becomes apparent after about 20 years of working night-shifts, but it is unclear if risk also increases with shorter duration. Nevertheless, since night work is a permanent feature of many occupations, certain steps can be taken to minimize circadian disruption that may help to reduce cancer risk:[78]

- Rapidly rotating shifts (one-two consecutive nights) cause less disruption of circadian rhythms than slowly rotating shifts (three or more consecutive shifts). Delay of circadian phase causes less disruption than advance of circadian phase and therefore forward- rather than backward-rotating shifts are preferable.

- Permanent night work is an option to avoid circadian disruption and may be feasible, particularly if a night-oriented rhythm during days off is possible. But, this requires avoiding bright light during the day and making certain that sleep is adequate.

- Modified light intensity during work at night can help, such as working in bright white light to increase adoption of a night rhythm or in dim red light to prevent adoption. Dim red light suppresses melatonin less than bright white light, but there may be a trade-off with alertness that is critical for performing many tasks.

- People working at night should be especially attentive to maintaining adequate levels of vitamin D.

- Considering the potential risks and benefits, most analysts do not recommend earlier or more intensive mammography screening in women night shift workers.

- Women who have breast cancer should be advised not to work night shifts because of the strong experimental evidence showing that suppression of melatonin secretion can facilitate tumor growth.

Ionizing radiation (Chapter 6)

Ionizing radiation is a firmly-established risk factor for breast cancer. In spite of this, excessive exposure to radiation from medical sources, including X-rays, CT scans, and other medical imaging, is a large and growing problem. To reduce exposures:

- Individuals should discuss with their health care providers the need for medical tests or procedures that involve radiation exposure. Key considerations include personal history of radiation exposure, the expected benefit of the test, and alternative ways of obtaining the same information.

- To help limit cumulative medical radiation exposure, individuals and their health care providers can create a record of all imaging or nuclear medicine tests and, if known, the estimated radiation dose for each test.

- Medical and nursing schools, schools training nuclear medicine and radiology health care workers, and professional organizations must undertake systematic education and evaluation of current standards of practice to make certain that radiation exposures are minimized without sacrificing quality of care.

- Improved equipment design, regular calibration, and maintenance can also help minimize exposures.

Electromagnetic fields (Chapter 6)

The International Agency for Research on Cancer (IARC) has classified both extra low frequency (ELF) and radio frequency (RF) electromagnetic fields (EMF) as possibly carcinogenic in humans, but whether or not they increase the risk of breast cancer is an important but unresolved question. But recent case reports of breast cancer in young women who carried cell phones in their bras are extremely disturbing. Proposed mechanisms by which EMFs could influence breast cancer risk for which there are varying levels of support include genotoxic effects, alterations in gene expression, oxidative stress, up-regulation of stress responses, changes in permeability of membranes and the blood brain barrier, reduced melatonin levels, and altered immune function.

Individuals, families, and communities will need to make their own decisions about how to respond to the concerns raised by a large and growing body of literature addressing potential health effects of ELF- and RF-EMF exposures. This has become a more urgent public health matter as wireless technologies are increasingly deployed in virtually all aspects of our daily lives.

For reducing exposures to ELF-EMF, these simple steps will help:

- Increase your distance from a source. For example, re-position electric alarm clocks and other electric appliances farther away from your body while in bed.
- Use electric blankets only to warm the bed, turning them off before getting into bed.
- Repair faulty wiring which may be generating higher than usual ELF-EMF. If high voltage power lines are close to your house you may want to obtain EMF measurements. In some instances, electric utility companies provide that service for free.
- Turn off electrical devices such as televisions and computers when not in use.

The best ways to reduce RF-EMF exposures from cell phones include:

- Keep conversations on cell phones as short and infrequent as possible; use a land line or send texts instead.
- Do not put it against your body. Put it in your purse, your backpack, or your case.
- Do not keep your cell phone in your bra or pocket.
- Always try to keep it a few inches away from your body. The strength of the antenna signal decreases quickly with increasing distance from the source.
- Do not call in vehicles (car, bus, train). If your mobile does not have an external antenna, the radiation levels go up in moving vehicles. This is because each time the cell phone connects to a new tower (the "handshake") an increase in power follows until an optimal level is established.

- Avoid placing mobile calls in places with poor reception such as cellars or elevators. The cell phone will increase its power (and thus the radiation) in such situations.
- Use the speaker phone feature.
- Plug in earphones while talking.
- Use the hands-free device.
- Keep the phone away from your head.
- Do not sleep with it under your pillow.
- Put your cell phone in airplane mode.

Other steps that will reduce exposures to RF-EMF:

- Avoid using cordless phones.
- Turn off wireless devices when not being used.

Stress reduction (Chapter 7)

Although many people feel that excessive stress can increase the risk of developing breast cancer, the evidence is inconsistent. Yet, based on growing understanding of the underlying biology, it's entirely plausible that unusual or chronic stress could speed the growth and development of an undiagnosed tumor. It is also increasingly apparent that after the diagnosis of breast cancer, stress reduction can be an important part of a comprehensive treatment plan that improves quality of life and can help to prevent or delay recurrence and improve prognosis.

A variety of psychotherapeutic interventions can reduce stress. Techniques subjected to fairly rigorous scrutiny in epidemiologic studies and clinical trials often involve varieties of mind-body-spirit interventions. They include meditation, yoga, mindfulness exercises, guided imagery, music, and cognitive behavioral therapy. Establishing and taking advantage of existing social support networks can also markedly reduce stress and improve outcomes after diagnosis and treatment.

Many studies show that stress reduction can significantly improve quality of life during the initial treatment of breast cancer and thereafter. In general, group therapy, education, structured and unstructured counseling, and cognitive behavioral therapy help to reduce anxiety, depression, and fatigue significantly and generally improve functional ability. For many people, guided imagery, music therapy, meditation, and relaxation training are highly beneficial. A number of these interventions also improve indicators of immune function.

The most significant associations of lower stress levels with improved survival are in women who do not have metastatic disease at the time of initial diagnosis and treatment. But even

with more advanced disease, in some individuals survival is prolonged. Indeed, there will always be individuals who will benefit more or less from a particular intervention.

Improved quality of life is clearly associated with stress reduction in women with all stages of breast cancer. In general, outcomes are more likely to improve when conventional therapy is combined with more comprehensive interventions that include stress reduction along with optimizing diet, exercise, sleep, and social support.

Designing strategies for breast cancer prevention and improved outcomes into daily life

Individual and societal-level variables associated with increased or decreased breast cancer risk do not only act independently. They also combine into an interactive set of system conditions that collectively increase or decrease risk—for individuals, groups of people, and entire populations. To illustrate the importance of interactions, the effects of combinations of dietary fat and chemical carcinogens on the mammary glands of rodents are among the most widely studied. Since the 1970s many investigators have shown that various kinds of dietary manipulations influence the susceptibility of the mammary gland to exposure to the carcinogen DMBA.[79]

For example:

- Sprague Dawley rats fed a diet consisting of 20 percent corn oil (high omega 6:3 fatty acid ratio) from weaning are much more susceptible to developing mammary gland cancer after exposure to the carcinogen DMBA than animals fed a low fat diet exposed to the same carcinogen[80] (see chapter 5 for discussion of DMBA as a mammary gland carcinogen). The rats fed the high corn oil diet also gained slightly more weight and reached puberty earlier. Rats fed a diet consisting of three percent corn oil and 17 percent olive oil were only slightly more likely to develop mammary tumors than low-fat control animals.

- Another rodent study showed that dietary fish oil (a source of long-chain omega 3 FAs) protected against DNA damage caused by exposure to DMBA while dietary corn oil accentuated the DNA damage.[81]

- Pre-pubertal dietary omega 3 FAs can help to protect against DMBA-induced mammary tumors in laboratory rodents, but exceptionally high levels of this kind of fat (39 percent of total calories) can actually promote mammary cancer development.[82]

- One study carried the analysis a step further and administered black tea to rodents that had been treated with DMBA and fed a high-fat corn oil diet. The high-fat diet had the expected promoting effect on DMBA-induced mammary tumors, but there were significantly fewer tumors in tea-drinking rats compared to water-drinking control animals.[83]

- Another rodent study evaluated the effect of vitamin D and calcium on combinations of high fat- and DMBA-induced mammary gland tumors.[84] Inadequate dietary vitamin D and calcium enhanced mammary tumor development with a high-fat diet (20 percent sunflower seed oil, with high levels of omega 6 FAs) while increased dietary levels of vitamin D and calcium were protective. Vitamin D and calcium levels had no significant effect on tumor development in animals fed a low fat diet.

- Demonstrating the importance of a lifespan and trans-generational perspective, a study in rodents found that in utero exposures to a high fat diet (43 percent of maternal calories from corn oil) or a regular rodent diet supplemented with 0.1 ppm ethinyl-estradiol resulted in increased risk of mammary gland tumors not only in offspring daughters but also in granddaughters and great-granddaughters.[85] Epigenetic mechanisms, resulting in heritable changes in gene expression without gene mutations, are likely to explain the findings.

In people the study of interactions among risk factors for breast cancer has been slow to evolve, although we're beginning to see more evidence of the added benefit of combining interventions in adults to prevent the disease or improve outcomes after diagnosis. This is also the case in studies of people at risk of developing diabetes, where combinations of a Mediterranean-like or heart-healthy diet, exercise, and weight control actually prevent the onset of disease more effectively than pharmaceuticals. Based on studies discussed in Appendix A, this is almost certain to decrease breast cancer risk as well. Moreover, comprehensive treatment programs that include a healthy diet, exercise, stress reduction, improved sleep patterns, and social support along with other conventional therapies significantly improve breast cancer prognosis.[86] But,§human data addressing combinations of efforts at prevention of breast cancer, across the life course, beginning with fetal development, are virtually non-existent.

Existing evidence shows that consuming a healthy diet beginning in infancy and childhood (see above), maintaining a healthy weight, getting regular exercise, maintaining adequate vitamin D levels, avoiding smoking, limiting alcohol consumption, and avoiding combination hormone replacement therapy and unnecessary radiation exposure are each associated with a significantly lower breast cancer risk. Current oral contraceptive use modestly increases breast cancer risk. For women who are mothers, breast feeding their infants also reduces

their own risk of breast cancer while providing numerous benefits to their children. Risk reduction based on these interventions is best documented for breast cancer developing after age 50, although some of these interventions are clearly tied to reduced risk in younger women as well.[87] Avoiding exposure to carcinogens and chemicals that alter breast development and increase cancer risk is almost certainly going to help as well.

These data help to show how important it is to consider an entire context—a web of interlocking strategic interventions, across the life-course—when looking for opportunities to reduce the risk of breast cancer and improve outcomes. Yet, the complexity of that context means that it will always be difficult to identify precisely what the contribution of each single intervention will be to outcomes. No study has looked at breast cancer links to combinations of childhood and adolescent diet, exercise, and fetal exposures to endocrine disrupting compounds. Nor, has any study examined how vitamin D status might influence those associations. These kinds of studies would be extremely complex and resource intensive—and nearly impossible to carry out. Yet, it is precisely these combinations of variables that influence system conditions, as described in the ecological framework (chapter 1), that make breast cancer more or less likely.

Incomplete data should not prevent us from acting, based on what we already know. Although most established evidence targets steps that adults can undertake, we know enough to conclude that more comprehensive efforts to prevent breast cancer need to begin with fetal development and continue through childhood, adolescence, and throughout adulthood. What might this look like?

- Establish optimal baseline conditions during pregnancy. That means healthy nutrition, appropriate exercise, optimal maternal vitamin status including vitamin D, and avoiding exposures to chemicals and other environmental agents that may alter fetal development, increasing the risk of cancer and other diseases in childhood and years later.

- Infants should be exclusively breast fed if at all possible for at least six months and given a vitamin D supplement as recommended by the American Academy of Pediatrics. When solid food is begun, children should be introduced to a varied, healthy diet, avoiding calorie-rich, nutrient-poor choices that are so commonly pushed onto them by the food industry. Growing evidence shows that unhealthy childhood and adolescent diets are strongly linked to adverse health outcomes in adulthood, including breast cancer.

- Throughout infancy, childhood, adolescence, and adulthood efforts should be undertaken to reduce or eliminate exposures to environmental chemicals and con-

taminants that can alter breast development or otherwise damage breast tissue, increasing cancer risk.

- Avoid unnecessary exposure to both ionizing (e.g., X-rays, CT scans) and non-ionizing radiation, as from cell phones carried close to the body. Early life is characterized by time-windows of vulnerability to environmental influences. As we learn more, it will not be at all surprising to find that breast cancer in younger women is particularly strongly linked to early-life combinations of environmental exposures, unhealthy diets, and sub-optimal vitamin D status, perhaps along with genetic variables that together establish a backdrop for other breast cancer risk factors.

- Regular exercise and physical activity within individual capabilities is an essential part of a healthy childhood and adolescence as well as adult life. Studies show that physical activity levels in early life significantly influence lifelong physical activity patterns. And based on what we know about the benefits of combinations of a healthy diet and regular exercise in adults, it would not be surprising to find them even more beneficial when adopted in childhood.

- Vitamin D supplementation should continue throughout childhood and adolescence and is likely to be necessary throughout life in most people to achieve optimal serum levels.

Individuals and families will of course make their own family planning and medical decisions. But many variables related to breast cancer risk must not only be addressed by individuals but also by communities, businesses, schools, and society more generally. For example, physical activity levels are not just a matter of personal choice. Land use planning and zoning also play an important role by helping to determine neighborhood walkability, access to parks, and availability of bike lanes for transportation. School policies can help to ensure that exercise is a regular part of every student's day. Ready access to farmers markets and other sources of healthy, affordable food influence what people actually eat. Consumer product reformulation, eliminating chemicals plausibly linked to breast cancer, will reduce exposures. Exposure to mammary gland carcinogens in the workplace can be reduced by using safer substitutes and improved worker protection. Individual efforts alone are not sufficient to reduce breast cancer risk.

Multi-level interventions should be combined in integrated breast cancer prevention strategies, just as the integrated approach to breast cancer care and treatment shows great promise.[88,89,90] This typically includes combinations of conventional medical therapy along with nutritional interventions, exercise, stress reduction, and other treatment modalities, depending on individual circumstances. Similarly, integrative approaches to breast cancer

prevention will require combinations of multi-level interventions, beginning with fetal development and continuing throughout the life course.

Historically, we have thought about breast cancer risk in individuals, and risk assessment tools, such as the Gail model, have been developed for individuals to use.[91] But, it looks as if we have collectively although unintentionally also designed current breast cancer patterns into the fabric of communities and society more generally. This argues for widespread interventions at the population level as well as targeted interventions for individuals at higher risk. In this way, we can imagine re-designing various aspects of the eco-social environment to reduce not only breast cancer risk but also the risk of other common, chronic diseases for everyone. Multi-factorial, multi-level changes will be necessary. Properly chosen, they will undoubtedly have co-benefits that will improve public health in many ways.

Conclusions

Reports from two expert committees—one convened by the Institute of Medicine (IOM) and the other a governmental interagency and non-governmental taskforce known as the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC)—acknowledge the importance of taking a more ecological view of the origins of breast cancer (see chapter 1).[92,93] Many of their observations and recommendations are also explicit in the President's Cancer Panel Report, "Reducing Environmental Cancer Risk: What we can do now?"

These reports and numerous studies discussed throughout earlier chapters make clear that successful efforts at breast cancer prevention must begin with fetal development and continue throughout life. Preventing breast cancer and improving outcomes following diagnosis will require a multi-pronged public health response as well as individual actions. Although we need a revised and expanded research agenda, individuals, communities, and governments do not need to wait to act. Combinations of a lifelong healthy eating, regular exercise, maintaining healthy weight, healthy sleep patterns, maintenance of normal vitamin D levels, avoidance of exposure to chemicals known or suspected to increase cancer risk, avoiding smoking, limited alcohol consumption, avoidance of unnecessary exposure to radiation, and reductions in chronic stress are almost certain to help prevent breast cancer.

Data also clearly show that lifelong healthy diet, regular exercise, healthy weight maintenance, and stress reduction improve quality of life and reduce mortality after initial diagnosis and treatment of breast cancer.

Individuals needing to make changes in their lives to address these opportunities can do that in whatever sequence and combination works for them. They deserve and many will need encouragement from health care providers, family, and support groups. From the perspective of population health, we must also more urgently, consistently, and comprehensively design our communities and public policies in ways that also help to prevent this disease and improve outcomes.

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Appendix A: Breast cancer, body weight, insulin resistance, and diabetes

Diet, physical activity levels, and body weight are major determinants of blood glucose levels, baseline insulin levels, insulin sensitivity, and general metabolic profiles.[1,2,3,4,5,6] Other factors that contribute to insulin resistance include stress and sleep deprivation. Newly emerging data also find an association between insulin resistance and exposure to certain environmental chemicals.[7,8]

Obesity is associated with increased risk of post-menopausal breast cancer as well as cancers of the colon, uterus, esophagus, gallbladder, pancreas, kidney, and thyroid.[9] Obesity is also a risk factor for diabetes among other disorders. Epidemiologic studies have found an increased risk of several kinds of cancer in association with diabetes, including liver, pancreatic, colorectal, gynecologic, and breast.

Type 2 diabetes is characterized by elevated blood glucose caused by insulin resistance and ultimate defects in insulin secretion. Early in the development of the disorder as insulin resistance develops, increased secretion of insulin helps to keep blood glucose levels relatively normal.[10, 11] Ultimately β-cell function in the pancreas declines, insulin levels fall, and blood glucose begins to rise.

Insulin increases the biologic activity of insulin-like growth factor I (IGF-I) by stimulating IGF-1 production and decreasing some IGF binding proteins. Both insulin and IGF-1 can promote tumor development and/or progression by stimulating cell proliferation and inhibiting apoptosis (programmed cell death).[12] Insulin and IGF-1 also decrease levels of sex hormone binding globulin (SHBG), thereby increasing bioavailable levels of testosterone and estrogen. Insulin also stimulates sex hormone production in the ovary, primarily androgens.[13] Solid tumors are able to utilize glucose for energy production, even in the presence of relatively low oxygen levels.[14] For these reasons, there is considerable interest and concern about the role of elevated blood glucose, insulin, and IGF-1 levels in breast cancer development, progression, and outcomes, whether or not clinical diabetes is present and recognized. A number of large prospective studies report increased risk of breast cancer with elevated levels of fasting blood glucose, although associations with insulin and IGF levels are mixed.

Studies of glucose metabolism and breast cancer occurrence

In the Italian (ORDET) cohort of 10,673 participants, after an average follow up of 13.5 years, women with the highest glucose levels at baseline had a significantly greater risk of breast cancer than those in the lowest. (RR 1.63)[15] This association remained significant when data from pre- and post-menopausal cases were analyzed separately. Highest insulin resistance was also significantly associated with higher risk. In women over 55 years old at

diagnosis, the relative risk was more than 2-fold higher in those with the highest quartile of glucose levels compared to the lowest.

In a population based study of 33,293 women and 31,304 men in Sweden, total cancer risk in women increased by 26 percent with higher fasting blood sugar compared to lowest. Pre-menopausal breast cancer risk was increased 2-fold with higher fasting blood sugar.[16]

In a population cohort study of 140,000 Austrian adults, after an average 8.4 yrs follow up highest fasting blood sugar was associated with an increased likelihood of all cancers combined (HR 1.20 in men; 1.28 in women). In post-menopausal women over 65, higher fasting blood sugar was associated with increased breast cancer risk (HR 1.38).[17]

A pooled cohort study of 290,000 women from Austria, Norway, Sweden identified increased risk of breast cancer incidence and mortality with increased glucose (RR=1.57) and BMI in women over 60 after 11 years of follow up. In women less than 50, breast cancer risk decreased with higher BMI but increased with higher levels of blood glucose.[18]

A nested case control study of 10,786 women who were 35-69 years old found significantly increased risk of breast cancer in premenopausal and heavier post-menopausal women with higher levels of fasting blood glucose after 5.5 years of follow up. With longer follow up, (see the ORDET study above; the same cohort) breast cancer risk was increased for all post-menopausal women with higher blood glucose. The findings were independent of insulin and IGF-1 levels [19]

In a study of 7,894 women aged 45-64 years from four U.S. communities, authors examined the association of breast cancer incidence with serum levels of insulin and glucose over an average follow-up period of 7.1 years. 187 breast cancer cases were identified. Breast cancer risk increased with higher BMI but not with serum insulin level. After adjustment for age, race, and study site, the incidence of breast cancer was 60 percent higher among diabetic women than among women with normal fasting glucose levels, but this increase was no longer statistically significant after adjustment for body mass index.[20]

A study of 5,450 participants enrolled in the Women's Health Initiative examined the relationship between glucose, insulin, and insulin resistance measures at baseline and the risk of breast cancer with an average 8-year follow-up period. All participants were post-menopausal (age 50-79 at entry); it included black, Hispanic, Asian-Pacific, and white women; during the follow up period 153 cases of invasive and 37 cases of carcinoma in situ were diagnosed. Mean serum glucose and insulin levels were measured at baseline and at years 1, 3, and for some at year 6 of follow up. Glucose levels were higher in women who developed

breast cancer than in those that did not, and this relationship was significantly greater in black women. Baseline insulin levels and insulin resistance were both significantly higher in women who developed breast cancer.[21]

One prospective study of 9738 women, however, with up to 24 years follow up, found no association of breast cancer with fasting blood sugar in pre- or post-menopausal women.[22]

Effect of diabetes on breast cancer outcome/prognosis

A meta-analysis of 8 studies showed a 49 percent increased risk of all cause mortality in women with diabetes and breast cancer during the follow up period that ranged from 1-12 years. The authors noted that women with diabetes tend to be diagnosed at a more advanced stage of breast cancer than non-diabetics and the presence of diabetes appeared to modify treatment choices in varying ways.[23]

A more recent study of 3003 early stage breast cancer survivors, not included in this meta-analysis, also found that chronically elevated blood sugar was associated with a shorter disease-free period and two-fold increased risk of all cause mortality compared to participants with normal blood sugar levels.[24]

A study of 331 African American and 257 white women with stage I, II, or III breast cancer found that diabetes significantly shortened the period of disease-free survival following initial treatment, adjusted for age, stage, nodal involvement, ER/PR status, and co-morbidities.[25]

A prospective cohort study of 527 multiethnic women diagnosed with stage I-III breast cancer evaluated the association between adiponectin, insulin, glucose, and insulin resistance levels and breast cancer mortality and all-cause mortality, over an average six years of follow-up. Most participants did not have diabetes. Increasing insulin resistance was associated with reduced breast cancer survival and reduced all-cause survival when all participants were considered as a group. When the data were analyzed by subsets, this relationship remained significant for African-American women and for women with ER positive tumors, but not for Hispanic/non-Hispanic white women or women with ER negative tumors. Higher levels of adiponectin were associated with longer breast cancer survival.[26]

Together, these studies show a less favorable prognosis in women with breast cancer who also have diagnosed or undiagnosed diabetes or patients with different forms of glucose intolerance, as measured by insulin resistance or elevated fasting blood glucose levels. As noted in an editorial in the *Journal of Oncology:*

> "The findings…highlight the influence of insulin resistance on breast cancer progression. In the era of treatment selectivity and molecular-targeted anti-cancer drugs, the accumulating evidence of common pathways linking breast cancer and impaired glucose intolerance or diabetes is increasingly pointing the way forward. The time has come to overcome the conventional tunnel vision that results in two diseases being treated by separate clinicians, and to move towards a comprehensive approach that ideally integrates oncologists, internists, nutritionists, and other health care professionals in an attempt to improve breast cancer prognosis in a significant proportion of patients."[27]

A number of plausible biologic pathways link obesity, insulin resistance, and diabetes to increased breast cancer risk, particularly post-menopausal, and less favorable outcomes after diagnosis and treatment regardless of menopausal status. These biologic pathways are favorably influenced by adoption of healthy dietary patterns, weight control, and regular exercise, and their benefits are demonstrated in epidemiologic studies.[28] They should be routinely included in the daily lives of individuals and encouraged via public health policy decisions.

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