The Ecology of Breast Cancer

The Promise of Prevention and the Hope for Healing

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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.

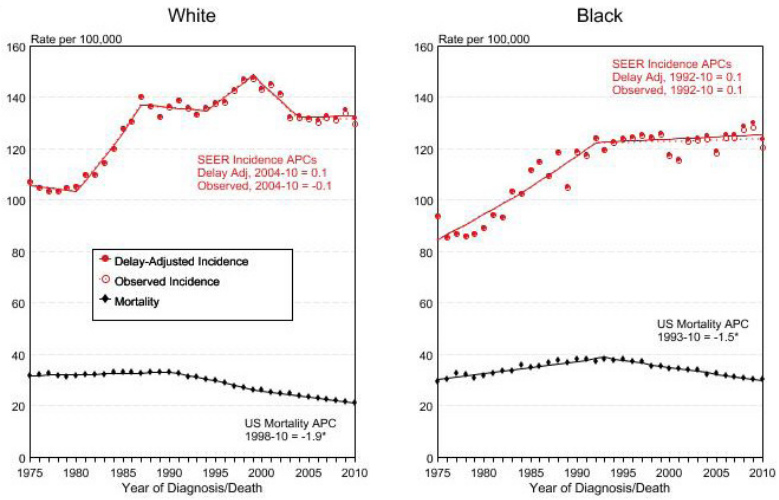
The National Cancer Institute and the Center for Disease Control's National Program of Cancer Registries regularly collect information to produce estimates of cancer incidence and mortality. Data collected by these surveillance systems indicated that approximately 227,000 new cases of invasive breast 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

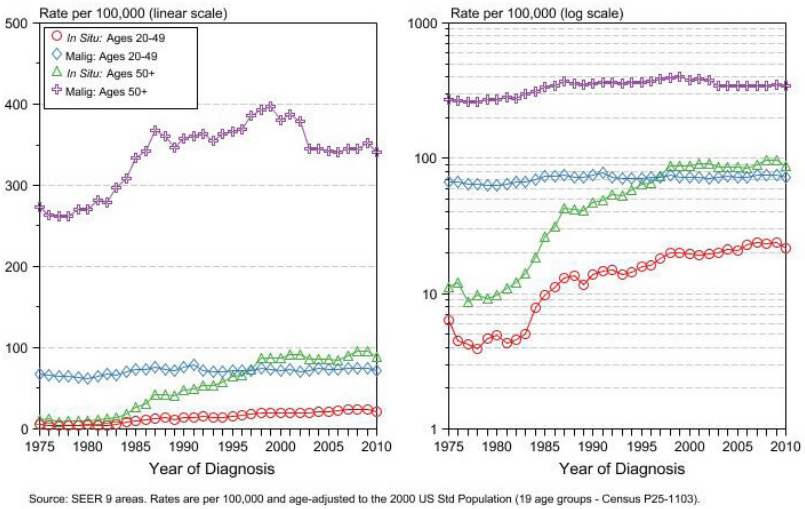


[a] Source: SEER * areas and US Mortality Files (National Center for Health Statistics, CDC).
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines and APCs are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer 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



Source: SEER 9 areas. Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).

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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