The Breast Cancer Landscape

Breast Cancer Incidence

Breast cancer is a global problem. Worldwide, breast cancer accounts for nearly a quarter of all cancers in women and as of 2020, female breast cancer has become the most commonly diagnosed cancer, with an estimated 2.3 million new cases.(1) In the United States, in 2021, it is estimated that 281,550 women and 2,650 men will be diagnosed with invasive breast cancer, and another 49,290 women will be diagnosed with ductal carcinoma in situ.(2, 3) The chance of a woman being diagnosed with breast cancer during her lifetime has increased from about 1 in 11 in 1975 to 1 in 8 today.(3) The number of women being diagnosed continues to increase as the number of women in age groups at risk of breast cancer increases. From 2004 to 2017, age-adjusted rates for new female breast cancer cases have been rising on average 0.5 percent each year.(4) The median age at diagnosis overall is 62 years, with slightly younger age for black women (60 years) than white women (63 year).(5) Studies have found that military active duty females have a 20 to 40 percent higher risk of breast cancer compared to the general population.(6) In 2008, 1 out of every 7 active duty individuals were women, the majority (>90%) of whom were under the age of 40.

Incidence rates of invasive breast cancer have remained relatively stable over the past several decades among women <50 years of age (Figure 1b).(5) However, recent trends(4) show that among adolescent and young adult females (age 15 to 39 years) where the incidence of invasive breast cancer is low (22.6 per 100,000), rates have been increasing by about 1.1 percent per year between 2010-2017. Meanwhile, the most substantial changes in rates have been observed over time among women ≥50 years of age. Rates for this age group increased sharply over the 1980s and then increased at a slower rate through 2000. These increases are largely attributed to the widespread introduction and utilization of mammographic screening and increases in the proportion of women using menopausal hormone-replacement therapy. A decline observed after 2003 has been attributed to the publication of the Women’s Health Initiative randomized trial demonstrating that the use of menopausal hormone-replacement therapy is associated with breast cancer risk and that, overall, the harms outweigh the benefits.(7) This led to a rapid reduction in the number of women using hormone-replacement therapy. Since this time, rates have stabilized.

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1 In past years, the annual incidence of carcinoma in situ reflected both ductal and lobular carcinoma in situ. However, LCIS was removed from the eighth edition (2017) of the AJCC breast cancer staging system and is no longer captured in annual incidence counts because it is generally believed to be a benign condition associated with increased breast cancer risk, but without the potential to progress to invasive cancer.
The increase in breast cancer screening has also resulted in a dramatic increase in the incidence of ductal carcinoma in situ (DCIS), a pre-invasive, stage zero breast condition (Figure 1a). The cause-specific survival rate of DCIS is nearly 100%, with a recent study estimating the standardized mortality ratio for death from invasive breast cancer among women previously diagnosed with DCIS at 3.36 out to 15 years. However, it is currently not possible to distinguish DCIS that will develop into invasive cancer from DCIS that will not progress. As a result, the overdiagnosis and overtreatment of DCIS remain persistent problems.(9)

While breast cancer screening in the general population with mammography has been shown in randomized controlled trials to reduce breast cancer-specific mortality, there remains ongoing controversy regarding the value of mammography and how it should be utilized. Ongoing screening trials(10, 11) are currently evaluating risk-stratified screening programs in the general population. However, there remains a need to identify novel approaches that improve breast cancer screening and early detection that reduces the problems of overdiagnosis and overtreatment, and that can detect cancers at a point where interventions can be made that avert morbidity and mortality.

Figure 1: US Incidence Rates of Invasive Female Breast Cancer by Age, 1975-2016(5)

Breast Cancer Deaths

In 2020, there were 684,996 deaths from breast cancer globally.(12) In the United States, in 2021, it is estimated that 43,600 women and 530 men will die of breast cancer. Between 2014-2018, the median age of death from breast cancer was 69.(5) In 2040, with no major changes in prevention or treatment, it is estimated that 1.04 million women will die from breast cancer worldwide.(13) Most breast cancer deaths are due to the spread of the disease to other parts of the body and its consequence on impairing the function of vital organs like lung, liver, and brain. Figure 2 presents incidence data retrieved from the SEER database following the November 2014 data submission.(14) Incidence data from 1975 through 2012 were stratified using SEER historic stage A to define three categories of breast cancer stage at diagnosis: localized, regional and distant breast cancer. As depicted in Figure 2, the rate of metastatic breast cancer at initial diagnosis in the United States has not changed appreciably since 1975 despite widespread use of mammography for early detection, a finding consistent with other reports.(15, 16) In fact, between 2001 and 2011, distant-stage disease increased by about 2.5% annually, although it has stabilized subsequent to 2011.(5)

Figure 2. Female Breast Cancer Incidence Rates by Stage, US, 1975-2012(14)

![Figure 2. Female Breast Cancer Incidence Rates by Stage, US, 1975-2012](chart)

Source: SEER 9 registries, November 2014 data submission. Rates are per 100,000 and age-adjusted to the 2000 US Standard Population. Localized – confined to the breast; regional – spread to regional lymph nodes; distant – metastatic disease.

Between 1975 and 1990, breast cancer mortality rates in the United States increased slightly, and then began decreasing in the late 1990s for all women. However, as seen in Figure 3, there are striking differences in the rate of breast cancer death by race and ethnicity with non-Hispanic (NH) black women having a 40 percent higher mortality rate compared with NH white women despite a lower incidence of breast cancer (Figure 4)(5).
Figure 3. Female Breast Cancer Mortality Rates by Race and Ethnicity, US, 1975-2015

Source: US Mortality Files, National Center for Health Statics, Centers for Disease Control and Prevention, 2019. Rates for American Indian/Alaska Native are based on the PRCDA counties and are 3-year moving averages. Rates are per 100,000 and age adjusted to the 2000 US standard population.

Figure 4. Female Breast Cancer Incidence (2012-2016) and Death (2013-2017) Rates by Race/Ethnicity, US

While breast cancer mortality rates have decreased annually from a peak in 1989 across all women, in more recent years there has been a deceleration in annual breast cancer deaths. Female breast cancer death rates decreased 2.3 percent per year on average during 2003-2007, 1.6 percent during 2007-2014, and 1.0 percent during 2014-2018.\(^{(4)}\) By race and ethnicity, the breast cancer death rates during 2014-2018 declined annually by 1.4 percent for NH black women, 1.1 percent for Hispanic women, and 0.9 percent for NH white women.\(^{(4)}\) Rates were stable for Asian/Pacific Islander and American Indian/Alaska Native women. The causes of the decline in mortality are multifactorial and have been attributed to such factors as earlier detection and improved treatments.

**Note:** Five-year survival rates, though often used, are not a sole indicator of progress. The National Cancer Institute reports that 5-year breast cancer survival is 99% for women who are diagnosed with localized disease.\(^{(5)}\) However, 5-year survival rates are skewed by screening as more women are being identified early in their disease course resulting in both a larger denominator of breast cancer cases (i.e., more women will be counted as alive at 5 years) and a lead time effect.\(^{(17)}\) Evidence suggests that many women would not have died of breast cancer in that time frame, even if they had not been screened. In addition, these numbers do not take recurrence into account. Among hormone positive breast cancer patients, the rate of breast cancer recurrences over the period of 5 to 20 years following five years of adjuvant hormone therapy ranged from 10 to 41 percent depending on the original tumor TN status and tumor grade.\(^{(18)}\) Moreover, among all breast cancer subtypes, a sizable proportion of the women reported to have survived for 5 years will have their breast cancer recur.

While incidence across global regions varies significantly, this is primarily a function of screening practices in more developed countries. Differences in mortality rates are much less appreciable (Figure 5).\(^{(1)}\)
Risk Factors

Epidemiologic studies have established a number of risk factors for breast cancer. These studies provide information about risk factors on a population level but have not proven to be effective in predicting an individual’s risk of breast cancer.

Risk factors that increase the relative risk for invasive breast cancer by more than four-fold include, age (65+ versus <65 years, although risk increases across all ages until age 80), diagnosis of atypical hyperplasia and/or lobular carcinoma in situ, or the presence of a pathogenic genetic variation (e.g., BRCA1, BRCA2, PALB2, TP53).
Risk factors that increase relative risk for invasive breast cancer by two to under four-fold include, prior diagnosis of DCIS, high endogenous hormone levels (postmenopausal), high-dose radiation to chest (e.g., Hodgkin lymphoma treatment), mammographically dense breasts, or two or more first-degree relatives with breast cancer.

Numerous other risk factors are known to increase risk modestly by up to two-fold including, alcohol consumption, early menarche (<11 years), excess body weight, high endogenous estrogen or testosterone levels (premenopausal), late age at first full-term pregnancy (>30 years), late menopause (≥55 years), never breastfed a child, no full-term pregnancies, one first-degree relative with breast cancer, obesity (postmenopausal), personal history of ovarian or endometrial cancer, physical inactivity, proliferative breast disease without atypia (usual ductal hyperplasia, fibroadenoma), recent and long-term use of menopausal hormone therapy containing estrogen and progestin, recent hormonal contraceptive use, weight gain in adulthood, and tall height.

However, it has been estimated using data collected as part of the first National Health and Nutrition Examination Survey (NHANES 1) and the Epidemiologic Follow-up Study (NHEFS), that no more than 41% of breast cancer cases in the United States were attributable to key risk factors identified through this analysis (i.e., later age at first birth, nulliparity, family history of breast cancer, and higher socioeconomic status).(19) Evidence attributes the majority of cancers to not one single factor but various physical, hormonal, environmental, and genetic factors.(5, 20) Factors affecting obesity, immunity, and the tumor’s environment within the body, as well as exogenous environmental exposures, can also influence development of disease.

Most risk factors are not modifiable, including age, family history, reproductive history, ages at menarche/menopause, BRCA status, and breast density. The amount of lifetime exposure of breast tissue to circulating ovarian hormones, which influences breast cancer risk, is only partially under one’s control—modifiable with respect to exogenous hormone use.

Potentially modifiable breast cancer risk factors include postmenopausal obesity, use of combined estrogen and progestin menopausal hormone-replacement therapy, alcohol consumption, smoking, and being physically inactive.(5) However, all of these factors are only weakly to moderately associated with breast cancer risk, with relative risks of <2.0.(5) There is also mixed evidence in relation to the impact of various commonly used medications on breast cancer risk, with some emerging evidence that perhaps bisphosphonates and metformin may lower breast cancer risk.(21-24)

Radiation exposure is a well-established risk factor for breast cancer,(25) and secondary breast cancer is strongly associated with high-dose radiation therapy to the chest for young women between the ages of 10 and 30 years treated for cancers, such as Hodgkin’s lymphoma.(5, 26) Studies have demonstrated that women who had their first exposure to medical radiation procedures during childhood, even at lower doses, had a greater increase in the risk of breast cancer than those who were first exposed at older ages.(25) This higher risk begins about 8 years after such exposure and continues to be elevated for more than 25 years.

Importantly, evidence is emerging that BRCA mutation carriers are exquisitely sensitive to the effect of radiation exposure through diagnostic procedures, with their risk of breast cancer increasing in a dose-dependent fashion.(27, 28)
There is also emerging evidence that risk factors vary in their relationships to different molecular subtypes of breast cancer, though the majority of studies have been small and further characterization of these differences is needed.

**Breast Cancer Heterogeneity**

It is well established that there are several different major molecular subtypes of breast cancer including luminal A, luminal B, HER2-overexpressing, and basal-like. Expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 can be used to approximate these four major subgroups (luminal A: ER+ and/or PR+/HER2-; luminal B: ER+ and/or PR+/HER2+; HER2 overexpressing: ER-/HER2+; and basal-like: ER-/PR-/HER2-). The latter group is also commonly called the triple-negative phenotype of which basal-like tumors are one of its primary components. Based on SEER (Surveillance, Epidemiology, and End Results) data, in the United States, 71% of tumors are ER+ and/or PR+/HER2-, 12% are triple-negative, 12% are ER+ and/or PR+/HER2+, and 5% are ER-/HER2+.(29) These proportions vary by a number of factors including age and race/ethnicity, as 15% of breast cancers among women <50 years of age and 23% of breast cancers among African American women are triple-negative. In addition to known molecular differences across subtypes, they also carry important clinical differences given the availability of targeted therapies for women with hormone receptor-positive and HER2-overexpressing tumors, but not for women with triple-negative disease. Further, data from the state of California indicate that survival rates vary across subtypes with triple-negative and HER2-overexpressing tumors carrying the poorest prognoses(30), though in recent years the prognosis for patients with advanced or metastatic HER2 positive breast cancer has improved.(31)

**Recurrence and Metastatic Disease**

We still do not know how to prevent recurrence and metastasis for any individual woman. An estimated 20% to 30% of women diagnosed with invasive breast cancer will have a recurrence and may eventually die of their disease.(32)

An estimated 90% of deaths due to breast cancer are a consequence of metastatic disease, whether the cancer was metastatic at diagnosis or a metastatic recurrence that developed later.(33, 34)

It has been estimated that approximately 155,000 women were living with metastatic breast cancer in the United States in 2017.(35) Of these women, three quarters were initially diagnosed with stage I–III breast cancer who later progressed to metastatic disease. This number is projected to rise to 168,292 by the year 2020.(35) The exact numbers are not known; neither is information available on historical trends. While researchers have identified treatments that sometimes shrink or slow metastatic tumors, such as estrogen blockers, radiation, and chemotherapy, they are most often temporary. *Treatments to permanently eradicate metastasis do not exist. There is no cure once metastatic disease has occurred.*

According to recent estimates, median survival with metastatic breast cancer is approximately 3 years(35-39), and varies depending on numerous factors, including age at diagnosis, tumor type,
whether metastatic disease was diagnosed \textit{de novo} or is recurrent, and the disease-free interval for recurrent cases, among other factors.

While the risk of recurrence is greater in the first 5 years after a diagnosis of ER-negative breast cancer, patients with ER-positive tumors have a consistent long-term risk of death from breast cancer and a greater risk after 7 years.\cite{40, 41} Approximately 75% of breast cancer is ER-positive, and most breast cancer deaths occur in ER-positive women. A 2014 publication of 2010 SEER data demonstrate that the proportion of patients with either node-positive disease or metastatic stage IV disease at diagnosis vary by breast cancer subtype as shown in Table 1, below.\cite{42}

### Table 1: Select clinical characteristics of breast cancer subtypes in women with invasive breast cancer, SEER-18, excluding Alaska, 2010\cite{42}

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Overall number</th>
<th>HR+/HER2−</th>
<th>Triple-negative</th>
<th>HR+/HER2+</th>
<th>HR−/HER2+</th>
<th>Unknown subtype</th>
</tr>
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<tr>
<td>All</td>
<td>n=57,483</td>
<td>n=36,810</td>
<td>n=6,193</td>
<td>n=5240</td>
<td>n=2,328</td>
<td>n=6,912</td>
</tr>
<tr>
<td>Positive nodal status</td>
<td>16,085 (28.0%)</td>
<td>10,185</td>
<td>1,875</td>
<td>1,800</td>
<td>890</td>
<td>1,335</td>
</tr>
<tr>
<td>(63.3% of this subtype)</td>
<td></td>
<td>(27.7% of</td>
<td>(30.3% of this</td>
<td>(34.4% of</td>
<td>(38.2% of</td>
<td>(19.3% of unknown subtype)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>positive node)</td>
<td>subtype)</td>
<td>subtype)</td>
<td>subtype)</td>
<td>unknown subtype)</td>
</tr>
<tr>
<td>AJCC 7th stage IV</td>
<td>3,203 (5.6%)</td>
<td>1,532</td>
<td>379</td>
<td>370</td>
<td>223</td>
<td>699</td>
</tr>
<tr>
<td>(47.8% of all stage IV)</td>
<td></td>
<td>(4.2% of this subtype)</td>
<td>(6.1% of this subtype)</td>
<td>(7.1% of this subtype)</td>
<td>(9.6% of this subtype)</td>
<td>(10.1% of unknown subtype)</td>
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<td></td>
<td></td>
<td>(11.8% of all stage IV)</td>
<td>(11.6% of all stage IV)</td>
<td>(7.0% of all stage IV)</td>
<td>(21.8% of all stage IV)</td>
<td></td>
</tr>
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</table>

Source: Howlader et al. 2014

**Breast Cancer Treatments**

For decades, breast cancer treatment has included surgery, radiation therapy, chemotherapy, and/or hormonal therapy, and within the past 15 years, targeted antibody or small-molecule therapy. Some of the most significant changes in treatment have involved doing less surgery; for example, moving from radical mastectomy to lumpectomy and radiation therapy, and removing fewer lymph nodes.\cite{43, 44} These two developments have had a major impact on improving quality of life. However, while important, these changes in standard of care do not change the mortality statistics.

As described above, breast cancer can be divided into different subtypes, based largely on the presence or absence of three key proteins: ER, PR, and HER2. Although breast cancers are highly heterogeneous, the majority of women with breast cancer still receive the same treatment, as though all breast cancers were the same within that subtype.\cite{45}
There are treatments targeted to some subtypes. For example, hormonal therapies, such as aromatase inhibitors and selective ER modulators, target ER-positive breast cancer. Trastuzumab, a monoclonal antibody, targets HER2-overexpressing breast cancer. Importantly, de novo and acquired resistance are major issues with all known targeted therapies. Unfortunately, no targeted therapies have been approved for triple-negative breast cancer (TNBC).

A meta-analysis of clinical studies on early breast cancer found a reduction in risk of recurrence for all women treated with chemotherapy, but a benefit in survival only for younger women.(46, 47)

For combination chemotherapy, studies showed an absolute improvement of only 7% to 11% in 10-year survival for younger women and of 2% to 3% for women ages 50-69, the age range when the majority of breast cancers are diagnosed.(48)

Standard adjuvant therapies have only a small (5% to 10%) impact on disease-specific survival. Currently, adjuvant therapies are given to all individuals with breast cancer but benefit only a small proportion. This nonspecific approach derives from the fact that we do not know how to reliably identify which cancers will recur, and we do not understand how the heterogeneity within each tumor affects therapy response or recurrence.

Radiation therapy (RT) is coupled with breast conserving surgery as a standard of care, based on the 1976 randomized trial that showed a 9% (although not statistically significant) decrease in breast cancer deaths with RT combined with lumpectomy.(49) A subsequent meta-analysis showed a 5% reduction in 15-year breast cancer mortality risk.(50)

In recent years, more research has been focused on determining whether breast cancer can be treated with immunological agents aimed at augmenting the immune response to cancer antigens. The goal of cancer immunotherapy is to activate a patient’s immune system to recognize and kill their tumors.(51) Monoclonal antibodies used to treat certain subtypes of breast cancer are passive immunotherapies that are already standard of care. Researchers are now also studying active immunotherapies (such as vaccines) for treating breast cancer. A number are in clinical trials including therapeutic vaccines directed against tumor-related antigens; checkpoint inhibitors and immune modulators; and adoptive cell therapy, primarily adoptive T cell transfer. On July 26, 2021, the U.S. FDA granted regular drug approval to the first PD-1 (programmed cell death protein 1) inhibitor combined with chemotherapy for patients with both metastatic TNBC whose tumors express PD-L1 (programmed death-ligand 1; Combined Positive Score ≥10) and for patients with high-risk, early stage TNBC.(52) There are also ongoing clinical trials involving oncolytic virus therapies, antibodies, adjuvant immunotherapies, and cytokines(53) as well as combined approaches of these agents.

While there is also ongoing research into preventative vaccines for breast cancer, this research is not yet testing in healthy populations.

The cost of treating breast cancer continues to rise. The national cost of cancer care overall in 2015 were shown to be $183 billion with a minimum projected increase by 34% to $246 billion by 2030 based solely on the aging and growth of the U.S. population.(54) This increase does not include anticipated increases in national costs for medical services and prescription drugs which
are projected to increase during this time by 34% and 40% respectively. The total national costs for medical services and oral prescription drug costs in 2015 were highest for female breast cancer ($26 billion).(54)

Morbidity and Mortality Caused by Treatments

Breast cancer treatments do carry risk of morbidity and even mortality. Morbidities reported include cardiac complications, second cancers, wound infections, peripheral neuropathy, lymphedema, impaired range of shoulder motion, and psychological distress. Of these, the morbidity of greatest incidence is lymphedema (swelling of lymph vessels because of fluid buildup). Immediate morbidity from RT is typically reported in the form of dermal reactions, but long-term consequences can include increased cardiac mortality and new cancers.(55)

An estimated 31% of all breast cancer cases (both invasive and DCIS) are considered to be overdiagnosed and overtreated.(56) Overdiagnosis is diagnosis of cancers that would not have presented within the life of the patient. Overtreatment can occur in two ways—either in overdiagnosis, where any treatment is unnecessary, or with the administration of more aggressive therapies than is necessary. It has recently been estimated that one to three deaths from overtreatment occur for every one breast cancer death avoided.(56)

Drug Development

In 2020, the Pharmaceutical Research and Manufacturers of America reported that there were over 1,300 medicines and vaccines (or other immunotherapies) in clinical testing for the treatment of cancer, including at least 108 specific for breast cancer.(57) In addition, there are many clinical trials evaluating existing drugs in new combinations or at different stages of disease. A recent search of ClinicalTrials.gov shows over 2,211 clinical trials currently ongoing or recruiting for the evaluation of drug interventions for breast cancer.(58) There are clearly many interventions and trials in breast cancer, but the expected impact on mortality has so far been lacking. What remains unknown is whether the current approaches to developing drugs and conducting clinical trials can be redesigned to accelerate the rate of progress to end breast cancer.

References


Department of Defense Breast Cancer Research Program, October 2021


