

# The Breast Cancer Landscape

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## Breast Cancer Incidence

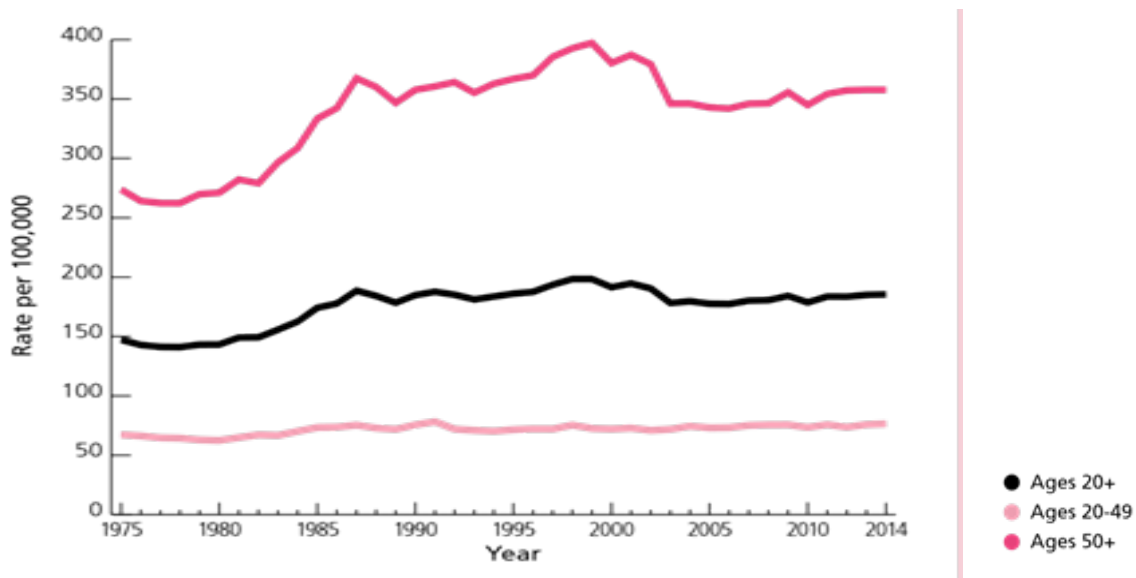
Breast cancer is a global problem. Worldwide, breast cancer accounts for nearly a quarter of all cancers in women and it is estimated that 1.7 million women are diagnosed with the disease annually.<sup>1</sup> In the United States, in 2017, it is estimated that 252,710 women and 2,470 men will be diagnosed with invasive breast cancer, and another 63,410 women will be diagnosed with in situ breast cancer.<sup>2</sup> 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.<sup>3</sup> The number of women being diagnosed continues to increase as the number of women in age groups at risk of breast cancer increases. From 2005 to 2014, the most recent 10 years for which data are available, overall invasive breast cancer incidence rates were stable in white women and increased slightly (by 0.4% per year) in black women.<sup>2</sup> The median age at diagnosis is 62.<sup>3</sup>

Incidence rates of invasive breast cancer have remained stable over the past several decades among women <50 years of age ([Figure 1](#)). However, substantial changes in rates have been observed over time among women  $\geq 50$  years of age. In particular, rates 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 therapy. The decline observed after 2000 has been attributed to the publication of the Women's Health Initiative randomized trial demonstrating that the menopausal hormones are associated with breast cancer risk and that, overall, their harms outweigh their benefits.<sup>4</sup> This led to a rapid reduction in the number of women using these hormones. Since this time, rates have stabilized.

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 form of breast cancer. The cause-specific survival rate of DCIS is nearly 100%, but it is currently not possible to distinguish DCIS that will develop into cancer from DCIS that will not progress. As a result, the overdiagnosis and overtreatment of DCIS remain persistent problems.<sup>5</sup>

While breast cancer screening 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. 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, 1975-2014**

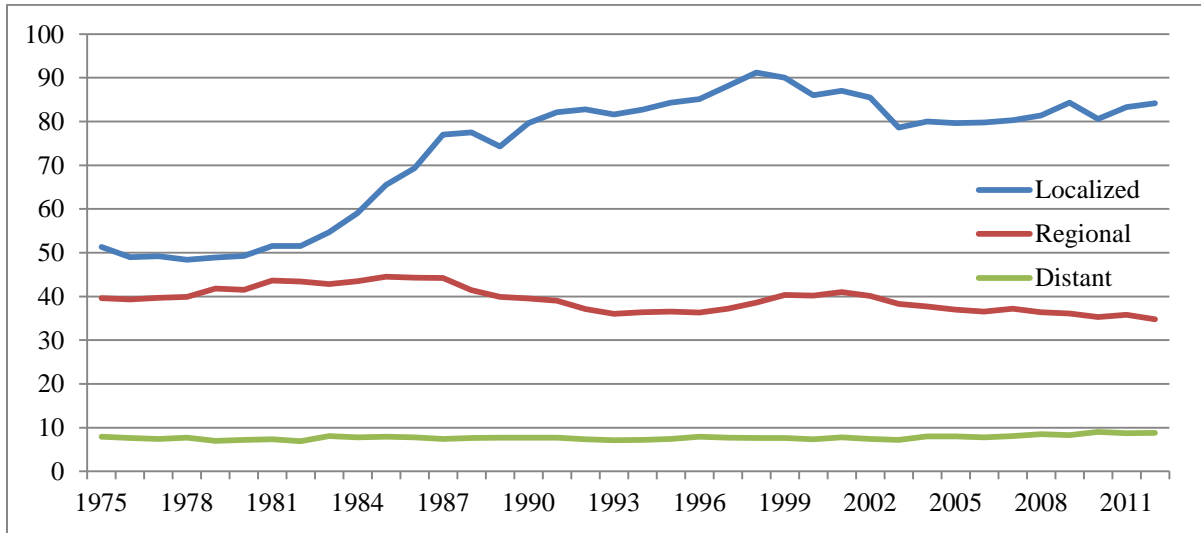


Source: SEER 9 registries, National Cancer Institute, 2017. American Cancer Society, Inc., Surveillance Research, 2017. Rates are per 100,000 and age-adjusted to the 2000 US Standard Population and are adjusted for reporting delay.

## Breast Cancer Deaths

In 2012 there were 522,000 deaths globally.<sup>1</sup> In the United States, in 2017, it is estimated that 40,610 women and 460 men will die of breast cancer.<sup>2</sup> The median age of death from breast cancer is 68.<sup>2</sup> In 2035, with no major changes in prevention or treatment, it is estimated that 846,241 women will die from breast cancer worldwide.<sup>6</sup> 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. As depicted in [Figure 2](#), the rate of metastatic breast cancer at initial diagnosis in the United States has not changed since 1975 despite widespread use of mammography for early detection.

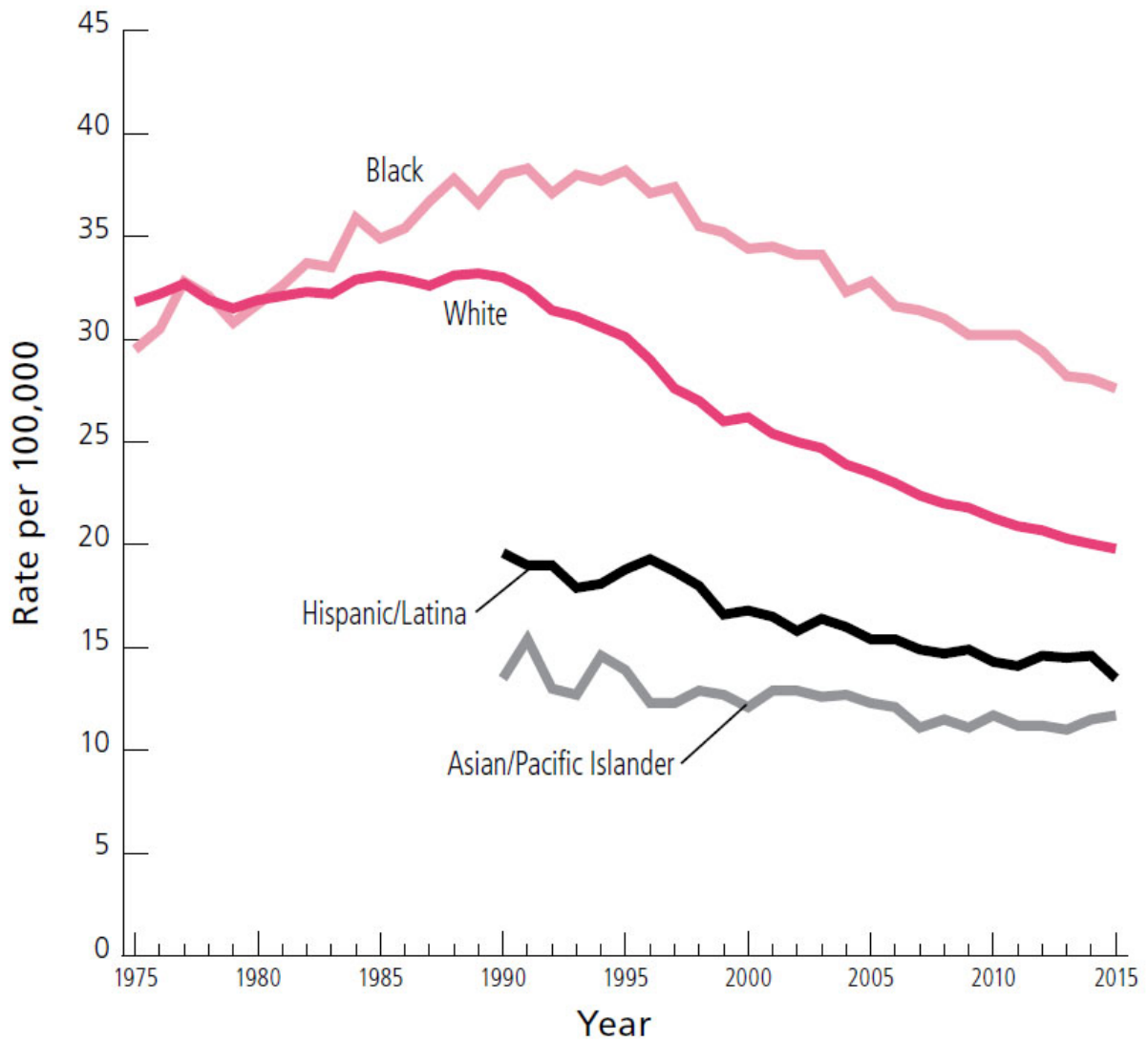
**Figure 2. Female Breast Cancer Incidence Rates by Stage, US, 1975-2012**



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, with the overall highest rate of decrease in white women (Figure 3). From 2000-2012, breast cancer mortality rates overall decreased at an average rate of 1.9%, then from 2010-2014, rates decreased at an average rate of 1.6% per year,<sup>7</sup> and this trend has continued through 2015 (Figure 3).

**Figure 3. Female Breast Cancer Mortality Rates by Race and Ethnicity, US, 1975-2015**



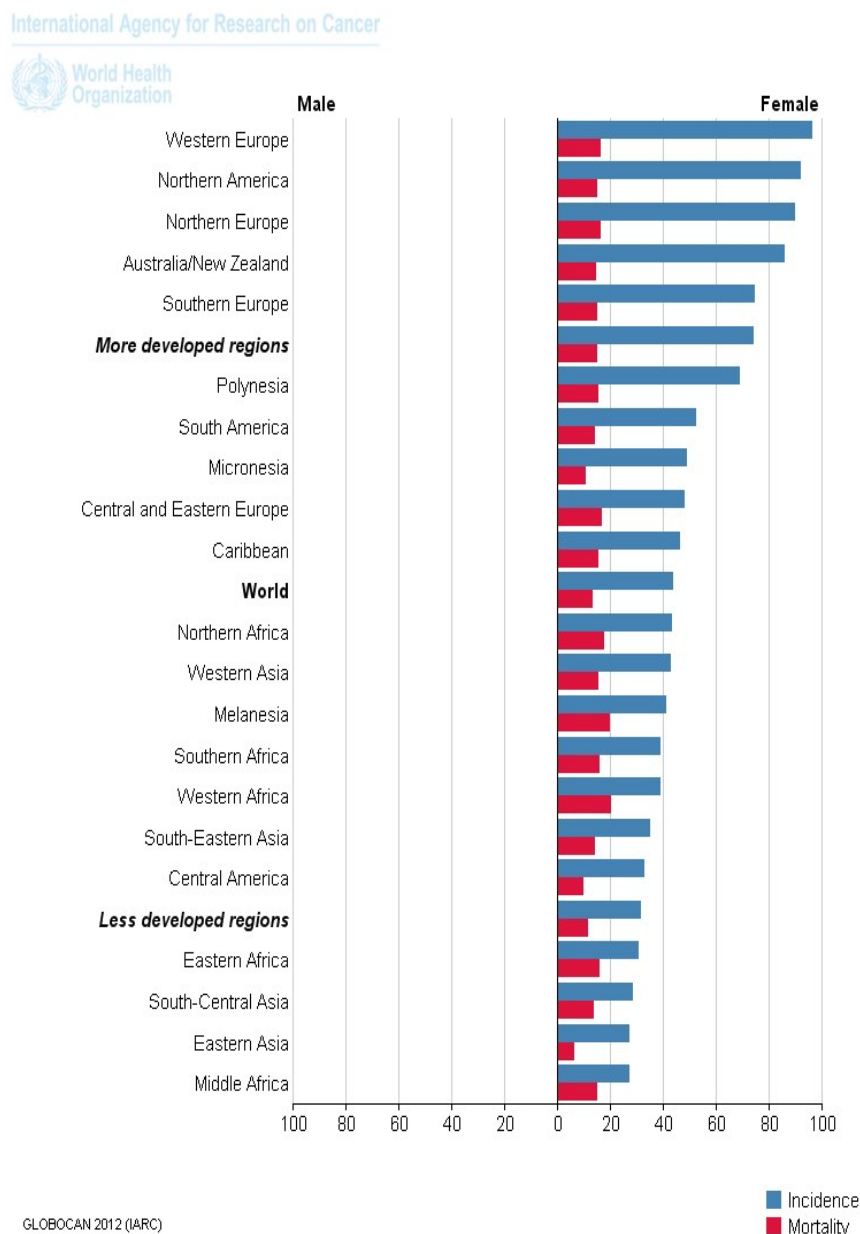
Source: US Mortality Files, National Center for Health Statics, Centers for Disease Control and Prevention, 2017. Rates for Hispanics exclude deaths from Louisiana, New Hampshire, and Oklahoma. Data for American Indian/Alaska Native not shown due to small counts and unstable rates. Rates are age adjusted to the 2000 US standard population.

There has been no acceleration in the rate of decrease in mortality since the 1990s. The causes of the decline in mortality are multifactorial and have been attributed to such factors as earlier detection and improved treatments.<sup>6</sup>

**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 98% for women who are diagnosed with localized disease. However, survival rates are skewed by screening: the more women that are screened, the earlier cancers are found, resulting in a larger denominator of breast cancer cases, i.e., more women will be counted as alive at 5 years. 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. A sizable proportion of the women reported to have survived for 5 years will have their breast cancer recur.<sup>8</sup>

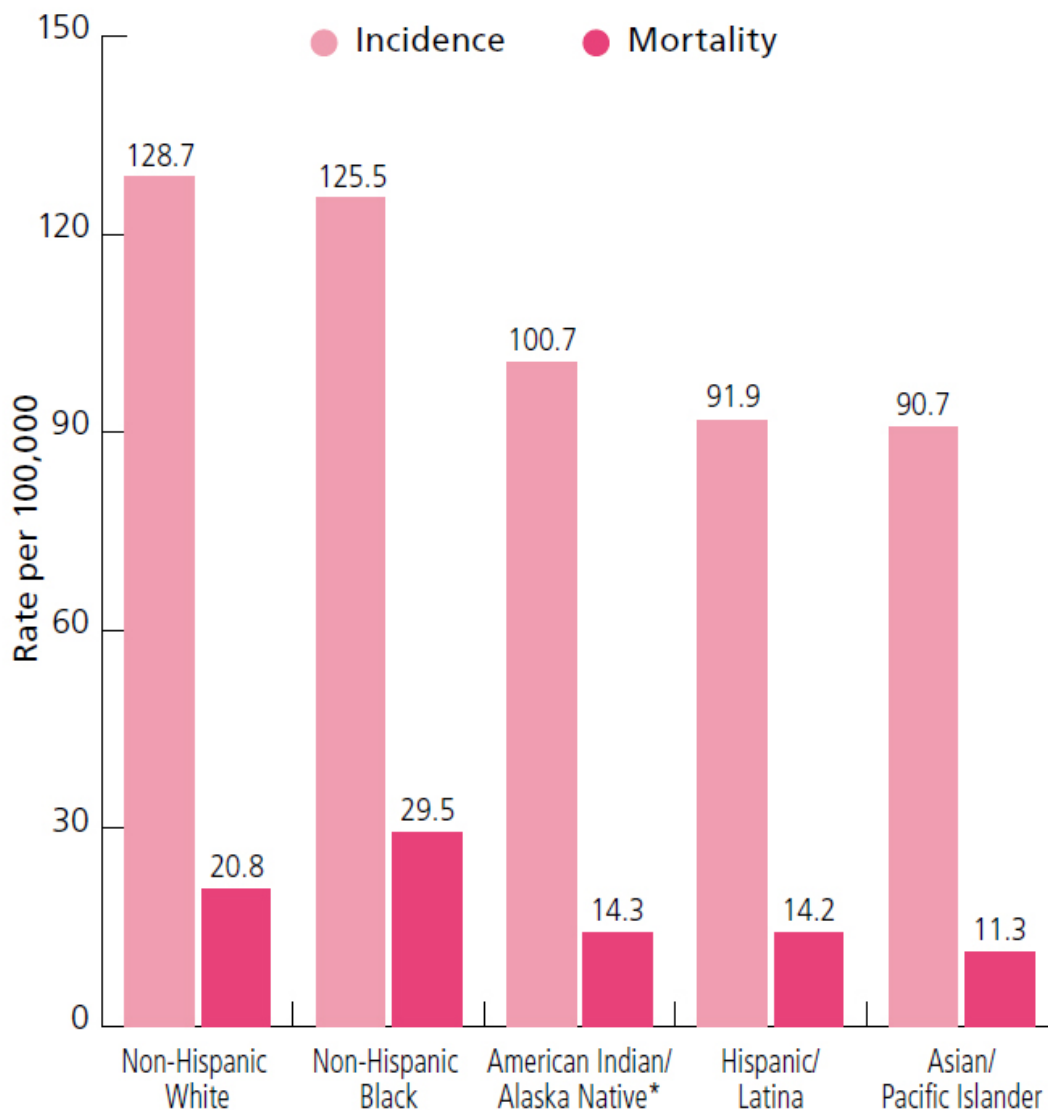
While incidence across global regions varies significantly, this is primarily a function of screening practices in more developed countries. Differences in mortality rates are much less appreciable ([Figure 4](#)).<sup>8</sup>

**Figure 4. World Breast Cancer Incidence and Mortality Rates**



In the United States, there is also considerable variation in breast cancer incidence and mortality rates by race/ethnicity. As shown in [Figure 5](#), incidence rates are highest among non-Hispanic white and non-Hispanic black populations, but mortality rates are the highest among non-Hispanic black women.

**Figure 5: Female Breast Cancer Incidence (2010-2014) and Mortality (2011-2015) Rates\* by Race and Ethnicity, US**



\*Statistics based on data from Contract Health Service Delivery Area (CHSDA) counties. Note: Rates are age adjusted to the 2000 US standard population.

**Sources:** Incidence – NAACCR, 2017. Mortality – National Center for Health Statistics, Centers for Disease Control and Prevention, 2017.

American Cancer Society, Inc., Surveillance Research, 2017.

## 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. Further, it has been estimated that no more than 55% of breast cancer is explained by the risk factors identified thus far.<sup>9</sup> Evidence attributes the majority of cancers to not one single factor but various physical, hormonal, environmental, and genetic factors. Factors affecting obesity, immunity, and the tumor's environment within the body, as well as exogenous environmental exposures, can also influence development of disease.<sup>2, 10</sup>

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 hormones, alcohol consumption, smoking, and being physically inactive. However, all of these factors are only weakly to moderately associated with breast cancer risk, with relative risks of <2.0. 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.<sup>11, 12, 13, 14</sup>

Radiation exposure is a well-established risk factor for breast cancer, 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.<sup>2</sup> 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.<sup>15</sup> 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.<sup>16, 17</sup>

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+.<sup>2</sup> 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.<sup>18</sup>

## 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.<sup>19</sup>

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.

It has been estimated that approximately 155,000 women are living with metastatic breast cancer in the United States, and this estimate was projected to rise to 162,000 by the end of 2011, according to one expert.<sup>20</sup> 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.***

Median survival with metastatic breast cancer is 3 years, and there has been no statistically significant change in over 20 years.<sup>21</sup> Estimates are that, with current historical trends, median survival will increase by 6 months by the year 2021.<sup>22</sup>

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.<sup>23, 24</sup> Approximately 75% of breast cancer is ER-positive, and most breast cancer deaths occur in ER-positive women. The proportion of patients with node-positive disease and widely metastatic stage IV disease at diagnosis are known to vary by breast cancer subtype (HR+/HER2-: 31.3%, ER-/PR-/HER2-: 34.3%, ER-/HER2+: 44.4%, and HR+/HER2-: 4.3%, ER-/PR-/HER2-: 6.2%, ER-/HER2+: 9.9%, respectively).<sup>25</sup>



## 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.<sup>26</sup> 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.<sup>27</sup>

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. 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.<sup>28, 29</sup>

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.<sup>30</sup>

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.<sup>31</sup> A subsequent meta-analysis showed a 5% reduction in 15-year breast cancer mortality risk.<sup>32</sup>

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.<sup>33</sup> 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. There are also ongoing clinical trials involving oncolytic virus therapies, antibodies, adjuvant immunotherapies,

and cytokines<sup>34</sup> as well as combined approaches of these agents. None have received approval by the US Food and Drug Administration or regulatory agencies in other countries to date.

While there is also ongoing research into preventative vaccines for breast cancer, this research is not yet in the clinical trial phase.

The cost of treating breast cancer continues to rise. The national cost of cancer care in 2010 was estimated to be \$124.6 billion, with female breast cancer care leading all cancer sites at an estimated \$16.5 billion.<sup>35</sup>

## 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 as a result 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.<sup>36</sup>

An estimated 30% of all breast cancer cases (both invasive and DCIS) are considered to be overdiagnosed and overtreated. 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.<sup>37</sup> It has recently been estimated that one to three deaths from overtreatment occur for every one breast cancer death avoided.<sup>38</sup>

## Drug Development

In 2015, the Pharmaceutical Research and Manufacturers of America reported that there were over 800 medicines and vaccines (or other immunotherapies) in clinical testing for the treatment of cancer, including 82 specific for breast cancer.<sup>39</sup> 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](http://ClinicalTrials.gov) shows over 1,600 clinical trials currently ongoing or recruiting for the evaluation of drug interventions for breast cancer.<sup>40</sup> 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.

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