The Breast Cancer Landscape

Breast Cancer Incidence

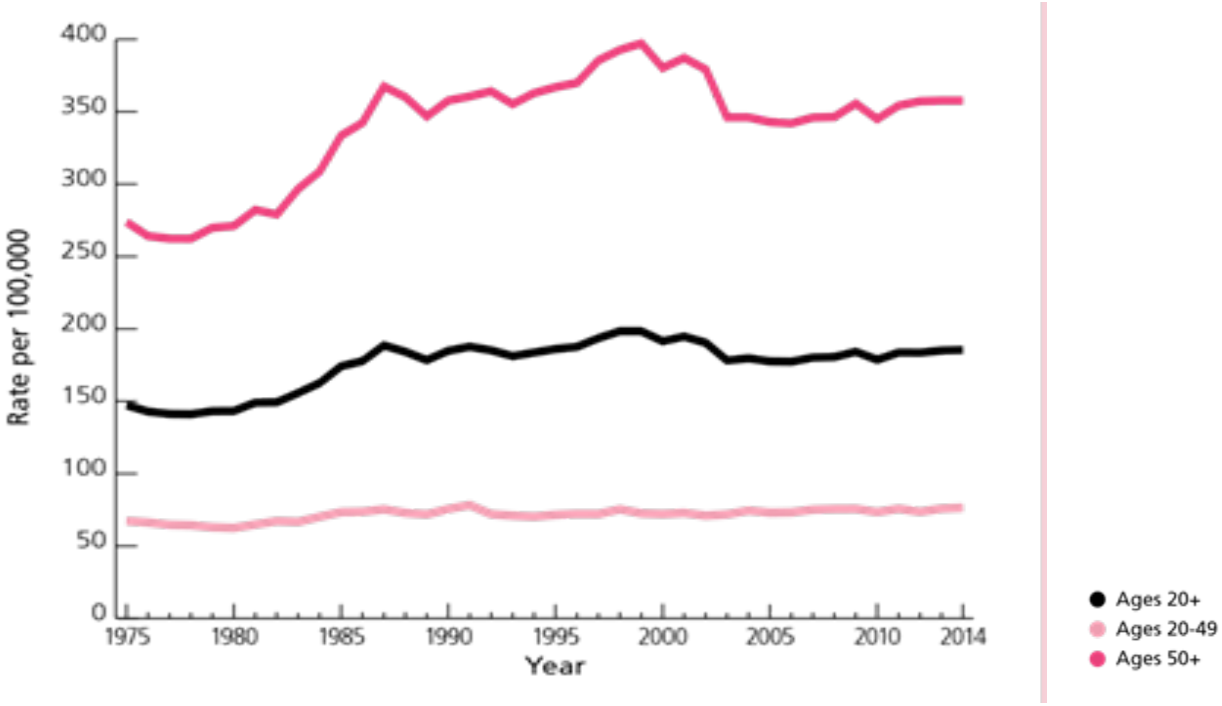
Breast cancer is a global problem. Worldwide, breast cancer accounts for nearly a quarter of all cancers in women and it is estimated that 2.1 million women will be diagnosed with the disease in 2018.(1) In the United States, in 2019, it is estimated that 268,600 women and 2,670 men will be diagnosed with invasive breast cancer, and another 62,930 women will be diagnosed with in situ breast cancer.(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.(2) 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 0.3% per year) in black women.(4) The median age at diagnosis overall is 62.(4) Recent studies have found that military active duty females have a 20 to 40 percent higher risk of breast cancer compared to the general population.(5) 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 stable over the past several decades among women <50 years of age (Figure 1).(4) However, substantial changes in rates have been observed over time among women ≥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-replacement therapy. The 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.(6) This led to a rapid reduction in the number of women using hormone-replacement therapy. 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), which is an abnormal proliferation of epithelial cells within the breast ducts that has not invaded into tissue and is not cancer. The cause-specific survival rate of DCIS is nearly 100%, but 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.(7)

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(4)

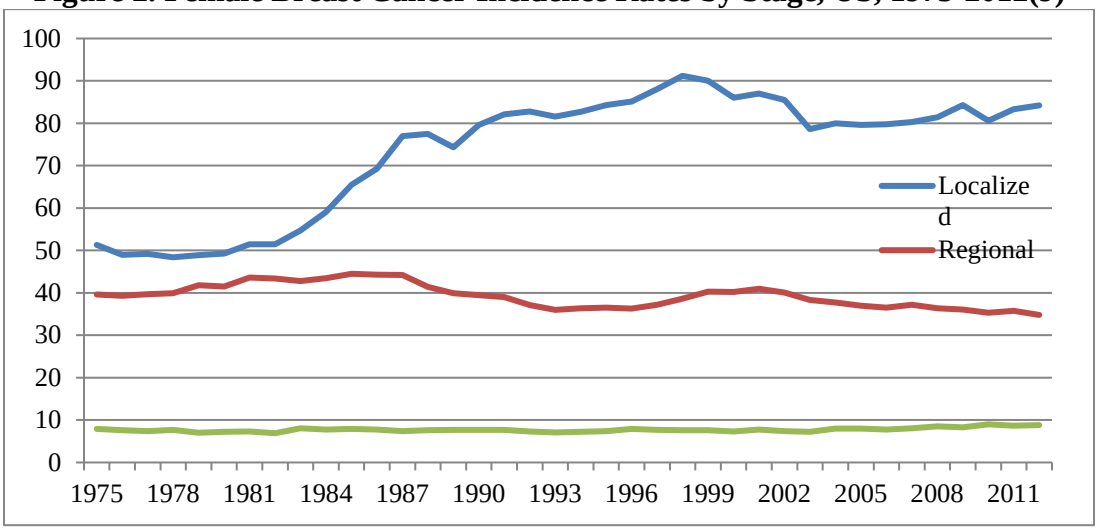


Source: SEER 9 registries, National Cancer Institute, 2017. American Cancer Society, Inc., Surveillance Research, 2017. Rates are per 100,000 and age-adjusted to the 2000 US Standard Population and are adjusted for reporting delay.

Breast Cancer Deaths

In 2018 there were 626,679 deaths globally.(1) In the United States, in 2019, it is estimated that 41,760 women and 500 men will die of breast cancer. The median age of death from breast cancer is 68.(4) In 2040, with no major changes in prevention or treatment, it is estimated that 991,904 women will die from breast cancer worldwide.(8) 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.(9) 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.(10, 11)

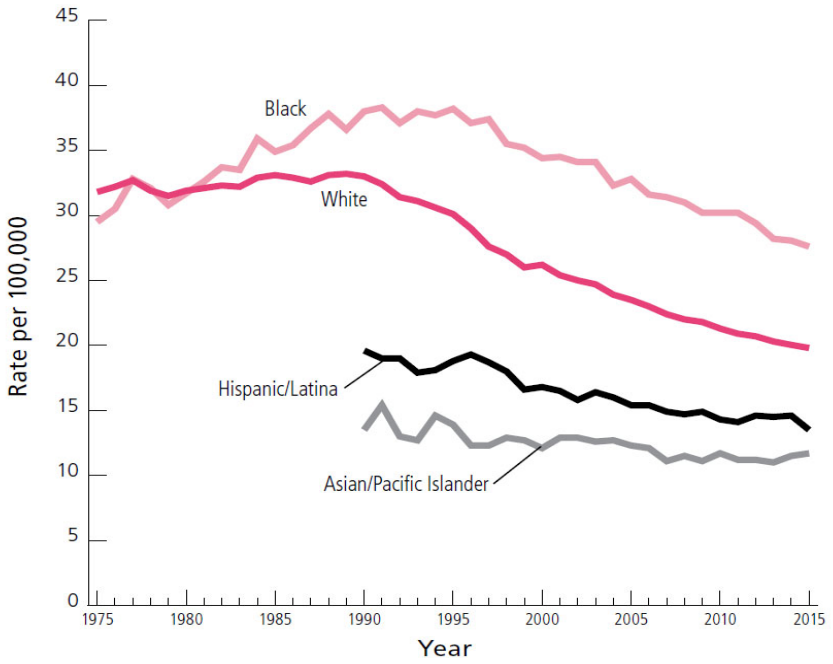
Figure 2. Female Breast Cancer Incidence Rates by Stage, US, 1975-2012(9)



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).(4) 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,(12) (Figure 3). Recent estimates examining the period between 2007 and 2016(3) suggest that the rate of decline per year was 1.8%.(3)

Figure 3. Female Breast Cancer Mortality Rates by Race and Ethnicity, US, 1975-2015(4)



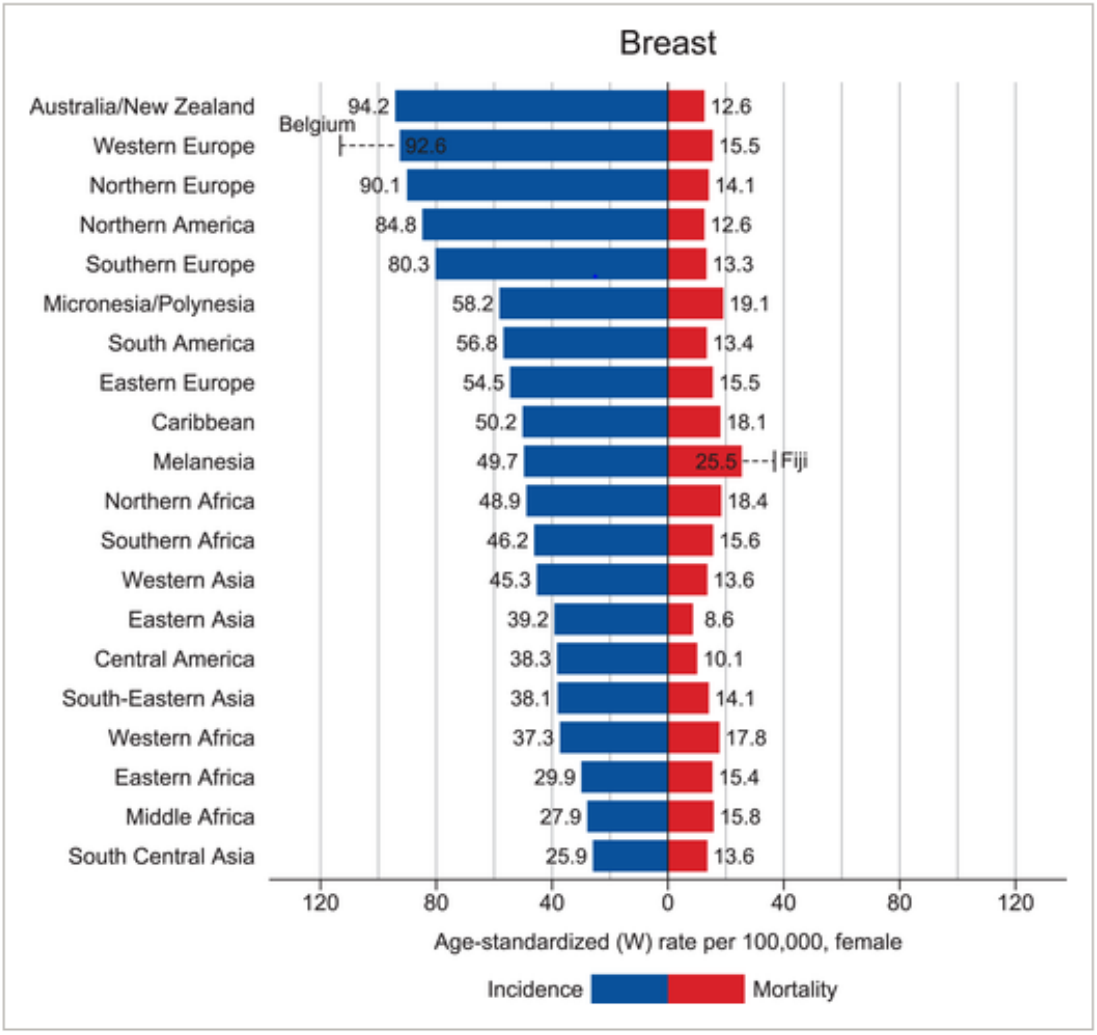
Source: US Mortality Files, National Center for Health Statics, Centers for Disease Control and Prevention, 2017. Rates for Hispanics exclude deaths from Louisiana, New Hampshire, and Oklahoma. Data for American Indian/Alaska Native not shown due to small counts and unstable rates. Rates are age adjusted 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.(3)

Note: Five-year survival rates, though often used, are not a sole indicator of progress.(13) The National Cancer Institute reports that 5-year breast cancer survival is 99% for women who are diagnosed with localized disease.(4) 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(13) 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.(14) 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 4).(1)

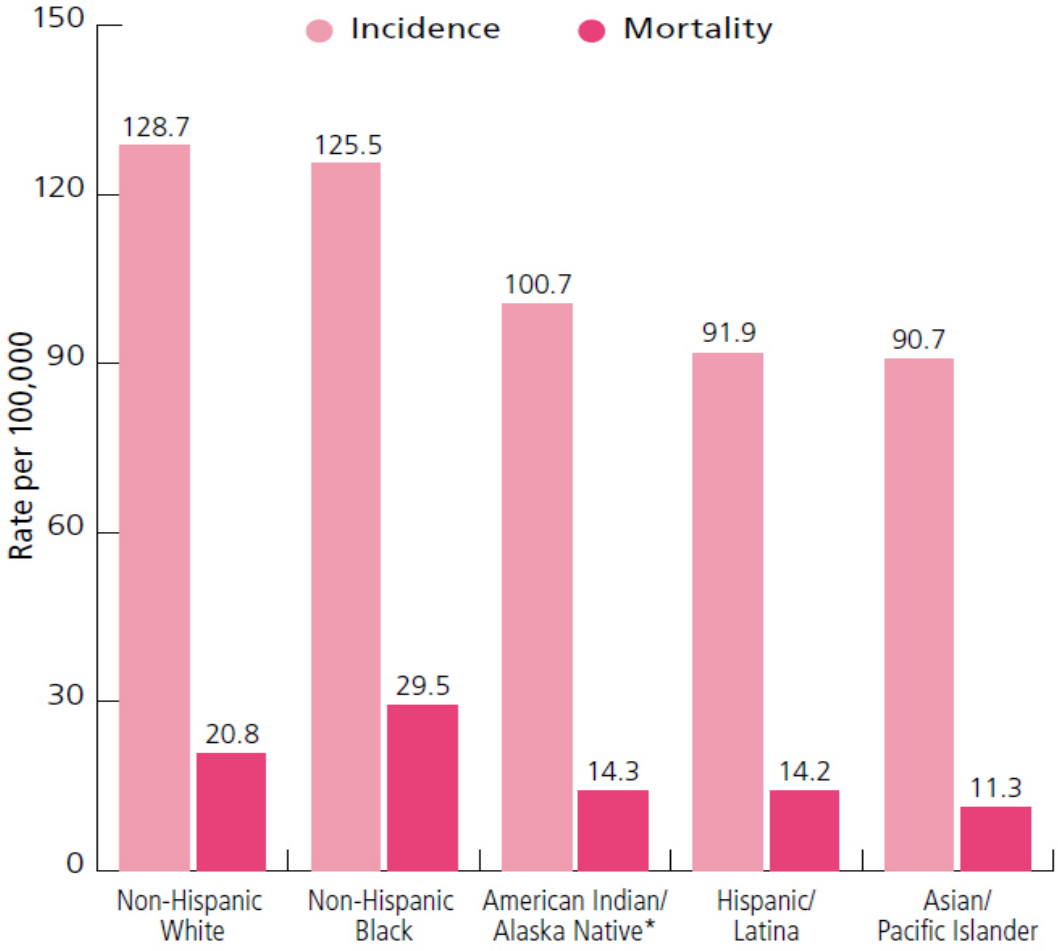
Figure 4. World Breast Cancer Incidence and Mortality Rates(1)



Source: Globocan 2018

In the United States, there is also considerable variation in breast cancer incidence and mortality rates by race/ethnicity. As shown in Figure 5,(4) 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(4)



*Statsitics 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 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).(15) Evidence attributes the majority of cancers to not one single factor but various physical, hormonal, environmental, and genetic factors.(4, 16) 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.(4) However, all of these factors are only weakly to moderately associated with breast cancer risk, with relative risks of <2.0.(4) 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.(17-20)

Radiation exposure is a well-established risk factor for breast cancer,(21) 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.(4) 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.(21) 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.(22, 23)

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+.(4) 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.(24)

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.(25)

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.(26, 27)

It has been estimated that approximately 155,000 women were living with metastatic breast cancer in the United States in 2017.(28) 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.(28) 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(28-31), and varies depending on a variety of factors, including age at diagnosis, tumor type, whether metastatic disease was diagnosed *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.(32, 33) 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.(34)

Table 1: Select clinical characteristics of breast cancer subtypes in women with invasive breast cancer, SEER-18, excluding Alaska, 2010(34)

		Overall number	Subtype				
			HR+/HER2−	Triple-negative	HR+/HER2+	HR−/HER2+	Unknown subtype
	All	n=57,483	n=36,810 (64%)	n=6,193 (10.8%)	n=5240 (9.1%)	n=2,328 (4%)	n=6,912 (12%)
Clinical Characteristic	Positive nodal status	16,085 (28.0%)	10,185 (27.7% of this subtype)	1,875 (30.3% of subtype)	1,800 (34.4% of subtype)	890 (38.2% of subtype)	1,335 (19.3% of unknown subtype)
			(63.3% of positive node)	(11.7% of positive node)	(11.2% of positive node)	(5.5% of positive node)	(8.3% of positive node)
	AJCC 7th stage IV	3,203 (5.6%)	1,532 (4.2% of this subtype)	379 (6.1% of this subtype)	370 (7.1% of this subtype)	223 (9.6% of this subtype)	699 (10.1% of unknown subtype)
			(47.8% of all stage IV)	(11.8% of all stage IV)	(11.6% of all stage IV)	(7.0% of all stage IV)	(21.8% of all stage IV)

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.(35, 36) 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.(37)

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.(38, 39)

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.(40)

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.(41) A subsequent meta-analysis showed a 5% reduction in 15-year breast cancer mortality risk.(42)

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.(43) 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(44) 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 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.(45)

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.(46)

An estimated 31% of all breast cancer cases (both invasive and DCIS) are considered to be overdiagnosed and overtreated.(47) 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.(47)

Drug Development

In 2018, the Pharmaceutical Research and Manufacturers of America reported that there were over 1,100 medicines and vaccines (or other immunotherapies) in clinical testing for the treatment of cancer, including at least 108 specific for breast cancer.(48) In addition, there are many clinical trials evaluating existing drugs in new combinations or at different stages of disease. A January 2019 search of ClinicalTrials.gov identifies 1,683 registered clinical trials currently ongoing or recruiting for the evaluation of drug interventions for breast cancer.(49) 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

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424. Epub 2018/09/13. doi: 10.3322/caac.21492. PubMed PMID: 30207593.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7-34. doi: 10.3322/caac.21551. PubMed PMID: 30620402.
3. American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019.
4. American Cancer Society. Breast Cancer. Facts & Figures 2017-2018. Atlanta: American Cancer Society; 2017.
5. Zhu K, Devesa SS, Wu H, Zahm SH, Jatoi I, Anderson WF, et al. Cancer incidence in the U.S. military population: comparison with rates from the SEER program. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009;18(6):1740-5. Epub 2009/06/10. doi: 10.1158/1055-9965.epi-09-0041. PubMed PMID: 19505907; PubMed Central PMCID: PMCPMC2780333.
6. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, et al. The decrease in breast-cancer incidence in 2003 in the United States. The New England journal of medicine. 2007;356(16):1670-4. Epub 2007/04/20. doi: 10.1056/NEJMsr070105. PubMed PMID: 17442911.
7. Allegra CJ, Aberle DR, Ganschow P, Hahn SM, Lee CN, Millon-Underwood S, et al. NIH state-of-the-science conference statement: diagnosis and management of ductal carcinoma in situ (DCIS). NIH consensus and state-of-the-science statements. 2009;26(2):1-27. Epub 2009/09/29. PubMed PMID: 19784089.
8. Globocan. Graph production: Global Cancer Observatory International Agency for Research on Cancer 2018 [cited International Agency for Research on Cancer]. Available from: http://gco.iarc.fr/.
9. SEER*Stat Database: (1975-2012). Bethesda, MD: National Cancer Institute Surveillance Research Program; 2015.
10. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness. The New England journal of

medicine. 2016;375(15):1438-47. Epub 2016/10/13. doi: 10.1056/NEJMoa1600249. PubMed PMID: 27732805.
11. Narod S, Iqbal J, AB M. Why have breast cancer mortality rates declined? Journal of Cancer Policy. 2015;5(September):8-17.
12. Noone A, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2015. https://seercancergov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Bethesda, MD: National Cancer Institute; 2018.
13. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? Jama. 2000;283(22):2975-8. Epub 2000/06/24. PubMed PMID: 10865276.
14. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. The New England journal of medicine. 2017;377(19):1836-46. doi: 10.1056/NEJMoa1701830. PubMed PMID: 29117498; PubMed Central PMCID: PMC5734609.
15. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. Journal of the National Cancer Institute. 1995;87(22):1681-5. Epub 1995/11/15. PubMed PMID: 7473816.
16. National Cancer Institute FactSheet: Breast Cancer Risk in American Woman. [cited 2017 November 29]. Available from: https://www.cancer.gov/types/breast/risk-fact-sheet.
17. Chlebowski RT, Chen Z, Cauley JA, Anderson G, Rodabough RJ, McTiernan A, et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(22):3582-90. Epub 2010/06/23. doi: 10.1200/jco.2010.28.2095. PubMed PMID: 20567009; PubMed Central PMCID: PMCPMC2917313.
18. Rennert G, Pinchev M, Rennert HS. Use of bisphosphonates and risk of postmenopausal breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(22):3577-81. Epub 2010/06/23. doi: 10.1200/jco.2010.28.1113. PubMed PMID: 20567021.
19. Gnant M. Can oral bisphosphonates really reduce the risk of breast cancer in healthy women? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(22):3548-51. Epub 2010/06/23. doi: 10.1200/jco.2010.29.6327. PubMed PMID: 20567005.
20. Chlebowski RT, McTiernan A, Wactawski-Wende J, Manson JE, Aragaki AK, Rohan T, et al. Diabetes, metformin, and breast cancer in postmenopausal women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(23):2844-52. Epub 2012/06/13. doi: 10.1200/jco.2011.39.7505. PubMed PMID: 22689798; PubMed Central PMCID: PMCPMC3826090.
21. Ma H, Hill CK, Bernstein L, Ursin G. Low-dose medical radiation exposure and breast cancer risk in women under age 50 years overall and by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast cancer research and treatment. 2008;109(1):77-90. Epub 2007/07/10. doi: 10.1007/s10549-007-9625-5. PubMed PMID: 17616809.
22. Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Nogues C, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations:

retrospective cohort study (GENE-RAD-RISK). BMJ (Clinical research ed). 2012;345:e5660. Epub 2012/09/08. doi: 10.1136/bmj.e5660. PubMed PMID: 22956590; PubMed Central PMCID: PMCPMC3435441.
23. Formenti SC, Preston-Martin S, Haffty BG. BRCA1/2 germline mutations: a marker for radioresistance or radiosensitivity? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2000;18(5):1159-60. Epub 2000/03/01. doi: 10.1200/jco.2000.18.5.1159. PubMed PMID: 10694571.
24. Tao L, Gomez SL, Keegan TH, Kurian AW, Clarke CA. Breast Cancer Mortality in African-American and Non-Hispanic White Women by Molecular Subtype and Stage at Diagnosis: A Population-Based Study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2015;24(7):1039-45. Epub 2015/05/15. doi: 10.1158/1055-9965.epi-15-0243. PubMed PMID: 25969506; PubMed Central PMCID: PMCPMC4490947.
25. Diseases of the Breast. 2nd ed. Harris J, Lippman M, Morrow M, al e, editors. Philadelphia: J.B. Lippincott, Williams & Wilkins; 2000.
26. Jin X, Mu P. Targeting Breast Cancer Metastasis. Breast cancer : basic and clinical research. 2015;9(Suppl 1):23-34. doi: 10.4137/BCBCR.S25460. PubMed PMID: 26380552; PubMed Central PMCID: PMC4559199.
27. Gupta GP, Massague J. Cancer metastasis: building a framework. Cell. 2006;127(4):679-95. doi: 10.1016/j.cell.2006.11.001. PubMed PMID: 17110329.
28. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2017;26(6):809-15. Epub 2017/05/20. doi: 10.1158/1055-9965.epi-16-0889. PubMed PMID: 28522448; PubMed Central PMCID: PMCPMC5833304.
29. Caswell-Jin JL, Plevritis SK, Tian L, Cadham CJ, Xu C, Stout NK, et al. Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review. JNCI cancer spectrum. 2018;2(4):pky062. doi: 10.1093/jncics/pky062. PubMed PMID: 30627694; PubMed Central PMCID: PMC6305243.
30. Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. Breast. 2017;31:46-50. doi: 10.1016/j.breast.2016.10.005. PubMed PMID: 27810699.
31. Tevaarwerk AJ, Gray RJ, Schneider BP, Smith ML, Wagner LI, Fetting JH, et al. Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: little evidence of improvement over the past 30 years. Cancer. 2013;119(6):1140-8. doi: 10.1002/cncr.27819. PubMed PMID: 23065954; PubMed Central PMCID: PMC3593800.
32. Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(13):1683-90. Epub 2007/04/04. doi: 10.1200/jco.2006.09.2106. PubMed PMID: 17404367.
33. Yu KD, Wu J, Shen ZZ, Shao ZM. Hazard of breast cancer-specific mortality among women with estrogen receptor-positive breast cancer after five years from diagnosis: implication for extended endocrine therapy. The Journal of clinical endocrinology and

metabolism. 2012;97(12):E2201-9. Epub 2012/09/21. doi: 10.1210/jc.2012-2423. PubMed PMID: 22993034.
34. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. Journal of the National Cancer Institute. 2014;106(5). Epub 2014/04/30. doi: 10.1093/jnci/dju055. PubMed PMID: 24777111; PubMed Central PMCID: PMCPMC4580552.
35. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. Jama. 2017;318(10):918-26. Epub 2017/09/13. doi: 10.1001/jama.2017.11470. PubMed PMID: 28898379; PubMed Central PMCID: PMCPMC5672806.
36. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. Jama. 2011;305(6):569-75. Epub 2011/02/10. doi: 10.1001/jama.2011.90. PubMed PMID: 21304082; PubMed Central PMCID: PMCPMC5389857.
37. National Comprehensive Cancer Network: Breast Cancer NCCN Guidelines for Patients: National Comprehensive Cancer Network; 2018 [cited 2019 January 10]. Available from: https://www.nccn.org/patients/guidelines/cancers.aspx.
38. EBCTCG. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. The New England journal of medicine. 1988;319(26):1681-92. Epub 1988/12/29. doi: 10.1056/nejm198812293192601. PubMed PMID: 3205265.
39. EBCTCG. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet (London, England). 1992;339(8784):1-15. Epub 1992/01/04. PubMed PMID: 1345950.
40. Multi-agent chemotherapy for early breast cancer. The Cochrane database of systematic reviews. 2002(1):CD000487. Epub 2002/03/01. doi: 10.1002/14651858.cd000487. PubMed PMID: 11869577.
41. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. The New England journal of medicine. 2002;347(16):1233-41. Epub 2002/10/24. doi: 10.1056/NEJMoa022152. PubMed PMID: 12393820.
42. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet (London, England). 2005;366(9503):2087-106. Epub 2005/12/20. doi: 10.1016/s0140-6736(05)67887-7. PubMed PMID: 16360786.
43. Mittendorf E, Hunt K. Breast cancer immunotherapy: Is it ready for prime time? Am J Hematol Oncol. 2015;11(9):6-9.

44. Emens L. How is Immunotherapy Changing the Outlook for Patients with Breast Cancer? New York, NY: Cancer Research Institute website; 2018 [cited 2019 January 14]. Available from: https://www.cancerresearch.org/we-are-cri/home/cancer-types/breast-cancer.
45. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. Journal of the National Cancer Institute. 2011;103(2):117-28. Epub 2011/01/14. doi: 10.1093/jnci/djq495. PubMed PMID: 21228314; PubMed Central PMCID: PMCPMC3107566.
46. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. The Lancet Oncology. 2005;6(8):557-65. Epub 2005/08/02. doi: 10.1016/s1470-2045(05)70251-5. PubMed PMID: 16054566.
47. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. The New England journal of medicine. 2012;367(21):1998-2005. Epub 2012/11/23. doi: 10.1056/NEJMoa1206809. PubMed PMID: 23171096.
48. PhRMA. Medicines in Development for Cancer. Washington, DC: Pharmaceutical Research and Manufacturers of America®; 2018. Available from: https://www.phrma.org/report/medicines-in-development-for-cancer-2018-report.
49. Clinicaltrials.gov search terms breast cancer and drug agents [cited 2019 January 22]. Available from: https://clinicaltrials.gov/.