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 (M) new cases.[1, 2] In the United States, in 2023, it is estimated that 297,790 women and 2,800 men will be diagnosed with invasive breast cancer, and another 55,720 women will be diagnosed with ductal carcinoma in situ (DCIS).[3][1] 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.[4] 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 2018, age-adjusted rates for new female breast cancer cases have been rising slightly by an average of 0.5% each year.[4, 5] The median age at diagnosis overall is 63 years, with slightly younger age for Black women (61 years) than White women (64 years).[6] Studies have found that military active-duty females have a 20% to 40% higher risk of breast cancer compared to the general population.[7] In 2022, approximately 17.5% of active-duty individuals were women.[8]

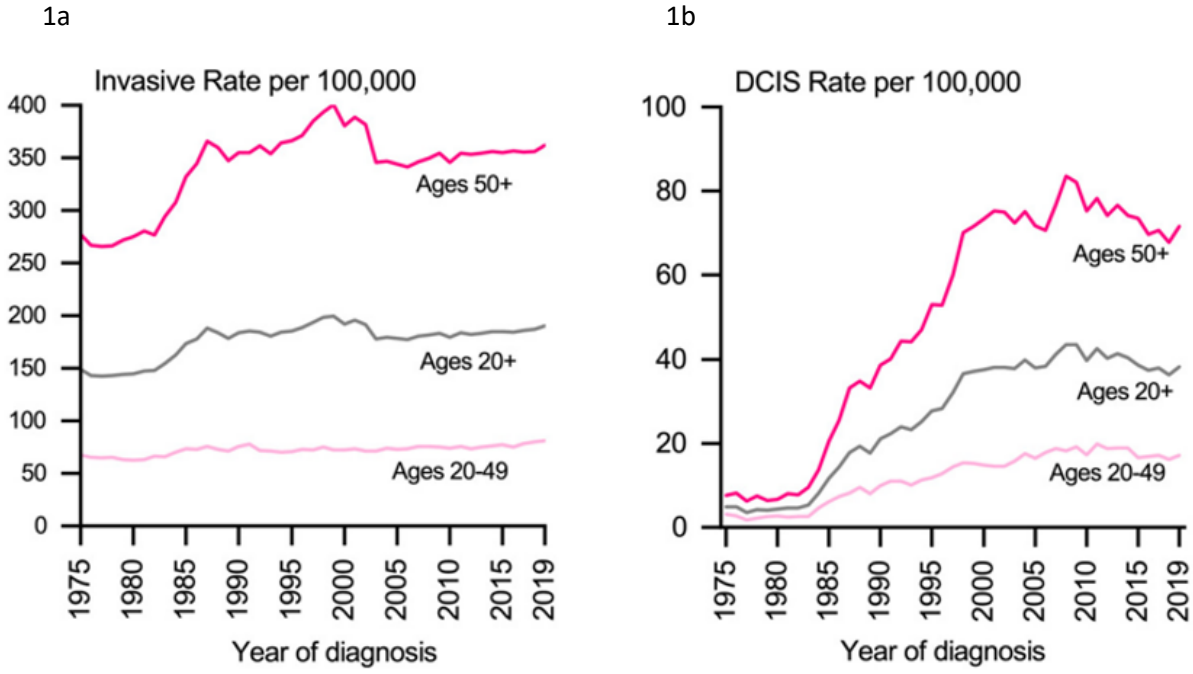
Incidence rates of invasive breast cancer among women <50 years of age have remained relatively stable over the past several decades (Figure 1a).[4] However, recent trends[5] show that among adolescent and young adult females (age 15 to 39 years), where the incidence of invasive breast cancer is relatively low (22.8 per 100,000), rates have been increasing by about 1.0% per year between 2010-2018. 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 in incidence among women over 50 years of age observed in 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.[9] This led to a rapid reduction in the number of women using hormone-replacement therapy. Since this time, rates have stabilized.

[1] In past years, the annual incidence of carcinoma in situ reflected both ductal and lobular carcinoma in situ (LCIS). However, LCIS was removed from the eighth edition (2017) of the American Joint Committee on Cancer (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 DCIS, a preinvasive, stage zero breast condition (Figure 1b). Prior to 1985, DCIS represented 2% of all breast cancer diagnoses. Following the introduction of screening, DCIS now represents nearly one-third of all screened-detected breast cancers.[10] The cause-specific survival rate of DCIS is nearly 100%, with recent studies[11, 12] estimating the standardized mortality ratio (SMR) for death from invasive breast cancer among women previously diagnosed with DCIS at just above 3.0 out to 15 years of follow-up. Notably, the SMR for breast cancer mortality decreases with increasing age at diagnosis of DCIS, being higher for women diagnosed with DCIS younger than the age of 50 years.[12] 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.[13]

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[14, 15] 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 reduce the problems of overdiagnosis and overtreatment, and that can detect cancers at a point where interventions can be made to avert morbidity and mortality.

Figure 1: U.S. Incidence Rates of Female Breast Cancer by Age, 1975-2019[4]



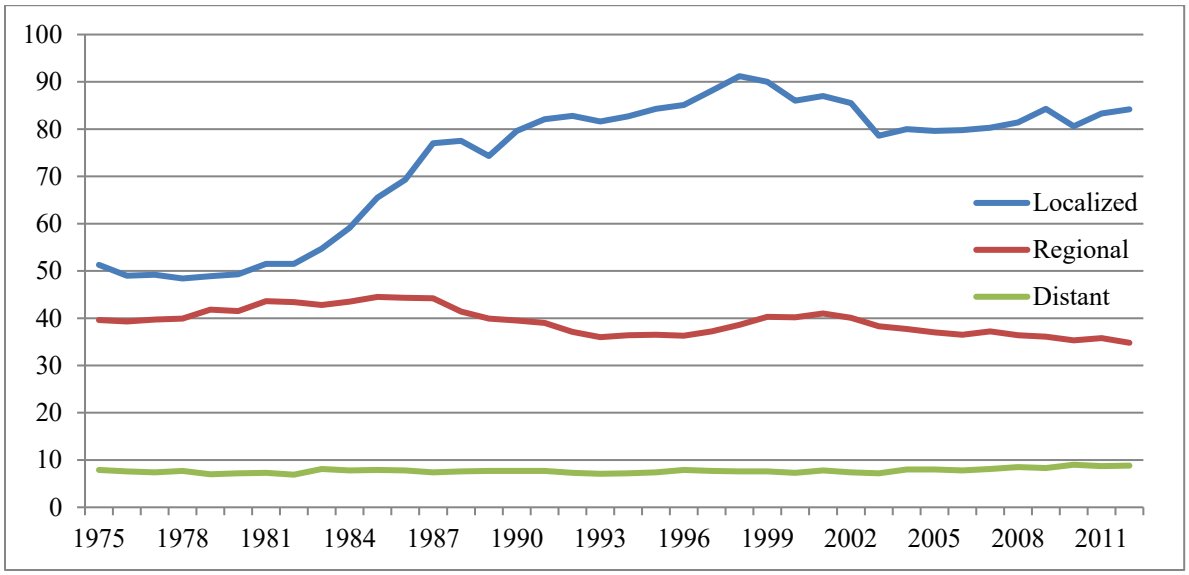
Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 8 Registries, National Cancer Institute, 2022. Rates are age adjusted to the 2000 U.S. standard population. Rates for invasive breast cancer are adjusted for delays in reporting.

Figure 2 presents long-term incidence data by stage at diagnosis retrieved from the Surveillance, Epidemiology, and End Results (SEER) 9 registries between the period of 1975 through 2012.[16] Figure 3 presents more recent trend data collected between the period of 2004 and 2019 from the SEER 22 registries.[4]

In Figure 2, incidence data were stratified using SEER historic staging criteria to define three categories of breast cancer stage at diagnosis: localized, regional, and distant breast cancer. As shown, the rate of metastatic breast cancer at initial diagnosis (i.e., distant disease) in the United States has not changed appreciably since 1975 despite widespread use of mammography for early detection, a finding consistent with other reports.[17, 18] In fact, between 2004 and 2011, distant-stage disease increased by about 2.4% annually.[4]

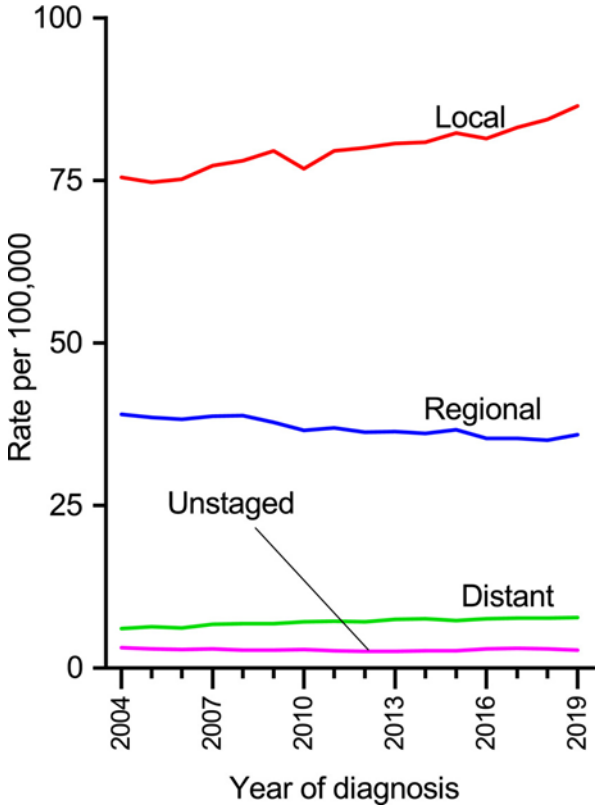
Figure 3 shows comparable data available between 2004 and 2019 from the SEER 22 registries which utilize an updated stage classification system (SEER Summary). As shown in Figure 3, the incidence rate for local-stage disease has been increasing by 0.9% per year and decreasing by about 0.7% per year for regional disease. Again, the incidence rate for distant-stage disease increased by 2.4% annually during 2004-2011 but has slowed to a 0.9% per year annual increase during 2015-2019.[4]

Figure 2. Female Breast Cancer Incidence Rates by Stage, U.S., 1975-2012[16]



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

Figure 3. Female Breast Cancer Incidence Rates by Stage, U.S., 2004-2019[4]



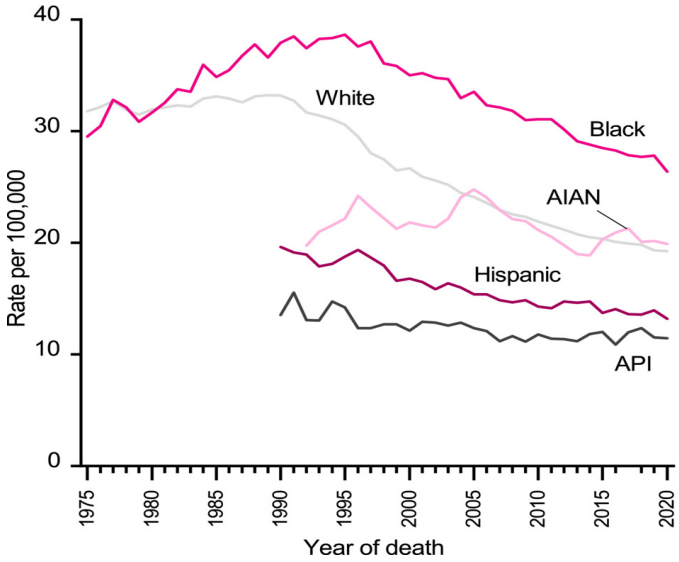
Source: SEER 22 areas (San Francisco, Connecticut, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, Georgia excluding ATL/RG, Idaho, New York, Massachusetts, Illinois, and Texas).

Breast Cancer Deaths

In 2020, there were 684,996 deaths from breast cancer globally.[1] In the United States, in 2023, it is estimated that 43,170 women and 530 men will die of breast cancer.[3] Between 2016-2020, the median age of death from breast cancer was 70 years.[19, 20] In 2040, with no major changes in prevention or treatment, it is estimated that 1.04M women will die from breast cancer worldwide.[2] 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.

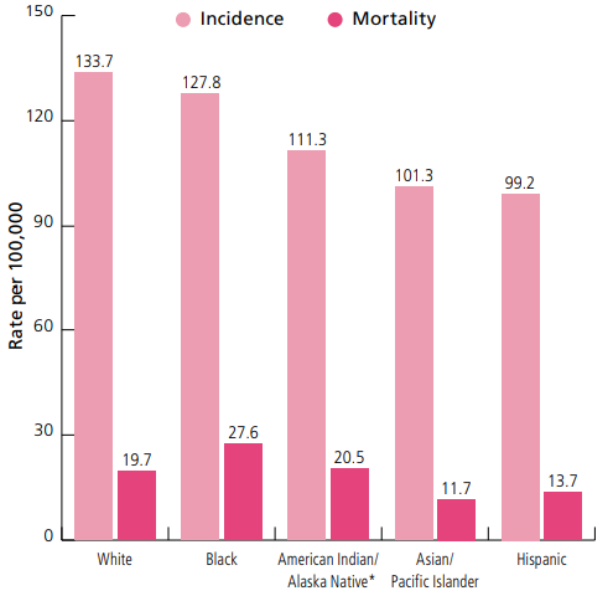
Between 1975 and 1990, breast cancer mortality rates in the United States increased, and then began decreasing in the late 1990s for all women. However, as seen in Figure 4, there are striking differences in the rate of breast cancer death by race and ethnicity, with non-Hispanic (NH) Black women having a 40% higher mortality rate compared with NH White women, despite a lower incidence of breast cancer (Figure 5).[4]

Figure 4. Female Breast Cancer Mortality Rates by Race and Ethnicity, U.S., 1975-2020[4]



Source: U.S. Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention, 2022. Rates are per 100,000 and age adjusted to the 2000 U.S. standard population. Race is exclusive of Hispanic origin, except for 1975-1989 for Black and White women. Rates for American Indian/Alaska Native (AIAN) are 3-year moving averages and are adjusted for racial misclassification. API refers to Asian/Pacific Islander.

Figure 5. Female Breast Cancer Incidence (2015-2019) and Death (2016-2020) Rates by Race/Ethnicity, U.S.[19]



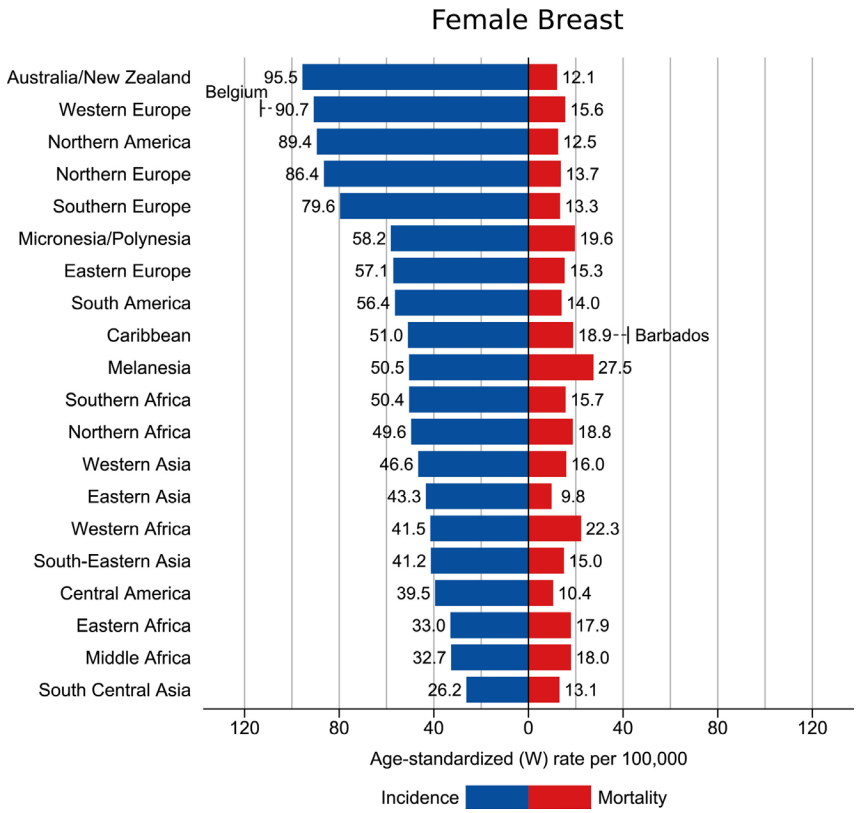
Source: Incidence – North American Association of Central Cancer Registries, 2022. Mortality – National Center for Health Statistics, Centers for Disease Control and Prevention, 2022. Rates are per 100,000 and age adjusted to the 2000 U.S. standard population. Incidence rates are confined to Purchased/Referred Care Delivery Area (PRCDA) counties, while mortality data are for the entire U.S. with adjustment factors for racial misclassification applied.

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 mortality reduction. The mortality rate was decreasing by about 1.9% annually between 1998 and 2011. Annual declines have slowed to 1.3% between 2011 and 2020, and to 1.1% between 2015 and 2019.[3, 4, 19] By race and ethnicity, the breast cancer death rates during 2014-2018 declined annually by 1.4% for NH Black women, 1.1% for Hispanic women, and 0.9% for NH White women.[19] 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.[4] However, screening influences the interpretation of 5-year survival rates because of lead-time bias and the detection of indolent cancer.[21] In addition, these numbers do not take breast cancer recurrence into account. The risk of local and distant (metastatic) recurrence varies greatly based on many factors. Estimates of long-term cumulative risk range from about 5% to 60%, with most estimates falling between 10% to 30%.[22-25] Among hormone-positive breast cancer patients with stage I or II disease, the rate of breast cancer metastatic recurrences over the period of 5 to 20 years following 5 years of adjuvant hormone therapy ranged from 10% to 41%, depending on the original tumor TN status and tumor grade.[24, 25]

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 6).[1]

Figure 6. World Breast Cancer Incidence and Mortality Rates[1]



Source: Globocan 2021

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), 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 (e.g., later age at first birth, nulliparity, family history of breast cancer, and higher socioeconomic status).[26] Evidence attributes the majority of cancers to not one single factor but various physical, hormonal, environmental, and genetic factors.[19] 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.[19] However, all of these factors are only weakly to moderately associated with breast cancer risk, with relative risks of <2.0.[19] Tamoxifen and raloxifene are the only drugs currently approved to reduce the risk of developing breast cancer; tamoxifen specifically in premenopausal women and raloxifene in postmenopausal women. A 2013 meta-analysis[27] of four randomized controlled trials of the use of tamoxifen in women at high-risk of developing breast cancer demonstrated a 33% reduction in risk, limited to estrogen receptor (ER)-positive (ER+) breast cancer. However, to date, a survival advantage has yet to be observed. There is also mixed evidence in relation to the impact of other commonly used medications on breast cancer risk, with observational and preclinical evidence that perhaps bisphosphonates and metformin may lower breast cancer risk.[28-32] However, recently published data from the MA.32 randomized adjuvant breast cancer trial reported that metformin (versus placebo) did not affect invasive disease-free, overall survival, or decrease the risk of developing any new invasive cancer, including a new contralateral invasive breast cancer.[33]

Radiation exposure is a well-established risk factor for breast cancer,[34] 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.[19, 35, 36] 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.[34] This higher risk begins about 8 years after such exposure and continues to be elevated for more than 25 years.

Importantly, evidence suggests 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.[37-41]

There is also emerging evidence[42] 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 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+ or HER2-negative but higher proliferation (Ki67); 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 data, in the United States, 68% of tumors are ER+ and/or PR+/HER2-, 10% are triple-negative, 10% are ER+ and/or PR+/HER2+, 4% are ER-/HER2+, and another 8% are classified as unknown.[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[43], though since the development of trastuzumab (Herceptin) the prognosis for patients with advanced or metastatic HER2+ breast cancer has improved.[44, 45]

At present, increased attention is being given to HER2 low-expressing breast cancer. That is, breast cancers that do possess low levels (1+ or 2+) of HER protein expression by immunohistochemistry and no HER2 gene amplification. Approximately 50% of non HER2+ breast cancers express low levels of HER2 protein. However, the clinical significance of this expression is yet unknown and is a field of ongoing study.[46-48] While there does not appear to be any biological difference in outcome for those with low levels of HER2 expression, new therapies are being developed that target chemotherapy to the HER2 protein expressed at low levels on cancer cells. Trastuzumab deruxtecan-nxki (T-DXd) was approved on August 5, 2022, for adult patients with unresectable or metastatic HER2-low breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Recurrence and Metastatic Disease

We still do not know how to prevent recurrence and metastasis for any individual woman. An estimated 10% to 30% of women diagnosed with invasive breast cancer will have a recurrence and may eventually die of their disease.[22-25]

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.[49, 50]

It has been estimated that approximately 140,230 women were living with metastatic breast cancer in the United States as of January 2018.[51] Of these women, nearly two-thirds (61.4%) were initially diagnosed with stages I to III breast cancer, who later progressed to metastatic disease. This number is projected to rise to 169,347 by the year 2025.[51] 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[45, 52-56], and varies depending on numerous 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.[25, 57, 58] Approximately 75% of breast cancer is ER-positive, and most breast cancer deaths occur in those with ER-positive disease. 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.[59]

Table 1: Select Clinical Characteristics of Breast Cancer Subtypes in Women with Invasive Breast Cancer, SEER-18, Excluding Alaska, 2010[59]

		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 20 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.[60, 61] 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 a given subtype.[62]

There are treatments targeted to some subtypes. For example, hormonal therapies, such as aromatase inhibitors and selective ER modulators, target ER-positive breast cancer. Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are used in combination with hormone therapy to treat advanced/metastatic and some high-risk early-stage ER-positive breast cancers. Trastuzumab, a monoclonal antibody, targets HER2-overexpressing breast cancer and, more recently, antibody drug conjugates (such as trastuzumab emtansine and trastuzumab deruxtecan), which target delivery of chemotherapy to HER2-expressing cells, have been approved. Importantly, *de* novo and acquired resistance are major issues with all known targeted therapies. Unfortunately, no targeted therapies in lieu of chemotherapy have been approved for triple-negative breast cancer (TNBC). Immune checkpoint inhibitors (e.g., pembrolizumab) combined with chemotherapy have been approved for patients with metastatic TNBC whose cancer cells express the PD-L1 protein (programmed death-ligand 1; Combined Positive Score ≥10) and for patients with high-risk, early-stage TNBC regardless of PD-L1 expression.[63]. Additionally, PARP inhibitors have been approved for patients with TNBC who have a BRCA mutation and whose cancer no longer responds to chemotherapy. A PARP inhibitor (olaparib) has also been approved for high-risk early-stage breast cancer in BRCA mutation carriers. BRCA carriers represent a small minority of patients with 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.[64, 65] 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 to 69, the age range when the majority of breast cancers are diagnosed.[66]

Standard adjuvant therapies have only a small (5% to 10%) impact on disease-specific survival. Until very recently, standard adjuvant therapies have been given to all individuals with breast cancer, with benefit to only a small proportion. This nonspecific approach derives from the fact that we do not know how to reliably identify which cancers will experience disease recurrence, and we do not understand how the heterogeneity within each tumor affects therapy response or recurrence. However, several genomic assays are now widely used in early-stage breast cancer to assess risk of cancer recurrence and to guide treatment decisions, including identification of patients who may safely forego adjuvant chemotherapy.[67-69]

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.[70] A subsequent meta-analysis showed a 5% reduction in 15-year breast cancer mortality risk.[71]

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.[72] 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.[73] A number are in clinical trials, including therapeutic vaccines directed against tumor-related antigens; checkpoint inhibitors combined with 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, as well as combined approaches of these agents.

Research related to breast cancer prevention has also recently expanded with two vaccines now in Phase 1 clinical trials.[2] Both trials are evaluating safety and immunogenicity of candidate vaccines in healthy individuals at high-risk of breast cancer.

Cost of Breast Cancer Treatment

The cost of treating breast cancer continues to rise. The national cost of cancer care overall in 2015 was shown to be $183 billion (B), with a minimum projected increase by 34% to $246B by 2030 based solely on the aging and growth of the U.S. population.[74] 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 ($26B).[74] Moreover, the out-of-pocket costs for patients in 2019 were highest for breast cancer at $3.14B.[75] Financial toxicity from both direct and indirect expenses linked to treatment is also high among breast cancer patients, with as many as 35% of breast cancer patients in high-income countries and 79% in low- and middle-income countries being affected.[76]

[2] See ClinicalTrials.gov, NCT04674306: a Phase 1b expansion cohort in this trial includes participants with a genetic risk for developing TNBC who plan to undergo prophylactic mastectomy. ClinicalTrials.gov, NCT04367675: an experimental vaccine among people with BRCA1 or BRCA2 mutations. It likewise includes a Phase 1b expansion cohort of cancer-free individuals.

Morbidity and Mortality Caused by Treatments

Traditional breast cancer treatments, such as chemotherapy and HER2-targeted agents, 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.[77]

The introduction of a host of targeted agents and immune checkpoint inhibitors have resulted in the emergence of a number of less-well characterized treatment-related toxicities. These include hematologic, endocrine, pulmonary, gastrointestinal, dermatologic, hepatic, and immune-mediated toxicities, among others. Varied combinations of drugs along with orally administered drugs are also an important cause of treatment-related morbidity. Side effects of targeted agents tend to present early in the course of treatment and require swift identification and multidisciplinary management, particularly for life-threatening toxicities such as interstitial lung disease and pneumonitis.[78, 79]

An estimated 31% of all breast cancer cases (both invasive and DCIS) are considered to be overdiagnosed and overtreated.[80] Overtreatment can occur in two ways—either in overdiagnosis, where any treatment subsequently administered is unnecessary, or with the administration of more aggressive therapies than is necessary.

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.[81] As of September 2023, there are 83 drugs including chemotherapy, targeted agents, and immune checkpoint inhibitors that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer, and four drugs approved for the prevention of breast cancer.[82] A total of 19 of these drugs were approved by the FDA, for a total of 30 different breast cancer indications between the period of 2010 and 2020. All but one of these drugs were targeted agents.[83] One additional new drug, elacestrant (Orserdu), an oral estrogen receptor antagonist was approved by the FDA between 2021 and 2023, along with expanded indications of previously approved breast cancer drugs. In addition, there are many clinical trials (interventional) evaluating new drugs, existing drugs in new combinations. or at different stages of disease. A recent search of ClinicalTrials.gov shows over 2,115 clinical trials currently ongoing (not recruiting) or recruiting for the evaluation of drug interventions for breast cancer.[84] 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. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* CA Cancer J Clin, 2021. **71**(3): p. 209-249.
2. Arnold, M., et al., *Current and future burden of breast cancer: Global statistics for 2020 and 2040.* Breast, 2022. **66**: p. 15-23.
3. Siegel, R.L., et al., *Cancer statistics, 2023.* CA Cancer J Clin, 2023. **73**(1): p. 17-48.
4. Giaquinto, A.N., et al., *Breast Cancer Statistics, 2022.* CA Cancer J Clin, 2022.
5. Cronin, K.A., et al., *Annual report to the nation on the status of cancer, part 1: National cancer statistics.* Cancer, 2022. **128**(24): p. 4251-4284.
6. *National Cancer Institute SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program*. 2023 [cited 2023 Sep 5]; Available from: https://seer.cancer.gov/statistics-network/explorer/.
7. Zhu, K., et al., *Cancer incidence in the U.S. military population: comparison with rates from the SEER program.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(6): p. 1740-5.
8. *Active Duty Master Personnel File, Military Academies*. 2022.
9. Ravdin, P.M., et al., *The decrease in breast-cancer incidence in 2003 in the United States.* N Engl J Med, 2007. **356**(16): p. 1670-4.
10. Punglia, R.S., et al., *Epidemiology, Biology, Treatment, and Prevention of Ductal Carcinoma In Situ (DCIS).* JNCI Cancer Spectr, 2018. **2**(4): p. pky063.
11. Giannakeas, V., V. Sopik, and S.A. Narod, *Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer.* JAMA Netw Open, 2020. **3**(9): p. e2017124.
12. Elshof, L.E., et al., *Cause-specific Mortality in a Population-based Cohort of 9799 Women Treated for Ductal Carcinoma In Situ.* Ann Surg, 2018. **267**(5): p. 952-958.
13. Allegra, C.J., et al., *NIH state-of-the-science conference statement: diagnosis and management of ductal carcinoma in situ (DCIS).* NIH Consens State Sci Statements, 2009. **26**(2): p. 1-27.
14. Shieh, Y., et al., *Breast Cancer Screening in the Precision Medicine Era: Risk-Based Screening in a Population-Based Trial.* J Natl Cancer Inst, 2017. **109**(5).
15. *MyPeBS (My Personalized Breast Screening) trial*. [cited 2021 September 22]; Available from: https://clinicaltrials.gov/ct2/show/NCT03672331.
16. *SEER*Stat Database: (1975-2012).* 2015, National Cancer Institute Surveillance Research Program: Bethesda, MD.
17. Welch, H.G., et al., *Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness.* N Engl J Med, 2016. **375**(15): p. 1438-1447.
18. Narod, S., J. Iqbal, and M. AB, *Why have breast cancer mortality rates declined?* Journal of Cancer Policy, 2015. **5**(September): p. 8-17.
19. *American Cancer Society. Breast Cancer. Facts & Figures 2022-2024*. 2022, American Cancer Society: Atlanta.
20. National Cancer Institute. Surveillance, E., and End Results Program, *Cancer Stat Facts: Female Breast Cancer*. 2022.
21. Welch, H.G., L.M. Schwartz, and S. Woloshin, *Are increasing 5-year survival rates evidence of success against cancer?* JAMA, 2000. **283**(22): p. 2975-8.

22. Saphner, T., D.C. Tormey, and R. Gray, *Annual hazard rates of recurrence for breast cancer after primary therapy.* J Clin Oncol, 1996. **14**(10): p. 2738-46.
23. Colleoni, M., et al., *Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V.* J Clin Oncol, 2016. **34**(9): p. 927-35.
24. Pan, H., et al., *20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years.* N Engl J Med, 2017. **377**(19): p. 1836-1846.
25. Pedersen, R.N., et al., *The Incidence of Breast Cancer Recurrence 10-32 Years After Primary Diagnosis.* J Natl Cancer Inst, 2022. **114**(3): p. 391-399.
26. Madigan, M.P., et al., *Proportion of breast cancer cases in the United States explained by well-established risk factors.* J Natl Cancer Inst, 1995. **87**(22): p. 1681-5.
27. Cuzick, J., et al., *Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data.* Lancet, 2013. **381**(9880): p. 1827-34.
28. Chlebowski, R.T., et al., *Oral bisphosphonate use and breast cancer incidence in postmenopausal women.* J Clin Oncol, 2010. **28**(22): p. 3582-90.
29. Rennert, G., M. Pinchev, and H.S. Rennert, *Use of bisphosphonates and risk of postmenopausal breast cancer.* J Clin Oncol, 2010. **28**(22): p. 3577-81.
30. Gnant, M., *Can oral bisphosphonates really reduce the risk of breast cancer in healthy women?* J Clin Oncol, 2010. **28**(22): p. 3548-51.
31. Chlebowski, R.T., et al., *Diabetes, metformin, and breast cancer in postmenopausal women.* J Clin Oncol, 2012. **30**(23): p. 2844-52.
32. Li, C.I., et al., *Bisphosphonate Use and Breast Cancer Risk among Women with Ductal Carcinoma In Situ.* Cancer Res, 2021. **81**(10): p. 2799-2802.
33. Goodwin, P.J., et al., *Effect of Metformin Versus Placebo on New Primary Cancers in Canadian Cancer Trials Group MA.32: A Secondary Analysis of a Phase III Randomized Double-Blind Trial in Early Breast Cancer.* J Clin Oncol, 2023: p. JCO2300296.
34. Ma, H., et al., *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 Res Treat, 2008. **109**(1): p. 77-90.
35. Ibrahim, E.M., et al., *Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis.* BMC Cancer, 2012. **12**: p. 197.
36. Holmqvist, A.S., et al., *Risk of solid subsequent malignant neoplasms after childhood Hodgkin lymphoma-Identification of high-risk populations to guide surveillance: A report from the Late Effects Study Group.* Cancer, 2019. **125**(8): p. 1373-1383.
37. Pijpe, A., et al., *Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK).* BMJ, 2012. **345**: p. e5660.
38. Formenti, S.C., S. Preston-Martin, and B.G. Haffty, *BRCA1/2 germline mutations: a marker for radioresistance or radiosensitivity?* J Clin Oncol, 2000. **18**(5): p. 1159-60.
39. Colin C, F.N., Di Leo G, Sardanelli F, *Radiation induced breast cancer risk in BRCA mutation carriers from low-dose radiological exposures: a systematic review.* Radioprotection, 2017. **52**(4): p. 231–240

40. Eidemuller, M., et al., *Evidence for Increased Susceptibility to Breast Cancer From Exposure to Ionizing Radiation Due to a Familial History of Breast Cancer: Results From the Swedish Hemangioma Cohort.* Am J Epidemiol, 2021. **190**(1): p. 76-84.
41. Jansen-van der Weide, M.C., et al., *Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis.* Eur Radiol, 2010. **20**(11): p. 2547-56.
42. Barnard, M.E., C.E. Boeke, and R.M. Tamimi, *Established breast cancer risk factors and risk of intrinsic tumor subtypes.* Biochim Biophys Acta, 2015. **1856**(1): p. 73-85.
43. Tao, L., et al., *Breast Cancer Mortality in African-American and Non-Hispanic White Women by Molecular Subtype and Stage at Diagnosis: A Population-Based Study.* Cancer Epidemiol Biomarkers Prev, 2015. **24**(7): p. 1039-45.
44. Howlader, N., et al., *Differences in Breast Cancer Survival by Molecular Subtypes in the United States.* Cancer Epidemiol Biomarkers Prev, 2018. **27**(6): p. 619-626.
45. Grinda, T., et al., *Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort.* ESMO Open, 2021. **6**(3): p. 100114.
46. Tarantino, P., et al., *HER2-Low Breast Cancer: Pathological and Clinical Landscape.* J Clin Oncol, 2020. **38**(17): p. 1951-1962.
47. Miglietta, F., et al., *Evolution of HER2-low expression from primary to recurrent breast cancer.* NPJ Breast Cancer, 2021. **7**(1): p. 137.
48. Marchio, C., et al., *Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond.* Semin Cancer Biol, 2021. **72**: p. 123-135.
49. Jin, X. and P. Mu, *Targeting Breast Cancer Metastasis.* Breast Cancer (Auckl), 2015. **9**(Suppl 1): p. 23-34.
50. Gupta, G.P. and J. Massague, *Cancer metastasis: building a framework.* Cell, 2006. **127**(4): p. 679-95.
51. Gallicchio, L., et al., *Estimation of the numbers of individuals living with metastatic cancer in the United States.* J Natl Cancer Inst, 2022.
52. Caswell-Jin, J.L., et al., *Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review.* JNCI Cancer Spectr, 2018. **2**(4): p. pky062.
53. Mariotto, A.B., et al., *Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States.* Cancer Epidemiol Biomarkers Prev, 2017. **26**(6): p. 809-815.
54. Sundquist, M., L. Brudin, and G. Tejler, *Improved survival in metastatic breast cancer 1985-2016.* Breast, 2017. **31**: p. 46-50.
55. Tevaarwerk, A.J., 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): p. 1140-8.
56. Gong, Y., et al., *Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study.* Sci Rep, 2017. **7**: p. 45411.
57. Jatoi, I., et al., *Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis.* J Clin Oncol, 2007. **25**(13): p. 1683-90.

58. Yu, K.D., et al., *Hazard of breast cancer-specific mortality among women with estrogen receptor-positive breast cancer after five years from diagnosis: implication for extended endocrine therapy.* J Clin Endocrinol Metab, 2012. **97**(12): p. E2201-9.
59. Howlader, N., et al., *US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status.* J Natl Cancer Inst, 2014. **106**(5).
60. Giuliano, A.E., 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): p. 918-926.
61. Giuliano, A.E., 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): p. 569-75.
62. *National Comprehensive Cancer Network: Breast Cancer NCCN Guidelines*. 2023 [cited 2023 September 29]; Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419
63. *FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer*. 2021 [cited 2021 September 20]; Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-high-risk-early-stage-triple-negative-breast-cancer.
64. 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.* N Engl J Med, 1988. **319**(26): p. 1681-92.
65. 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, 1992. **339**(8784): p. 1-15.
66. *Multi-agent chemotherapy for early breast cancer.* Cochrane Database Syst Rev, 2002(1): p. CD000487.
67. Sparano, J.A., et al., *Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer.* N Engl J Med, 2018. **379**(2): p. 111-121.
68. Audeh, W., et al., *Prospective Validation of a Genomic Assay in Breast Cancer: The 70-gene MammaPrint Assay and the MINDACT Trial.* Acta Med Acad, 2019. **48**(1): p. 18-34.
69. Taylor, C., J. Meisel, and K. Kalinsky, *Are we closer to being able to select patients with node-positive hormone receptor-positive breast cancer who can safely omit chemotherapy?* Ther Adv Med Oncol, 2022. **14**: p. 17588359221084769.
70. Fisher, B., 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.* N Engl J Med, 2002. **347**(16): p. 1233-41.
71. Clarke, M., 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, 2005. **366**(9503): p. 2087-106.
72. Mittendorf, E. and K. Hunt, *Breast cancer immunotherapy: Is it ready for prime time?* Am J Hematol Oncol., 2015. **11**(9): p. 6-9.
73. Zhang, L., et al., *Recent Progress on Therapeutic Vaccines for Breast Cancer.* Front Oncol, 2022. **12**: p. 905832.

74. Mariotto, A.B., et al., *Medical Care Costs Associated with Cancer Survivorship in the United States.* Cancer Epidemiol Biomarkers Prev, 2020. **29**(7): p. 1304-1312.
75. Yabroff, K.R., et al., *Annual Report to the Nation on the Status of Cancer, Part 2: Patient Economic Burden Associated With Cancer Care.* J Natl Cancer Inst, 2021.
76. Ehsan, A.N., et al., *Financial Toxicity Among Patients With Breast Cancer Worldwide: A Systematic Review and Meta-analysis.* JAMA Netw Open, 2023. **6**(2): p. e2255388.
77. Darby, S.C., et al., *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.* Lancet Oncol, 2005. **6**(8): p. 557-65.
78. Anders, C.K., et al., *What's the Price? Toxicities of Targeted Therapies in Breast Cancer Care.* Am Soc Clin Oncol Educ Book, 2020. **40**: p. 55-70.
79. Cazzaniga, M.E., et al., *Management of toxicities associated with targeted therapies for HR-positive metastatic breast cancer: a multidisciplinary approach is the key to success.* Breast Cancer Res Treat, 2019. **176**(3): p. 483-494.
80. Bleyer, A. and H.G. Welch, *Effect of three decades of screening mammography on breast-cancer incidence.* N Engl J Med, 2012. **367**(21): p. 1998-2005.
81. PhRMA. *Medicines in Development for Cancer.* 2020; Available from: https://www.phrma.org/medicines-in-development/medicines-in-development-for-cancer-2020-report.
82. *NCI. Drugs Approved for Breast Cancer*. [cited 2023 September 29]; Available from: https://www.cancer.gov/about-cancer/treatment/drugs/breast.
83. Arora, S., et al., *U.S. FDA Drug Approvals for Breast Cancer: A Decade in Review.* Clin Cancer Res, 2022. **28**(6): p. 1072-1086.
84. *Clinicaltrials.gov search terms breast cancer and interventions*. [cited 2023 September 29]; Available from: https://clinicaltrials.gov/.