American Cancer Society®

Breast Cancer
Facts & Figures 2022-2024

Contents

This publication attempts to summarize current scientific information about breast cancer. Except when specified, it does not represent the official policy of the American Cancer Society.

Suggested citation: American Cancer Society. *Breast Cancer Facts & Figures 2022-2024.* Atlanta: American Cancer Society, Inc. 2022.

Breast Cancer Basic Facts

What is breast cancer?

Breast cancer is a group of diseases in which cells in a person's breast tissue change and divide uncontrolled, typically resulting in a lump or mass. Most breast cancers begin in the milk glands (lobules) or in the tubes (ducts) that connect the milk glands to the nipple.

What are the signs and symptoms of breast cancer?

Breast cancer typically has no symptoms when the tumor is small and most easily treated, which is why breast cancer screening is important for early detection. The most common physical sign is a painless lump. Sometimes breast cancer can spread to underarm lymph nodes and cause a lump or swelling even before the original breast tumor is large enough to be felt. Less common signs and symptoms include breast pain or heaviness; dimpling, swelling, thickening, or redness of the breast skin; and nipple changes, such as spontaneous discharge (especially if bloody), scaliness, or retraction. Any persistent change in the breast should be evaluated by a physician.

How is breast cancer diagnosed?

Breast cancer is typically detected during mammography screening, before symptoms have developed (asymptomatic), or after a woman notices a lump or change in the breast (symptomatic). Detection after symptoms develop is more common among younger women who have not started breast cancer screening, older women who are no longer recommended for screening, and those who lack access to preventive screening. Most screen-detected masses turn out to be benign (not cancerous). When cancer is suspected, a biopsy is needed to establish the diagnosis through microscopic analysis. A needle biopsy (fine-needle or larger core-needle) is most common, but sometimes a surgical biopsy is performed. Selection of the type of biopsy is based on multiple factors, including the size and location of the mass, patient factors and preferences, and resources.

How is breast cancer staged?

The extent of cancer and its spread at the time of diagnosis, as well as microscopic characteristics of the tumor, determine its stage. Cancer stage is the best predictor of prognosis (disease outcome) and is essential for guiding treatment options. The two main staging systems for breast cancer are the American Joint Committee on Cancer (AJCC) staging system, typically used in clinical settings, and the Surveillance, Epidemiology, and End Results (SEER) summary staging system, reported by cancer registries and used in surveillance research to measure the success of cancer control efforts.

The AJCC staging system incorporates anatomic and biologic information about the cancer to create a prognostic stage. Anatomic stage is based on TNM classification, including the size of the tumor (T) and whether cancer cells have spread to regional lymph nodes (N) or have metastasized (M) to distant lymph nodes and/or organs. Prognostic stage additionally includes information on biomarkers, such as estrogen receptor (ER) and progesterone receptor (PR) status, level of human epidermal growth factor 2 (HER2, a growth-promoting protein), and grade (similarity of the cancer's microscopic appearance to normal breast tissue).[1] In this document, we refer to SEER summary stage except in the section on breast cancer treatment (page 25), which is described using AJCC staging.

According to the SEER summary stage system:

- In situ refers to the presence of abnormal cells that are confined to the layer of cells where they originated.
- Local stage refers to invasive cancer that is confined to the breast.
- Regional stage refers to cancer that has spread to surrounding tissue and/or lymph nodes.
- Distant stage refers to cancer that has spread to distant organs and/or lymph nodes, including nodes above the collarbone.

What are the types of breast cancer?

Breast cancer is a collection of many related diseases with different biologic, clinical, and prognostic characteristics. In addition to being classified by their stage (as previously described), breast cancers are further grouped based on microscopic appearance and molecular traits.

Ductal carcinoma in situ

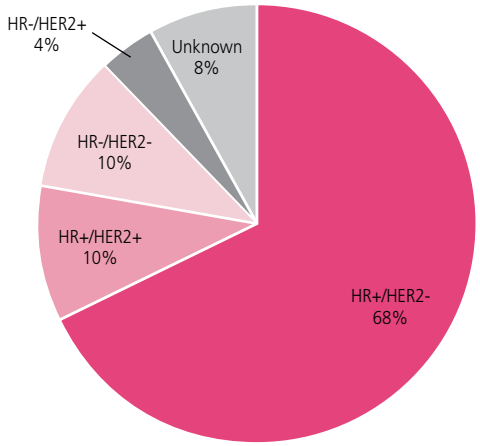
Although ductal carcinoma in situ (DCIS) is not a true cancer, it represents about one in six newly diagnosed breast cancers overall, and even more screen-detected cancers. DCIS, or stage 0 breast cancer, refers to presumably malignant cells that are confined to the mammary ducts. It is considered a precursor to invasive cancer and is associated with increased risk of subsequent invasive breast cancer. However, not all DCIS lesions progress to invasive cancer.[1, 2] Although long-term follow-up studies of women with untreated DCIS report progression to invasive breast cancer ranging from 10% to 53%,[3-5, 6] a recent modeling study suggests that over 64% of DCIS progresses.[7] The wide range is likely due to the heterogeneity of DCIS. Women with DCIS who are premenopausal and those with large or high-grade masses that can be felt are at greatest risk of future invasive breast cancer.[8, 9] Multiple studies are investigating how to distinguish high-risk DCIS that requires treatment from low-risk DCIS that can be safely managed with active surveillance (close monitoring) to reduce risk of overtreatment.[6]

See breast cancer risk factors on page 12 for information on LCIS (lobular carcinoma in situ) and additional information on DCIS.

Invasive

Most (83%) breast cancers are invasive, or infiltrating, which means the cancer cells have broken through the wall of the glands or ducts where they originated and grown into surrounding breast tissue with the potential to spread to other parts of the body.

Figure 1. Distribution of Female Breast Cancer Subtypes, US, 2015-2019



HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.
Source: North American Association of Central Cancer Registries (NAACCR), 2022.

Histologic subtypes

Histologic subtypes are based on the size, shape, and arrangement of cancer cells. Approximately 75% of invasive breast cancers are histologically categorized as "invasive ductal carcinoma." The second most common subtype is invasive lobular carcinoma, representing about 10% of invasive breast cancers. Medullary, tubular, mucinous, and cribriform carcinomas are rare subtypes that are generally associated with a favorable prognosis.[10-12] Inflammatory breast carcinoma is an uncommon (0.3% of invasive breast cancers) but aggressive subtype that spreads to the skin of the breast, which becomes red and swollen.

Molecular subtypes

Breast cancer is further classified by molecular characteristics that are associated with clinical presentation, response to therapy, and prognosis. The four broad molecular subtypes are Luminal A, Luminal B, basal-like, and HER2-enriched. These subtypes were originally defined by gene expression profiling but are often approximated based on simpler tests that determine ER, PR, and HER2 status. Hormone receptor positive (HR+) cancers are those that test positive for ER or PR, or both. Information about tumor grade and proliferation (rate of cell division) is also sometimes used to assign subtype.[13]

- **HR+/HER2-** Surrogate for Luminal A. This is the most common molecular subtype of breast cancer, accounting for 68% of all cases (Figure 1). This subtype tends to be slower-growing and less aggressive than other subtypes and responds to hormone therapy (see page 28).[14]
- **HR+/HER2+** Surrogate for Luminal B. This subtype was originally characterized as always HER2+, but is now defined as being positive for HER2 and/or a specific protein indicative of rapidly dividing cells (Ki67). It accounts for approximately 10% of all breast cancers and is often higher grade than Luminal A and associated with poorer outcomes.[15]
- **HR-/HER2-** Surrogate for basal-like. These cancers are also called triple-negative breast cancer (TNBC) because they are negative for all three biomarkers. This is generally a more aggressive type of tumor, with higher risk of metastasis and recurrence.[16, 17] TNBC accounts for 10% of breast cancers overall, but nearly 20% among African American women, who have the highest incidence. Risk is also higher among young women and those with a *BRCA1* gene variant.[18-20]
- **HR-/HER2+** Surrogate for HER2-enriched. This is the least common breast cancer subtype, accounting for 4% of all diagnoses. In the past, this subtype had the worst prognosis; however, the development of targeted therapies for HER2+ cancers has substantially improved outcomes.[3, 21, 22]

For information about the treatment of breast cancer subtypes, see page 25.

Breast Cancer Occurrence

How many cases and deaths are expected to occur in 2022?

In the US in 2022, an estimated 287,850 new cases of invasive breast cancer will be diagnosed among women and 43,250 women will die from the disease (Table 1). In addition, an estimated 51,400 cases of DCIS will be diagnosed among women. Although breast cancer is predominantly a female disease, approximately 2,710 new cases and 530 deaths (about 1% of all breast cancer cases and deaths) will occur among men.

Table 1. Estimated New DCIS and Invasive Breast Cancer Cases and Deaths Among Women by Age, US, 2022

	DCIS cases		Invasive cases		Deaths	
Age	**Number**	**%**	**Number**	**%**	**Number**	**%**
<40	1,230	2%	10,850	4%	1,090	3%
40-49	8,050	16%	36,710	13%	2,950	7%
50-59	12,830	26%	65,980	23%	7,150	17%
60-69	16,030	31%	84,200	29%	10,270	24%
70-79	10,450	20%	61,470	21%	10,010	23%
80+	2,810	5%	28,640	10%	11,780	27%
All ages	**51,400**		**287,850**		**43,250**	

Estimates are rounded to the nearest 10. Percentages may not sum to 100 due to rounding. DCIS = Ductal carcinoma in situ.

How many women alive today have ever had breast cancer?

More than 4 million US women with a history of invasive breast cancer were alive on January 1, 2022.[23] Some of these women were cancer-free, while others still had evidence of cancer and may have been undergoing treatment. More than 150,000 breast cancer survivors are living with metastatic (stage IV) disease, three-fourths of whom were originally diagnosed with stage I-III cancer.[24]

What is the risk of breast cancer diagnosis or death?

Approximately 1 in 8 women (13%) will be diagnosed with invasive breast cancer in her lifetime and 1 in 39 women (3%) will die from breast cancer (Table 2). Lifetime risk is an average risk for all women and accounts

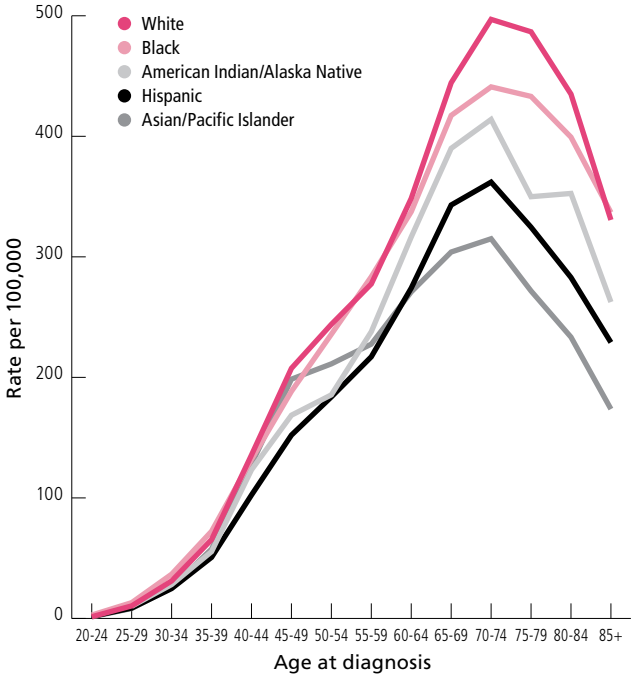
Table 2. Age-specific Ten-year Probabilities of Breast Cancer Diagnosis or Death for US Women, 2017-2019

Current age	Diagnosed with invasive breast cancer	Dying from breast cancer
20	0.1% (1 in 1,439)	<0.1% (1 in 18,029)
30	0.5% (1 in 204)	<0.1% (1 in 2,045)
40	1.6% (1 in 63)	0.1% (1 in 674)
50	2.4% (1 in 41)	0.3% (1 in 324)
60	3.5% (1 in 28)	0.5% (1 in 203)
70	4.1% (1 in 24)	0.7% (1 in 137)
80	3.0% (1 in 33)	1.0% (1 in 100)
Lifetime risk	**12.9% (1 in 8)**	**2.5% (1 in 39)**

Note: Probability is among those who have not been previously diagnosed with breast cancer and reflects the likelihood of diagnosis/death within 10 years of current age. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.

Source: DevCan, Version 6.8.0

Figure 2. Age-specific Female Breast Cancer Incidence Rates by Race/Ethnicity, US, 2015-2019



Note: Rates are per 100,000 and age adjusted to the 2000 US standard population. Race is exclusive of Hispanic origin. Data for American Indians/Alaska Natives are based on Purchased/Referred Care Delivery Area (PRCDA) counties.

Source: NAACCR, 2022.

for deaths from other causes that may preempt a breast cancer diagnosis. A woman's individual risk varies by age and race/ethnicity, as well as family, medical, and reproductive history.[25]

Age

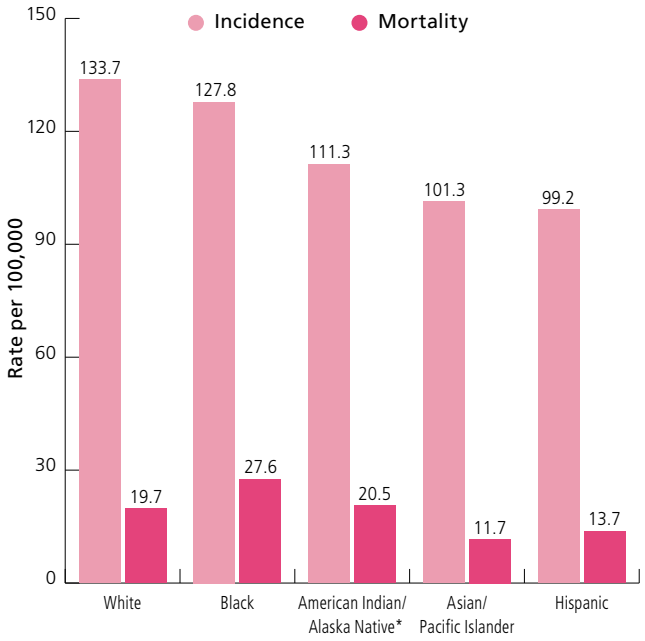
Breast cancer incidence increases with age until the seventh decade of life (Figure 2). The decrease in incidence that occurs in women 80 years of age and older likely reflects lower rates of screening. During 2015-2019, the median age at breast cancer diagnosis was 62. This means that half of women who developed breast cancer were 62 years of age or younger at the time of diagnosis. The median age of diagnosis is younger for Hispanic (57), Asian/Pacific Islander (58), Black (60), and American Indian/Alaska Native (61) women than White women (64), partly reflecting differences in population age structure, as well as age-specific risk.

Race/Ethnicity

Breast cancer incidence and death rates differ substantially by race and ethnicity (Figure 3). Incidence rates are highest among White women (133.7 per 100,000), followed closely by Black women (127.8), then America Indian/Alaska Native (111.3), Asian/Pacific Islander (101.3), and Hispanic (99.2) women. In contrast, death rates are highest among Black women, exceeding those in White women by 40% and almost 2.5 times higher than Asian/Pacific Islander (API) women, who have the lowest rates. Thus, both Black and American Indian/Alaska Native women have higher mortality rates than White women despite lower incidence.

The disproportionate mortality burden among Black women in part reflects the higher risk of TNBC (Figure 4) and later-stage diagnosis (Figure 5), although Black women have worse survival across all stages and subtypes. Breast cancer is the leading cause of cancer death in the US for Black and Hispanic women (due to lower lung cancer mortality rates) and the second-leading cause of cancer death, following lung cancer, among API, American Indian/Alaska Native (AIAN), and White women. Globally, breast cancer has surpassed lung cancer as the leading cause of cancer death among women.[26]

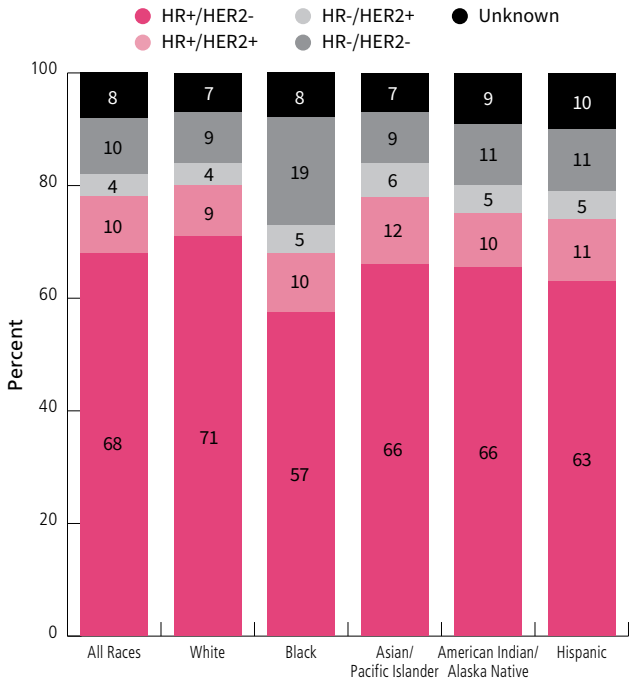
Figure 3. Female Breast Cancer Incidence (2015-2019) and Death (2016-2020) Rates by Race/Ethnicity, US



Note: Rates are per 100,000 and age adjusted to the 2000 US standard population. Race is exclusive of Hispanic origin. *To reduce racial misclassification, incidence data are confined to PRCDA counties, while mortality data are for the entire US with adjustment factors for racial misclassification applied. (See Sources of Statistics, page 34).

Sources: Incidence – NAACCR, 2022. Mortality – National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2022.

Figure 4. Distribution of Breast Cancer Subtypes by Race/Ethnicity, Ages 20 and Older, US 2015-2019



HR = hormone receptor; HER2 = human epidermal growth factor receptor 2. Note: Except for all races, race is exclusive of Hispanic origin. Data for American Indians/Alaska Natives are based on Purchased/Referred Care Delivery Area (PRCDA) counties.

Source: NAACCR, 2022.

What percentage of women are diagnosed with early-stage breast cancer?

Two-thirds (66%) of female breast cancer patients in the US are diagnosed with localized-stage disease, when treatment is more likely to be successful and less extensive. Black, Hispanic, and AIAN women are less likely to be diagnosed with localized-stage disease (57%-60%), compared to API and White women (65%-68%) (Figure 5). Differences in stage at diagnosis by race/ethnicity reflect inequities in access and quality of breast cancer screening[27] and varying risk of aggressive forms of cancer.

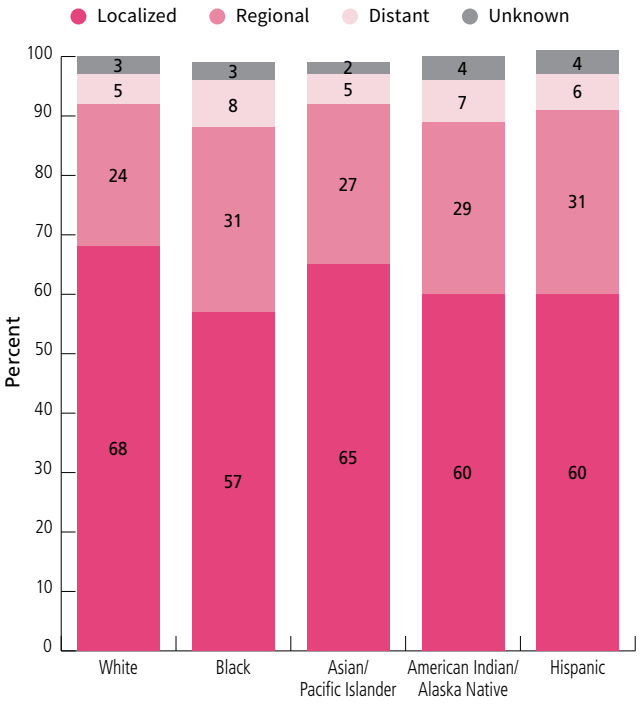
How has breast cancer occurrence changed over time?

Incidence

Breast cancer incidence rates have been increasing in the United States for the past several decades. The rapid rise during the 1980s and 1990s (Figure 6) largely reflects the widespread dissemination and rapid uptake of mammography screening, mostly in women 50 years of age and older.[28] From 1980 to 2000, rates of invasive breast cancer increased by nearly 40% among women ages 50 and older (from 275 cases to 380 cases per 100,000), compared to an increase of 15% (from 63 to 72 cases per 100,000) among younger women. During the same time period, the diagnosis of DCIS, which is almost exclusively diagnosed during screening mammograms, increased among both women 50 years of age and older (10-fold; from 7 cases to 73 cases per 100,000) and women ages 20 to 49 years (5-fold; from 3 cases to 15 cases per 100,000).

Among women older than 20 years of age, the long-term, steady increase of invasive breast cancer incidence was interrupted by a brief drop in the early 2000s. This decline is likely due to decreased use of menopausal hormone therapy following the 2002 publication of results from a clinical trial that found an association

Figure 5. Female Breast Cancer Stage Distribution, by Race/Ethnicity, Ages 20 and Older, US, 2015-2019



Note: Race is exclusive of Hispanic origin. Estimates may not sum to 100 due to rounding. Data for American Indians/Alaska Natives are based on Purchased/ Referred Care Delivery Area (PRCDA) counties.

Source: NAACCR, 2022.

between use of estrogen and progestin therapy and increased risk of breast cancer.[29, 30] After 2004, invasive breast cancer incidence began to increase again steadily. During the most recent decade of data (2010-2019), invasive breast cancer incidence rose by 0.4% per year among women older than 50 and 1% per year among women ages 20-49 years compared to declines in DCIS of 0.7% and 0.8% per year in each age group, respectively. The increase in invasive breast cancer is largely driven by hormone-receptor positive cancer, a disease that is more easily detected by screening and less aggressive compared to other subtypes. Behavioral risk factors for hormone-receptor positive breast cancer include no childbirths, older age at first birth, excess body weight (postmenopausal), physical inactivity, and alcohol consumption, all of which have been increasing in the US.[31, 32]

Race/Ethnicity

Figure 7 presents trends in invasive female breast cancer incidence by race and ethnicity since 2000. (The shorter time period compared to Figure 6 allows for greater population coverage, 48% versus 9%). During the most recent 5 years of available data (2015-2019), breast cancer incidence rates increased among all racial and ethnic groups, with a faster pace among API (2.1% per year), AIAN (2.0% per year), and Hispanic (1.4% per year) women than White (0.5% per year) and Black (0.7% per year) women.

Stage

The increase in breast cancer incidence is largely driven by localized-stage disease, which increased by 0.9% annually from 2015 to 2019. Regional-stage disease decreased by 0.7% annually, and distant-stage disease increased by 0.9% annually, from 7.3 per 100,000 in 2015 to 7.7 per 100,000 in 2019.

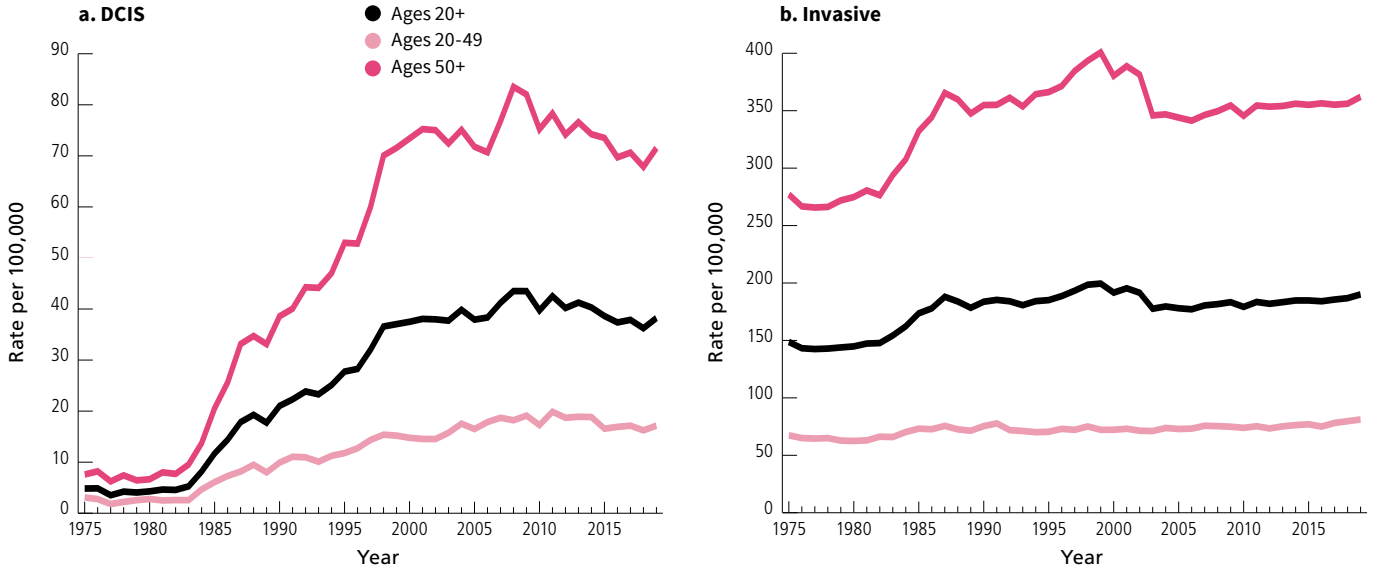
Mortality

The overall breast cancer death rate increased by 0.4% per year from 1975 to 1989, but since has decreased steadily, for a total decline of 43% through 2020. As a result, 460,000 breast cancer deaths were averted in US women from 1989 through 2020. The decline in breast cancer mortality has been attributed to better and more targeted treatment and earlier detection.[33-35] The decline in breast cancer mortality has slowed slightly in the most recent time period, from an annual decrease of 1.9% during 2002-2011 to 1.3% during 2011-2020. Breast cancer death rates declined in Hispanic, Black, and White women by 1% to 1.4% per year, in API women by 0.6% per year, and were stable among AIAN women (Figure 8).

Race/Ethnicity

All women have not benefited equally from advancements in breast cancer early detection and treatment, as indicated by the striking divergence in mortality trends between Black and White women beginning in the early 1980s (Figure 8). This disparity also likely reflects a combination of factors, including later stage at diagnosis, higher rates of unfavorable tumor characteristics (e.g., TNBC), and higher prevalence of other health conditions among Black women. These inequities are largely underpinned by less access to high-quality health care across the cancer continuum from prevention to treatment because of longstanding systemic racism and its impact on the social determinants of health, such as

Figure 6. Trends in Incidence Rates of Ductal Carcinoma In Situ (DCIS) and Invasive Female Breast Cancer by Age, US, 1975-2019



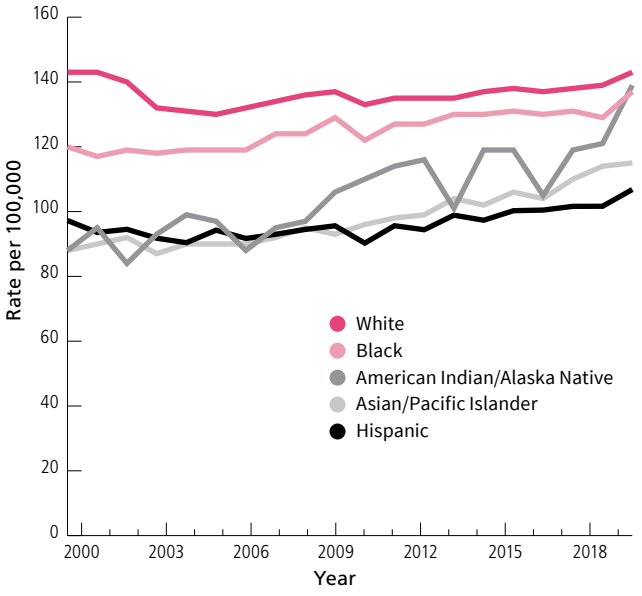
Note: Rates are age adjusted to the 2000 US standard population. Rates for invasive breast cancer are adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 8 Registries, National Cancer Institute, 2022.

health insurance coverage.[36-39] Although national screening rates are similar between White and Black women, Black women are more likely to be screened at lower resourced and nonaccredited facilities and also to experience longer intervals between mammograms and between abnormal results and follow-up.[27, 40-42] The Black-White breast cancer mortality disparity continued to widen through the 2000s as breast cancer treatment improved, peaking in 2011 with rates in Black women 44% higher than those in Whites. In the most recent period (2016-2020), the breast cancer death rate was 40% higher in Black women versus White women (Figure 3).

Are there geographic differences in breast cancer rates?

Table 3 shows variation in state-level breast cancer incidence and death rates by race/ethnicity. Although the national incidence rate for breast cancer remains slightly higher in White women compared to Black women, rates are higher in Black women in 4 of the 42 states with sufficient data (Alabama, Louisiana, Mississippi, and Virginia), and are not statistically different in 21 other states and the District of Columbia.

Figure 7. Trends in Female Breast Cancer Incidence Rates by Race/Ethnicity, US, 2000-2019



Note: Rates are per 100,000 and age adjusted to 2000 US standard population and adjusted for delays in reporting. Race is exclusive of Hispanic origin. Data for American Indians/Alaska Natives are based on Purchased/Referred Care Delivery Area (PRCDA) counties.
Source: SEER Program, SEER 22 Registries, National Cancer Institute, 2022.

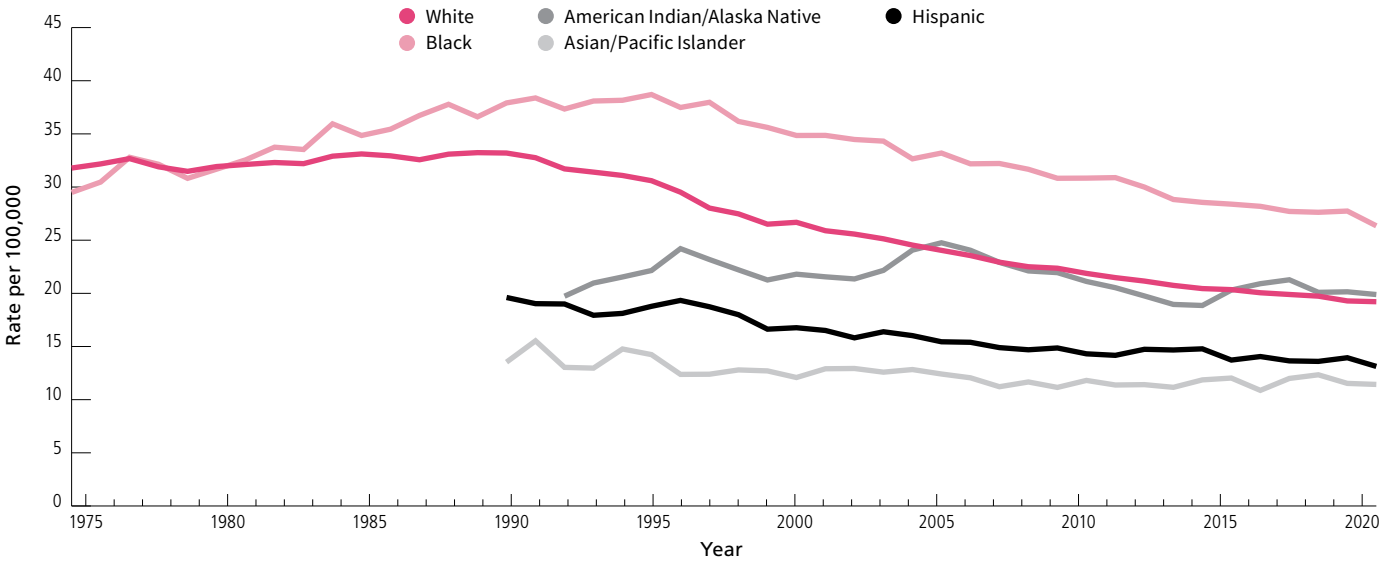
Table 3. Female Breast Cancer Incidence and Death Rates by Race/Ethnicity and State

State	Incidence Rates (2015-2019)				Death Rates (2016-2020)			
	White	Black	Hispanic	Asian/ Pacific Islander	White	Black	Hispanic	Asian/ Pacific Islander
Alabama	121.9	128.0	56.6	80.7	19.4	26.6	*	*
Alaska	122.4	98.2	133.0	80.1	17.0	*	*	*
Arizona	124.0	104.0	95.1	85.0	18.8	28.1	14.5	13.8
Arkansas	121.0	123.9	94.2	106.7	18.7	27.6	*	*
California	138.9	126.1	96.5	108.4	21.5	29.3	14.1	13.0
Colorado	135.3	119.5	108.5	89.3	19.2	24.9	16.4	8.4
Connecticut	145.5	132.2	123.8	88.8	17.5	24.0	11.4	7.7
Delaware	138.2	139.6	101.9	99.6	20.4	26.8	*	*
District of Columbia	145.4	137.9	80.3	82.4	15.6	31.0	*	*
Florida	127.9	112.9	106.8	79.3	18.9	25.3	13.5	11.2
Georgia	130.0	132.0	114.8	94.9	18.9	27.0	11.3	11.8
Hawaii	139.2	126.3	165.1	141.3	21.1	*	23.7	14.5
Idaho	130.7	*	105.6	104.9	20.8	*	7.7	*
Illinois	139.2	136.6	101.7	105.5	20.0	31.6	11.6	11.0
Indiana	125.8	122.2	95.4	88.0	20.2	28.7	12.5	*
Iowa	137.1	133.1	72.5	94.3	18.2	19.5	12.4	*
Kansas	134.9	130.3	96.7	81.6	19.7	26.5	14.6	*
Kentucky	128.7	132.9	96.2	73.7	21.6	26.7	*	*
Louisiana	128.2	135.6	91.7	85.3	20.2	29.1	11.3	*
Maine	128.7	79.4	92.0	69.6	17.7	*	*	*
Maryland	140.9	133.9	88.2	100.1	19.3	27.6	11.2	11.0
Massachusetts	142.9	122.4	92.3	96.8	16.6	19.5	11.7	8.6
Michigan	127.0	119.6	73.5	89.1	19.4	28.4	12.6	10.1
Minnesota	139.0	105.6	103.4	82.9	17.5	23.2	9.6	7.6
Mississippi	122.0	129.1	49.6	81.0	20.0	30.9	*	*
Missouri	133.3	133.0	77.1	99.1	19.1	28.4	9.4	9.8
Montana	136.8	*	104.4	94.7	18.0	*	*	*
Nebraska	134.3	121.7	103.3	69.0	20.8	29.5	*	*
Nevada†	185.5	107.1	77.7	92.9	23.9	31.4	12.1	16.9
New Hampshire	144.3	96.0	121.0	74.8	18.2	*	*	*
New Jersey	148.6	136.0	110.3	106.1	21.1	28.0	12.8	10.3
New Mexico	123.6	114.0	106.4	87.9	22.9	26.0	17.5	*
New York	146.1	127.6	109.3	106.3	18.8	25.1	12.8	9.7
North Carolina	140.6	136.5	97.5	85.3	18.8	26.3	10.4	8.6
North Dakota	136.1	*	*	*	17.3	*	*	*
Ohio	132.8	127.1	71.9	86.2	20.7	27.4	9.0	10.3
Oklahoma	123.4	126.2	91.8	92.4	22.5	28.9	14.6	12.4
Oregon	133.8	110.7	107.3	95.1	19.8	24.4	11.2	12.9
Pennsylvania	135.0	127.4	98.9	83.3	19.9	28.8	11.9	8.4
Rhode Island	147.5	121.0	98.5	110.5	17.7	20.7	9.1	*
South Carolina	132.9	129.3	88.6	80.6	19.9	27.6	8.2	10.7
South Dakota	127.8	*	74.1	107.9	18.9	*	*	*
Tennessee	125.1	122.0	91.1	73.0	20.7	29.1	11.6	8.6
Texas	130.1	123.6	93.5	84.1	20.3	29.0	15.2	12.0
Utah	116.7	96.1	115.4	85.8	20.4	*	14.5	11.2
Vermont	132.6	*	*	*	16.7	*	*	*
Virginia	129.3	132.3	77.9	77.9	20.0	27.9	9.0	10.4
Washington	136.7	112.0	106.5	102.6	20.2	19.1	12.2	11.3
West Virginia	122.2	122.4	70.1	89.9	21.1	30.9	*	*
Wisconsin	136.7	141.1	94.6	81.1	18.3	26.0	12.7	*
Wyoming	115.5	*	83.2	*	18.9	*	*	*
United States	133.7	127.8	99.2	101.3	19.7	27.6	13.7	11.7

Note: Race is exclusive of Hispanic origin. Rates are per 100,000 and age adjusted to 2000 US standard population. *Statistic not displayed due to fewer than 25 cases or deaths. †Incidence data from this registry did not meet NAACCR high-quality standards and were obtained from *Cancer in North America CINA Volumes 2015-2019*, and are not included in the overall US incidence rate. US rates also do not include Puerto Rico, which identifies as 99% Hispanic but does not report cancer data by race or ethnicity. In 2015-2019, breast cancer incidence was 98.5 per 100,000 and mortality 17.3 per 100,000 for women in Puerto Rico.

Sources: Incidence: NAACCR, 2022. Mortality: NCHS, 2022.

Figure 8. Trends in Female Breast Cancer Death Rates by Race/Ethnicity, US, 1975-2020



Note: Rates are per 100,000 and age adjusted to the 2000 US standard population. Race is exclusive of Hispanic origin, except for 1975-1989 for Black and White women. Rates for American Indian/Alaska Native are 3-year moving averages and are adjusted for racial misclassification (see Sources of Statistics, page 34).

Source: NCHS, 2022.

In contrast to incidence, breast cancer death rates are higher among Black women than White women in every state except Washington, with rates 50% higher in some states (e.g., Mississippi and Illinois) and two-fold higher in the District of Columbia (Table 3). Breast cancer death rates among API and Hispanic women did not surpass Black or White women in any state. Among White women, rates tend to be highest in the North Central, Mid-Atlantic, and Western regions of the US, whereas among Black women they are highest in some of the South Central and Mid-Atlantic states, as well as California. Factors that contribute to geographic disparities in incidence and mortality include variations in risk factors and access to screening and treatment, which are influenced by socioeconomic status, legislative policies, and distance to medical services.[43]

Data for AIAN women are too sparse to analyze by state; however, a recent study that examined breast cancer incidence by region found that rates during 2014-2018 were more than two-fold higher in the Southern Plains (166.8 per 100,000), where rates were highest, than in the Southwest (69.9 per 100,000), where they were lowest.[44]

Breast cancer survival

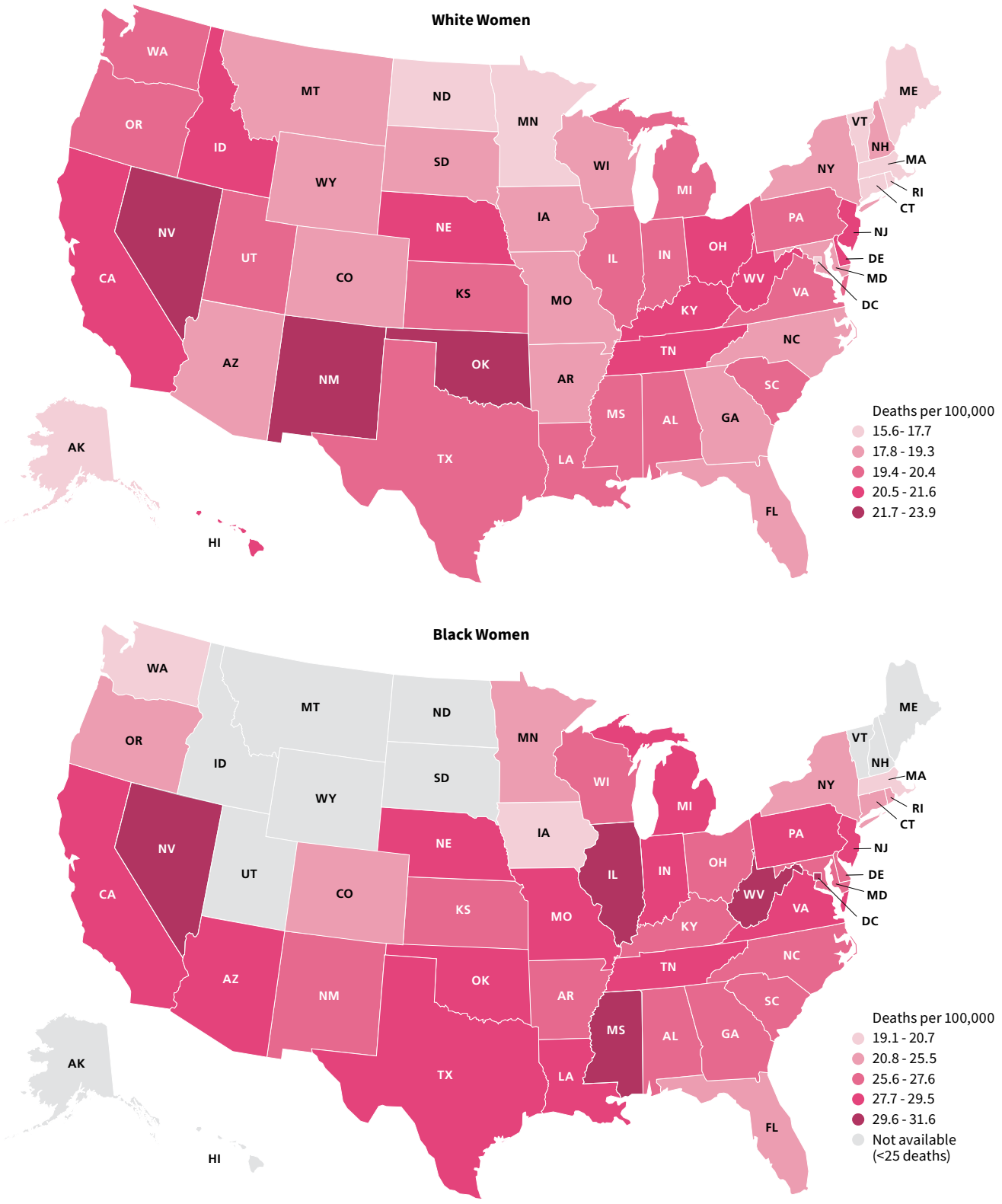
Relative survival rates are an estimate of the percentage of patients who survive for a given time period (usually 5 years) following cancer diagnosis, after accounting for death from all causes based on the experience of people of the same age who have not been diagnosed with cancer.

Relative survival rates should be interpreted with caution because they are based on the average experience of all patients with breast cancer and do not account for individual variation in factors that influence survival, such as excess body weight and other illnesses. In addition, long-term survival rates are based on data from patients diagnosed and treated many years ago and thus, do not reflect the most recent improvements in early detection and treatment.

Based on the most recent data, overall relative survival rates for women diagnosed with breast cancer are:

- 91% at 5 years after diagnosis
- 84% at 10 years after diagnosis
- 80% at 15 years after diagnosis

Figure 9. Geographic Variation in Female Breast Cancer Death Rates by Race/Ethnicity, 2016-2020



Note: Rates are per 100,000 and age adjusted to the 2000 US standard population. Race is exclusive of Hispanic origin.
Source: NCHS, 2022.

Thus, although 5-year cancer survival is often considered "cured," death can occur well after 5 years.

Stage at diagnosis

Stage at diagnosis is one of the most important factors affecting prognosis because treatment is typically more effective when the cancer is less extensive. Five-year relative survival rates for breast cancer are:

- 99% for localized disease
- 86% for regional disease
- 30% for distant disease

Breast cancer subtype (HR/HER2)

Breast cancer survival also varies by tumor subtype. Five-year relative survival rates are:

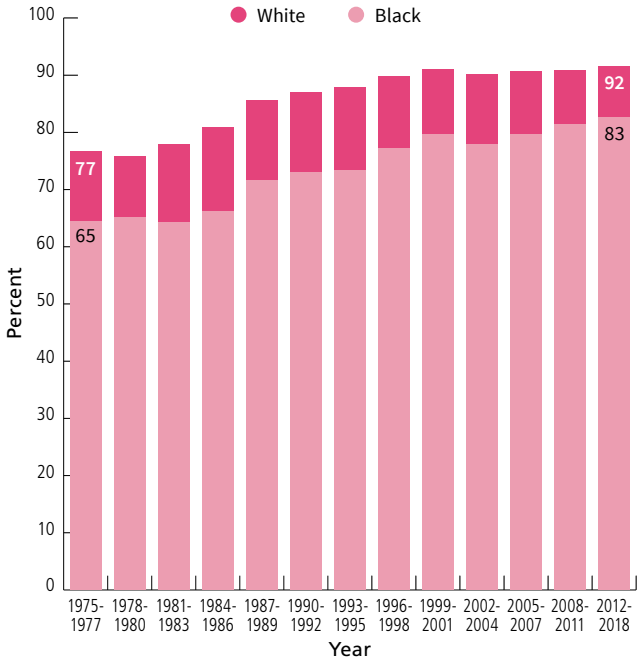
- 94% for HR+/HER2-
- 91% for HR+/HER2+
- 85% for HR-/HER2+
- 77% for HR-/HER2-

Importantly, 5-year relative survival is 90% or greater for all subtypes when diagnosed at a localized stage.

Race/ethnicity

Since the 1970s, breast cancer survival has improved significantly in both Black and White women in the US (Figure 10). However, the most recent data show that progress continues to lag among Black women. The 5-year relative survival rate during 2012-2018 was only 83% among Black women, compared to 92% among White and API women. Black women have the lowest survival for every stage at diagnosis (Figure 11) and breast cancer subtype compared to women of other racial/ethnic groups. (Importantly, survival rates may be underestimated for Hispanic and API women, who are more likely to be foreign-born, and thus have less complete follow-up information in cancer registry data.[45,46]) Thus, in addition to reflecting differences in tumor biology, racial and ethnic disparities in breast cancer survival also reflect differences in access to care and insurance status, which in turn are associated with a history of structural racism in the US.[47-49]

Figure 10. Trends in Female Breast Cancer 5-year Relative Survival Rates (%) by Race, US, 1975-2018



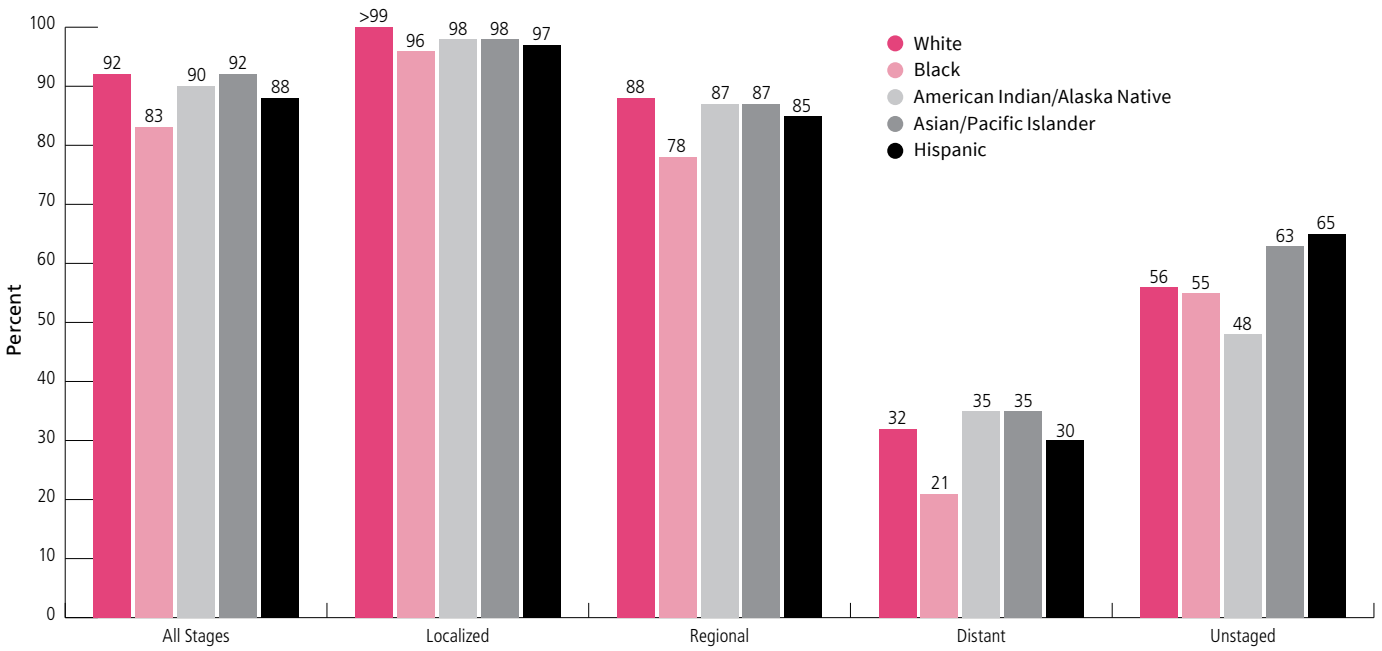
Source: SEER Program, 17 SEER registries for 2002-2018, 8 SEER registries for 1975-2001, National Cancer Institute, 2022. SEER 17-based survival rates are exclusive of Hispanic ethnicity.

A recent study found that among stage IV breast cancer patients, survival disparities between White women and other racial/ethnic groups were no longer present after Medicaid expansion.[50]

Male breast cancer

Breast cancer in men is rare, accounting for less than 1% of breast cancer cases in the US. Male breast cancer incidence was 1.2 cases per 100,000 men during 2015-2019, a rate that has held steady over the past 3 decades. Men are more likely than women to be diagnosed with advanced (regional- or distant-stage) breast cancer (49% versus 33%),[51] which likely reflects delayed detection due to lack of awareness in addition to the absence of screening.[52] The death rate for male breast cancer has decreased slightly from 0.4 (per 100,000) during 1975-1979 to 0.3 (per 100,000) during 2016-2020 due to improvements in treatment.[53] Survival rates for men with breast cancer are lower compared with those of women, possibly reflecting unfavorable stage distribution and limited knowledge about effective treatment.[54]

Figure 11. Five-year Relative Survival Rates (%) by Stage at Diagnosis and Race/Ethnicity, US, 2012-2018



Note: Race is exclusive of Hispanic origin. Survival rates are based on patients diagnosed during 2012-2018 and followed through 2019. Survival for AIAN individuals is based on patients diagnosed in PRCDA counties.

Source: SEER Program, 17 SEER registries, National Cancer Institute, 2022.

Much less is known about breast cancer in men than in women. Similar to women, the incidence of male breast cancer increases with age. Other risk factors include radiation exposure, *BRCA1/2* gene variations, family history of breast or ovarian cancer (likely due to genetic predisposition), Klinefelter syndrome, testicular disorders, diabetes, gynecomastia (enlarged breasts), and obesity.[55-57]

In contrast to women, Black men appear to have the highest breast cancer incidence rates among men, both overall and across molecular subtype.[58] Studies suggest that risk factors for breast cancer among women, such as smoking, alcohol consumption, and physical inactivity, do not increase risk in men.[59-61]

Breast Cancer Risk Factors

The most well-established risk factors for breast cancers are summarized in Table 4. Approximately 30% of postmenopausal breast cancer cases can be attributed to potentially modifiable risk factors, such as excess body weight, physical inactivity, and alcohol consumption.[62] Other potentially modifiable factors that influence risk include use of menopausal hormones and breastfeeding.[63, 64] Many risk factors affect lifetime exposure of breast tissue to hormones, which are thought to influence breast cancer risk by increasing cell division and thus the likelihood of DNA damage, as well as promoting cancer growth. Although exposures that influence risk accumulate throughout a woman's life, research suggests that early-life exposures during breast development may be particularly critical.[65] Many established risk factors for breast cancer have been consistently associated with HR+/luminal breast cancer; less is known about risk factors for HR-, HER2+, and basal-like breast cancers.[66] The following sections present current knowledge about factors associated with breast cancer risk.

Table 4. Factors That Increase the Relative Risk for Invasive Breast Cancer in Women

Relative risk	Factor
>4.0	Age (65+ versus <65 years, although risk increases across all ages until age 80)
	Biopsy-confirmed atypical hyperplasia
	Certain inherited genetic mutations for breast cancer (e.g., *BRCA1*, *BRCA2*, *PALB2*, *TP53*)
	Lobular neoplasia
	Personal history of early-onset (<40 years) breast cancer
2.1-4.0	Ductal carcinoma in situ
	High endogenous estrogen or testosterone levels (postmenopausal)
	High-dose radiation to chest (e.g., Hodgkin lymphoma treatment)
	Mammographically dense (26% or more) breasts (compared to 11%-25% breast density)
	Personal history of breast cancer (40+ years)
	Two or more first-degree relatives with breast cancer
1.1-2.0	Alcohol consumption
	Early menarche (<11 years)
	Height (tall)
	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 endometrium or ovarian 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
	Type 2 diabetes
	Weight gain in adulthood

Note: Relative risks for some factors vary by breast cancer molecular subtype.

Family history, personal characteristics, and medical history

Family history and genetic predisposition

Women (and men) with a family history of breast cancer, especially in a first-degree relative (parent, child, or sibling), are at increased risk for the disease. Compared to women without a family history, risk of breast cancer is about 1.5 times higher for women with one affected first-degree female relative and 2-4 times higher for women with more than one first-degree relative.[70-72] Risk is further increased when the affected female relative was diagnosed at a young age or was diagnosed with cancer in both breasts, or if the affected relative is male. However, the majority of women with one or more affected first-degree relatives will never develop breast cancer, and most women who develop breast cancer do not have a family history of the disease.[70]

Women should discuss their family history with their health care provider because it may signal the presence of a genetic predisposition to cancer and the need for individualized screening and risk reduction. For example, a family history of ovarian, endometrial, pancreatic, or prostate cancer, and possibly gastric or biliary cancer, is associated with increased breast cancer risk, at least some of which has a genetic component.[68, 73]

Inherited pathogenic (disease-causing) genetic variations in *BRCA1* and *BRCA2*, the most well-studied breast cancer susceptibility genes, account for 5%-10% of all female breast cancers and 15%-20% of all familial breast cancers.[74, 75] These variations are rare (about 1 in 400) in the general population, but occur slightly more often in certain ethnic or geographically isolated groups, such as those of Ashkenazi (Eastern European) Jewish descent (about 1 in 40).[76] *BRCA1/2* variations may occur more frequently in Black and Hispanic breast cancer patients compared to those who are White,[77, 78] although the prevalence of pathogenic variants overall is similar in Black and White women.[79, 80] Frequency of genetic testing has historically been lower among Black compared to White women, which previously resulted in misleading information about *BRCA* mutation patterns by race.[81, 82]

Compared to women in the general population, who have a 10% risk of developing breast cancer by 80 years of age, risk in women with *BRCA1/2* variations is estimated to be about 70% by the same age.[83] The risk of developing breast cancer by age 70 in women with variations in *PALB2*, a gene related to *BRCA2*, is estimated to range from 35% to 53%.[84, 85] Inherited variations in other genes are also associated with increased breast cancer risk, including *TP53* (associated with Li-Fraumeni syndrome), *PTEN* (Cowden syndrome/PTEN hamartoma tumor syndrome), *STK11* (Peutz-Jeghers syndrome), *ATM*, *CHEK2*,

What is the difference between absolute, lifetime, and relative risk?

Absolute risk is the likelihood of being diagnosed with cancer over a certain period of time. For example, the absolute risk of breast cancer increases with age: 13 out of 10,000 women ages 40-44 versus 23 out of 10,000 women ages 50-54 will be diagnosed with breast cancer in the next year.[67]

Lifetime risk is the absolute risk of being diagnosed with cancer anytime between birth and death. Lifetime risk of breast cancer reflects the average probability of a female being diagnosed with breast cancer in the US. A woman living in the US has a 13% chance of being diagnosed with invasive breast cancer in her lifetime (Table 2). Another way to say this is that 1 out of every 8 women will be diagnosed with breast cancer in her lifetime. However, it is important to keep in mind that risk varies substantially based on individual factors.

Relative risk compares the absolute risk of disease among people with a particular exposure to the risk among people without that exposure. If the relative risk is above 1.0, then risk is higher among those with the exposure than without it, whereas if the relative risk is below 1.0, the exposure reduces the risk of disease. For example, one study found women ages 50-59 who were current users of combined estrogen and progestin menopausal hormones had a relative risk of developing breast cancer of 1.2, meaning they had a 20% higher risk compared to women who have not used hormone therapy.[69] While relative risks are useful for comparisons, they do not provide information about the absolute risk of the exposed group. In fact, when the absolute risk is low, even a large relative risk has little influence. In this example, 27 breast cancers per year would be expected to be diagnosed among 10,000 women ages 50-59 who had never used menopausal hormones compared to 33 breast cancers among 10,000 women of the same age who had used estrogen and progestin. Thus, the 20% increased relative risk is the equivalent of 6 additional breast cancers per 10,000 women per year.

and *CDH1* (associated with diffuse gastric and lobular breast cancer syndrome). In addition, there are 300-plus more common genetic variants that are associated with a slightly elevated risk, ranging from a lifetime risk of 10% to 50%.[86-88] Genetic variations are often associated with specific molecular subtypes.[89] For example, women with *BRCA1/2* variations are more likely than the general population to be diagnosed with triple-negative disease, with the highest risk among *BRCA1* variation carriers.[90] Variations in *ATM* and *CHEK2* are more commonly associated with ER+ breast cancer.[86, 89]

The US Preventive Services Task Force recommends that primary care providers routinely collect and update family medical history, as well as ancestry. Women with a personal or family history of breast, ovarian, tubal, or primary peritoneal cancer or those with ancestry associated with *BRCA1/2* gene variations should be screened with one of several brief questionnaires to determine if there is a need for genetic counseling.[91, 92] Genetic counseling is strongly encouraged to help in the decision making about testing so that the benefits and potential consequences can be understood and carefully considered.

Personal history of breast cancer

About 5% of breast cancer survivors will develop a new breast cancer (also referred to as a subsequent primary breast cancer), with 70% of these occurring in the opposite (contralateral) breast.[93, 94] One population-based study found that Black and Hispanic breast cancer survivors have a 44% and 11% higher risk, respectively, of developing subsequent contralateral breast cancer compared to Whites.[95] Notably, the incidence of contralateral breast cancer has been declining steadily since 1985,[96] predominantly among ER+ breast cancer survivors. This may reflect advances in hormone therapy (i.e., tamoxifen and aromatase inhibitors) and other adjuvant treatments used to lower risk of breast cancer recurrence, as well as steep increases in the election of bilateral mastectomy for breast cancer treatment (see page 26).[94, 97, 98]

DCIS and LCIS

DCIS is considered a potential precursor to invasive cancer.[99] Similar to women with a prior invasive breast cancer, women diagnosed with DCIS have a small excess risk of developing a new invasive breast cancer that is greatest near the site of DCIS. Although the natural progression is difficult to study because most women with DCIS undergo treatment, a recent study of untreated women found a 10-year risk of invasive breast cancer of 10.5% in the same breast and 3.9% in the opposite breast.[6] Invasive cancer may be more likely with ER-positive DCIS.[100]

In contrast, LCIS is not generally considered a breast cancer precursor, but it is associated with an increased risk of developing breast cancer. Classic LCIS likely reflects hyperproliferative (rapidly growing) breast tissue, evidenced by the comparable risk of developing cancer in either breast regardless of the site where LCIS was detected. The 10- and 20-year risks of being diagnosed with DCIS or an invasive breast cancer after LCIS are 11% and 20%, respectively.[101 102] Risk may be higher among Black and Asian women, compared to other racial/ethnic groups.[102, 103] Pleomorphic and/or florid LCIS are more aggressive subtypes that are linked to a higher risk of invasive cancer than classic LCIS and are often treated as a cancer precursors (similarly to DCIS).[104]

Benign breast disease

Doctors often categorize benign breast conditions into 3 general groups reflecting the associated degree of cancer risk: nonproliferative lesions, proliferative lesions without atypia (abnormal cells or patterns of cells), and proliferative lesions with atypia.

- **Nonproliferative lesions** are not associated with overgrowth of breast tissue and include fibrosis and simple cysts (also known as fibrocystic changes) and mild hyperplasia. Nonproliferative conditions are associated with little to no increased breast cancer risk.[105]
- **Proliferative lesions without atypia** are associated with a small (1.5 to 2 times higher) increased breast cancer risk and include usual ductal hyperplasia (without atypia) and fibroadenoma.[105]
- **Proliferative lesions with atypia** are associated with about 4 times higher than average breast cancer risk. These include atypical ductal hyperplasia, atypical lobular hyperplasia, and florid epithelial atypia.[105, 106] The 15-year risk of developing in situ or invasive breast cancer exceeds 30% in women diagnosed with atypical hyperplasia.[106, 107] When atypia is detected in a needle biopsy, a follow-up surgery is usually necessary to rule out a co-existing breast cancer.

A recent study found that benign breast disease is also associated with increased risk of interval cancer, which is a breast cancer diagnosis after a normal routine screening.[108] This suggests that benign disease may be associated with faster-growing tumors or that it may decrease screening sensitivity. Women should keep detailed records of any benign breast biopsy results because they are valuable for risk assessment, screening, and counseling for chemoprevention and other risk-reduction strategies. The majority of breast cancers that develop among women with a history of benign breast disease are ER+; however, Black women with a history of the condition are four times more likely than White women to develop triple-negative breast cancer.[109]

Mammographic breast density

Mammographic breast tissue density is determined based on the amount of glandular and connective tissue relative to fatty tissue measured during a mammogram. Breast tissue is categorized according to a standardized system developed by the American College of Radiology called the Breast Imaging-Reporting and Data System (BI-RADS). The categories include A) almost entirely fatty; B) scattered areas of fibroglandular density; C) heterogeneously dense; and D) extremely dense. Women with breasts classified as BI-RADS C or D are referred to as having "mammographically dense breasts." The risk of breast cancer increases with mammographic breast density, and women with BI-RADS C or D have a 1.5 to 2-fold higher risk of breast cancer compared to those with average density (BI-RADS B).[110] High mammographic breast density can also mask the appearance of breast tumors on a mammogram.[111, 112]

Mammographic dense breasts are common. About 36% of US women ages 40-74 have heterogeneously dense breasts, and about 7% have extremely dense breasts.[113] Breast density is influenced by genetics and other factors and typically decreases with age, higher body weight, and after pregnancy and menopause.[114] Some drugs also affect breast density, including tamoxifen (decreases density) and combined menopausal hormone therapy, estrogen and progestin, (increases density).[111, 114]

In early 2019, Congress passed legislation directing the US Food and Drug Administration to ensure that mammogram reports include information about breast density.[115] Thirty-eight states and the District of Columbia have passed some form of breast density legislation. Research has found that additional testing, such as ultrasound or MRI, may improve cancer detection among women with dense breasts, and some state laws require that these women be told they may benefit from these supplement imaging tests.[116-119] A recent study found that among women with dense breasts, digital breast tomosynthesis (DBT) screening decreased the need for additional diagnostic imaging and increased cancer detection compared to conventional digital mammography alone.[120] See page 22 for more information on DBT.

Height

Many studies have found that taller women have a higher risk of breast cancer than shorter women.[121-123] A pooled study of more than 5 million women estimated that every 10 centimeters (about 4 inches) increase in height was associated with a 17% higher risk of breast cancer.[122] Although reasons are not fully understood, this may reflect differences in early growth, as well as hormonal or genetic factors. Height is also associated with increased risk for a number of other cancers.

Puberty and menstruation

Breast cancer risk increases with earlier breast development,[124] earlier menstruation, and later menopause.[124, 125] Breast cancer risk is about 20% higher among those who begin menstruating before age 11, compared to those who begin at age 14 or older. Likewise, women who experience menopause at age 55 or older have about a 12% higher risk compared to those who do so between ages 50 and 54.[125] The increased risk is likely due to longer lifetime exposure to reproductive hormones and has been more strongly linked to HR+ breast cancer than other subtypes.[66]

Bone mineral density

High bone mineral density in postmenopausal women has been associated with a 60% to 80% increased risk for breast cancer compared to low bone density, which appears to be strongest for HR+ disease.[126, 127] Bone density is not thought to be an independent risk factor but rather a marker of cumulative estrogen exposure.[128, 129] However, routine bone density testing that is often conducted to screen for osteoporosis may help identify women at increased risk of breast cancer.

Type 2 diabetes

Type 2 diabetes shares several modifiable risk factors with cancer, including excess body weight, poor diet, and lack of physical activity. Evidence suggests that type 2 diabetes independently increases risk for several cancers, including breast cancer.[130] A recent prospective study reported a 26% increased risk of breast cancer among women with diabetes compared to those without the disease after controlling for demographic and lifestyle factors and body weight.[131] Although early studies of women treated with metformin (the most common drug used to treat diabetes) found it to be associated with decreased breast cancer risk, more recent research is inconclusive.[132]

Endogenous sex hormones

Postmenopausal women with naturally high levels of certain endogenous sex hormones (e.g., estrogen, progesterone) have about twice the risk of developing breast cancer compared to women with the lowest levels, with the strongest association for HR+ tumors.[133, 134] High levels of endogenous testosterone also appear to increase breast cancer risk among postmenopausal women.[135, 136] High circulating hormone levels are associated with, and may reflect, the effects of other breast cancer risk factors, such as postmenopausal obesity[137] and alcohol use.[134]

Although it is challenging to study endogenous hormones in premenopausal women because of variation across the menstrual cycle, there is some evidence that high levels of circulating estrogens and androgens are associated with a small excess risk in premenopausal women, particularly for HR+ breast cancer.[134, 138, 139]

Postmenopausal hormones

Use of combined estrogen and progestin hormones after menopause (also referred to as hormone therapy or hormone replacement therapy) increases breast cancer incidence[66, 137, 140, 141] and mortality.[142, 143] Discontinuation of menopausal hormones diminishes but does not eliminate excess risk.[137, 144] Combined hormone therapy also increases mammographic breast density.[111]

Postmenopausal estrogen-only therapy increases risk of endometrial cancer and is therefore only prescribed to women who have undergone a hysterectomy. Studies are conflicted about the effect of estrogen-only therapy on breast cancer risk. Clinical trial data indicate a reduction in both breast cancer incidence and mortality[143] with estrogen-only therapy, whereas observational studies report an increase in both.[137, 142] Reasons for the disagreement may include differences in the age of study participants or study methodology; in the utilization of mammography; and in the timing and duration of hormone use.

Gender-affirming hormone therapy

Gender-affirming hormone therapy is a medical intervention to help align the characteristics of an individual with their gender identity. Although data are sparse, one long-term retrospective cohort study in the Netherlands found that transgender women who received hormone therapy, including antiandrogens and estrogens, had increased breast cancer risk compared to cisgender men, while both transgender men and women receiving therapy had a lower risk of breast cancer compared to cisgender women.[145] There are currently no breast cancer screening recommendations for transgender individuals, so these patients and their health care providers should be aware of the risks associated with exogenous hormones and alert to the signs and symptoms of breast cancer.

Reproductive factors

Pregnancy

Pregnancy has a dual effect on breast cancer risk.[146] In the short term, women who have had a full-term pregnancy have an increased risk of both HR+ and HR- breast cancers that peaks 5 years after childbirth. However, after about two decades, the relative risk of HR+ breast cancer becomes slightly lower (by about 20%-25%) in women who have given birth compared to those who have not. Risk is further reduced among women who have their first child at a younger age or have a greater number of children. In contrast, the increased risk for HR- breast cancer persists following a full-term pregnancy except among women who breastfeed.[147] See below for more information on breastfeeding and breast cancer risk.

Fertility drugs

More research is needed on the relationship between the use of ovulation-stimulating drugs and breast cancer risk.[148, 149] Most studies to date have found that breast cancer risk is not elevated in women who undergo in vitro fertilization.[150-155] However, the data are less clear for clomiphene (Clomid), a drug that is often used as a first-line treatment for infertility.[151, 153, 154] A recent study from Norway found no association between fertility drugs, including clomiphene, and breast cancer risk after 20 years of follow- up,[155] while other studies have reported an elevated risk for certain subgroups, such as women who underwent more than 12 clomiphene treatment cycles,[153] or who had given birth.[154]

Breastfeeding

Most studies suggest that breastfeeding for a year or more slightly reduces a woman's overall risk of breast cancer, with longer duration associated with greater reduction. In a review of 47 studies in 30 countries, the risk of breast cancer was reduced by 4% for every 12 months of breastfeeding.[156] The protective effect may be stronger for, or even limited to, triple-negative cancers.[147, 157-159]

Hormonal birth control

Most studies have found that current or recent use of oral contraceptives (combined estrogen and progesterone) is associated with a small (about 20%) relative increase in breast cancer risk, particularly among women who begin use before first pregnancy.[160, 161] Results from studies evaluating whether this risk is modified by genetic factors, such as among *BRCA* variant carriers, are inconsistent.[162] Risk appears to diminish when women stop use, and at about 10 years is similar to never-users. Data are limited and less clear for "ultra low-dose" (20 micrograms) estrogen formulations.[163]

Studies of the progestin-only intrauterine device have produced conflicting results,[164-167] but a large study from Denmark found that use increases breast cancer risk by about 20%.[160] In contrast, the injectable progestin-only contraceptive depot-medroxyprogesterone acetate (Depo-Provera) does not seem to be linked with breast cancer, although the number of users may be insufficient to detect an association.[160, 168] Overall, it has been estimated that one extra breast cancer is diagnosed for every 7,690 women using hormonal contraception for one year.[160]

Body weight, physical inactivity, diet, alcohol, and tobacco

Body weight

The risk of postmenopausal HR+ breast cancer is about 1½ to 2 times higher in women who are overweight or obese than in those who are a healthy weight.[169] Even within the normal range of BMI (18.5-24.9), higher levels of body fat are associated with increased risk of breast cancer after menopause.[170] This is likely due, in part, to higher estrogen levels because fat tissue is the largest source of estrogen in postmenopausal women, but may also be related to other mechanisms, including higher levels of insulin among heavier women.[170-172]

Weight gain also increases risk of postmenopausal breast cancer.[173, 174] A large meta-analysis found that for each 5 kilograms (about 11 pounds) gained during adulthood, risk of postmenopausal breast cancer increases by 11%.[174] The increased risk was only observed among women who did not use menopausal hormones. Weight loss in early adulthood and after menopause is associated with reduced breast cancer risk in some, but not all studies.[171, 172] Weight loss is more difficult to examine because it is often not sustained long term.

In contrast, studies have found that excess body weight reduces risk of breast cancer in premenopausal women. One large observational study found that the risk reduction occurred even among heavier women who were classified as a healthy weight and was strongest for the youngest women (ages 18 to 24) and for HR+ tumors.[175] The underlying mechanisms for this inverse relationship are not well understood, but may be related to interrupted menstrual cycles and lower estrogen levels associated with excess body weight among premenopausal women.[176, 177]

Physical inactivity

Women who get regular physical activity have a 10%-20% lower risk of breast cancer compared to women who are inactive, with greater risk reduction associated with increasing levels of activity.[178-182] The protective effect is likely independent of BMI and may be limited to women who have never used menopausal hormone therapy.[181, 182] The benefit may be due to the effects of physical activity on systemic inflammation, hormone levels, and energy balance.[181, 183]

Diet

Numerous studies have examined the relationship between food consumption (including fat, fiber, soy, dairy, meat, and fruits and vegetables) and breast cancer, with mixed results. A limitation of most of these studies is that they are based on self-reported information in food frequency questionnaires. A meta-analysis concluded there was no association between breast cancer risk and overall dietary fat consumption, but was suggestive of differences by fat type,[184] similar to findings of other studies.[185-187] It has been suggested that soy consumption may reduce breast cancer risk, in part because of historically low breast cancer rates among Asian women, who have a diet high in soy. Another meta-analysis showed that soy intake was inversely associated with breast cancer risk in Asian but not Western populations, perhaps because Asian women generally consume more soy

products beginning at an earlier age than Western women.[188] Further, a recent cohort study among women in the US found no association between soy consumption and breast cancer.[189]

There is limited but growing evidence that high levels of fruit and/or vegetable consumption may reduce the risk of HR- breast cancer.[190-192] These findings are supported by studies linking lower breast cancer risk to higher blood levels of carotenoids (micronutrients found in fruits and vegetables).[193-196] Some studies also suggest that calcium-rich diets may be linked to a lower risk of breast cancer,[191] although a pooled analysis of over 1 million women found no association.[197] The effect of diet on breast cancer risk remains an active area of research, with studies particularly focused on the timing of exposure, specific dietary components, and risk differences by cancer subtype.

Alcohol

Alcohol is estimated to account for approximately 16% of breast cancer cases in the US.[62] Alcohol consumption increases the risk of breast cancer in women by about 7%-10% for each 10 grams (roughly one drink) of alcohol consumed per day on average.[191, 198] Women who have 2-3 alcoholic drinks per day have a 20% higher risk of breast cancer compared to non-drinkers. There is also some evidence that alcohol consumption before first pregnancy may particularly affect risk.[198, 199] Although mechanisms are not well understood, alcohol may increase risk indirectly by increasing estrogen and other hormone levels[200] and/or increasing breast density.[201] Alcohol use appears more strongly associated with risk for HR+ than HR- breast cancer.[66, 202]

Tobacco

Accumulating research indicates that smoking may slightly increase breast cancer risk, particularly among women with a heavy smoking history and who start smoking at a young age.[203, 204] A family history of breast cancer may heighten this risk.[205] Some studies suggest secondhand smoke may increase risk, particularly when exposure happens in childhood and for premenopausal breast cancer.[206-208]

Environmental and other risk factors

Radiation

Radiation exposure has been shown to increase breast cancer risk in studies of atomic bomb survivors and females treated with high-dose radiation therapy to the chest between 10 and 30 years of age, such as for Hodgkin lymphoma. This may be because breast tissue is most susceptible to carcinogens before it is fully differentiated, which occurs with first childbirth. Breast cancer risk starts to rise about 8 years after radiation treatment and continues to be elevated for more than 35 years.[209] Although radiation treatments have evolved to include lower doses given over smaller areas, recent studies suggest that elevated breast cancer risk persists.[210] In 2020, the International Late Effects of Childhood Cancer Guideline Harmonization Group recommended that young female cancer survivors who were treated with chest radiation begin yearly breast cancer screenings at age 25.[211] In 2007, the American Cancer Society recommended that such young female cancer survivors should be considered "high risk" and begin screening at age 30.

Diethylstilbestrol (DES) exposure

From the 1940s through 1971, some pregnant women were given the drug diethylstilbestrol (DES) because it was thought to lower the risk of miscarriage. These women have about a 30% increased risk of developing breast cancer compared to women who have not taken DES.[212] It remains unclear whether women born to mothers who took DES also have a higher risk.[212-215]

Environmental chemicals and pollutants

Many occupational, environmental, and chemical exposures have been proposed as causes of breast cancer. In general, epidemiological studies have not found clear relationships between environmental pollutants, such as organochlorine pesticides, and breast cancer. Studies to date have found no association between increased concentrations of organochlorines (e.g., dichlorodiphenyltrichloroethane, or DDT) in blood and fat tissue of adults and breast cancer risk,[216] although exposure to DDT during certain developmental windows, such as in utero, during infancy, or prior to puberty, is associated with elevated breast cancer risk later in life.[217, 218] Animal

studies have demonstrated that prolonged, high-dose exposure to many chemicals can increase mammary tumor development, but it is unknown whether the much lower dose exposures that occur in the general environment increase human breast cancer risk. Many relevant chemicals have not been adequately studied in humans, and this is an active area of research.[219-223] Study results from examinations of a relationship between hair dyes/relaxers and breast cancer risk are inconsistent, and more research is needed.[224-226]

Night shift work

A recent meta-analysis reported that short-term (but not long-term) night shift employment was associated with a slight increase in breast cancer risk.[227] Elevated risk appears to be most strongly associated with shift working during early adulthood.[228, 229] Exposure to light at night disrupts the production of melatonin, a hormone that regulates sleep. Experimental evidence suggests that melatonin may also inhibit the growth of small, established tumors and prevent new tumors from developing.[230] In 2019, based on an updated review of studies in humans and animals, the International Agency for Research on Cancer concluded that "night shift work," as opposed to "shift work" identified in 2007, was probably carcinogenic to humans based on its association with breast, prostate, and colorectal cancers.[231]

Factors that are not associated with breast cancer risk

Abortion

There are persistent claims that women who have had an abortion are at increased risk for developing breast cancer based on early studies that have since been deemed methodologically flawed by the American College of Obstetricians and Gynecology.[232, 233] Indeed, a large body of scientific evidence, including an expert panel review convened in 2003 by the National Cancer Institute, confirms that there is no link between breast cancer and abortion (either spontaneous or induced).[234]

Bras

Although internet rumors have suggested that bras cause breast cancer by obstructing lymph flow, there is no scientific basis or evidence to support this claim. The only credible study investigating this relationship found no association between wearing a bra and breast cancer.[235]

Breast implants

No association has been found between breast implants and risk of breast cancer; however, there is evidence that women with textured implants are at increased risk for a rare type of lymphoma that occurs in the breast.[236, 237] In addition, breast implants can obstruct the view of breast tissue during mammography. Women with breast implants should inform the mammography facility about the implants during scheduling so that additional x-ray pictures (called implant displacement views) may be collected to allow for more complete breast imaging.

Chemoprevention and prophylactic surgery

Chemoprevention

The use of drugs to reduce the risk of disease is called chemoprevention. Currently, the US Food and Drug Administration (FDA) has approved two drugs to help lower the risk of breast cancer in high-risk women: tamoxifen and raloxifene (for postmenopausal women only). These drugs are classified as selective estrogen receptor modulators (SERMs) because they block estrogen in some tissues of the body, but act like estrogen in others.

A large meta-analysis including more than 83,000 high-risk women found that SERMs reduced in situ and invasive breast cancer risk by 38% over 10 years,[238] although the benefit was limited to ER+ disease. SERMs are associated with some side effects, including hot flashes, nausea, and fatigue. Premenopausal women taking tamoxifen can also experience menstrual changes. More serious side effects are rare but include blood clots and endometrial cancer, particularly in women over 50.[238]

Aromatase inhibitors have also been shown to reduce breast cancer risk (by more than half) among high-risk postmenopausal women in clinical trials.[239] While these drugs have not yet been approved by the FDA for this purpose, the US Preventive Services Task Force recommendation for breast cancer risk reduction in high-risk women includes aromatase inhibitors and SERMS.[240] Aromatase inhibitors can decrease bone density, so women taking these drugs must be monitored for osteoporosis.

Prophylactic surgery

Women at very high risk of breast cancer (such as those with pathogenic *BRCA* gene variants) may elect prophylactic (preventive) mastectomy. Removal of both breasts reduces the risk of breast cancer by 90% or more,[241] depending upon the type of mastectomy and the amount of tissue removed. Since prophylactic mastectomy is risk-reducing but not risk-eliminating (because residual breast tissue can be hidden in the mastectomy skin flaps and/or axillary fat pad), women undergoing this surgery should continue to be aware of breast cancer symptoms and seek medical attention if any develop. Prophylactic salpingo-oophorectomy (surgical removal of the fallopian tubes and ovaries) reduces the risk of ovarian cancer, but the benefit for breast cancer in high-risk women is less clear and may be limited to *BRCA2* variant carriers.[242] Importantly, not all women who elect prophylactic surgery would have developed cancer, and surveillance may be just as effective for reducing breast cancer mortality for some women.[243] Women considering these options should discuss the benefits and limitations with their doctor, and a second opinion is strongly recommended. See page 26 for further discussion of contralateral prophylactic mastectomy in women diagnosed with unilateral breast cancer.

Breast Cancer Screening

American Cancer Society recommendations for the early detection of breast cancer vary depending on a woman's age and include mammography, as well as magnetic resonance imaging (MRI) for women at high risk. The recommendations for average-risk women were most recently updated in 2015 (see sidebar, right),[244] and for high-risk women in 2007.[245]

Mammography

Mammography is a low-dose x-ray image of breast tissue. Although early mammographic images were on x-ray film, digital mammography (DM), in which a 2-dimensional (2D) image of breast tissue is captured electronically and viewed on a monitor, has largely replaced screen-film mammography. DM has improved sensitivity for women under age 50 and those with mammographically dense breast tissue.[246] 2D mammography is more commonly being accompanied with digital breast tomosynthesis (DBT) to create 3D images of the breast. More information on DBT can be found on page 22.

American Cancer Society Guideline for Breast Cancer Screening, 2015[244]

The following recommendations are for women at average risk of breast cancer (i.e., women without a personal history of breast cancer, a suspected or a confirmed genetic variant known to increase risk of breast cancer [e.g., *BRCA1* or *BRCA2*], a strong family history, or a history of previous radiotherapy to the chest at a young age). All women should become familiar with the benefits, limitations, and potential harms associated with breast cancer screening.

- Women should have the opportunity to begin annual screening between the ages of 40 and 44.
- Women ages 45 to 54 should be screened annually.
- Women ages 55 and older should transition to biennial screening or have the opportunity to continue screening annually.
- Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or more.

Early detection of breast cancer by mammography reduces the risk of breast cancer death as it increases treatment options, including less extensive surgery and/or the use of chemotherapy. This can result in fewer side effects, and sometimes even the option to forgo chemotherapy. Beginning in the late 1960s, a succession of randomized trials demonstrated the efficacy of early breast cancer detection with mammography, and breast cancer screening with mammography was adopted as a preventive health strategy.[247] More recent results from organized mammography programs in Europe and Canada indicate that the risk of breast cancer death is reduced by more than 40% among women who participated in screening.[248-251] Additionally, women who undergo mammography screening have a 25% reduction in advanced-stage breast cancers compared to women who received no screening.[251]

Women should be informed of the limitations of mammography. Mammography will not detect all breast cancers, and some breast cancers detected by screening still have a poor prognosis. Mammography screening can also lead to overdiagnosis. That is, some breast tumors or lesions detected by mammography, particularly ductal carcinoma in situ (DCIS), would never have progressed or otherwise been detected in the absence of screening. Unfortunately, however, we are currently unable to distinguish the biologically indolent breast cancers from the majority of cases that will progress in the absence of treatment. Ongoing research seeks to clarify this distinction. The prevalence of overdiagnosis is difficult to measure, but a recent study found that among women 50 to 74 years of age, overdiagnosis occurs in about 1 out of 7, or 15%, of screen-detected breast cancers.[252] Mammography may also result in false-positive results, which lead to follow-up examinations, including biopsies, when there is no cancer. False positives are most likely at the first screening. About 12% of women screened with modern digital mammograms require follow-up imaging or biopsy, but most (95%) do not have cancer.[253] Cumulative radiation exposure from repeated mammograms slightly increases the risk of breast cancer;[254] however, the dose of radiation during a mammogram is relatively small and the benefit of screening substantially outweighs the harm.[255] Reducing radiation exposure through more effective imaging is an area of current research. For example, use of artificial intelligence to analyze images can lower the need for unnecessary follow-up testing.[256]

The Affordable Care Act requires that Medicare and all new private health insurance plans fully cover biannual screening mammograms for women 50 and older without any out-of-pocket expense for patients. There are also programs, such as the Centers for Disease Control and Prevention's National Breast and Cervical Cancer Early Detection Program, that offer mammography services for low-income, uninsured, and underserved women. For help locating a free or low-cost screening mammogram in your area, contact the American Cancer Society at 1-800-227-2345.

Digital breast tomosynthesis (DBT)

In 2011, the FDA approved the use of DBT (also referred to as 3D mammography) for breast cancer screening. DBT takes multiple breast images, in combination with digital 2D mammography, which can be used to construct a 3D image of the breast. Some studies have found that DBT may be more sensitive (i.e., detects more cancers); has fewer false positives; reduces advanced-staged cancers among women with extremely mammographic dense breasts; and has lower recall rates than 2D mammography alone.[116, 257, 258] However, when DBT is performed with a 2D mammogram, women receive about twice the dose of radiation compared to standard mammogram. The FDA has approved the use of tomographic images to produce synthetic 2D images, which reduces the radiation dose to that similar to conventional digital mammography, although this practice is not yet widespread. Approximately 83% of mammography facilities have at least one DBT unit; however not all health plans cover reimbursement for DBT.[259]

Mammography prevalence

- In 2019, 54% of women ages 45-54 had received a mammogram within the past year, and about 76%-78% of women ages 55-74 had received a mammogram within the past two years (Table 5). Overall, 65% of women ages 45 and older were up to date with breast cancer screening according to the American Cancer Society recommendations.

- In 2019, the prevalence of up-to-date mammography was lower in AIAN (54%) and Asian (60%) women than among White (65%), Hispanic (67%), and Black (69%) women (Table 5). However, studies have documented that self-reported survey data overestimate mammography screening prevalence, particularly among Black and Hispanic women.[260-262]
- In 2019, only 37% of uninsured women were up to date with breast cancer screening, compared to 70% of privately insured women (Table 5). Screening rates were also among the lowest in recent immigrants (47%) and women without a high school education (57%).
- Recent studies have provided evidence of declines in breast cancer screening during the COVID-19 pandemic; receipt of a mammogram within the past two years declined from 62% in 2018 to 58% in 2020 among women ages 50-74.[263]
- In 2020, the prevalence of up-to-date mammography among women ages 45 and older ranged from 56% in Wyoming to 76% in Hawaii (Table 6).

Magnetic resonance imaging (MRI)

Breast MRI uses high-powered magnets along with radio waves instead of x-rays to produce an image. In 2007, the American Cancer Society published recommendations for the use of MRI for screening women at high risk of breast cancer.[245]

Beginning at age 30, annual screening with MRI, in addition to mammography, is recommended for women with an estimated lifetime risk of breast cancer of at least 20%-25% due to the presence of a high-risk variation in the breast cancer susceptibility genes *BRCA1* or *BRCA2*, a first-degree relative with a *BRCA1* or *BRCA2* variant (if the woman herself has not been tested), a strong family history of breast and/or ovarian cancer, and prior chest radiation therapy (e.g. for Hodgkin lymphoma), as well as women with Li-Fraumeni, Cowden, and Bannayan-Riley-Ruvalcaba syndromes and their first-degree relatives.[245]

Table 5. Mammography (%), Women 45 and Older, US, 2019

	Up-to-date* (≥ 45 years)	Within the past 2 years (50-74 years)
Overall	**65**	**76**
Age (years)		
45-54	54	–
55-64	76	–
65-74	78	78
75+	54	–
Race/Ethnicity		
Hispanic/Latina	67	79
White	65	76
Black	69	79
Asian/Pacific Islander	60	74
American Indian/Alaska Native	54	63
Education		
Some high school or less	57	69
High school diploma or GED	61	73
Some college/Assoc. degree	66	76
College graduate	72	83
Sexual orientation		
Gay/Lesbian	57	74
Straight	66	77
Bisexual	65	†
Health insurance status (age ≤64 years)		
Uninsured (ages < 65 years)	36	44
Private	70	80
Medicaid/pub/dual	61	72
Medicare (ages ≥65 years)	68	78
Other	69	79
Immigration		
Born in US/US Territory	65	77
In US fewer than 10 years	47	59
In US 10 or more years	67	78
Region		
Northeast	68	81
Midwest	66	76
South	64	75
West	65	75

GED = General Educational Development high school equivalency. *According to the American Cancer Society recommendations: mammogram within the past year (ages 45-54 years) or past two years (ages ≥55 years). †Estimate not provided due to instability. Note: Race is exclusive of Hispanic origin. Mammography prevalence estimates do not distinguish between examinations for screening and diagnosis.

Source: National Health Interview Survey, 2019.

Women with an estimated 15%-20% lifetime risk[264] should talk with their doctors about the benefits and limitations of adding MRI screening to their annual mammogram. MRI screening is not recommended for

Table 6. Mammography (%) by State, Women 45 and Older, 2020

	Up-to-date* (≥ 45 years)		Within the past 2 years (50-74 years)	
	All	Uninsured (Ages 45-64)	All	Uninsured (Ages 50-64)
Alabama	67	28	73	38
Alaska	56	27	65	40
Arizona	63	42	66	49
Arkansas	66	50	67	54
California	60	25	69	^
Colorado	60	31	66	37
Connecticut	73	44	74	60
Delaware	68	51	70	†
District of Columbia	66	†	72	†
Florida	65	35	72	35
Georgia	67	35	70	45
Hawaii	76	56	78	†
Idaho	60	30	65	40
Illinois	67	†	76	†
Indiana	62	32	67	37
Iowa	70	25	75	28
Kansas	64	29	70	36
Kentucky	66	†	70	†
Louisiana	74	44	73	56
Maine	72	23	76	34
Maryland	70	43	69	39
Massachusetts	75	†	80	†
Michigan	64	42	75	70
Minnesota	67	40	72	47
Mississippi	64	36	70	40
Missouri	67	26	72	35
Montana	63	21	69	35
Nebraska	64	36	72	42
Nevada	65	†	71	†
New Hampshire	67	23	69	28
New Jersey	66	38	68	50
New Mexico	61	32	71	39
New York	71	48	71	58
North Carolina	70	44	76	50
North Dakota	72	†	76	†
Ohio	67	35	69	40
Oklahoma	62	35	66	33
Oregon	67	39	73	56
Pennsylvania	68	†	70	†
Rhode Island	74	39	76	†
South Carolina	70	41	73	53
South Dakota	72	30	75	45
Tennessee	67	46	69	29
Texas	65	35	70	49
Utah	60	35	66	41
Vermont	63	46	69	†
Virginia	70	39	72	43
Washington	63	35	67	40
West Virginia	68	36	75	55
Wisconsin	70	53	76	†
Wyoming	56	27	60	33
United States (median)	**67**	**35**	**71**	**40**

*According to American Cancer Society recommendations: mammogram within the past year (ages 45-54 years) or past two years (ages ≥55 years). Note: Mammography prevalence estimates do not distinguish between examinations for screening and diagnosis.

Source: Behavioral Risk Factor Surveillance System, 2016.

women whose lifetime risk of breast cancer is less than 15%. Studies indicate that MRI is underutilized among high-risk women[265] and overutilized by women who are not at high risk for breast cancer.[266] MRI should supplement – not replace – mammography screening and should be done at facilities that are accredited by the American College of Radiology. Although MRI is more expensive than mammography, most major insurance companies will cover some portion of the cost if a woman is demonstrated to be at sufficiently high risk.

Breast ultrasound

Breast ultrasound is sometimes used to evaluate abnormal findings from a mammogram or physical exam. Most often, it is done with a device that captures images of the breast using sound waves. For women with mammographically dense breast tissue, ultrasound combined with mammography may be more sensitive than mammography alone; however, it also increases the likelihood of false-positive results.[267] The use of ultrasound instead of mammograms for breast cancer screening is not recommended at this time. However, using artificial intelligence to improve accuracy of breast ultrasound results and reduce false positives is a current area of research.[268]

Clinical breast examination (CBE)

The American Cancer Society no longer recommends CBE for breast cancer screening in average-risk asymptomatic women because of a lack of clear benefits for CBE alone or in conjunction with mammography.[244] Furthermore, there is some evidence that adding CBE to mammography screening increases the rate of false positives.

Breast self-awareness

Although the American Cancer Society also no longer recommends that women perform monthly breast self-exams (BSE), all women should become familiar with both the appearance and feel of their breasts and report any changes promptly to their doctor. If a lump or other symptoms develop, women should contact a doctor immediately, even after a recent normal mammogram.

Breast Cancer Treatment

Treatment decisions should be made jointly by the patient and the physician after consideration of the cancer stage and biological characteristics; patient age, menopausal status, and preferences; and the risks and benefits associated with each option.

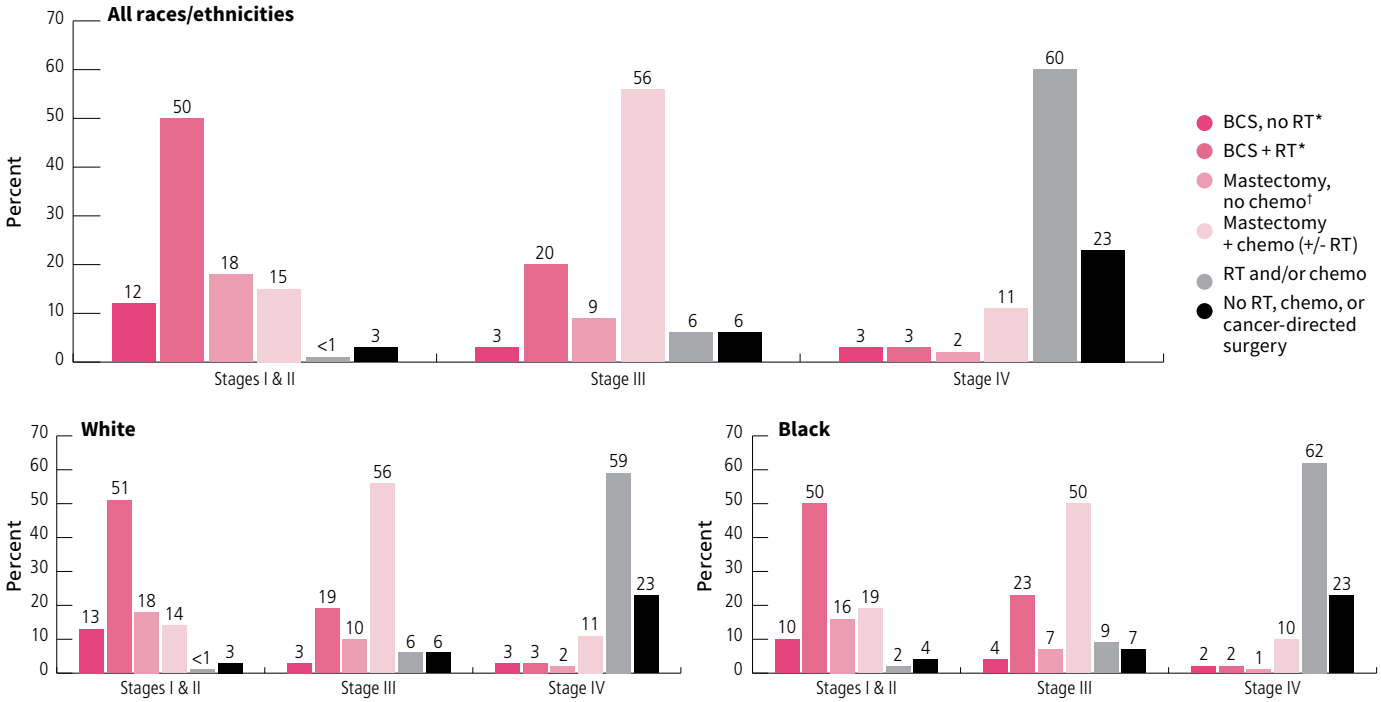
Ductal carcinoma in situ (DCIS)

There is currently no certain way to determine the progressive potential of DCIS, so these lesions are usually treated with surgery and sometimes radiation and/or hormone therapy after surgery. However, there is likely a group of DCIS patients who could safely forgo surgery.[6] Several clinical trials currently underway in the US and internationally are comparing standard treatment to active monitoring (with or without hormone therapy) in women with "low-risk" DCIS, although results will not be available for several years.[269] Ongoing research also seeks to identify molecular markers of DCIS that could predict recurrence or progression to invasive cancer. Currently, active monitoring is extremely rare; a national study found that <1% of DCIS patients diagnosed from 2004 to 2015 underwent active surveillance.[270]

Invasive breast cancer

Figure 12 shows treatment patterns among US women with invasive breast cancer in 2018 by stage at diagnosis and race. Most women with non-metastatic breast cancer will have some type of surgery, which is often combined with other treatments, such as radiation therapy, chemotherapy, hormone therapy, and/or targeted drug therapy, to reduce the risk of recurrence. Patients with metastatic disease are primarily treated with systemic therapies, which can include chemotherapy, targeted drug therapy, hormonal therapy, and/or immunotherapy.

Figure 12. Female Breast Cancer Treatment Patterns (%), by Stage, 2018



White and Black race excludes persons of Hispanic ethnicity. BCS = breast conserving surgery, i.e., lumpectomy/partial mastectomy, in which only cancerous tissue plus a surrounding layer of normal tissue is removed; Mastectomy = surgical removal of the entire breast(s); RT = radiation therapy; Chemo = chemotherapy and includes targeted therapy and immunotherapy. *A small number of these patients received chemotherapy. †A small number of these patients received radiation therapy. NOTE: Many patients may have received hormonal therapy in addition to the above treatments.

Source: National Cancer Data Base, 2021.

Surgery

The primary goals of breast cancer surgery are to remove the cancer and determine its stage. Surgical treatment involves mastectomy (surgical removal of the entire breast) or breast-conserving surgery (BCS). With BCS (also known as partial mastectomy or lumpectomy), only cancerous tissue, plus a rim of normal tissue (tumor margin), is removed. BCS is generally not an option in patients with high tumor-to-breast ratio, multiple tumors within the same breast, or inflammatory or locally advanced cancers. In most cases, BCS is coupled with radiation to the breast, whereas mastectomy is more commonly preceded or followed by chemotherapy, particularly for stage III disease. However, receipt of treatment differs by race; Black women are less likely than White women to receive surgery (56% versus 64%) and more likely to receive radiation or chemotherapy alone (9% versus 6%) for stage III disease, which has the largest stage-specific survival disparity.[23]

BCS-eligible patients in the US are increasingly electing contralateral mastectomy, which has risen among women with breast cancer from 4% in the early 2000s to 13% in 2012, despite equivalent survival when BCS is combined with radiation.[271] Reasons for this include fear of recurrence, reluctance or contraindication to receiving radiation (e.g., prior ipsilateral radiation), and desire for breast symmetry.[272-274] Structural obstacles to receiving radiation therapy, such as distance to treatment and/or transportation availability, also play a role.[275] Some women who are diagnosed with breast cancer in one breast also choose to have the unaffected breast removed, which is known as bilateral mastectomy or contralateral prophylactic mastectomy (CPM). Younger women (<40 years of age) and patients with larger and/or more aggressive tumors are more likely to be treated with mastectomy[276, 277] and to have a contralateral prophylactic mastectomy (CPM).[278] Among women with early-stage disease who choose mastectomy, the percentage who also underwent CPM increased from <2% in 1998 to 28%-30% in 2010-2012,[277] but appears to have leveled off in recent years.[279] Although a proportion of this increase may be due to the broader availability of genetic testing and increased awareness among women at high risk of contralateral disease,[280] CPM rates in Europe are remarkably lower than those in the US.[281] Decision-making tools to help women better understand their individual risk of contralateral breast cancer currently in development may help reduce unnecessary CPM.[282]

Women who undergo mastectomy may have breast reconstruction, which is done either at the time of mastectomy or after further cancer treatment. Reconstruction is done with either a saline or silicone implant, tissue from another part of the body, or a combination of the two. A woman considering breast reconstruction should discuss this option with her breast surgeon and a trained breast plastic surgeon prior to the mastectomy in order to coordinate the treatment.

Both BCS and mastectomy are usually accompanied by removal of one or a few regional lymph nodes from the armpit (axilla) to determine if the disease has spread beyond the breast. This procedure, called sentinel lymph node biopsy (SLNB), identifies the lymph node(s) to which cancer is most likely to spread. The presence of cancer cells in the lymph nodes increases the risk of recurrence, so results from the SLNB can help determine whether further treatment is needed. Breast cancer patients who are ≥70 years of age who have early-stage HR+ tumors may not require an SLNB.[277] Some breast cancer patients need more extensive lymph node surgery, called an axillary lymph node dissection (ALND). However, ALND use has rapidly declined across the US, from 44% in 2011 to 25%-28% in 2013, following clinical trial results that the procedure does not improve survival or recurrence in low-risk patients appropriately treated with BCS and radiation.[277] Patients with a negative/non-cancerous SLNB do not need to consider ALND, and axillary radiation can be considered as a substitute for the ALND in patients that are found to have cancer in the SLNB.

Surgery involving the axillary lymph nodes is the primary risk factor for the development of lymphedema, a serious swelling of the arm caused by retention of lymph fluid. Other risk factors may include axillary radiation, excess body weight, and older age.[283, 284] The precise incidence of breast cancer-related lymphedema is difficult to determine due to the condition's long latency, with incidence generally peaking 12-30 months following initial treatment.[283] Studies estimate that lymphedema affects

about 20% of women who undergo ALND and about 6% of patients who receive SLNB.[285] However, the risk of chronic lymphedema may be greatly reduced through prospective surveillance and early management; in one meta-analysis examining the efficacy of this approach, the cumulative incidence of chronic arm lymphedema at 2 years follow-up among women who underwent ALND was only 6%.[286] Among the clinical trials included in the analysis, surveillance and early management reduced the risk of chronic lymphedema by nearly 70%. The use of early preventive measures, such as compression sleeves, also reduces the risk of swelling in high-risk patients.[287] However, in large part because of limited access to these services, Women of lower socioeconomic status, including Black and Hispanic women, are disproportionately burdened by the condition; for example, Medicare does not provide coverage for compression sleeves even among symptomatic patients.[284]

For more information about breast cancer survivorship and the side effects of treatment, visit cancer.org/statistics to see *Cancer Treatment & Survivorship Facts & Figures*.

Radiation therapy

Radiation therapy is often used after surgery to destroy cancer cells remaining in the breast, chest wall, or underarm area and reduce the risk local of recurrence. Radiation therapy after BCS is standard for most patients, as it has been shown to reduce the risk of cancer recurrence by about 50% at 10 years and the risk of breast cancer death by almost 20% at 15 years.[288] However, evidence from randomized control trials has suggested adjuvant radiation may be omitted without impacting survival in certain subsets of patients receiving BCS, such as women ≥70 years of age with small, localized, hormone receptor (HR) positive tumors taking hormone therapy.[289, 290] Older patients with HR+ tumors who opt to omit radiation must be aware of the heightened importance of adhering to their prescribed hormone therapy regimen.

Patients treated with mastectomy can also benefit from radiation if their tumor is larger than 5 centimeters, growing into nearby tissues, or if cancer is found in the lymph nodes. Radiation can also be used to treat the symptoms of advanced breast cancer, especially when it has spread to the central nervous system or bones.

Radiation therapy may be administered as external beam radiation or internal radiation therapy (brachytherapy). The method depends on the type, stage, and location of the tumor, as well as patient characteristics and doctor and patient preferences. External beam radiation is the standard type of radiation, whereby radiation from a machine outside the body is focused on the area affected by cancer.[291] Brachytherapy uses a radioactive source placed in catheters or other devices that are put into the breast cavity left after BCS and is sometimes an option for patients with early-stage cancers. Accumulating evidence suggests that radiation therapy given in hypofractionated schedules (in which the total dose of radiation is divided into a smaller number of larger doses compared to standard schedules) over fewer days may be as effective as conventional therapy.[292-294] Intraoperative radiation therapy, in which a single fraction of radiation is given directly into the breast cavity after BCS, is also sometimes an option in very select cancers.

Systemic drug therapy

Systemic therapies are drugs that travel through the bloodstream, reaching most parts of the body, and work using different mechanisms. For example, chemotherapy drugs generally attack all cells that grow quickly, such as cancer cells, but may attack normal cells (e.g., those that produce hair) as well. Hormonal therapy works by either blocking or decreasing the level of the body's natural hormones, which sometimes promote cancer growth. Targeted drug therapies work by attacking specific proteins on cancer cells (or nearby cells) that help them grow. Immunotherapy stimulates the patient's immune system to attack cancer cells. Systemic therapies often are used in combination with each other, particularly for advanced or recurrent disease.

When systemic drug therapy is given to patients before surgery, it is called neoadjuvant or preoperative therapy. For larger breast tumors, it is often used to shrink the tumor enough to make surgical removal easier and less extensive (such as BCS in women who would otherwise have required mastectomy).[295] Systemic drug treatment

given to patients after surgery is called adjuvant drug therapy. Systemic drug therapy destroys any undetected tumor cells (micrometastases) that may have migrated to other parts of the body and is the main treatment option for women with metastatic breast cancer.

Systemic drug therapy can affect fertility in premenopausal women, so young breast cancer patients who are interested in future childbearing should consult with a reproductive endocrinologist as soon as possible to determine fertility preservation strategies. Recent studies have suggested that modest breast cancer treatment delays to allow for fertility preservation (e.g., cryopreservation of eggs) do not significantly increase all-cause or breast cancer-specific mortality or recurrence.[296-298] Chemotherapy can also lead to premature ovarian failure. Hormone therapy for breast cancer can lead to menstrual irregularities and even amenorrhea, but normal ovarian function can return once the medication is stopped. However, the drugs used for hormone therapy can affect the fetus, so treatment is delayed for women who are pregnant.

Chemotherapy

The benefit of chemotherapy depends on multiple factors, including the size of the tumor and the number of lymph nodes involved, as well as HR and HER2 status. Triple-negative and HER2+ breast cancers tend to be more sensitive to chemotherapy than HR+ tumors.[299] Gene expression panels (such as Oncotype DX, and MammaPrint) may help assess the risk of distant recurrence and potentially identify those who would more likely benefit from adjuvant chemotherapy. The Oncotype Dx 21-Gene Recurrence Score is used most widely in the US, but it is only applicable for patients with HR+/HER2- breast cancer. A high recurrence score identifies women who are more likely to benefit from adjuvant chemotherapy (in addition to hormone therapy), whereas a low score identifies women who could safely avoid it. Evidence is less clear for patients with intermediate risk scores, although recent clinical trial results based on 9 years of follow-up suggest that most patients over age 50 with intermediate scores are unlikely to benefit from the addition of chemotherapy.[300]

Although most women who are treated with chemotherapy receive it after surgery, the use of neoadjuvant chemotherapy, particularly among patients with HER2+ and triple-negative breast cancers, appears to be increasing.[301] A meta-analysis of 10 clinical trials concluded that neoadjuvant chemotherapy is as effective as the same therapy given after surgery in terms of breast cancer-specific survival and distant recurrence.[295] Although surgery is still necessary after neoadjuvant chemotherapy, even when the preoperative treatment appears to have completely cleared all clinical evidence of the cancer, studies are exploring whether they may be less invasive if disease becomes substantially reduced.[302] Recent clinical trials have identified therapies that can improve outcomes among neoadjuvant-treated breast cancer patients (with triple-negative and HER2 positive cancers) who have residual disease detected during surgery.[303, 304]

Hormone (endocrine) therapy

About 77% of breast cancers are HR+ (Figure 1) and can be treated with hormone therapy to block or lower the effects of estrogen and progesterone on the growth of breast cancer cells. These drugs are different than menopausal hormone therapies, which actually increase hormone levels. About 84% of women with HR+ tumors receive hormone therapy, although receipt is lower for Black women compared to White women, especially for those diagnosed with metastatic disease (69% versus 77%).[305]

For premenopausal women, tamoxifen for up to 10 years is standard treatment; however, for women with a high risk of recurrence, the combination of ovarian suppression and either tamoxifen or an aromatase inhibitor (i.e., letrozole, anastrozole, and exemestane) is recommended.[306] For postmenopausal women, aromatase inhibitors are the preferred hormone treatment. The decision to treat with an aromatase inhibitor beyond 5 years is individualized based on patient factors and the expected benefit from the reduction in risk of subsequent breast cancers. Studies have found that adherence to hormone therapies remains suboptimal, particularly among Black women, and is due in part to side effects, and perhaps the out-of-pocket cost.[307-309]

Targeted drug therapy

Multiple medications are available for the treatment of HER2+ cancers, which account for about 14% of all female breast cancers in the US (Figure 1). All invasive breast cancers should be tested for HER2 to identify women who would benefit from targeted drug therapies. Trastuzumab, the first approved targeted drug for breast cancer, is a monoclonal antibody that directly targets the HER2 protein. Several new drugs that target the HER2 protein are now available and can be used in combination with trastuzumab or if trastuzumab is no longer working.[310] For example, trastuzumab emtansine and trastuzumab deruxtecan are antibody-drug conjugates (drugs that include both a targeted antibody and a chemotherapy agent) that may be used in patients with metastatic HER2+ disease, typically after other treatments have been tried.[311] Trastuzumab deruxtecan was also recently found to improve overall survival in previously treated metastatic patients with very low levels of HER2 expression (referred to as HER2-low disease) compared to standard chemotherapy.[312]

Additional targeted therapy drugs, such as CDK4/6 and PI3K inhibitors, are available for treatment of select patients with advanced disease, often along with hormone therapy. Targeted drugs known as PARP inhibitors are also available to patients with germline *BRCA* variations,[313, 314] and an antibody-drug conjugate (sacituzumab govitecan) may be used in patients with metastatic triple-negative breast cancer that has recurred or progressed.[315]

Immunotherapy

Immunotherapy drugs are an emerging area of breast cancer treatment. These drugs stimulate a person's own immune system to recognize and destroy cancer cells more effectively. For example, the immune system normally uses certain "checkpoint" proteins to keep the immune system in check, which can stop it from attacking cancer cells. Immunotherapy drugs known as checkpoint inhibitors, such as pembrolizumab, can be used to treat some triple-negative breast cancers.[316-318] Research is ongoing to develop novel immunotherapy drugs and regimens, particularly for metastatic and triple-negative disease. However, several challenges remain, including identifying effective biomarker targets.[319, 320]

What Is the American Cancer Society Doing About Breast Cancer?

For more than 100 years, the American Cancer Society (ACS) has helped lead an evolution in the way the world prevents, detects, treats, and thinks about breast cancer – and all cancers. As the nation's preeminent cancer-fighting organization, we fund and conduct research, share expert information, support people impacted by cancer, spread the word about ways to reduce cancer risk, and through our advocacy affiliate, the American Cancer Society Cancer Action Network[SM] (ACS CAN), advocate for public policy change. We are the only organization that integrates discovery, advocacy, and direct patient support to measurably improve lives.

ACS is working to ensure that all people have a fair and just opportunity to prevent, find, treat, and survive cancer. ACS and ACS CAN also believe all people should have a fair and just opportunity to live a longer, healthier life free from cancer regardless of how much money they make, the color of their skin, their sexual orientation, gender identity, their disability status, or where they live. (For more information on these initiatives, see the Advocacy section on page 32.)

This work could not be accomplished without the strength of our dedicated volunteers to drive every part of our mission. With the support of our professional staff, volunteers raise funds to support innovative research, provide rides to treatment for people with cancer, and offer peer-to-peer support to those facing a cancer diagnosis – and that's just the beginning. Thanks in part to our contributions, 3.2 million cancer deaths have been

averted in the US since 1991, when cancer death rates were at their peak.

Patient support

The American Cancer Society works to ensure no one feels alone at any point on their cancer journey, from prevention to detection and diagnosis, through treatment and survivorship, and for some, the end of life. We ensure people impacted by cancer have the support, information, and resources they need, all aimed toward eliminating cancer disparities.

Cancer information

Caring, trained American Cancer Society staff provide people with information and support about breast cancer when they need it, including a free 24/7 cancer helpline, cancer.org website, and online peer communities for people with cancer, caregivers, and survivors. Our website, cancer.org, offers reliable and accurate breast cancer information and news, including current information on treatments and side effects, and programs and services available nearby. We can also help people who speak languages other than English or Spanish find the assistance they need at cancer.org/cancer-information-in-other-languages.

People can visit cancer.org/breastcancer to find information on every aspect of the breast cancer experience, from prevention to survivorship. We also publish a wide variety of pamphlets and books that cover a multitude of topics, from patient education, quality-of-life, and caregiving issues to healthy living. Visit cancer.org/bookstore for a complete list of books that are available for order. All of our books are also available from all major book retailers such as Amazon and Barnes & Noble. Call 1-800-227-2345 or visit cancer.org for brochures.

Programs and services

Survivorship: The American Cancer Society's survivorship work aims to help people living with and beyond cancer from diagnosis through long-term survivorship to the end of life. Efforts focus on helping survivors understand and access treatment; manage their ongoing physical, psychosocial, and functional problems; and engage in healthy behaviors to optimize their wellness. Our post-treatment survivorship care guidelines are designed to promote survivor health and quality of life by facilitating the delivery of high-quality, comprehensive, coordinated clinical follow-up care. Our survivorship research efforts focus on understanding the impact of cancer on multiple facets of survivors' lives and on developing and testing interventions to help survivors actively engage in their health care and improve their health and well-being through and beyond treatment. Through the National Cancer Survivorship Resource Center, a collaboration between the American Cancer Society and the George Washington University Cancer Center funded by the Centers for Disease Control and Prevention, we created the Cancer Survivorship E-Learning Series for Primary Care Providers. The free e-learning program is designed to teach clinicians how to care for survivors of adult-onset cancers.

Support for caregivers: Contemporary estimates of caregiver prevalence range between 1.1 million and 6.1 million individuals, and the American Cancer Society is committed to meeting their information, education, and support needs. We support the notion that cancer is not isolated only to the individual diagnosed, but also impacts an entire family unit and network of close friends. One of the informational tools we offer caregivers is our *Caregiver Resource Guide* (cancer.org/caregiverguide), which can help them: learn to care for themselves as a caregiver, better understand what their loved one is going through, develop skills for coping and caring, and take steps to help protect their own health and well-being. Also, our *Caregiver Support Video Series* (cancer.org/caregivervideos) provides educational support to caregivers as they assist with the everyday needs of people with cancer and provide self-care techniques to improve their quality of life.

Help navigating the health care system

Learning how to navigate the cancer journey and the health care system can be overwhelming for anyone, but it is particularly difficult for those who are medically underserved, those who experience language or health literacy barriers, and those with limited resources. The

American Cancer Society aims to reach those most in need through our National Cancer Information Center (NCIC), where we can help find transportation to treatment and other cancer-related appointments; assist with medical financial issues, including insurance navigation; identify resources; and provide information on a patient's cancer diagnosis and treatment process.

Breast cancer support

The American Cancer Society connects people facing breast cancer with one-on-one support – from diagnosis through survivorship – with trained volunteers who are breast cancer survivors. Our Reach To Recovery® volunteers help people facing breast cancer cope with diagnosis, treatment, side effects, and more. Visit reach.cancer.org for more information.

Finding hope and inspiration

The American Cancer Society provides information and support through our online communities. These virtual communities provide people facing breast cancer – or any cancer – and survivors the opportunity to learn more and connect with others who can be a source of support and comfort. Our Cancer Survivors Network (csn.cancer.org) is a safe online community where survivors and caregivers can share their stories, ask questions, and support each other.

Transportation to treatment

American Cancer Society volunteers help people with cancer get free transportation to medical appointments and treatment. Our Road To Recovery® program removes barriers to cancer treatment by providing people with cancer transportation through volunteer drivers.

Lodging during treatment

American Cancer Society Hope Lodge® communities provide free, temporary lodging for people facing cancer and their caregivers when treatment is far from home. Hope Lodge guests don't just find a place to stay – they find a community of support and an emotional connection with others facing the same journey.

Hair-loss and mastectomy products

The American Cancer Society helps women cope with appearance-related side effects of cancer treatment through our *"tlc" Tender Loving Care®* program. The *"tlc"*™ program offers a variety of affordable wigs, hats, and scarves, as well as a full range of mastectomy programs – all available for purchase from the privacy of home. Call 1-800-850-9445 or visit the *"tlc"* website at tlcdirect.org to order products or catalogs.

Support after treatment

The end of breast cancer treatment does not mean the end of a cancer journey. Cancer survivors may experience long-term or late effects resulting from the disease or its treatment. *The Life After Treatment: The Next Chapter in Your Survivorship Journey* guide may help cancer survivors as they begin the next phase of their journey. Visit cancer.org/survivorshipguide to download a free copy of the guide.

The American Cancer Society offers a follow-up care guideline for breast cancer survivors based on available evidence, surveillance guidelines, and standard clinical practice and designed to facilitate the provision of high-quality, standardized, clinical care by primary care providers.[321] The breast cancer guideline addresses the assessment and management of potential long-term and late effects, as well as recommendations for health promotion, surveillance for recurrence, screening for second primary cancers, and the coordination of care between specialists and primary care clinicians.

Research

The American Cancer Society has played a role in most of the cancer research breakthroughs in recent history. We invest more in breast cancer research than any other cancer type. Our funded research has led to the development of potentially lifesaving breast cancer drugs such as tamoxifen and Herceptin, as well as improved understanding of genes linked to breast cancer. Ongoing research studies span the cancer continuum from prevention and early detection to treatment and beyond. As of March 31, 2022, the American Cancer Society is funding more than $72 million in breast cancer research through 162 research and training grants.

Examples of projects in which researchers in Extramural Discovery Science are engaged span the six ACS Research Priority Areas (indicated in parentheses below) and include:

- Identifying new targets for treating triple-negative breast cancers (treatment)
- Developing a wearable device to image breast cancers for assessing effectiveness of ongoing treatments (treatment)
- Understanding the role of the immune system in the spread of breast cancer to other parts of the body (etiology/causes of cancer)
- Evaluating the effects of a high-protein, low-calorie diet on breast tissue and the risk of breast cancer recurrence (etiology/causes of cancer; survivorship)
- Examining the impact of breast density legislation on women's breast cancer knowledge and screening decisions (screening and diagnosis)
- Elucidating biobehavioral mechanisms of breast cancer racial disparities (health equity across the cancer continuum)
- Testing strategies to improved participation in exercise for Hispanic breast cancer survivors (health equity across the cancer continuum; obesity and Healthy Eating and Active Living [HEAL])
- Addressing gaps and disparities in genetic risk prevention in breast cancer patients and their families

Internally, the American Cancer Society also conducts epidemiologic studies of breast cancer and performs surveillance and health services research to understand the factors that underlie racial and socioeconomic disparities in breast cancer screening, incidence, treatment, survival, and mortality. Using information collected from more than 600,000 women in the American Cancer Society Cancer Prevention Study-II, our epidemiologists study the influence of many risk factors, including alcohol consumption, physical activity, menopausal hormones, family history of cancer, obesity, smoking, and spontaneous abortion on the risk of death from breast cancer. In order to continue to explore the effects of changing exposures and to provide greater opportunity to integrate biological and genetic factors into studies of other risk factors, more than 304,000 men and women were enrolled in the American Cancer Society Cancer Prevention Study-3 (CPS-3), and nearly all provided a blood sample at the time of enrollment. When female participants are diagnosed with breast cancer, consent is requested to bank tumor tissue specimens to better understand differences in risk and prognostic factors by molecular subtypes of breast cancer. The blood and tissue specimens together with the questionnaire data collected from CPS-3 participants will provide unique opportunities for research in the US.

Advocacy

The American Cancer Society Cancer Action Network℠ (ACS CAN), the nonprofit, nonpartisan advocacy affiliate of the American Cancer Society, advocates in city halls, statehouses, and Congress to increase access to quality breast cancer screenings, diagnostic and treatment services, and care for all women; increase government funding for breast cancer research; and provide a voice for the concerns of breast cancer patients and survivors. Following are some of the efforts that ACS CAN has been involved with in the past few years:

Improving Access to Affordable Care through Health Care Reform: The Affordable Care Act (ACA) was signed into law on March 23, 2010, giving people with cancer access to quality, affordable health care. All health insurance plans that must comply with the ACA, including those offered through state health insurance exchanges, are required to cover preventive services rated "A" or "B" by the US Preventive Services Task Force, including mammography screening, at no cost to patients. Additionally, the ACA removed cost sharing for any preventive services covered by Medicare. ACS CAN advocates for clear, comprehensive coverage of these preventive services, including breast cancer screening, and encourages states to broaden access to health care coverage for all low-income Americans through state Medicaid programs.

The National Breast and Cervical Cancer Early Detection Program (NBCCEDP): Protecting and increasing funding for the NBCCEDP is a high priority for ACS CAN at both the state and federal levels. Administered by the Centers for Disease Control and Prevention, this successful program provides community-based breast and cervical cancer screenings to low-income, uninsured, and underinsured women. Women who are uninsured are much less likely to be screened for cervical and breast cancer than those who are insured. The NBCCEDP helps to decrease this disparity in screening. Unfortunately, only one in 10 eligible women can be served by the program due to lack of federal and state funding. ACS CAN is asking Congress and state legislatures to increase funding to ensure that more women have access to cancer screening.

Protecting the Breast and Cervical Cancer Prevention and Treatment Act (BCCPTA): In 2000, Congress passed the BCCPTA, ensuring that low-income women diagnosed with cancer through the NBCCEDP were provided a pathway to treatment services through their state Medicaid program.

In recent years, a number of states have considered proposals to eliminate the treatment program due to misconceptions around coverage needs following implementation of the ACA. Additionally, states have considered proposals that could jeopardize access to this program through the 1115 demonstration waiver process. ACS CAN has opposed these efforts and is working to protect this Medicaid eligibility category.

Breast Density and Mammography Reporting: Mammography sensitivity is lower for women with mammographically dense breasts because dense breast tissue makes it harder for doctors to see cancer on mammograms. The Food and Drug Administration proposed a rule to incorporate breast density reporting on mammography reports for the first time in 2019. That rule has not been finalized yet. ACS CAN has advocated for several years for a national standard developed through an evidence-based process to inform women about breast density and risk.

Patient Navigation: Patient navigation can improve quality of cancer care, particularly in vulnerable populations. In 2017, the American Cancer Society established the National Navigation Roundtable (NNRT), a national coalition of over 100 organizations dedicated to achieving health equity and access to quality care across the cancer continuum through effective patient navigation. ACS CAN advocates for the coverage of patient navigation services because clinical navigation services are not covered by most insurers. The organization also advocates to improve health equity by increasing access to quality cancer care among communities that have been marginalized and to extend the reach of navigation services to populations that have been underserved so that they can access resources that help eliminate other barriers to care.

ACS CAN supports the federal Patient Navigation Assistance Act, which would require state Medicaid programs to cover navigation services. In collaboration with the NNRT, the organization also is working on proposals to encourage public and private insurance coverage of patient navigation services to ensure the financial stability of patient navigation programs because patient navigation services are not covered by most insurers and are frequently supported through short-term grant funding.

Funding for Cancer Research: ACS CAN continues to work to increase government funding for cancer research at the National Institutes of Health, including the National Cancer Institute and the National Center on Minority Health and Health Disparities.

It is important to note that the preceding references to ACA provisions and other federal laws and guidance reflect current law as of 2022, and do not take into account potential changes to the ACA or other federal laws and guidance subsequently considered by Congress and the administration.

Sources of Statistics

Unless otherwise stated, the statistics and statements in this publication refer to invasive (not in situ) female breast cancer.

Estimated new breast cancer cases. The number of invasive breast cancer cases and DCIS diagnosed in 2022 was calculated by estimating complete case counts during 2004-2018 in all 50 states and the District of Columbia using a spatiotemporal model that considers state variation in sociodemographic and lifestyle factors, medical settings, and cancer screening behaviors, and also accounts for expected delays in case reporting. Input data for the model was cancer occurrence information from cancer registries that consented to participate and met the North American Association of Central Cancer Registries' (NAACCR) high-quality data standards. The NAACCR is an umbrella organization that sets standards and aggregates and disseminates incidence data collected by cancer registries in the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program and/or the Centers for Disease Control and Prevention's National Program of Cancer Registries. Modeled counts are then projected forward 4 years based on the most recent 4-year average annual percent change (AAPC) in cases. Age-specific estimates were calculated using the proportions of cases that occurred in each age group during 2015-2019 applied to the overall 2022 estimate.

Incidence rates. Breast cancer incidence rates are defined as the number of people who are diagnosed with cancer divided by the number of people who are at risk for the disease in the population during a given time period. Incidence rates in this publication are typically presented per 100,000 female population per year (or 100,000 male population for male breast cancer) and are age adjusted to the 2000 US standard population based on 19 age groups. Breast cancer incidence rates for the US in the most recent time period (2015-2019) were based on nationwide cancer registry data provided by NAACCR. Incidence rates presented herein may differ slightly from those on the NAACCR website (naaccr.org) because NAACCR has begun adjusting rates based on 20 age groups instead of 19, which is the standard of the National Cancer Institute and the Centers for Disease Control and Prevention. Long-term (1975-2019) incidence trends are based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 8 registries, which account for about 8% of the US population. Analyses of trends by race/ethnicity (2000-2019) and by stage at diagnosis (2004-2019) were based on SEER 22 and 17 registry incidence data, respectively, and adjusted for reporting delay using delay factors.

Estimated cancer deaths. The overall estimated number of breast cancer deaths in the US is calculated by fitting the number of breast cancer deaths for 2006-2020 to a statistical model that forecasts the number of deaths expected to occur in 2022. Data on the number of deaths are obtained from the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC). Similar to cases, proportions of breast cancer deaths by age (2016-2020) were applied to obtain age-specific estimates.

Mortality rates. Similar to incidence rates, breast cancer mortality rates (or death rates) are defined as the number of people who die from cancer divided by the number of people at risk in the population during a given time period. Breast cancer death rates were calculated using data on cancer deaths compiled by NCHS and population data collected by the US Census Bureau. Death rates specific to the AIAN population were adjusted with classification ratios by using the approach of Arias, et al.[322] due to known issues with misclassification of AIAN race on death certificates. All death rates in this publication were age adjusted to the 2000 US standard population. Mortality rates for Puerto Rico were obtained from the NCI's State Cancer Profiles, which also includes incidence rates and risk factors for states and counties. Trends of mortality rates from 1990 onward by race and ethnicity exclude states during years they did not collect Hispanic ethnicity data: Louisiana (1990); New Hampshire (1990-1992); and Oklahoma (1990-1996).

Survival. Five-year survival statistics are based on breast cancer patients diagnosed during 2012-2018; 10-year survival rates are based on diagnoses during 2004-2018; and 15-year survival rates are based on diagnoses during 2001-2018. All patients were followed through 2019.

Probability of breast cancer diagnosis or death. Probabilities of developing or dying from breast cancer were calculated using DevCan 6.8.0 (Probability of Developing Cancer Software), developed by the National Cancer Institute. These probabilities reflect the average experience of women in the US who were not previously diagnosed with breast cancer and do not take into account individual behaviors and risk factors (e.g., utilization of mammography screening and family history of breast cancer).

Screening. State-level prevalence estimates of mammography are based on Behavioral Risk Factor Surveillance System (BRFSS) data. The BRFSS is an ongoing system of surveys conducted by the state health departments in cooperation with the CDC. Data from the CDC's National Health Interview Survey were used to generate national prevalence estimates of mammography.

Important note about estimated cases and deaths. While these estimates provide a reasonably accurate portrayal of the current cancer burden in the absence of actual data, they should be interpreted with caution because they are model-based projections that may vary from year to year for reasons other than changes in cancer occurrence. As such, they are not informative for tracking cancer trends. Instead, trends in cancer occurrence should be analyzed using age-adjusted incidence rates reported by population-based cancer registries and mortality rates reported by the NCHS.

References

1. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67:93-99.

2. Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67:290-303.

3. Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: a review. *Breast Cancer Res Treat*. 2006;97:135-144.

4. Sanders ME, Schuyler PA, Simpson JF, Page DL, Dupont WD. Continued observation of the natural history of low-grade ductal carcinoma in situ reaffirms proclivity for local recurrence even after more than 30 years of follow-up. *Mod Pathol*. 2015;28:662-669.

5. Collins LC, Tamimi RM, Baer HJ, Connolly JL, Colditz GA, Schnitt SJ. Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. *Cancer*. 2005;103:1778-1784.

6. Ryser MD, Weaver DL, Zhao F, et al. Cancer Outcomes in DCIS Patients Without Locoregional Treatment. *J Natl Cancer Inst*. 2019;111:952-960.

7. Chootipongchaivat S, van Ravesteyn NT, Li X, et al. Modeling the natural history of ductal carcinoma in situ based on population data. *Breast Cancer Res*. 2020;22:53-53.

8. Punglia RS, Bifolck K, Golshan M, et al. Epidemiology, Biology, Treatment, and Prevention of Ductal Carcinoma In Situ (DCIS). *JNCI Cancer Spectr*. 2018;2:pky063.

9. Visser LL, Groen EJ, van Leeuwen FE, Lips EH, Schmidt MK, Wesseling J. Predictors of an Invasive Breast Cancer Recurrence after DCIS: A Systematic Review and Meta-analyses. *Cancer Epidemiol Biomarkers Prev*. 2019;28:835-845.

10. Jenkins S, Kachur ME, Rechache K, Wells JM, Lipkowitz S. Rare Breast Cancer Subtypes. *Curr Oncol Rep*. 2021;23:54.

11. Dieci MV, Orvieto E, Dominici M, Conte P, Guarneri V. Rare breast cancer subtypes: Histological, molecular, and clinical peculiarities. *Oncologist*. 2014;19:805-813.

12. Renshaw A. *Rosen's Breast Pathology, 4th Edition*. Philadelphia PA: Wolters Kluwer; 2014.

13. Cheang MCU, Martin M, Nielsen TO, et al. Defining breast cancer intrinsic subtypes by quantitative receptor expression. *Oncologist*. 2015;20:474-482.

14. Parise CA, Caggiano V. Risk of mortality of node-negative, ER/PR/HER2 breast cancer subtypes in T1, T2, and T3 tumors. *Breast Cancer Res Treat*. 2017;165:743-750.

15. Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in Breast Cancer Survival by Molecular Subtypes in the United States. *Cancer Epidemiol Biomarkers Prev*. 2018;28:28.

16. Prat A, Adamo B, Cheang MC, Anders CK, Carey LA, Perou CM. Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. *Oncologist*. 2013;18:123-133.

17. Yin L, Duan JJ, Bian XW, Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Res*. 2020;22:61.

18. Sharma P. Biology and Management of Patients With Triple-Negative Breast Cancer. *Oncologist*. 2016;21:1050-1062.

19. Howard FM, Olopade OI. Epidemiology of Triple-Negative Breast Cancer: A Review. *Cancer J*. 2021;27:8-16.

20. Emborgo TS, Saporito D, Muse KI, et al. Prospective Evaluation of Universal BRCA Testing for Women With Triple-Negative Breast Cancer. *JNCI Cancer Spectr*. 2020;4:pkaa002-pkaa002.

21. Pernas S, Tolaney SM. Management of Early-Stage Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer. *JCO Oncol Pract*. 2021;17:320-330.

22. Plevritis SK, Munoz D, Kurian AW, et al. Association of Screening and Treatment With Breast Cancer Mortality by Molecular Subtype in US Women, 2000-2012. *JAMA*. 2018;319:154-164.

23. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin*. 2022:1-23.

24. 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 Epidemiol Biomarkers Prev*. 2017;26:809-815.

25. National Cancer Institute. Breast cancer risk assessment tool. Available at: https://bcrisktool.cancer.gov. Accessed May 31 2022.

26. 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 Cancer J Clin*. 2018;68:394-424.

27. Warnecke RB, Campbell RT, Vijayasiri G, Barrett RE, Rauscher GH. Multilevel Examination of Health Disparity: The Role of Policy Implementation in Neighborhood Context, in Patient Resources, and in Healthcare Facilities on Later Stage of Breast Cancer Diagnosis. *Cancer Epidemiol Biomarkers Prev*. 2019;28:59-66.

28. Breen N, Gentleman JF, Schiller JS. Update on mammography trends: comparisons of rates in 2000, 2005, and 2008. *Cancer*. 2011;117:2209-2218.

29. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356:1670-1674.

30. Coombs NJ, Cronin KA, Taylor RJ, Freedman AN, Boyages J. The impact of changes in hormone therapy on breast cancer incidence in the US population. *Cancer Causes Control*. 2010;21:83-90.

31. Pfeiffer RM, Webb-Vargas Y, Wheeler W, Gail MH. Proportion of U.S. Trends in Breast Cancer Incidence Attributable to Long-term Changes in Risk Factor Distributions. *Cancer Epidemiol Biomarkers Prev*. 2018;1:1.

32. Anderson WF, Katki HA, Rosenberg PS. Incidence of breast cancer in the United States: current and future trends. *J Natl Cancer Inst*. 2011;103:1397-1402.

33.Munoz D, Near AM, van Ravesteyn NT, et al. Effects of screening and systemic adjuvant therapy on ER-specific US breast cancer mortality. *J Natl Cancer Inst*. 2014;106.

34.Tong CWS, Wu M, Cho WCS, To KKW. Recent Advances in the Treatment of Breast Cancer. *Front Oncol*. 2018;8.

35. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353:1784-1792.

36. Krieger N, Wright E, Chen JT, Waterman PD, Huntley ER, Arcaya M. Cancer Stage at Diagnosis, Historical Redlining, and Current Neighborhood Characteristics: Breast, Cervical, Lung, and Colorectal Cancers, Massachusetts, 2001–2015. *Am J Epidemiol*. 2020;189:1065-1075.

37. Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL. Racial and Ethnic Disparities in Cancer Survival: The Contribution of Tumor, Sociodemographic, Institutional, and Neighborhood Characteristics. *J Clin Oncol*. 2018;36:25-33.

38. Newman LA. Parsing the Etiology of Breast Cancer Disparities. *J Clin Oncol*. 2016;34:1013-1014.

39. Daly B, Olopade OI. A perfect storm: How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. *CA Cancer J Clin*. 2015;65:221-238.

40. Lawson MB, Bissell MCS, Miglioretti DL, et al. Multilevel Factors Associated With Time to Biopsy After Abnormal Screening Mammography Results by Race and Ethnicity. *JAMA Oncol*. 2022;8(8):1115-1126. doi:10.1001/jamaoncol.2022.1990.

41. Star J, Bandi P, A KM, Jemal A, S AF. A first look at breast cancer screening in over 1000 community health centers in the United States. *Prev Med*. 2022;161:107115.

42. Nyante SJ, Abraham L, Aiello Bowles EJ, et al. Diagnostic Mammography Performance across Racial and Ethnic Groups in a National Network of Community-Based Breast Imaging Facilities. *Cancer Epidemiol Biomarkers Prev*. 2022;31:1324-1333.

43. Coughlin SS. Social determinants of breast cancer risk, stage, and survival. *Breast Cancer Res Treat*. 2019;177:537-548.

44. American Cancer Society. *Cancer Facts & Figures 2022*. Atlanta: American Cancer Society; 2022.

45. Loo LWM, Williams M, Hernandez BY. The high and heterogeneous burden of breast cancer in Hawaii: A unique multiethnic U.S. Population. *Cancer Epidemiol*. 2019;58:71-76.

46. Pinheiro PS, Morris CR, Liu L, Bungum TJ, Altekruse SF. The impact of follow-up type and missed deaths on population-based cancer survival studies for Hispanics and Asians. *J Natl Cancer Inst Monogr*. 2014;2014:210-217.

47. Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL. Trends in Cancer Survival by Health Insurance Status in California From 1997 to 2014. *JAMA Oncol*. 2018;4:317-323.

48. Singh GK, Jemal A. Socioeconomic and Racial/Ethnic Disparities in Cancer Mortality, Incidence, and Survival in the United States, 1950-2014: Over Six Decades of Changing Patterns and Widening Inequalities. *J Environ Public Health*. 2017;2017:2819372.

49. Shariff-Marco S, DeRouen MC, Yang J, et al. Neighborhood archetypes and breast cancer survival in California. *Ann Epidemiol*. 2021;57:22-29.

50. Malinowski C, Lei X, Zhao H, Giordano SH, Chavez-MacGregor M. Association of Medicaid Expansion With Mortality Disparity by Race and Ethnicity Among Patients With De Novo Stage IV Breast Cancer. *JAMA Oncol*. 2022;8:863-870.

51. SEER*Stat Database: NAACCR Incidence Data - CiNA Analytic File, 1995-2019, for NHIAv2 Origin, Custom File With County, ACS Facts and Figures projection Project (which includes data from CDC's National Program of Cancer Registries (NPCR), CCCR's Provincial and Territorial Registries, and the NCI's Surveillance, Epidemiology and End Results (SEER) Registries), certified by the North American Association of Central Cancer Registries (NAACCR) as meeting high-quality incidence data standards for the specified time periods, submitted December 2021.

52. Anderson WF, Devesa SS. Breast carcinoma in men. *Cancer*. 2005;103:432-433; author reply 433.

53. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality – All COD, Aggregated With State, Total U.S. (1990-2020) <Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2022. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

54. Yadav S, Karam D, Bin Riaz I, et al. Male breast cancer in the United States: Treatment patterns and prognostic factors in the 21st century. *Cancer*. 2020;126(1):26-36. doi:10.1002/cncr.32472.

55. Gucalp A, Traina TA, Eisner JR, et al. Male breast cancer: a disease distinct from female breast cancer. *Breast Cancer Res Treat*. 2019;173:37-48.

56. Brinton LA, Cook MB, McCormack V, et al. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. *J Natl Cancer Inst*. 2014;106:djt465.

57. Ruddy KJ, Winer EP. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. *Ann Oncol*. 2013;24:1434-1443.

58. Sung H, DeSantis C, Jemal A. Subtype-Specific Breast Cancer Incidence Rates in Black versus White Men in the United States. *JNCI Cancer Spectr*. 2019;4.

59. Cook MB, Guenel P, Gapstur SM, et al. Tobacco and alcohol in relation to male breast cancer: An analysis of the male breast cancer pooling project consortium. *Cancer Epidemiol Biomarkers Prev*. 2015;24:520-531.

60. Arem H, Brinton LA, Moore SC, et al. Physical Activity and Risk of Male Breast Cancer. *Cancer Epidemiol Biomarkers Prev*. 2015;24: 1898-1901.

61. Choi YJ, Myung SK, Lee JH. Light Alcohol Drinking and Risk of Cancer: A Meta-Analysis of Cohort Studies. *Cancer Res Treat*. 2018;50:474-487.

62. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2018;68:31-54.

63. Morra A, Jung AY, Behrens S, et al. Breast Cancer Risk Factors and Survival by Tumor Subtype: Pooled Analyses from the Breast Cancer Association Consortium. *Cancer Epidemiol Biomarkers Prev*. 2021;30:623-642.

64. Tamimi RM, Spiegelman D, Smith-Warner SA, et al. Population Attributable Risk of Modifiable and Nonmodifiable Breast Cancer Risk Factors in Postmenopausal Breast Cancer. *Am J Epidemiol*. 2016;184:884-893.

65. Dall GV, Britt KL. Estrogen Effects on the Mammary Gland in Early and Late Life and Breast Cancer Risk. *Front Oncol*. 2017;7:110.

66. Gaudet MM, Gierach GL, Carter BD, et al. Pooled Analysis of Nine Cohorts Reveals Breast Cancer Risk Factors by Tumor Molecular Subtype. *Cancer Res*. 2018;78:6011-6021.

67. DevCan: Probability of Developing or Dying of Cancer Software, Version 6.8.0; Statistical Research and Applications Branch, National Cancer Institute, April 2022. surveillance.cancer.gov/devcan.

68. Momozawa Y, Sasai R, Usui Y, et al. Expansion of Cancer Risk Profile for *BRCA1* and *BRCA2* Pathogenic Variants. *JAMA Oncol*. 2022.

69. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310:1353-1368.

70. Shiyanbola OO, Arao RF, Miglioretti DL, et al. Emerging Trends in Family History of Breast Cancer and Associated Risk. *Cancer Epidemiol Biomarkers Prev*. 2017;26:1753-1760.

71. Kharazmi E, Chen T, Narod S, Sundquist K, Hemminki K. Effect of multiplicity, laterality, and age at onset of breast cancer on familial risk of breast cancer: a nationwide prospective cohort study. *Breast Cancer Res Treat*. 2014;144:185-192.

72. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet*. 2001;358:1389-1399.

73. Beebe-Dimmer JL, Yee C, Cote ML, et al. Familial clustering of breast and prostate cancer and risk of postmenopausal breast cancer in the Women's Health Initiative Study. *Cancer*. 2015;121:1265-1272.

74. Tung N, Lin NU, Kidd J, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. *J Clin Oncol*. 2016;34:1460-1468.

75. Turnbull C, Rahman N. Genetic predisposition to breast cancer: past, present, and future. *Annu Rev Genomics Hum Genet*. 2008;9: 321-345.

76. Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *Proc Natl Acad Sci U S A*. 2014;111:14205-14210.

77. Pal T, Bonner D, Cragun D, et al. A high frequency of *BRCA* mutations in young black women with breast cancer residing in Florida. *Cancer*. 2015;121:4173-4180.

78. Weitzel JN, Clague J, Martir-Negron A, et al. Prevalence and type of BRCA mutations in Hispanics undergoing genetic cancer risk assessment in the southwestern United States: a report from the Clinical Cancer Genetics Community Research Network. *J Clin Oncol*. 2013;31:210-216.

79. Domchek SM, Yao S, Chen F, et al. Comparison of the Prevalence of Pathogenic Variants in Cancer Susceptibility Genes in Black Women and Non-Hispanic White Women With Breast Cancer in the United States. *JAMA Oncol*. 2021;7:1045-1050.

80. Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. *N Engl J Med*. 2021;384:440-451.

81. McCarthy AM, Bristol M, Domchek SM, et al. Health Care Segregation, Physician Recommendation, and Racial Disparities in BRCA1/2 Testing Among Women With Breast Cancer. *J Clin Oncol*. 2016;34:2610-2618.

82. Palmer JR, Polley EC, Hu C, et al. Contribution of Germline Predisposition Gene Mutations to Breast Cancer Risk in African American Women. *J Natl Cancer Inst*. 2020;112:1213-1221.

83. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA*. 2017;317:2402-2416.

84. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med*. 2014;371:497-506.

85. Yang X, Leslie G, Doroszuk A, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. *J Clin Oncol*. 2020;38:674-685.

86. Dorling L, Carvalho S, Allen J, et al. Breast Cancer Risk Genes – Association Analysis in More than 113,000 Women. *N Engl J Med*. 2021;384:428-439.

87. Ferreira MA, Gamazon ER, Al-Ejeh F, et al. Genome-wide association and transcriptome studies identify target genes and risk loci for breast cancer. *Nat Commun*. 2019;10:1741.

88. Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat Genet*. 2015;47:373-380.

89. Consortium BCA. Pathology of Tumors Associated With Pathogenic Germline Variants in 9 Breast Cancer Susceptibility Genes. *JAMA Oncol*. 2022;8:e216744-e216744.

90. Chen H, Wu J, Zhang Z, et al. Association Between BRCA Status and Triple-Negative Breast Cancer: A Meta-Analysis. *Front Pharmacol*. 2018;9:909.

91. Force UPST. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2019;322:652-665.

92. Moyer VA. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160:271-281.

93. Sung H, Freedman RA, Siegel RL, et al. Risks of subsequent primary cancers among breast cancer survivors according to hormone receptor status. *Cancer*. 2021;127:3310-3324.

94. Kramer I, Schaapveld M, Oldenburg HSA, et al. The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype. *J Natl Cancer Inst*. 2019;30:30.

95. Watt GP, John EM, Bandera EV, et al. Race, ethnicity and risk of second primary contralateral breast cancer in the United States. *Int J Cancer*. 2021;148:2748-2758.

96. Nichols HB, Berrington de Gonzalez A, Lacey JV, Jr., Rosenberg PS, Anderson WF. Declining incidence of contralateral breast cancer in the United States from 1975 to 2006. *J Clin Oncol*. 2011;29:1564-1569.

97. Gierach GL, Curtis RE, Pfeiffer RM, et al. Association of Adjuvant Tamoxifen and Aromatase Inhibitor Therapy With Contralateral Breast Cancer Risk Among US Women With Breast Cancer in a General Community Setting. *JAMA Oncol*. 2017;3:186-193.

98. Ramin C, Withrow DR, Davis Lynn BC, Gierach GL, Berrington de González A. Risk of contralateral breast cancer according to first breast cancer characteristics among women in the USA, 1992-2016. *Breast Cancer Res*. 2021;23:24.

99. Morrow M, Schnitt SJ, Norton L. Current management of lesions associated with an increased risk of breast cancer. *Nat Rev Clin Oncol*. 2015;12:227-238.

100. Stout NK, Cronin AM, Uno H, et al. Estrogen-receptor status and risk of contralateral breast cancer following DCIS. *Breast Cancer Res Treat*. 2018;171:777-781.

101. Wong SM, King T, Boileau JF, Barry WT, Golshan M. Population-Based Analysis of Breast Cancer Incidence and Survival Outcomes in Women Diagnosed with Lobular Carcinoma In Situ. *Ann Surg Oncol*. 2017;24:2509-2517.

102. Dania V, Liu Y, Ademuyiwa F, Weber JD, Colditz GA. Associations of race and ethnicity with risk of developing invasive breast cancer after lobular carcinoma in situ. *Breast Cancer Res*. 2019;21:120.

103. Liu Y, West R, Weber JD, Colditz GA. Race and risk of subsequent aggressive breast cancer following ductal carcinoma in situ. *Cancer*. 2019;125:3225-3233.

104. Masannat YA, Husain E, Roylance R, et al. Pleomorphic LCIS what do we know? A UK multicenter audit of pleomorphic lobular carcinoma in situ. *Breast*. 2018;38:120-124.

105. Dyrstad SW, Yan Y, Fowler AM, Colditz GA. Breast cancer risk associated with benign breast disease: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2015;149:569-575.

106. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast--risk assessment and management options. *N Engl J Med*. 2015;372:78-89.

107. Mazzola E, Coopey SB, Griffin M, et al. Reassessing risk models for atypical hyperplasia: age may not matter. *Breast Cancer Res Treat*. 2017;165:285-291.

108. Gaudet MM, Deubler E, Diver WR, et al. Breast cancer risk factors by mode of detection among screened women in the Cancer Prevention Study-II. *Breast Cancer Res Treat*. 2021;186:791-805.

109. Newman LA, Stark A, Chitale D, et al. Association Between Benign Breast Disease in African American and White American Women and Subsequent Triple-Negative Breast Cancer. *JAMA Oncol*. 2017;3:1102-1106.

110. Bertrand KA, Tamimi RM, Scott CG, et al. Mammographic density and risk of breast cancer by age and tumor characteristics. *Breast Cancer Res*. 2013;15:R104.

111. Byrne C, Ursin G, Martin CF, et al. Mammographic Density Change With Estrogen and Progestin Therapy and Breast Cancer Risk. *J Natl Cancer Inst*. 2017;109.

112. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356:227-236.

113. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst*. 2014;106.

114. Huo CW, Chew GL, Britt KL, et al. Mammographic density-a review on the current understanding of its association with breast cancer. *Breast Cancer Res Treat*. 2014;144:479-502.

115. Hoeven J. Agriculture, Rural Development, Food and Drug Administration and Related Agencies Appropriations Bill of 2019. 2 ed; 2018.

116. Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. *N Engl J Med*. 2019;381:2091-2102.

117. Weinstein SP, Slanetz PJ, Lewin AA, et al. ACR Appropriateness Criteria® Supplemental Breast Cancer Screening Based on Breast Density. *J Am Coll Radiol*. 2021;18:S456-s473.

118. Keating NL, Pace LE. New Federal Requirements to Inform Patients About Breast Density: Will They Help Patients? *JAMA*. 2019;9:9.

119. Rafferty EA, Durand MA, Conant EF, et al. Breast Cancer Screening Using Tomosynthesis and Digital Mammography in Dense and Nondense Breasts. *JAMA*. 2016;315:1784-1786.

120. Lowry KP, Coley RY, Miglioretti DL, et al. Screening Performance of Digital Breast Tomosynthesis vs Digital Mammography in Community Practice by Patient Age, Screening Round, and Breast Density. *JAMA Netw Open*. 2020;3:e2011792-e2011792.

121. Elands RJJ, Offermans NSM, Simons C, et al. Associations of adult-attained height and early life energy restriction with postmenopausal breast cancer risk according to estrogen and progesterone receptor status. *Int J Cancer*. 2019;144:1844-1857.

122. Zhang B, Shu XO, Delahanty RJ, et al. Height and Breast Cancer Risk: Evidence From Prospective Studies and Mendelian Randomization. *J Natl Cancer Inst*. 2015;107:11.

123. Green J, Cairns BJ, Casabonne D, Wright FL, Reeves G, Beral V. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. *Lancet Oncol*. 2011;12:785-794.

124. Goldberg M, D'Aloisio AA, O'Brien KM, Zhao S, Sandler DP. Pubertal timing and breast cancer risk in the Sister Study cohort. *Breast Cancer Res*. 2020;22:112.

125. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol*. 2012;13:1141-1151.

126. Qu X, Zhang X, Qin A, et al. Bone mineral density and risk of breast cancer in postmenopausal women. *Breast Cancer Res Treat*. 2013;138:261-271.

127. Grenier D, Cooke AL, Lix L, Metge C, Lu H, Leslie WD. Bone mineral density and risk of postmenopausal breast cancer. *Breast Cancer Res Treat*. 2011;126:679-686.

128. Kerlikowske K, Shepherd J, Creasman J, Tice JA, Ziv E, Cummings SR. Are breast density and bone mineral density independent risk factors for breast cancer? *J Natl Cancer Inst*. 2005;97:368-374.

129. Zhang Y, Mao X, Yu X, Huang X, He W, Yang H. Bone mineral density and risk of breast cancer: A cohort study and Mendelian randomization analysis. *Cancer*. 2022.

130. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin*. 2010;60:207-221.

131. Hu Y, Zhang X, Ma Y, et al. Incident Type 2 Diabetes Duration and Cancer Risk: A Prospective Study in Two US Cohorts. *J Natl Cancer Inst*. 2021;113:381-389.

132. Cejuela M, Martin-Castillo B, Menendez JA, Pernas S. Metformin and Breast Cancer: Where Are We Now? *Int J Mol Sci*. 2022;23:2705.

133. Sampson JN, Falk RT, Schairer C, et al. Association of Estrogen Metabolism with Breast Cancer Risk in Different Cohorts of Postmenopausal Women. *Cancer Res*. 2017;77:918-925.

134. Brown SB, Hankinson SE. Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. *Steroids*. 2015;99:8-10.

135. Tin Tin S, Reeves GK, Key TJ. Endogenous hormones and risk of invasive breast cancer in pre- and post-menopausal women: findings from the UK Biobank. *Br J Cancer*. 2021;125:126-134.

136. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002;94:606-616.

137. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet*. 2019;394:1159-1168.

138. Key TJ, Appleby PN, Reeves GK, al. e. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol*. 2013;14:1009-1010.

139. Fortner RT, Eliassen AH, Spiegelman D, Willett WC, Barbieri RL, Hankinson SE. Premenopausal endogenous steroid hormones and breast cancer risk: results from the Nurses' Health Study II. *Breast Cancer Res*. 2013;15:R19.

140. Li K, Anderson G, Viallon V, et al. Risk prediction for estrogen receptor-specific breast cancers in two large prospective cohorts. *Breast Cancer Res*. 2018;20:147.

141. Chlebowski RT, Manson JE, Anderson GL, et al. Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. *J Natl Cancer Inst*. 2013;105:526-535.

142. Beral V, Peto R, Pirie K, Reeves G. Menopausal hormone therapy and 20-year breast cancer mortality. *Lancet*. 2019;394:1139.

143. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. *JAMA*. 2020;324:369-380.

144. Chlebowski RT, Rohan TE, Manson JE, et al. Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone: Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol*. 2015;1:296-305.

145. de Blok CJM, Wiepjes CM, Nota NM, et al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands. *BMJ*. 2019;365:l1652.

146. Nichols HB, Schoemaker MJ, Cai J, et al. Breast Cancer Risk After Recent Childbirth: A Pooled Analysis of 15 Prospective Studies. *Ann Intern Med*. 2018;11:11.

147. Fortner RT, Sisti J, Chai B, et al. Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies. *Breast Cancer Res*. 2019;21:40.

148. Brinton LA. Fertility Status and Cancer. *Semin Reprod Med*. 2017;35:291-297.

149. Beebeejaun Y, Athithan A, Copeland TP, Kamath MS, Sarris I, Sunkara SK. Risk of breast cancer in women treated with ovarian stimulation drugs for infertility: a systematic review and meta-analysis. *Fertil Steril*. 2021;116:198-207.

150. van den Belt-Dusebout AW, Spaan M, Lambalk CB, et al. Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer. *JAMA*. 2016;316:300-312.

151. Gennari A, Costa M, Puntoni M, et al. Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. *Breast Cancer Res Treat*. 2015;150:405-413.

152. Williams CL, Jones ME, Swerdlow AJ, et al. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2 million person years of observation. *BMJ*. 2018;362:k2644.

153. Brinton LA, Scoccia B, Moghissi KS, et al. Long-term relationship of ovulation-stimulating drugs to breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2014;23:584-593.

154. Reigstad MM, Storeng R, Myklebust T, et al. Cancer Risk in Women Treated with Fertility Drugs According to Parity Status-A Registry-based Cohort Study. *Cancer Epidemiol Biomarkers Prev*. 2017;26:953-962.

155. Guleria S, Kjær SK, Albieri V, Frederiksen K, Jensen A. A Cohort Study of Breast Cancer Risk after 20 Years of Follow-Up of Women Treated with Fertility Drugs. *Cancer Epidemiol Biomarkers Prev*. 2019;28:1986-1992.

156. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet*. 2002;360:187-195.

157. Ma H, Ursin G, Xu X, et al. Reproductive factors and the risk of triple-negative breast cancer in white women and African-American women: a pooled analysis. *Breast Cancer Res*. 2017;19:6.

158. Islami F, Liu Y, Jemal A, et al. Breastfeeding and breast cancer risk by receptor status – a systematic review and meta-analysis. *Ann Oncol*. 2015;26:2398-2407.

159. Sanderson M, Pal T, Beeghly-Fadiel A, et al. A Pooled Case-only Analysis of Reproductive Risk Factors and Breast Cancer Subtype Among Black Women in the Southeastern United States. *Cancer Epidemiol Biomarkers Prev*. 2021;30:1416-1423.

160. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. *N Engl J Med*. 2017;377:2228-2239.

161. Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: relative and attributable risks of cardiovascular disease, cancer, and other health outcomes. *Ann Epidemiol*. 2015;25:193-200.

162. Huber D, Seitz S, Kast K, Emons G, Ortmann O. Use of oral contraceptives in BRCA mutation carriers and risk for ovarian and breast cancer: a systematic review. *Arch Gynecol Obstet*. 2020;301: 875-884.

163. Westhoff CL, Pike MC. Hormonal contraception and breast cancer. *Am J Obstet Gynecol*. 2018;219:169.e161-169.e164.

164. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity, hormones and breast cancer subtypes – results from a large nested case-control study in a national screening program. *Breast Cancer Res*. 2017;19:10.

165. Soini T, Hurskainen R, Grenman S, Maenpaa J, Paavonen J, Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. *Obstet Gynecol*. 2014;124:292-299.

166. Dinger J, Bardenheuer K, Minh TD. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. *Contraception*. 2011;83:211-217.

167. Conz L, Mota BS, Bahamondes L, et al. Levonorgestrel-releasing intrauterine system and breast cancer risk: A systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2020;99:970-982.

168. Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. *Cancer Res*. 2012;72:2028-2035.

169. Jiralerspong S, Goodwin PJ. Obesity and Breast Cancer Prognosis: Evidence, Challenges, and Opportunities. *J Clin Oncol*. 2016;34:4203-4216.

170. Iyengar NM, Arthur R, Manson JE, et al. Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study. *JAMA Oncol*. 2018;6:6.

171. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. *CA Cancer J Clin*. 2017;67:378-397.

172. Teras LR, Patel AV, Wang M, et al. Sustained Weight Loss and Risk of Breast Cancer in Women 50 Years and Older: A Pooled Analysis of Prospective Data. *J Natl Cancer Inst*. 2020;112:929-937.

173. Rosner B, Eliassen AH, Toriola AT, et al. Weight and weight changes in early adulthood and later breast cancer risk. *Int J Cancer*. 2017;140:2003-2014.

174. Keum N, Greenwood DC, Lee DH, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. *J Natl Cancer Inst*. 2015;107.

175. Schoemaker MJ, Nichols HB, Wright LB, et al. Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women. *JAMA Oncol*. 2018;4:e181771.

176. García-Estévez L, Cortés J, Pérez S, Calvo I, Gallegos I, Moreno-Bueno G. Obesity and Breast Cancer: A Paradoxical and Controversial Relationship Influenced by Menopausal Status. *Front Oncol*. 2021;11:705911-705911.

177. Barnard ME, Boeke CE, Tamimi RM. Established breast cancer risk factors and risk of intrinsic tumor subtypes. *Biochim Biophys Acta*. 2015;1856:73-85.

178. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. *Med Sci Sports Exerc*. 2019;51:1252-1261.

179. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol*. 2017;18:e457-e471.

180. Moore SC, Lee IM, Weiderpass E, et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. *JAMA Intern Med*. 2016;176:816-825.

181. Pizot C, Boniol M, Mullie P, et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. *Eur J Cancer*. 2016;52:138-154.

182. Guo W, Fensom GK, Reeves GK, Key TJ. Physical activity and breast cancer risk: results from the UK Biobank prospective cohort. *Br J Cancer*. 2020;122:726-732.

183. Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. *Cancer Epidemiol Biomarkers Prev*. 2009;18:11-27.

184. Cao Y, Hou L, Wang W. Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: A meta-analysis of prospective cohort studies. *Int J Cancer*. 2016;138:1894-1904.

185. Guo F, Wang M, Guo X, et al. The association between fatty acid intake and breast cancer based on the NHANES and Mendelian randomization study. *Cancer Epidemiol*. 2021;73:101966.

186. Matta M, Huybrechts I, Biessy C, et al. Dietary intake of trans fatty acids and breast cancer risk in 9 European countries. *BMC Med*. 2021;19:81.

187. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. *BMJ*. 2013;346:f3706.

188. Chen M, Rao Y, Zheng Y, et al. Association between soy isoflavone intake and breast cancer risk for pre- and post-menopausal women: A meta-analysis of epidemiological studies. *PloS One*. 2014;9:e89288.

189. Fraser GE, Jaceldo-Siegl K, Orlich M, Mashchak A, Sirirat R, Knutsen S. Dairy, soy, and risk of breast cancer: those confounded milks. *Int J Epidemiol*. 2020;49:1526-1537.

190. Farvid MS, Chen WY, Rosner BA, Tamimi RM, Willett WC, Eliassen AH. Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up. *Int J Cancer*. 2019;144:1496-1510.

191. World Cancer Research Fund and American Institute for Cancer Research. Continuous Update Project Report Expert Report 2018. Diet, nutrition, physical activity, and breast cancer. Available at: dietandcancerreport.org.

192. Jung S, Spiegelman D, Baglietto L, et al. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. *J Natl Cancer Inst*. 2013;105:219-236.

193. Bakker MF, Peeters PH, Klaasen VM, et al. Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Clin Nutr*. 2016;103:454-464.

194. Wang Y, Gapstur SM, Gaudet MM, Furtado JD, Campos H, McCullough ML. Plasma carotenoids and breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Causes Control*. 2015.

195. Eliassen AH, Hendrickson SJ, Brinton LA, et al. Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. *J Natl Cancer Inst*. 2012;104:1905-1916.

196. Kim JA, Jang J-H, Lee S-Y. An Updated Comprehensive Review on Vitamin A and Carotenoids in Breast Cancer: Mechanisms, Genetics, Assessment, Current Evidence, and Future Clinical Implications. *Nutrients*. 2021;13:3162.

197. Wu Y, Huang R, Wang M, et al. Dairy foods, calcium, and risk of breast cancer overall and for subtypes defined by estrogen receptor status: a pooled analysis of 21 cohort studies. *Am J Clin Nutr*. 2021;114:450-461.

198. Liu Y, Nguyen N, Colditz GA. Links between alcohol consumption and breast cancer: A look at the evidence. *Womens Health* (Lond). 2015;11:65-77.

199. Jayasekara H, MacInnis RJ, Hodge AM, et al. Is breast cancer risk associated with alcohol intake before first full-term pregnancy? *Cancer Causes Control*. 2016;27:1167-1174.

200. Assi N, Rinaldi S, Viallon V, et al. Mediation analysis of the alcohol-postmenopausal breast cancer relationship by sex hormones in the EPIC cohort. *Int J Cancer*. 2019;10:10.

201. Rustagi AS, Scott CG, Winham SJ, et al. Association of Daily Alcohol Intake, Volumetric Breast Density, and Breast Cancer Risk. *JNCI Cancer Spectr*. 2021;5:pkaa124.

202. Jung S, Wang M, Anderson K, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. *Int J Epidemiol*. 2016;45:916-928.

203. Gram IT, Park SY, Maskarinec G, Wilkens LR, Haiman CA, Le Marchand L. Smoking and breast cancer risk by race/ethnicity and oestrogen and progesterone receptor status: the Multiethnic Cohort (MEC) study. *Int J Epidemiol*. 2019;18:18.

204. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active smoking and breast cancer risk: original cohort data and meta-analysis. *J Natl Cancer Inst*. 2013;105:515-525.

205. Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ. Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res*. 2017;19:118-118.

206. White AJ, D'Aloisio AA, Nichols HB, DeRoo LA, Sandler DP. Breast cancer and exposure to tobacco smoke during potential windows of susceptibility. *Cancer Causes Control*. 2017;28:667-675.

207. Macacu A, Autier P, Boniol M, Boyle P. Active and passive smoking and risk of breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2015;154:213-224.

208. Gram IT, Wiik AB, Lund E, Licaj I, Braaten T. Never-smokers and the fraction of breast cancer attributable to second-hand smoke from parents during childhood: the Norwegian Women and Cancer Study 1991–2018. *Int J Epidemiol*. 2021;50:1927-1935.

209. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N Engl J Med*. 2015;373:2499-2511.

210. Ehrhardt MJ, Howell CR, Hale K, et al. Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE). *J Clin Oncol*. 2019;10.

211. Mulder RL, Hudson MM, Bhatia S, et al. Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group. *J Clin Oncol*. 2020;38:4194-4207.

212. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100A-16, Pharmaceuticals. Diethylstilbestrol. A review of human carcinogens. Lyon: International Agency for Research on Cancer; 2012.

213. Hilakivi-Clarke L. Maternal exposure to diethylstilbestrol during pregnancy and increased breast cancer risk in daughters. *Breast Cancer Res*. 2014;16:208.

214. Reed CE, Fenton SE. Exposure to diethylstilbestrol during sensitive life stages: a legacy of heritable health effects. *Birth Defects Res C Embryo Today*. 2013;99:134-146.

215. Troisi R, Hatch EE, Titus L, et al. Prenatal diethylstilbestrol exposure and cancer risk in women. *Environ Mol Mutagen*. 2019;60:395-403.

216. Loomis D, Guyton K, Grosse Y, et al. Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. *Lancet Oncol*. 2015;16: 891-892.

217. Cohn BA, La Merrill M, Krigbaum NY, et al. DDT Exposure in Utero and Breast Cancer. *J Clin Endocrinol Metab*. 2015;100:2865-2872.

218. Cohn BA, Cirillo PM, Terry MB. DDT and Breast Cancer: Prospective Study of Induction Time and Susceptibility Windows. *J Natl Cancer Inst*. 2019;111:803-810.

219. Rodgers KM, Udesky JO, Rudel RA, Brody JG. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. *Environ Res*. 2018;160:152-182.

220. Ahern TP, Broe A, Lash TL, et al. Phthalate Exposure and Breast Cancer Incidence: A Danish Nationwide Cohort Study. *J Clin Oncol*. 2019;17.

221. Gaudet MM, Deubler EL, Kelly RS, et al. Blood levels of cadmium and lead in relation to breast cancer risk in three prospective cohorts. *Int J Cancer*. 2019;144:1010-1016.

222. Zeinomar N, Oskar S, Kehm RD, Sahebzeda S, Terry MB. Environmental exposures and breast cancer risk in the context of underlying susceptibility: A systematic review of the epidemiological literature. *Environ Res*. 2020;187:109346-109346.

223. White AJ, Keller JP, Zhao S, Carroll R, Kaufman JD, Sandler DP. Air Pollution, Clustering of Particulate Matter Components, and Breast Cancer in the Sister Study: A U.S.-Wide Cohort. *Environ Health Perspect*. 2019;127:107002.

224. Coogan PF, Rosenberg L, Palmer JR, Cozier YC, Lenzy YM, Bertrand KA. Hair product use and breast cancer incidence in the Black Women's Health Study. *Carcinogenesis*. 2021;42:924-930.

225. Rao R, McDonald JA, Barrett ES, et al. Associations of hair dye and relaxer use with breast tumor clinicopathologic features: Findings from the Women's circle of Health Study. *Environ Res*. 2022;203:111863.

226. Xu S, Wang H, Liu Y, et al. Hair chemicals may increase breast cancer risk: A meta-analysis of 210319 subjects from 14 studies. *PLoS One*. 2021;16:e0243792.

227. Manouchehri E, Taghipour A, Ghavami V, Ebadi A, Homaei F, Latifnejad Roudsari R. Night-shift work duration and breast cancer risk: an updated systematic review and meta-analysis. *BMC Womens Health*. 2021;21:89.

228. Wegrzyn LR, Tamimi RM, Rosner BA, et al. Rotating Night-Shift Work and the Risk of Breast Cancer in the Nurses' Health Studies. *Am J Epidemiol*. 2017;186:532-540.

229. Cordina-Duverger E, Menegaux F, Popa A, et al. Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol*. 2018;33:369-379.

230. Stevens RG, Brainard GC, Blask DE, Lockley SW, Motta ME. Breast cancer and circadian disruption from electric lighting in the modern world. *CA Cancer J Clin*. 2014;64:207-218.

231. group. IMV. Carcinogenicity of night shift work. *Lancet Oncol*. 2019;20:1058-1059.

232. ACOG Committee Opinion No. 434: induced abortion and breast cancer risk. *Obstet Gynecol*. 2009;113:1417-1418.

233. Rookus MA, van Leeuwen FE. Induced abortion and risk for breast cancer: reporting (recall) bias in a Dutch case-control study. *J Natl Cancer Inst*. 1996;88:1759-1764.

234. Couzin J. Cancer risk. Review rules out abortion-cancer link. *Science*. 2003;299:1498.

235. Chen L, Malone KE, Li CI. Bra wearing not associated with breast cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2014;23:2181-2185.

236. Leberfinger AN, Behar BJ, Williams NC, et al. Breast Implant-Associated Anaplastic Large Cell Lymphoma: A Systematic Review. *JAMA Surg*. 2017;152:1161-1168.

237. Cordeiro PG, Ghione P, Ni A, et al. Risk of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) in a cohort of 3546 women prospectively followed long term after reconstruction with textured breast implants. *J Plast Reconstr Aesthet Surg*. 2020;73:841-846.

238. Cuzick J, Sestak I, Bonanni B, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. *Lancet*. 2013;381:1827-1834.

239. Nelson HD, Fu R, Zakher B, Pappas M, McDonagh M. Medication Use for the Risk Reduction of Primary Breast Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2019;322:868-886.

240. Force UPST. Medication Use to Reduce Risk of Breast Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2019;322:857-867.

241. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *Am J Surg*. 2016;212:660-669.

242. Kotsopoulos J, Lubinski J, Gronwald J, et al. Bilateral Oophorectomy and the Risk of Breast Cancer in BRCA1 Mutation Carriers: a Reappraisal. *Cancer Epidemiol Biomarkers Prev*. 2022.

243. Heemskerk-Gerritsen BAM, Jager A, Koppert LB, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat*. 2019;177:723-733.

244. Oeffinger KC, Fontham ET, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. *JAMA*. 2015;314:1599-1614.

245. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57:75-89.

246. Souza FH, Wendland EM, Rosa MI, Polanczyk CA. Is full-field digital mammography more accurate than screen-film mammography in overall population screening? A systematic review and meta-analysis. *Breast*. 2013.

247. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer*. 2013;108:2205-2240.

248. Coldman A, Phillips N, Wilson C, et al. Pan-Canadian study of mammography screening and mortality from breast cancer. *J Natl Cancer Inst*. 2014;106.

249. Paci E, Broeders M, Hofvind S, Puliti D, Duffy SW. European breast cancer service screening outcomes: a first balance sheet of the benefits and harms. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1159-1163.

250. Tabar L, Dean PB, Chen TH, et al. The incidence of fatal breast cancer measures the increased effectiveness of therapy in women participating in mammography screening. *Cancer*. 2019;125:515-523.

251. Duffy SW, Tabár L, Yen AMF, et al. Mammography screening reduces rates of advanced and fatal breast cancers: results in 549,091 women. *Cancer*. 2020;126:2971-2979.

252. Ryser MD, Lange J, Inoue LYT, et al. Estimation of Breast Cancer Overdiagnosis in a U.S. Breast Screening Cohort. *Ann Intern Med*. 2022;175:471-478.

253. Lehman CD, Arao RF, Sprague BL, et al. National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium. *Radiology*. 2017;283:49-58.

254. Miglioretti DL, Lange J, van den Broek JJ, et al. Radiation-Induced Breast Cancer Incidence and Mortality From Digital Mammography Screening: A Modeling Study. *Ann Intern Med*. 2016;164:205-214.

255. Yaffe MJ, Mainprize JG. Risk of radiation-induced breast cancer from mammographic screening. *Radiology*. 2011;258:98-105.

256. Freeman K, Geppert J, Stinton C, et al. Use of artificial intelligence for image analysis in breast cancer screening programmes: systematic review of test accuracy. *BMJ*. 2021;374:n1872.

257. Bahl M, Mercaldo S, McCarthy AM, Lehman CD. Imaging Surveillance of Breast Cancer Survivors with Digital Mammography versus Digital Breast Tomosynthesis. *Radiology*. 2021;298:308-316.

258. Kerlikowske K, Su Y-R, Sprague BL, et al. Association of Screening With Digital Breast Tomosynthesis vs Digital Mammography With Risk of Interval Invasive and Advanced Breast Cancer. *JAMA*. 2022;327:2220-2230.

259. 2022 Scorecard Statistics. Available at: https://www.fda.gov/radiation-emitting-products/mqsa-insights/2022-scorecard-statistics#jun. Accessed July 7, 2022.

260. Allgood KL, Rauscher GH, Whitman S, Vasquez-Jones G, Shah AM. Validating self-reported mammography use in vulnerable communities: findings and recommendations. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1649-1658.

261. Cronin KA, Miglioretti DL, Krapcho M, et al. Bias associated with self-report of prior screening mammography. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1699-1705.

262. Rauscher GH, Johnson TP, Cho YI, Walk JA. Accuracy of self-reported cancer-screening histories: A meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2008;17:748-757.

263. Fedewa SA, Star J, Bandi P, et al. Changes in Cancer Screening in the US During the COVID-19 Pandemic. *JAMA Netw Open*. 2022;5:e2215490.

264. Comstock CE, Gatsonis C, Newstead GM, et al. Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection Among Women With Dense Breasts Undergoing Screening. *JAMA*. 2020;323:746-756.

265. Miles R, Wan F, Onega TL, et al. Underutilization of Supplemental Magnetic Resonance Imaging Screening Among Patients at High Breast Cancer Risk. *J Womens Health* (Larchmt). 2018;27:748-754.

266. Haas JS, Hill DA, Wellman RD, et al. Disparities in the use of screening magnetic resonance imaging of the breast in community practice by race, ethnicity, and socioeconomic status. *Cancer*. 2016;122:611-617.

267. Yang L, Wang S, Zhang L, et al. Performance of ultrasonography screening for breast cancer: a systematic review and meta-analysis. *BMC Cancer*. 2020;20:499.

268. Shen Y, Shamout FE, Oliver JR, et al. Artificial intelligence system reduces false-positive findings in the interpretation of breast ultrasound exams. *Nat Commun*. 2021;12:5645.

269. Kanbayashi C, Thompson AM, Hwang ES, et al. The international collaboration of active surveillance trials for low-risk DCIS (LORIS, LORD, COMET, LORETTA). *J Clin Oncol*. 2019;37:TPS603.

270. Fan B, Pardo JA, Alapati A, Hopewood P, Mohammad Virk Z, James TA. Analysis of active surveillance as a treatment modality in ductal carcinoma in situ. *Breast J*. 2020;26:1221-1226.

271. Wong SM, Freedman RA, Sagara Y, Aydogan F, Barry WT, Golshan M. Growing Use of Contralateral Prophylactic Mastectomy Despite no Improvement in Long-term Survival for Invasive Breast Cancer. *Ann Surg*. 2017;265:581-589.

272. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg*. 2015;150:9-16.

273. Albornoz CR, Matros E, Lee CN, et al. Bilateral Mastectomy versus Breast-Conserving Surgery for Early-Stage Breast Cancer: The Role of Breast Reconstruction. *Plast Reconstr Surg*. 2015;135:1518-1526.

274. Montagna G, Morrow M. Contralateral prophylactic mastectomy in breast cancer: what to discuss with patients. *Expert Rev Anticancer Ther*. 2020;20:159-166.

275. Lautner M, Lin H, Shen Y, et al. Disparities in the Use of Breast-Conserving Therapy Among Patients With Early-Stage Breast Cancer. *JAMA Surg*. 2015;150:778-786.

276. Freedman RA, Virgo KS, Labadie J, He Y, Partridge AH, Keating NL. Receipt of locoregional therapy among young women with breast cancer. *Breast Cancer Res Treat*. 2012;135:893-906.

277. Wang T, Baskin AS, Dossett LA. Deimplementation of the Choosing Wisely Recommendations for Low-Value Breast Cancer Surgery: A Systematic Review. *JAMA Surg*. 2020;155:759-770.

278. Nash R, Goodman M, Lin CC, et al. State Variation in the Receipt of a Contralateral Prophylactic Mastectomy Among Women Who Received a Diagnosis of Invasive Unilateral Early-Stage Breast Cancer in the United States, 2004-2012. *JAMA Surg*. 2017;152:648-657.

279. Baskin AS, Wang T, Bredbeck BC, Sinco BR, Berlin NL, Dossett LA. Trends in Contralateral Prophylactic Mastectomy Utilization for Small Unilateral Breast Cancer. *J Surg Res*. 2021;262:71-84.

280. Basu NN, Hodson J, Chatterjee S, et al. The Angelina Jolie effect: Contralateral risk-reducing mastectomy trends in patients at increased risk of breast cancer. *Sci Rep*. 2021;11:2847.

281. Guth U, Myrick ME, Viehl CT, Weber WP, Lardi AM, Schmid SM. Increasing rates of contralateral prophylactic mastectomy – a trend made in USA? *Eur J Surg Oncol*. 2012;38:296-301.

282. Gail MH, Jatoi I. Tools for Contralateral Prophylactic Mastectomy Decision Making. *J Clin Oncol*. 2022:Jco2102782.

283. McLaughlin SA, Brunelle CL, Taghian A. Breast Cancer-Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment. *J Clin Oncol*. 2020;38:2341-2350.

284. Montagna G, Zhang J, Sevilimedu V, et al. Risk Factors and Racial and Ethnic Disparities in Patients With Breast Cancer-Related Lymphedema. *JAMA Oncol*. 2022.

285. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14:500-515.

286. Rafn BS, Christensen J, Larsen A, Bloomquist K. Prospective Surveillance for Breast Cancer-Related Arm Lymphedema: A Systematic Review and Meta-Analysis. *J Clin Oncol*. 2022;40:1009-1026.

287. Paramanandam VS, Dylke E, Clark GM, et al. Prophylactic Use of Compression Sleeves Reduces the Incidence of Arm Swelling in Women at High Risk of Breast Cancer-Related Lymphedema: A Randomized Controlled Trial. *J Clin Oncol*. 2022;40:2004-2012.

288. Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378:1707-1716.

289. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16:310-320.

290. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, investigators PI. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015;16:266-273.

291. Mutter RW, Choi JI, Jimenez RB, et al. Proton Therapy for Breast Cancer: A Consensus Statement From the Particle Therapy Cooperative Group Breast Cancer Subcommittee. *Int J Radiat Oncol Biol Phys*. 2021;111:337-359.

292. Alterio D, La Rocca E, Volpe S, et al. Hypofractionated proton therapy in breast cancer: where are we? A critical review of the literature. *Breast Cancer Res Treat*. 2022;192:249-263.

293. Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*. 2020;395:1613-1626.

294. Hickey BE, James ML, Lehman M, et al. Fraction size in radiation therapy for breast conservation in early breast cancer. *Cochrane Database Syst Rev*. 2016;7:CD003860.

295. Early Breast Cancer Trialists' Collaborative G. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19:27-39.

296. Letourneau JM, Wald K, Sinha N, et al. Fertility preservation before breast cancer treatment appears unlikely to affect disease-free survival at a median follow-up of 43 months after fertility-preservation consultation. *Cancer*. 2020;126:487-495.

297. Rodriguez-Wallberg KA, Eloranta S, Krawiec K, Lissmats A, Bergh J, Liljegren A. Safety of fertility preservation in breast cancer patients in a register-based matched cohort study. *Breast Cancer Res Treat*. 2018;167:761-769.

298. Greer AC, Lanes A, Poorvu PD, et al. The impact of fertility preservation on the timing of breast cancer treatment, recurrence, and survival. *Cancer*. 2021;127:3872-3880.

299. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384:164-172.

300. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med*. 2018;379:111-121.

301. Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. Neoadjuvant Chemotherapy Use in Breast Cancer is Greatest in Excellent Responders: Triple-Negative and HER2+ Subtypes. *Ann Surg Oncol*. 2018;25:2241-2248.

302. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *J Clin Oncol*. 2021;39:1485-1505.

303. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med*. 2019;380:617-628.

304. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med*. 2017;376:2147-2159.

305. American College of Surgeons, Commission on Cancer. National Cancer Database. 2019 Data Submission. American College of Surgeons.; 2021.

306. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2019;37:423-438.

307. Reeder-Hayes KE, Troester MA, Wheeler SB. Adherence to Endocrine Therapy and Racial Outcome Disparities in Breast Cancer. *Oncologist*. 2021;26:910-915.

308. Wheeler SB, Spencer J, Pinheiro LC, et al. Endocrine Therapy Nonadherence and Discontinuation in Black and White Women. *J Natl Cancer Inst*. 2019;111:498-508.

309. Farias AJ, Du XL. Association Between Out-Of-Pocket Costs, Race/Ethnicity, and Adjuvant Endocrine Therapy Adherence Among Medicare Patients With Breast Cancer. *J Clin Oncol*. 2017;35:86-95.

310. Miles D, Ciruelos E, Schneeweiss A, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. *Ann Oncol*. 2021;32:1245-1255.

311. Cortes J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med*. 2022;386:1143-1154.

312. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med*. 2022.

313. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. *N Engl J Med*. 2021;384:2394-2405.

314. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation. *N Engl J Med*. 2018;379:753-763.

315. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med*. 2021;384:1529-1541.

316. Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. *Ann Oncol*. 2021;32:983-993.

317. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med*. 2020;382:810-821.

318. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020;396:1090-1100.

319. Hall PE, Schmid P. Emerging drugs for the treatment of triple-negative breast cancer: a focus on phase II immunotherapy trials. *Expert Opin Emerg Drugs*. 2021;26:131-147.

320. Hall PE, Schmid P. Emerging strategies for TNBC with early clinical data: new chemoimmunotherapy strategies. *Breast Cancer Res Treat*. 2022;193:21-35.

321. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol*. 2016;34:611-635.

322. Arias E, Xu J, Curtin S, Bastian B, Tejada-Vera B. Mortality Profile of the Non-Hispanic American Indian or Alaska Native Population, 2019. *Natl Vital Stat Rep*. 2021;70(12):1-27.

Acknowledgments

We gratefully acknowledge all cancer registries and their staff for their hard work and diligence in collecting cancer information, without which this report would not exist. We also would like to acknowledge the following individuals for their valuable contributions: Rick Alteri; Priti Bandi; Rachel Cannady; Joseph Cotter; Ellie Daniels; Lynn Elmore; Ted Gansler; Mamta Kalidas; Joan Kramer; Katie McMahon; Kimberly Miller; Adair Minihan; Lisa A Newman; Ampy Rougeau; Scott Simpson; Robert Smith; Hyuna Sung; Lauren Teras; Lynn Urquhart; Dana Wagner; and Kathy Zamora.

Breast Cancer Facts & Figures is a publication of the American Cancer Society, Atlanta, Georgia.

For more information, contact:
Rebecca Siegel; Angela Giaquinto; or Ahmedin Jemal
Surveillance and Health Equity Science Department

American Cancer Society®

cancer.org | 1-800-227-2345

BBB ACCREDITED CHARITY
bbb.org/charity

PUTTING PATIENTS FIRST
National Health Council
Standards of Excellence
Certification Program ®