



# Breast Cancer Facts & Figures 2013-2014

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# Breast Cancer Basic Facts

## What is breast cancer?

Cancer is a group of diseases that cause cells in the body to change and grow out of control. Most types of cancer cells eventually form a lump or mass called a tumor, and are named after the part of the body where the tumor originates.

Breast cancer begins in the breast tissue that is made up of glands for milk production, called lobules, and the ducts that connect the lobules to the nipple. The remainder of the breast is made up of fatty, connective, and lymphatic tissues.

Breast cancer typically is detected either during a screening examination, before symptoms have developed, or after symptoms have developed, when a woman feels a lump. Most masses seen on a mammogram and most breast lumps turn out to be benign; that is, they are not cancerous, do not grow uncontrollably or spread, and are not life-threatening. When cancer is suspected based on clinical breast exam or breast imaging, microscopic analysis of breast tissue is necessary for a definitive diagnosis and to determine the extent of spread (in situ or invasive) and characterize the pattern of the disease. The tissue for microscopic analysis can be obtained via a needle or surgical biopsy. Selection of the type of biopsy is based on individual patient clinical factors, availability of particular biopsy devices, and resources.

## In situ

- Ductal carcinoma in situ (DCIS) is a spectrum of abnormal breast changes that start in the cells lining the breast ducts. DCIS is considered a noninvasive form of breast cancer because the abnormal cells have not grown beyond the layer of cells where they originated. It is the most common type of in situ breast cancer, accounting for about 83% of in situ cases diagnosed during 2006-2010. DCIS may or may not progress to

invasive cancer; in fact, some of these tumors grow so slowly that even without treatment they would not affect a woman's health. Studies suggest that about one-third, and possibly more, of DCIS cases will progress to invasive cancer if left untreated.<sup>1</sup> Identifying subtypes of DCIS that are most likely to recur or progress to invasive cancer is an active area of research.<sup>2</sup>

- Lobular carcinoma in situ (LCIS, also known as lobular neoplasia) is not a true cancer or precancer, but an indicator of increased risk for developing invasive cancer. LCIS is much less common than DCIS, accounting for about 12% of female in situ breast cancers diagnosed during 2006-2010. See page 12 for more information on LCIS.
- Other in situ breast cancers have characteristics of both ductal and lobular carcinomas or have unknown origins.

## Invasive

Most breast cancers are invasive, or infiltrating. These cancers have broken through the ductal or glandular walls where they originated and grown into surrounding breast tissue.

The prognosis (forecast or outcome) of invasive breast cancer is strongly influenced by the stage of the disease – that is, the extent or spread of the cancer when it is first diagnosed. There are two main staging systems for cancer. The TNM classification of tumors uses information on tumor size and how far it has spread within the breast (T), the extent of spread to the nearby lymph nodes (N), and the presence or absence of distant metastases (spread to distant organs) (M).<sup>3</sup> Once the T, N, and M are determined, a stage of 0, I, II, III, or IV is assigned, with stage 0 being in situ, stage I being early stage invasive cancer, and stage IV being the most advanced disease. The TNM staging system is commonly used in clinical settings.

The Surveillance, Epidemiology, and End Results (SEER) Summary Stage system is more simplified and is commonly used in reporting cancer registry data and for public health research and planning.<sup>4</sup>

According to this system:

- Local stage refers to cancers that are confined to the breast (corresponding to stage I and some stage II cancers in the TNM staging system).
- Regional stage refers to tumors that have spread to surrounding tissue or nearby lymph nodes (generally corresponding to stage II or III cancers, depending on size and lymph node involvement).
- Distant stage refers to cancers that have metastasized (spread) to distant organs or lymph nodes above the collarbone (corresponding to stages IIIc and IV).

**Table 1. Estimated New Female Breast Cancer Cases and Deaths by Age, US, 2013\***

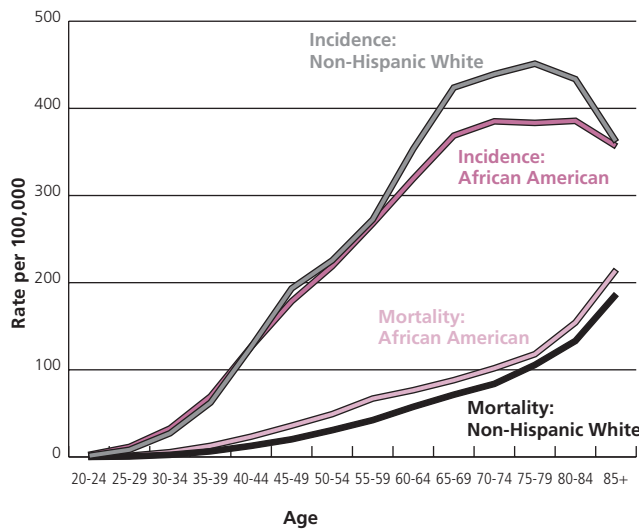
| Age (Yrs)       | In Situ Cases | Invasive Cases | Deaths        |
|-----------------|---------------|----------------|---------------|
| <40             | 1,900         | 10,980         | 1,020         |
| <50             | 15,650        | 48,910         | 4,780         |
| 50-64           | 26,770        | 84,210         | 11,970        |
| 65+             | 22,220        | 99,220         | 22,870        |
| <b>All ages</b> | <b>64,640</b> | <b>232,340</b> | <b>39,620</b> |

\*Rounded to the nearest 10.

**Source:** Total estimated cases are based on 1995-2009 incidence rates from 49 states as reported by the North American Association for Central Cancer Registries. Total estimated deaths are based on data from US Mortality Data, 1995-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

American Cancer Society, Surveillance and Health Services Research, 2013

**Figure 1. Age-specific Female Breast Cancer Incidence and Mortality Rates, US, 2006-2010**



**Sources:** Incidence: North American Association of Central Cancer Registries. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the Surveillance, Epidemiology, and End Results Program, National Cancer Institute. American Cancer Society, Surveillance and Health Services Research, 2013

Breast cancer is increasingly considered to be not one disease, but a group of diseases distinguished by different molecular subtypes, risk factors, clinical behaviors, and responses to treatment. Distinct molecular subtypes of breast cancer have been identified using gene expression profiles, a process that is both complex and costly.<sup>5</sup> More convenient approximations of molecular subtypes have been identified using biological markers, including the presence or absence of estrogen receptors (ER+/ER-), progesterone receptors (PR+/PR-), and human epidermal growth factor receptor 2 (HER2+/HER2-).<sup>6</sup> Molecular subtypes are increasingly being used for research purposes; however, questions remain about their usefulness to further tailor breast cancer treatments and predict breast cancer prognosis.<sup>6,7</sup>

- **Luminal A.** About 40% of breast cancers are luminal A, making it the most common breast cancer subtype.<sup>8</sup> These tumors tend to be ER+ and/or PR+ and HER2-, slow-growing, and less aggressive than other subtypes. Luminal A tumors are associated with the most favorable short-term prognosis, in part because expression of hormone receptors is predictive of a favorable response to hormonal therapy (see page 25); however, long-term survival is similar to or even lower than some other subtypes.<sup>9</sup>

- **Luminal B.** About 10% to 20% of breast cancers are luminal B.<sup>8,10</sup> Like luminal A tumors, most luminal B tumors are ER+ and/or PR+, but they are distinguished by either expression of HER2 or high proliferation rates (high numbers of cancer cells actively dividing).<sup>11</sup>
- **Basal-like.** About 10% to 20% of breast cancers are basal-like, and the majority of basal-like breast cancers are referred to as “triple negative” because they are ER-, PR-, and HER2-.<sup>10,12</sup> Basal-like tumors are more common in African American women, premenopausal women, and those with a *BRCA1* gene mutation.<sup>8</sup> Women diagnosed with basal-like breast cancer have a poorer short-term prognosis than those diagnosed with other breast cancer types because there are no targeted therapies for these tumors.
- **HER2 enriched.** About 10% of breast cancers produce excess HER2 (a growth-promoting protein) and do not express hormone receptors (ER- and PR-).<sup>8</sup> Similar to the basal-like subtype, these cancers tend to grow and spread more aggressively than other breast cancers and are associated with poorer short-term prognosis compared to ER+ breast cancers.<sup>9</sup> However, the use of targeted therapies for HER2+ cancers has reversed much of the adverse prognostic impact of HER2 overexpression. For more information about the treatment of HER2+ breast cancers, see the section on targeted therapy on page 25.

## What are the signs and symptoms of breast cancer?

Breast cancer typically produces no symptoms when the tumor is small and most easily cured. Therefore, it is very important for women to follow recommended screening guidelines for detecting breast cancer at an early stage. When breast cancer has grown to a size that can be felt, 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; persistent changes to the breast, such as swelling, thickening, or redness of the breast’s skin; and nipple abnormalities such as spontaneous discharge (especially if bloody), erosion, inversion, or tenderness. It is important to note that pain (or lack thereof) does not indicate the presence or the absence of breast cancer. Any persistent abnormality in the breast should be evaluated by a physician as soon as possible.

**Table 2. Female Breast Cancer Incidence and Mortality Rates\* by Race, Ethnicity, and State, 2006-2010**

| State                          | Non-Hispanic White |           | African American |           | Hispanic  |           |
|--------------------------------|--------------------|-----------|------------------|-----------|-----------|-----------|
|                                | Incidence          | Mortality | Incidence        | Mortality | Incidence | Mortality |
| Alabama                        | 117.9              | 21.0      | 121.2            | 31.5      | 56.8      | †         |
| Alaska                         | 130.7              | 25.2      | 147.5            | †         | 90.3      | †         |
| Arizona                        | 117.1              | 21.5      | 95.7             | 27.7      | 84.4      | 16.4      |
| Arkansas                       | 109.6              | 22.3      | 100.8            | 32.9      | 50.7      | †         |
| California                     | 140.6              | 24.7      | 120.7            | 31.8      | 89.9      | 15.2      |
| Colorado                       | 127.9              | 20.2      | 121.5            | 23.3      | 98.3      | 14.2      |
| Connecticut                    | 140.2              | 21.8      | 110.9            | 27.0      | 119.6     | 11.9      |
| Delaware                       | 126.9              | 23.3      | 126.7            | 23.4      | 112.8     | †         |
| Dist. of Columbia <sup>‡</sup> | 160.5              | 22.6      | 133.6            | 34.7      | 71.8      | –         |
| Florida                        | 119.7              | 21.5      | 105.4            | 29.1      | 96.5      | 15.0      |
| Georgia                        | 124.0              | 21.9      | 120.9            | 29.6      | 85.8      | 6.0       |
| Hawaii                         | 130.4              | 19.9      | 128.5            | †         | 112.9     | 18.4      |
| Idaho                          | 121.6              | 22.3      | †                | †         | 80.2      | †         |
| Illinois                       | 131.6              | 23.2      | 123.4            | 33.4      | 87.2      | 10.8      |
| Indiana                        | 118.1              | 23.6      | 117.6            | 31.6      | 70.9      | 8.8       |
| Iowa                           | 124.6              | 21.6      | 114.0            | 28.3      | 68.8      | †         |
| Kansas                         | 123.1              | 22.3      | 124.0            | 28.1      | 88.7      | 11.2      |
| Kentucky                       | 121.5              | 22.7      | 129.4            | 32.9      | 60.5      | †         |
| Louisiana                      | 119.9              | 22.7      | 124.6            | 33.8      | 80.0      | 9.6       |
| Maine                          | 127.3              | 20.8      | †                | †         | †         | †         |
| Maryland                       | 131.3              | 22.8      | 125.7            | 31.7      | 82.6      | 10.5      |
| Massachusetts <sup>§</sup>     | 137.9              | 21.8      | 97.7             | 23.2      | –         | 10.0      |
| Michigan                       | 118.7              | 22.8      | 119.4            | 34.3      | 80.1      | 15.8      |
| Minnesota <sup>¶</sup>         | –                  | 21.1      | –                | 21.9      | –         | †         |
| Mississippi                    | 112.3              | 20.8      | 117.3            | 33.4      | 35.1      | †         |
| Missouri                       | 121.5              | 23.7      | 130.9            | 32.4      | 70.5      | †         |
| Montana                        | 123.5              | 20.0      | †                | †         | 113.5     | †         |
| Nebraska                       | 123.7              | 20.0      | 122.8            | 27.5      | 97.9      | 19.3      |
| Nevada                         | 120.6              | 24.9      | 103.7            | 26.6      | 79.9      | 9.9       |
| New Hampshire                  | 133.1              | 21.5      | 107.3            | †         | 90.9      | †         |
| New Jersey                     | 139.4              | 26.2      | 117.1            | 30.9      | 91.8      | 13.2      |
| New Mexico                     | 122.9              | 22.4      | 83.4             | †         | 93.3      | 19.3      |
| New York                       | 138.4              | 22.9      | 109.0            | 25.8      | 99.8      | 15.6      |
| North Carolina                 | 127.2              | 21.9      | 123.0            | 29.9      | 79.4      | 6.7       |
| North Dakota <sup>‡</sup>      | 122.9              | 21.1      | †                | †         | †         | –         |
| Ohio                           | 119.2              | 24.2      | 116.2            | 31.6      | 64.0      | 9.3       |
| Oklahoma                       | 120.0              | 24.0      | 129.4            | 34.7      | 106.4     | 11.4      |
| Oregon                         | 130.2              | 22.3      | 106.7            | 22.0      | 100.4     | 12.6      |
| Pennsylvania                   | 126.5              | 23.4      | 127.8            | 32.1      | 90.9      | 12.6      |
| Rhode Island                   | 137.3              | 21.5      | 104.0            | 19.7      | 67.2      | †         |
| South Carolina <sup>‡</sup>    | 124.0              | 21.3      | 118.5            | 29.8      | 74.6      | –         |
| South Dakota                   | 119.0              | 20.7      | †                | †         | †         | †         |
| Tennessee                      | 118.9              | 21.8      | 122.7            | 35.4      | 57.1      | †         |
| Texas                          | 124.6              | 22.0      | 117.2            | 33.5      | 89.4      | 16.7      |
| Utah                           | 113.7              | 22.8      | 96.7             | †         | 83.4      | 13.6      |
| Vermont                        | 133.2              | 20.7      | †                | †         | †         | †         |
| Virginia                       | 126.8              | 22.8      | 127.3            | 33.2      | 87.3      | 12.2      |
| Washington                     | 134.8              | 22.7      | 116.4            | 24.5      | 83.4      | 9.4       |
| West Virginia                  | 110.7              | 22.2      | 105.7            | 25.8      | †         | †         |
| Wisconsin                      | 123.4              | 21.3      | 116.5            | 29.1      | 85.2      | 9.8       |
| Wyoming                        | 113.2              | 21.4      | †                | †         | 91.0      | †         |
| United States <sup>††</sup>    | 127.3              | 22.7      | 118.4            | 30.8      | 91.1      | 14.8      |

\*Rates are per 100,000 and age adjusted to 2000 US standard population. †Statistic not displayed due to fewer than 25 cases or deaths. ‡Mortality rates for white women in these states are not exclusive of Hispanic origin and are not shown for Hispanic women due to unreliable ethnicity data. §The incidence rate for white women in Massachusetts is not exclusive of Hispanic origin and is not available for Hispanic women. ¶This state's registry did not submit 2006-2010 incidence data to the North American Association of Central Cancer Registries. ††Overall US incidence rates do not include data from Arkansas, Minnesota, Nevada, Ohio, and Virginia.

**Sources:** Incidence: Copeland et al.<sup>15</sup> Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the Surveillance, Epidemiology, and End Results Program, National Cancer Institute.

American Cancer Society, Surveillance and Health Services Research, 2013

# Breast Cancer Occurrence

## How many cases and deaths are estimated to occur in 2013?

- In 2013, an estimated 232,340 new cases of invasive breast cancer will be diagnosed among women, as well as an estimated 64,640 additional cases of in situ breast cancer (Table 1, page 1).
- In 2013, approximately 39,620 women are expected to die from breast cancer (Table 1, page 1). Only lung cancer accounts for more cancer deaths in women.
- In 2013, about 2,240 men will be diagnosed with breast cancer and 410 men will die from the disease.

## How many women alive today have ever had breast cancer?

More than 2.9 million US women with a history of breast cancer were alive on January 1, 2012.<sup>13</sup> Some of these women were cancer-free, while others still had evidence of cancer and may have been undergoing treatment.

## Who gets breast cancer?

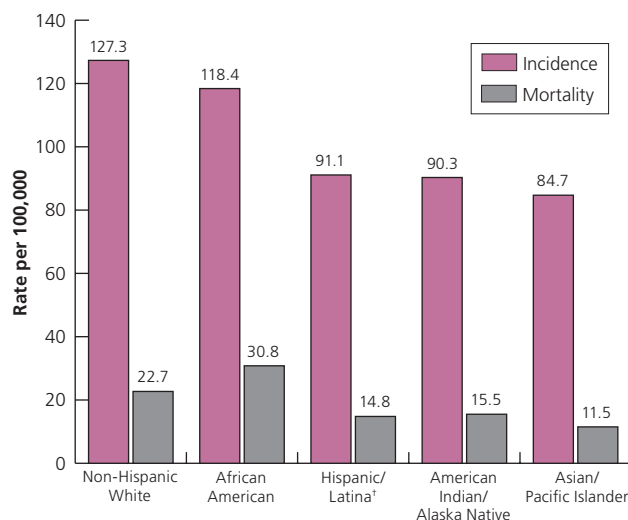
### Sex

- Excluding cancers of the skin, breast cancer is the most common cancer among US women, accounting for 29% of newly diagnosed cancers.
- Men are generally at low risk for developing breast cancer; however, they should report any change in their breasts to a physician.

### Age

- Breast cancer incidence and death rates generally increase with age (Figure 1, page 2). Seventy-nine percent of new cases and 88% of breast cancer deaths occurred in women 50 years of age and older.
- The decrease in incidence rates that occurs in women 80 years of age and older may reflect lower rates of screening, the detection of cancers by mammography before 80 years of age, and/or incomplete detection.
- During 2006-2010, the median age at the time of breast cancer diagnosis was 61.<sup>14</sup> This means that half of women who developed breast cancer were 61 years of age or younger at the time of diagnosis.
- A woman living in the US has a 12.3%, or a 1 in 8, lifetime risk of being diagnosed with breast cancer. In the 1970s, the lifetime risk of being diagnosed with breast cancer was

Figure 2. Female Breast Cancer Incidence and Mortality Rates\* by Race and Ethnicity, US, 2006-2010



\*Rates are age adjusted to the 2000 US standard population.

†Persons of Hispanic origin may be any race.

Sources: Incidence: Copeland et al.<sup>15</sup> Mortality: Howlander et al.<sup>14</sup>

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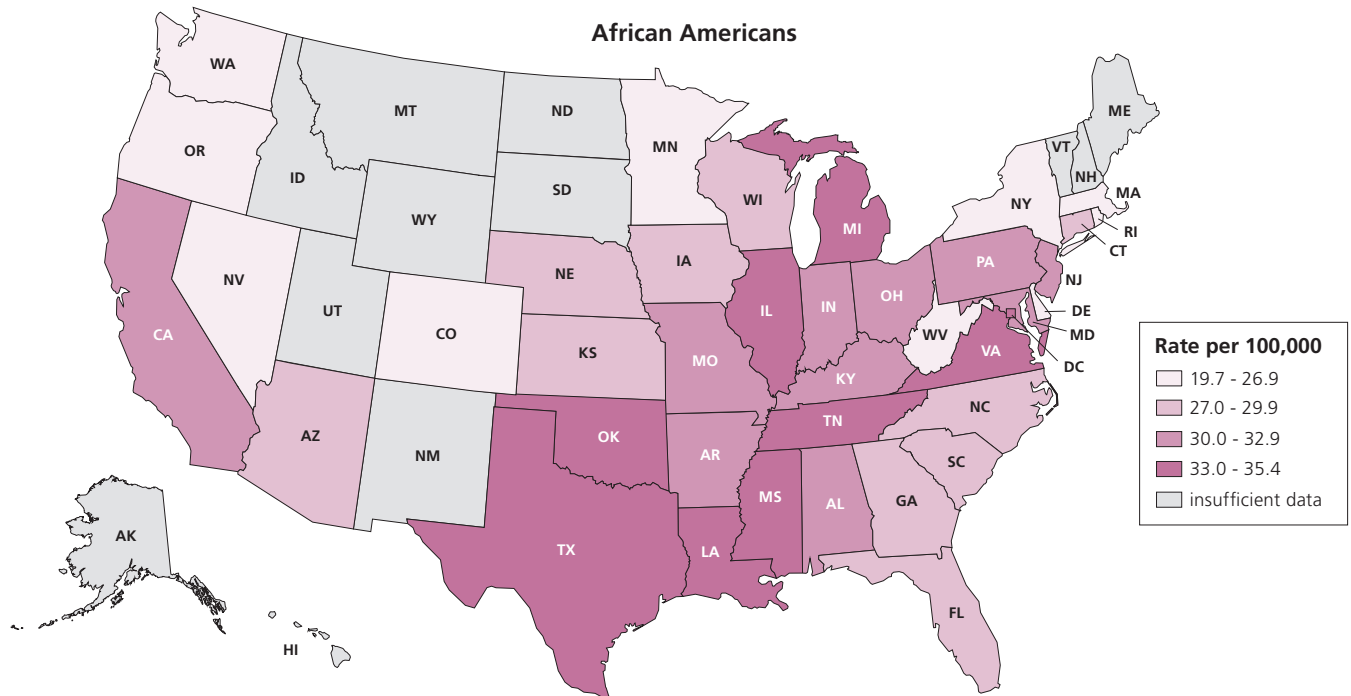
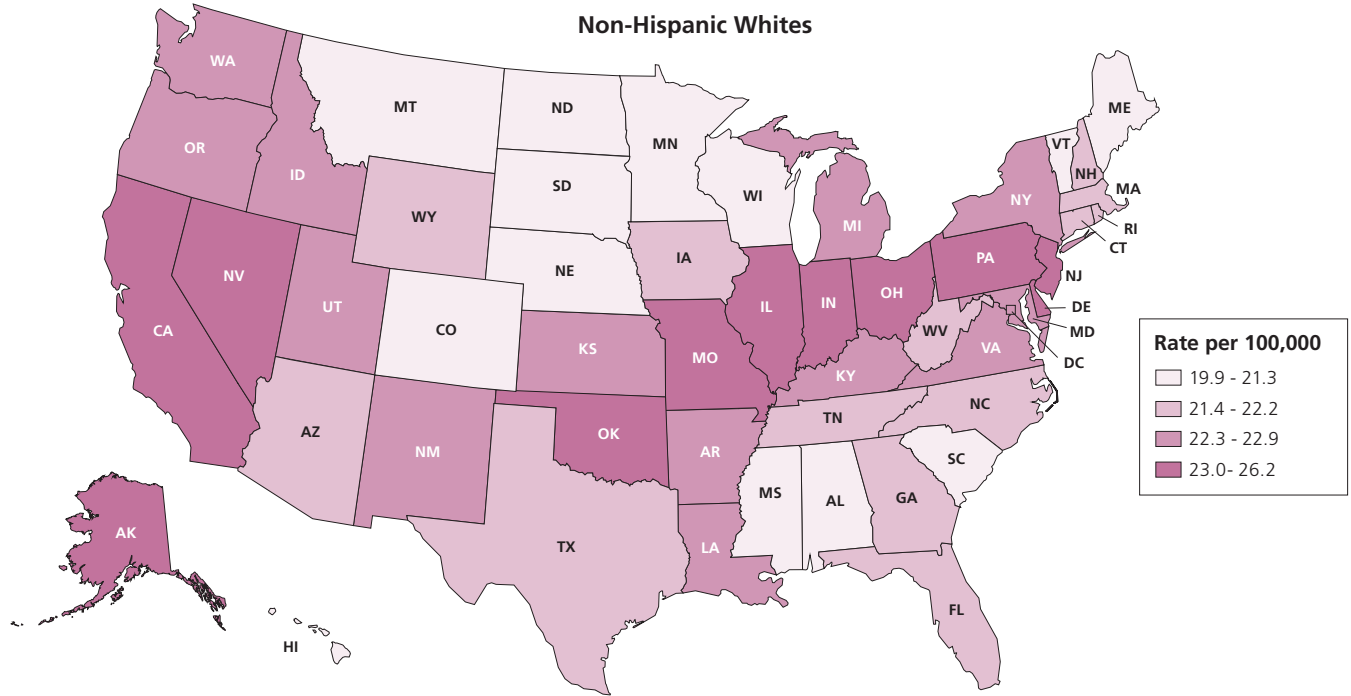
1 in 11. This increase in risk is due to longer life expectancy, as well as increases in breast cancer incidence due in part to changes in reproductive patterns, menopausal hormone use, the rising prevalence of obesity, and increased detection through screening. Lifetime risk reflects an average woman's risk over an entire lifetime, including the possibility that she may die from another cause before she would have been diagnosed with breast cancer, and should not be confused with risk over a shorter time period.

### Race/Ethnicity

- Breast cancer incidence rates are higher in non-Hispanic white women than African American women for most age groups (Figure 1, page 2). However, African American women have a higher incidence rate before age 40 and are more likely to die from breast cancer at every age. In addition, African American women have lower rates of ER+ breast cancer and higher rates of ER- breast cancer than white women in every age group.
- Figure 2 shows breast cancer incidence and death rates by race and ethnicity during the most recent time period (2006-2010).<sup>14,15</sup> Incidence and death rates for breast cancer are lower among women of other racial and ethnic groups than among non-Hispanic white and African American women. Asian/Pacific Islander women have the lowest incidence and death rates.



**Figure 3. Female Breast Cancer Death Rates\* by Race and Ethnicity, US, 2006-2010**



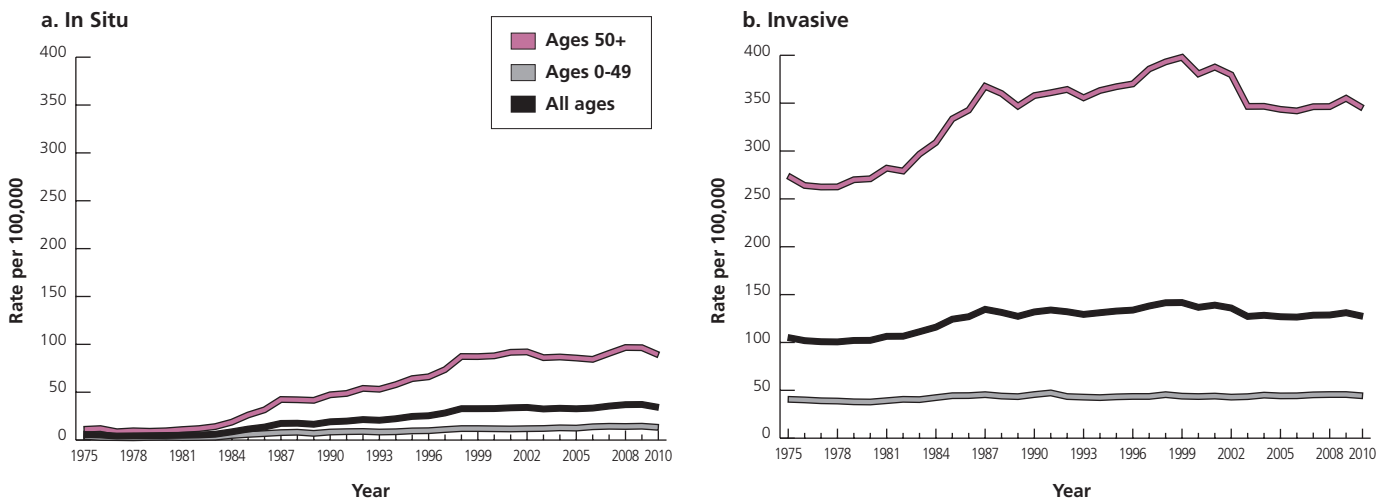
\*Per 100,000 and age adjusted to the 2000 US standard population.

Note: Statistic not displayed for states with fewer than 25 deaths. Death rates for whites in DC, ND, and SC are not exclusive of Hispanic origin due to unreliable ethnicity data.

Source: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the Surveillance, Epidemiology, and End Results Program, National Cancer Institute.

American Cancer Society, Surveillance and Health Services Research, 2013

**Figure 4. Incidence Rates\* of In Situ and Invasive Female Breast Cancer by Age, Adjusted for Delayed Reporting, US, 1975-2010**



\*Rates are age adjusted to the 2000 US standard population within each age group.  
**Source:** Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 Registries, National Cancer Institute.

American Cancer Society, Surveillance and Health Services Research, 2013

### Are there geographic differences in breast cancer rates?

Table 2 (page 3) shows breast cancer incidence and death rates per 100,000 women for non-Hispanic white, African American, and Hispanic women by state. Breast cancer incidence rates range from 109.6 (cases per 100,000 women) in Arkansas to 160.5 in the District of Columbia among non-Hispanic white women; 83.4 in New Mexico to 147.5 in Alaska among African American women; and 35.1 in Mississippi to 119.6 in Connecticut among Hispanic women. Incidence rates reflect disease occurrence, as well as how completely the population is screened.

Despite higher incidence rates, breast cancer death rates are generally lower among non-Hispanic white women compared to African American women. Death rates reflect both cancer incidence rates and survival. Breast cancer death rates range from 19.9 in Hawaii to 26.2 in New Jersey among non-Hispanic white women and from 19.7 in Rhode Island to 35.4 in Tennessee among African American women. Breast cancer death rates are lowest for Hispanic women and range from 6.0 in Georgia to 19.3 in Nebraska.

Breast cancer mortality rates among non-Hispanic white women tend to be highest in the West, Midwest, and Mid-Atlantic regions of the US. Among African American women, the highest death rates are found in some of the Southern and Mid-western states (Figure 3, page 5).

### How has the occurrence of breast cancer changed over time?

#### Incidence trends – women

Figure 4 presents trends for in situ and invasive breast cancer incidence rates since 1975, when population-based cancer registration began in the nine oldest cancer registries.

#### In situ breast cancer

Incidence rates of in situ breast cancer rose rapidly during the 1980s and 1990s (Figure 4a), largely because of increases in mammography screening. The increase in incidence was greater in women 50 years of age and older than in those younger than 50. Since 1999, incidence rates of in situ breast cancer have stabilized among women 50 and older, but continue to increase in younger women (1.9% per year from 1998 to 2010). The stabilization in incidence among women 50 years of age and older likely reflects trends in mammography screening rates, which peaked in 2000 and then stabilized at a slightly lower rate.<sup>16</sup> It may also reflect a reduced pool of prevalent cases as a result of widespread screening.

#### Invasive breast cancer

Much of the historic increase in breast cancer incidence reflects changes in reproductive patterns, such as delayed childbearing and having fewer children, which are recognized risk factors for breast cancer. However, between 1980 and 1987, breast cancer incidence rates increased rapidly, due largely to greater use of

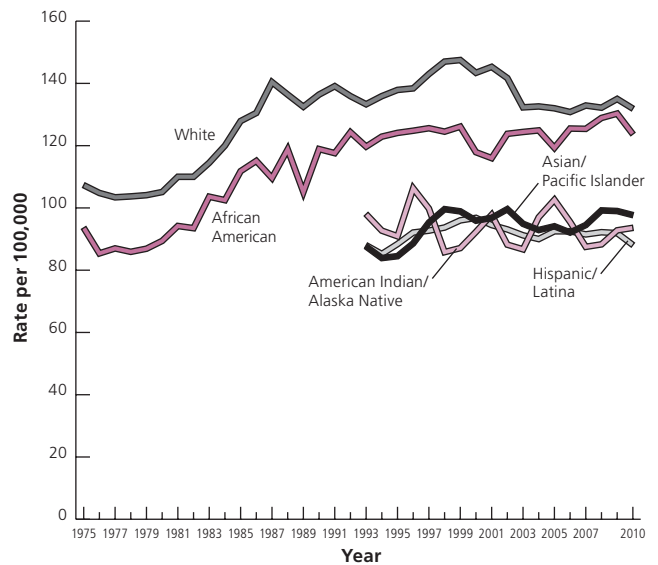


mammography screening, which can detect breast cancers too small to be felt. The widespread uptake of mammography screening inflated the incidence rate because cancers were being diagnosed 1 to 3 years earlier than they would have in the absence of screening. Rates stabilized in the early 1990s, followed by a slower increase during the latter half of the decade. This trend may reflect further increases in the prevalence of mammography screening, as well as rising rates of obesity and the use of menopausal hormones, both of which increase breast cancer risk. Between 2002 and 2003, breast cancer rates dropped sharply (nearly 7%), likely due to the decreased use of menopausal hormones following the 2002 publication of the Women's Health Initiative randomized trial results.<sup>17,18</sup> The decline occurred primarily in white women, in women ages 50 and older, and for ER+ disease.<sup>17,19</sup> This trend may also reflect declines in mammography screening. The percentage of women 40 years of age and older who reported having a mammogram within the past 2 years peaked in 2000, declined slightly, and has since stabilized.<sup>16</sup> Similar reversals in breast cancer trends have been observed internationally, as well.<sup>20-24</sup> Since 2004, overall breast cancer incidence rates have remained relatively stable.<sup>14</sup>

**Race/Ethnicity:** Figure 5a presents trends in invasive female breast cancer incidence rates by race and ethnicity. Incidence data are available for white and African American women since 1975 and for women of other races and ethnicities since 1992. During 2006-2010 (the most recent 5 years of data available), overall breast cancer incidence rates increased slightly (0.2% per year) among African American women, decreased by 0.6% per year in Hispanic women, and did not change significantly among whites, Asians/Pacific Islanders (API), or American Indians/Alaska Natives (AI/AN).<sup>14</sup> Notably, rates for white and African American women are converging. Please note that rates for white and African American women were adjusted for delays in case reporting; delay-adjusted rates are not available for other races/ethnicities, resulting in slightly underestimated rates, particularly for the most recent data years. Also, rates for American Indians/Alaska Natives are based on limited geographic areas with high-quality data.

**Age:** Trends for invasive breast cancer by age at diagnosis are shown in Figure 4b. Overall breast cancer incidence rates have been relatively stable for both women under the age of 50 and those ages 50 and older during the most recent time period (2006-2010). However, trends by age at diagnosis vary by race and ethnicity. Although the overall incidence trends for white and API women were stable, rates increased slightly during 2006-2010 for white and API women younger than 50 by 0.1% and 0.8% per year, respectively.<sup>14</sup> Among women 50 years of age and older, incidence rates decreased slightly in Hispanics (0.7% per year) and increased slightly (0.3% per year) in African Americans.<sup>14</sup> Incidence rates were stable for white, Asian/Pacific Islander, and American Indian/Alaska Native women 50 years of age and older during 2006-2010.<sup>14</sup>

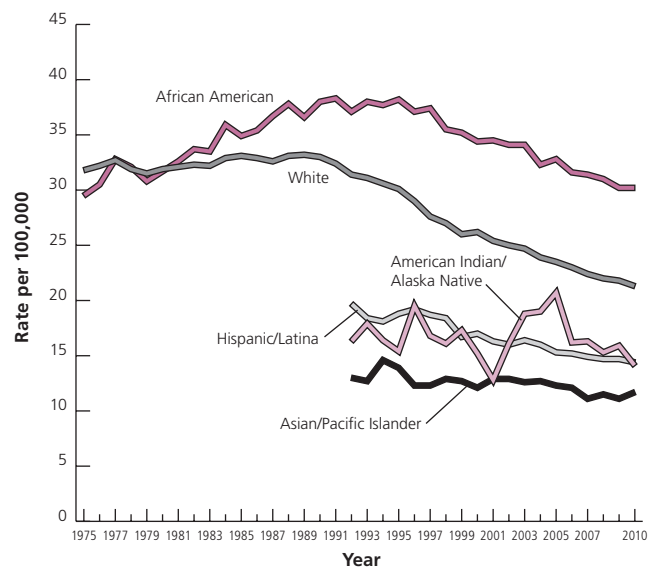
**Figure 5a. Trends in Female Breast Cancer Incidence Rates\* by Race and Ethnicity, US, 1975-2010**



\*Rates are age adjusted to the 2000 US standard population.

**Source:** Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. Data for whites and African Americans are from the 9 SEER registries and were adjusted for reporting delay. Data for other races/ethnicities are 2-year moving averages from the 13 SEER registries. For Hispanics, incidence data do not include cases from the Alaska Native Registry. Incidence data for American Indians/Alaska Natives are based on Contract Health Service Delivery Area (CHSDA) counties.

**Figure 5b. Trends in Female Breast Cancer Death Rates\* by Race and Ethnicity, US, 1975-2010**

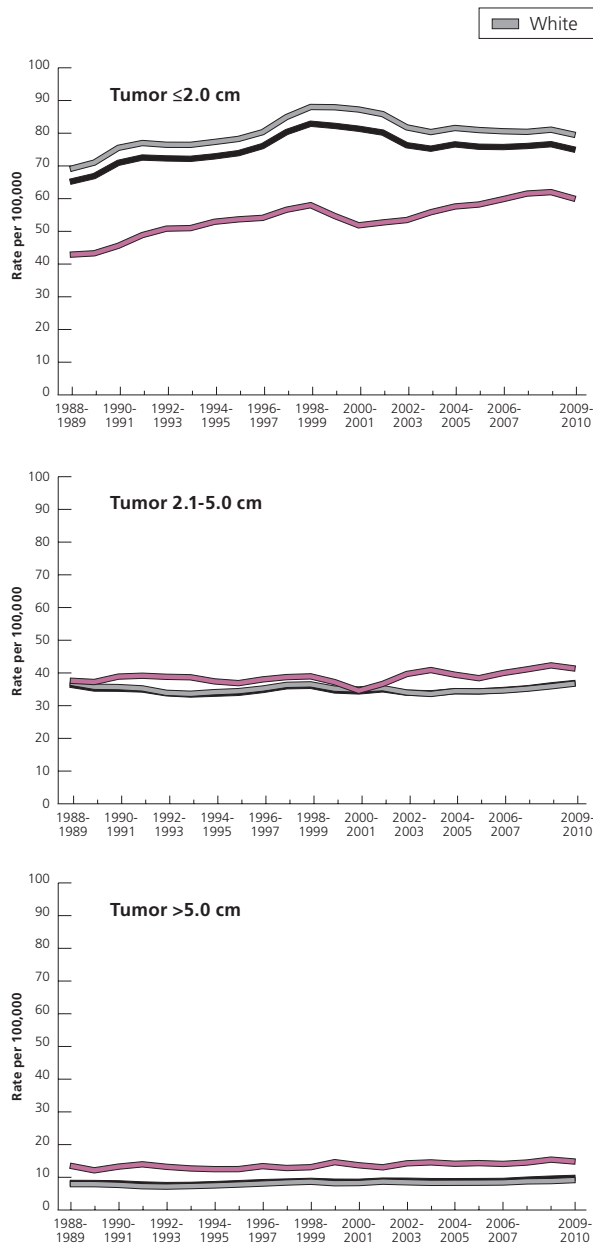


\*Rates are age adjusted to the 2000 US standard population.

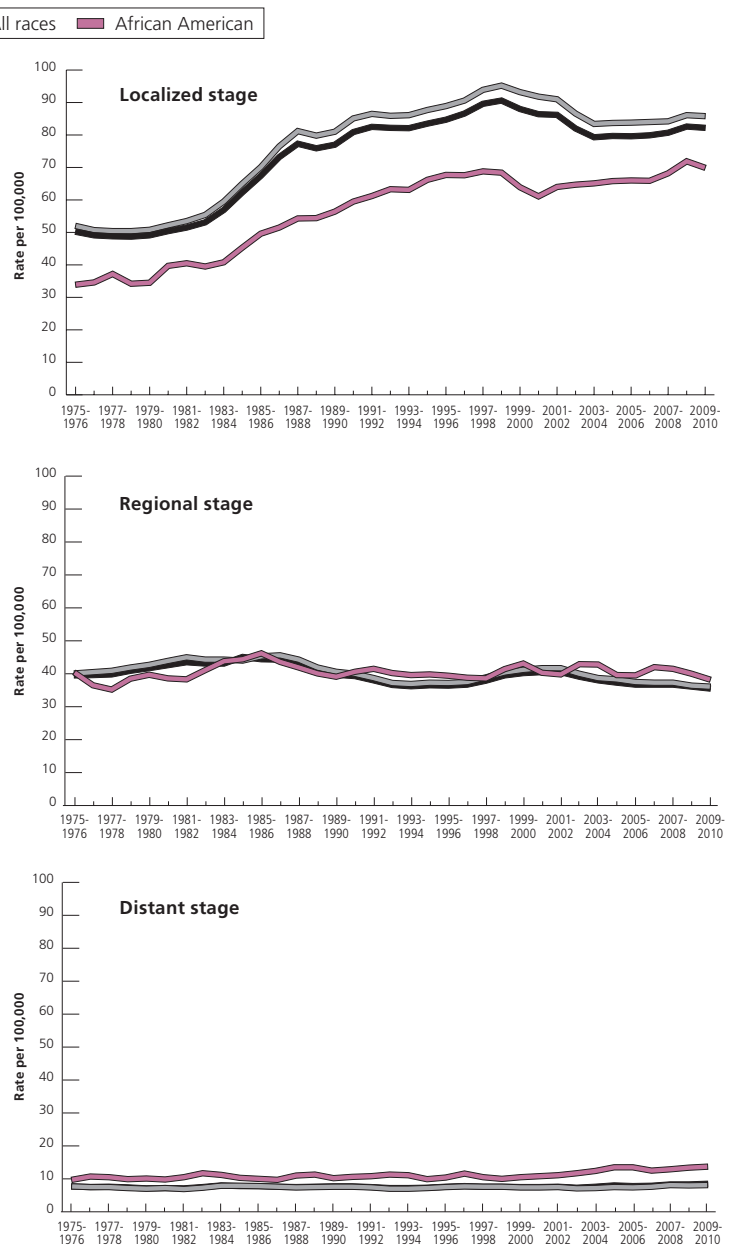
**Source:** National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the Surveillance, Epidemiology, and End Results Program, National Cancer Institute. Rates for American Indians/Alaska Natives are based on data from the Contract Health Service Delivery Area (CHSDA) counties. For Hispanics, mortality rates do not include data from Connecticut, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, Vermont, and the District of Columbia.

American Cancer Society, Surveillance and Health Services Research, 2013

**Figure 6a. Trends in Female Breast Cancer Incidence Rates\* by Tumor Size and Race, US, 1988-2010**



**Figure 6b. Trends in Female Breast Cancer Incidence Rates\* by Stage and Race, US, 1975-2010**



\*Rates are two-year moving averages and age adjusted to the 2000 US standard population.

Source: Surveillance, Epidemiology, and End Results (SEER) Program, 9 SEER Registries, National Cancer Institute.

American Cancer Society, Surveillance and Health Services Research, 2013

**Tumor size:** Incidence rates of breast cancer by tumor size differ between white and African American women. African American women are less likely to be diagnosed with smaller tumors ( $\leq 2.0$  cm) and more likely to be diagnosed with larger tumors ( $> 5.0$  cm) than white women.

Figure 6a describes trends in incidence rates by tumor size and race. For smaller tumors ( $\leq 2.0$  cm), incidence rates decreased by 1.1% per year during 2006-2010 among white women, but were stable among African American women. The incidence rate for tumors 2.1-5.0 cm increased during 2006-2010 for both white and African American women, by 1.1% and 0.5% per year, respec-

tively. For the largest tumors (>5.0 cm), incidence rates were relatively stable among white women during the most recent time period, but increased slightly by 0.7% per year on average for African American women.

**Stage:** Figure 6b presents incidence trends by race and stage at diagnosis. Among both African American and white women, incidence rates of localized breast cancer increased through most of the 1980s and 1990s, but have been relatively stable during the most recent time period (2006-2010). Among white women, incidence rates of regional-stage disease decreased on average 1.6% per year during 2006-2010, whereas the rate of distant-stage tumors increased over this period (1.8% per year). This shift toward later stage at diagnosis may reflect improvements in tumor staging. Rates of distant-stage breast cancer also increased among African American women by 1.4% per year from 2006-2010.

### Mortality trends – women

After slowly increasing for many years (0.4% per year from 1975-1990), breast cancer death rates decreased by 34% from 1990 to 2010. The decline has been faster among women younger than 50 (3.1% per year) than women 50 and older (1.9% per year).<sup>14</sup> From 2001 through 2010, breast cancer death rates declined annually by 1.8% in non-Hispanic whites, 1.7% in Hispanics/Latinas, 1.6% in African Americans, and 1.0% in Asians/Pacific Islanders, but remained unchanged among American Indians/Alaska Natives.<sup>14</sup>

The drop in breast cancer mortality has been attributed to both improvements in breast cancer treatment and early detection.<sup>25</sup> However, not all segments of the population have benefited equally from these advances. A striking divergence in long-term breast cancer mortality trends between African American and white women began in the early 1980s (Figure 5b, page 7). This mortality difference may reflect earlier uptake and greater mammography usage by whites during the 1980s, as well as differences in access and response to new treatments, including tamoxifen, which is used to treat hormone receptor-positive breast cancers, which are less common among African American women.<sup>26,27</sup> By 2010, breast cancer death rates were 41% higher in African American than white women.

Trends in breast cancer death rates also vary by state. During 2001-2010, breast cancer death rates among all women combined significantly decreased in 36 states, but remained relatively unchanged in the remaining 14 states (Alaska, Arkansas, Delaware, Hawaii, Idaho, Maine, Montana, Nebraska, Nevada, New Mexico, South Dakota, Utah, West Virginia, and Wyoming) and the District of Columbia. The lack of a decline in these states is likely related to variations in the prevalence and quality of mammography screening, as well as state differences in racial and socioeconomic composition.

**Figure 7. Trends in Male Breast Cancer Incidence and Mortality Rates\*, US, 1975-2010**



\*Rates are age adjusted to the 2000 US standard population.

**Sources:** Incidence: Surveillance, Epidemiology, and End Results (SEER) Program, 9 SEER Registries, National Cancer Institute. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the SEER program.

American Cancer Society, Surveillance and Health Services Research, 2013

### Incidence and mortality trends – men

Figure 7 presents incidence and mortality trends for male breast cancer. Breast cancer in men is rare, accounting for approximately 1% of breast cancer cases in the US. However, since 1975, the incidence rate increased 0.8% annually, from 1.0 case per 100,000 men during 1975-1979 to 1.2 cases per 100,000 men during 2005-2010. The increase has been limited to in situ and local-stage tumors, which may reflect a shift to earlier diagnoses due to increased awareness and follow up of breast symptoms.<sup>28</sup>

Mammography is not recommended for men because of the rarity of the disease. Similar to female breast cancer, the incidence of male breast cancer increases with age; however, unlike female breast cancer, incidence rates are higher in African American men than white men.<sup>29</sup> Death rates for male breast cancer have decreased 1.8% per year since 2000.

Due to the infrequency of male breast cancer, much less is known about the disease than female breast cancer. Risk factors include radiation exposure, *BRCA* gene mutations, Klinefelter syndrome, testicular disorders, family history of male or female breast cancer, and obesity.<sup>30</sup>

### Breast cancer survival and stage at diagnosis

Relative survival rates are an estimate of the percentage of patients who will survive for a given period of time after a cancer diagnosis. It differs from observed survival in that it accounts for deaths from other causes by comparing survival among cancer

patients to survival among people of the same age and race who have not been diagnosed with cancer.

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

- 89% at 5 years after diagnosis
- 83% after 10 years
- 78% after 15 years

Relative survival rates should be interpreted with caution. First, they do not predict individual prognosis because many patient and tumor characteristics that influence breast cancer survival are not taken into account. Second, long-term survival rates are based on the experience of women treated many years ago and do not reflect the most recent improvements in early detection or treatment.

### Stage at diagnosis

Five-year relative survival is lower among women with a more advanced stage at diagnosis (Figure 8a). Considering all races, 5-year relative survival is 99% for localized disease, 84% for regional disease, and 24% for distant-stage disease.<sup>14</sup> Larger tumor size at diagnosis is also associated with decreased survival. For example, among women with regional disease, the 5-year relative survival is 95% for tumors less than or equal to 2.0 cm, 83% for tumors 2.1-5.0 cm, and 65% for tumors greater than 5.0 cm.

### Age at diagnosis

The 5-year relative survival rate is lower among women diagnosed with breast cancer before age 40 (85%) compared to women diagnosed at 40 years of age or older (90%). This may be due to tumors diagnosed at younger ages being more aggressive and/or less responsive to treatment.<sup>31,32</sup>

### Race/ethnicity and socioeconomic factors

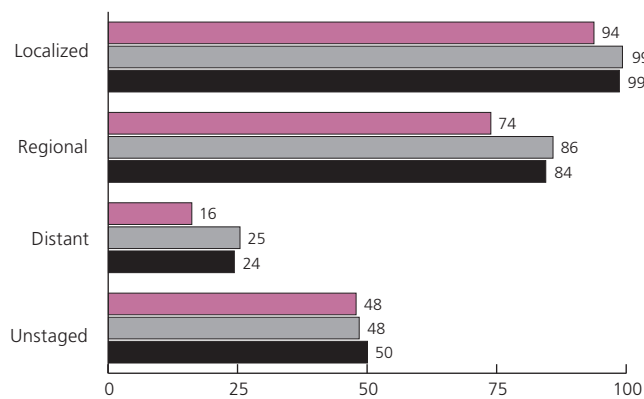
Since 1975, the breast cancer 5-year relative survival rate has increased significantly for both African American and white women; nevertheless, there remains a substantial racial gap (Figure 9). In the most recent period, the 5-year relative survival rate was 79% for African American women and 92% among white women.<sup>14</sup> This survival disparity is attributed to both later stage at detection and poorer stage-specific survival among African American women (Figure 8).

Table 3 presents 5-year cause-specific breast cancer survival rates by race and ethnicity. Cause-specific survival instead of relative survival is used to describe the cancer experience of racial and ethnic minorities because estimates of normal life expectancy are not available for most racial groups. Cause-specific survival is the probability of not dying of breast cancer within 5 years of diagnosis. African American women have the lowest survival rate of any racial or ethnic group.

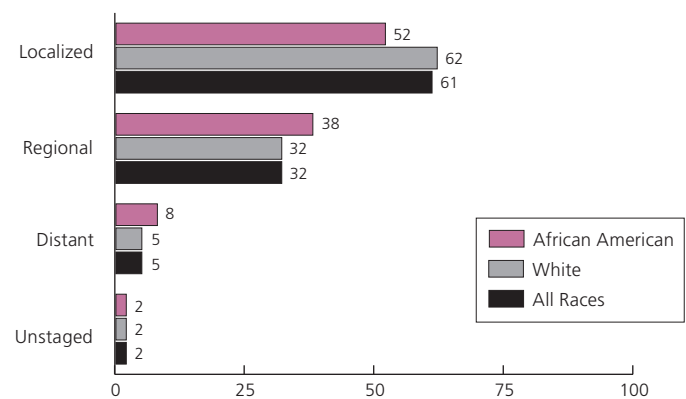
Poverty, less education, and a lack of health insurance are also associated with lower breast cancer survival.<sup>33,34</sup> Breast cancer patients who reside in lower-income areas have lower 5-year survival rates than those in higher-income areas at every stage of diagnosis.<sup>35</sup> The presence of additional illnesses, unequal access to medical care, and disparities in receipt of treatment likely contribute to differences in breast cancer survival.<sup>36-41</sup> Aggressive tumor characteristics associated with poorer prognosis appear to be more common in African American women and may also contribute to lower survival rates.<sup>12,42</sup>

**Figure 8. Female Breast Cancer Survival and Stage Distribution, 2003-2009\***

**a. Five-year Relative Survival Rates (%) by Stage at Diagnosis and Race**



**b. Stage Distribution (%) by Race**

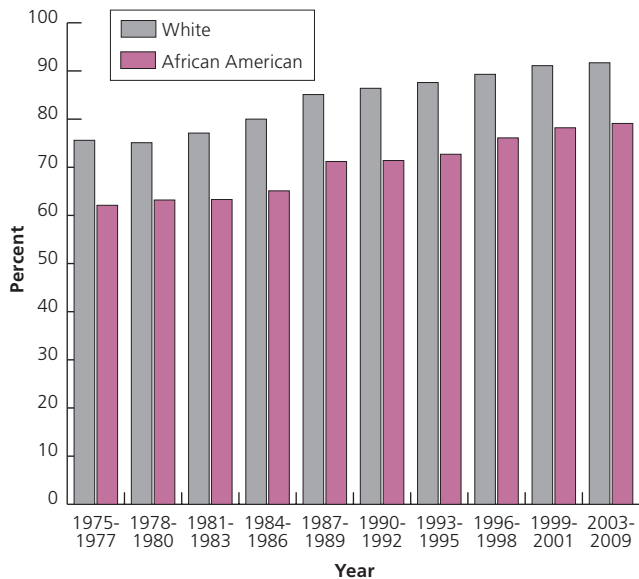


\*Survival rates are based on patients diagnosed between 2003 and 2009 and followed through 2010.

Source: Howlader et al.<sup>14</sup>

American Cancer Society, Surveillance and Health Services Research, 2013

**Figure 9. Trends in Female Breast Cancer 5-year Relative Survival by Race, 1975-2009\***



\*Survival rates are based on follow up of patients through 2010.

Source: Howlader et al.<sup>14</sup>

American Cancer Society, Surveillance and Health Services Research, 2013

**Table 3. Five-year Cause-specific Breast Cancer Survival by Race and Ethnicity, 2003-2009\***

|                                      | Percent |
|--------------------------------------|---------|
| <b>Non-Hispanic White</b>            | 88.6    |
| <b>African American</b>              | 78.9    |
| <b>American Indian/Alaska Native</b> | 85.4    |
| <b>Asian</b>                         | 91.4    |
| Asian Indian, Pakistani              | 89.7    |
| Chinese                              | 91.7    |
| Filipino                             | 90.0    |
| Japanese                             | 92.8    |
| Korean                               | 92.1    |
| Vietnamese                           | 91.4    |
| Other Asian                          | 92.8    |
| <b>Pacific Islander</b>              | 86.8    |
| Hawaiian                             | 89.7    |
| Other Pacific Islander               | 80.8    |
| <b>Hispanic</b>                      | 87.0    |

\*Survival rates are based on patients diagnosed between 2003 and 2009 and followed through 2010.

Source: Howlader et al.<sup>14</sup>

American Cancer Society, Surveillance and Health Services Research, 2013

## Breast Cancer Risk Factors

Many of the known breast cancer risk factors listed in Table 4 (page 12), such as sex, age, family history, early menarche, and late menopause, are not modifiable, that is they cannot be changed. However, other factors associated with increased breast cancer risk, including postmenopausal obesity, use of combined estrogen and progestin menopausal hormones, cigarette smoking, and alcohol consumption are modifiable. Many risk factors affect lifetime exposure of breast tissue to hormones (early menarche, late menopause, obesity, and hormone use). Reproductive hormones are thought to influence breast cancer risk by increasing cell proliferation, thereby increasing the likelihood of DNA damage, as well as promotion of cancer growth. Many of the known risk factors for breast cancer are specifically associated with the ER+/luminal A subtype; less is known about risk factors for ER- and triple negative (basal-like) breast cancers.

Strategies that may help reduce the risk of breast cancer include avoiding weight gain and obesity, engaging in regular physical activity, and minimizing alcohol intake (see American Cancer Society guidelines, page 15).<sup>43</sup> Women who choose to breastfeed for an extended period of time (studies suggest a year or more) may also reduce their breast cancer risk. Women should consider the increased risk of breast cancer associated with the use of estrogen and progestin when evaluating treatment options for menopausal symptoms. Treatment with tamoxifen or raloxifene

can also reduce the risk of breast cancer among women at high risk (see page 17 for section on chemoprevention). Breast cancer risk factors, along with factors that may decrease the risk of breast cancer, are discussed below.

### Personal and family history

#### Family history of breast cancer

Women (as well as men) with a family history of breast cancer, especially in a first-degree relative (mother, sister, daughter, father, or brother), are at increased risk of developing breast cancer; this risk is higher if more than one first-degree relative developed breast cancer. Compared to women without a family history, risk of breast cancer is 1.8 times higher for women with one first-degree female relative who has been diagnosed, nearly 3 times higher for women with two relatives, and nearly 4 times higher for women with three or more relatives.<sup>44</sup> Risk is further increased when the affected relative was diagnosed at a young age.

It is important to note that the majority of women with one or more affected first-degree relatives will never develop breast cancer and that most women who develop breast cancer do not have a family history of the disease. A family history of ovarian cancer is also associated with increased breast cancer risk in both men and women. Women with a history of breast or ovarian



cancer in their immediate family or in either parent's extended family should discuss this with their physicians because it may signal the presence of a genetic predisposition to cancer.

### Genetic predisposition

It is estimated that 5% to 10% of breast cancer cases result from inherited mutations, including those in the breast cancer susceptibility genes *BRCA1* and *BRCA2*.<sup>45</sup> These mutations are present in less than 1% of the general population, but occur more often in certain ethnic groups such as those of Ashkenazi (Eastern European) Jewish descent.<sup>45</sup> The estimates of the risk of breast cancer in women with these mutations vary; by age 70, between 44% and 78% of women with *BRCA1* mutations and between 31% and 56% of women with *BRCA2* mutations will develop breast cancer.<sup>46,47</sup>

Only about 15%-20% of familial breast cancers are attributed to *BRCA1* or *BRCA2* gene mutations.<sup>48</sup> Other inherited conditions associated with smaller increased breast cancer risk include Li-Fraumeni and Cowden syndromes and a number of more common genetic mutations.<sup>48</sup> These mutations can be inherited from either parent and by sons as well as daughters.

In addition, low-risk variations in the genetic code may affect breast cancer risk. Scientists believe that much of the occurrence of breast cancer in families results from the interaction between lifestyle factors and these low-risk variations that may be shared within a family.<sup>49</sup>

Molecular tests are commercially available to identify some of the *BRCA* mutations, as well as many of the family cancer syndromes responsible for inherited forms of breast cancer; however, the interpretation of these tests and treatment decisions remains complicated.<sup>50</sup> It is not yet possible to predict if or when women who carry a particular genetic abnormality will develop breast cancer. Furthermore, tests are not available for all of the genes that affect breast cancer risk.

The US Preventive Services Task Force (USPTF) currently recommends that only women with a strong family history (about 2% of US women) be evaluated for genetic testing for *BRCA* mutations (see recommendations, opposite page).<sup>51</sup> The American Cancer Society, the American Society for Clinical Oncology, and other organizations strongly recommend that any person who is considering genetic testing talk with a genetic counselor before making a decision about testing so that the benefits and potential consequences can be understood and carefully considered. For more information, see the American Cancer Society document called *Genetic Testing: What You Need to Know*, which is available at cancer.org.

### Personal history of breast cancer

Women with a history of breast cancer are at increased risk for developing a second breast cancer. The risk is higher if the diagnosis was at a younger age. Women diagnosed with early onset

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

| Relative Risk | Factor  |
|---------------|---|
| >4.0          | <ul style="list-style-type: none"> <li>• Age (65+ vs. &lt;65 years, although risk increases across all ages until age 80)</li> <li>• Biopsy-confirmed atypical hyperplasia</li> <li>• Certain inherited genetic mutations for breast cancer (<i>BRCA1</i> and/or <i>BRCA2</i>)</li> <li>• Lobular carcinoma in situ</li> <li>• Mammographically dense breasts</li> <li>• Personal history of early onset (&lt;40 years) breast cancer</li> <li>• Two or more first-degree relatives with breast cancer diagnosed at an early age</li> </ul>   |
| 2.1-4.0       | <ul style="list-style-type: none"> <li>• Personal history of breast cancer (40+ years)</li> <li>• High endogenous estrogen or testosterone levels (postmenopausal)</li> <li>• High-dose radiation to chest</li> <li>• One first-degree relative with breast cancer</li> </ul>   |
| 1.1-2.0       | <ul style="list-style-type: none"> <li>• Alcohol consumption</li> <li>• Ashkenazi (Eastern European) Jewish heritage</li> <li>• Diethylstilbestrol (DES) exposure</li> <li>• Early menarche (&lt;12 years)</li> <li>• Height (tall)</li> <li>• High socioeconomic status</li> <li>• Late age at first full-term pregnancy (&gt;30 years)</li> <li>• Late menopause (&gt;55 years)</li> <li>• Never breastfed a child</li> <li>• No full-term pregnancies</li> <li>• Obesity (postmenopausal)/adult weight gain</li> <li>• Personal history of endometrium, ovary, or colon cancer</li> <li>• Recent and long-term use of menopausal hormone therapy containing estrogen and progestin</li> <li>• Recent oral contraceptive use</li> </ul> |

breast cancer (age <40) have almost a 4.5-fold increased risk of subsequent breast cancer.<sup>52</sup> Genetic predisposition, such as mutations in *BRCA1* and *BRCA2* genes, probably contribute to some of the excess risk of subsequent breast cancers, particularly among women diagnosed at a young age.<sup>53</sup>

### Lobular carcinoma in situ

This uncommon condition is the result of abnormal cells forming in the lobules or milk-producing glands of the breast. Although LCIS seldom becomes invasive cancer, women with LCIS are 7 to 12 times more likely to develop invasive cancer in either breast than women without LCIS.<sup>54</sup> LCIS is not usually apparent on a mammogram and is typically discovered during a biopsy performed for another reason, such as an abnormal mammogram. Pure LCIS should be distinguished from DCIS and pleomorphic LCIS, as both of these conditions are considered precursor lesions for breast cancer and require cancer-directed therapy.



## Benign breast disease

Some types of benign breast conditions are linked to breast cancer risk. Doctors often categorize these conditions into 3 general groups, reflecting the degree of 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 have little to no effect on breast cancer risk. Examples of nonproliferative lesions include fibrosis (also known as fibrocystic changes), simple cysts, and mild hyperplasia. Proliferative lesions without atypia are associated with a small increase in the risk of breast cancer (1.5 to 2 times the risk of those who do not have one of these lesions) and include non-atypical (or usual) ductal hyperplasia and fibroadenoma.<sup>55-58</sup> Proliferative lesions with atypia are associated with the greatest breast cancer risk – 4 to 5 times higher than average risk.<sup>55,56,58</sup> These include atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). Women should keep detailed records of any benign breast biopsy results, as this information is valuable for risk assessment, screening, and counseling for chemoprevention and risk-reduction strategies.

## Breast density

High breast tissue density (a mammographic indicator of the amount of breast and connective tissue relative to fatty tissue in the breast) has been shown to be a strong, independent risk factor for the development of breast cancer.<sup>59</sup> A number of factors can affect breast density, such as age, menopausal status, the use of certain drugs (such as menopausal hormone therapy), pregnancy, and genetics. Breast density is influenced by inherited genetic factors, but decreases with age and is further reduced by pregnancy and menopause.<sup>60,61</sup> Percent breast density is generally lower among women with higher body weight because of the higher proportion of fatty tissue.<sup>62</sup> Some drugs affect breast density, including tamoxifen (decreases density) and combined menopausal hormone therapy (increases density).<sup>63</sup> The risk of breast cancer increases with increasing breast density; women with very high breast density have a 4- to 6-fold increased risk of breast cancer compared to women with the least dense breasts.<sup>59,64,65</sup> In addition, mammographic detection of breast cancer is impaired for dense breast tissue.<sup>64</sup> Some states have laws requiring that women be informed if they have higher than average breast tissue density, along with the other findings on their mammogram. In addition, some states also require that women with dense breasts be told that they may benefit from additional screening.<sup>66</sup> However, at this time there is no expert consensus about what other tests, if any, should be done in addition to mammograms to screen for breast cancer in women with dense breasts.

## US Preventive Services Task Force recommendations for genetic testing for BRCA mutations<sup>51</sup>

**Women who are not of Ashkenazi (Eastern European) Jewish heritage should be referred for genetic evaluation if they have any of the following:**

- Two first-degree female relatives (mother, sisters, daughters) with breast cancer, one of whom was diagnosed when they were younger than age 50
- Three or more first- or second-degree female relatives (includes grandmothers and aunts) diagnosed with breast cancer
- Both breast and ovarian cancer among first- and second-degree relatives
- A first-degree relative diagnosed with cancer in both breasts
- Two or more first- or second-degree relatives diagnosed with ovarian cancer
- A male relative with breast cancer

**Women of Ashkenazi (Eastern European) Jewish heritage should be referred for genetic evaluation if they have:**

- A first-degree relative with breast or ovarian cancer
- Two second-degree relatives on the same side of the family with breast or ovarian cancer

## Endogenous hormone levels

Postmenopausal women with high levels of endogenous hormones (estrogen or testosterone produced naturally in the body) have about twice the risk of developing breast cancer compared to women with the lowest levels.<sup>67-69</sup> High circulating hormone levels are associated with and may reflect the effects of other breast cancer risk factors, such as postmenopausal obesity and alcohol use.<sup>70</sup>

The relationship in premenopausal women is less clear, which likely reflects the complexity of measuring hormone levels that vary during the menstrual cycle. Nevertheless, there is growing evidence linking high levels of testosterone to breast cancer risk in premenopausal women.<sup>71-73</sup> A recent study reported that premenopausal women in the highest quintiles of total and free testosterone had an 80% greater breast cancer risk compared to women in the lowest quintiles.<sup>71</sup> Two recent reviews concluded that high estrogen levels are also associated with a slight increase in breast cancer risk in premenopausal women.<sup>68,74</sup>

## Menstrual cycles

Women who have had more menstrual cycles because they started menstruating early (before age 12) and/or went through menopause later (after age 55) have a slightly higher risk of breast cancer.<sup>75,76</sup> The increased risk may be due to longer lifetime exposure to reproductive hormones.

## Pregnancy

Younger age at first full-term pregnancy (<30 years) and a greater number of pregnancies decrease the risk of breast cancer over the long term; however, there appears to be a transient increase in breast cancer risk following a full-term pregnancy, particularly among women who are older at first birth.<sup>75,77</sup> Pregnancy-related risk factors seem to be more strongly related to hormone receptor-positive than hormone receptor-negative breast cancers.<sup>78,79</sup>

## Breastfeeding

Most studies suggest that breastfeeding for a year or more slightly reduces a woman's overall risk of breast cancer.<sup>80</sup> The protective effect may be greater for basal-like breast cancers.<sup>80</sup> Longer duration is associated with greater risk reduction. In a review of 47 studies in 30 countries, the risk of breast cancer was reduced by 4.3% for every 12 months of breastfeeding.<sup>81</sup> One possible explanation for this effect may be that breastfeeding inhibits menstruation, thus reducing the lifetime number of menstrual cycles. Another possible explanation relates to structural changes that occur in the breast following lactation and weaning.

## Bone mineral density

High bone mineral density in postmenopausal women has been associated with increased risk for breast cancer in many, but not all, studies; risk appears to be most strongly related to ER+ disease.<sup>82-86</sup> Bone density is not an independent risk factor for breast cancer, but a marker for cumulative estrogen exposure.<sup>86</sup> Bone density is routinely measured to identify women at increased risk for osteoporosis (high bone density indicates absence of osteoporosis) and may help determine a woman's risk for developing breast cancer.

## Lifestyle-related factors

### Postmenopausal hormone use

Recent use of menopausal hormones (also referred to as hormone therapy or HT) with combined estrogen and progestin increases the risk of developing and dying from breast cancer, with higher risk associated with longer use.<sup>87,88</sup> Risk is also greater for women who start hormone therapy soon after the onset of menopause compared to those who begin use later.<sup>89-91</sup> The increased risk appears to diminish within 5 years of discontinuation of hormone use.<sup>88,89,92</sup>

Estrogen alone can be prescribed for women without a uterus, and it is less clear if this therapy increases risk of breast cancer.

### What is the difference between absolute, lifetime, and relative risks?

**Absolute risk:** Absolute risk is the likelihood of being diagnosed with cancer over a certain period of time. For example, the risk for a 50-year-old cancer-free woman of being diagnosed with breast cancer over the next 10 years is 2% (Table 5, page 17). Another way to say this is that 1 out of every 43 women who are 50 years old will be diagnosed with breast cancer by the age of 60.

**Lifetime risk:** Lifetime risk refers to the likelihood of being diagnosed with cancer over the course of a lifetime from birth to death. Lifetime risk reflects the average probability; an individual will have a higher or lower risk based on their age and other risk factors. A woman living in the US has a 12% chance of being diagnosed with breast cancer in her lifetime (Table 5, page 17). Another way to say this is that 1 out of every 8 women will be diagnosed with breast cancer in her lifetime (Table 5, page 17).

**Relative risk:** Relative risk compares the absolute risk of disease among people with a particular risk factor to the risk among people without that risk factor. If the relative risk is above 1.0, then risk is higher among those with the risk factor than among those without the factor. Relative risks below 1.0 reflect an inverse association between the exposure and the disease, or a protective effect. For example, one study found current users of combined estrogen and progestin menopausal hormones have a relative risk of developing breast cancer of 1.26, or a 26% increased risk compared to women who have not used hormone therapy.<sup>87</sup> While relative risks are useful for comparisons, they do not provide information about the absolute amount of additional risk experienced by the exposed group. In this example, 38 breast cancers would be expected to be diagnosed among 10,000 women who use estrogen and progestin for 5.2 years (that is the absolute risk among this group). Among 10,000 women of the same ages who never used menopausal hormones, 30 cases would be expected over the same period. Therefore, the 26% increased relative risk results in a total of 8 additional breast cancer cases per 10,000 women over a period of 5.2 years.

Updated results from the Women's Health Initiative randomized trial found that use of estrogen-only therapy for an average of 6 years is associated with decreased risk of breast cancer;<sup>93</sup> however, several other observational studies have found a slight increase in risk, particularly among lean women and for women who began therapy soon after menopause.<sup>89,92,94</sup>

### Obesity and weight gain

Obesity increases the risk of postmenopausal breast cancer.<sup>95</sup> The risk of postmenopausal breast cancer is about 1.5 times higher in overweight women and about 2 times higher in obese women than

in lean women.<sup>96</sup> Breast cancer risk associated with excess weight is likely due to high estrogen levels because fat tissue is the largest source of estrogen in postmenopausal women.

Obesity is also a risk factor for type II diabetes, which some studies have linked to modestly increased risk for postmenopausal breast cancer.<sup>97</sup> The inconsistencies likely reflect the complex relationship between obesity and diabetes, as well as the fact that diabetic treatments may further affect risk.<sup>98</sup>

In contrast, some studies have found that obesity protects against developing breast cancer before menopause. A large meta-analysis found that among women ages 40-49, the risk for developing breast cancer was about 14% lower in overweight women and about 26% lower in obese women compared to women who are normal weight.<sup>99</sup> The underlying mechanisms for this inverse relationship are not well understood, but the protective effect may be limited to ER+ breast cancers.<sup>78,100,101</sup>

Many studies have looked at whether the timing of weight gain influences breast cancer risk. Results from a study of more than 80,000 registered nurses found that women who gained 55 pounds or more after age 18 had almost 50% greater risk of breast cancer; a gain of 22 pounds or more after menopause was associated with an increased risk of 18%.<sup>102</sup> Although some studies have found weight loss to be associated with reduced risk, results are not consistent.<sup>102-104</sup> It is more difficult to examine the effect of weight loss on breast cancer because weight loss is often not sustained.

## Physical activity

Growing evidence suggests that women who get regular physical activity have a 10%-20% lower risk of breast cancer compared to women who are inactive, with stronger evidence for postmenopausal than premenopausal women.<sup>95,105-107</sup> A recent report from the Nurses' Health Study of more than 95,000 women found that increases in physical activity after menopause lowered breast cancer risk by 10%.<sup>105</sup> The benefit may be due to the effects of physical activity on body mass, hormones, and energy balance.<sup>108</sup>

## Diet

Although numerous studies have examined the relationship between food consumption (including fat, soy, dairy, meat, and fruits and vegetables) and breast cancer, there is no conclusive evidence that diet influences breast cancer risk.<sup>109,110</sup> A recent meta-analysis of animal fat intake and breast cancer, which included more than 20,000 breast cancer cases, concluded there was no association.<sup>111</sup> Similarly, reducing dietary fat in postmenopausal women did not affect risk of breast cancer in the Women's Health Initiative dietary intervention. However, the timing of the exposure may be important, as findings from the Nurses' Health Study showed that a high-fat diet during adolescence was associated with a moderate increase in premenopausal breast cancer risk.<sup>112</sup>

## American Cancer Society Guidelines for Nutrition and Physical Activity for Cancer Prevention<sup>43</sup>

### ***Achieve and maintain a healthy weight throughout life.***

- Be as lean as possible throughout life without being underweight.
- Avoid excess weight gain at all ages. For those who are currently overweight or obese, losing even a small amount of weight has health benefits and is a good place to start.
- Engage in regular physical activity and limit consumption of high-calorie foods and beverages as key strategies for maintaining a healthy weight.

### ***Adopt a physically active lifestyle.***

- Adults should engage in at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity activity each week, or an equivalent combination, preferably spread throughout the week.
- Children and adolescents should engage in at least 1 hour of moderate- or vigorous-intensity activity each day, with vigorous-intensity activity occurring at least 3 days each week.
- Limit sedentary behavior such as sitting, lying down, watching television, or other forms of screen-based entertainment.
- Doing some physical activity above usual activities, no matter what the level of activity, can have many health benefits.

### ***Consume a healthy diet, with an emphasis on plant foods.***

- Choose foods and beverages in amounts that help achieve and maintain a healthy weight.
- Limit consumption of processed meat and red meat.
- Eat at least 2½ cups of vegetables and fruits each day.
- Choose whole grains instead of refined-grain products.

### ***If you drink alcoholic beverages, limit consumption.***

- Drink no more than 1 drink per day for women or 2 per day for men.

### ***Maintain a healthy weight throughout life.***

- Balance calorie intake with physical activity.
- Avoid excessive weight gain throughout life.
- Achieve and maintain a healthy weight if currently overweight or obese.

It has been suggested that soy consumption may reduce breast cancer risk, in part because of historically low breast cancer rates among Asian women. A meta-analysis showed that soy intake was inversely associated with breast cancer risk in Asian but not Western populations.<sup>113</sup> There is growing evidence that



high levels of fruit and vegetable consumption may be associated with reduced risk of hormone receptor negative breast cancer.<sup>114-116</sup> The effect of diet on breast cancer risk remains an active area of research, with studies particularly focusing on timing of exposure, specific dietary components, and whether risks may differ by tumor hormone receptor status.

## Alcohol

Numerous studies have confirmed that alcohol consumption increases the risk of breast cancer in women by about 7% to 12% for each 10g (roughly one drink) of alcohol consumed per day.<sup>117-119</sup> The increased risk is dose-dependent and exists regardless of the type of alcoholic beverage consumed.<sup>119</sup> One of the mechanisms by which alcohol increases risk of breast cancer is by increasing estrogen and androgen levels.<sup>120</sup> Alcohol use has been more strongly related with increased risk for ER+ than ER- breast cancers.<sup>121,122</sup>

## Tobacco

In 2009, the International Agency for Research on Cancer concluded that there was limited evidence that tobacco smoking causes breast cancer in women based on a review of 150 studies.<sup>123</sup> A recent meta-analysis by American Cancer Society researchers found that current smokers had a 12% higher risk of breast cancer than women who never smoked.<sup>124</sup> Research also suggests that risk may be greater for women who begin smoking before first childbirth.<sup>125,126</sup>

In 2006, the US Surgeon General characterized the evidence linking secondhand smoke and breast cancer as “suggestive but not sufficient” to infer a causal relationship.<sup>127</sup> However, a subsequent meta-analysis concluded that there was no association between secondhand smoke and breast cancer, regardless of the time of onset of exposure.<sup>128</sup> The results of more recent studies have also failed to show a clear relationship between passive smoking and breast cancer risk.<sup>124,129,130</sup> Nevertheless, it is clear that avoiding exposure to secondhand smoke has multiple health benefits.

## Oral contraceptive use

Recent use of oral contraceptives may increase the risk of breast cancer by about 10% to 30%; however, since most studies have looked at older, high-dose estrogen forms of oral contraceptives, the risk with current, low-dose formulations is not clear.<sup>131</sup> Women who have stopped using oral contraceptives for 10 years or more have the same risk as women who never used the pill.<sup>131</sup>

## Other risk factors

### Radiation

The link between radiation exposure and breast cancer has been demonstrated in studies of atomic bomb survivors and women who have received high-dose radiation therapy to the chest, particularly for those who were first exposed at younger

ages.<sup>132,133</sup> This may be because breast tissue is most susceptible to carcinogens before it is fully differentiated, which occurs with first childbirth.<sup>134</sup>

Breast cancer is one of the most common types of second cancers among childhood cancer survivors. Secondary breast cancer is most strongly associated with high-dose radiation therapy to the chest for women treated between 10 and 30 years of age, such as for Hodgkin lymphoma.<sup>135</sup> Breast cancer risk among women with such exposure start to rise about 8 years after radiation treatment and continue to be elevated for more than 25 years.<sup>133</sup>

### Diethylstilbestrol exposure

From the 1940s through the 1960s, some pregnant women were given the drug diethylstilbestrol (DES) because it was thought to lower the risk of miscarriage. These women have increased risk (about 30% higher) of developing breast cancer compared to women who have not taken DES.<sup>136</sup> Some studies have found that women whose mothers took DES during pregnancy also have a slightly higher risk of breast cancer.<sup>137</sup>

### Environmental pollutants

Concerns have been raised among some advocacy groups and survivors that rising breast cancer incidence in the latter half of the 20th century may have been caused by environmental pollutants such as organochlorine pesticides. However, studies to date have found no association between increased concentrations of organochlorines in blood and fat tissue and breast cancer risk.<sup>138-141</sup>

Although animal studies have demonstrated that prolonged, high-dose exposure to many industrial chemicals can increase mammary tumor development, it is difficult to determine whether exposure to much lower concentrations of these chemicals in the general environment – which occur alone or in combination, in air, drinking water, and consumer products – increases the risk of human breast cancer.<sup>142</sup> In general, epidemiological studies have not found clear relationships between environmental pollutants and breast cancer, though these studies have had limited capability to study effects on population subgroups or to quantify exposures at potentially critical periods of life, such as adolescence. An association between environmental exposures and breast cancer may be difficult to quantify because it may reflect an indirect pathway (e.g., an effect of these exposures on early onset puberty). This continues to be an active area of research.

### Occupational exposures

A few occupations have been linked to breast cancer risk. One study found an increased risk of breast cancer among women employed in commercial sterilization facilities who were exposed to high levels of ethylene oxide.<sup>143</sup> This chemical has been shown to cause breast cancer in experimental animals.

Night shift work may also be associated with increased breast cancer risk. Most studies of nurses who work night shifts and flight attendants who experience circadian rhythm disruption caused by crossing multiple time zones have found increased risks of breast cancer associated with long-term employment.<sup>144,145</sup> Animal studies suggest that exposure to light at night causes circadian rhythm disruption and increases cancer incidence.<sup>146</sup> Some researchers suggest that the increased risk of breast cancer may be due to decreases in melatonin levels that occur as a result of exposure to light at night; melatonin may affect estrogen levels, as well as act as a tumor suppressor.<sup>146</sup> Based on the results of studies in humans and experimental animals, the International Agency for Research on Cancer concluded in 2007 that shift work, particularly at night, was probably carcinogenic to humans.<sup>147</sup> Additional studies are needed to confirm this relationship because shift work at night is a common exposure, involving about 15% to 20% of workers in the US and Europe, and because much of the population in industrialized countries is exposed to artificial light at night.

## 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.<sup>148</sup> Indeed, a large body of solid scientific evidence, including a review by a panel of experts convened by the National Cancer Institute in 2003, confirms that there is no link between breast cancer and abortion (either spontaneous or induced).<sup>149</sup> For more information, see the American Cancer Society document called *Is Abortion Linked to Breast Cancer?*, which is available at [cancer.org](http://cancer.org).

### Hair dyes and antiperspirants

A combined analysis of 14 studies found no association between the use of permanent hair dyes and breast cancer.<sup>150</sup> Although antiperspirant use has been less well-studied, there is presently no conclusive scientific evidence that links breast cancer risk to the use of antiperspirants.<sup>151,152</sup>

### Breast implants

No association has been found between breast implants and an increased risk of breast cancer; however, there is growing concern that women with implants may be at increased risk of a rare type of lymphoma.<sup>153-155</sup>

Breast implants can make it harder to see breast tissue by mammography. A woman with breast implants should inform the mammography facility about the implants when scheduling her mammogram. The use of additional x-ray pictures (called

**Table 5. Age-specific Probabilities of Developing Invasive Female Breast Cancer\***

| If current age is ... | The probability of developing breast cancer in the next 10 years is: | or 1 in: |
|-----------------------|--|----------|
| 20                    | 0.06%  | 1,732    |
| 30                    | 0.44%  | 228      |
| 40                    | 1.45%  | 69       |
| 50                    | 2.31%  | 43       |
| 60                    | 3.49%  | 29       |
| 70                    | 3.84%  | 26       |
| <b>Lifetime risk</b>  | <b>12.29%</b>  | <b>8</b> |

\*Among those free of cancer at beginning of age interval. Based on cases diagnosed 2008-2010. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.

Probability derived using NCI DevCan Software, Version 6.7.0.

American Cancer Society, Surveillance and Health Services Research, 2013

implant displacement views) may be used 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. Clinical trials have shown that the drugs tamoxifen and raloxifene significantly reduce the risk of breast cancer in women known to be at increased risk.<sup>156</sup>

Tamoxifen has been used for more than 30 years as a treatment for some breast cancers. In 1998, a large, randomized trial of more than 13,000 women first demonstrated that tamoxifen can also be used to reduce the risk of invasive and in situ ER+ breast cancer in women at high risk for developing the disease.<sup>157</sup> After an average of 7 years of follow up, breast cancer risk was decreased by 42% in the group that received tamoxifen. A protective effect was also observed in an international randomized prevention trial involving more than 7,000 women.<sup>158</sup> Long-term follow-up results indicate that the reduction in risk persists after completion of the 5-year treatment schedule.<sup>158,159</sup> Side effects of tamoxifen include increased risk of endometrial cancer, thromboembolic events, and cataracts.<sup>156</sup>

Raloxifene's efficacy in the prevention of breast cancer was discovered by accident. In a study looking at raloxifene for the prevention of osteoporosis, researchers noticed that patients taking raloxifene had a lower risk of breast cancer than the control group.<sup>160</sup> The Study of Tamoxifen and Raloxifene (STAR) trial, which compared the effectiveness of tamoxifen and raloxifene, found that although raloxifene was somewhat less effective in preventing invasive breast cancer, it was associated with lower risks of certain side effects (endometrial cancer, blood clots in the legs or lungs, and cataracts).<sup>161</sup> Similar to tamoxifen,

the benefit of raloxifene appears to be limited to reducing the risk of developing ER+ breast cancer.<sup>162</sup> Unlike tamoxifen, raloxifene is only approved for use in postmenopausal women.

Chemoprevention is not appropriate for all women who are eligible because of potential side effects. An estimated 19% of white women and 6% of African American women 35 to 79 years of age are eligible (based on criteria from the US Food and Drug Administration) for chemoprevention, but the benefit would be expected to outweigh the risks for only 5% of white women and about 1% of African American women.<sup>163</sup> However, according to the 2010 National Health Interview Survey, only 0.03% of US women 35 to 79 years of age without a personal history of breast cancer were taking tamoxifen and 0.21% of women 50 to 79 reported using raloxifene.<sup>164</sup>

Clinical trials are also examining another class of drugs – aromatase inhibitors – to see if they may be effective for reducing breast cancer risk. Aromatase inhibitors target the enzyme that is responsible for producing estrogen in the fat tissue. Currently, these drugs are only approved to prevent breast cancer recurrence. Early results are promising; women at moderately increased risk taking exemestane had a 65% lower risk of developing invasive breast cancer after three years compared to women taking a placebo.<sup>165</sup> These drugs are only effective in women without functioning ovaries, such as postmenopausal women. Women taking aromatase inhibitors must be monitored for osteoporosis, as these medications can decrease bone density.

### Prophylactic surgery

Women at very high risk of breast cancer may elect prophylactic (preventive) mastectomy. This operation removes one or both

breasts before breast cancer has been discovered. Some women may also choose to have their breasts reconstructed after the surgery. Breast reconstruction can be performed at the same time as the mastectomy (immediate reconstruction) or months to years after the mastectomy (delayed reconstruction). There are several techniques for breast reconstruction. The conventional or traditional mastectomy involves removal of the nipple and areolar skin, but some recent studies are demonstrating that selected patients may be able to safely undergo a nipple-sparing mastectomy. However, long-term data regarding the safety of nipple preservation are limited. Removing both breasts before cancer is diagnosed reduces the risk of breast cancer by 90% or more.<sup>166-169</sup> Prophylactic salpingo-oophorectomy (surgical removal of the fallopian tubes and ovaries) reduces the risk of both breast and ovarian cancers in women who carry *BRCA* mutations.<sup>169,170</sup>

It is important to note that not all women who elect to have these surgeries would have developed cancer. A woman considering these operations should discuss this carefully with her doctor. A second opinion is strongly recommended.

Some women who are diagnosed with breast cancer in one breast choose to have the unaffected breast removed as well. This is known as contralateral prophylactic mastectomy (CPM). Recent studies have shown marked increases in the rate of CPM for women diagnosed with invasive breast cancer, as well as DCIS.<sup>171-173</sup> Although CPM nearly eliminates the risk of developing breast cancer, there is less evidence that it improves long-term breast cancer survival.<sup>171</sup> Studies suggest that a survival advantage may be limited to certain subgroups, such as women diagnosed before 50 years of age and those with ER-breast cancers.<sup>174-175</sup>

## Breast Cancer Screening

American Cancer Society guidelines for the early detection of breast cancer vary depending on a woman's age and include mammography and clinical breast examination (CBE), as well as magnetic resonance imaging (MRI) for women at high risk.

### Mammography

Mammography is a low-dose x-ray procedure that allows visualization of the internal structure of the breast. Dedicated mammography units used today result in higher-quality images with a considerably lower x-ray dose than the general-purpose x-ray equipment used in the past. Conventional (film) mammography has been largely replaced by digital mammography, which appears to be even more accurate for women younger than age 50 and for those with dense breast tissue.<sup>176-178</sup>

The American Cancer Society recommends that women receive an annual mammogram beginning at age 40.<sup>179</sup> It is especially important that women are regularly screened to increase the chance that a breast cancer would be detected early before it has spread. Recommended screening intervals are based on the duration of time a breast cancer is detectable by mammography before symptoms develop. Combined results from randomized screening trials suggest that mammography reduces the risk of dying from breast cancer by 15% to 20%, whereas studies of modern mammography screening programs in Europe found that the risk of breast cancer death was reduced by more than one-third.<sup>180-184</sup> Early detection of breast cancer by mammography also leads to a greater range of treatment options, including less-extensive surgery (e.g., breast-conserving surgery like



lumpectomy versus mastectomy) and the use of chemotherapy with fewer serious side effects, or even, in some cases, the option to forgo chemotherapy. However, mammography screening does have potential harms.

### False-positive results

Mammography sometimes leads to follow-up examinations, including biopsies, when there is no cancer; these are referred to as false-positive test results. A false-positive is most likely following a woman's initial screening mammogram.<sup>185</sup> On average, 10% of women will be recalled from each screening examination for further testing, but only 5% of these women will have cancer.<sup>186</sup> According to one US study, over the course of 10 screening examinations, about one-half of women will experience a false-positive, and about 19% will undergo biopsy.<sup>187</sup>

### Overdiagnosis

Mammography likely results in some overdiagnosis; that is, the detection of cancers that would not have progressed or otherwise been detected unless a woman underwent screening. Since it is not currently possible to distinguish a nonprogressive cancer from a progressive one, overdiagnosis is estimated from long-term evaluation of observed versus expected cases in a screening program. Estimates of the rate of overdiagnosis are highly variable, ranging from 0% to more than 30%.<sup>181,184,188-190</sup>

### Radiation exposure

Although many people are concerned about radiation exposure, the dose required for a mammogram is very small and the risk of harm is minimal.<sup>191,192</sup>

### Limitations of mammography

As with all screening tests, mammography is not 100% effective. Not all breast cancer will be detected by a mammogram, and some breast cancers that are screen-detected still have poor prognosis. Although the lifetime risk of breast cancer is substantial (1 in 8), most women will not be diagnosed with breast cancer in their lifetime, but will undergo regular screening and many will experience one or more "false alarms." In an effort to maximize the benefits and minimize the harms of screening, some scientists are attempting to determine which combinations of conventional and new risk factors could be used to individualize screening recommendations (e.g., determine which women could start screening at older ages and/or be screened less often).<sup>193</sup>

Despite these limitations, mammography is the single most effective method of early detection since it can often identify cancer several years before physical symptoms develop. It is the position of the American Cancer Society that the balance of benefits to possible harms strongly supports the value of regular breast cancer screening in women who are 40 years of age or older.

**Table 6. Mammography Prevalence\*, Women 40 and Older, US, 2010**

| Characteristic                   | % mammogram within the past year | % mammogram within the past 2 years |
|----------------------------------|----------------------------------|-------------------------------------|
| <b>Age</b>                       |                                  |                                     |
| 40-49                            | 47                               | 62                                  |
| 50-64                            | 56                               | 73                                  |
| 65+                              | 49                               | 64                                  |
| <b>Race/Ethnicity</b>            |                                  |                                     |
| Non-Hispanic White               | 52                               | 67                                  |
| African American                 | 51                               | 66                                  |
| Asian American†                  | 48                               | 62                                  |
| American Indian/Alaska Native‡   | 50                               | 69                                  |
| Hispanic/Latina                  | 46                               | 64                                  |
| <b>Education (years)</b>         |                                  |                                     |
| 11                               | 38                               | 52                                  |
| 12                               | 48                               | 64                                  |
| 13-15                            | 53                               | 69                                  |
| 16 or more                       | 57                               | 75                                  |
| <b>Health insurance coverage</b> |                                  |                                     |
| No                               | 17                               | 32                                  |
| Yes                              | 55                               | 71                                  |
| <b>Immigration§</b>              |                                  |                                     |
| Born in US                       | 52                               | 67                                  |
| Born in US territory             | 43                               | 68                                  |
| In US fewer than 10 years        | 27                               | 37                                  |
| In US 10 or more years           | 48                               | 65                                  |
| <b>Total</b>                     | <b>51</b>                        | <b>67</b>                           |

\*Percentages are age adjusted to 2000 US standard population. † Does not include Native Hawaiians and other Pacific Islanders. ‡ Estimates should be interpreted with caution because of small sample sizes. § Definition has changed such that individuals born in the US or in a US territory are reported separately from individuals born outside the US. Individuals born in a US territory have been in the US for any length of time.

**Source:** National Health Interview Survey Public Use Data File 2010, National Center for Health Statistics, Centers for Disease Control and Prevention.  
American Cancer Society, Surveillance and Health Services Research, 2013

According to the American Cancer Society guidelines, there is no specific age at which mammography screening should be discontinued. Rather, the decision to stop regular mammography screening should be individualized based on the potential benefits and risks of screening within the context of overall health status and estimated longevity. As long as a woman is in good health and would be a candidate for breast cancer treatment, she should continue to be screened with mammography.

The Affordable Care Act requires that Medicare and all new health insurance plans fully cover screening mammograms without any out-of-pocket expense for patients. For help locating a free or low-cost screening mammogram in your area, contact the American Cancer Society at 1-800-227-2345.

## Prevalence of mammography

According to the National Health Interview Survey, the percentage of women 40 years of age and older who reported having had a mammogram within the past 2 years was 67% in 2010 (Table 6, page 19). Mammography prevalence increased from 29% in 1987 to 70% in 2000, declined slightly (by 3.4%) from 2000 to 2005, and then stabilized.<sup>16</sup> Women who have less than a high school education, who have no health insurance coverage, or who are recent immigrants to the US are least likely to have had a recent mammogram. Similarly, poor and near poor women are less likely to have had a mammogram within the past 2 years than non-poor women, and declines in mammography usage have generally been greater among poorer women (Table 7).<sup>194</sup> Efforts to increase screening should specifically target socioeconomically disadvantaged women and recent immigrants, who are most likely to have the lowest rates of mammographic screening.

Table 8 (page 22) shows the percentage of US women 40 years of age and older who have had a mammogram within the past year by state, based on data from the 2010 Behavioral Risk Factor Surveillance System. Among women 40 years of age and older, reported annual screening rates range from 47% in Wyoming, to 72% in Massachusetts.

The Centers for Disease Control and Prevention's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) was established in 1990 to improve access to breast cancer screening and diagnostic services for low-income women and was recently shown to save lives from breast cancer.<sup>195</sup> However, the CDC estimates that the program is currently only reaching about 12% of the women eligible to receive a screening mammogram, due in part to funding shortages.<sup>196</sup> The American Cancer Society is committed to helping protect and increase funding for NBCCEDP in order to expand the number of women who can be served through the program.

## Magnetic resonance imaging (MRI)

An expert panel convened by the Society published recommendations for the use of MRI for screening women at increased risk for breast cancer in 2007.<sup>197</sup> The panel recommended annual MRI screening in addition to mammography for women at high lifetime risk (~20%-25% or greater) beginning at 30 years of age. Women at moderately increased risk (15%-20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram. See risk criteria for MRI screening (right). MRI screening is not recommended for women whose lifetime risk of breast cancer is less than 15%.

MRI uses magnetic fields instead of x-rays to produce very detailed, cross-sectional images of the body. MRI exams for breast imaging use a contrast material (usually gadolinium DTPA) that is injected into a vein in the arm before or during the exam to improve the

### American Cancer Society Risk Criteria for Breast MRI Screening as an Adjunct to Mammography

#### **Women at high lifetime risk (~20%-25% or greater) of breast cancer include those who:**

- Have a known *BRCA1* or *BRCA2* gene mutation
- Have a first-degree relative (mother, father, brother, sister, or child) with a *BRCA1* or *BRCA2* gene mutation, but have not had genetic testing themselves
- Have a lifetime risk of breast cancer of approximately 20% to 25% or greater
- Had radiation therapy to the chest when they were between 10 and 30 years of age
- Have Li-Fraumeni syndrome or Cowden syndrome, or have a first-degree relative with one of these syndromes

#### **Women at moderately increased (15%-20% lifetime risk) risk include those who:**

- Have a lifetime risk of breast cancer of 15% to 20%, according to risk assessment tools that are based mainly on family history
- Have a personal history of breast cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia, or atypical lobular hyperplasia
- Have extremely dense breasts or unevenly dense breasts when viewed by mammograms

ability to capture detailed images of breast tissue.<sup>197</sup> MRIs should supplement, but not replace, mammography screening.

Just as mammography uses x-ray machines designed especially to image the breasts, breast MRI also requires special equipment. Higher-quality images are produced by dedicated breast MRI equipment than by machines designed for head, chest, or abdominal MRI scanning. However, many hospitals and imaging centers do not have dedicated breast MRI equipment available. It is important that screening MRIs are done at facilities that are capable of performing an MRI-guided breast biopsy in case abnormalities are found. Otherwise, the scan must be repeated at another facility if a biopsy is necessary. Although MRI is more expensive than mammography, most major insurance companies will cover some portion of the costs if a woman can be shown to be at high risk.

## Clinical breast examination (CBE)

For average-risk, asymptomatic women in their 20s and 30s, it is recommended that a breast exam be a part of a regular health examination, preferably at least every 3 years. For women 40 or older, annual CBE can be an important complement to mammography, since a small percentage of cancers may be missed by mammography.

**Table 7. Mammography Prevalence (%) within the Past Two Years by Age and Poverty Status\*, US, Selected Years 1987-2010**

| Year | 40-49 years |           |          | 50-64 years |           |          | 65 years and over |           |          |
|------|-------------|-----------|----------|-------------|-----------|----------|-------------------|-----------|----------|
|      | Poor        | Near poor | Non-poor | Poor        | Near poor | Non-poor | Poor              | Near poor | Non-poor |
| 1987 | 19          | 18        | 44       | 15          | 24        | 45       | 13                | 20        | 35       |
| 1990 | 32          | 39        | 69       | 30          | 40        | 72       | 31                | 39        | 61       |
| 1991 | 33          | 44        | 70       | 37          | 50        | 73       | 35                | 42        | 63       |
| 1993 | 36          | 48        | 70       | 47          | 47        | 79       | 40                | 48        | 71       |
| 1994 | 43          | 48        | 70       | 46          | 49        | 78       | 44                | 49        | 73       |
| 1998 | 45          | 47        | 73       | 53          | 62        | 83       | 52                | 58        | 71       |
| 1999 | 51          | 53        | 77       | 63          | 65        | 83       | 58                | 60        | 77       |
| 2000 | 47          | 44        | 76       | 62          | 68        | 87       | 55                | 60        | 82       |
| 2003 | 51          | 54        | 72       | 58          | 64        | 85       | 57                | 63        | 73       |
| 2005 | 42          | 50        | 74       | 50          | 59        | 81       | 52                | 56        | 73       |
| 2008 | 47          | 47        | 73       | 57          | 59        | 84       | 49                | 59        | 78       |
| 2010 | 48          | 46        | 74       | 55          | 57        | 83       | 51                | 56        | 75       |

\*Poor persons are defined as below the poverty threshold. Near poor persons have income of 100%-199% of the poverty threshold. Non-poor persons have an income 400% or more than the poverty level.

Source: *Health, United States, 2012*.<sup>194</sup>

American Cancer Society, Surveillance and Health Services Research, 2013.

Ideally, women should have their CBE shortly before their annual mammogram. During a CBE, the clinician uses the pads of the fingers to gently feel the breasts, giving special attention to shape, texture, location of any lumps, and whether such lumps are attached to the skin or to deeper tissues. The breasts should also be inspected for skin irregularities (e.g., dimpling, redness) and asymmetry. The area under both arms will also be examined. CBE is also an opportunity for a woman and her health care provider to discuss changes in her breasts and early detection testing, to review and update family history information, and to discuss any questions she may have about breast cancer.

### Breast self-awareness

All women should become familiar with both the appearance and feel of their breasts and report any changes promptly to their physician. Although the American Cancer Society no longer recommends that all women perform monthly breast self-exams (BSE), women should be informed about the potential benefits and limitations associated with BSE. Experts have concluded that self-awareness seems to be at least as effective for detecting breast cancer as structured BSE.<sup>198-200</sup> Women who detect their own breast cancer usually find it outside of a structured breast self-exam while bathing or getting dressed. A woman who wishes to perform periodic BSE should receive instruction from her health care provider and/or have her technique reviewed periodically.

If symptoms develop, women should contact a doctor immediately, even after a recent normal mammogram. However, lumps are not necessarily abnormal, and for women who are still menstruating, they can appear and disappear with the menstrual cycle. Most breast lumps are not cancerous.

### Breast ultrasound

Breast ultrasound is sometimes used to evaluate abnormal findings from a screening or diagnostic mammogram or physical exam. Some studies have suggested that ultrasound may detect more cancer than mammography alone when screening women with dense breast tissue; however, it also increases the likelihood of false-positive results.<sup>201</sup> The use of ultrasound instead of mammograms for breast cancer screening is not recommended.

**Table 8. Mammography and Clinical Breast Exam, Women 40 and Older, by State, 2012**

|                      | % Recent Mammogram* |                |                    |                                  |                      | % Recent Mammogram and Clinical Breast Exam† |                |                    |                                  |                      |
|----------------------|---------------------|----------------|--------------------|----------------------------------|----------------------|--|----------------|--------------------|----------------------------------|----------------------|
|                      | 40 years and older  | 40 to 64 years | 65 years and older | No usual source of medical care‡ | No health insurance§ | 40 years and older                           | 40 to 64 years | 65 years and older | No usual source of medical care‡ | No health insurance§ |
| Alabama              | 59                  | 58             | 60                 | 28                               | 31                   | 48   | 50             | 42                 | 20                               | 26                   |
| Alaska               | 54                  | 53             | 58                 | 35                               | –                    | 47   | 47             | 46                 | 29                               | –                    |
| Arizona              | 53                  | 50             | 60                 | 27                               | 22                   | 43   | 42             | 45                 | 21                               | 15                   |
| Arkansas             | 50                  | 47             | 54                 | 29                               | 25                   | 39   | 40             | 36                 | –                                | 21                   |
| California           | 59                  | 57             | 62                 | 29                               | 33                   | 47   | 49             | 42                 | 23                               | 28                   |
| Colorado             | 52                  | 51             | 56                 | 22                               | 23                   | 42   | 43             | 41                 | 17                               | 17                   |
| Connecticut          | 66                  | 67             | 64                 | 28                               | 39                   | 57   | 61             | 50                 | 23                               | 31                   |
| Delaware             | 68                  | 66             | 70                 | –                                | –                    | 58   | 59             | 55                 | –                                | –                    |
| District of Columbia | 63                  | 62             | 65                 | –                                | –                    | 54   | 56             | 51                 | –                                | –                    |
| Florida              | 59                  | 55             | 65                 | 28                               | 29                   | 46   | 46             | 47                 | 21                               | 21                   |
| Georgia              | 62                  | 59             | 70                 | 33                               | 27                   | 52   | 52             | 54                 | 27                               | 22                   |
| Hawaii               | 59                  | 59             | 59                 | 36                               | 30                   | 44   | 47             | 37                 | –                                | –                    |
| Idaho                | 49                  | 46             | 55                 | 21                               | –                    | 43   | 42             | 45                 | 17                               | –                    |
| Illinois             | 58                  | 57             | 60                 | –                                | 37                   | 48   | 49             | 45                 | –                                | 33                   |
| Indiana              | 52                  | 50             | 57                 | 18                               | 23                   | 41   | 42             | 39                 | –                                | 13                   |
| Iowa                 | 61                  | 60             | 63                 | 35                               | –                    | 51   | 53             | 46                 | 30                               | –                    |
| Kansas               | 60                  | 60             | 61                 | 30                               | 30                   | 50   | 52             | 44                 | 24                               | 26                   |
| Kentucky             | 57                  | 56             | 59                 | 26                               | 29                   | 46   | 49             | 40                 | 17                               | 23                   |
| Louisiana            | 60                  | 60             | 61                 | 37                               | 41                   | 49   | 51             | 44                 | 29                               | 31                   |
| Maine                | 65                  | 65             | 66                 | 24                               | 34                   | 55   | 57             | 51                 | –                                | 27                   |
| Maryland             | 65                  | 64             | 66                 | 38                               | 36                   | 55   | 57             | 51                 | 26                               | 27                   |
| Massachusetts        | 72                  | 72             | 72                 | 40                               | 44                   | 62   | 64             | 58                 | 30                               | 36                   |
| Michigan             | 59                  | 58             | 62                 | 21                               | 29                   | 50   | 51             | 48                 | –                                | 25                   |
| Minnesota            | 63                  | 61             | 68                 | 39                               | 35                   | 55   | 55             | 55                 | 34                               | 34                   |
| Mississippi          | 52                  | 51             | 55                 | 27                               | 27                   | 43   | 44             | 40                 | 23                               | 22                   |
| Missouri             | 58                  | 56             | 64                 | 25                               | 29                   | 46   | 47             | 44                 | 20                               | 20                   |
| Montana              | 50                  | 49             | 53                 | 19                               | 27                   | 42   | 42             | 42                 | 15                               | 24                   |
| Nebraska             | 54                  | 54             | 55                 | 26                               | 35                   | 45   | 47             | 40                 | 22                               | 30                   |
| Nevada               | 50                  | 48             | 54                 | 28                               | 23                   | 39   | 40             | 35                 | 24                               | –                    |
| New Hampshire        | 65                  | 64             | 67                 | –                                | 36                   | 54   | 56             | 51                 | –                                | 30                   |
| New Jersey           | 61                  | 62             | 60                 | 41                               | 44                   | 52   | 55             | 46                 | 34                               | 35                   |
| New Mexico           | 50                  | 48             | 53                 | 25                               | 28                   | 41   | 42             | 39                 | 18                               | 25                   |
| New York             | 62                  | 63             | 61                 | 42                               | 37                   | 53   | 54             | 50                 | –                                | 28                   |
| North Carolina       | 62                  | 59             | 67                 | 29                               | 27                   | 52   | 52             | 50                 | 23                               | 22                   |
| North Dakota         | 58                  | 56             | 61                 | –                                | –                    | 50   | 50             | 48                 | –                                | –                    |
| Ohio                 | 60                  | 59             | 63                 | 28                               | 29                   | 49   | 51             | 45                 | 24                               | 26                   |
| Oklahoma             | 52                  | 51             | 55                 | 24                               | 25                   | 41   | 43             | 38                 | 20                               | 21                   |
| Oregon               | 54                  | 50             | 62                 | –                                | –                    | 39   | 39             | 39                 | –                                | –                    |
| Pennsylvania         | 60                  | 59             | 62                 | 28                               | 31                   | 49   | 50             | 45                 | 22                               | 25                   |
| Rhode Island         | 67                  | 66             | 70                 | –                                | 44                   | 58   | 58             | 56                 | –                                | 36                   |
| South Carolina       | 54                  | 52             | 60                 | 25                               | 23                   | 43   | 42             | 44                 | 18                               | 16                   |
| South Dakota         | 62                  | 61             | 62                 | 37                               | 29                   | 52   | 55             | 46                 | 30                               | 25                   |
| Tennessee            | 57                  | 55             | 60                 | 28                               | 25                   | 48   | 48             | 49                 | 26                               | 23                   |
| Texas                | 54                  | 51             | 60                 | 23                               | 21                   | 44   | 45             | 44                 | 19                               | 18                   |
| Utah                 | 50                  | 49             | 53                 | 30                               | 28                   | 37   | 38             | 34                 | 21                               | 21                   |
| Vermont              | 61                  | 61             | 63                 | –                                | –                    | 51   | 53             | 47                 | –                                | –                    |
| Virginia             | 64                  | 64             | 65                 | 42                               | 44                   | 55   | 57             | 51                 | 36                               | 40                   |
| Washington           | 56                  | 53             | 61                 | 28                               | 27                   | 43   | 44             | 43                 | 20                               | 22                   |
| West Virginia        | 58                  | 58             | 59                 | 25                               | 36                   | 47   | 49             | 43                 | –                                | 33                   |
| Wisconsin            | 63                  | 61             | 68                 | –                                | 36                   | 56   | 56             | 57                 | –                                | –                    |
| Wyoming              | 47                  | 46             | 51                 | 27                               | 26                   | 39   | 40             | 35                 | 24                               | 24                   |
| United States        | 59                  | 58             | 61                 | 28                               | 29                   | 48   | 49             | 45                 | 22                               | 25                   |
| Range                | 47-72               | 46-72          | 51-72              | 18-42                            | 21-44                | 37-62  | 38-64          | 34-58              | 13-36                            | 12-40                |

\*A mammogram within the past year. †Both a mammogram and clinical breast exam within the past year. ‡Women who reported that they did not have a personal doctor or health care provider. §Women ages 40 to 64 who reported that they did not have any kind of health care coverage.

**Source:** Behavioral Risk Factor Surveillance System (BRFSS) 2012, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention. Statistic not shown if based on fewer than 50 respondents. Note: The 2012 BRFSS cancer screening data results should be considered baseline and are not directly comparable to previous years of BRFSS data because of the changes in weighting methodology and the addition of the cell phone sampling frame.

American Cancer Society, Surveillance and Health Services Research, 2013



# Breast Cancer Treatment

Treatment decisions are made by the patient and the physician after consideration of the optimal treatment available for the stage and biological characteristics of the cancer, the patient's age and preferences, and the risks and benefits associated with each treatment protocol. Most women with breast cancer will have some type of surgery. Surgery is often combined with other treatments such as radiation therapy, chemotherapy, hormone therapy, and/or targeted therapy.

## Surgery

The primary goals of breast cancer surgery are to remove the cancer from the breast and to determine the stage of disease. Surgical treatment for breast cancer involves breast-conserving surgery (BCS) or mastectomy. With BCS (also known as partial mastectomy, quadrantectomy, and lumpectomy), only cancerous tissue plus a rim of normal tissue are removed. Simple or total mastectomy includes removal of the entire breast. Modified radical mastectomy includes removal of the entire breast and lymph nodes under the arm, but does not include removal of the underlying chest wall muscle, as with a radical mastectomy. Radical mastectomy is rarely used because in most cases removal of the underlying chest muscles is not needed to remove all of the cancer.

Fifty-seven percent of women diagnosed with early stage (I or II) breast cancer have BCS, 36% have mastectomy, 6% have no surgery, and about 1% do not receive any treatment (Figure 10, page 24).<sup>13</sup> In contrast, among women with late-stage (III or IV) breast cancer, 13% undergo BCS, 60% have mastectomy, 18% have no surgical treatment, and 7% do not receive any treatment (Figure 10, page 24).<sup>13</sup>

Depending on age at diagnosis, 20%-40% of women who undergo mastectomy elect to have breast reconstruction, either with an implant, tissue from another part of the body, or a combination of the two.<sup>202-207</sup> A woman considering breast reconstruction should discuss this option with her breast surgeon prior to her mastectomy. The plastic surgeon and the surgeon performing the mastectomy will work together to coordinate treatment plans. Some types of reconstruction can begin during the mastectomy itself, so reconstruction may influence the surgical facility (inpatient versus outpatient) and other aspects of the mastectomy. Since 1999, the Women's Health and Cancer Rights Act (WHCRA) has required group health plans, insurance companies, and health maintenance organizations that offer mastectomy coverage to also pay for reconstructive surgery after mastectomy for breast cancer. Reconstruction is also covered by Medicare and Medicaid, though Medicaid benefits vary by state.

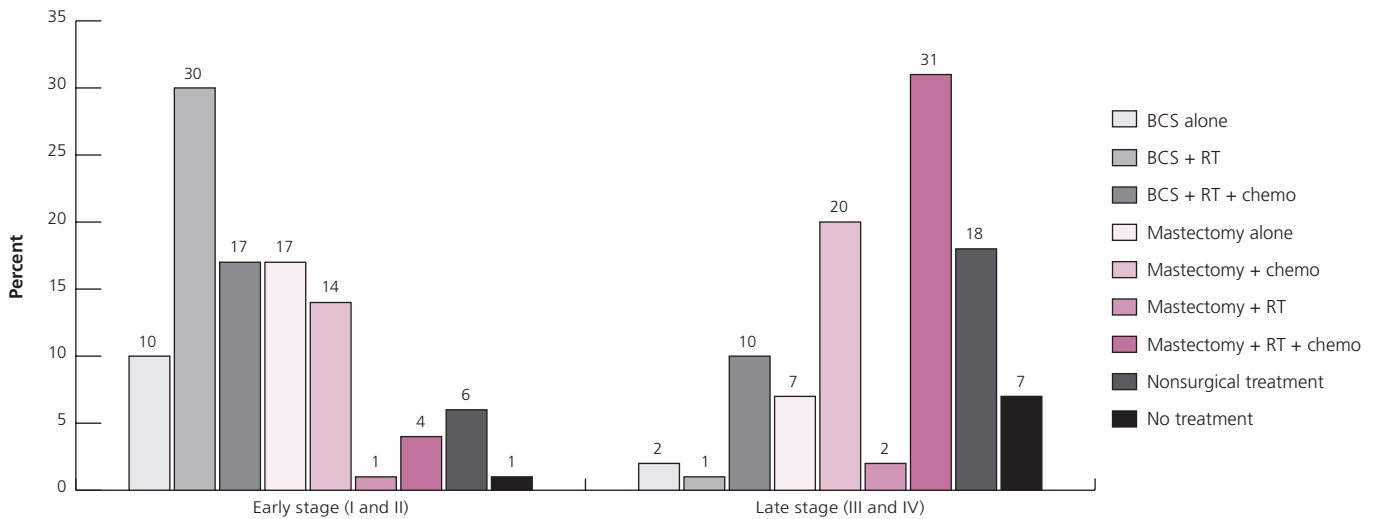
Both BCS and mastectomy are usually accompanied by removal of regional lymph nodes from the armpit to determine if the disease has spread beyond the breast. The presence of any cancer cells in the lymph nodes will help determine the need for subsequent therapy and the course it should take. Sentinel lymph node biopsy (SLNB), in which selected lymph nodes are removed and tested before any others are excised, reduces the need for full axillary lymph node dissections among most women with no evidence of sentinel lymph node involvement.<sup>208</sup> Furthermore, findings from a recent clinical trial suggest that for some breast cancer patients treated by lumpectomy and radiation, the axillary lymph node dissection can be avoided even if cancer cells are found in one or two sentinel lymph nodes.<sup>209</sup> Prior to surgery, patients should talk with their doctors to determine whether they intend to perform SLNB. If a woman is eligible for SLNB and wishes to have this procedure, her breast cancer surgery should be performed at a facility with a medical care team experienced with the technique. SLNB is widely available in the US.

Surgery and radiation therapy involving the axillary lymph nodes can lead to lymphedema, a serious swelling of the arm caused by retention of lymph fluid. Breast cancer patients who undergo axillary lymph node dissection are about 3 times more likely to develop lymphedema compared to those who have SLNB.<sup>210</sup> It has been estimated that about 5% of patients with SLNB and 16%-18% of patients undergoing axillary lymph node dissection following SLNB will develop clinically measurable lymphedema.<sup>211,212</sup> Some evidence suggests that upper body exercises may reduce the risk and lessen the severity of this condition.<sup>213</sup>

## Radiation therapy

Radiation therapy is the use of high-energy beams or particles to kill cancer cells. Radiation may be used after potentially curative surgery to destroy cancer cells remaining in the breast, chest wall, or underarm area. BCS is almost always followed by radiation therapy because it has been shown to reduce the risk of cancer recurrence by about 50% and the risk of breast cancer death by about 20%.<sup>214</sup> Although there is a higher risk of local recurrence (cancer returning to the breast) with BCS, clinical trials with more than 20 years of follow-up data have confirmed that a woman who chooses BCS and radiation will have the same expected long-term survival as if she had chosen mastectomy.<sup>215-217</sup> Some mastectomy patients also require radiation if their tumor is larger than 5 cm or when 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.

**Figure 10. Female Breast Cancer Treatment Patterns (%), by Stage, US, 2008**



BCS= breast conserving surgery; RT = radiation therapy; Chemo = chemotherapy and may include common targeted therapies.

**Source:** National Cancer Database, 2008.

American Cancer Society, Surveillance and Health Services Research, 2013

Radiation therapy may be administered internally or externally. Some patients are treated with both types of radiation in combination. The way the radiation therapy is given depends on the type, stage, and location of the tumor, as well as doctor and patient preference.

External beam radiation is the standard type of radiation for women with breast cancer. Radiation is focused from a machine outside the body on the area affected by cancer. This usually includes the whole breast and, depending on the size and extent of the cancer, may include the chest wall and underarm area as well. External beam radiation therapy is typically administered daily over a period of 5 to 6 weeks; however, in recent studies, shortening the treatment to 3 weeks (referred to as accelerated breast irradiation or ABI) appears to be just as effective.<sup>218</sup>

Internal radiation therapy, known as brachytherapy, is a form of accelerated partial breast irradiation (APBI) which uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The ability to target radiation therapy accurately has increased dramatically in recent decades, which has greatly diminished side effects and can also reduce treatment time.<sup>219</sup> For example, the most common form of brachytherapy used for breast cancer, intracavitary brachytherapy, is given for only 5 days.<sup>220,221</sup> However, a recent retrospective study reported that women who were treated with brachytherapy were more likely to have certain complications and receive a subsequent mastectomy than those treated with whole breast radiation therapy.<sup>222</sup> Additional follow-up data are needed to determine the long-term efficacy and risks associated with APBI and to identify which patients are the best candidates.

Clinical trials are also investigating other forms of APBI that are designed to give radiation to a smaller segment of the breast, also over a period of 5 days.<sup>223</sup>

## Systemic therapy

Systemic therapy is treatment that travels through the bloodstream and affects all parts of the body, not just the cancer. These cancer drugs are injected into a vein or given by mouth. Systemic therapy includes chemotherapy, hormone therapy, and targeted therapy, all of which work through different mechanisms. For example, chemotherapy drugs work by attacking cells that grow quickly, such as cancer cells. Hormone therapy works by either blocking the body's natural hormones or lowering the levels of those hormones, which sometimes act to promote cancer growth. Newer targeted drugs work by attacking specific parts of cancer cells.

When systemic treatment is given to patients before surgery, it is called neoadjuvant therapy. It is often used to shrink the tumor enough to make surgical removal possible or allow for less extensive surgery (such as BCS in women who would otherwise have required mastectomy). Neoadjuvant systemic therapy has been found to be as effective as therapy given after surgery in terms of survival, disease progression, and distant recurrence.<sup>224</sup>

Systemic treatment given to patients after surgery is called adjuvant therapy. It is used to kill any undetected tumor cells that were left behind during surgery or had migrated to other parts of the body. The use of adjuvant systemic therapy is primarily determined by the tumor stage and histopathological characteristics (hormone receptor and HER2 status).



Systemic therapy is the main treatment option for women with metastatic breast cancer who may not benefit from surgery due to the extensive spread of the disease.

## Chemotherapy

The benefit of chemotherapy is dependent on multiple factors, including the size of the cancer, the number of lymph nodes involved, the presence of estrogen or progesterone receptors, and the amount of HER2 protein made by the cancer cells. Basal-like and HER2-enriched breast cancers tend to be more sensitive to chemotherapy, while luminal A tumors are generally less responsive.<sup>225</sup>

Research has established that in most cases, combinations of drugs are more effective than one drug alone for breast cancer treatment. Many combinations are being used, and it is not clear that any single combination is the best. Depending on the combination of drugs used, chemotherapy is usually given for 3 to 6 months. Chemotherapy is most effective when the full dose and cycle of drugs are completed in a timely manner.

## Hormone therapy

Estrogen, a hormone produced by the ovaries, promotes the growth of many breast cancers. Women whose breast cancers test positive for estrogen or progesterone receptors can be given hormone therapy to lower estrogen levels or to block the effects of estrogen on the growth of breast cancer cells. Tamoxifen and toremifene (Fareston) are drugs that prevent estrogen from binding to breast cancer cells and are effective in both postmenopausal and premenopausal women. Treatment of ER+ breast cancer with tamoxifen for 5 years has been shown to reduce the rate of recurrence by 39% throughout the first decade, and reduces breast cancer mortality by about one-third throughout the first 15 years.<sup>226</sup> Recently released results of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) study showed that extended use of tamoxifen (10 years versus 5 years) may further reduce the risk of breast cancer recurrence and mortality.<sup>227</sup> Fulvestrant (Faslodex) is a newer drug (given by injection once a month) that blocks estrogen binding and then reduces the number of estrogen receptors on breast tumors. It is often effective in postmenopausal women even if the breast cancer is no longer responding to tamoxifen.

Premenopausal women with hormone-sensitive tumors may also benefit from the removal or suppression of the ovaries (ovarian ablation), which are the main source of estrogen prior to menopause. Ovarian ablation may also allow some other hormone therapies to work better.<sup>228</sup> Permanent ovarian ablation can be done by surgically removing the ovaries (oophorectomy). More often, potentially reversible ovarian ablation is achieved with a class of drugs called luteinizing hormone-releasing hormone (LHRH) analogs (e.g., goserelin [Zoladex] or leuprolide [Lupron]). Studies have shown that the addition of these drugs

to tamoxifen and/or chemotherapy reduces the risk of breast cancer recurrence and death among premenopausal women with early stage, hormone-sensitive breast cancer.<sup>229</sup>

Aromatase inhibitors (AIs), such as letrozole, anastrozole, and exemestane, are another class of drugs that are used to treat both early and advanced hormone receptor positive breast cancer in postmenopausal women. They work by interfering with the body's ability to produce estrogen. AIs are not usually an effective treatment in women with functioning ovaries (including premenopausal women). Clinical trials have demonstrated a clear advantage to using either an AI instead of tamoxifen for a total of 5 years or switching to an AI after at least 2 to 3 years of tamoxifen, compared to tamoxifen alone for 5 years.<sup>230</sup>

In 2010, clinical guidelines were issued recommending that AIs be included in the treatment of postmenopausal women with hormone receptor positive breast cancer.<sup>231</sup> Clinical trials continue to assess the optimal timing and duration of treatment. Although AIs have fewer serious side effects than tamoxifen, they can cause osteoporosis (with resulting bone fractures), joint pain, and other musculoskeletal symptoms because they completely deplete postmenopausal women of estrogen.

## Targeted therapy

### Therapy aimed at HER2

Approximately 15% to 20% of breast cancers overproduce the growth-promoting protein HER2.<sup>12</sup> These tumors tend to grow faster and are generally more likely to recur than tumors that do not overproduce HER2. Trastuzumab (Herceptin) is a monoclonal antibody that directly targets the HER2 protein. The combined results of two large trials indicate that adding trastuzumab to standard chemotherapy for early stage HER2-positive breast cancer reduces the risk of recurrence and death by 52% and 33%, respectively, compared to chemotherapy alone.<sup>232</sup> This drug is also a standard part of the treatment for advanced (metastatic) HER2-positive breast cancer. In 2006, the US Food and Drug Administration (FDA) approved trastuzumab for all HER2-positive breast cancers. All invasive breast cancers should be tested for the HER2 gene amplification or protein overexpression in order to identify women who would benefit from this therapy. Guidelines were released in 2007 aimed at improving the accuracy of HER2 testing.<sup>233</sup>

Like trastuzumab, pertuzumab is a monoclonal antibody that attaches to the HER2 protein, though it seems to target a different location. This drug is used to treat HER2-positive, metastatic breast cancer. When given along with docetaxel (Taxotere) and trastuzumab to patients who have not yet received chemotherapy, it has been shown to cause tumors to shrink or stop growing for about 6 months longer than giving docetaxel and trastuzumab alone.<sup>234</sup>

Another drug, ado-trastuzumab emtansine (Kadcyla, formerly called TDM-1), was recently approved by the FDA to treat HER2-positive metastatic breast cancer, and has been shown to shrink tumors and extend survival. It is made up of the same monoclonal antibody found in trastuzumab attached to a chemotherapy drug known as DM-1. The antibody acts as a homing device, taking the chemotherapy drug directly to the cancer cells.<sup>235</sup>

Lapatinib (Tykerb) is another drug that has been found to be effective in delaying disease progression in women with HER2-positive advanced breast cancers that have become resistant to trastuzumab.<sup>236</sup>

### Other targeted drugs

Everolimus (Afinitor) is a type of targeted therapy that blocks mTOR, a protein that promotes cell growth and division. By blocking this protein, everolimus can help stop cancer cells from growing. Everolimus may also stop tumors from developing new blood vessels, which can also limit growth. This drug seems to improve the effectiveness of hormone therapy drugs in treating breast cancer. Everolimus was recently approved to treat advanced, hormone receptor-positive, HER2-negative breast cancer in postmenopausal women. It is meant to be used with exemestane in those women whose cancers have grown while they were being treated with either letrozole or anastrozole. Everolimus is also being studied in combination with other hormone therapy drugs.<sup>237,238</sup>

### Clinical trials

A clinical trial is an experiment that is used to assess the safety and efficacy of treatments or other interventions for human disease and health problems. Generally, participants receive either the state-of-the-art standard treatment or a new therapy that may offer improved survival and/or fewer side effects. Participation in clinical trials provides essential information on the effectiveness and risks of a new treatment. For more information about clinical trials, including how to enroll, call the American Cancer Society at 1-800-303-5691 or visit [cancer.org/clinicaltrials](http://cancer.org/clinicaltrials). Information can also be obtained by visiting the National Cancer Institute's Web site at [cancer.gov/clinicaltrials](http://cancer.gov/clinicaltrials) or by calling 1-800-4-CANCER. Patients should consult their personal doctors and cancer specialists for detailed information about appropriate treatment options.

Bevacizumab (Avastin) is a drug that targets the vascular endothelial growth factor (VEGF) protein, which helps tumors form new blood vessels. After granting accelerated approval of bevacizumab (Avastin) for the treatment of HER2-negative, metastatic breast cancer in 2008, the FDA revoked approval of the drug in November 2011 based on subsequent studies that demonstrated minimal benefit combined with some potentially dangerous side effects.

## What is the American Cancer Society doing about breast cancer?

The American Cancer Society works relentlessly to save lives from breast cancer by helping people stay well and get well, by finding cures, and by fighting back against the disease. This section provides highlights and information on some of these efforts.

### Stay Well and Get Well

The American Cancer Society helps women stay well by encouraging them to take steps to reduce the risk of breast cancer or detect it early, when there are more treatment options. For women who are diagnosed with breast cancer, the Society provides the information, day-to-day help, and emotional support to guide them through every step of their experience and to help them get well.

### Information, 24 Hours a Day, Seven Days a Week

Help and information are available 24 hours a day, seven days a week online at [cancer.org](http://cancer.org) and by calling the American Cancer Society at 1-800-227-2345. Callers are connected with a Cancer Information Specialist who can help them locate a hospital,

understand breast cancer and treatment options, learn what to expect and how to plan, address insurance concerns, find financial resources, find a local support group, and more. The Society can also help people who speak languages other than English or Spanish find the assistance they need, offering services in 150 languages in total.

Information on every aspect of the breast cancer experience, from prevention to survivorship, is also available at [cancer.org/breastcancer](http://cancer.org/breastcancer). The Society also publishes 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. A complete list of Society books is available for order at [cancer.org/bookstore](http://cancer.org/bookstore).

### Day-to-day Help and Emotional Support

The American Cancer Society offers patients and their families the resources they need to guide them through every step of the breast cancer experience so they can focus on getting well.

## Breast cancer support

Breast cancer survivors provide one-on-one support, information, and inspiration to help people facing the disease cope with breast cancer through the American Cancer Society Reach To Recovery® program. Volunteer survivors are trained to respond in person or by telephone to people facing breast cancer diagnosis, treatment, recurrence, or recovery.

## Support during treatment

When women are in active breast cancer treatment, they want to look their best, and Look Good Feel Better® helps them do just that. The free program, which is a collaboration of the American Cancer Society, the Personal Care Products Council Foundation, and the Professional Beauty Association, helps women learn beauty techniques to restore their self-image and cope with appearance-related side effects of breast cancer treatment. Certified beauty professionals, trained as Look Good Feel Better volunteers, provide tips on makeup, skin care, nail care, and head coverings. Information and materials are also available for men and teens.

## Transportation to treatment

Breast cancer patients cite transportation to and from treatment as a critical need, second only to direct financial assistance. The American Cancer Society Road To Recovery® program matches these patients with specially trained volunteer drivers. In addition, the program offers patients the benefit of companionship and moral support during the drive to medical appointments. In those cases where a Road To Recovery driver isn't available, the Society may be able to provide other transportation assistance.

## Lodging during treatment

When a woman diagnosed with breast cancer must travel away from home for the best treatment, where to stay and how to afford accommodations are immediate concerns and can sometimes affect treatment decisions. American Cancer Society Hope Lodge® facilities provide free, home-like temporary lodging for patients and their caregivers close to treatment centers, thereby easing the emotional and financial burden of finding affordable lodging.

## Finding hope and inspiration

Women with breast cancer and their loved ones do not have to face their cancer experience alone. They can connect with others who have "been there" through the American Cancer Society Cancer Survivors Network®. The online community is a welcoming and safe place that was created by and for cancer survivors and their families.

## Hair-loss and mastectomy products

Some women wear wigs, hats, breast forms, and bras to help cope with the effects of mastectomy and hair loss. The American Cancer Society "tlc" *Tender Loving Care*®, which is a magazine and catalog in one, offers helpful articles and a line of products to help

women battling cancer restore their appearance and dignity at a difficult time. All proceeds from product sales go back into the Society's programs and services for patients and survivors.

## Cancer education materials

Women with breast cancer and their caretakers need help coping with the challenges of living with the disease. Doctors, nurses, social workers, and other health care professionals can help guide patients and their families through their cancer journey using the American Cancer Society I Can Cope® educational materials. Free classes are also available online at [cancer.org/onlineclasses](http://cancer.org/onlineclasses).

## 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* guide may help cancer survivors as they begin the next phase of their journey. The free guide can be downloaded at [cancer.org/survivorshipguide](http://cancer.org/survivorshipguide).

## Find Cures

The American Cancer Society, the largest nongovernmental, not-for-profit funding source of cancer research and training in the United States, invests more in breast cancer research than any other cancer type. From 1971 to 2010, the Society awarded approximately \$450.7 million in research and training grants associated with the disease. Recently, the Society changed how it reports dollars committed to funding research and training by cancer types. Since 2011, the Society has awarded \$46.4 million in breast cancer research and training grants. Society-funded research has led to the development of lifesaving breast cancer drugs such as tamoxifen and Herceptin, as well as the discovery of genes linked to breast cancer (e.g., *BRCA1*).

The Society is currently funding \$86 million in breast cancer research through 220 research and training grants. These grants are awarded in multiple areas relevant to the disease, including genetics, etiology, diagnostics (imaging and biomarkers), drug development; and preclinical, clinical, and epidemiological studies in prevention, diagnosis, treatment, and quality of life.

Specific examples of ongoing breast cancer research being conducted by Society grantees include:

- Establishing an animal model for triple negative breast cancers that are resistant to chemotherapy in order to evaluate new targeted therapies
- Identifying the unmet needs of African American breast cancer survivors in order to develop a program to support and assist in meeting those unique needs
- Evaluating whether known genetic factors for established risk factors, such as age at menarche and height, are associated with breast cancer risk



- Identifying factors associated with joint pain resulting from aromatase inhibitor therapy and investigating ways that it can be effectively managed
- Exploring new therapies for the treatment of breast cancer that activate cells of the immune system and evaluating whether the immune system plays a role in inflammatory responses that promote cancer progression
- Evaluating factors that influence mammography interpretation by radiologists, developing a test set that identifies radiologists who could benefit from additional training, and creating a continuing medical education course that reduces recall rates while maintaining or improving cancer detection. This project, co-funded by the National Cancer Institute, was designed in direct response to the Institute of Medicine's report "Improving Breast Imaging Quality Standards," which highlighted the need to decrease variability in mammography interpretation in the US and identified issues stalling the reauthorization of the Mammography Quality Standards Act.

The Society also internally conducts epidemiologic studies of breast cancer and performs surveillance research to monitor racial and socioeconomic disparities in breast cancer screening, incidence, survival, and mortality. Using information collected from more than 600,000 women in the Cancer Prevention Study II (CPS-II), American Cancer Society epidemiologists study the influence of many risk factors, including alcohol consumption, diethylstilbestrol (DES), estrogen hormone use, family history of cancer, obesity, smoking, and spontaneous abortion on the risk of death from breast cancer. Recently published papers have also examined the effect of smoking, weight loss, and vitamin D levels on breast cancer risk. The Society is enrolling cancer-free adults in the Cancer Prevention Study-3 (CPS-3) through December 2013, with the goal of 300,000 participants. This multiyear survey will study lifestyle, behavioral, environmental, and genetic factors that may cause or prevent cancer, with the ultimate goal of eliminating cancer as a major health problem for this and future generations.

American Cancer Society epidemiologists have also studied the influence of mammography on breast cancer prognostic factors, conducted long-term follow up of major breast cancer screening studies, modeled the cost-effectiveness of chemoprevention strategies, and recommended breast cancer surveillance strategies that can be applied at the local and national levels.

The Society's Behavioral Research Center is currently conducting a study of survivors of 10 cancers, including breast cancer, to examine the determinants of good quality of life. Specific areas of research include healthy lifestyle behaviors (e.g., diet, physical activity, and smoking), body image issues, sexuality and intimacy, and overall quality of life among breast cancer survivors and their caregivers. One recent analysis of this survey found that although the majority of breast cancer survivors 70 years of age and older

were reportedly doing well, a subset of survivors had ongoing concerns about symptoms, comorbidities, emotional health, and the lack of social support.

The Society's Surveillance and Health Services Research group recently reported that breast cancer incidence rates have stabilized among white women in the US, following the sharp drop in rates related to declines in use of menopausal hormones. Another study found that breast cancer ER status varies among African American women depending on region of birth, with higher rates found among Western African-born and Jamaican-born African Americans compared to Eastern African-born African American women. This group also published findings that African American breast cancer patients are less likely than whites to receive recommended breast cancer care, even after controlling for insurance and socioeconomic factors.

## Fight Back

The American Cancer Society and its nonprofit, nonpartisan advocacy affiliate, the American Cancer Society Cancer Action Network<sup>SM</sup> (ACS CAN), are involved in advocacy efforts at both the federal and state levels that seek to increase access to quality breast cancer screenings, diagnostic services and treatment, 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. Below are some of the efforts that the Society and ACS CAN have been involved with in the past few years to fight back against breast cancer – and all cancers:

- **Improving Access to Affordable Care through Health Care Reform:** The Affordable Care Act (ACA) was signed into law on March 23, 2010, giving cancer patients access to quality, affordable health care. As of 2011, all new health insurance plans and Medicare are required to cover preventive services rated "A" or "B" by the US Preventive Services Task Force (USPSTF), including mammography screening, at no cost to patients. This requirement will be extended in 2014 to cover all insurance companies enrolled in state health insurance exchanges and individuals newly covered through the ACA's expansion of Medicaid.
- **The National Breast and Cervical Cancer Early Detection Program (NBCCEDP):** Protecting and increasing funding for the NBCCEDP is a high priority for the Society and ACS CAN at both the state and federal levels. This successful program provides community-based breast and cervical cancer screenings to low-income, uninsured, and underinsured women. More than 50% of the women screened are from racial/ethnic minority groups. While the Affordable Care Act will greatly improve insurance coverage, the NBCCEDP will remain an essential program for our nation's most vulnerable populations. Unfortunately, funding has been cut for the program. In 2013, federal funding was reduced by 10% compared to 2012 due to sequestration and other federal funding cuts,

which will result in tens of thousands of fewer cancer screenings. ACS CAN is asking Congress to increase funding to the full \$275 million the program was authorized for in 2007 to ensure that more women have access to cancer screening.

- **Protecting the Breast and Cervical Cancer Prevention and Treatment Act:** This act ensures that low-income women diagnosed with cancer through the NBCCEDP are eligible for Medicaid coverage for treatment. ACS CAN continues to advocate at the state level to protect Medicaid dollars so that there is sufficient funding for treatment of these women.
- **Patient Navigation:** Patient navigation is a critical component in reducing breast cancer deaths and improving quality of care, particularly in vulnerable populations. ACS CAN supports the Patient Navigation Assistance Act, which would create a coverage solution that incentivizes providers to use patient navigators; the end result will be better team-based care coordination for patients with cancer and other chronic illnesses. The organization also supports funding for patient navigator programs and is working with Congress and federal agencies to help increase funding for grant programs for patient navigation.
- **Funding for Cancer Research:** The Society and ACS CAN continue 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.

## Additional Resources

### ABCD After Breast Cancer Diagnosis

Toll-free number: 1-800-977-4121

Web site: [abcdbreastcancersupport.org](http://abcdbreastcancersupport.org)

ABCD provides free, personalized information and one-to-one support to people affected by breast cancer – patients, families, and friends.

### Living Beyond Breast Cancer

Toll-free number: 1-888-753-5222

Web site: [lbbc.org](http://lbbc.org)

This nonprofit organization is dedicated to empowering all women affected by breast cancer to live as long as possible with the best quality of life.

### National Breast and Cervical Cancer Early Detection Program

Toll-free number: 1-800-CDC-INFO or 1-800-232-4636

Web site: [cdc.gov/cancer/nbccedp/](http://cdc.gov/cancer/nbccedp/)

This Centers for Disease Control and Prevention (CDC) program helps low-income women gain access to timely, high-quality screening programs for the detection of breast and cervical cancer.

### Sisters Network

Toll-free number: 1-866-781-1808

Web site: [sistersnetworkinc.org](http://sistersnetworkinc.org)

This national African American breast cancer survivor's support group is committed to increasing local and national attention to the devastating impact that breast cancer has in the African American community.

## Sources of Statistics

**General information.** Unless otherwise stated, the statistics and statements in this booklet refer to invasive (not in situ) breast cancer.

**Estimated new cancer cases.** The estimated numbers of new US cancer cases are projected using a spatiotemporal model based on incidence data from 49 states and the District of Columbia for the years 1995-2009 that met the North American Association of Central Cancer Registries' (NAACCR) high-quality data standard for incidence, which covers about 98% of the US population. This method considers geographic variations in sociodemographic and lifestyle factors, medical settings, and cancer screening behaviors as predictors of incidence, as well as accounting for expected delays in case reporting.

**Incidence rates.** Incidence rates are defined as the number of people per 100,000 who develop a disease during a given time period. Breast cancer incidence rates for the US in the most recent time period were calculated using data on cancer cases collected

by the North American Association of Central Cancer Registries (NAACCR) and population data collected by the US Census Bureau. When referenced as such, NAACCR incidence data were made available on the NAACCR Web site ([naaccr.org](http://naaccr.org)) and within the Cancer in North America publications.<sup>15,239</sup> Long-term incidence trends are based on American Cancer Society analysis of the SEER 9 Registries Public Use Dataset, 1973-2010, November 2012 submission, using SEER\*Stat 8.0.4, a statistical software package from the National Cancer Institute. Short-term trends (2006-2010) are based on incidence rates from the SEER 13 registries. When referenced as such, US SEER incidence rates and trends were previously made available on SEER's Web site ([seer.cancer.gov](http://seer.cancer.gov)) and within the *SEER Cancer Statistics Review 1975-2010*.<sup>14</sup>

Note that because of delays in reporting newly diagnosed cancer cases to the cancer registries, cancer incidence rates for the most recent diagnosis years may be underestimated. Incidence rates adjusted for delays in reporting are used when available and are referenced as such.

**Estimated cancer deaths.** The estimated number of breast cancer deaths in the US is calculated by fitting the numbers of breast cancer deaths for 1995-2009 to a statistical model that forecasts the numbers of deaths expected to occur in 2013. Data on the number of deaths are obtained from the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention.

**Mortality rates.** Similar to incidence rates, mortality rates are defined as the number of people per 100,000 who die from a disease during a given time period. Death rates used in this publication were previously made available by SEER on their Web site ([seer.cancer.gov](http://seer.cancer.gov)) and within the *SEER Cancer Statistics Review 1975-2010*.<sup>14</sup> Death rates were calculated using data on cancer deaths compiled by NCHS and population data collected by the US Census Bureau. All death rates in this publication were age-adjusted to the 2000 US standard population.

**Survival.** Five-year survival statistics are based on cancer patients diagnosed during 2003-2009; 10-year survival rates are based on diagnoses during 1997-2009; and 15-year survival rates are based on diagnoses during 1992-2009. All patients were followed through 2010. Relative survival rates are used to adjust for normal life expectancy (and events such as death from heart disease, accidents, and diseases of old age). Relative survival is calculated by dividing the percentage of observed 5-year survival for cancer patients by the 5-year survival expected for people in the general population who are similar to the patient group with respect to age, sex, race, and calendar year of observation. Relative survival rates are not calculated for Hispanics/Latinas, Asians/Pacific Islanders, and American Indians/Alaska Natives because reliable estimates of normal life expectancy are

not available for these groups; therefore, cause-specific survival rates are presented. Cause-specific survival rates are the probability of not dying of breast cancer within 5 years after diagnosis. Cause-specific survival does not account for stage and age at diagnosis. When referenced as such, 5-year survival statistics were originally published in *SEER Cancer Statistics Review, 1975-2010*.<sup>14</sup>

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

**Screening.** Prevalence estimates of mammography by age and state were obtained through analysis of data from the Behavioral Risk Factor Surveillance System (BRFSS). The BRFSS is an ongoing system of surveys conducted by the state health departments in cooperation with the Centers for Disease Control and Prevention. Prevalence estimates of mammography by race/ethnicity, poverty, and other demographic factors are from the National Health Interview Survey.

**Important note about estimated cases and deaths.** The projected number of new cancer cases and deaths for the current year is model-based and may produce numbers that vary considerably from year to year. For this reason, we discourage the use of our estimates to track cancer trends. Incidence and mortality rates reported by SEER and NCHS are the conventional statistics used to tracking cancer incidence and mortality trends for the US. Rates from state cancer registries are useful for tracking local trends.

## References

1. Allred DC. Ductal carcinoma in situ: terminology, classification, and natural history. *J Natl Cancer Inst Monogr*. 2010;2010(41):134-8.
2. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst*. May 15 2013;105(10):701-10.
3. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FG, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
4. Young JL Jr, Roffers SD, Ries LAG, Fritz AG, Hurlbut A, eds. *SEER Summary Staging Manual - 2001: Codes and Coding Instructions*. Bethesda, MD: National Cancer Institute; 2001. NIH Pub. No. 01-4969.
5. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. Aug 17 2000;406(6797):747-52.
6. Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification, prognostication, and prediction. *Lancet*. Nov 19 2011; 378(9805):1812-23.
7. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. Aug 2011;22(8):1736-47.
8. Perou CM, Borresen-Dale AL. Systems biology and genomics of breast cancer. *Cold Spring Harb Perspect Biol*. Feb 2011;3(2).
9. Blows FM, Driver KE, Schmidt MK, et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. *PLoS Med*. May 2010;7(5):e1000279.
10. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol*. Apr 1 2010;28(10):1684-91.
11. Cheang MC, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst*. May 20 2009;101(10):736-50.



12. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. Jun 7 2006; 295(21):2492-502.
13. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*. Jul-Aug 2012;62(4):220-41.
14. Howlader N, Noone AM, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2010. Bethesda, MD: National Cancer Institute; 2013. [http://seer.cancer.gov/csr/1975\\_2010/](http://seer.cancer.gov/csr/1975_2010/), based on November 2012 SEER data submission.
15. Copeland G, Lake A, Firth R, et al., eds. *Cancer in North America: 2006-2010. Volume One: Combined Cancer Incidence for the United States, Canada and North America*. Springfield, IL: North American Association of Central Cancer Registries, Inc; 2013.
16. Breen N, Gentleman JF, Schiller JS. Update on mammography trends: comparisons of rates in 2000, 2005, and 2008. *Cancer*. May 15 2011; 117(10):2209-18.
17. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. Apr 19 2007; 356(16):1670-4.
18. 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*. Jan 2010;21(1):83-90.
19. DeSantis C, Howlader N, Cronin KA, Jemal A. Breast cancer incidence rates in US women are no longer declining. *Cancer Epidemiol Biomarkers Prev*. Feb 28 2011.
20. Parkin DM. Is the recent fall in incidence of post-menopausal breast cancer in UK related to changes in use of hormone replacement therapy? *Eur J Cancer*. Jun 2009;45(9):1649-53.
21. Antoine C, Ameye L, Paesmans M, Rozenberg S. Update of the evolution of breast cancer incidence in relation to hormone replacement therapy use in Belgium. *Maturitas*. Aug 2012;72(4):317-23.
22. Hemminki E, Kyyronen P, Pukkala E. Postmenopausal hormone drugs and breast and colon cancer: Nordic countries 1995-2005. *Maturitas*. Dec 20 2008;61(4):299-304.
23. Canfell K, Banks E, Moa AM, Beral V. Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Aust*. Jun 2 2008;188(11):641-4.
24. De P, Neutel CI, Olivotto I, Morrison H. Breast cancer incidence and hormone replacement therapy in Canada. *J Natl Cancer Inst*. Oct 6 2010;102(19):1489-95.
25. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. Oct 27 2005;353(17):1784-92.
26. Menashe I, Anderson WF, Jatoi I, Rosenberg PS. Underlying causes of the black-white racial disparity in breast cancer mortality: a population-based analysis. *J Natl Cancer Inst*. Jul 15 2009;101(14):993-1000.
27. Jatoi I, Becher H, Leake CR. Widening disparity in survival between white and African-American patients with breast carcinoma treated in the U. S. Department of Defense Healthcare system. *Cancer*. Sep 1 2003;98(5):894-9.
28. Anderson WF, Devesa SS. Breast carcinoma in men. *Cancer*. Jan 15 2005;103(2):432-3; author reply 33.
29. Goodman MT, Tung KH, Wilkens LR. Comparative epidemiology of breast cancer among men and women in the US, 1996 to 2000. *Cancer Causes Control*. Mar 2006;17(2):127-36.
30. Ruddy KJ, Winer EP. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. *Ann Oncol*. Jun 2013;24(6):1434-43.
31. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. *Semin Oncol*. Jun 2009;36(3):237-49.
32. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. *PLoS One*. 2009;4(11):e7695.
33. Sprague BL, Trentham-Dietz A, Gangnon RE, et al. Socioeconomic status and survival after an invasive breast cancer diagnosis. *Cancer*. Apr 1 2011;117(7):1542-51.
34. Halpern MT, Bian J, Ward EM, Schrag NM, Chen AY. Insurance status and stage of cancer at diagnosis among women with breast cancer. *Cancer*. Jun 11 2007.
35. Harper S, Lynch J, Meersman SC, Breen N, Davis WW, Reichman MC. Trends in area-socioeconomic and race-ethnic disparities in breast cancer incidence, stage at diagnosis, screening, mortality, and survival among women ages 50 years and over (1987-2005). *Cancer Epidemiol Biomarkers Prev*. Jan 2009;18(1):121-31.
36. Curtis E, Quale C, Haggstrom D, Smith-Bindman R. Racial and ethnic differences in breast cancer survival: how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics? *Cancer*. Jan 1 2008;112(1):171-80.
37. Baquet CR, Mishra SI, Commiskey P, Ellison GL, DeShields M. Breast cancer epidemiology in blacks and whites: disparities in incidence, mortality, survival rates and histology. *J Natl Med Assoc*. May 2008;100(5):480-8.
38. Newman LA, Griffith KA, Jatoi I, Simon MS, Crowe JP, Colditz GA. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. *J Clin Oncol*. Mar 20 2006;24(9):1342-9.
39. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA*. Oct 12 2005;294(14):1765-72.
40. Smedley B, Stith A, Nelson A, eds. *Unequal treatment: confronting racial and ethnic disparities in health care*. Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. Institute of Medicine, Washington, DC: National Academy Press; 2002.
41. Fedewa SA, Edge SB, Stewart AK, Halpern MT, Marlow NM, Ward EM. Race and ethnicity are associated with delays in breast cancer treatment (2003-2006). *J Health Care Poor Underserved*. 2011;22(1):128-41.
42. DeSantis C, Jemal A, Ward E. Disparities in breast cancer prognostic factors by race, insurance status, and education. *Cancer Causes Control*. Sep 2010;21(9):1445-50.
43. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. Jan-Feb 2012;62(1):30-67.
44. 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*. Oct 27 2001;358(9291):1389-99.
45. Schwartz GF, Hughes KS, Lynch HT, et al. Proceedings of the international consensus conference on breast cancer risk, genetics, & risk management, April, 2007. *Cancer*. Nov 15 2008;113(10):2627-37.
46. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*. May 2003;72(5):1117-30.
47. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*. Apr 10 2007;25(11):1329-33.

48. Turnbull C, Rahman N. Genetic predisposition to breast cancer: past, present, and future. *Annu Rev Genomics Hum Genet.* 2008;9:321-45.
49. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med.* Jul 13 2000;343(2):78-85.
50. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol.* Feb 10 2010;28(5):893-901.
51. U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. *Ann Intern Med.* Sep 6 2005;143(5):355-61.
52. American Cancer Society. *Cancer Facts & Figures 2009.* Atlanta, GA: American Cancer Society, 2009.
53. Schottenfeld D, Beebe-Dimmer J. Multiple Primary Cancers. In: Schottenfeld D, Fraumeni JF, Jr., eds. *Cancer Prevention and Early Detection Third Edition.* New York: Oxford University Press; 2006:1269-80.
54. Kilbride KE, Newman LA. Chapter 25: Lobular carcinoma in situ: Clinical management. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast.* 4th ed: Lippincott Williams & Wilkins; 2010.
55. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med.* Jul 21 2005;353(3):229-37.
56. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. *JAMA.* Feb 19 1992;267(7):941-4.
57. Wang J, Costantino JP, Tan-Chiu E, Wickerham DL, Paik S, Wolmark N. Lower-category benign breast disease and the risk of invasive breast cancer. *J Natl Cancer Inst.* Apr 21 2004;96(8):616-20.
58. Kabat GC, Jones JG, Olson N, et al. A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer. *Cancer Causes Control.* Jun 2010;21(6):821-8.
59. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* Aug 1 2007;99(15):1178-87.
60. Boyd NF, Dite GS, Stone J, et al. Heritability of mammographic density, a risk factor for breast cancer. *N Engl J Med.* Sep 19 2002;347(12):886-94.
61. Ursin G, Lillie EO, Lee E, et al. The relative importance of genetics and environment on mammographic density. *Cancer Epidemiol Biomarkers Prev.* Jan 2009;18(1):102-12.
62. Harris HR, Tamimi RM, Willett WC, Hankinson SE, Michels KB. Body size across the life course, mammographic density, and risk of breast cancer. *Am J Epidemiol.* Oct 15 2011;174(8):909-18.
63. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. *Breast Cancer Res.* 2011;13(6):223.
64. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med.* Jan 18 2007;356(3):227-36.
65. Cummings SR, Tice JA, Bauer S, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *J Natl Cancer Inst.* Mar 18 2009;101(6):384-98.
66. Brower V. Breast density legislation fueling controversy. *J Natl Cancer Inst.* Apr 17 2013;105(8):510-1.
67. Fuhrman BJ, Schairer C, Gail MH, et al. Estrogen metabolism and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* Feb 22 2012;104(4):326-39.
68. Key TJ. Endogenous oestrogens and breast cancer risk in premenopausal and postmenopausal women. *Steroids.* Jul 2011;76(8):812-5.
69. Hankinson SE, Eliassen AH. Endogenous estrogen, testosterone and progesterone levels in relation to breast cancer risk. *J Steroid Biochem Mol Biol.* Aug-Sep 2007;106(1-5):24-30.
70. Endogenous Hormones Breast Cancer Collaborative Group, Key TJ, Appleby PN, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. *Br J Cancer.* Aug 23 2011;105(5):709-22.
71. Zeleniuch-Jacquotte A, Afanasyeva Y, Kaaks R, et al. Premenopausal serum androgens and breast cancer risk: a nested case-control study. *Breast Cancer Res.* 2012;14(1):R32.
72. Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA. Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. *Breast Cancer Res.* 2010;12(6):R98.
73. Kaaks R, Berrino F, Key T, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst.* May 18 2005;97(10):755-65.
74. Walker K, Bratton DJ, Frost C. Premenopausal endogenous oestrogen levels and breast cancer risk: a meta-analysis. *Br J Cancer.* Oct 25 2011;105(9):1451-7.
75. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev.* 1993;15(1):36-47.
76. 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.* Nov 2012;13(11):1141-51.
77. Lambe M, Hsieh C, Trichopoulos D, Ekblom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. *N Engl J Med.* Jul 7 1994;331(1):5-9.
78. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst.* Feb 2 2011;103(3):250-63.
79. Phipps AI, Buist DS, Malone KE, et al. Reproductive history and risk of three breast cancer subtypes defined by three biomarkers. *Cancer Causes Control.* Mar 2011;22(3):399-405.
80. Faupel-Badger JM, Arcaro KF, Balkam JJ, et al. Postpartum remodeling, lactation, and breast cancer risk: summary of a National Cancer Institute-sponsored workshop. *J Natl Cancer Inst.* Feb 6 2013;105(3):166-74.
81. 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.* Jul 20 2002;360(9328):187-95.
82. 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.* Apr 2011;126(3):679-86.
83. Chen Z, Arendell L, Aickin M, Cauley J, Lewis CE, Chlebowski R. Hip bone density predicts breast cancer risk independently of Gail score: results from the Women's Health Initiative. *Cancer.* Sep 1 2008;113(5):907-15.
84. Zhang Y, Kiel DP, Kreger BE, et al. Bone mass and the risk of breast cancer among postmenopausal women. *N Engl J Med.* Feb 27 1997;336(9):611-7.
85. Zmuda JM, Cauley JA, Ljung BM, Bauer DC, Cummings SR, Kuller LH. Bone mass and breast cancer risk in older women: differences by stage at diagnosis. *J Natl Cancer Inst.* Jun 20 2001;93(12):930-6.
86. 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.* Mar 2 2005;97(5):368-74.

87. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. Jul 17 2002;288(3):321-33.
88. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. Oct 20 2010;304(15):1684-92.
89. Beral V, Reeves G, Bull D, Green J. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst*. Feb 16 2011;103(4):296-305.
90. Chlebowski RT, Anderson GL. The influence of time from menopause and mammography on hormone therapy-related breast cancer risk assessment. *J Natl Cancer Inst*. Feb 16 2011;103(4):284-5.
91. Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol*. May 15 2008;167(10):1207-16.
92. Calle EE, Feigelson HS, Hildebrand JS, Teras LR, Thun MJ, Rodriguez C. Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. *Cancer*. Jan 20 2009;115(5):936-45.
93. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol*. May 2012;13(5):476-86.
94. Bakken K, Fournier A, Lund E, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. Jan 1 2011;128(1):144-56.
95. World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition, physical activity, and the prevention of cancer: a global perspective*. Washington, DC: AICR, 2007.
96. La Vecchia C, Giordano SH, Hortobagyi GN, Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. *Oncologist*. 2011;16(6):726-9.
97. Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer*. Oct 23 2012;107(9):1608-17.
98. Goodwin PJ, Thompson AM, Stambolic V. Diabetes, metformin, and breast cancer: lilac time? *J Clin Oncol*. Aug 10 2012;30(23):2812-4.
99. Nelson HD, Zakher B, Cantor A, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Ann Intern Med*. May 1 2012;156(9):635-48.
100. Ritte R, Lukanova A, Berrino F, et al. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. *Breast Cancer Res*. 2012;14(3):R76.
101. Rose DP, Vona-Davis L. Interaction between menopausal status and obesity in affecting breast cancer risk. *Maturitas*. May 2010;66(1):33-8.
102. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA*. Jul 12 2006;296(2):193-201.
103. Teras LR, Goodman M, Patel AV, Diver WR, Flanders WD, Feigelson HS. Weight loss and postmenopausal breast cancer in a prospective cohort of overweight and obese US women. *Cancer Causes Control*. Apr 2011;22(4):573-9.
104. Wolin KY, Colditz GA. Can weight loss prevent cancer? *Br J Cancer*. Oct 7 2008;99(7):995-9.
105. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. *Arch Intern Med*. Oct 25 2010;170(19):1758-64.
106. Peters TM, Schatzkin A, Gierach GL, et al. Physical activity and postmenopausal breast cancer risk in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev*. Jan 2009;18(1):289-96.
107. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. *Br J Sports Med*. Aug 2008;42(8):636-47.
108. 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*. Jan 2009;18(1):11-27.
109. Vera-Ramirez L, Ramirez-Tortosa MC, Sanchez-Rovira P, et al. Impact of diet on breast cancer risk: a review of experimental and observational studies. *Crit Rev Food Sci Nutr*. 2013;53(1):49-75.
110. Thomson CA. Diet and breast cancer: understanding risks and benefits. *Nutr Clin Pract*. Oct 2012;27(5):636-50.
111. Alexander DD, Morimoto LM, Mink PJ, Lowe KA. Summary and meta-analysis of prospective studies of animal fat intake and breast cancer. *Nutr Res Rev*. Jun 2010;23(1):169-79.
112. Linos E, Willett WC, Cho E, Frazier L. Adolescent diet in relation to breast cancer risk among premenopausal women. *Cancer Epidemiol Biomarkers Prev*. Mar 2010;19(3):689-96.
113. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. *Br J Cancer*. Jan 15 2008;98(1):9-14.
114. 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*. Feb 6 2013;105(3):219-36.
115. Aune D, Chan DS, Vieira AR, et al. Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Breast Cancer Res Treat*. Jul 2012;134(2):479-93.
116. Hui C, Qi X, Qianyong Z, Xiaoli P, Jundong Z, Mantian M. Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. *PLoS One*. 2013;8(1):e54318.
117. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*. Nov 18 2002;87(11):1234-45.
118. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA*. Nov 2 2011;306(17):1884-90.
119. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst*. Mar 4 2009;101(5):296-305.
120. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA*. Nov 7 2001;286(17):2143-51.
121. Li CI, Chlebowski RT, Freiberg M, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. *J Natl Cancer Inst*. Sep 22 2010;102(18):1422-31.
122. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis of epidemiological studies. *Int J Cancer*. Apr 15 2008;122(8):1832-41.
123. Secretan B, Straif K, Baan R, et al. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*. Nov 2009;10(11):1033-4.



124. 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.* Apr 17 2013;105(8):515-25.
125. Luo J, Margolis KL, Wactawski-Wende J, et al. Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. *BMJ.* 2011;342:d1016.
126. DeRoo LA, Cummings P, Mueller BA. Smoking before the first pregnancy and the risk of breast cancer: a meta-analysis. *Am J Epidemiol.* Aug 15 2011;174(4):390-402.
127. US Department of Health and Human Services, *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General.* Department of Health and Human Services, 2006.
128. Pirie K, Beral V, Peto R, Roddam A, Reeves G, Green J. Passive smoking and breast cancer in never smokers: prospective study and meta-analysis. *Int J Epidemiol.* Oct 2008;37(5):1069-79.
129. Xue F, Willett WC, Rosner BA, Hankinson SE, Michels KB. Cigarette smoking and the incidence of breast cancer. *Arch Intern Med.* Jan 24 2011;171(2):125-33.
130. Anderson LN, Cotterchio M, Mirea L, Ozcelik H, Kreiger N. Passive cigarette smoke exposure during various periods of life, genetic variants, and breast cancer risk among never smokers. *Am J Epidemiol.* Feb 15 2012;175(4):289-301.
131. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet.* Jun 22 1996;347(9017):1713-27.
132. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD, Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res.* Aug 2002;158(2):220-35.
133. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA.* Jul 23 2003;290(4):465-75.
134. Russo J, Hu YF, Yang X, Russo IH. Developmental, cellular, and molecular basis of human breast cancer. *J Natl Cancer Inst Monogr.* 2000(27):17-37.
135. Clemons M, Loijens L, Goss P. Breast cancer risk following irradiation for Hodgkin's disease. *Cancer Treat Rev.* Aug 2000;26(4):291-302.
136. Titus-Ernstoff L, Hatch EE, Hoover RN, et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer.* Jan 5 2001;84(1):126-33.
137. Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med.* Oct 6 2011;365(14):1304-14.
138. Salehi F, Turner MC, Phillips KP, Wigle DT, Krewski D, Aronson KJ. Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors. *J Toxicol Environ Health B Crit Rev.* Mar 2008;11(3-4):276-300.
139. Calle EE, Frumkin H, Henley SJ, Savitz DA, Thun MJ. Organochlorine and breast cancer risk. *CA Cancer J Clin.* September/October 2002;52(5):301-09.
140. Lopez-Cervantes M, Torres-Sanchez L, Tobias A, Lopez-Carrillo L. Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. *Environ Health Perspect.* Feb 2004;112(2):207-14.
141. Gammon MD, Wolff MS, Neugut AI, et al. Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. *Cancer Epidemiol Biomarkers Prev.* Aug 2002;11(8):686-97.
142. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. Environmental pollutants and breast cancer. *Cancer.* June 15 2007;109(S12):2667-711.
143. Steenland K, Whelan E, Deddens J, Stayner L, Ward E. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control.* Aug 2003;14(6):531-9.
144. Jia Y, Lu Y, Wu K, et al. Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol.* Jun 2013;37(3):197-206.
145. Kamdar BB, Tergas AI, Mateen FJ, Bhayani NH, Oh J. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat.* Feb 2013;138(1):291-301.
146. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol.* Dec 2007;8(12):1065-6.
147. International Agency for Research on Cancer. *IARC monographs on the evaluation of carcinogenic risks to humans. Volume 98. Shift-work, painting and fire-fighting.* Lyon, France: International Agency for Research on Cancer, 2007.
148. ACOG Committee Opinion No. 434: induced abortion and breast cancer risk. *Obstet Gynecol.* Jun 2009;113(6):1417-8.
149. Couzin J. Cancer risk. Review rules out abortion-cancer link. *Science.* Mar 7 2003;299(5612):1498.
150. Takkouche B, Etmann M, Montes-Martinez A. Personal use of hair dyes and risk of cancer: a meta-analysis. *JAMA.* May 25 2005;293(20):2516-25.
151. Mirick DK, Davis S, Thomas DB. Antiperspirant use and the risk of breast cancer. *J Natl Cancer Inst.* Oct 16 2002;94(20):1578-80.
152. Gikas PD, Mansfield L, Mokbel K. Do underarm cosmetics cause breast cancer? *Int J Fertil Womens Med.* Sep-Oct 2004;49(5):212-4.
153. Lipworth L, Tarone RE, Friis S, et al. Cancer among Scandinavian women with cosmetic breast implants: a pooled long-term follow-up study. *Int J Cancer.* Jan 15 2009;124(2):490-3.
154. Brinton LA, Lubin JH, Burich MC, Colton T, Brown SL, Hoover RN. Breast cancer following augmentation mammoplasty (United States). *Cancer Causes Control.* Oct 2000;11(9):819-27.
155. US Food and Drug Administration. FDA Medical Device Safety Communication: Reports of Anaplastic Large Cell Lymphoma (ALCL) in Women with Breast Implants, vol. 2011, 2011.
156. Nelson HD, Smith ME, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* Apr 16 2013;158(8):604-14.
157. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* Sep 16 1998;90(18):1371-88.
158. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst.* Feb 21 2007;99(4):272-82.
159. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst.* Nov 16 2005;97(22):1652-62.
160. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA.* Jun 16 1999;281(23):2189-97.
161. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. *Cancer Prev Res (Phila).* Jun 2010;3(6):696-706.

162. Grady D, Cauley JA, Geiger MJ, et al. Reduced incidence of invasive breast cancer with raloxifene among women at increased coronary risk. *J Natl Cancer Inst.* Jun 18 2008;100(12):854-61.
163. Freedman AN, Graubard BI, Rao SR, McCaskill-Stevens W, Ballard-Barbash R, Gail MH. Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention. *J Natl Cancer Inst.* Apr 2 2003;95(7):526-32.
164. Waters EA, McNeel TS, Stevens WM, Freedman AN. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. *Breast Cancer Res Treat.* Jul 2012;134(2):875-80.
165. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med.* Jun 23 2011;364(25):2381-91.
166. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev.* 2010(11):CD002748.
167. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst.* Nov 7 2001;93(21):1633-7.
168. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. *J Clin Oncol.* 2004;22(6):1055-62.
169. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA.* Sep 1 2010;304(9):967-75.
170. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst.* Jan 21 2009;101(2):80-7.
171. Brewster AM, Parker PA. Current knowledge on contralateral prophylactic mastectomy among women with sporadic breast cancer. *Oncologist.* 2011;16(7):935-41.
172. Stucky CC, Gray RJ, Wasif N, Dueck AC, Pockaj BA. Increase in contralateral prophylactic mastectomy: echoes of a bygone era? Surgical trends for unilateral breast cancer. *Ann Surg Oncol.* Oct 2010;17 Suppl 3:330-7.
173. Tuttle TM, Jarosek S, Habermann EB, et al. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. *J Clin Oncol.* Feb 17 2009.
174. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. *J Natl Cancer Inst.* Mar 17 2010;102(6):401-9.
175. Brewster AM, Bedrosian I, Parker PA, et al. Association between contralateral prophylactic mastectomy and breast cancer outcomes by hormone receptor status. *Cancer.* Nov 15 2012;118(22):5637-43.
176. Pisano ED, Hendrick RE, Yaffe MJ, et al. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology.* Feb 2008;246(2):376-83.
177. Kerlikowske K, Hubbard RA, Miglioretti DL, et al. Comparative effectiveness of digital versus film-screen mammography in community practice in the United States: a cohort study. *Ann Intern Med.* Oct 18 2011;155(8):493-502.
178. 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.* Mar 11 2013.
179. Smith RA, Brooks D, Cokkinides V, Saslow D, Brawley OW. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. *CA Cancer J Clin.* Mar-Apr 2013;63(2):88-105.
180. Independent U. K. Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet.* Nov 17 2012;380(9855):1778-86.
181. Nelson HD, Tyne K, Naik A, et al. *Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force.* Rockville MD, 2009.
182. Tabar L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology.* Sep 2011;260(3):658-63.
183. Paci E, Euroscreen Working Group. Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. *J Med Screen.* 2012;19 Suppl 1:5-13.
184. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev.* Jun 4 2013;6:CD001877.
185. Hubbard RA, Kerlikowske K, Flowers CI, Yankaskas BC, Zhu W, Miglioretti DL. Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. *Ann Intern Med.* Oct 18 2011;155(8):481-92.
186. Rosenberg RD, Yankaskas BC, Abraham LA, et al. Performance benchmarks for screening mammography. *Radiology.* Oct 2006;241(1):55-66.
187. Elmore JG, Barton MB, Mocerri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med.* Apr 16 1998;338(16):1089-96.
188. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med.* Nov 22 2012;367(21):1998-2005.
189. Duffy SW, Tabar L, Olsen AH, et al. Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England. *J Med Screen.* 2010;17(1):25-30.
190. Puliti D, Zappa M, Miccinesi G, Falini P, Crocetti E, Paci E. An estimate of overdiagnosis 15 years after the start of mammographic screening in Florence. *Eur J Cancer.* Dec 2009;45(18):3166-71.
191. Yaffe MJ, Mainprize JG. Risk of radiation-induced breast cancer from mammographic screening. *Radiology.* Jan 2011;258(1):98-105.
192. de Gelder R, Draisma G, Heijnsdijk EA, de Koning HJ. Population-based mammography screening below age 50: balancing radiation-induced vs prevented breast cancer deaths. *Br J Cancer.* Mar 29 2011;104(7):1214-20.
193. Brawley OW. Risk-based mammography screening: an effort to maximize the benefits and minimize the harms. *Ann Intern Med.* May 1 2012;156(9):662-3.
194. National Center for Health Statistics. *Health, United States, 2012: With Special Feature on Emergency Care.* Hyattsville, MD, 2013.
195. Hoerger TJ, Ekwueme DU, Miller JW, et al. Estimated effects of the National Breast and Cervical Cancer Early Detection Program on breast cancer mortality. *Am J Prev Med.* Apr 2011;40(4):397-404.
196. Centers for Disease Control and Prevention. National Breast and Cervical Cancer Early Detection Program (NBCCEDP), vol. 2013 Atlanta, GA.
197. 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.* Mar-Apr 2007;57(2):75-89.
198. Smith RA, Saslow D, Sawyer KA, et al. American Cancer Society guidelines for breast cancer screening: update 2003. *CA Cancer J Clin.* May-Jun 2003;53(3):141-69.
199. Thomas DB, Gao DL, Ray RM, et al. Randomized trial of breast self-examination in Shanghai: final results. *J Natl Cancer Inst.* Oct 2 2002;94(19):1445-57.



200. Semiglazov VF, Moiseenko VM, Manikhas AG, et al. Interim results of a prospective randomized study of self-examination for early detection of breast cancer. *Vopr Onkol.* 1999;45(3):265-71.
201. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA.* Apr 4 2012;307(13):1394-404.
202. Kruper L, Holt A, Xu XX, et al. Disparities in reconstruction rates after mastectomy: patterns of care and factors associated with the use of breast reconstruction in Southern California. *Ann Surg Oncol.* Aug 2011;18(8):2158-65.
203. Tseng WH, Stevenson TR, Canter RJ, et al. Sacramento area breast cancer epidemiology study: use of postmastectomy breast reconstruction along the rural-to-urban continuum. *Plast Reconstr Surg.* Dec 2010;126(6):1815-24.
204. Reuben BC, Manwaring J, Neumayer LA. Recent trends and predictors in immediate breast reconstruction after mastectomy in the United States. *Am J Surg.* Aug 2009;198(2):237-43.
205. Alderman AK, Wei Y, Birkmeyer JD. Use of breast reconstruction after mastectomy following the Women's Health and Cancer Rights Act. *JAMA.* Jan 25 2006;295(4):387-8.
206. Rosson GD, Singh NK, Ahuja N, Jacobs LK, Chang DC. Multilevel analysis of the impact of community vs patient factors on access to immediate breast reconstruction following mastectomy in Maryland. *Arch Surg.* Nov 2008;143(11):1076-81; discussion 81.
207. Christian CK, Niland J, Edge SB, et al. A multi-institutional analysis of the socioeconomic determinants of breast reconstruction: a study of the National Comprehensive Cancer Network. *Ann Surg.* Feb 2006;243(2):241-9.
208. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer.* Jan 1 2006;106(1):4-16.
209. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* Feb 9 2011;305(6):569-75.
210. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. *Ann Surg Oncol.* Jul 2009;16(7):1959-72.
211. Wernicke AG, Shamis M, Sidhu KK, et al. Complication rates in patients with negative axillary nodes 10 years after local breast radiotherapy after either sentinel lymph node dissection or axillary clearance. *Am J Clin Oncol.* Feb 2013;36(1):12-9.
212. McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: patient perceptions and precautionary behaviors. *J Clin Oncol.* Nov 10 2008;26(32):5220-6.
213. Lawenda BD, Mondry TE, Johnstone PA. Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. *CA Cancer J Clin.* Jan-Feb 2009;59(1):8-24.
214. 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.* Nov 12 2011;378(9804):1707-16.
215. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* Oct 17 2002;347(16):1233-41.
216. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* Oct 17 2002;347(16):1227-32.
217. Litiere S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol.* Apr 2012;13(4):412-9.
218. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* Feb 11 2010;362(6):513-20.
219. Beitsch PD, Shaitelman SF, Vicini FA. Accelerated partial breast irradiation. *J Surg Oncol.* Mar 15 2011;103(4):362-8.
220. Shaitelman SF, Vicini FA, Beitsch P, Haffty B, Keisch M, Lyden M. Five-year outcome of patients classified using the American Society for Radiation Oncology consensus statement guidelines for the application of accelerated partial breast irradiation: an analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. *Cancer.* Oct 15 2010;116(20):4677-85.
221. Vicini F, Beitsch P, Quiet C, et al. Five-year analysis of treatment efficacy and cosmesis by the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial in patients treated with accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys.* Mar 1 2011;79(3):808-17.
222. Smith GL, Xu Y, Buchholz TA, et al. Association between treatment with brachytherapy vs whole-breast irradiation and subsequent mastectomy, complications, and survival among older women with invasive breast cancer. *JAMA.* May 2 2012;307(17):1827-37.
223. Cox JA, Swanson TA. Current modalities of accelerated partial breast irradiation. *Nat Rev Clin Oncol.* Apr 30 2013.
224. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst.* Feb 2 2005;97(3):188-94.
225. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol.* May 20 2012;30(15):1796-804.
226. Early Breast Cancer Trialists' Collaborative Group, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet.* Aug 27 2011;378(9793):771-84.
227. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet.* Dec 5 2012.
228. National Comprehensive Cancer Network. NCCN Guidelines for patients: Breast cancer. Version 3.2013, 2013.
229. Cuzick J, Ambrosine L, Davidson N, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet.* May 19 2007;369(9574):1711-23.
230. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol.* Jan 20 2010;28(3):509-18.
231. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol.* Aug 10 2010;28(23):3784-96.

232. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. Oct 20 2005;353(16):1673-84.

233. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Arch Pathol Lab Med*. Jan 1 2007;131(1):18.

234. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. Jan 12 2012;366(2):109-19.

235. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. Nov 8 2012;367(19):1783-91.

236. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist*. 2010;15(9):924-34.

237. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol*. Aug 1 2012;30(22):2718-24.

238. Baselga J, Semiglazov V, van Dam P, et al. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. *J Clin Oncol*. Jun 1 2009;27(16):2630-7.

239. Copeland G, Lake A, Firth R, et al., eds. *Cancer in North America: 2006-2010. Volume Two: Registry-specific Cancer Incidence for the United States, Canada and North America*. Springfield, IL: North American Association of Central Cancer Registries, Inc; 2013.

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