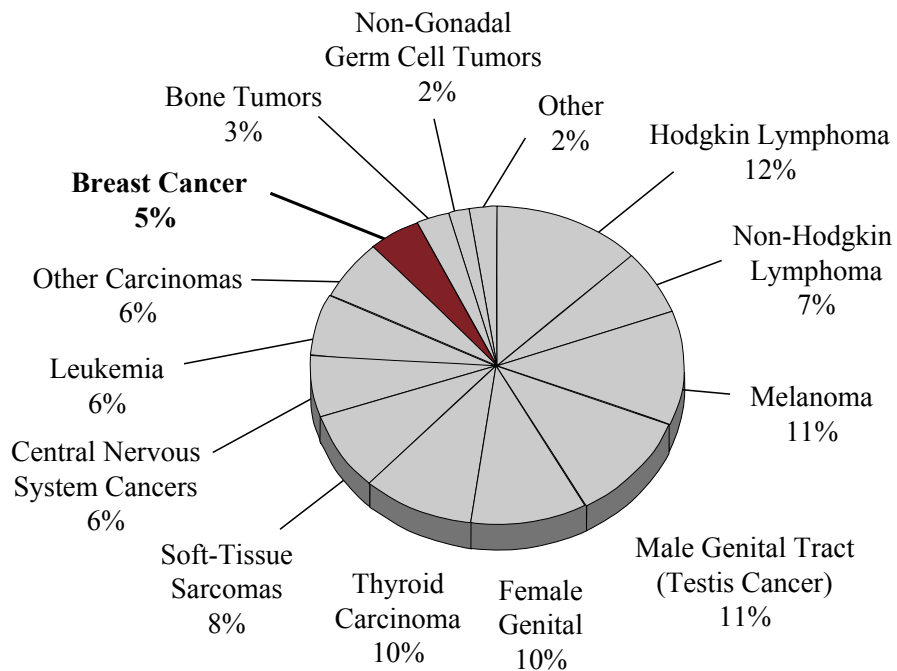


# Chapter 9

## Breast Cancer

Cancer in 15- to 29-Year-Olds in the United States



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## HIGHLIGHTS

*Incidence*

- Breast cancer in adolescents and young adults is rare. From 1975 to 2000, less than 0.1% of all breast cancer occurred in young women under 30 years of age.
- There was an increase in the average incidence of breast cancer per million females per year across the adolescent and young adult age groups during the period 1975 to 2000: incidence was 1.3 in 15- to 19-year-olds, 12.1 in 20- to 24-year-olds, rising to 81.1 in 25- to 29-year-olds.
- Breast cancer incidence for African American/black adolescents and young adults was more than twice that of white non-Hispanic women of similar age. This incidence trend reversed between the ages of 45 and 50 years; African American/black women 45 years and older had a lower incidence than white women.
- American Indian/Alaska Native women had the lowest incidence of breast cancer, regardless of age.

*Mortality & Survival*

- Death rates for breast cancer rose steadily with increasing age.
- Mortality was much higher for African Americans/blacks and to a lesser extent those of Hispanic ethnicity at all ages than for white, non-Hispanic young women.
- Survival rates have improved over time. White non-Hispanic patients experienced greater improvements in survival rates than Hispanic and African American/black patients.
- Survival is lower for women 15 to 29 years of age than for older women, regardless of histologic subtype and stage.
- Socioeconomic factors, including access to care and health insurance coverage, affect mortality.

*Risk Factors*

- The primary risk factor for the development of breast cancer in women of all ages is a family history of breast cancer.
- Risk factors in adolescence and young adulthood include germline mutations of BRCA1, BRCA2, p53 (Li Fraumeni syndrome), Muir's Syndrome and PTEN (Cowden's syndrome).
- Prior mantle radiation for Hodgkin disease is a risk factor for the development of breast cancer in young women.
- Age younger than 35 years at diagnosis is a risk factor for the development of aggressive disease.
- African American/black race, particularly for those younger than 45 years of age, and increased parity in young African/black women are risk factors.
- Increased breast tissue density in women over the age of 35 is considered a risk factor.

## INTRODUCTION

Breast cancer is rare in adolescent girls and young women, and even more rare in males of this age group. Due to lack of data about male breast cancer, this chapter will present data pertaining to female patients only. When breast cancer occurs in adolescents and young women, it tends to be more aggressive and has a worse prognosis than when it occurs in older women.<sup>1-</sup>

<sup>3</sup> Adolescents and young women tend to have more advanced disease, in part due to the poor correlation

of standard mammography findings with extent of disease.<sup>1,4</sup> Age is an independent prognostic factor even when size and nodal status are considered—younger aged patients have a worse prognosis.<sup>1,2</sup> These patients have a higher incidence of invasive ductal carcinoma with an aggressive biological behavior and are more likely to have lymphovascular invasion.<sup>3</sup> Young women are more likely to have tumors that are estrogen-receptor negative.<sup>1,4,5</sup>

**METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS**

The International Classification of Childhood Cancer (ICCC) has no specific category for breast cancer. These cancers are contained with category XI(f), *Other and Unspecified Carcinomas*, as one of the *Carcinomas and Other Epithelial Neoplasms* (category XI). Hence, the SEER site recode based on the International Classification of Diseases for Oncology (ICD-O) was used exclusively for this chapter.

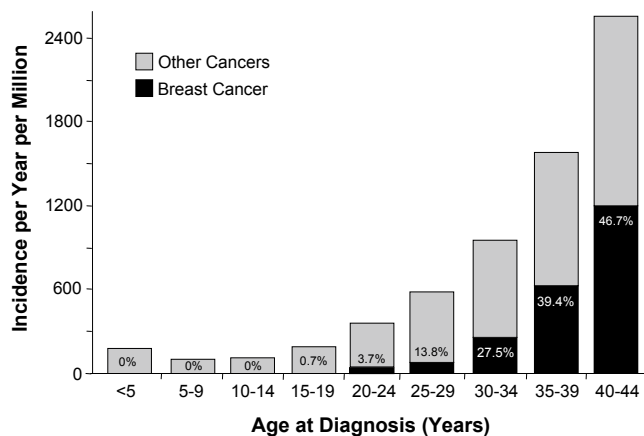
For breast cancer, the ICD-O Topography codes are C50.0-C50.9 (all tissues in the breast except overlying skin) and the ICD-O categories include general carcinomas and adenocarcinomas (8010-8041, 8140, many others) and specific carcinomas of the breast. The latter are found in the ICD-O group *Ductal and Lobular Neoplasms* (8500-8543) and include intraductal, lobular, inflammatory, comedo-, intracystic, and Paget’s types, and various combinations of these histologies.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

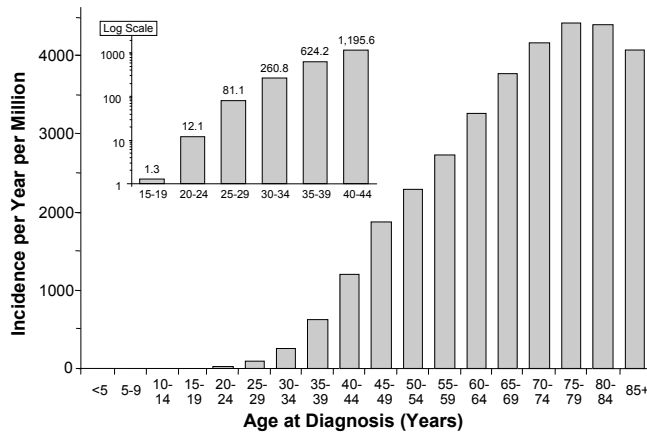
Since the ICCC was set up as a classification for childhood cancer, it does not have a separate category for breast cancer. Topography and histology from ICD-O can be used to examine differences among very young breast cancer patients compared to older patients, but it is unclear whether this is sufficient to explain all of the biologic differences, given that the younger breast cancer patients in general experience poorer survival than older breast cancer patients.

**INCIDENCE**

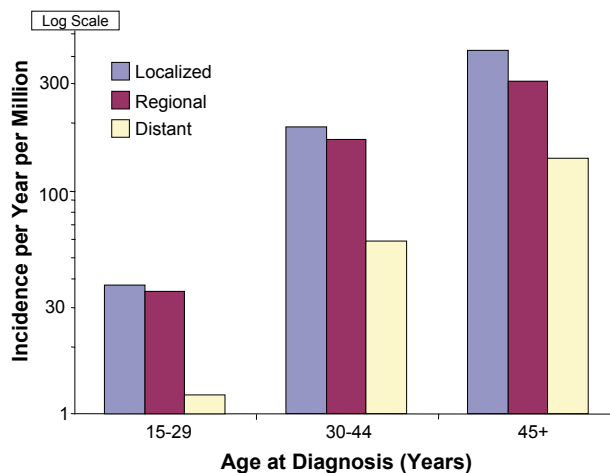
The SEER incidence data in this section were collected between 1975 and 2000. Less than 1% of all breast cancer cases occurred in women under the age of 30. Breast cancer incidence rose steadily with age, stabilized, and then dropped slightly after 80 years of age (Figures 9.1, 9.2).



**Figure 9.1:** Incidence of Breast Cancer Relative to All Cancer in Females, U.S., SEER 1975-2000



**Figure 9.2:** Incidence of Breast Cancer in Females, SEER 1975-2000



**Figure 9.3:** Incidence of Breast Cancer in Females by Extent of Disease at Diagnosis, SEER 1975-2000

**Table 9.1:** Incidence of Breast Cancer in Persons Younger Than 30 Years of Age, U.S., 1975-2000

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions), females	9.365	10.026	10.008	9.829	9.276	9.583
Average incidence per million, 1975-2000, SEER	^	^	^	1.3	12.1	81.1
Average annual % change in incidence, 1975-2000, SEER	^	^	^	0	0	0
Estimated incidence per million, year 2000, U.S.	^	^	^	1.3	12.1	81.1
Estimated number persons diagnosed, year 2000, U.S.	^	^	^	13	112	777

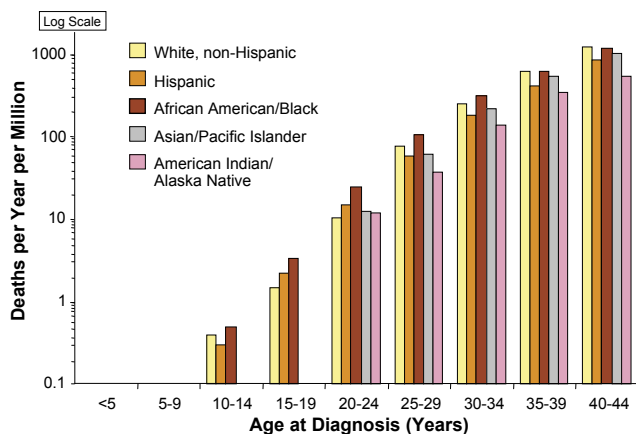
^ Too few for a reliable estimate

Over the period 1975 to 2000, there was an increase in incidence of breast cancer with increasing age, from an average incidence per million of 1.3 in 15- to 19-year-olds, to 12.1 in 20- to 24-year-olds, to 81.1 in 25- to 29-year-olds (Table 9.1). However, there was no annual increase within each age group apparent over the same time period.

As shown in Figure 9.3, the incidence of regional spread of disease was higher for adolescents and young adults than for women older than 30 years of age.

*Racial/Ethnic Differences in Incidence*

From 1992 to 2002, African American/black women from 10 to 34 years of age had a higher rate of breast cancer than any other race/ethnicity (Figure 9.4). Above age 50, however, breast cancer predominated in non-Hispanic white women (data not shown). At all ages, American Indian/Alaska Native women had the lowest incidence of breast cancer (Figure 9.4; data not shown for older females).



**Figure 9.4:** Incidence of Breast Cancer in Females by Race/Ethnicity, SEER 1992-2001

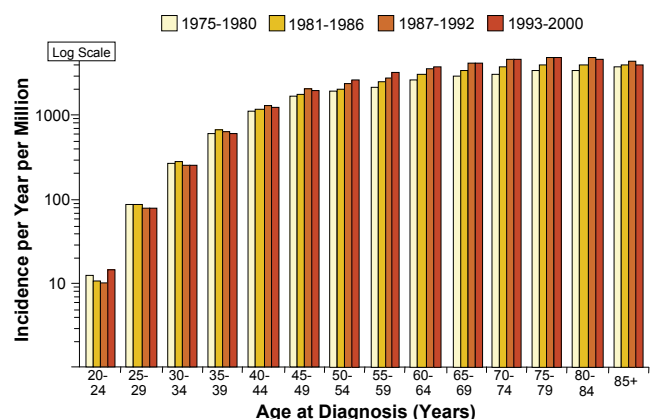
*Trends in Incidence*

The incidence of breast cancer in young women has remained relatively stable over the period 1975 to 2000 (Figures 9.5).

OUTCOME

*Mortality*

During the period 1975 to 2000, breast cancer mortality rose steadily with age (Figure 9.6), reflecting an increasing breast cancer incidence (Figure 9.2). The mortality:incidence ratio was lower in the 15- to 29-year age range than in the 30- to 44-year range (Figure 9.7), implying that survival was better among the younger patients. This apparent advantage for the younger age group may be due either to a higher cure rate or to a longer interval to death, such that the deaths from breast cancer among those diagnosed between 15 and 29 years of age occur primarily after age 30. Survival data shown below indicate that it was not due to a higher survival rate.



**Figure 9.5:** Change in Incidence of Breast Cancer in Females by Era, SEER

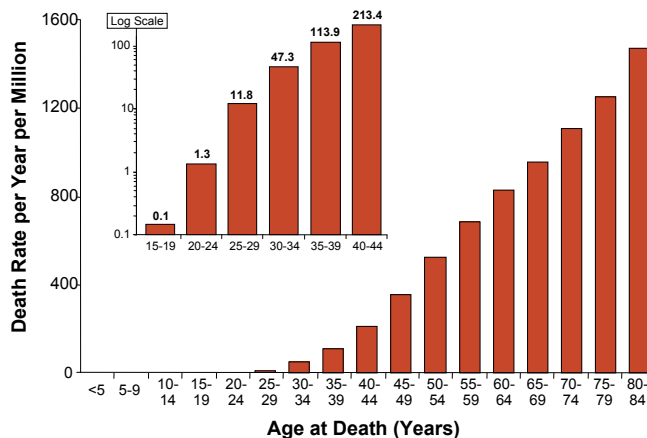
Mortality for all age groups remained stable or dropped since 1981. The decrease in mortality was more pronounced for those over 30 years of age, particularly in the most recent treatment era (Figure 9.8), and likely reflects the use of screening programs, improved diagnostic techniques, and adjuvant chemotherapy and radiation therapy. There was a more significant improvement in mortality over time for older age groups.

*Racial/Ethnic Differences in Mortality*

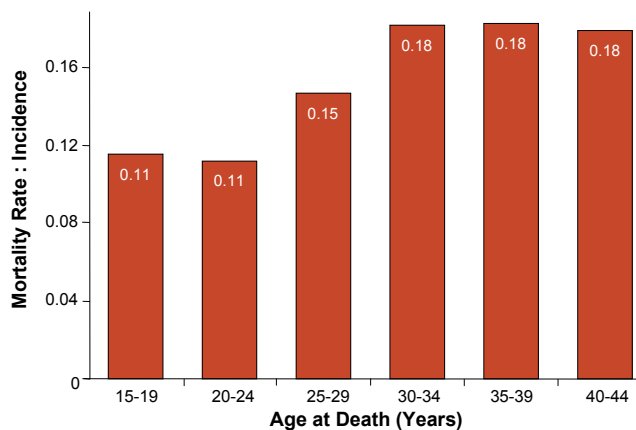
For women younger than 45 years of age, mortality for African Americans/blacks was nearly twice as high as for other racial/ethnic groups (Figure 9.9). Although African Americans/blacks had an increased incidence of breast cancer compared to other groups, the death rate for this group was disproportionately higher than the incidence difference (Figure 9.4). African American/black patients have been reported to present with higher stage or more advanced disease.<sup>6,7</sup> White non-Hispanic women were significantly more likely to be older and to have smaller tumors, have less lymph node involvement, have tumors with positive estrogen receptor and progesterone receptor status compared with Hispanic or African American/black women.<sup>6</sup>

An additional analysis of treatment modalities used for women under 35 years of age with invasive breast cancer revealed that African American/black women—and to some extent Hispanic females—received less aggressive initial therapy than white non-Hispanic women, despite similar prognostic variables. These analyses were multivariate and were adjusted for stage, grade, lymph node status, and treatment. Overall, 9% of the women in this study were registered on clinical trials, yet African American/black women were less likely than others to be among those registered. African American/black and Hispanic women had poorer outcomes and a higher mortality than white, non-Hispanic women.<sup>6</sup>

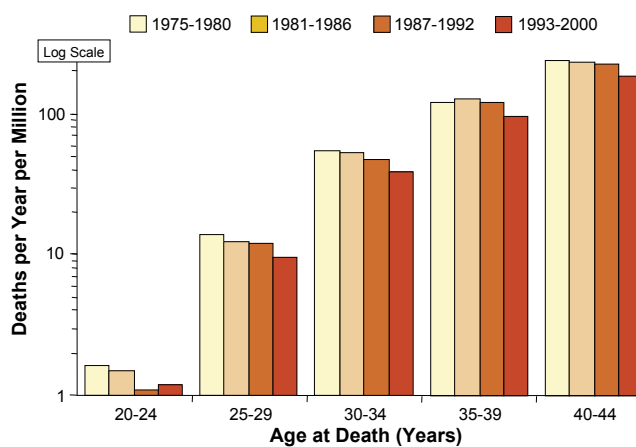
Figure 9.10 displays mortality data for white and African American/black women over the period 1975 to 2000. For white Americans there was a relatively consistent decline in the death rate across all age groups, but for African Americans/blacks, either an increase in death rate or stable death rate was observed.



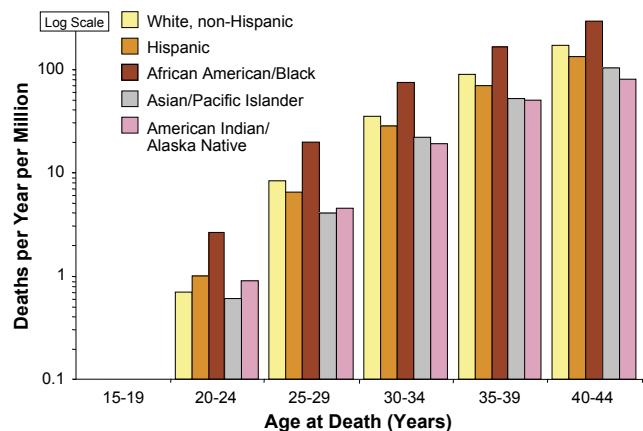
**Figure 9.6:** National Mortality for Breast Cancer in Females, U.S., 1975-2000



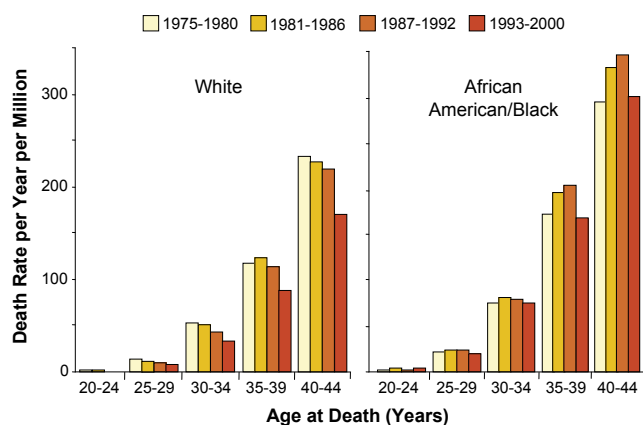
**Figure 9.7:** Ratio of National Mortality to SEER Incidence for Breast Cancer in Females, U.S., 1975-2000



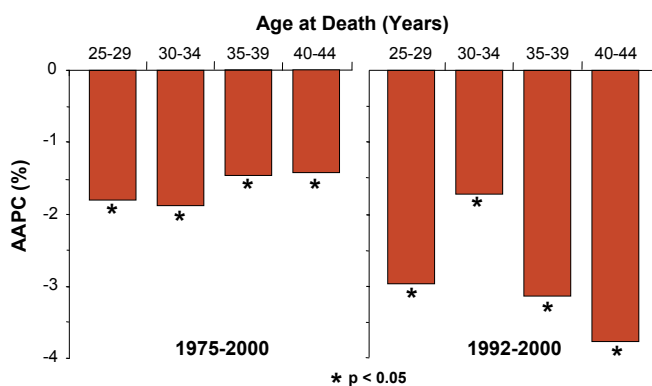
**Figure 9.8:** National Mortality for Breast Cancer in Females, U.S., by Era



**Figure 9.9:** National Mortality for Breast Cancer in Females by Race/Ethnicity, 1990-2000



**Figure 9.10:** National Mortality for Breast Cancer in Females by Era, 1975-2000



**Figure 9.11:** Average Annual Percent Change (AAPC) in National Mortality for Breast Cancer in Females, 1975-2000

Data analysis of death from breast cancer (1973 to 2000) and its association to age at diagnosis, stage, and ethnicity indicates that breast cancer was the cause of death more often in younger patients as compared to older patients, and was associated with advanced stage and race. African American/black women did not achieve survival rates similar to white non-Hispanic women.<sup>8</sup>

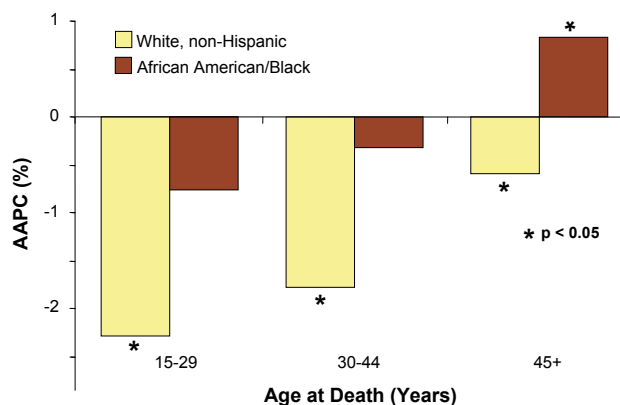
*Trends in Mortality*

A reduction in breast cancer mortality occurred over time, and was significant for each age group. This improvement has been considerable in more recent years (Figure 9.11).

The average annual percent change in mortality for whites compared to African Americans/blacks reveals a significant discrepancy between the two racial groups. Whites experienced substantial improvements in survival in all age groups in the period 1975 to 2000—improvements not observed in the African American/black population. Decreases in mortality during this period were three times greater for whites than for African Americans/blacks (Figure 9.12).

*Survival*

Five-year survival rates for breast cancer, by age, revealed that survival was lowest for those in the adolescent and young adult age group. Within that group, 25- to 29-year-old women had slightly lower survival rates than those younger or older (Figure 9.13). This lower survival rate for 15- to 29-year-old women may be due to several factors: breast cancer in young women is typically invasive, more aggressive and associated with a worse prognosis



**Figure 9.12:** Average Annual Percent Change (AAPC) in National Mortality for Breast Cancer in Females, by Race, 1975-2000

than in older women,<sup>1,2</sup> detection rates are lower due to lack of suspicion in the general population and medical community, and breast tissue in younger women is commonly more dense than in older women, resulting in mammography results which may be inconclusive.

Five-year survival rates, by era, revealed that although survival rates for the adolescent and young adult population remained relatively stable over time, slight improvement was seen in the most recent era (Figure 9.14).

Breast cancer survival is consistently lower for adolescent and young adult women than for other age groups, regardless of histologic type. For all age groups, 5-year survival is limited for women with inflammatory disease (Figure 9.15). Lower survival rates reflect the aggressive biologic and pathologic characteristics of tumors specific to this age group, and the fact that routine screening for breast cancer is not the standard of care in adolescents and young adults. Although treatment modalities have improved considerably over the last 30 years, due to National Cancer Institute initiatives for the care of breast cancer patients, improvements in survival have not been observed in adolescents and young adults to the extent seen in older females.

Five-year survival rates were generally low for 20- to 24-year-old women, except for those with localized disease at diagnosis. For localized disease, women in the age groups 20 to 24 and 40 to 44 had high survival rates, although rates were relatively high for all ages (Figure 9.16). For regional and distant disease, survival rates increased with age. As expected, survival for all women was best for those with localized disease, followed by those with regional disease. Survival was poor for all women with distant disease (Figure 9.16).

The average annual percent change in 5-year survival rates from 1975 to 2000 is shown in Figure 9.17. For young women 15 to 29 years of age, decreases in 5-year survival rates were noted for localized and regional disease. Decreases were also seen for women 30 to 44 years of age with regional disease, but significantly better survival was noted for those with localized or distant disease. For those over 45 years of age, improvement—which was significant—was observed only for those with localized disease. This may indicate the benefit of awareness campaigns and breast cancer screening in the older population.

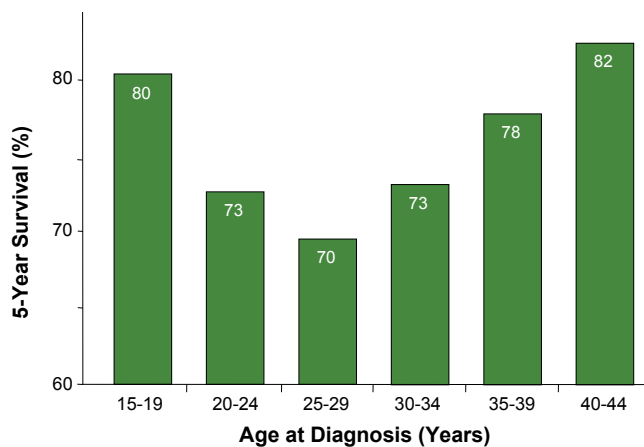


Figure 9.13: 5-Year Survival Rate for Breast Cancer in Females, SEER 1975-1999

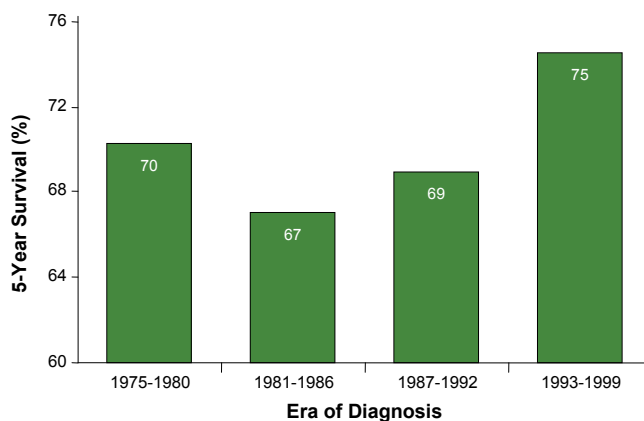


Figure 9.14: 5-Year Survival Rate for Breast Cancer in 15- to 29-Year-Old Females, by Era, SEER 1975-1999

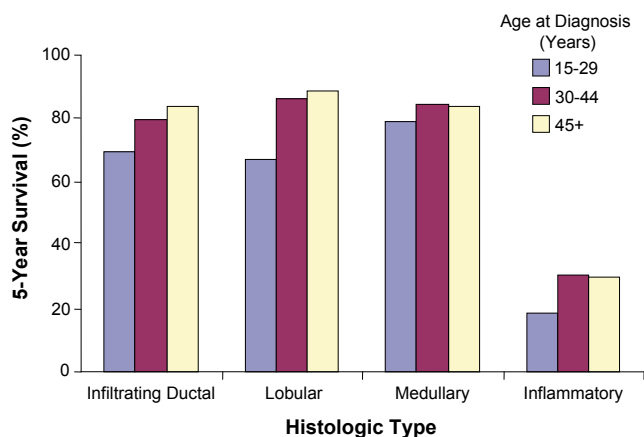


Figure 9.15: 5-Year Survival Rate for Breast Cancer in Females by Histologic Type and Age, SEER 1975-1999

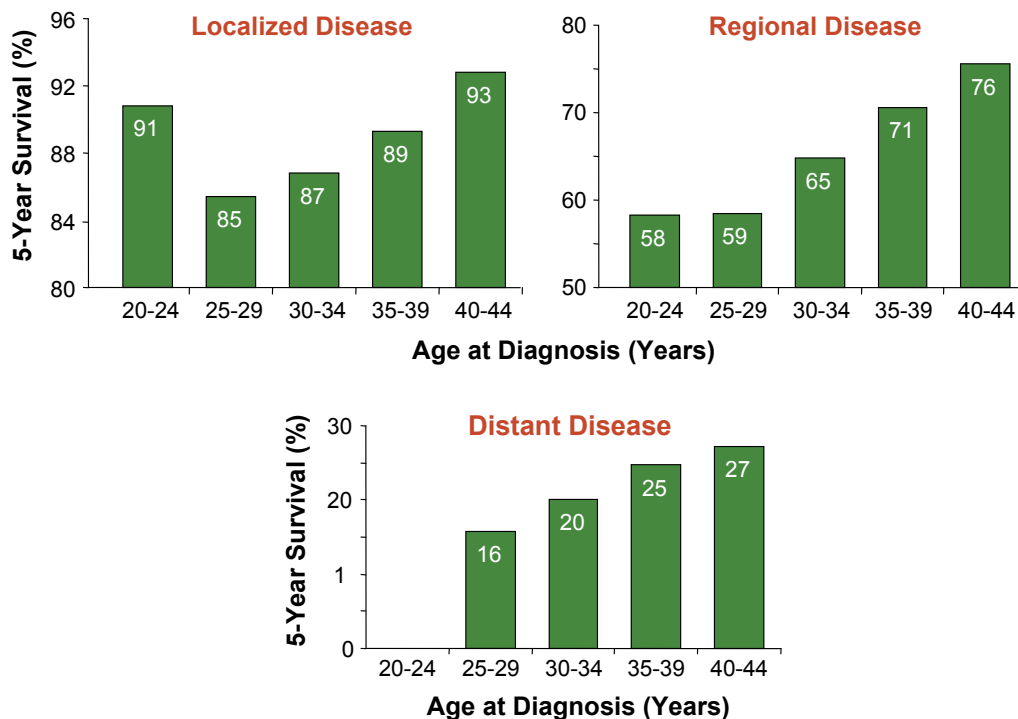


Figure 9.16: 5-Year Survival Rate for Breast Cancer in Females by Age and Extent of Disease at Diagnosis, SEER 1975-1999

RISK FACTORS

Due to the low incidence of breast cancer in adolescents and young adults, relatively few epidemiological studies have been undertaken with the focus on this age group. Much of the information listed below is based on studies of women under 35 or 40 years of age; in a few studies age was stratified at above and below 50 years.

General risk factors for the development of breast cancer include age, reproductive history, personal or family history of breast cancer, and environmental exposure to carcinogens.<sup>9</sup> A significant risk factor for breast cancer is family history—specifically in a first- or second-degree relative. However, even with increased risk, only 5 percent of familial breast cancers studied are consistent with hereditary breast cancer.<sup>10-12</sup>

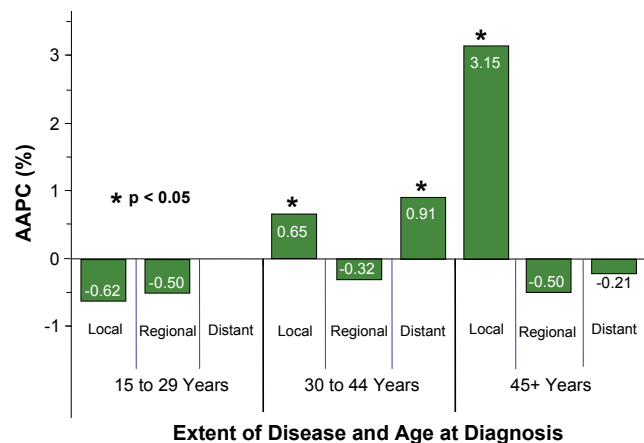


Figure 9.17: Average Annual Percent Change (AAPC) in 5-Year Survival Rates for Breast Cancer in Females by Age and Extent of Disease, SEER 1975-2000

Young women with germline mutations in BRCA1, BRCA2, p53 (Li Fraumeni syndrome), Muir syndrome, or PTEN (Cowden’s syndrome) are at increased risk for breast cancer.<sup>9,13</sup> Women who carry a BRCA1 or BRCA2 mutation have a lifetime risk of breast cancer as high as 80-90%, although lower risk estimates of 37-56% have also been reported.<sup>14</sup>

Young female patients are more likely to carry p53 mutations, and perturbations of the p53 pathway are associated with more aggressive and therapeutically refractory tumors.<sup>15</sup> Li Fraumeni syndrome is a rare, dominantly inherited condition caused by a germline mutation in the Tp53 gene on chromosome 17.<sup>16</sup> Affected



patients have a 50% risk of developing cancer by age 35 and a 90% risk of developing cancer in their lifetime. Muir syndrome is a familial cancer family variant with basal cell carcinomas and benign and malignant colon tumors.<sup>17</sup> Cowden's syndrome is caused by a rare mutation in PTEN gene on chromosome 10.<sup>18</sup> Affected patients have an increased risk of developing breast or thyroid carcinoma at a young age and often have multiple hamartomas.

Race/ethnicity is a risk factor for the development of breast cancer. Incidence is higher in African Americans/black women younger than 50 years of age than for other racial/ethnic groups, even in the adolescent and young adult subset.<sup>19</sup> African American/black women more often present with distant disease than white women, and mortality in this group exceeds that of the white population. Yet for women born after 1950, mortality has decreased, and the African American/black population has experienced more benefit than the white population.<sup>20</sup>

Reasons for these racial/ethnic disparities include age, tumor histology, premenopausal endogenous hormones and growth factors levels, and parity. African American/black women younger than 45 years of age were more likely to develop breast cancer than those over 45, whereas white women over the age of 45 were more likely to develop breast cancer than those under 45.<sup>7</sup> African American/black women under the age of 50 were also noted to have more aggressive tumor histology.<sup>19</sup> In a population-based study of women with breast cancer, a significant difference in the expression of p53, late stage tumors, larger tumors, positive lymph nodes, and higher histologic grade was seen in African American/black women as compared to white women.<sup>21</sup> Racial differences in levels of endogenous hormones and growth factors indicate that African American/black women under 45 years of age are at higher risk of developing breast cancer than their white counterparts.<sup>22</sup> African American/black women were more likely to have had an early first birth (when younger than 20 years of age) and higher parity than white women, with a higher risk of breast cancer at younger ages.<sup>23,24</sup> African American/black women were more likely to have estrogen-receptor negative tumors than white women, which is a risk factor in itself.<sup>25</sup> In

regards to treatment for breast cancer, African American/black women are more likely than white women to undergo breast-conserving surgery or have no surgery for their disease.<sup>26</sup> They are also less likely to receive post-operative radiation therapy than white women.<sup>6</sup> Treatment is affected by socioeconomic factors such as access to care, lack of health insurance, and type of health insurance coverage.<sup>26</sup>

Age is an independent risk factor; women under 35 years more often have a palpable mass at diagnosis, undifferentiated tumors, grade 3 tumors, negative hormone receptor status, and microscopic lymph node involvement.<sup>1,2</sup> An increase in the incidence of infiltrating ductal carcinoma in women younger than 39 years of age was noted in a British study, with a decrease in regional and distant disease with advancing age.<sup>3</sup> A French study found that women younger than 40 years of age had tumor histology associated with high nuclear grade and vascular invasion.<sup>27</sup>

Other risk factors include circulating enzyme and hormone levels and breast tissue density. A recent study indicated that increased cytochrome P450 1A2 function may be associated with an increased risk of developing breast cancer.<sup>28</sup> The risk of developing estrogen-negative breast cancer may be higher in women with particular enzyme genotypes.<sup>29</sup> In women over 35 years of age and particularly over age 50, increased density of breast tissue—independent of ethnicity—is a risk factor for the development of breast cancer.<sup>30</sup>

A unique group at risk for the development of breast cancer consists of adolescent and young adult survivors of Hodgkin lymphoma. The risk of developing breast cancer appears to be related to the quantity and location (chest/mantle) of prior radiation therapy, with or without alkylating agent-based chemotherapy; this risk increases over time.<sup>13,31,32</sup>

## SUMMARY

Breast cancer is rare in adolescents and young women but has a worse prognosis than for older women. Young females with breast cancer are more likely to present with regional spread prior to diagnosis.<sup>5</sup> Adolescents and young women are not considered at risk for breast

cancer, therefore they may not seek early medical attention or concerns may be dismissed by medical practitioners. Breast cancer in this age group may also be more difficult to detect due to dense breast tissue. Nonetheless, there is evidence that breast cancer is more virulent in young females, with a worse prognosis for the same stage of disease at diagnosis. There is a higher incidence of germline mutations of BRCA1, BRCA2, Tp53, and PTEN in this age group.

Survival data demonstrate striking racial differences. African Americans/blacks—and to a lesser degree Hispanics—fare poorly compared to whites. Although progress has been made, there is much to accomplish for the youngest women and women of color. Effective screening programs are needed to help identify early disease in these at-risk groups. These young women should be encouraged to participate in such programs at an early age and throughout their lives.

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