Special Section: Breast Carcinoma In Situ

An estimated 60,290 new cases of female breast carcinoma in situ are expected to be diagnosed in 2015, accounting for about 20% of all breast tumors in women. The vast majority (83%) will be ductal carcinoma in situ (DCIS), and 12% will be lobular carcinoma in situ (LCIS) (which is also called lobular neoplasia). The clinical significance of a breast carcinoma in situ diagnosis and optimal approaches to treatment are topics of uncertainty and concern for both patients and clinicians.[1-3] In this special section, we summarize what is known and not known about female DCIS and LCIS, present statistics on their occurrence and treatment, and highlight promising areas of research. Because DCIS and LCIS are quite distinct in their natural history and treatment, they are discussed separately.

What is "carcinoma" and "carcinoma in situ"?

The term "carcinoma" is used to describe cancer arising in epithelial cells (cells that cover the surface of the body and the lining of "hollow" internal organs). This is why most cancers of the skin, mouth, throat, esophagus, stomach, intestines, reproductive system, and most other organs are classified as carcinomas. Although most people do not think of a breast as being hollow, its system of glands and ducts are, which is why most breast cancers are carcinomas. One of the most important features that distinguishes benign (non-cancerous) cells from those of carcinoma is that carcinoma cells can invade beyond the epithelium into nearby tissues. Thus, when examination of a biopsy sample shows abnormal epithelial cells that have spread from their origin into other tissues, this is a sign of carcinoma.

The term "carcinoma in situ" was coined long ago to describe abnormal epithelial cells that have not invaded nearby tissues, but that look very similar to cells of invasive carcinoma when viewed under a microscope. For many years, it was assumed that these cells could become invasive in the absence of treatment. More recent research indicates that the transition from normal tissue to carcinoma in situ to invasive carcinoma involves a series of molecular changes that are more complex and subtle than the older view based on microscopic appearances. Long-term follow-up studies of patients with carcinoma in situ also find that even without treatment, not all patients develop invasive cancer.[4]

Adding to this complexity, abnormal yet noninvasive epithelial cells in different organs are often given various names (such as carcinoma in situ, high-grade dysplasia, high-grade intraepithelial neoplasia), and doctors still disagree about the best way to classify these conditions. The clinical consequences of this uncertainty are perhaps most evident and controversial in breast cancer. For this reason, a review of carcinoma in situ of the breast is particularly timely and important.

What is DCIS?

DCIS refers to abnormal cells that replace the normal epithelial cells of breast ducts, but are still within the tissue layer of origin; under a microscope, these cells appear similar to those of invasive breast cancers. Although DCIS can present as a palpable mass, it is most often detected by a mammogram, where it commonly is identified by the appearance of microcalcifications (tiny bits of calcium that appear as clustered white dots). The microcalcificactions are harmless but indicate the possible presence of in situ or invasive cancer.

Because the abnormal DCIS cells are contained within the layer of cells where they originated, they cannot spread to other organs and cause serious illness or death. However, if left untreated, DCIS has the potential to evolve into invasive cancer and is considered a true cancer precursor. The main goal of treatment for DCIS is to prevent progression to invasive cancer.

Table 1. Ductal carcinoma in situ incidence rates* by race, ethnicity and age group, US, 2007-2011

Age	All races	Non-Hispanic White	Non-Hispanic Black	Asian and Pacific Islander	American Indian and Alaska Native†	Hispanic/Latina
All ages	**25.8**	**26.6**	**26.5**	**23.9**	**14.4**	**17.9**
20-39 years	3.4	3.7	3.5	3.4	1.9	2.1
40-49 years	37.9	40.7	32.8	42.1	20.5	25.9
50-59 years	57.9	59.8	56.9	57.0	33.4	41.7
60-69 years	81.8	82.9	91.3	70.1	49.6	58.2
70-79 years	84.3	85.8	94.6	66.8	46.3	57.2
≥80 years	47.4	47.6	55.8	33.2	19.4	32.2

Hispanic origin is not mutually exclusive from Asian/Pacific Islander or American Indian/Alaska Native. *Per 100,000 females and age adjusted to the 2000 US standard population. †Data based on Indian Health Service Contract Health Service Delivery Areas. Rates exclude data from Kansas.

Source: North American Association of Central Cancer Registries (NAACCR), 2014.

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There is some uncertainty and debate about the benefits and harms of detecting and treating DCIS. Data are very limited about the proportion of detected DCIS lesions that will progress to invasive cancer because almost all women receive some treatment. Long-term follow-up studies of women whose DCIS was untreated because it was originally misclassified as benign found that 20-53% were diagnosed with an invasive cancer over the course of 10 years or more.[5-9] These studies suggest that untreated DCIS has the potential to eventually become invasive. On the other hand, it also follows that some women treated for DCIS might not have developed an invasive breast cancer in the absence of treatment.

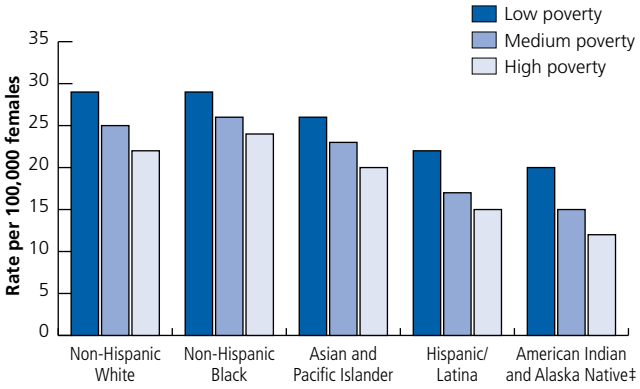
Overdiagnosis and overtreatment of DCIS (terms that are used to describe diagnosis and treatment of diseases that would have gone undetected in the absence of screening) are of concern because the diagnosis, treatment, and follow-up can affect long-term health and quality of life. Overdiagnosis of DCIS does not mean that the patient had a benign condition that was mistakenly classified as DCIS. Rather, it means that some cases of DCIS would not progress to invasive carcinoma, and that current diagnostic methods are not yet accurate enough to reliably distinguish these cases from DCIS cases that should be treated to avoid progression to invasive cancer.

Like invasive breast cancers, DCIS lesions are diverse in many ways, some of which may influence the likelihood of progression to invasive cancer or recurrence. Factors that are measured to estimate the likelihood of progression or recurrence are referred to as "prognostic factors," while those that indicate responsiveness to a particular treatment are referred to as "predictive factors." Prognostic and predictive factors that are measured for DCIS include nuclear grade, histology, size, and estrogen receptor status.[10] Many of these factors also influence the risk of a DCIS lesion containing or bordering an area of invasive cancer.

- **Nuclear grade** describes how different the nuclei of tumor cells (the central part of cells that contains their DNA) look compared to those of normal cells. Higher-grade tumors have more cells with abnormal-looking nuclei and have a greater probability of progression and recurrence.
- **Histology** identifies subtypes of DCIS based on how the cells are arranged when viewed under a microscope. DCIS is generally classified as papillary, solid, comedo, micropapillary, or cribriform. The comedo type of DCIS typically has more aggressive characteristics, such as high nuclear grade and high proliferation (growth) rate.[11]
- **Size** of the DCIS lesion can be difficult to measure because, rather than being a solid mass, the lesion often follows the branching structure along several milk ducts. The size of the DCIS is associated with recurrence, in part because it is more difficult to ensure complete removal of widespread branching lesions. The extent of breast tissue harboring DCIS is also associated with the likelihood of having a microscopic component of invasive cancer within the affected breast.
- **Estrogen receptor status** influences the recommendation for hormonal therapy. Like invasive breast cancers, DCIS tumors may contain estrogen receptors (ER). Treatment guidelines recommend that ER status be measured for DCIS because tamoxifen therapy may be recommended for women with ER positive (ER+) tumors in order to decrease the risk of recurrence or reduce the risk of new breast cancers developing.

Other tumor characteristics that are routinely measured for invasive breast cancers may also be measured in DCIS lesions, but are not considered clinically relevant for DCIS because they do not influence treatment, include progesterone receptor (PR) status and human epidermal growth factor receptor 2 (HER2) status.

Figure 1. Ductal carcinoma in situ incidence rates* by race, ethnicity, and county-level poverty†, US, 2007-2011



Hispanic origin is not mutually exclusive from Asian/Pacific Islander or American Indian/Alaska Native. *Per 100,000 females and age adjusted to the 2000 US standard population. †Low poverty: county poverty rate <10%; medium poverty: county poverty rate 10.0% - 19.9%; high poverty: county poverty rate ≥20.0%. ‡Data based on Indian Health Service Contract Health Service Delivery Areas. Rates exclude data from Kansas.

Source: NAACCR, 2014.

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DCIS incidence in the most recent time period (2007-2011)

Diagnosis of DCIS rarely occurs among women younger than 40, the age at which it is recommended for women of average risk of breast cancer to begin mammography screening.[12] In general, DCIS incidence rates increase with age and peak at ages 70-79 (Table 1). Overall incidence rates are similar for non-Hispanic white, non-Hispanic black, and Asian/Pacific Islander women; lower among Hispanic women; and lowest for American Indian/Alaska Native women (Table 1). Lower incidence rates of DCIS in Hispanic and American Indian/Alaska Native women may be in part because of inaccurate identification of race and ethnicity for these populations, as well as lower access to and utilization

of mammography. Within each racial and ethnic subgroup, DCIS rates vary consistently with county poverty level. The highest DCIS incidence rates are observed in low poverty areas (county poverty rate <10%), and the lowest incidence rates are observed for high poverty areas (county poverty rate of 20% or higher) (Figure 1, page 27). Patterns of DCIS incidence by county poverty level may largely reflect lower prevalence of mammography in low-income and uninsured women.[13]

The incidence rate for DCIS also varies by state. Among women 40 and older, the average annual age-adjusted incidence rates from 2007 to 2011 were lowest in New Mexico (38.1 per 100,000 women), West Virginia (42.5), and Wyoming (43.2), and were highest in Connecticut (80.1), Massachusetts (76.3), and Hawaii (73.0). This more than 2-fold variation reflects differences in screening prevalence, as well as the racial and ethnic makeup of US states. Incidence of DCIS by state is strongly associated (r=0.72) with prevalence of mammography screening (Figure 2).

Table 2 shows the distribution of prognostic factors among DCIS lesions diagnosed in the most recent time period. The majority are small (< 2cm: 51%), higher grade (70% are grade II or higher) or have unspecified histologic type (DCIS, NOS: 68%). Similar to invasive breast cancer, most DCIS lesions are ER+ (72% versus 74% of invasive breast cancers). The distribution of ER status does not differ markedly by race, which is unlike invasive breast cancer, for which non-Hispanic black women have a notably higher percentage of ER- tumors than women of other race/ethnicities (28% versus 15-19%, respectively). Invasive ER- breast tumors tend to be more aggressive and are more difficult to treat because there are no targeted therapies available.

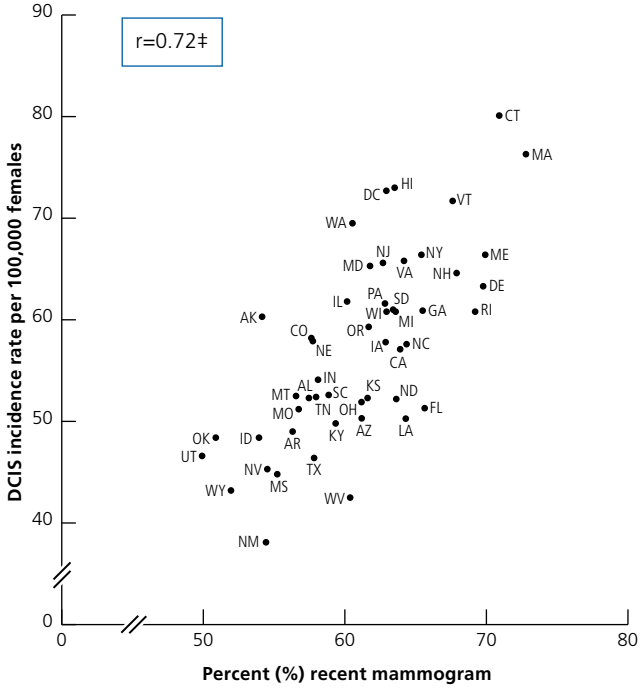
DCIS incidence trends

The incidence of DCIS increased rapidly following the introduction of mammography as a population screening tool in the US from the late 1980s until about 1998, after which it increased at a much slower rate.[14-16] From 2007 to 2011, the DCIS incidence rate for all ages combined increased 0.8% per year on average. Figure 3 shows trends in incidence rates from 1992-2011 for 3 age groups of women. All 3 groups show rapidly increasing trends through the late 1990s, followed by a slower rate of increase for women ages 40-49 and 70-79 and stable rates for women ages 50-69. This pattern is likely explained by the leveling-off of mammography screening in the early 2000s.[13]

Declines in invasive breast cancer rates were observed when many women stopped taking combined menopausal hormone therapy (MHT) after the 2002 release of the Women's Health Initiative findings of an increased risk of invasive breast cancer among users.[17] Although the statistical model (Joinpoint) used to detect changes in trend does not find a significant change in incidence rates of DCIS beginning in 2002 for any of the 3 age groups of women displayed in Figure 3, the data points suggest a drop in DCIS incidence from 2002 to 2006 for women ages 50 to 79. This decline is supported by the results of a study conducted in a regularly screened population of women within the Breast Cancer Screening Consortium (BCSC), which found that the incidence of DCIS declined significantly in women ages 50 to 79 from 2002 to 2006.[18] The BCSC study also found that MHT use among women 50 to 69 declined from a steady state of 4,800 per 10,000 screening mammograms from 1997 to 2001 to approximately 1,300 per 10,000 screening mammograms in 2006.

When incidence rates from 1992 to 2011 are examined by race and ethnicity, it appears that the rise and plateau in incidence of DCIS in US women occurred earlier in non-Hispanic whites than in non-Hispanic blacks and Asians/Pacific Islanders, although their incidence rates and trends have been similar in recent years (Figure 4, page 30). DCIS incidence rates rose much more

Figure 2. Association between state-level prevalence of mammography screening* (2008) and incidence rates† of ductal carcinoma in situ (2007-2011) among women ≥40 years



DCIS: ductal carcinoma in situ. *Percent of women ≥40 years who reported having a mammogram within the past year. †Rates are per 100,000 females and age adjusted to the 2000 US standard population. ‡Pearson correlation coefficient.

Source: Mammography screening prevalence – Behavior Risk Factor Surveillance System 2008, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2010. Incidence – NAACCR, 2014. Not all states met high-quality standards for all years according to NAACCR. DCIS incidence rate for Arkansas is based on incidence data for the years 2007-2009; for Nevada, the rate is based on incidence data for the years 2007-2010. Minnesota did not submit 2007-2011 incidence data to NAACCR and is not included.

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Table 2. Distribution of prognostic characteristics among ductal carcinoma in situ cases by race and ethnicity, US, 2007-2011

Prognostic characteristic	All races	Non-Hispanic White	Non-Hispanic Black	Asian and Pacific Islander	American Indian and Alaska Native*	Hispanic/ Latina
Estrogen receptor (ER) status†						
ER+	72%	71%	75%	75%	66%	70%
ER-	13%	13%	11%	12%	14%	11%
Missing	16%	15%	15%	14%	20%	19%
Grade‡						
Grade I	14%	14%	15%	13%	16%	14%
Grade II	34%	33%	36%	40%	31%	34%
Grade III/IV	36%	37%	31%	36%	34%	34%
Missing	16%	16%	18%	12%	19%	18%
Histologic subtype						
DCIS, NOS	68%	68%	68%	68%	66%	69%
Comedocarcinoma	10%	10%	9%	9%	13%	9%
Papillary	4%	4%	6%	4%	4%	5%
Cribriform	10%	10%	10%	11%	10%	10%
Solid	8%	8%	7%	7%	7%	7%
Size (cm)						
<2.0	51%	52%	46%	53%	53%	48%
2.0-4.9	13%	12%	14%	18%	12%	14%
≥5.0	4%	4%	6%	4%	4%	4%
Missing	33%	33%	34%	24%	31%	34%

DCIS, NOS: ductal carcinoma in situ, not otherwise specified. ER+ includes borderline status. Hispanic origin is not mutually exclusive from Asian/Pacific Islander or American Indian/Alaska Native. *Data based on Indian Health Service Contract Health Service Delivery Areas and exclude cases from Kansas. †Based on cases diagnosed between 2009-2011 with more complete data. ‡Although nuclear grade for DCIS is usually reported on a scale of 1-3, cancer registry data are reported on a scale of I-IV.

Source: NAACCR, 2014.

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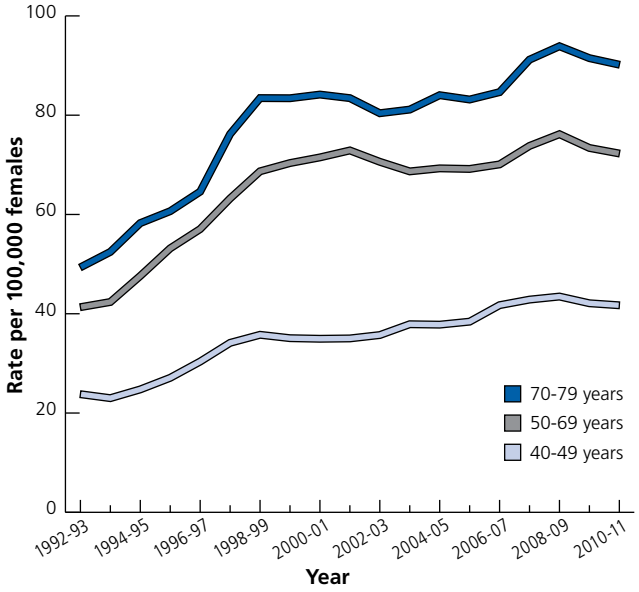
slowly among Hispanics and American Indians/Alaska Natives, likely due to slower rates of mammography uptake, as well as potential misclassification of race and ethnicity. Incidence trends for DCIS also showed variation by county poverty level, similarly reflecting slower mammography screening uptake among low-income women (Figure 5, page 31).

Risk factors for DCIS

Mammography screening can be considered a risk factor for DCIS because the incidence is much lower in women who are not screened. However, while mammography screening results in the detection of DCIS lesions, it does not actually cause the disease. Until recently, there has been little information about the risk factors for DCIS, as many epidemiologic studies of breast cancer risk factors either exclude women with DCIS, or have relatively small numbers of women with DCIS. However, in recent years greater clarity about DCIS risk factors has begun to emerge.

In general, studies suggest that DCIS and invasive breast cancer share many similar risk factors.[15,19-21] Results from one of these recent studies are summarized in Table 3 (page 32).[19] In this study, which included 1.2 million women living in the United Kingdom, the risk of DCIS was higher for women who had fewer

Figure 3. Trends in ductal carcinoma in situ incidence rates* by age, US, 1992-2011



*Per 100,000 females, two-year moving averages, age adjusted to the 2000 US standard population, and adjusted for reporting delay.

Source: Surveillance, Epidemiology, and End Results (SEER) Program, 13 SEER registries, National Cancer Institute, 2014.

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or no children, were older at the time of first birth, or reached menopause after age 50. DCIS incidence was not associated with age at menarche in this study; however, this study also found no association between earlier age at menarche and invasive breast cancer unlike most other studies (Table 3, page 32). With respect to nonreproductive risk factors, the study found no association between DCIS and body mass index (BMI) or alcohol consumption, but risk was increased among women with a family history of breast cancer and current and past users of MHT.

The Women's Health Initiative (WHI) study, which documented the association between MHT use and invasive breast cancer, also reported on associations between MHT use and DCIS.[22] While not statistically significant, the results for DCIS were in the same direction as the results for invasive breast cancer, suggesting that estrogen plus progestin use may be associated with an increased risk of DCIS, while use of estrogen alone may be associated with a decreased risk.[22] An important feature of this study was that all participants had regular screening mammography, which ensured that hormone and non-hormone users had equal probability of DCIS detection.

High breast density is a risk factor for invasive breast cancer and may also increase risk for DCIS. A pooled analysis of six studies including more than 10,000 women found that the association between breast density and DCIS risk was largest for women younger than age 55.[23] In this age group, higher mammographic density was associated with about a 2-fold increased risk for DCIS as compared to women with lower breast density. For women ages 55-64, high density was associated with about a 1½-fold increased risk.

Breast density is also a risk factor for the development of contralateral breast cancer (i.e., breast cancer in the unaffected breast) after DCIS treatment. In one prospective study of women treated with lumpectomy for DCIS between 1993 and 2005, high breast density was associated with about a 3-fold increased risk of invasive breast cancer in the contralateral breast as compared to women with low and average breast density.[24]

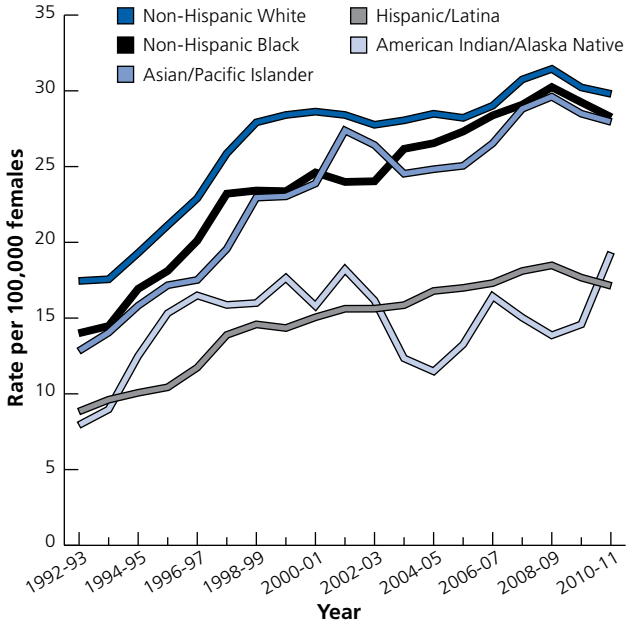
The use of drugs to reduce the risk of disease is called chemoprevention. Clinical trials of chemoprevention agents for women at high risk of breast cancer have found decreased incidence of DCIS among women receiving tamoxifen or raloxifene.[25]

Treatment for DCIS

Treatment for DCIS usually involves either breast-conserving surgery (BCS) with radiation therapy or mastectomy.

BCS removes a part of the affected breast, including the area where DCIS is found, along with a margin of healthy tissue. If the removed tissue is later found to also contain invasive cancer, staging of the axillary (underarm) lymph nodes is needed. This is most often done using a minimally invasive staging procedure called a sentinel lymph node biopsy.

Figure 4. Trends in ductal carcinoma in situ incidence rates* by race and ethnicity, US, 1992-2011



Hispanic origin is not mutually exclusive from Asian/Pacific Islander or American Indian/Alaska Native. *Per 100,000 females, two-year moving averages, age adjusted to the 2000 US standard population, and adjusted for reporting delay. †Data based on Indian Health Service Contract Health Service Delivery Areas.

Source: SEER Program, 13 SEER registries, National Cancer Institute, 2014.
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Radiation therapy is recommended for most women who have BCS because randomized trials show strong and consistent evidence that radiation therapy after BCS approximately halves the rate of recurrence in the affected breast. A recent combined analysis of four clinical trials found that at 5 years after treatment, 18% of women who had BCS alone had experienced a recurrence, compared to 8% of women who had BCS plus radiation therapy.[26] After 10 years of follow-up, 28% of women who received BCS alone had experienced a recurrence, compared to 13% of women who received BCS plus radiation therapy. In both treatment groups, about half of the recurrences were DCIS and half were invasive breast cancer.

Although radiation therapy has a clear benefit in reducing the risk of recurrence among DCIS patients who receive BCS, there are some drawbacks and risks. Radiation is delivered to the whole breast and requires a commitment to daily treatment for six weeks. Patients receiving radiation therapy may experience short-term side effects including fatigue and skin toxicity, as well as a slightly increased risk of secondary cancers.[27,28]

A number of studies have tried to identify patients with DCIS who have a low enough risk of recurrence that they can safely be treated by BCS alone. While some studies have demonstrated radiation therapy can be safely omitted in carefully selected low-risk patients (based on Van Nuys Prognostic Index), others have

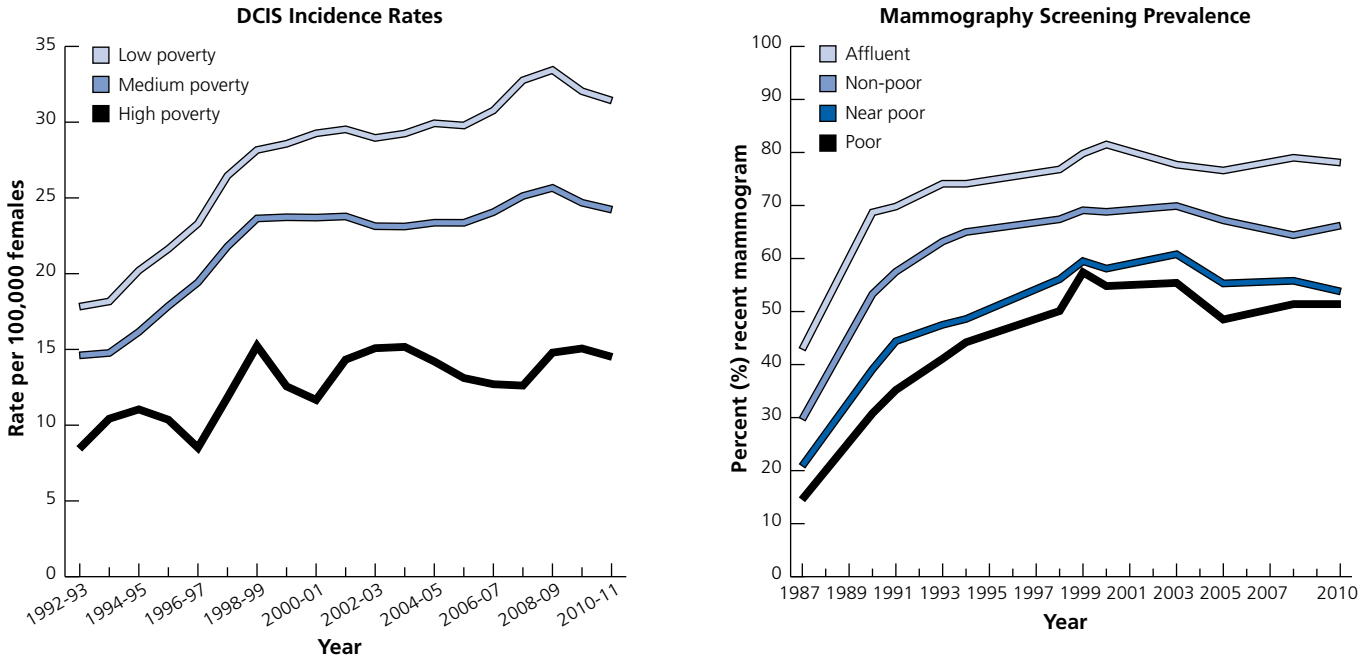
found similar rates of recurrence across risk groups.[29-31] The National Comprehensive Cancer Network (NCCN) treatment guidelines suggest that BCS followed by observation is a reasonable option for some women with low-risk disease.[32]

Mastectomy, removal of the entire breast, is the most common alternative to BCS plus radiation for the treatment of DCIS. Because a lesion thought to be DCIS can contain an area of invasive cancer, mastectomy for DCIS may be accompanied by a sentinel lymph node biopsy. Until the early 1990s, mastectomy was the standard treatment for DCIS. The evolution of BCS and radiation therapy as the standard treatment was brought about by increased detection of asymptomatic DCIS diagnosed in the mammography era, the acceptance of BCS plus radiation therapy as standard therapy for invasive cancers, and the publication of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial, which reported that the addition of radiation to BCS reduced the risk of local recurrence.[33] As a result, mastectomy rates among DCIS patients decreased from 46% in 1991 to 25% in 2005.[34]

While it is no longer the standard treatment for DCIS, mastectomy remains an acceptable option and is the recommended treatment for some women, including patients with DCIS involving 4-5 cm of disease or more than one area of the breast, those with a large tumor-to-breast ratio, those who should not receive radiation due to certain medical conditions or have received prior radiation therapy, and those for whom negative margins could not be achieved with BCS.[35] Women who have a mastectomy for DCIS have a very low probability of recurrence in the treated breast, but remain at increased risk of developing DCIS or invasive breast cancer in the untreated (contralateral) breast. A study of 18,845 patients diagnosed with DCIS in 1973-1996 found that the cumulative risk of contralateral invasive or in situ breast cancer was 3% at 5 years, 6% at 10 years, 9% at 15 years, and 11% at 20 years.[36] Women treated with unilateral mastectomy are followed with clinical breast examination and mammography to screen for DCIS or invasive cancers in the contralateral breast. Magnetic resonance imaging (MRI) of the breast may also be an option for women with a history of DCIS who are at high risk due to certain other risk factors.[37]

Some women with unilateral DCIS choose to have bilateral mastectomy to prevent cancer in the unaffected breast.[38] This is more common in younger women. Studies suggest that the decision to have a bilateral mastectomy may be influenced by the presence of other breast cancer risk factors, including a family history. However, some women make this decision primarily based on worry about recurrence.[39]

Figure 5. Trends in ductal carcinoma in situ incidence rates* (1992-2011) by county-level poverty† (left) and mammography screening‡ prevalence (1987-2010) by individual-level poverty§ (right), US



*Per 100,000 females, two-year moving averages, age adjusted to the 2000 US standard population, and adjusted for reporting delay. †Low poverty: county poverty rate <10%; medium poverty: county poverty rate 10.0% - 19.9%; high poverty: county poverty rate ≥20.0%. ‡Screening mammogram within the past 2 years. §Poor: below federal poverty level; near poor: 100% to 199% of federal poverty level; non-poor: 200%-399%; affluent: 400% or more.

Source: Incidence – SEER Program, 13 SEER registries, National Cancer Institute, 2014. Mammography screening prevalence – National Center for Health Statistics. Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD; 2014.

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Table 3. Risk factors for in situ and invasive ductal breast cancer among postmenopausal women

	In Situ Disease Relative Risk*	Invasive Disease Relative Risk*
Reproductive risk factors		
Age at menarche		
<12 years	1.02	1.03
12-13 years	1.00 (ref.)	1.00 (ref.)
≥14 years	0.99	0.98
Number of children		
0	1.00 (ref.)	1.00 (ref.)
1	0.81†	0.87†
2	0.76†	0.81†
≥3	0.66†	0.71†
Age at first birth		
<20 years	1.00 (ref.)	1.00 (ref.)
20-24 years	1.07†	1.01
25-29 years	1.15†	1.11†
≥30 years	1.31†	1.24†
Age at menopause‡		
<45 years	0.64†	0.76†
45-49 years	0.77†	0.88†
50-54 years	1.00 (ref.)	1.00 (ref.)
≥55 years	1.08	1.24†
Nonreproductive risk factors		
BMI (kg/m^2)‡		
<25	0.98	0.82
25-29.9	1.00 (ref.)	1.00 (ref.)
≥30	0.99	1.18
Family history of breast cancer		
Yes	1.57†	1.60†
No	1.00 (ref.)	1.00 (ref.)
Alcohol intake (units/day)		
Non-drinkers	0.97	1.00
<0.3	1.00 (ref.)	1.00 (ref.)
0.3-0.9	0.96	1.05†
1.0-2.0	0.97	1.12†
>2.0	1.11	1.28†
MHT use		
Never	1.00 (ref.)	1.00 (ref.)
Past	1.14†	1.07†
Current	1.51†	1.67†

BMI: body mass index; MHT: menopausal hormone therapy. *Relative risk compares the risk of disease among people with a particular "exposure" to the risk among people without that exposure. If the relative risk is more than 1.00, then the risk is higher among exposed than unexposed. Relative risks less than 1.00 indicate a protective effect. †Relative risk is significant (p<0.05). ‡Among never users of MHT.

Source: Adapted with permission from Reeves GK, Pirie K, Green J, et al. Comparison of the effects of genetic and environmental risk factors on in situ and invasive ductal breast cancer. *Int J Cancer.* 2012; 131(4):930-7.

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Women who undergo mastectomy for DCIS may also elect to have breast reconstruction. In a population-based study of DCIS patients in Southern California who were treated with mastectomy between 2003 and 2007, nearly half (46%) had immediate reconstruction, with higher utilization of reconstruction among younger women, non-Hispanic white women, and privately insured women.[40]

For women with ER+ DCIS, hormonal therapy with tamoxifen is associated with a significantly decreased risk of invasive cancer and DCIS in either breast.[41, 42] Treatment guidelines in the US recommend tamoxifen as an option for women with ER+ DCIS treated with either BCS or unilateral mastectomy to reduce their risk of developing another DCIS lesion or invasive breast cancer as long as they do not have specific contraindications (e.g., history of deep vein thrombosis, pulmonary embolism, or uterine cancer).[43] Clinical trials are currently underway to determine whether medications called aromatase inhibitors can be used as an alternative to tamoxifen in postmenopausal patients.[44]

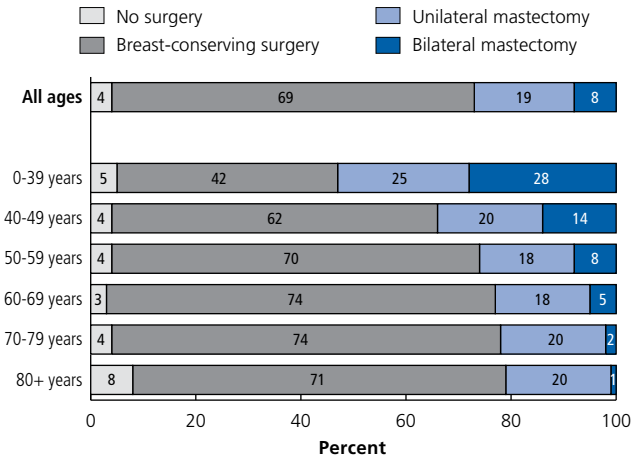
Several initiatives are underway to identify additional biomarkers that can improve prediction of the risk of recurrence to better tailor treatment to risk. For example, the Oncotype DCIS Score, which measures the expression of a group of cancer genes in the tumor tissue, has been developed and validated as a predictor of recurrence in selected patients treated with BCS without radiation.[45] So far, however, it has not been studied to see how well it predicts the benefit of radiation. Although HER2 status is not routinely measured, a clinical trial is currently evaluating whether treatment with trastuzumab in addition to BCS and radiation therapy is beneficial for high-risk HER2+ DCIS patients.[46]

Treatment patterns for DCIS

Among women of all ages diagnosed with a primary DCIS in the US from 2007 to 2011, the most common surgical treatment was BCS (69%), followed by unilateral mastectomy (19%), bilateral mastectomy (8%), and no surgery (4%) (Figure 6). Patterns of surgical treatment showed only modest variation by race/ethnicity (data not shown). The majority of women (68%) who received BCS also received radiation therapy (Table 4). The percentage of women who had breast reconstruction was 33% for those who had unilateral mastectomy and 62% for those with bilateral mastectomy. Only 39% of patients with ER+DCIS were noted to have received hormonal therapy (e.g., tamoxifen) in registry records (Table 4). However, cancer registry data are less complete for chemotherapy and hormonal treatment than for other forms of therapy, so the actual proportion may be higher.

Age at diagnosis was strongly associated with the type of treatment received (Figure 6). Younger women were substantially more likely to undergo mastectomy. In fact, the majority of breast cancer patients younger than 40 underwent mastectomy (53%), opting for bilateral mastectomy slightly more often than

Figure 6. Treatment patterns for primary ductal carcinoma in situ patients by age at diagnosis, US, 2007-2011



Based on patients with known treatment information and excludes treatment coded Surgery, not otherwise specified (NOS).

Source: NAACCR, 2014.

American Cancer Society, Inc., Surveillance Research, 2015

unilateral mastectomy (28% versus 25%, respectively). The proportion of DCIS patients undergoing bilateral mastectomy has increased over the past 2 decades, from 2% of patients in 1998 to 8% in 2011. Women ages 40-69 were most likely to receive radiation therapy after BCS and hormone therapy for ER+ breast cancer (Table 4).

Although NCCN treatment guidelines do not formally stratify by age, it is one of the factors considered in the University of Southern California/Van Nuys Prognostic Index, which is used to predict local recurrences for women with DCIS.[47] Clinical trials and population studies of DCIS outcomes generally find higher recurrence rates for younger women (younger than age 50) compared to older women.[48] In addition, younger women have a longer life expectancy and, therefore, a longer opportunity to experience a second breast event and/or multiple diagnostic mammograms and biopsies, which may influence preferences for mastectomy over BCS for younger women.[49]

What is LCIS?

Lobular carcinoma in situ (LCIS) refers to cells that look like cancer cells growing within the walls of the lobules, the milk-producing glands of the breast. LCIS is not generally thought to be a precursor of invasive cancer. Instead, it is considered a marker for increased risk of developing invasive breast cancer. The exception is a relatively uncommon variant of LCIS known as pleomorphic LCIS, in which the cells look more atypical under the microscope. Pleomorphic LCIS is linked to a higher risk of invasive cancer and is often treated as though it is a cancer precursor.[50]

The strongest evidence that LCIS is more of a risk indicator than a direct cancer precursor comes from registry-based studies. One study of women diagnosed with LCIS from 1973 to 1998 and treated with BCS found that 7% of women developed invasive breast cancer within 10 years, with the increased risk of invasive disease equally distributed between both breasts.[51] Care for women with LCIS emphasizes medical surveillance and risk reduction strategies for both breasts rather than local treatment, such as BCS plus radiation therapy, as is recommended for DCIS patients.

LCIS incidence and trends

The incidence rate of LCIS was 3.9 per 100,000 women during 2007-2011 (Table 5, page 34), about one-seventh the rate of DCIS. The incidence of LCIS peaks in women ages 50-59 and is higher for non-Hispanic white women compared to other racial and ethnic groups (Table 5, page 34). LCIS is not easily detectable by mammography, but is often detected in biopsies performed to investigate mammographic abnormalities. Thus, like the incidence of DCIS, the incidence of LCIS increased in conjunction with increasing use of mammography from 1992 to 2000. LCIS incidence rates among women ages 50-69 show a pronounced decline beginning around 2002, although the trend is not significant (Figure 7, page 34). This finding is notable because for invasive breast cancer, studies have shown stronger associations between MHT use and lobular than ductal tumors.[52]

Treatment for LCIS

If LCIS is found when a mammographically suspicious lesion is biopsied, the entire suspicious area is often removed as part of the diagnostic workup. This is usually done to rule out the presence of DCIS or invasive cancer. Generally, however, no attempt is made to remove all of the LCIS. There is some debate about

Table 4. Use of radiation therapy (RT) and hormone therapy among primary ductal carcinoma in situ patients by age at diagnosis, US, 2007-2011

	RT among patients receiving BCS	Hormone therapy among patients with ER+ DCIS*
All ages	**68%**	**39%**
0-39 years	67%	34%
40-49 years	73%	43%
50-59 years	73%	44%
60-69 years	71%	41%
70-79 years	61%	32%
≥80 years	37%	19%

BCS: breast-conserving surgery; ER+: Estrogen receptor positive. *Excludes patients with bilateral mastecomy.

Source: NAACCR, 2014.

American Cancer Society, Inc., Surveillance Research, 2015

Table 5. Lobular carcinoma in situ incidence rates* by race, ethnicity, and age group, 2007-2011

Age	All races	Non-Hispanic White	Non-Hispanic Black	Asian and Pacific Islander	Hispanic/ Latina
All ages	**3.9**	**4.4**	**2.6**	**2.1**	**2.7**
20-39 years	0.6	0.7	0.4	0.5	0.4
40-49 years	9.4	10.8	5.5	6.0	6.6
50-59 years	11.2	12.7	7.2	5.5	7.4
60-69 years	8.6	9.3	6.4	3.5	6.3
70-79 years	6.0	6.5	5.1	2.2	3.6
≥80 years	2.4	2.6	2.0	1.3	1.5

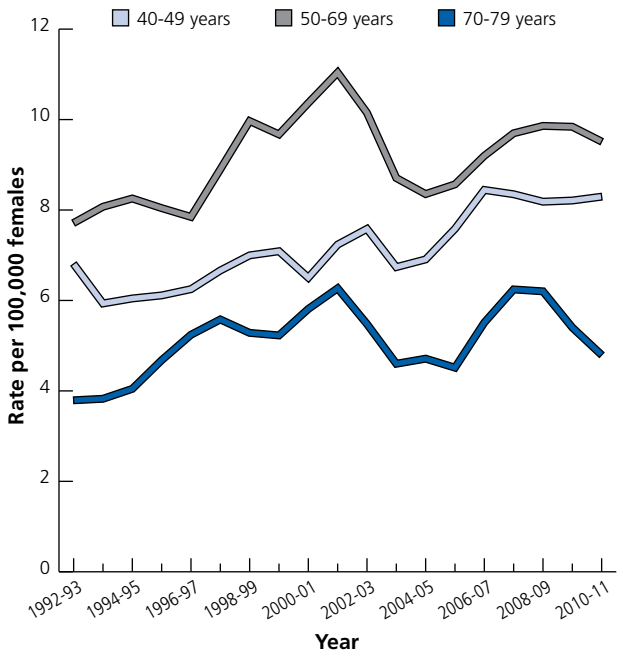
Hispanic origin is not mutually exclusive from Asian/Pacific Islander. Rates for American Indian/Alaska Natives not shown due to sparse data. *Per 100,000 females and age adjusted to the 2000 US standard population.

Source: NAACCR, 2014.

American Cancer Society, Inc., Surveillance Research, 2015

whether a surgical biopsy is necessary for all women diagnosed with LCIS on core biopsy.[32] Since pure LCIS will not cause any clinical findings, such as a lump or a mammographic abnormality, a follow-up surgical biopsy may be necessary to ensure that the lesion prompting the biopsy has been adequately investigated. Complete removal with negative margins is considered important for the more histologically aggressive pleomorphic LCIS.[32]

Figure 7. Trends in lobular carcinoma in situ incidence rates* by age, US, 1992-2011



*Per 100,000 females, two-year moving averages, age adjusted to the 2000 US standard population, and adjusted for reporting delay.

Source: SEER Program, 13 SEER registries, National Cancer Institute, 2014.

American Cancer Society, Inc., Surveillance Research, 2015

Guidelines do not recommend unilateral mastectomy as a standard treatment for LCIS because risk of future breast cancer is equal for both breasts. Bilateral mastectomy may be considered as a risk reduction strategy, especially for women with LCIS and a strong family history of breast cancer. Among US women with a primary LCIS diagnosed during 2007 to 2011, 81% underwent BCS**, 9% had mastectomy (4% unilateral, 5% bilateral), and 11% did not receive surgical treatment (Figure 8). Mastectomy was most common among women younger than age 40, with 9% of LCIS patients in this age group undergoing bilateral mastectomy and 4% undergoing unilateral mastectomy (Figure 8). The proportion of women with LCIS who received mastectomy has increased significantly over time, from 12% in 2000 to 18% in 2009.[53]

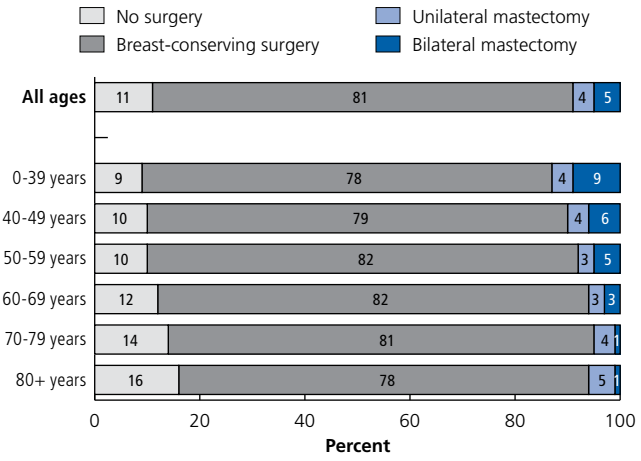
Medical surveillance recommendations from the NCCN for women with LCIS include annual mammography and clinical breast exam every 6-12 months.[54] Although the lifetime risk of invasive breast cancer for a woman with LCIS may exceed 20% (depending on the age at diagnosis), the American Cancer Society guidelines do not support routine use of MRI screening for surveillance of women with LCIS because the evidence for its effectiveness as an addition to mammography has not been demonstrated.[37] Both the American Society of Clinical Oncology (ASCO) and NCCN recommend discussing chemoprevention therapy with LCIS patients; tamoxifen is the only option for premenopausal women, and tamoxifen or raloxifene may be recommended for postmenopausal women, depending on other health conditions.[41,43] ASCO also lists exemestane, an aromatase inhibitor, as an option in postmenopausal women; however, this is not an FDA-approved indication for this drug.

Conclusion

Although carcinoma in situ is a relatively common diagnosis, it is not as widely known or understood as invasive breast cancer. Many patients may find it difficult to understand the implications of the diagnosis for their health and the advantages and

** Coding of surgical procedures includes surgical removal of the involved segment of a breast in the code for "excision or BCS." Although women with DCIS and LCIS are both treated with "excision or BCS," there are some differences in the approach to the two lesions. For DCIS, the presence of negative margins is considered essential, while for LCIS it is not. Thus, women with DCIS may have to have another resection if their surgical margins are not considered adequate. Re-excision is uncommon for LCIS as the primary purpose of the excision is diagnostic rather than therapeutic.*

Figure 8. Treatment patterns for primary lobular carcinoma in situ patients by age at diagnosis, US, 2007-2011



Based on patients with known treatment information and excludes treatment coded Surgery, NOS. Percents may not sum to 100 due to rounding.

Source: Source: NAACCR, 2014.

American Cancer Society, Inc., Surveillance Research, 2015

disadvantages of different treatment options. We hope that this information will be useful to patients who are facing the disease, as well as to friends, family, and others who can provide support and perspective for women who are newly diagnosed and those living after a diagnosis of DCIS or LCIS.

Please see page 9 for information on invasive breast cancer. Additional information can be found in *Breast Cancer Facts & Figures* available at cancer.org/statistics.

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