

ARTICLE

Ductal Carcinoma In Situ of the Breast: A Systematic Review of Incidence, Treatment, and Outcomes

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Background The National Institutes of Health Office of Medical Applications of Research commissioned a structured literature review on the incidence, treatment, and outcomes of ductal carcinoma in situ (DCIS) as a background article for the State of the Science Conference on Diagnosis and Management of DCIS.

Methods Published studies were identified and abstracted from MEDLINE and other sources. We include articles published between 1965 and January 31, 2009; 374 publications were identified that addressed DCIS incidence, staging, treatment, and outcomes in adult women.

Results In the United States, DCIS incidence rose from 1.87 per 100 000 in 1973–1975 to 32.5 in 2004. Incidence increased in all ages but more so in women older than 50 years. Increased use of mammography explains some but not all of the increased incidence. Risk factors for incident DCIS include older age and family history. Although tamoxifen treatment prevented both invasive breast cancer and DCIS, raloxifene treatment decreased incidence of invasive breast cancer but not DCIS. Among patients with DCIS, magnetic resonance imaging was more sensitive than mammography for detecting multicentric disease and estimating tumor size. Because about 15% of patients with DCIS identified on core needle biopsy are diagnosed with invasive breast cancer after excision or mastectomy, the accuracy of sentinel lymph node biopsy after excision is relevant to surgical management of DCIS. Most studies demonstrated that sentinel lymph node biopsy is feasible after breast-conserving surgery (BCS). Younger age, positive surgical margins, tumor size and grade, and comedo necrosis were consistently related to DCIS recurrence. DCIS outcomes after either mastectomy or BCS plus radiation therapy were superior to BCS alone. Tamoxifen treatment after DCIS diagnosis reduced risk of recurrent disease.

Conclusions Scientific questions deserving further investigation include the relationship between mammography use and DCIS incidence and whether imaging technologies and treatment guidelines can be modified to focus on lesions that are most likely to become clinically problematic.

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Ductal carcinoma in situ (DCIS) is noninvasive breast cancer that encompasses a wide spectrum of diseases ranging from low-grade lesions that are not life threatening to high-grade lesions that may harbor foci of invasive breast cancer. DCIS is characterized histologically by the proliferation of malignant epithelial cells that are bounded by the basement membrane of the breast ducts. DCIS is typically classified according to architectural pattern (solid, cribriform, papillary, and micropapillary), tumor grade (high, intermediate, and low), and the presence or absence of comedo necrosis. Before the advent of widespread screening mammography, DCIS was usually diagnosed by surgical removal of a suspicious breast mass. DCIS was rarely diagnosed before 1980, but currently about 25% of breast cancers that are diagnosed in the United States are DCIS (Figure 1) (1).

The fundamental question underlying treatment and detection of DCIS is whether it should be considered a direct precursor of

invasive breast cancer. Although studies of the natural history of invasive breast cancer are rare, there is general consensus that DCIS represents an intermediate step between normal breast tissue and invasive breast cancer. Because excisional biopsy (and, to a lesser extent, core needle biopsy) removes a substantial portion of the targeted lesion, the natural history of untreated DCIS is unknown. Data from population-based studies indicate that the 10-year breast cancer mortality rate for patients with DCIS is less than 2% after excision or mastectomy (2).

The following is a summary of a report requested by the National Institutes of Health Office of Medical Applications of Research as a background paper for the State of the Science Conference on Diagnosis and Management of DCIS. The report, which is available at <http://www.ahrq.gov/clinic/epcix.htm>, addresses four key questions: 1) What are the incidence and prevalence of DCIS and its specific pathologic subtypes, and how

are incidence and prevalence influenced by mode of detection, population characteristics, and other risk factors? 2) How does the use of magnetic resonance imaging (MRI) or sentinel lymph node biopsy (SLNB) impact important outcomes in patients diagnosed with DCIS? 3) How do local control and systemic outcomes vary in DCIS based on tumor and patient characteristics? 4) In patients with DCIS, what is the impact of surgery, radiation, and systemic treatment on outcomes?

Methods

Studies were sought from a wide variety of sources, including MEDLINE via PubMed, Scirus, Cochrane databases, Web sites of the Sloane Project and of the International Breast Cancer Screening Network, and manual searches of reference lists from systematic reviews and consensus conferences. We include articles published from 1965 through January 31, 2009.

We searched Medical Subject Headings (MESH) headings, titles, and abstracts for the terms Ductal Carcinoma In Situ, DCIS, noninfiltrating intraductal carcinoma, carcinoma in situ, intraductal carcinoma, ductal carcinoma in situ of the breast, localized breast cancer, and stage 0 breast cancer. Because this is a state-of-the-science report, we did not exclude studies by level of evidence. We reviewed abstracts to confirm eligible target populations of female adults. We excluded studies of invasive breast cancer only, non-breast ductal cancers (eg, pancreatic ductal cancer), animal or in vitro experiments, analysis of results from other publications, letters, comments, and case reports. We conducted a pilot test to assess agreement in eligibility status among the principal investigator and research assistants. We detected the reasons for disagreement to clarify eligibility criteria. The principal investigator reviewed randomly selected excluded cohort studies and clinical trials to confirm eligibility status.

Study quality was analyzed using the framework recommended in the manual of comparative effectiveness reviews (http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf). First, studies were classified on the basis of whether they were comparative study, whether investigators assigned exposure, and presence and strategy for random allocation. From this information, studies were classified as interventional or observational studies and by design (eg, randomized clinical trial, prospective cohort, and nested case-control).

Second, we evaluated the quality of observational studies using criteria for internal and external validity (3). We evaluated quality of interventional studies using criteria from the Cochrane manual, including randomization, adequacy of randomization and allocation concealment, masking of the treatment status, intention-to-treat principles, and justification of the sample size (4). We abstracted the following criteria of internal validity: masking of the treatment status, preplanned intention-to-treat analysis, adequacy of allocation concealment, randomization scheme, adequacy of randomization, similarity of comparison groups, validation of the methods to measure the outcomes, loss of follow-up, strategy to reduce bias in design, control for confounding factors in analyses, and reported estimates (crude and adjusted).

CONTEXT AND CAVEATS

Prior knowledge

Ductal carcinoma in situ (DCIS) is composed of noninvasive malignant-appearing cells confined to breast ducts.

Study design

Systematic review of the DCIS literature from 1965 through January 2009.

Contributions

DCIS incidence, risk factors, effects of preventive treatments, outcomes of chemotherapy, screening methods, and prognostic factors were highlighted.

Implications

Additional questions require further investigation: associations between mammography use and DCIS incidence and the modification of guidelines for imaging technologies and treatment to focus on clinically relevant tumors.

Limitations

Unpublished or ongoing studies could not be included, and studies that combined DCIS and invasive breast cancer were not included in the analysis.

From the Editors

Finally, we rated quality of the studies based on the *Manual of Comparative Effectiveness Reviews* (5). Studies were categorized into three groups: well designed (low risk of bias), fair (susceptible to some bias), and poor (high risk of bias).

Results

We abstracted results from 374 publications. The first question included 63 publications addressing incidence and 29 addressing risk factors; the second question included 64 publications for MRI and 50 for SLNB. Studies of outcomes were addressed in 10 articles reporting the results of randomized clinical trials and 133 publications describing observational experience. Some publications were used for more than one question. This article includes a highly abbreviated reference list.

Question 1: What Are the Incidence and Prevalence of DCIS and Its Specific Pathologic Subtypes, and How Are Incidence and Prevalence Influenced by Mode of Detection, Population Characteristics, and Other Risk Factors?

The incidence of DCIS has increased dramatically since the early 1970s. For example, the estimated incidence of DCIS in 2004 was 32.5 per 100 000 women. Although considerably higher than the 5.8 per 100 000 in 1975, the rate is considerably less than the invasive breast cancer incidence estimated to be 124.3 per 100 000 in 2004 (1). The incidence of comedo DCIS, a subtype that is considered particularly aggressive, has not increased as rapidly as the less aggressive noncomedo form. For example, an analysis based on the Surveillance, Epidemiology, and End Results cancer registries found that between 1991 and 2001, the age-adjusted incidence of comedo DCIS was unchanged at approximately seven per 100 000,

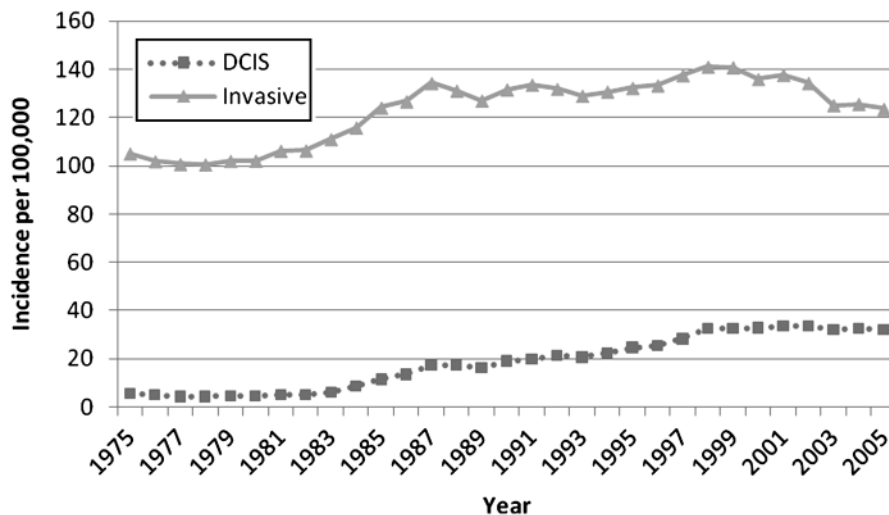


Figure 1. Trends in the age-adjusted incidence of ductal carcinoma in situ (DCIS) and invasive cancer (1975–2005).

whereas the age-adjusted incidence of non-comedo DCIS rose from 16.5 to 31 per 100 000 (Figure 2) (6).

Many of the key risk factors for DCIS are similar to those for invasive breast cancer. Table 1 summarizes the similarities and differences in these associations for DCIS risk factors.

Use of Hormone Replacement Therapy (HRT). The increased risk of invasive breast cancer associated with HRT with estrogen plus progestin is well established and reported in both observational and randomized studies. The association between HRT and DCIS was examined in five observational studies and one of two large randomized trials (7–11). None of the population-based studies found an association between ever use of HRT and DCIS incidence (9,10,12). Studies comparing current users with never users were inconsistent. The Iowa Women’s Health Study, a large prospective cohort, found no association between HRT use and DCIS for either women who were current users for less than 5 years or current users for more than 5 years (0.94 and 1.35, respectively) (9). The breast cancer surveillance consortium found current users for less than 5 years to have decreased risk and current users for more than 5 years to have increased risk of DCIS compared with never users (0.77 and 1.41, respectively) (10). The Women’s Health Initiative, a large randomized trial of HRT and breast cancer risk, found no increased risk of DCIS associated with HRT (13,14). The large Million Women Study cohort did not comment on whether they observed any increase in DCIS associated with HRT use.

Screening Using Mammography. The strongest evidence that the high incidence of DCIS can be attributed to the use of screening mammography comes from eight population-based trials of mammography screening. These trials were initiated between 1963 and 1982: the Health Insurance Plan study (15), the Malmö study (16), the Swedish Two-County trial (17), the Edinburgh trial (18), the Stockholm trial (19), the Canadian National Breast Screening Studies 1 and 2 (20,21), and the Gothenburg Breast Screening Trial (22). Mammographic screening consistently was more likely to lead to the diagnosis of invasive

breast cancer than of DCIS—all trials reported that less than 20% of screen-detected breast cancers were DCIS.

The conclusions from the randomized trials are supported by several population-based studies from the United States and around the world. Namely, although mammography results in increased detection of DCIS, the number of invasive cancers always outnumbers DCIS cases (23–25).

There is considerable evidence that the detection of DCIS is greatest at baseline screening. For example, the breast cancer surveillance consortium reported DCIS incidence of 150 per 1000 screening mammograms on first screening and incidence of 0.83 per 1000 for subsequent screening mammograms (26).

Chemoprevention of DCIS. Although several trials have been used to assess the value of tamoxifen or raloxifene for preventing DCIS, the trials, in reality, were designed to assess the value of the agents for preventing invasive breast cancer, with DCIS as a secondary outcome. Two large, placebo-controlled, double-blind, randomized clinical trials showed that tamoxifen had a protective role on the development of DCIS (and invasive breast cancer), whereas two smaller studies did not report this association (27–29). The NSABP-P1 and IBIS studies found reductions in both invasive and in situ breast cancer associated with tamoxifen use. The NSABP-P1 trial found similar relative risks (RRs) for DCIS and invasive cancer (RR = 0.63 and 0.57, respectively), whereas the IBIS study found a 69% reduction in DCIS incidence and only 25% reduction in invasive breast cancer. In contrast, the considerably smaller Royal Marsden trial found no difference in DCIS incidence and a non-statistically significant 22% reduction in invasive breast cancer. The Italian Randomized Tamoxifen Prevention Trial focused on women who had undergone hysterectomy and found a nonstatistically significant decrease in the cumulative incidence of combined invasive and noninvasive breast cancer associated with tamoxifen use [hazard ratio (HR) = 0.84 (30)].

The Study of Tamoxifen and Raloxifene (STAR) trial was a trial of more than 19 000 women who were randomly assigned to tamoxifen or raloxifene for preventing breast cancer. Women in the raloxifene group had 40% higher incidence of DCIS than

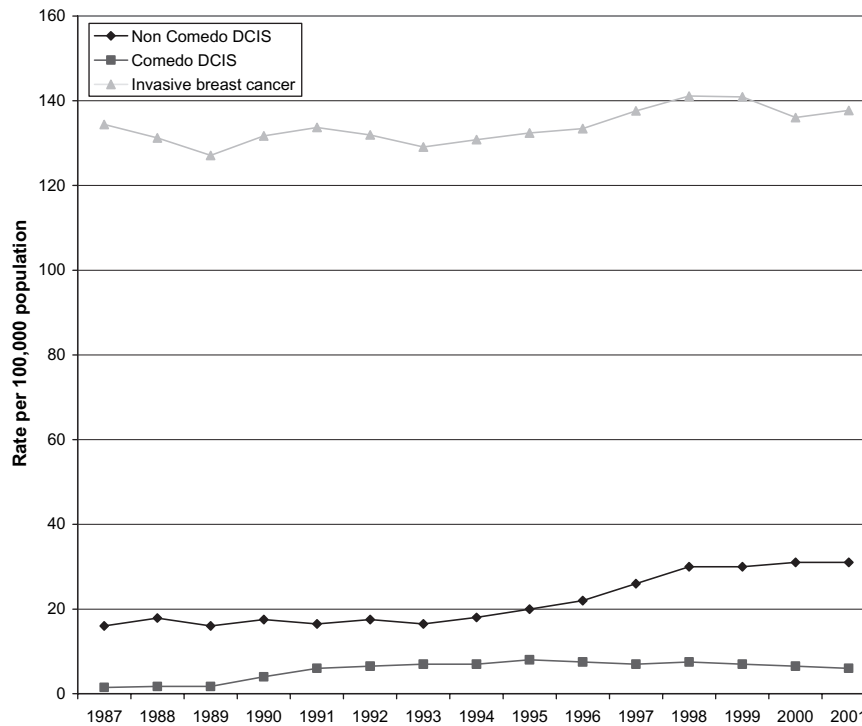


Figure 2. Trends in the age-adjusted incidence of comedo and non-comedo ductal carcinoma in situ (DCIS) and invasive breast cancer.

women in the tamoxifen group. However, the study also found with both treatments that the risk of invasive breast cancer decreased by half. Offsetting the higher incidence of DCIS was the observation that the women randomly assigned to raloxifene after 4 years had 36% fewer uterine cancers and 29% fewer blood clots than the women assigned to tamoxifen (31).

The Continuing Outcomes Relevant to Evista (CORE) and Multiple Outcomes of Raloxifene Evaluation (MORE) are placebo-controlled, randomized, double-blind trials examining the impact of raloxifene for preventing invasive breast cancer among postmenopausal women with osteoporosis (32). The CORE trial represents increased follow-up of the MORE population. The CORE study found statistically significantly reduced incidence of invasive breast cancer associated with raloxifene (HR = 0.41, 95% confidence interval [CI] = 0.24 to 0.71; $P < .001$) but a non-statistically significant increase in the incidence of DCIS among the treated women (HR = 1.78, 95% CI = 0.37 to 8.61, $P = .47$). The inconsistent impact of raloxifene and tamoxifen on DCIS and invasive breast cancer incidence deserves further investigation and may, ultimately, shed light on the biology of DCIS and invasive breast cancer and the factors that control invasive progression.

Question 2: How Does the Use of MRI or SLNB Impact Important Outcomes in Patients Diagnosed With DCIS?

Breast MRI is increasingly used in the pretreatment evaluation of patients with invasive breast cancer. The treatment of invasive cancer may be modified by MRI findings that may lead to wider excisions, unilateral mastectomy, and/or treatment of the contralateral breast. The use of breast MRI for patients with DCIS is not yet established. Because the presence of multicentric disease is generally considered a contraindication to breast-conserving sur-

gery (BCS), MRI can influence treatment recommendations for some patients. Among patients with DCIS, three studies found that the sensitivity of detecting multicentric disease is higher with MRI compared with mammography (33–35). These studies have reported sensitivities for detecting multicentric disease with MRI to range from 42% to 94%, whereas the sensitivities of mammogram range from 26% to 40%.

Breast MRI can potentially influence treatment decisions by providing more accurate information on the size and extent of the known DCIS. Such findings may determine the choice of BCS vs mastectomy or the width of excision margins. Given the growth pattern of DCIS, accurate histological determination of size and extent can be difficult. Moreover, limitations inherent in tissue processing make tumor measurement difficult. Finally, determining DCIS size is limited by the difficulty in reconstructing the three-dimensional extent by use of two-dimensional pathology slides. As a result, pathological examination can misestimate tumor sizes, depending on the plane of section. Two of three studies that compared MRI with mammography for determining the extent of DCIS found that MRI was more likely to overestimate tumor size. Likewise, two of three found that MRI was more likely than mammography to underestimate tumor size (35–37).

Because current technology evaluates both breasts, MRI can potentially identify occult contralateral breast cancer. This finding would necessitate excision or contralateral mastectomy. In the largest study to date that included 196 patients, Lehman et al. (38) reported that MRI detected occult contralateral breast cancer in five patients (2.6%).

The potential benefits of MRI include fewer re-excisions after BCS, decreased local recurrence rates after excision, and earlier detection and treatment of contralateral breast cancer. However,

Table 1. Comparison of risk factors for ductal carcinoma in situ (DCIS) and invasive breast cancer*

Risk factor	DCIS	Invasive breast cancer
Time	Rare before 1980s, increased until 1999 and then stable	Increased until mid 1990s, declining since 2001
Age	Unusual before age 35 years, peaks at age 60–74 years, and then declines	Unusual before age 30 years, peaks at age 75–79 years, and then declines
Race	Less common among African American, Asian, and Hispanic women than white women	Less common among African American, Asian, and Hispanic women than white women
Family history and/or genetics	Increased risk among women with positive family history or positive for BRCA1/2 genes	Increased risk among women with positive family history or positive for BRCA1/2 genes
Breast density	Increased risk of DCIS among women with increased breast density	Increased risk among women with increased breast density
BMI	No consistent association with BMI	Increased risk with increased BMI in postmenopausal women
Parity	Increased risk among women with no children or one child, increased risk with older age at first birth	Increased risk among women with no children or one child, increased risk with older age at first birth
HRT with estrogen plus progestin	No association between HRT use and DCIS incidence in randomized trials, and observational studies were inconsistent	Increased invasive cancer with HRT
Chemoprevention	Decreased DCIS with tamoxifen relative to raloxifene	Decreased invasive breast cancer with tamoxifen and raloxifene
Mammography	Increased DCIS with screening	Increased invasive cancer with screening

* BMI = body mass index; HRT = hormone replacement therapy.

no studies to date have reported that MRI yields these improved patient outcomes. Breast MRI may also have potential disadvantages for patients with DCIS. In the American College of Radiology Imaging Network study, Lehman et al. (38) reported that MRI prompted biopsies of the contralateral breast in 18 patients; the biopsies were benign in 13 patients (72%). As a result, MRI may increase patient anxiety and costs. The routine use of MRI may also result in overtreatment of some patients with DCIS. Because MRI overestimates the extent and size of DCIS in some patients, MRI may lead to unnecessary wider excisions with less favorable cosmetic outcomes and more mastectomies.

SLNB is recommended for patients with invasive breast cancer to determine prognosis and to guide adjuvant treatment decisions. In general, SLNB is not recommended for patients with a “final” or definitive diagnosis of DCIS because the preinvasive cells do not metastasize. However, about 15% of patients who are initially diagnosed with DCIS on core needle biopsy have invasive breast cancer identified in the excision or mastectomy specimen (39). Thus, some patients may require axillary lymph node staging after definitive surgical treatment for DCIS. Although SLNB is feasible for most patients after excision, it is not feasible after mastectomy (40).

Among the published studies, the incidence of SLN metastasis among patients with an initial diagnosis of DCIS is substantially higher than among those with a final diagnosis of DCIS (after excision or mastectomy) (9.8% vs 5.0%) (41,42). The risk of SLN metastasis is higher for patients with a final diagnosis of DCIS with microinvasion compared with pure DCIS (9.3% vs 4.8%) (43,44). For patients with pure DCIS, the overall risk of AJCC pN1(mic) or pN1 SLN metastases is less than 1%. Therefore, SLNB is not likely to affect important outcomes (survival, recurrence, and quality of life) for most patients with DCIS, especially if excision is planned. However, the findings of SLNB [AJCC pN0(i+)] may

lead to overtreatment (axillary lymph node dissection and cytotoxic chemotherapy), which may negatively affect patient’s quality of life.

Question 3: How Do Local Control and Systemic Outcomes Vary in DCIS Based on Tumor and Patient Characteristics?

Many of the prognostic factors that are shared between DCIS and invasive cancer point to similar associations. However, in contrast to the invasive breast cancer literature, the literature addressing the impact of these characteristics on survival shows a surprising lack of depth and, largely, is limited to studies of recurrence. This primary focus on studies of recurrence is likely because of the low incidence of outcomes other than DCIS and invasive recurrence, which is between 10% and 24% after 10 years (45–47). Mortality due to breast cancer 10 years after DCIS diagnosis is less than 2% (48). Younger age at diagnosis is a consistent adverse prognostic factor for DCIS outcomes. Women older than 40 or 50 years consistently have reduced risk of DCIS or invasive recurrence than younger women, with many studies reporting a relative risk around 0.5 for older vs younger women (49–51).

Surveillance, Epidemiology, and End Results–based studies report higher all-cause mortality among African American women than white women diagnosed with DCIS and higher breast cancer mortality for African American women than white women (49,52,53). Studies of racial differences in DCIS recurrence point to a somewhat complex story. When adjusting for demographic factors alone (49,54), African American women with DCIS are more likely than white women to die from breast cancer (RR = 1.35, 95% CI = 1.12 to 1.62) or experience an invasive recurrence (RR = 1.4, 95% CI = 1.2 to 1.7). However, the studies such as that conducted by Warren et al. (53) that adjust for a more detailed set of tumor factors find no difference between racial groups and risk

of DCIS or invasive recurrence (RR = 1.12, 95% CI = 0.61 to 2.06). This difference in assessment of the impact of race on DCIS outcomes before and after adjusting for tumor characteristics suggests that there may be differences in the tumors between African American and white women. This finding needs to be further explored.

Positive surgical margins are consistently associated with increased DCIS and invasive breast cancer recurrence, although the magnitude of excess risk varies considerably (53,55). There is considerable debate, however, regarding whether width of a negative margin is (width of a margin negative for tumor cells) associated with a decreased risk of recurrence, and classification of the margins makes summary statements difficult. For example, in some studies, 0-mm negative margins are compared with margins clear up to 10 mm, supporting the conclusion that wider negative margins confer the greatest protection (RR = .02) (56). However, no study comparing women whose margins were above or below a specific threshold (ie, 2, 4, or 10 mm) found any benefit to being above vs below the threshold. Regardless, the prognostic value of positive margins is evidenced by their presence in the Van Nuys index, a multifactor prognostic index for DCIS (57). In general, larger tumors were associated with higher rates of local DCIS and invasive recurrence than smaller tumors (48,53). For example, Li et al. studied 37 692 women and found increased risk of recurrence for women with large tumors compared with small tumors (RR = 1.3) but not for medium-sized tumors compared with small tumors (RR = 0.9) (54). Although the tumors were labeled somewhat inconsistently, a higher pathological or nuclear grade (grade 3) was consistently associated with a higher probability of local DCIS or invasive recurrence than an intermediate or low grade (grade 2 or 1) (58). Comedo necrosis, a factor unique to DCIS, is strongly and consistently associated with poorer outcomes and increased risk of DCIS or invasive recurrence (53,55,54).

Few of the important markers of tumor aggressiveness in invasive breast cancer are well studied in DCIS. Estrogen receptor positivity has been reported to be linked with a decreased risk of recurrence in several small studies, all with less than 400 subjects (range = 0.2–0.74) (59,60). The rate of estrogen receptor testing reported in the literature, however, is quite low (20%) (52). Ongoing trials of tamoxifen and aromatase inhibitors may contribute to more routine testing of estrogen receptor status in the future.

DCIS is rarely tested for HER2 positivity but, nonetheless, has been linked to increased risk of recurrence (RR = 1.5–3.7) in several small studies, all with less than 130 subjects (60,61). The possibility of treating HER2-positive tumors with trastuzumab is being studied in ongoing trials and points to the possibility that HER2 evaluation in women with DCIS might become more common.

Beyond DCIS and invasive breast cancer recurrence, very few studies have addressed the impact of a DCIS diagnosis on quality of life or psychological well-being and even fewer have used a design that allows for comparison of women with DCIS over time or against another group. Although the population size in the study was small (64 women with DCIS and 164 women with invasive breast cancer), Rakovitch et al. (62) reported that DCIS is associated with levels of anxiety and depression that are equivalent to those experienced by women diagnosed with an early-stage invasive breast cancer. The study found no differences between women diagnosed with DCIS and invasive breast cancer in their estimated probability of dying of breast cancer (27% for both) or developing a local recurrence (53% and 45%, respectively) (62). Partridge et al. (63) noted that anxiety that was associated with a diagnosis of DCIS decreased with time but was associated with elevated perceptions of risk of DCIS recurrence or breast cancer mortality.

Question 4: In Patients With DCIS, What Is the Impact of Surgery, Radiation, and Systemic Treatment on Outcomes?

We identified five randomized trials that addressed the value of tamoxifen or adding radiation therapy (RT) to BCS for the treatment of DCIS. We were unable to find any randomized trials comparing BCS plus RT with mastectomy analogous to the NSABP-B06 trial for invasive breast cancer. In addition to information from randomized trials, we identified numerous observational studies that address the impact of treatment on DCIS outcomes. The most consistently measured outcomes were local DCIS and invasive recurrence.

BCS With or Without Radiation Therapy. In randomized trials including NSABP-17 and the European Organization for Research and Treatment of Cancer (EORTC) randomized phase III trial 10853, whole-breast RT following BCS was associated with a reduction of local DCIS or invasive carcinoma recurrence of approximately between 45% (NSABP) and 55% (EORTC) (NSABP, RR = 0.56, 95% CI = 0.44 to 0.73; EORTC, RR = 0.459, 95% CI = .34 to .59). In spite of the reduced recurrence, use of RT had no impact on either breast cancer mortality (NSABP, RR = 1.12, 95% CI = 0.57 to 2.23; EORTC, RR = 0.33, 95% CI = 0.34 to 3.16) or total mortality (NSABP, RR = 1.18, 95% CI = 0.71 to 1.93; EORTC, RR = 0.87, 95% CI = 0.59 to 1.28) (55,64–67). Although the number of events prevented per 1000 treated women was statistically significant in these two studies, it is typically less than 10%. Table 2 summarizes the results of these trials and translates the observed effects into a metric of events reduced by treating 1000

Table 2. Events reduced by treating 1000 women with radiation therapy after breast-conserving therapy (statistically significant effects only)*

First author, year (reference)	Local DCIS recurrence, No.	Local invasive carcinoma, No.	DCIS or invasive carcinoma, No.	Regional recurrence, No.
Bijker, 2006 (64)	62.2	52.3	114.5	18.0
Holmberg, 2008 (65)	98.6	50.8	149.5	—
Houghton, 2003 (66)	48.0	30.3	80.3	—
Fisher, 2001 (55)	—	79.3 (total invasive)	158.9	—

* — = estimates not statistically significant from zero; DCIS = ductal carcinoma in situ.

women with RT; only statistically significant effects are shown. The findings from randomized studies are consistent with the results from multiple observational studies, namely that treating DCIS reduces risk of recurrence, but treatment reduces any recurrence for approximately 10% of women (53,54,68). The trials found no increase in contralateral breast cancer (DCIS or invasive) (RR = 1.382; 95% CI = 0.86 to 2.21).

Neither randomized nor observational studies pointed to compelling evidence that BCS plus radiation is more or less effective than BCS without radiation in the presence or absence of adverse prognostic factors. For example, two studies found a similar effect of radiation for women with positive or negative margins (RR = 1.84 for both). This lack of differential effect can be seen for the most important prognostic factors, including tumor grade and size and comedo necrosis (48,58,69). Although studies of positive vs negative margins point to equal effectiveness of RT, Silverstein et al. (70) evaluated 469 women and reported a lack of benefit of RT when margins were greater than 1 mm wide.

Although outcomes between mastectomy and BCS or BCS+RT were not studied in a randomized fashion, several observational studies compared them. These studies reported that women undergoing mastectomy were less likely than women undergoing lumpectomy or lumpectomy plus radiation to experience local DCIS or invasive recurrence (71,72). We found no study showing a mortality reduction associated with mastectomy over BCS with or without radiation.

Analogous to the experience with early-stage breast cancer (73), it is possible, however, that low statistical power explains the apparent lack of mortality benefit when comparing BCS+RT or BCS alone to mastectomy. Because the breast cancer mortality after DCIS diagnosis is so low, it is possible that few studies have included a sufficient numbers of cases to support identification of a mortality benefit. We found no study that compared survival after an invasive recurrence with survival after a primary of the same stage, size, and grade. Thus, it is not possible to quantify the impact of a local invasive recurrence on long-term survival after diagnosis of DCIS.

The NSABP-24 assessed the value of tamoxifen following DCIS diagnosis and found tamoxifen use to reduce risk of recurrent DCIS or invasive carcinoma. Tamoxifen was associated with statistically reductions in local recurrence (RR = 0.60, 95% CI = 0.38 to 0.96) and contralateral disease (RR = 0.56, 95% CI = 0.34 to 0.90) (55).

Ongoing studies such as the NSABP-37 are examining the comparative effectiveness of tamoxifen and aromatase inhibitors, and the NSABP B-43 is examining use of trastuzumab for women with HER2-positive tumors.

Discussion

This review is limited by the quality and clarity of the published literature. We do not include results that are not published yet and cannot control for ongoing publication bias. Publications that do not include adjusted or unadjusted estimates are not included in this analysis. Likewise, studies that pool DCIS and invasive breast cancer are not included.

The relationship between DCIS and invasive breast cancer remains unclear. Ethical factors make it impossible to do any sort of natural experiment to assess the rate at which untreated DCIS evolves into invasive cancer. It is entirely clear that much DCIS either would not develop into invasive disease or would do so much later in life, perhaps never becoming clinically relevant. This DCIS that would either not progress or progress much later in life if ever is often considered to represent overdiagnosis. This issue of potentially overdiagnosed breast cancer as the result of screening is by no means limited to DCIS and is part of an active policy discussion related to invasive breast cancer, too. The potential for overdiagnosis is not the only issue associated with DCIS. There is also an aspect of underdiagnosis that must be considered. In fact, in some instances, DCIS may be underdiagnosed invasive cancer for which the pathology sections simply missed the invasive area. Overall, the arguments for a close relationship between in situ and invasive breast cancer can be found in the similarity of risk factors for both the incidence of the diseases and their similar responses to treatment.

From a clinical perspective, it seems prudent to approach DCIS and invasive breast cancer as being related. Certainly, screening makes no effort to distinguish them nor should it. Given the rate of error in needle biopsies, presumptive DCIS should be treated as potential invasive cancer until a more definitive pathological sample is available. Likewise, the aggressiveness of treatment of DCIS should presumably differ between DCIS and invasive breast cancer, just as it presently does for invasive breast cancer by stage of diagnosis.

In clinical settings, efforts should be made to make full use of markers such as estrogen receptor and progesterone receptor status, HER2 status, and necrosis to differentiate women at high risk from those at lower risk of developing invasive disease. This would allow for focusing aggressive treatment on those who have the greatest probability of benefit.

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