Ductal Carcinoma In Situ

Brittany L. Bychkovsky, MD, MSc[a,b,c], Sara Myers, MD, PhD[c,d], Laura E.G. Warren, MD[c,e], Pietro De Placido, MD[b], Heather A. Parsons, MD, MPH[b,c,f,*]

KEYWORDS

- Ductal carcinoma in situ • DCIS • Breast cancer precursor lesions
- Breast cancer detection

KEY POINTS

- Ductal carcinoma in situ (DCIS) is a precancerous lesion of the breast and is most often detected after mammogram screening.
- Endocrine therapy has an established role in both primary and secondary prevention among females identified with DCIS or high-risk lesions who have intact breast tissue.
- Preliminary DCIS vaccine studies appear safe and can elicit sustained response, though further research is necessary to determine their clinical effectiveness.

BIOLOGY AND NATURAL CLINICAL HISTORY OF DUCTAL CARCINOMA IN SITU

In breast cancer (BC) pathogenesis models, normal cells acquire somatic mutations and there is a stepwise progression from high-risk lesions (HRLs include atypical ductal hyperplasia [ADH], atypical lobular hyperplasia [ALH], and lobular carcinoma in situ [LCIS]) and ductal carcinoma in situ (DCIS) to invasive cancer. The precancer biology of mammary tissue warrants better characterization to understand how different BC subtypes emerge. Currently, research efforts are underway to improve our understanding of premalignant biology and immunosurveillance in the precancer microenvironment to guide prevention and interception trials.[1,2]

DCIS is a precancerous lesion of the breast and is most often detected after mammogram screening. Microscopically, DCIS appears morphologically similar to invasive BCBC with uncontrolled proliferation of neoplastic cells that obliterate the normal lobular and ductal structures; however, unlike invasive BCBC, DCIS does not invade across the basement membrane.[3]

[a] Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, MA, USA; [b] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [c] Harvard Medical School, Boston, MA, USA; [d] Brigham and Women's Hospital, Boston, MA, USA; [e] Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [f] Broad Institute of MIT and Harvard, Cambridge, MA, USA
* Corresponding author. Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115.
E-mail address: heather_parsons@dfci.harvard.edu

Hematol Oncol Clin N Am 38 (2024) 831–849
https://doi.org/10.1016/j.hoc.2024.05.014 **hemonc.theclinics.com**

At diagnosis, the estrogen receptor (ER) status of DCIS is determined as this influences recommendations for endocrine therapy (and radiation therapy [RT] among older patients). Tamoxifen or an aromatase inhibitor (AI) can reduce the risk of recurrence and a second BCBC diagnosis.[4–10] Increased expression of ER distinguishes precancer lesions from normal breast tissue, and is an important regulator of BC pathogenesis.[11] In contrast, ER-negative DCIS is perceived as a more aggressive phenotype and is seen more frequently in palpable DCIS versus asymptomatic screen-detected DCIS[12]; however, this perception may be influenced by the fact that there are no established preventative systemic therapies for ER-negative DCIS at this time.

High-grade DCIS with comedonecrosis is associated with an increased risk of invasive disease,[13,14] ipsilateral disease recurrence,[15] and tumor-infiltrating lymphocytes (TILs).[3] A high number of TILs and the distribution of TILs in the DCIS microenvironment are correlated with DCIS outcomes.[16] TILs in DCIS are associated with somatic *TP53* mutations, which are more common with ER-negative HER2-positive DCIS, and higher nuclear grade.[3] Prior work has also demonstrated that the immune microenvironment differs between DCIS alone, DCIS with microinvasion, and invasive BC, and these differences can be further stratified by ER status.[17] In sum, at least a subset of DCIS is immunogenic and therefore, vaccination or immunomodulatory therapies may have a role in BC prevention and risk-reduction for patients with DCIS or HRLs.

PRIMARY AND SECONDARY PREVENTION

Endocrine therapy has an established role in both primary and secondary prevention among females identified with DCIS or an HRL who have intact breast tissue. Premenopausal females are eligible for tamoxifen 20 mg, and postmenopausal females are eligible for tamoxifen 20 mg, tamoxifen 5 mg, raloxifene, exemestane, or anastrozole. The approach to endocrine therapy in this patient population is evolving due new data showing good efficacy of low-dose tamoxifen for prevention and risk-reduction.[9,10]

The impact of tamoxifen 20 mg/d for a duration of 5 years (compared to placebo) was examined among patients with DCIS who had received a breast conservation surgery (BCS) and radiation in the National Surgery Adjuvant Breast and Bowel Project (NSABP) B-24 (A Clinical Trial to Evaluate the Worth of Tamoxifen in Conjunction with Lumpectomy and Breast Irradiation for the Treatment of Noninvasive Intraductal Carcinoma (DCIS) of the Breast) study.[4] ER testing was not required for study enrollment, but was available for 41% of the cohort. On subset analyses, tamoxifen 20 mg/d for 5 years was found to reduce the rates of any subsequent DCIS or invasive cancer event among patients with ER-positive DCIS (hazard ratio [HR] 0.58; 95% confidence interval [CI]: 0.415–0.81; P=.0015), but not in those with ER-negative DCIS (HR 0.88; 95% CI: 0.49–1.59; P=.68). For those with ER-positive DCIS, the benefit was primarily due to a statistically significant reduction in contralateral BC (CBC) events (HR 0.50; 95% CI: 0.28–0.88; P<.02). Statistical significance was not reached for ipsilateral breast events (HR 0.68; 95% CI: 0.44–1.03; P<.07) demonstrating that the primary benefit of tamoxifen is to reduce the risk of future CBCs. For those with ER-negative DCIS, tamoxifen 20 mg for 5 years did not have a statistically significant benefit at reducing any future BC diagnosis, ipsilateral BC, or CBC; however, the event rate was low for CBC with 7 CBCs in those that received placebo and 3 among those who received tamoxifen.[4] Among those with invasive disease, ER status is not necessarily predictive of the BC subtype that may emerge when a patient develops a second BC: among females with ER-negative invasive BC who develop a second BC, ER concordance occurs 53% of the time and among females with ER-positive invasive BC who develop a second BC, ER concordance is 82%.[18]

Tamoxifen 20 mg for 5 years also has efficacy for primary prevention. In the NSABP P-1 (A Clinical Trial to Determine the Worth of Tamoxifen for Preventing Breast Cancer) trial,[5] premenopausal or postmenopausal females aged more than 60, or females aged 35 to 60 at elevated risk for BC as defined by the presence of an HRL (ADH, ALH, LCIS) or a Gail 5-year risk score of $\geq$ 1.67, were randomized to tamoxifen 20 mg/day for 5 years (n = 6597) or placebo (n = 6610).[5] At 7 years of follow-up, tamoxifen reduced the risk of invasive BC (rate ratio[RR] 0.57; 95% CI: 0.46–0.70) and noninvasive disease (DCIS) compared to placebo (RR 0.63; 95% CI: 0.45–0.89).[5] Tamoxifen also had a benefit of reducing osteoporotic fractures by 32%, but did increase the risk of endometrial cancer, primarily in females aged 50 and older (RR 5.33; 95% CI: 2.47–13.17) compared to those aged 49 or younger (RR 1.42; 95% CI: 0.55–3.81).[5] The cumulative risk of endometrial cancer at 7 years of follow-up was 0.468% in the placebo group and 1.5% with tamoxifen (P<.001)[5]; importantly, all were early-stage cancers and were treated with simple hysterectomy. Tamoxifen 20 mg also statistically increased the risk of pulmonary embolism (PE) (0.69 per 1000 for tam vs 0.32 per 1000 for placebo, RR 2.15; 95% CI: 1.08–4.51), and there was a trend toward an increased risk of deep vein thrombosis (DVT) (1.21 per 1000 for tamoxifen vs 0.84 per 1000 for placebo, RR 1.44; 95% CI: 0.91–2.3).[5]

Subsequent to the NSABP P-1 study, 3 additional trials demonstrated that tamoxifen 20 mg for 5 years reduces the risk of BC.[6–8] In the IBIS-1 (Tamoxifen for the Prevention of Breast Cancer in High-Risk Women) study, females were followed for a median of 16.0 years and it was demonstrated that 5 years of endocrine therapy with tamoxifen has a long-lasting effect on risk reduction.[6] The risk reduction of developing BC with tamoxifen 20 mg for 5 years was similar between years 0 to 10 (HR 0.72; 95% CI: 0.59–0.88, P=.001) and after 10 years (HR 0.69; 95% CI: 0.53–0.91, P=.009).[6]

After 2 studies found that a subset of older patients with ER-positive DCIS could avoid adjuvant radiation without an increased risk of ipsilateral recurrence if they received adjuvant endocrine therapy,[19,20] 2 randomized control trials were conducted comparing tamoxifen to an AI: IBIS-II DCIS (An International Multi-Centre Trial of Tamoxifen Versus Anastrozole in Postmenopausal Women who have had a Recent Hormone Receptor Positive Ductal Carcinoma In Situ) and NSABP B-35 (Anastrozole or Tamoxifen in Treating Postmenopausal Women With Ductal Carcinoma in Situ Who Are Undergoing Lumpectomy and Radiation Therapy).[21,22] In the IBIS-II DCIS study,[21] there was no difference in recurrence rates at median follow-up of 7.2 years for patients who received anastrozole versus tamoxifen (HR 0.89; 95% CI: 0.64–1.23). In IBIS-II DCIS, 71% received radiation and this was balanced between the 2 arms.[21] NSABP B-35 was also a randomized controlled trial comparing tamoxifen 20 mg to anastrozole; however, all participants received radiation.[22] In contrast, NSABP B-35 showed that anastrozole reduced the risk of all breast events (HR 0.73; 95% CI: 0.56–0.96; P=.02) and contralateral breast events (HR 0.64; 95% CI: 0.43–0.96; P=.03) compared to tamoxifen.[22] The benefit was limited to postmenopausal females aged less than 60 compared to those aged 60 and older, which is noteworthy as women often have more musculoskeletal problems and bone loss as they age. In IBIS-II DCIS, there were higher rates of musculoskeletal side effects (64% with anastrozole vs 54% with tamoxifen) and fractures (9% vs 7%) with AI therapy compared to tamoxifen.[21] At this time in clinical practice, AIs are available for prevention among those with DCIS or HRLs of the breast, and the recommended approach must consider patient preferences and the risks of therapy.

Recent work has suggested that measurement of serum estradiol and testosterone levels could guide care decisions among postmenopausal patients on an AI for prevention. At a median follow-up of ~10 years, the IBIS-II (Anastrozole in Preventing

Breast Cancer in Postmenopausal Women at Increased Risk of Breast Cancer) prevention trial found a benefit to anastrozole among patients with estradiol/sex hormone binding globulin ratios of $\geq$ 0.167,[23] but less relative benefit when ratio was less than 0.167 (relative benefit 0.18; 95% CI: −0.60–0.59). These findings suggest that biomarker monitoring could inform clinical care.

Despite the known benefit of endocrine therapy in primary and secondary prevention for women with a diagnosis of DCIS, many do not start or are unable to tolerate AI or tamoxifen due to adverse effects.[24–26] Approaches to maintain the benefits but avoid toxicity may help with endocrine therapy uptake. More recently, there is robust data supporting low-dose tamoxifen for primary and secondary prevention among females who are high risk or have a personal diagnosis of DCIS. In TAM-01 (Trial of Low Dose Tamoxifen in Women With Breast Intraepithelial Neoplasia - Long Term Follow-up) trial, low-dose tamoxifen 5 mg was compared to placebo, and included 500 women with a diagnosis of DCIS, ADH, or LCIS who received breast conservation therapy.[9] Most patients in the study had a diagnosis of DCIS (69% in the low-dose tamoxifen arm and 70% in the placebo arm; yet ER status was only known in 80% of cases with DCIS and only 45% of patients received RT). At a median follow-up of 9.7 years,[10] there was a benefit to low-dose tamoxifen: 9.8% in the tamoxifen 5 mg arm were diagnosed with BC compared to 16.6% who were in the placebo group (HR 0.58; 95% CI: 0.35–0.95, P=.03).[10] Most recurrences were invasive (77%) and ipsilateral (59%).[10] Regarding the CBC rate, there were 6 BCs with tamoxifen 5 mg and 16 with placebo (HR 0.36; 95% CI: 0.14–0.92, P=.025).[10] Within subgroup analyses, patients with DCIS had a 50% reduction in BC recurrence with low-dose tamoxifen for 3 years (HR 0.50; 95% CI: 0.28–0.91, P=.02). The reduction in BC events occurred while patients were on tamoxifen 5 mg for 3 years and were durable for 7 years after therapy cessation demonstrating a role for low-dose tamoxifen for primary and secondary prevention.

Low-dose tamoxifen has an exceptional side effect profile.[10] In TAM-01, there were no differences in rates of DVT/PE, coronary heart disease, bone fracture, cataract, endometrial polyps, and endometrial cancer rates between patients who received low-dose tamoxifen for 3 years versus those who received placebo. There are more hot flashes with tamoxifen 5 mg compared to placebo (P=.02); this effectively translated into 1 more hot flash per day.[9] There were no differences between hot flash intensity (P=.16), vaginal dryness (P=.40), or musculoskeletal pain or arthralgias (P=.41) between the 2 study arms.

Subset analyses of TAM-01 showed that postmenopausal females, with estradiol less than 15.8 pg/mL, menopausal symptoms at baseline, and those who were never smokers benefited most from low-dose tamoxifen.[27] Among postmenopausal women, low-dose tamoxifen had a favorable HR (HR = 0.30; 95% CI: 0.11–0.82) compared to premenopausal women (HR = 0.73; 95% CI: 0.30–1.76) and this was borderline statistically significant $P_{interaction}$ = 0.13. More work is needed to better understand if low levels of active tamoxifen metabolites (with low-dose tamoxifen) are less effective in premenopausal women compared to postmenopausal women due to the higher baseline levels of estrogen in premenopausal women. Body mass index (BMI) did not influence tamoxifen 5 mg efficacy,[27] which is consistent with prior work that efficacy of tamoxifen 20 mg is not influence by BMI.[28,29] This finding is similar to what has been observed with AIs where BMI is not a modulating factor of outcome in the prevention setting.[30]

Patients with baseline menopausal symptoms are unlikely to take either selective estrogen receptor modulators (SERMs) or an AI, and ongoing work is investigating bazedoxifene combined with conjugated estrogen (CE) (BZE + CE, Duavee) in the

prevention setting. Preclinical data suggest that BZE + CE downregulates ERalpha and Ki67 expression similar to BZE alone and distinct from CE, and therefore may have a role for BC prevention.[31] Ongoing work has demonstrated that BZE can induce epigenetic changes in 17beta-estradiol (E2) and other estrogen compounds that mediate ERalpha regulator changes to target gene proliferative pathways.[32] Clinical data are also promising showing favorable effects on BC risk biomarkers when women were treated for 6 months with BZE + CE,[33] and a phase II trial is ongoing (NCT04821141).

At this time, there is a need to better understand the immunomodulatory effects of SERMs and AI in the prevention setting since our understanding of anticancer immunity and the breast microenvironment has evolved since these agents were first studied.[34,35] It is unclear if there are different immunologic effects between SERMs and AIs that could be combined synergically with novel therapies to enhance BC prevention among those with HRLs and DCIS.

SURGICAL CONSIDERATIONS

Surgery is the mainstay of treatment for DCIS.[36] The National Comprehensive Cancer Network treatment guidelines indicate that appropriate candidates may be offered either BCS or mastectomy.[37] Traditionally, contraindications to BCS for DCIS included extensive disease,[38] multicentricity, and multifocality.[39] It is estimated that for unilateral DCIS, 70% of women receive BCS compared to 20% who undergo unilateral mastectomy; bilateral mastectomy is pursued by 10% of women.[40]

Local recurrence varies by surgical approach: compared to the 1% to 2% local recurrence rate after mastectomy, recurrence after BCS depends on tumor characteristics, margin status, receipt of endocrine (ER+) and radiation treatments in the adjuvant setting.[41] In patients $\geq$ 40 years old who receive BCS for unifocal DCIS followed by radiation, society guidelines advocate for a margin of at least 2 mm to minimize the risk of local recurrence.[42] Optimal margin width in younger patients with large or multifocal disease is unclear based on existing data. The Memorial Sloan Kettering Cancer Center has a freely available prognostic nomogram to assist in understanding DCIS recurrence rates after BCS allowing for individualized approach to adjuvant treatment (ie, radiation and/or endocrine therapy).[43] Other prediction tools that aid in understanding recurrence and may be used to guide shared decision-making with respect to choice of surgical treatment include the Oncotype DX DCIS Score[44] and DCISionRT Prelude DX.[20] Discussion of how these tools can be leveraged for decisions to pursue adjuvant radiation and endocrine therapy will be discussed elsewhere.

Axillary staging is not generally recommended for patients undergoing BCS. There is variability in surgeon practice; however, with data from the National Cancer Database indicating that 19% of patients undergoing BCS for DCIS receive sentinel lymph node biopsy (SLNB).[45] Features such as tumor size greater than 3 cm, high histologic grade, and necrosis may motivate some to pursue SLNB[46] despite the low probability of pathologic node positivity. Studies advocating for the omission of SLNB include a meta-analysis of 9803 patients from 48 studies that demonstrated safety in patients with high-grade DCIS smaller than 2 cm and low to intermediate grade DCIS over 2 cm.[47] A Surveillance, Epidemiology, and End Results population database analysis corroborated these findings in patients 67 years of age or older in who there were no differences in locoregional recurrence or survival based on receipt of SLNB.[48] In the case of mastectomy, SLNB is usually performed given concern that postoperative assessment in the setting of upstage to invasive carcinoma would be compromised after removal of the breast.

Existing data indicate that only 20% to 30% of DCIS progresses to invasive ductal carcinoma (IDC).[49,50] Unfortunately, factors that confer risk of progression are incompletely understood.[51] As such, clinical trials are underway investigating whether surveillance is a safe alternative to operative management.[52–55] Forthcoming data from these trials will be helpful in deciphering a subpopulation of patients who may be surveilled with or without endocrine therapy in lieu of surgical resection (**Tables 1** and **2**).

Radiation

Several studies dating back to the 1980s to 1990s examined the benefit of RT following BCS for DCIS. A meta-analysis of 3729 patients from 4 trials—NSABP B-17 (A Protocol to Evaluate Natural History and Treatment of Patients with Noninvasive Intraductal Adenocarcinoma), EORTC 10853, SweDCIS (Swedish Breast Cancer Group Ductal Carcinoma in Situ), and UK ANZ DCIS (UK, Australia, and New Zealand Ductal Carcinoma In Situ)—randomizing patients to RT or not following BCS showed that RT approximately halved the rate of ipsilateral breast events (RR, 0.46; standard error (SE) 0.05; $P<.00001$) with an absolute benefit of 15.2% at 10 years.[56] RT was beneficial regardless of other risk factors including age, grade, pathologic size, extent of BCS, whether tamoxifen was planned, and whether or not comedonecrosis was present. Investigators defined a lower risk subgroup as patients with negative margins and low-grade DCIS measuring 1 to 20 mm, and RT still proved beneficial in lowering the 10-year risk of an ipsilateral event from 30.1% to 12.1% (RR, 0.48; SE 0.17; $P = .002$). Despite the substantial reduction in recurrence, there was no difference in BC mortality or overall survival, likely due to the success of salvage therapy in the event of a recurrence. These data provided strong support for the routine use of adjuvant RT for patients with DCIS, irrespective of clinical or pathologic features, as a means by which to decrease the risk of in-breast recurrence (IBR) following BCS.

However, patients treated for DCIS in the modern era have a lower absolute risk of IBR, likely due to of a combination of increased mammographic screening, improved imaging quality and pathologic evaluation, and increased utilization of adjuvant RT and endocrine therapy. Recent efforts have focused on better identifying a low-risk subgroup of patients who might safely avoid RT. The Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) trial E5194 (Evaluation of Breast Cancer Recurrence Rates Following Surgery in Women With Ductal Carcinoma In Situ) enrolled 2 cohorts of patients with DCIS to evaluate omission of RT: (1)lLow-grade or intermediate-grade DCIS measuring 2.5 cm or smaller (n = 561) or (2) high-grade DCIS measuring 1 cm or smaller (n = 104).[20] Surgical margins were 3 mm or greater. The 12-year rate of an ipsilateral local recurrence was 14.4% and 24.6% in cohorts 1 and 2, respectively, and continued to increase over the follow-up period without plateau. For patients with high-grade DCIS, these data are often referenced in support of a recommendation for adjuvant RT given the high risk of local recurrence with the omission of RT.

The Radiation Therapy Oncology Group 9804 (Radiation Therapy With or Without Optional Tamoxifen in Treating Women With Ductal Carcinoma in Situ) trial similarly attempted to identify a group of patients at low risk of IBR who may be candidates for omission of RT. This was a randomized, prospective trial of 636 patients with good-risk DCIS, defined as mammographically detected, low-grade or intermediate-grade DCIS, measuring 2.5 cm or less with margins 3 mm or greater. Patients meeting these criteria were randomized to RT or observation after BCS. Of the enrolled patients, 76% were postmenopausal, 44% had grade 1 DCIS, the median pathologic size was 0.6 cm, and 65% had margins $\geq$1.0 cm. At a median follow-up time of 7.2 years, RT decreased the 7-year risk of local failure from 6.7% (95% CI, 3.2%–9.6%) to 0.9%

Table 1
Trials of active surveillance for ductal carcinoma in situ

	LOw RISk DCIS (LORIS) Trial	Comparison of Operative versus Monitoring and Endocrine Therapy (COMET) Trial	The Low Risk DCIS (LORD) Trial
Study design	RCT	RCT	RCT
Primary endpoint	5 y—ipsilateral invasive breast cancer–free survival	2–5 y ipsilateral invasive cancer diagnosis	10 y ipsilateral invasive breast cancer and cancer-free survival
Inclusion criteria	≥46 y with a histologically confirmed diagnosis of grade I/II DCIS	≥46 y with any extent of ER/PR + grade I/II DCIS who had confirmed diagnosis based on biopsy or lumpectomy (positive margins allowed) ≤120 d of registration	≥45 y with any extent of grade I/II DCIS
Exclusion criteria	• Previous ipsilateral DCIS or invasive breast cancer • Mass lesion not biopsy-proven benign • High-risk group for developing breast cancer • Comedonecrosis	• Previous history of DCIS or invasive breast cancer • HER2 + disease	• Previous history of DCIS or invasive breast cancer • Family history of BRCA 1/2 mutation • Symptomatic DCIS
Imaging schedule	Annual bilateral mammography	Ipsilateral mammography every 6 m; Contralateral mammography annually	Annual bilateral mammography
Endocrine therapy	Optional	Optional	Not allowed

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor 2; PR, progesterone receptor; RCT, randomized controlled trial.

Adapted from Hwang ES, Malek V. Estimating the magnitude of clinical benefit of local therapy in patients with DCIS. Breast. Nov 2019;48 Suppl 1:S34-S38. (https://doi.org/10.1016/S0960-97761931120-8)

Table 2
Overview of prediction models predicting subsequence breast events after ductal carcinoma in situ

	Oncotype DCIS (Solin et al,[61] 2013)	DCISionRT PreludeDX (Bremer et al,[44] 2018)	Van Nuys Prognostic Index (Silverstein et al, 1995)	MSKCC DCIS Nomogram (Rudlof et al,[43] 2010)	Patient Prognostic Score (Sagara et al, 2016)	CBC Risk Model (Choudhury et al, 2017)
Country	USA	Sweden	USA	USA	USA	USA
Format	On order*	On order**	On paper	Web-based***	On paper	On paper
Predicted outcome	Ipsilateral in situ or invasive breast event	Ipsilateral in situ or invasive breast event	Disease-free survival	Ipsilateral in situ or invasive breast event	Breast cancer–specific death	Contralateral invasive breast cancer
Tool based on	Multigene assay	Clinicopathological factors	Clinicopathological factors	Clinicopathological factors	Clinicopathological factors	Clinicopathological factors
Type of data	Trial cohort	Multicenter	Single-center	Trial cohort	Population-based	Population-based
Number of patients	327	526	238	1868	32,144	7,684
Number of events	46	Not reported	31	202	304	1,921
Intended to support decision making about:	Adjuvant radiotherapy	Adjuvant radiotherapy	Type of surgery and adjuvant radiotherapy	Adjuvant radiotherapy	Adjuvant radiotherapy	Screening or prophylactic mastectomy
Risk of bias based on CHARMS	Moderate	Moderate	Moderate/high	Moderate	Moderate	Moderate
Number of validation studies retrieved	3	2	10	3	0	0

Type of data validation studies	Trial and population-based	Trial and single center	Single-center and Multicenter	Single-center	N.A.	N.A.
Number of patients validation studies (range)	718–1102	455–504	159–949	467–734	N.A.	N.A.
Number of events validation studies (range)	65–100	54–90	11–165	42–63	N.A.	N.A.
C-index/AUC	0.68	None reported	None reported	0.61–0.68	None reported	None reported
Clinical utility	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Adapted from Dabbs D, Mittal K, Heineman S, Whitworth P, Shah C, Savala J, Shivers SC and Bremer T (2023) Analytical validation of the 7-gene biosignature for prediction of recurrence risk and radiation therapy benefit for breast ductal carcinoma in situ. Front. Oncol. 13:1069059. https://doi.org/10.3389/fonc.2023.1069059.

(95% CI, 0.0% to 2.2%); HR 0.11 (95% CI, 0.03–0.47; $P<.001$).[57] Long-term follow-up demonstrated a persistent reduction in IBR with the utilization of RT; 15-year IBR decreased from 15.1% (95% CI, 10.8–20.2) to 7.1% (95% CI, 4.0–11.5) with the addition of RT (HR = 0.36; 95% CI, 0.20–0.66; $P = .0007$).[58] There was no significant difference in subsequent mastectomy rates between treatment arms and no difference in overall survival. These data demonstrate that the risk of IBR continues to increase over time, particularly after 10 years of follow-up, and that adjuvant RT significantly decreases this risk. Specifically, and importantly, these studies demonstrate a reduction in the risk of both in situ and invasive recurrences with the utilization of RT.

In the hopes of better quantifying and personalizing estimates of the risk of IBR and the benefits of adjuvant RT for patients with DCIS, multigene molecular profiling assays have been developed. The Oncotype DX DCIS Score (Genomic Health) is a 12-gene prognostic test that was developed to estimate the 10-year risk of IBR following BCS alone. Its prognostic value was initially validated in a cohort of over 3000 women with DCIS[59] and it was subsequently shown to be predictive of the benefit of RT.[60] All patients benefited from RT but those with a higher score derived a greater absolute benefit from RT compared to those with lower scores, approximately 13% versus 5% absolute risk reduction in the modern era, respectively. Oncotype DX DCIS score was calculated for a subset of patients from the ECOG-ACRIN 5194 study (n = 327) and was found to be significantly associated with local control at 10 years, independent of other traditional clinical and pathologic features.[61] Despite enrollment eligibility based on perceived lower risk features, 30% of patients enrolled on ECOG-ACRIN 5194 were categorized into the intermediate-risk or high-risk groups based on their DCIS score. The DUCHESS (Evaluation of the DCIS Score for Decisions on Radiotherapy in Patients With Low/Intermediate Risk DCIS) trial attempted to assess the impact of the DCIS score, in conjunction with traditional clinical-pathologic features, on the recommendation for RT in a cohort of 217 patients. The score changed the treatment recommendation in 35.2% (95% CI, 29.1%–41.8%) of patients, improved patient satisfaction, and reduced decisional conflict.[62]

DCISionRT (Prelude Dx) is a genomic assay that risk stratifies patients into low and elevated risk based on data from 7 genes and 4 clinical-pathologic factors. On multivariate analysis, DCISionRT was independently associated with 10-year IBR.[44] Patients defined as low risk by DCISionRT had similar IBR with or without RT; the elevated risk group had significantly decreased rates of IBR with the receipt of RT (HR, 0.3; $P = .003$). The PREDICT (The PREDICT Registry for DCIS Patients With DCISionRT Testing) study is a prospective cohort study that is evaluating the effect of DCISionRT on treatment recommendations for patients with DCIS following BCS. DCISionRT testing resulted in a substantial change in RT recommendations with 42% of recommendations changing after receipt of the score and overall adjuvant RT being recommended in 20% fewer patients.[63] Although additional data are forthcoming, there are to date no randomized data supporting routine incorporation of molecular profiling to guide recommendations for adjuvant RT and the cost-effectiveness of this testing should also be considered before widespread adoption.[64]

In conclusion, prospective trials have demonstrated that even in patients with DCIS felt to be at low risk for IBR following BCS, the risk of IBR increases with time and adjuvant RT lowers this risk. RT does not, however, confer an overall survival benefit. While adjuvant RT has been shown to decrease the risk of IBR, there are potential side effects including radiation dermatitis and fatigue in the acute setting and breast discomfort, skin color changes, and, modest but non-zero, risks of RT-related pneumonitis, ischemic heart disease, and secondary malignancy in the longer term. While increasing utilization of shorter, hypofractionated courses of radiation decreases the risk of

financial toxicity that is another potential consideration when deciding to proceed with adjuvant RT.[65] Therefore, for many patients, whether to proceed with adjuvant RT is a shared decision informed by the patient's perceived value of the decreased risk of IBR weighed against the potential side effects.

Future Approaches in Detection and Risk Stratification

Given the high incidence and local recurrence rate of DCIS, future research efforts are vital in this field. Priority areas include (a) enhancing early detection through novel body fluid biomarkers; (b) refining risk stratification according to genetics, radiological, and clinical features; and (c) preventive interventions incorporating immunomodulation via vaccines.

EARLY DETECTION

Current approaches to DCIS detection rely on mammography. Successful advancements in early detection should enable increased DCIS diagnoses, while also differentiating between high-risk and low-risk cases. If successful, this would allow for a reduction in the number of tumors presenting as IDC and for treatment tailoring across risk scenarios. This goal might be achieved via newly emerging technologies to detect blood-based biomarkers with recent investigations illustrating the current strengths and limitations of this approach.

Progress in genomics, sequencing, and machine learning have facilitated the development of blood tests for cancer detection, monitoring, and selecting treatment.[66–72] These technologies rely on detection of circulating nucleic acids, usually cell-free DNA (cfDNA) released by precancerous cells, or circulating tumor DNA (ctDNA). Initial studies investigating early detection of DCIS and invasive BC have been limited by test sensitivity. In a study conducted in Japan using the Oncomine Pan-Cancer cell-free assay to detect ctDNA, 1/12 (8%) patients with stage 0 disease, out of a cohort of 109 with early and metastatic BC (BC), were identified by the assay.[73] The PATHFINDER study (NCT04241796) is an excellent example of scientific progress in this field using a multi-cancer early detection (MCED) test based on cancer-specific DNA methylation patterns from cfDNA. The test can detect a cancer signal and predict the origin discriminating more than 50 distinct cancer types.[68,70] Results show a cancer signal detected in 92/6621 pan-cancer participants, anticipating the diagnosis in 35 confirmed to be true positives,[74] and demonstrating the feasibility of MCED testing in screening. However, performance in BC was limited. Results are awaited from newly designed trials: The PATHFINDER2 cohort study (NCT05155605), the UK's NHS Galleri study (ISRCTN91431511),[75] and the Oxford's SYMPLIFY study (ISRCTN10226380),[76] all evaluating the MCED testing as a screening procedure.

Some assays instead rely on the detection of molecular profiles of microRNA (miRNA). Shimomura and colleagues[77] examined 5 miRNA expression profiles in the serum of both BC patients and healthy women, demonstrating a sensitivity of 98.0% with DCIS. The authors are now working on moving this into prospective clinical studies. Early detection is key to achieve better outcomes in early-stage cancers such as DCIS and further advancements are required in diagnostic tools to enhance affordability, speed, and ease of use. Future combined approaches could improve analytical sensitivity of screening procedures through detection of ctDNA and circulating tumor cells in plasma or urine.

RISK STRATIFICATION AND TREATMENT TAILORING STRATEGIES

To optimize therapeutic strategies, risk stratification is essential and includes understanding patients' intrinsic predisposition, and radiological and clinical features.

Risk-stratified prevention programs are typically evaluated in randomized trials or prospective studies integrating data from screening for inherited pathogenic variants in high-risk genes, along with tumor radiological characteristics, and disease clinical features, all constituting factors which dynamically interact over time. Such studies take a long time to be finalized and simulation models can complement trial results.[78–82]

Evidence of DCIS sharing the same genetic predisposition with IDC come from a UK's King College study in which data pooled from 38 studies with a total of 5067 cases of DCIS, 24,584 cases of IDC and nearly 38,000 controls, all genotyped using a custom Illumina iSelect genotyping array, designed as part of the Collaborative Oncological Gene-Environment Study (iCOGS chip) showed no significant difference analyzing the 76 known BC predisposition loci.[83]

Conventional radiology can serve as a backbone diagnostic to be complemented by additional testing. Dynamic contrast-enhanced breast MRI is the most sensitive imaging to detect and characterize DCIS.[84] A small MRI radiomics study showed that heterogeneity features could differentiate DCIS nuclear grades.[85] The artificial intelligence may bridge radiomics and DCIS management in the future. In a pilot study, semiquantitative MRI features could discriminate DCIS nuclear grades and identify low-risk DCIS based on the Van Nuys score.[86,87]

DCIS evaluation with contrast-enhanced mammography (CEM) is still challenging, even though proven to be non-inferior to MRI in less than 5-mm lesions[88,89]; from retrospective evidence, CEM shows high sensitivity, suggesting that the enhancement may correlate with nuclear grade.[90,91]

With around 20% to 30% progressing to invasive BC if left untreated, DCIS management needs focused-research interventions.[92,93] This indicates that much of the treatment provided may be overtreatment. Low-risk DCIS has emerged as a distinct subtype that could potentially be managed with active surveillance (AS), as some patients will never develop invasive BC.[53,94,95]

The COMET trial (NCT02926911) is a currently ongoing phase III randomized controlled clinical trial for low-risk DCIS designed with a specific objective: to determine the risks and benefits of guideline concordant care (GCC) compared with those of AS for low-risk DCIS. In this study, low-risk disease is defined as 40 years of age or older, grade I/II DCIS without invasive BC diagnosed on biopsy; ER+ and/or progesterone receptor+; HER2-; and no mass on physical examination or imaging.[53] In addition, The LOw Risk dcIS study (LORIS trial; ISRCTN27544579) is a randomized controlled trial of AS versus GCC in the UK, which opened to accrual in 2015.[52] The principal investigators of the LORIS study collaborated with the COMET study team to coordinate studies endpoints, facilitating future meta-analysis.[53]

Multidisciplinary collaboration, intrinsic predisposition, and advanced imaging techniques play crucial roles in guiding treatment decisions and addressing the challenges associated with DCIS.

Future directions in treatment: vaccination

Currently, primary methods for BC prevention or risk reduction include lifestyle changes, surgery, and chemoprevention. Surgical intervention for BC prevention involves risk-reducing prophylactic mastectomy, typically performed either synchronously with the treatment of a primary tumor or as a bilateral procedure in high-risk women. Chemoprevention with endocrine therapy carries adherence-limiting toxicity. New, effective strategies for BC prevention are an unmet need, and cancer vaccines represent a promising potential approach.

Cancer immunosurveillance is critical for interception and elimination of evolving neoplastic cells.[96] High CD8 + T cells concentration in a tumor and adjacent stroma is

associated with improved BC prognosis, indicating that malignant cells have been identified and an immune response elicited.[97] BC vaccines are a developing approach leveraging the host immune system to offer defense against cancer, preventing the advancement of HRLs to invasive ones. Studies of dendritic cell (DC) vaccines have shown promise, with vaccine administration initiating an immune response in vaccinated individuals. Success with BC vaccines have been limited to DCIS and early stage disease. This may be due DCs' failure to generate a robust immune response in advanced disease and to counteract the highly immunosuppressive tumor microenvironment.[96,97]

In a 2007 study, Czerniecki and colleagues,[98] in a HER2 + DCIS presurgical population, demonstrated an 18% pathological complete response (pCR) rate after 4 doses of DC vaccination. In participants with residual DCIS, 50% had no remaining HER2 expression in residual DCIS. The same research group, years later, demonstrated that a type I polarized DC vaccine loaded with HER2 peptides (HER2-DC1) elicited robust anti-HER2 CD4 + T cell immune responses in vaccinated patients with either ER+ or ER-/HER2 + BC. This led to enhanced pCR rates in patients with HER2 + DCIS and early-stage BC. In the same population, DC1 vaccination plus antiestrogen therapy elicited HER2-specific Th1 immunity. The study demonstrated vaccine safety and a showed a signal of recurrence rate reduction, though it was underpowered for this endpoint.[99–101]

In a more recent trial (NCT02636582), NeuVax, an HER2-derived MHC class I peptide E75 vaccine (nelipepimut-S [NPS]) was combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) and compared with GM-CSF alone in patients with DCIS. In this study, HER2-positivity was not required for eligibility. After randomizing 13 patients 2:1, the investigators showed numerically greater increase—though not statistically significant—NPS-specific cytotoxic T lymphocyte responses in the NPS + GM-CSF arm.[102]

In the HER2-negative setting, the NCT06218303 trial employs the prototype DAA/TAA vaccine targeting MUC1 in postmenopausal women with ER-positive DCIS. Patients are randomized to receive neoadjuvant endocrine therapy for 12 weeks before surgery, alone or in combination with the experimental vaccine. The trial will measure immunogenicity by evaluating the increase of serum anti-MUC1 IgG from baseline. And in BRCA1/2 mutation carriers in the primary prevention setting, another study will evaluate a combination of hTERT, WT1, and prostate-specific membrane antigen with or without IL-12 plasmid (NCT04367675).

Preliminary DCIS vaccine studies appear safe, and can elicit sustained response, though further research is necessary to determine their clinical effectiveness. Most strategies for reducing treatment intensity rely on precise risk assessment, which is increasingly influenced by research in genetics and biomarkers. As our comprehension of the genetic and biological basis of DCIS advances, ongoing research efforts hold promise for personalized management approaches tailored to individual patient risks, where cure optimization will result in better patient outcomes.

ACKNOWLEDGMENT

The authors would like to acknowledge Kaitlyn T. Bifolck, BA, for her editorial support. She is a full-time employee of Dana-Farber Cancer Institute and was not compensated beyond her regular salary.

REFERENCES

1. Spira A, Yurgelun MB, Alexandrov L, et al. Precancer atlas to drive precision prevention trials. Cancer Res 2017;77(7):1510–41.

2. Stanton SE, Castle PE, Finn OJ, et al. Advances and challenges in cancer immunoprevention and immune interception. J Immunother Cancer 2024;12(3). https://doi.org/10.1136/jitc-2023-007815.
3. Sanati S. Morphologic and molecular features of breast ductal carcinoma in situ. Am J Pathol 2019;189(5):946–55.
4. Allred DC, Anderson SJ, Paik S, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol 2012;30(12):1268–73.
5. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97(22):1652–62.
6. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol 2015;16(1):67–75.
7. Powles TJ, Ashley S, Tidy A, et al. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 2007;99(4):283–90.
8. Veronesi U, Maisonneuve P, Rotmensz N, et al. Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. J Natl Cancer Inst 2003;95(2):160–5.
9. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. J Clin Oncol 2019;37(19):1629–37.
10. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent recurrence in breast noninvasive neoplasia: A 10-Year Follow-Up of TAM-01 study. J Clin Oncol 2023;41(17):3116–21.
11. Allred DC, Brown P, Medina D. The origins of estrogen receptor alpha-positive and estrogen receptor alpha-negative human breast cancer. Breast Cancer Res 2004;6(6):240–5.
12. Sundara Rajan S, Verma R, Shaaban AM, et al. Palpable ductal carcinoma in situ: analysis of radiological and histological features of a large series with 5-year follow-up. Clin Breast Cancer 2013;13(6):486–91.
13. Schwartz GF, Patchefsky AS, Finklestein SD, et al. Nonpalpable in situ ductal carcinoma of the breast. Predictors of multicentricity and microinvasion and implications for treatment. Arch Surg 1989;124(1):29–32.
14. Silverstein MJ, Waisman JR, Gamagami P, et al. Intraductal carcinoma of the breast (208 cases). Clinical factors influencing treatment choice. Cancer 1990;66(1):102–8.
15. Fisher ER, Dignam J, Tan-Chiu E, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 1999;86(3):429–38.
16. Toss MS, Miligy I, Al-Kawaz A, et al. Prognostic significance of tumor-infiltrating lymphocytes in ductal carcinoma in situ of the breast. Mod Pathol 2018;31(8):1226–36.
17. Risom T, Glass DR, Averbukh I, et al. Transition to invasive breast cancer is associated with progressive changes in the structure and composition of tumor stroma. Cell 2022;185(2):299–310 e18.
18. Lowry KP, Ichikawa L, Hubbard RA, et al. Variation in second breast cancer risk after primary invasive cancer by time since primary cancer diagnosis and estrogen receptor status. Cancer 2023;129(8):1173–82.

19. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011;103(6):478–88.
20. Solin LJ, Gray R, Hughes LL, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol 2015;33(33):3938–44.
21. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet 2016;387(10021):866–73.
22. Margolese RG, Cecchini RS, Julian TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. Lancet 2016;387(10021):849–56.
23. Cuzick J, Chu K, Keevil B, et al. Effect of baseline oestradiol serum concentration on the efficacy of anastrozole for preventing breast cancer in postmenopausal women at high risk: a case-control study of the IBIS-II prevention trial. Lancet Oncol 2023. https://doi.org/10.1016/S1470-2045(23)00578–8.
24. Mitchell JM, DeLeire T, Isaacs C. Adherence to hormonal therapy after surgery among older women with ductal carcinoma in situ: Implications for breast cancer-related adverse health events. Cancer 2024;130(1):107–16.
25. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999 Nov 3; 91(21):1829–46. Erratum in: J Natl Cancer Inst 2000 Feb 2;92(3):275.
26. Port ER, Montgomery LL, Heerdt AS, et al. Patient reluctance toward tamoxifen use for breast cancer primary prevention. Ann Surg Oncol 2001;8:580–5.
27. DeCensi A, Puntoni M, Johansson H, et al. Effect Modifiers of Low-Dose Tamoxifen in a Randomized Trial in Breast Noninvasive Disease. Clin Cancer Res 2021; 27(13):3576–83.
28. Sestak I, Distler W, Forbes JF, et al. Effect of body mass index on recurrences in tamoxifen and anastrozole treated women: an exploratory analysis from the ATAC trial. J Clin Oncol 2010;28(21):3411–5.
29. Pfeiler G, Konigsberg R, Fesl C, et al. Impact of body mass index on the efficacy of endocrine therapy in premenopausal patients with breast cancer: an analysis of the prospective ABCSG-12 trial. J Clin Oncol 2011;29(19):2653–9.
30. Smith SG, Sestak I, Morris MA, et al. The impact of body mass index on breast cancer incidence among women at increased risk: an observational study from the International Breast Intervention Studies. Breast Cancer Res Treat 2021; 188(1):215–23.
31. Ethun KF, Wood CE, Register TC, et al. Effects of bazedoxifene acetate with and without conjugated equine estrogens on the breast of postmenopausal monkeys. Menopause 2012;19(11):1242–52.
32. Messier TL, Boyd JR, Gordon JAR, et al. Epigenetic and transcriptome responsiveness to ER modulation by tissue selective estrogen complexes in breast epithelial and breast cancer cells. PLoS One 2022;17(7):e0271725. https://doi.org/10.1371/journal.pone.0271725.
33. Fabian CJ, Nye L, Powers KR, et al. Effect of bazedoxifene and conjugated estrogen (duavee) on breast cancer risk biomarkers in high-risk women: a pilot study. Cancer Prev Res (Phila) 2019;12(10):711–20.
34. Behjati S, Frank MH. The effects of tamoxifen on immunity. Curr Med Chem 2009;16(24):3076–80.

35. Huang H, Zhou J, Chen H, et al. The immunomodulatory effects of endocrine therapy in breast cancer. J Exp Clin Cancer Res 2021;40(1):19.
36. Punglia RS, Bifolck K, Golshan M, et al. Epidemiology, biology, treatment, and prevention of ductal carcinoma in situ (DCIS). JNCI Cancer Spectr 2018;2(4): pky063. https://doi.org/10.1093/jncics/pky063.
37. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 1998;16(2):441–52.
38. Jordan RM, Oxenberg J. Breast cancer conservation therapy. StatPearls Publishing; 2024 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK547708/.
39. Rakovitch E, Pignol JP, Hanna W, et al. Significance of multifocality in ductal carcinoma in situ: outcomes of women treated with breast-conserving therapy. J Clin Oncol 2007;25(35):5591–6.
40. Hwang ES, Malek V. Estimating the magnitude of clinical benefit of local therapy in patients with DCIS. Breast 2019;48(Suppl 1):S34–8.
41. Ward EM, DeSantis CE, Lin CC, et al. Cancer statistics: breast cancer in situ. CA Cancer J Clin Nov-Dec 2015;65(6):481–95.
42. Morrow M, Van Zee KJ, Solin LJ, et al. Society of surgical oncology-american society for radiation oncology-american society of clinical oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. J Clin Oncol 2016;34(33):4040–6.
43. Rudloff U, Jacks LM, Goldberg JI, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol 2010;28(23):3762–9.
44. Bremer T, Whitworth PW, Patel R, et al. A biological signature for breast ductal carcinoma in situ to predict radiotherapy benefit and assess recurrence risk. Clin Cancer Res 2018;24(23):5895–901.
45. Miller ME, Kyrillos A, Yao K, et al. Utilization of axillary surgery for patients with ductal carcinoma in situ: a report from the national cancer data base. Ann Surg Oncol 2016;23(10):3337–46.
46. National Comprehensive Cancer Network. Clinical practice guidelines in oncology-breast cancer version 4. 2020. Available at: http://www.nccn.com.
47. El Hage Chehade H, Headon H, Wazir U, et al. Is sentinel lymph node biopsy indicated in patients with a diagnosis of ductal carcinoma in situ? a systematic literature review and meta-analysis. Am J Surg 2017;213(1):171–80.
48. Hung P, Wang SY, Killelea BK, et al. Long-term outcomes of sentinel lymph node biopsy for ductal carcinoma in situ. JNCI Cancer Spectr 2019;3(4):pkz052. https://doi.org/10.1093/jncics/pkz052.
49. Eusebi V, Feudale E, Foschini MP, et al. Long-term follow-up of in situ carcinoma of the breast. Semin Diagn Pathol 1994;11(3):223–35.
50. Sanders ME, Schuyler PA, Dupont WD, et al. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer 2005;103(12):2481–4.
51. Sanders ME, Schuyler PA, Simpson JF, et al. Continued observation of the natural history of low-grade ductal carcinoma in situ reaffirms proclivity for local recurrence even after more than 30 years of follow-up. Mod Pathol 2015;28(5):662–9.
52. Francis A, Thomas J, Fallowfield L, et al. Addressing overtreatment of screen detected DCIS; the LORIS trial. Eur J Cancer 2015;51(16):2296–303.
53. Hwang ES, Hyslop T, Lynch T, et al. The COMET (Comparison of Operative versus Monitoring and Endocrine Therapy) trial: a phase III randomised controlled clinical

trial for low-risk ductal carcinoma in situ (DCIS). BMJ Open 2019;9(3):e026797. https://doi.org/10.1136/bmjopen-2018-026797.
54. Elshof LE, Tryfonidis K, Slaets L, et al. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - The LORD study. Eur J Cancer 2015;51(12):1497–510.
55. Kanbayashi C, Iwata H. Current approach and future perspective for ductal carcinoma in situ of the breast. Jpn J Clin Oncol 2017;47(8):671–7.
56. Early Breast Cancer Trialists' Collaborative Group, Correa C, McGale P, Wang Y, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010;2010(41):162–77.
57. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol 2015;33(7):709–15.
58. McCormick B, Winter KA, Woodward W, et al. Randomized phase III trial evaluating radiation following surgical excision for good-risk ductal carcinoma in situ: long-term report from NRG oncology/RTOG 9804. J Clin Oncol 2021;39(32):3574–82.
59. Rakovitch E, Nofech-Mozes S, Hanna W, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat 2015;152(2):389–98.
60. Rakovitch E, Nofech-Mozes S, Hanna W, et al. Multigene expression assay and benefit of radiotherapy after breast conservation in ductal carcinoma in situ. J Natl Cancer Inst 2017;109(4). https://doi.org/10.1093/jnci/djw256.
61. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 2013;105(10):701–10.
62. Rakovitch E, Parpia S, Koch A, et al. DUCHESS: an evaluation of the ductal carcinoma in situ score for decisions on radiotherapy in patients with low/intermediate-risk DCIS. Breast Cancer Res Treat 2021;188(1):133–9.
63. Shah C, Bremer T, Cox C, et al. The clinical utility of DCISionRT((R)) on radiation therapy decision making in patients with ductal carcinoma in situ following breast-conserving surgery. Ann Surg Oncol 2021;28(11):5974–84.
64. Raldow AC, Sher D, Chen AB, et al. Cost effectiveness of the oncotype DX DCIS score for guiding treatment of patients with ductal carcinoma in situ. J Clin Oncol 2016;34(33):3963–8.
65. D'Rummo KA, Miller L, TenNapel MJ, et al. Assessing the financial toxicity of radiation oncology patients using the validated comprehensive score for financial toxicity as a patient-reported outcome. Pract Radiat Oncol Sep-Oct 2020;10(5):e322–9.
66. Liu MC. Transforming the landscape of early cancer detection using blood tests-Commentary on current methodologies and future prospects. Br J Cancer 2021;124(9):1475–7.
67. Beer TM. Novel blood-based early cancer detection: diagnostics in development. Am J Manag Care 2020;26(14 Suppl):S292–9.
68. Liu MC, Oxnard GR, Klein EA, et al. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol 2020;31(6):745–59.
69. Cristiano S, Leal A, Phallen J, et al. Genome-wide cell-free DNA fragmentation in patients with cancer. Nature 2019;570(7761):385–9.

70. Lennon AM, Buchanan AH, Kinde I, et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science 2020; 369(6499). https://doi.org/10.1126/science.abb9601.
71. Rossi SH, Stewart GD. Re: clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation Set. Eur Urol 2022;82(4):442–3.
72. Hackshaw A, Clarke CA, Hartman AR. New genomic technologies for multi-cancer early detection: Rethinking the scope of cancer screening. Cancer Cell 2022;40(2):109–13.
73. Chin YM, Takahashi Y, Chan HT, et al. Ultradeep targeted sequencing of circulating tumor DNA in plasma of early and advanced breast cancer. Cancer Sci 2021;112(1):454–64.
74. Schrag D, Beer TM, McDonnell CH 3rd, et al. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. Lancet 2023; 402(10409):1251–60.
75. Neal RD, Johnson P, Clarke CA, et al. Cell-Free DNA-based multi-cancer early detection test in an asymptomatic screening population (NHS-Galleri): design of a pragmatic, prospective randomised controlled trial. Cancers (Basel) 2022; 14(19). https://doi.org/10.3390/cancers14194818.
76. Nicholson BD, Oke J, Virdee PS, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. Lancet Oncol 2023;24(7): 733–43.
77. Shimomura A, Shiino S, Kawauchi J, et al. Novel combination of serum microRNA for detecting breast cancer in the early stage. Cancer Sci 2016;107(3): 326–34.
78. Clift AK, Dodwell D, Lord S, et al. The current status of risk-stratified breast screening. Br J Cancer 2022;126(4):533–50.
79. Aleshin-Guendel S, Lange J, Goodman P, et al. A Latent Disease Model to Reduce Detection Bias in Cancer Risk Prediction Studies. Eval Health Prof 2021; 44(1):42–9.
80. Trentham-Dietz A, Alagoz O, Chapman C, et al. Reflecting on 20 years of breast cancer modeling in CISNET: Recommendations for future cancer systems modeling efforts. PLoS Comput Biol 2021;17(6):e1009020. https://doi.org/10.1371/journal.pcbi.1009020.
81. Shen Y, Dong W, Gulati R, et al. Estimating the frequency of indolent breast cancer in screening trials. Stat Methods Med Res 2019;28(4):1261–71.
82. Fitzgerald RC, Antoniou AC, Fruk L, et al. The future of early cancer detection. Nat Med 2022;28(4):666–77.
83. Petridis C, Brook MN, Shah V, et al. Genetic predisposition to ductal carcinoma in situ of the breast. Breast Cancer Res 2016;18(1):22.
84. Lamb LR, Lehman CD, Oseni TO, et al. Ductal Carcinoma In Situ (DCIS) at Breast MRI: Predictors of Upgrade to Invasive Carcinoma. Acad Radiol 2020; 27(10):1394–9.
85. Chou SS, Gombos EC, Chikarmane SA, et al. Computer-aided heterogeneity analysis in breast MR imaging assessment of ductal carcinoma in situ: Correlating histologic grade and receptor status. J Magn Reson Imaging 2017; 46(6):1748–59.
86. Rahbar H, Partridge SC, Demartini WB, et al. In vivo assessment of ductal carcinoma in situ grade: a model incorporating dynamic contrast-enhanced and

diffusion-weighted breast MR imaging parameters. Radiology 2012;263(2):374–82.
87. Grimm LJ, Rahbar H, Abdelmalak M, et al. Ductal Carcinoma in Situ: State-of-the-Art Review. Radiology 2022;302(2):246–55.
88. Yang ML, Bhimani C, Roth R, et al. Contrast enhanced mammography: focus on frequently encountered benign and malignant diagnoses. Cancer Imag 2023;23(1):10.
89. Cozzi A, Magni V, Zanardo M, et al. Contrast-enhanced Mammography: A Systematic Review and Meta-Analysis of Diagnostic Performance. Radiology 2022;302(3):568–81.
90. Vignoli C, Bicchierai G, De Benedetto D, et al. Role of preoperative breast dual-energy contrast-enhanced digital mammography in ductal carcinoma in situ. Breast J 2019;25(5):1034–6.
91. Cheung YC, Juan YH, Lin YC, et al. Dual-Energy Contrast-Enhanced Spectral Mammography: Enhancement Analysis on BI-RADS 4 Non-Mass Microcalcifications in Screened Women. PLoS One 2016;11(9):e0162740.
92. Erbas B, Provenzano E, Armes J, et al. The natural history of ductal carcinoma in situ of the breast: a review. Breast Cancer Res Treat 2006;97(2):135–44.
93. Ozanne EM, Shieh Y, Barnes J, et al. Characterizing the impact of 25 years of DCIS treatment. Breast Cancer Res Treat 2011;129(1):165–73.
94. Wallis MG, Clements K, Kearins O, et al. The effect of DCIS grade on rate, type and time to recurrence after 15 years of follow-up of screen-detected DCIS. Br J Cancer 2012;106(10):1611–7.
95. National Comprehensive Cancer Network. NCCN Guidelines for Patients® Ductal Carcinoma in Situ Breast Cancer. 2024. Available at: https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients/guidelines-for-patients-details?patientGuidelineId=30.
96. Zachariah NN, Basu A, Gautam N, et al. Intercepting premalignant, preinvasive breast lesions through vaccination. Front Immunol 2021;12:786286.
97. De La Cruz LM, Nocera NF, Czerniecki BJ. Restoring anti-oncodriver Th1 responses with dendritic cell vaccines in HER2/neu-positive breast cancer: progress and potential. Immunotherapy 2016;8(10):1219–32.
98. Czerniecki BJ, Koski GK, Koldovsky U, et al. Targeting HER-2/neu in early breast cancer development using dendritic cells with staged interleukin-12 burst secretion. Cancer Res 2007;67(4):1842–52.
99. Sharma A, Koldovsky U, Xu S, et al. HER-2 pulsed dendritic cell vaccine can eliminate HER-2 expression and impact ductal carcinoma in situ. Cancer 2012;118(17):4354–62.
100. Datta J, Berk E, Xu S, et al. Anti-HER2 CD4(+) T-helper type 1 response is a novel immune correlate to pathologic response following neoadjuvant therapy in HER2-positive breast cancer. Breast Cancer Res 2015;17(1):71.
101. Lowenfeld L, Zaheer S, Oechsle C, et al. Addition of anti-estrogen therapy to anti-HER2 dendritic cell vaccination improves regional nodal immune response and pathologic complete response rate in patients with ER(pos)/HER2(pos) early breast cancer. OncoImmunology 2017;6(9):e1207032.
102. O'Shea AE, Clifton GT, Qiao N, et al. Phase II Trial of Nelipepimut-S Peptide Vaccine in Women with Ductal Carcinoma In Situ. Cancer Prev Res (Phila) 2023;16(6):333–41.