Does Progesterone Receptor Matter in the Risk of Recurrence for Patients With Ductal Carcinoma in Situ?

Lubna N. Chaudhary, MD, MS; Zeeshan Jawa, MD; Ahmad Hanif, MD; Aniko Szabo, PhD; Sailaja Kamaraju, MD; Yee Chung Cheng, MD; Christopher R. Chitambar, MD

ABSTRACT

Background: Local recurrence is a major concern in patients diagnosed with ductal carcinoma in situ (DCIS). In invasive breast cancers, estrogen receptor (ER) (+)/progesterone receptor (PR) (-) subtype is considered more aggressive with poorer prognosis as compared to ER+/PR+ tumors. It is unclear whether this holds true in DCIS.

Methods: Six hundred ninety-three patients diagnosed and treated for DCIS at Froedtert & Medical College of Wisconsin Cancer Center (February 2002 to March 2015) were studied to determine if the recurrence rates were significantly different between ER+/PR- and ER+/PR+ tumors. Recurrence was defined as either noninvasive or invasive ipsilateral, contralateral, or distant disease. Probabilities of recurrences were calculated using Kaplan-Meier estimator. Cox proportional hazards model was used to evaluate the effect of prognostic factors on DCIS recurrence.

Results: Median follow-up was 5.2 years. The 5-year recurrence-free survival (RFS) was 91% (95% CI, 88.2-93.3) while estimated 7-year RFS was 86% (95% CI, 81.9-89.2). Seventy-five patients had a recurrence during their follow-up. Patients with ER-/PR- tumors (n = 118) had a significantly higher risk of recurrence (Hazard Ratio 3.7, 95% CI, 1.9-7.2, $P = 0.0001$) whereas those with ER+/PR- subtype (n = 77) did not have a significant difference in recurrence risk (HR 1.75, 95% CI, 0.92-3.32, $P = 0.085$) when compared to ER+/PR+ tumors (n = 482). No endocrine therapy for ER+ DCIS and lumpectomy alone were also significant predictors of recurrence ($P = 0.0073$ and $P = 0.005$, respectively).

Conclusions: ER+/PR- subtype was not a significant predictor of recurrence in DCIS patients. This finding is in contrast to the recurrence risk seen in invasive breast cancers. Mastectomy and postlumpectomy radiation were associated with improved outcomes as was adjuvant endocrine therapy.

• • •

Author Affiliations: Division of Hematology and Oncology (Chaudhary, Jawa, Kamaraju, Cheng, Chitambar); Department of Internal Medicine (Hanif); Division of Biostatistics (Szabo); Medical College of Wisconsin, Milwaukee, Wis.

Corresponding Author: Lubna N. Chaudhary, MD, MS, Assistant Professor of Medicine, Division of Hematology/Oncology, Froedtert and Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226; phone 414.805.4600; fax 414.805.4606; email lchaudhary@mcw.edu.

INTRODUCTION

Ductal carcinoma in situ (DCIS) is a non-invasive 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.[1-4] Local recurrence is the most common adverse outcome experienced by women receiving treatment for DCIS. Estimates of 5- or 10-year recurrence rates are remarkably variable across studies, ranging from 2.4% to 15% for 5 years to 10% to 24% for 10-year recurrence,[5-9] although the older studies may be overestimating the risk. While the recurrence rates for DCIS have fallen over time with increase in screening detection, better surgical techniques, and use of adjuvant therapies, survival after recurrence has been addressed by only a few studies.[10-13] Solin et al reported on the experience of 42 cases with local recurrence and estimated an actual 5-year breast cancer mortality rate of about 16%.[11] In a multi-institutional cohort, the local recurrence rate was 16.7% (n = 45/268) for women who received treatment for DCIS, while the 15-year cause-specific survival was 96%.[12] More recently, Narod et al reported 20-year breast cancer-specific mortality rate of only 3.3% for a large cohort of women (n = 108,196) diagnosed with DCIS.[13] Younger age, black ethnicity, high tumor grade, and negative estrogen receptor (ER) were significant predictors of breast cancer-specific mortality. Progesterone receptor (PR) status was not assessed in this study. Despite the high survival rates, local recurrence is a serious problem and understanding the risk factors to prevent recurrence is essential.

ER+/PR- are highly relevant biomarkers for invasive breast carcinoma as well as DCIS. Generally ER+/PR+ and ER+/PR- invasive breast cancers are treated similarly and are thought to be hormone-sensitive tumors; however ER+/PR- subtype is now recognized as a distinct biological and clinical entity associated with a worse outcome. In the setting of ER+ breast cancer, studies have shown that the absence of PR is an independent predictor of poor response to endocrine therapy, associated with higher recurrence rates and shorter survival times for invasive disease.[14] However, it is unclear if this holds true in DCIS, and the association between PR status and patient outcomes is not as extensively reviewed.

The aim of this study was to determine the association of PR- status with outcomes (recurrence ie, noninvasive or invasive ipsilateral, contralateral, or distant disease) in DCIS patients with the primary objective to assess if a significant difference exists in the recurrence rates for ER+/PR- tumors when compared to ER+/PR+ tumors.

METHODS

Patient Population and Data Collection

Patients with DCIS diagnosed and treated at the Froedtert & Medical College of Wisconsin Cancer Center from February 2002 to March 2015 were included in our study. In all, 969 patient charts were reviewed, of which 693 were included in this analysis. Charts were not included if they had incomplete patient information and/or single clinic visit with no additional follow-up. Patients with previous history of DCIS or invasive breast cancer were excluded, as were patients with micro invasion or presence of invasive breast cancer on final surgical staging. Data on patient and tumor characteristics were collected. The study was approved by the Institutional Review Board and the Protocol Review and Monitoring Committee of the Medical College of Wisconsin.

Estrogen and progesterone receptors were evaluated by immunohistochemistry (IHC) on formalin-fixed paraffin-embedded tissue using clone 1 D5 for ER and clone PgR 636 for PR (Dako, Carpenteria, CA). In 2008, our institution switched to clone SP1 for ER and clone SP2 for PR (Ventana, Tucson, AZ). Detection utilized a monoclonal polymer. In 2012, the nuclear staining criteria for ER and PR was revised to consider any nuclear staining in 1% or more of the malignant cells to be positive and less than 1% to be considered negative, it being ≥ 10% for positivity prior to 2012.

Statistical Analysis

Descriptive statistics were used to summarize sample characteristics. Probabilities of recurrences were calculated using Kaplan-Meier estimator. Loglog-transformed 95% confidence intervals for recurrence probabilities were calculated. Cox proportional hazards model was used to evaluate the effect of prognostic factors on DCIS recurrence. Multivariate models were built using the forward selection with significance level of 0.05. The primary objective of this study was to assess if a significant difference exists in the recurrence rates for ER+/PR- tumors when compared to ER+/PR+ tumors; therefore the variable for ER/PR status was held in the model at each step. Other variables considered were age at diagnosis, body mass index (BMI), menopausal status, history of oral contraceptive use and/or hormone replacement therapy, tumor size, tumor histology, grade, necrosis, surgery, radiation, and endocrine therapy. Recurrence was defined as either noninvasive or invasive ipsilateral, contralateral, or distant disease. All the *P* values are 2-sided. SAS Studio 9.4 was used to perform all statistical analysis.

Table 1. Patient and Tumor Characteristics

Patient Characteristics	**N (%)**	**Median (range)**
Total number of patients	693	
Median age		53 (21-91)
Median body mass index		27 (17-65)
Postmenopausal	480 (69)	
Oral contraceptive pill use	301 (43)	
Hormone replacement therapy use	201 (29)	
Tumor Characteristics	**N (%)**	**Median (range)**
Median size		0.8 cm (0.2-6.5)
Histology		
Solid	349 (52)	
Cribriform	290 (43)	
Micro papillary/papillary	35 (5)	
Comedo necrosis	423 (61)	
ER/PR status		
ER+/PR+ tumors	482 (71.2)	
ER+/PR- tumors	77 (11.4)	
ER-/PR- tumors	118 (17.4)	
Tumor nuclear grade		
Low	125 (18)	
Intermediate	305 (45)	
High	250 (37)	
Negative surgical margins	671 (97)	
Treatment		
Lumpectomy	517 (75)	
Mastectomy	169 (25)	
Radiation (postlump)	450 (87)	
Endocrine therapy (ER+ pts)	286 (51)	
Patients with recurrence	75 (11)	
Type of recurrence		
In-situ	44 (6)	
Invasive	31 (5)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

RESULTS

Patient Characteristics

Patient and tumor characteristics are summarized in Table 1. Six hundred ninety-three patients were included in our study. Median age at diagnosis was 53 years (range 21-91) and median BMI was 27 (range 17-65). Most women were postmenopausal (69%) and were primi or multiparous (65%). Median tumor size on pathologic evaluation was 0.8 cm. Most of the tumors were intermediate (45%) or high nuclear grade (37%). ER+/PR+ tumors comprised 71.2% of the tumors. Most of the patients underwent

Figure 1. Kaplan-Meier Estimate of Being Recurrence Free in Patients With Ductal Carcinoma in Situ

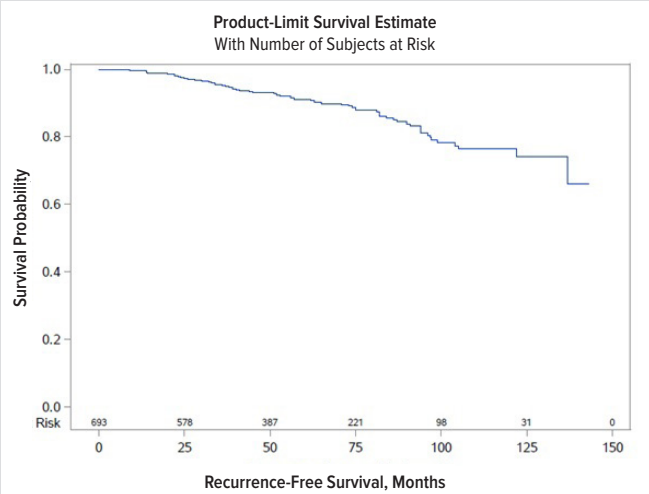
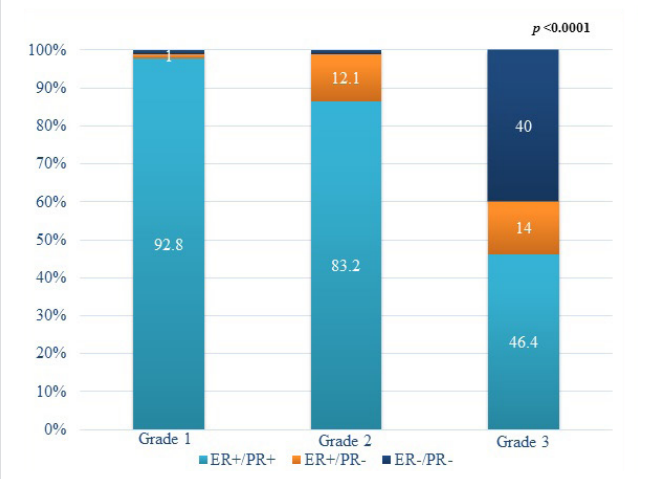


Figure 2. Association of ER/PR Status With DCIS Tumor Grade



Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Results of Multivariate Analysis for Recurrence in DCIS Patients

Variable	HR (95% CI)	*P* Value
ER/PR status		**0.0004**
ER+/PR+	1.00	
ER+/PR-	1.75 (0.92-3.32)	0.085
ER-/PR-	3.7 (1.9-7.2)	**0.0001**
Endocrine Therapy/ER Status		**0.0073**
ER+ with endocrine therapy	1.00	
ER+ without endocrine therapy	2.2 (1.23-3.92)	
Surgery/Radiation		**0.0003**
Lumpectomy+RT	1.00	
Lumpectomy alone	2.5 (1.32-4.93)	**0.005**
Mastectomy	0.34 (0.15-0.8)	**0.014**

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; RT, radiation therapy.

lumpectomy (n=517, 75%) and a large proportion of them received post lumpectomy radiation (n=450, 87%). Endocrine therapy was received by 51% of ER+ patients. It is to be noted that the proportion of patients not receiving endocrine therapy was similar between ER+/PR+ and ER+/PR- cohorts.

Outcomes

Median follow-up was 5.2 years. Five-year recurrence-free survival (RFS) was 91% (95% CI, 88.2-93.3) while 7-year RFS was 86% (95% CI, 81.9-89.2) as shown in Figure 1.

Seventy-five patients were found to have a recurrence during their follow-up. Forty-four patients had DCIS recurrence, 4 of whom had both ipsilateral and contralateral DCIS recurrence. Most of these patients had intermediate or high nuclear grade tumors at their initial DCIS diagnosis (n=16 and n=22, respectively) with only 6 patients having low-grade tumors at diagnosis.

Thirty-one patients had invasive ductal carcinoma (IDC) at recurrence, 3 of whom had distant disease. Assessment of their DCIS tumor grade at diagnosis showed grade 2 and 3 tumors for the majority of these patients (n=13 for grade 2 and n=12 for grade 3). Seven patients had human epidermal growth factor receptor 2 (HER2/neu) positive disease at their invasive recurrence.

ER/PR Status and DCIS Tumor Nuclear Grade

Most of the grade 1 tumors were ER+/PR+ whereas almost all of the ER-/PR- subtype were high-grade tumors. ER+/PR- tumors were mainly intermediate and high grade ($P < 0.0001$) as shown in Figure 2. In our cohort, there were no ER-/PR+ DCIS cases identified.

Multivariate Analysis

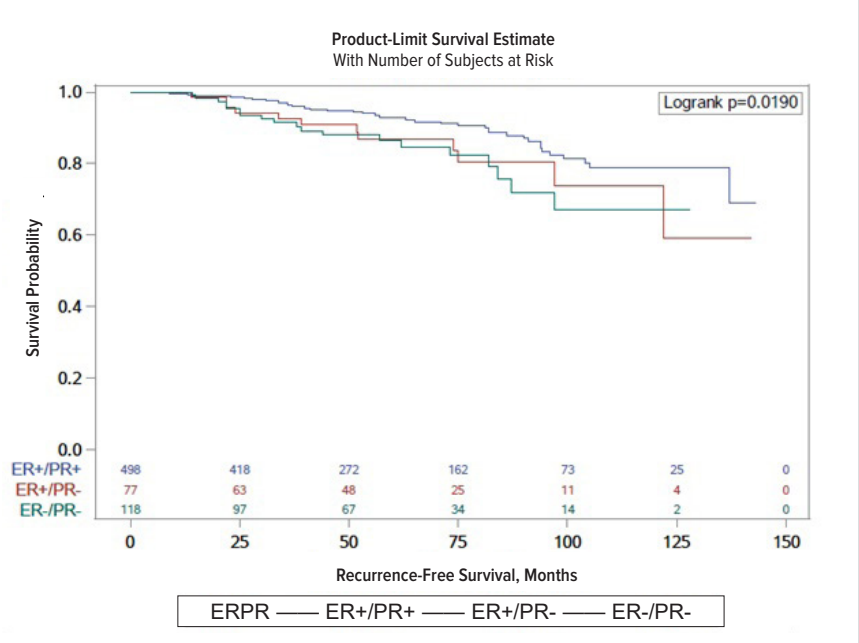
Multivariate analysis showed that among all covariates assessed, ER/PR status, endocrine therapy, surgery, and radiation were found to be significant predictors of recurrence in DCIS patients (Table 2). As compared to ER+/PR+ tumors, patients with ER-/PR- tumors had a significantly higher risk of recurrence ($P = 0.0001$) whereas ER+/PR- tumor subtype did not have a statistically significant difference in risk of recurrence ($P = 0.085$) as shown in Figure 3.

Patients not receiving endocrine therapy for their ER+ DCIS had a significantly higher risk of recurrence as compared to those who received it ($P = 0.0073$). When compared to lumpectomy/radiation, lumpectomy alone had a significantly higher risk of recurrence ($P = 0.005$) whereas mastectomy was associated with a significantly lower risk of recurrence ($P = 0.014$).

Given the significantly lower risk of recurrence after mastectomy, we performed a subgroup analysis of patients without the mastectomy cohort. The recurrence rate was 13.2% among the patients who underwent lumpectomy for their DCIS (n = 68/517). Multivariate analysis of this cohort still showed ER-/PR- status (Hazard Ratio 3.93; 95% CI, 1.96-7.87; $P = 0.0001$), no endocrine therapy within the ER+ cohort (HR 2.4; 95% CI, 1.31-4.41; $P = 0.004$) and not receiving post-

lumpectomy radiation (HR 2.49; 95% CI, 1.29-4.80; $P = 0.006$) to be associated with a significantly higher risk of recurrence. ER+/PR- tumor subtype was not a significant predictor of recurrence (HR 1.39; 95% CI, 0.67-2.8; $P = 0.36$).

Figure 3. Recurrence-Free Estimates by ER/PR Status



Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

DISCUSSION

DCIS of the breast is the most common type of noninvasive breast cancer and is considered a direct precursor for invasive breast cancer.[15,16] Local recurrence denotes a major concern in patients diagnosed with DCIS, as its invasive component—if present—can be associated with high rates of distant disease and mortality.[11,17] Therefore, the need to identify patients at risk for DCIS recurrence, as early and efficiently as possible, appears as a significant priority.

In invasive breast cancers, ER+/PR- subtype is now recognized as a more aggressive tumor phenotype with poorer prognosis as compared to ER+/PR+ tumors.[18] Whether this finding holds true in DCIS is not yet clear. Several studies have assessed the association between hormone receptors and patient outcomes in DCIS with conflicting results. Generally, most of the studies are consistent in their findings that positive ER status is associated with reduced likelihood of local DCIS or invasive recurrence.[19-22] Some of these studies showed a tendency toward less local DCIS or invasive cancer recurrence in PR-positive women.[19,20,23-25]

A nested case control study by Provenzano et al reported a significant risk reduction for local recurrence by 80% (adjusted OR 0.2; 95% CI, 0.1-0.8, $P = 0.02$) for ER+ and 60% (adjusted OR 0.4; 95% CI, 0.2-0.9, $P = 0.03$) for PR+ patients.[20] A recent study by Meattini et al reported 5-year and 10-year local recurrence rates of 4.9% and 10.2%, respectively, in 278 patients with DCIS and a median follow-up of 10.8 years.[22] Inadequate final surgical margins and negative ER status negatively influenced the local recurrence rates.

Our study had a much larger sample size and similarly showed that ER-/PR- tumors were associated with a significantly increased risk of recurrence as compared to ER+/PR+ DCIS. However, ER+/PR- subtype was not a significant predictor of recurrence. This finding is in contrast to the risk of recurrence and tumor aggressiveness seen in invasive breast cancers, which raises the question of tumor biology and carcinogenesis. It is often difficult to differentiate between true recurrence and a second primary carcinoma, especially when it involves the ipsilateral side. There has also been growing interest in HER2/neu status in DCIS and its correlation with tumor aggressiveness and recurrence rates, however the significance of HER2 status in DCIS is not yet clear. We did not have information on HER2 status in our study population as routine testing for HER2 in DCIS is not currently recommended.

Our study also showed significantly higher risk of recurrence for patients undergoing lumpectomy alone as compared to those receiving post-lumpectomy radiation, whereas mastectomy has a significantly lower risk of recurrence. These findings are in agreement with the published literature. Mastectomy provides excellent local control, approximately 90% at 7 years, with an overall recurrence rate of 1.5%.[26] However, it is difficult to justify mastectomy for a pre-invasive condition that should be curable with adequate local excision. There are no randomized trials comparing breast conservation plus radiation with mastectomy in DCIS analogous to the NSABP B-06 trial for invasive breast cancer. The benefit of adjuvant radiation in reducing local recurrence in those undergoing breast conservation has been well established given the long-term data from the NSABP B-17 and NSABP B-24 trials.[27] Recently Sagara et al reported a significant correlation of a patient prognostic score comprised of age, tumor size, and grade with survival benefit from post lumpectomy radiation.[28]

Endocrine therapy has been well established in reducing the risk of local ipsilateral and contralateral recurrence in ER+ DCIS patients. The addition of tamoxifen for 5 years after breast conservation and radiation significantly reduced the risk of recurrent DCIS or invasive carcinoma in the NSABP B-17 and B-24 trials.[6,27] Similar risk reduction was seen in the UK/ANZ DCIS trial in tamoxifen treated patients.[29] Aromatase inhibitors in postmenopausal women with ER+ DCIS also have shown reduc-

tion in breast cancer recurrence risk, with NSABP B-35 showing anastrozole to be superior to tamoxifen[30] whereas the IBIS-II DCIS study reported them to be equivalent.[31] Our study further supports and adds to the current literature by showing that patients who did not receive endocrine therapy for their ER+ DCIS had a significantly higher risk of recurrence as compared to those who received endocrine therapy.

The primary clinical dilemma in the management of DCIS patients relies on the fact that traditional clinicopathological features may not accurately predict disease recurrence in every patient. Great advances have been made in the use of molecular genomic profiling of invasive cancer for risk assessment; however, its implementation in clinical practice for the study of DCIS is lagging behind. The field of DCIS is growing and there are efforts to incorporate detailed genomic and molecular predictors into clinical practice. Recently, a modified form of the Oncotype DX recurrence score for invasive breast cancer (Genomic Health, Redwood City, CA) has been developed for DCIS. The DCIS score may be helpful in facilitating patient-specific recommendations for adjuvant radiation based on the risk of an ipsilateral breast event and recurrence risk. However, it is unclear how this information will fit beyond the decision making for postlumpectomy radiation. Furthermore, incorporating the DCIS score into everyday clinical practice for all patients with DCIS may not be cost effective[32] and needs to be further validated to confirm how much additional prognostic information could be derived from its use. Currently, clinicians and medical oncologists still rely very strongly on tumor biology and molecular subtypes for their clinical decision making and discussion of management and prognosis of such patients.

We acknowledge that our study has a number of limitations. Retrospective design, small sample size, short median follow-up and therefore the small number of recurrences in this study may have decreased the power to detect statistically significant differences.

CONCLUSION

Unlike invasive breast cancer, we did not find the ER+/PR- subtype to be a significant predictor of recurrence in DCIS. However, it is worth mentioning that although the hazard ratio of 1.75 was not significant, the confidence interval (0.92-3.32) is wide and the estimated effect would be important if true. Given the low event rate and the small number of the ER+/PR- group in our study, the effect would have had to be fairly large to be detectable. Although currently the treatment of ER+ DCIS does not differ based on PR status, knowing if PR status is independently prognostic of recurrence would be important for patient counseling, decision on postlumpectomy radiation, and encouraging compliance with endocrine therapy. It would be important to assess this further in larger confirmatory studies that would help elucidate the value of PR expression in recurrence risk determination of DCIS.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Hoorntje LE, Schipper ME, Peeters PH, Bellot F, Storm RK, Borel Rinkes IH. The finding of invasive cancer after a preoperative diagnosis of ductal carcinoma-in-situ: causes of ductal carcinoma-in-situ underestimates with stereotactic 14-gauge needle biopsy. *Ann Surg Oncol.* 2003;10(7):748-753.

2. Yen TW, Hunt KK, Ross MI, et al. Predictors of invasive breast cancer in patients with an initial diagnosis of ductal carcinoma in situ: a guide to selective use of sentinel lymph node biopsy in management of ductal carcinoma in situ. *J Am Coll Surg.* 2005;200(4):516-526. doi:10.1016/j.jamcollsurg.2004.11.012.

3. Li CI, Malone KE, Saltzman BS, Daling JR. Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988-2001. *Cancer.* 2006;106(10):2104-2112. doi:10.1002/cncr.21864.

4. Dillon MF, McDermott EW, Quinn CM, O'Doherty A, O'Higgins N, Hill AD. Predictors of invasive disease in breast cancer when core biopsy demonstrates DCIS only. *J Surg Oncol*. 2006;93(7):559-563. doi:10.1002/jso.20445.

5. Fisher B, Costantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med.* 1993;328(22):1581-1586. doi:10.1056/NEJM199306033282201.

6. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353(9169):1993-2000. doi:10.1016/S0140-6736(99)05036-9.

7. Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet.* 2003;362(9378):95-102.

8. EORTC Breast Cancer Cooperative Group, EORTC Radiotherapy Group, Bijker N, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol.* 2006;24(21):3381-3387. doi:10.1200/JCO.2006.06.1366.

9. Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. *J Clin Oncol.* 2008;26(8):1247-1252. doi:10.1200/JCO.2007.12.7969.

10. Subhedar P, Olcese C, Patil S, Morrow M, Van Zee KJ. Decreasing recurrence rates for ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery over 30 years. *Ann Surg Oncol.* 2015;22(10):3273-3281. doi:10.1245/s10434-015-4740-8.

11. Solin LJ, Fourquet A, McCormick B, et al. Salvage treatment for local recurrence following breast-conserving surgery and definitive irradiation for ductal carcinoma in situ (intraductal carcinoma) of the breast. *Int J Radiat Oncol Biol Phys.* 1994;30(1):3-9.

12. Solin LJ, Kurtz J, Fourquet A, et al. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. *J Clin Oncol.* 1996;14(3):754-763. doi:10.1200/JCO.1996.14.3.754.

13. Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast cancer mortality after a diagnosis of ductal carcinoma in situ. *JAMA Oncol.* 2015;1(7):888-896. doi:10.1001/jamaoncol.2015.2510.

14. Rakha EA, El-Sayed ME, Green AR, et al. Biologic and clinical characteristics of breast cancer with single hormone receptor positive phenotype. *J Clin Oncol.* 2007;25(30):4772-4778. doi:10.1200/JCO.2007.12.2747.

15. Ernster VL, Ballard-Barbash R, Barlow WE, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. *J Natl Cancer Inst.* 2002;94(20):1546-1554.

16. Holland R, Peterse JL, Millis RR, et al. Ductal carcinoma in situ: a proposal for a new classification. *Semin Diagn Pathol.* 1994;11(3):167-180.

17. Silverstein MJ, Lagios MD, Martino S, et al. Outcome after invasive local recurrence in patients with ductal carcinoma in situ of the breast. *J Clin Oncol.* 1998;16(4):1367-1373. doi:10.1200/JCO.1998.16.4.1367.

18. Viani GA, Stefano EJ, Afonso SL, et al. Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomized trials. *Radiat Oncol.* 2007;2:28. doi:10.1186/1748-717X-2-28.

19. Kepple J, Henry-Tillman RS, Klimberg VS, et al. The receptor expression pattern in ductal carcinoma in situ predicts recurrence. *Am J Surg*. 2006;192(1):68-71. doi:10.1016/j.amjsurg.2006.04.002.

20. Provenzano E, Hopper JL, Giles GG, Marr G, Venter DJ, Armes JE. Biological markers that predict clinical recurrence in ductal carcinoma in situ of the breast. *Eur J Cancer*. 2003;39(5):622-630.

21. Jiveliouk I, Corn B, Inbar M, Merimsky O. Ductal carcinoma in situ of the breast in Israeli women treated by breast-conserving surgery followed by radiation therapy. *Oncology.* 2009;76(1):30-35. doi:10.1159/000178162.

22. Meattini I, Saieva C, Bastiani P, et al. Impact of hormonal status on outcome of ductal carcinoma in situ treated with breast-conserving surgery plus radiotherapy: long-term experience from two large-institutional series. *Breast.* 2017;33:139-144. doi:10.1016/j.breast.2017.03.017.

23. de Roos MA, de Bock GH, de Vries J, van der Vegt B, Wesseling J. P53 overexpression is a predictor of local recurrence after treatment for both in situ and invasive ductal carcinoma of the breast. *J Surg Res.* 2007;140(1):109-114. doi:10.1016/j.jss.2006.10.045.

24. Roka S, Rudas M, Taucher S, et al. High nuclear grade and negative estrogen receptor are significant risk factors for recurrence in DCIS. *Eur J Surg Oncol.* 2004;30(3):243-247. doi:10.1016/j.ejso.2003.11.004.

25. Ringberg A, Anagnostaki L, Anderson H, Idvall I, Ferno M, South Sweden Breast Cancer Group. Cell biological factors in ductal carcinoma in situ (DCIS) of the breast-relationship to ipsilateral local recurrence and histopathological characteristics. *Eur J Cancer.* 2001;37(12):1514-1522.

26. Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. *Cancer.* 1999;85(3):616-628.

27. 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):478-488. doi:10.1093/jnci/djr027.

28. Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. *J Clin Oncol.* 2016;34(11):1190-1196. doi:10.1200/JCO.2015.65.1869.

29. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol.* 2011;12(1):21-29. doi:10.1016/S1470-2045(10)70266-7.

30. 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):849-856. doi:10.1016/S0140-6736(15)01168-X.

31. 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):866-873. doi:10.1016/S0140-6736(15)01129-0.

32. Raldow AC, Sher D, Chen AB, Recht A, Punglia RS. Cost effectiveness of the Oncotype DX DCIS Score for guiding treatment of patients with ductal carcinoma in situ. *J Clin Oncol.* 2016;34(33):3963-3968. doi:10.1200/JCO.2016.67.8532.

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.