

Association Between Patient and Tumor Characteristics With Clinical Outcomes in Women With Ductal Carcinoma In Situ

Tatyana Shamliyan, Shi-Yi Wang, Beth A. Virnig, Todd M. Tuttle, Robert L. Kane

Correspondence to: Tatyana Shamliyan, MD, Division of Health Policy and Management, University of Minnesota School of Public Health, D330-5 Mayo (MMC 729), 420 Delaware St SE, Minneapolis, MN 55455 (e-mail: sham1005@umn.edu).

We synthesized the evidence of the association between patient and tumor characteristics with clinical outcomes in women with ductal carcinoma in situ of the breast. We identified five randomized controlled clinical trials and 64 observational studies that were published in English from January 1970 to January 2009. Younger women with clinically presented ductal carcinoma in situ had higher risk of ipsilateral recurrent cancer. African Americans had higher mortality and greater rates of advanced recurrent cancer. Women with larger tumor size, comedo necrosis, worse pathological grading, positive surgical margins, and at a higher risk category, using a composite prognostic index, had worse outcomes. Inconsistent evidence suggested that positive HER2 receptor and negative estrogen receptor status were associated with worse outcomes. Synthesis of evidence was hampered by low statistical power to detect significant differences in predictor categories and inconsistent adjustment practices across the studies. Future research should address composite prediction indices among race groups for all outcomes.

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We identified five randomized controlled clinical trials (1–9) and 64 observational studies that were presented in 133 publications, including 10 publications that reported the results of the Surveillance, Epidemiology, and End Results (SEER) database analyses (10–19) and 65 articles based on analyses of the American cancer registries and large academic centers (20–84).

Age

Observational studies and randomized controlled clinical trials reported increased risk of recurrent cancer in younger women after adjustment for treatment, patient's characteristics, and tumor factors (Table 1). Randomized trials demonstrated that women younger than 40 years experienced an 89% increase in risk of ipsilateral breast tumor recurrence (IBTR) (adjusted hazard ratio [HR] = 1.89, 95% confidence interval [CI] = 1.12 to 3.19) (1). Women younger than 49 years experienced a 117% increase in relative risk of IBTR local ductal carcinoma in situ (DCIS) or invasive carcinoma recurrence (adjusted HR = 2.17, 95% CI = 1.61 to 2.94) (5). Observational studies also demonstrated that younger age was a predictor of poor recurrence independent of treatment and tumor characteristics, with an increased risk of IBTR by 100% (72), 125% (85), or 130% (13). Older women experienced a reduction in risk of local DCIS recurrence by 6% for every additional year of age (adjusted relative risk [RR] = 0.94, 95% CI = 0.89 to 0.99) (16) and incremental decrease in true recurrence by 7% (21,24) and IBTR by 6%–8% per year of age (25).

Premenopausal women had increased risk of local invasive recurrence by 90% (RR = 1.9, 95% CI = 1 to 3.7) (13) to 490%

(RR = 5.9, 95% CI = 1.8 to 19.3) (10) when compared with postmenopausal women after adjustment for age.

Race

Surprisingly, few studies examined racial differences in DCIS outcomes (13,15–17,19,49). Several analyses of the SEER database (13,15–19) found that overall mortality was 35% higher (RR = 1.35, 95% CI = 1.12 to 1.62) in African American vs Caucasian women with DCIS (17). The analyses that adjusted for prognostic variables including tumor size, grade, or necrosis (15,16,18) did not find differences in IBTR, local DCIS recurrence, or local invasive carcinoma recurrence in race subgroups (Figure 1). The analyses that adjusted for age, year, site, and treatments but not for tumor prognostic factors (17,19) reported worse outcomes among black women compared with white women with DCIS. Black women had higher rates of local invasive carcinoma recurrence (RR = 1.5, 95% CI = 1.2 to 2) or any invasive carcinoma (RR = 1.4, 95% CI = 1.2 to 1.7) (19). Risk of advanced invasive carcinoma, stage III/IV, was 130% higher in Hispanic vs white women with DCIS (RR = 2.3, 95% CI = 1.1 to 4.8) (19) and 170% in black vs white women (RR = 2.7, 95% CI = 1.7 to 4.4) (19).

External Hormone Use

Hormone replacement therapy before or after diagnosis and treatment for DCIS was not associated with IBTR (10). Relative risk of IBTR was not significant in women who used oral contraceptives when compared with those who never used them (10).

Table 1. Summary of the evidence: association between women and tumor characteristics and patient outcomes*

Risk factor	No. of publications	No. of patients	Estimates of risk	Evidence
Age	5 RCTs (1–5); 51 (10,12–17,19–25,40,43,47–49,62,67,71–76,79,81,83–91,93–105)	173937	Women younger than 40 y had worse outcomes	Moderate
Race	12; 1980 (57); 1997 (75); 2003 (13,15–19,49,73,83,84)	123853	African American women had higher mortality and advanced cancer	Low
Menopause	8 (10,13,25,67,71,73,84,87)	3718	Premenopausal women had worse outcomes than postmenopausal women	Low
Menarche age	1 (10)	709	NS	Low
Marital status	2 (10,15)	1812	Single or unmarried women had worse outcomes	Low
Education	1 (10)	709	NS	Low
Hormone replacement therapy	4 (10,84,89,104)	1899	NS	Low
Oral contraceptives	1 (10)	709	NS	Low
Age at first birth	1 (10)	709	NS	Low
Parity	1 (10)	709	NS	Low
Family history	12 (10,13,43,48,73,75,76,83,86–89)	4595	Women with family history had worse outcomes	Low
Alcohol intake	1 (10)	709	NS	Low
Body mass index; weight	2 (10,13); 1 (73)	1745; 198	Obese women may have worse outcomes	Low
Comorbidity	2 (15,16)	4512	Women with one or more comorbidities had worse outcomes	Low
Breast density	2 (27,64)	6466	Women with higher density had worse outcomes	Low
Methods of detection	2 RCTs (1,5); 23 (13,21,24,43,48,71,73,85–95,100,103,106–108)	2579; 8878	Women with clinical symptoms had worse outcomes	Moderate
Year of diagnosis; time since diagnosis	1 (12); 2 (11,49)	7072; 25476	Women diagnosed with DCIS after screening mammography became common had lower standardized to the general population 10-y breast cancer mortality ratio. Incidence of contralateral DCIS immediately after diagnosis of the primary DCIS dramatically increased due to active surveillance	Low
Total volume; volume of excision	1 (24); 3 (21,24,94)	148; 1309	Women with less excision volume (≤ 60 cm ³) had worse outcomes	Low
No. of slides with DCIS	1 (24)	148	Women with greater number of slides with DCIS in the specimen had worse outcomes	Low
Composed risk estimation	1 RCT (2); 13 (16,18,22,36–38,45,63,89,99,106,109,110)	775; 20736	Women at higher risk category using Van Nuys index had worse outcomes	Moderate
Microinvasion	1 RCT (2); 4 (50,80,83,104)	1065	NS	Low
Tumor size	2 RCTs (3,9); 39 (10,15,16,19,24,37,40,45,47,62,67,71,73,74,83–87,89–91,93,94,97,99–101,103,104,106,107,111,116)	1095; 53344	Women with larger tumors may have worse ipsilateral cancer	Low
Architecture: columnar cell change, comedo; cribriform, micropapillary, and solid types; necrosis	2 RCTs (1,9); 25 (10,16,19,23,30,33,43,48,67,71,73,75,86,91,93,95,96,100,103,107,111,113,117,118); 8 (20–22,24,45,49,72,107); 19 (15,23,28,40,45,47,48,62,71,83,85,91,100,103,113–115,117,118); 3 RCTs (2,5,9)	1693; 47346; 24709; 4525; 2869	Consistent evidence that women with comedo necrosis DCIS had worse outcomes. Solid, cribriform, or papillary DCIS were associated with worse outcomes	High; low
Calcification	6 (20,21,23,24,91,103)	808	The lack of calcification was strongly associated with DCIS or invasive carcinoma recurrence	Low
Antiapoptotic Bcl-2 gene expression	1 (119); 1 (92)	216	High vs low NS; women with positive Bcl-2 vs negative had lower odds of recurrence	Low; low
Expression of p21 cyclin-dependent kinase inhibitor	4 (92,104,116,121)	435	NS	Low
Estrogen receptors; progesterone receptors; HER2	8 (53,84,85,92,104,105,116,119); 6 (53,84,92,104,116,119); 5 (104,105,116,120,121)	1421; 1447; 660	Inconsistent evidence that women with positive ER had lower risk of recurrence. Women with HER2-positive status tended having worse ipsilateral cancer. HER4-positive women with expression had lower risk of recurrent cancer	Low
Tumor grade	2 RCTs (2,9); 20 (16,19,24,25,45,48,53,55,62,74,85,87,88,90,93,108,114,116,120,122)	1401; 45765	Consistent evidence that women with high-grade DCIS had worse ipsilateral cancer	High
Tumor suppressor protein 53	4 (92,104,116,119)	435	NS	Low
Positive surgical margins	3 RCTs (1,3,9); 11 with adjusted estimates (15,40,73,85,90,93,95,102,105,116,123)	2362	Women with positive margins had worse outcomes. Involved, close, and unknown margins were associated with worse outcomes. Women with negative margins of 10 mm or more had better outcomes	High

* DCIS = ductal carcinoma in situ; ER = estrogen receptor; NS = not significant; RCT = randomized controlled clinical trial.

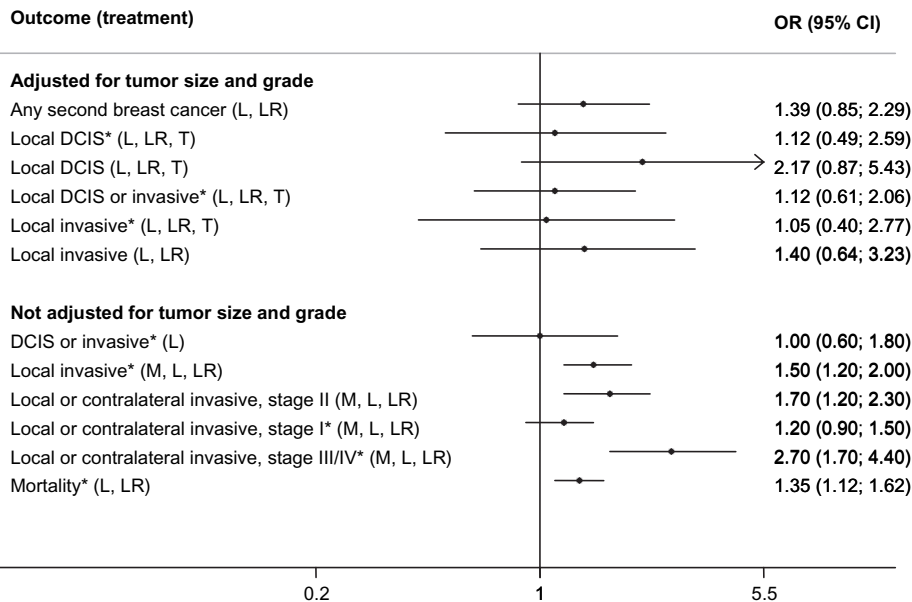


Figure 1. Patient outcomes in African Americans compared with whites, Surveillance, Epidemiology, and End Results database analyses (13,15–17,19). DCIS, ductal carcinoma in situ; L, breast conserving surgery; LR, breast conserving surgery and radiation; T, tamoxifen; M, mastectomy; *, analyses did not compare treatments.

Body Mass Index

Limited evidence from observational studies (10,13) suggested that obese women (body mass index >31 kg/m²) had a 130% increased risk of IBTR (RR = 2.3, 95% CI = 1.1 to 4.8). The risk of local invasive carcinoma recurrence was significantly greater in overweight (RR = 2.8, 95% CI = 1.0 to 8.1) and obese women (RR = 5.0, 95% CI = 1.1 to 10.8). One study found that women with increased weight (>200 vs ≤200 pounds) had 800% greater odds of grade 2 maximal acute toxicity (moderate to brisk erythema, patchy moist desquamation, mostly confined to skin folds and creases or moderate edema) from adjuvant radiotherapy (odds ratio [OR] = 9.0, 95% CI = 2.6 to 31.7) (73).

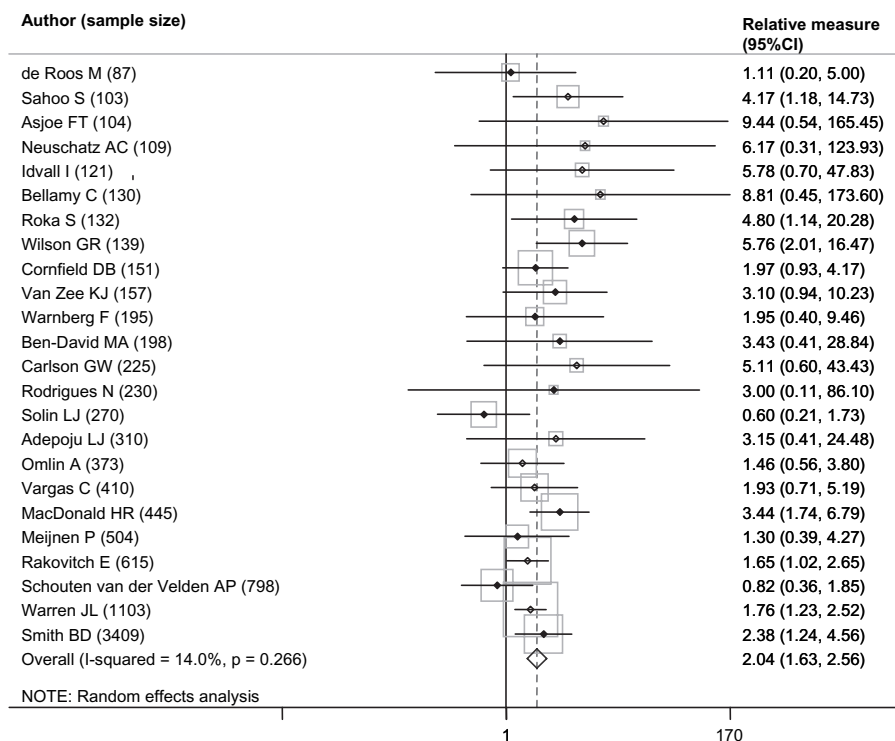
Marital Status

Two observational studies demonstrated greater risk of IBTR in single women (HR = 2.2, 95% CI = 1 to 4.9) (10) or unmarried women (HR = 1.52, 95% CI = 1.08 to 2.13) (15).

Family History

Positive family history of breast cancer defined as breast cancer in a first- or second-degree relative was significantly associated with local recurrence in one (HR = 3.08, 95% CI = 1.04 to 9.1) (73) of the four studies that examined this association (10,13,73,86). Other studies reported that crude recurrence rates in women older than

Figure 2. Local ductal carcinoma in situ (DCIS) or invasive cancer in women with high vs low grade of tumor (results from individual observational studies pooled with random-effects models) (15,16,25,40,45,47,48,62,71,73,74,83,85,90,93,98,100,104,108,116,122,124).



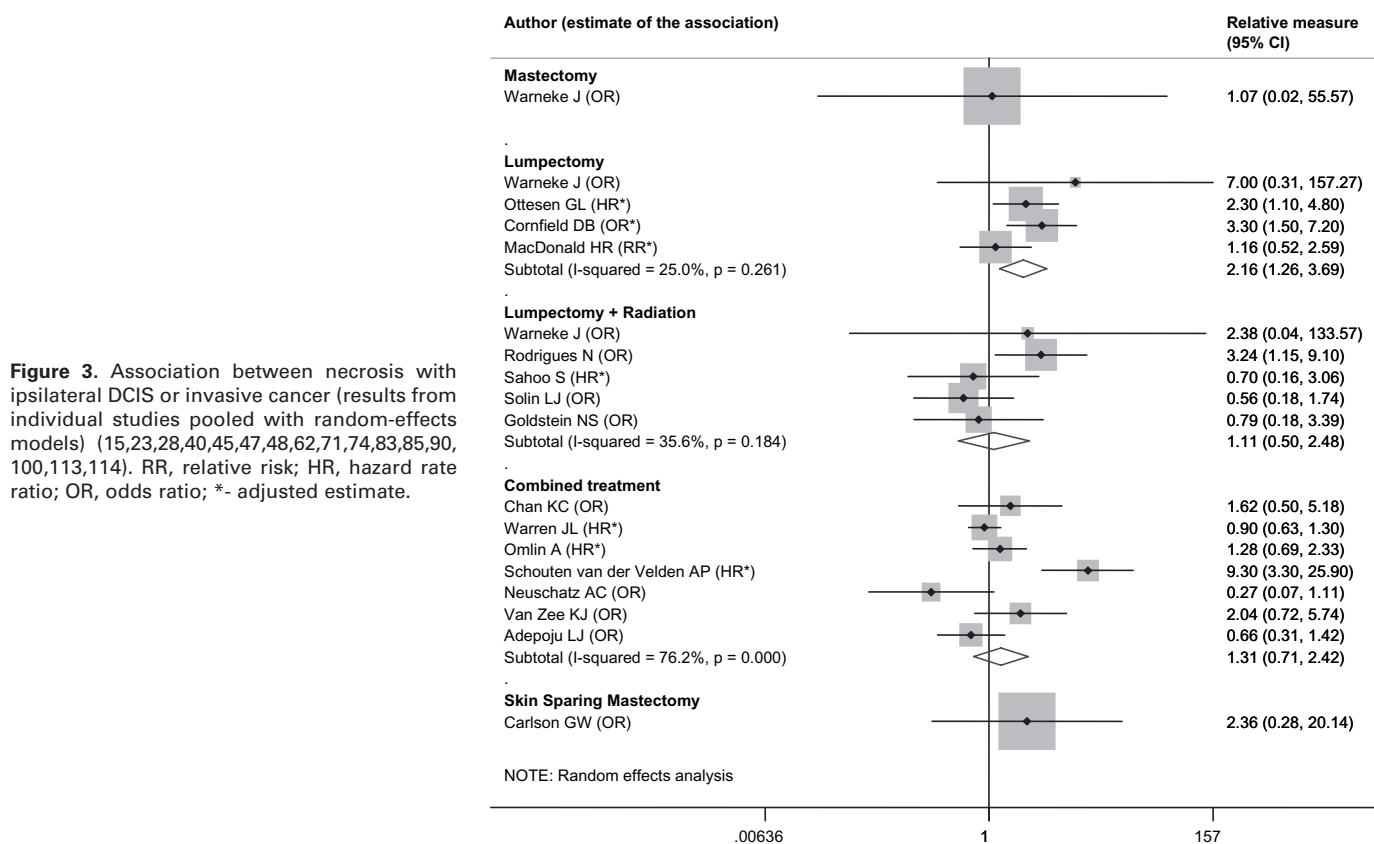


Figure 3. Association between necrosis with ipsilateral DCIS or invasive cancer (results from individual studies pooled with random-effects models) (15,23,28,40,45,47,48,62,71,74,83,85,90,100,113,114). RR, relative risk; HR, hazard rate ratio; OR, odds ratio; *- adjusted estimate.

50 years with positive family history were greater than those rates in those without family history (43,48,75,76,83,87–89).

Methods of Detection

Women with clinical symptoms had a 55% increase in risk of IBTR (RR = 1.55, 95% CI = 1.11 to 2.16) (1) to 90% (RR = 1.9, 95% CI = 1.36 to 2.65) (5) when compared to DCIS detected by mammography only in randomized controlled clinical trials. The results from observational studies were less consistent, and an increased risk of 100% (HR of IBTR = 2.05, 95% CI = 1.1 to 3.81) (72) to 170% (RR of invasive carcinoma = 2.7, 95% CI = 1.2 to 6.1) (13) was reported in three (13,72,90) of the nine studies that analyzed the association (10,13,72,85,86,90–93).

Year of Diagnosis

Generally, observational studies suggested reduction in breast cancer mortality after implementation of mammographic screening in the United States (12,49,87,94). Women diagnosed with DCIS after screening mammography became common (1984–1989; 5547 in SEER database) compared with those diagnosed from 1978 to 1983 (1525 women in SEER database) had a 40% reduction in relative risk of breast cancer death after adjustment for age and race (12). When data was standardized to the general population mortality ratio, women diagnosed with DCIS before screening mammography was common had greater 10-year breast cancer mortality, compared with those diagnosed after wide implementation of breast cancer screening (3.4, 95% CI 2.4 to 4.5 vs 1.9, 95% CI 1.5 to 2.3 respectively) (12).

Mammographic Breast Density

The results from the National Surgical Adjuvant Breast and Bowel Project B-17 trial (64) suggested that women with higher mammographic breast density (>75% vs <25%) experienced local recurrence (adjusted RR = 3, 95% CI = 1.2 to 3) or any recurrence (adjusted RR = 2.8, 95% CI = 1.3 to 2.8) more often. The Breast Cancer Surveillance Consortium findings suggested that women with high vs low breast density had higher risk of contralateral (HR adjusted for age = 3.1, 95% CI = 1.6 to 6.1) but not ipsilateral invasive recurrence after lumpectomy (27).

Comorbidity

A study of 1103 women who were diagnosed with DCIS between 1991 and 1992 found that women with one or more comorbidities were more likely to experience IBTR than women with no comorbidities (RR = 1.62) (15). The likelihood of receiving adjuvant radiotherapy is similar in women with and without comorbidities ($P = .747$) (15). Younger women and women receiving radiotherapy, however, were oversampled. In contrast, another analysis of the same SEER-Medicare database included only women older than 66 years and reported that those with comorbidities did not have an increased risk of IBTR when compared with women without comorbidities (16). Although both analyses used the Charlson comorbidity index, the study of older women did not obtain surgical margin status. Sampling and methodological differences may contribute to different results.

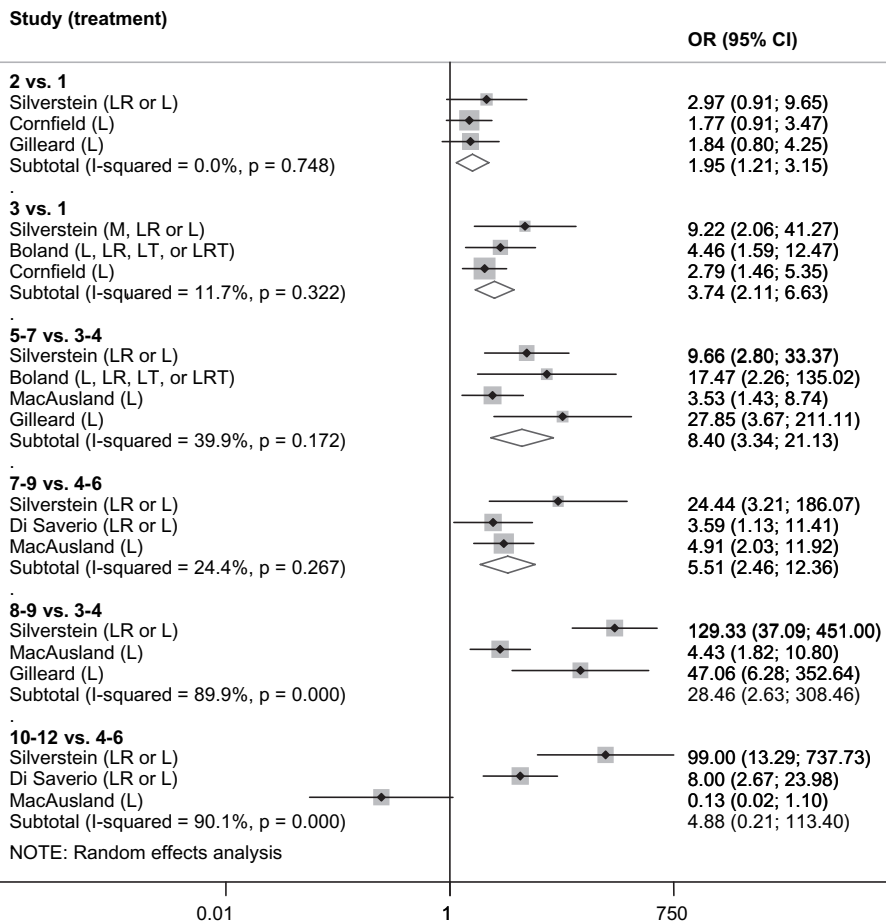


Figure 4. The association between Van Nuys Prognostic Index Score* with Ipsilateral Cancer. *, higher score indicated greater risk of ipsilateral cancer; L, breast conserving surgery; LR, breast conserving surgery and radiation; T, tamoxifen (34,36,38,45,63,89,97,99).

Positive Surgical Margins

Positive surgical margins were consistently associated with increased IBTR in observational studies and randomized controlled clinical trials (Table 1) despite considerable variability in definitions. The association was significant after adjustment for treatments including adjuvant radiotherapy and tamoxifen (1,5,15,40,73,85,95,124). An analysis of adjusted relative risk suggests that risk of IBTR is reduced with larger widths of negative margins. Margins of 10 mm or more were associated with the largest reduction (98%) in the risk of IBTR, whereas no differences were seen using a cutoff of 2 or 4 mm (40,94,124).

Tumor Characteristics

Tumor size was positively associated with higher rates of IBTR, though many of the estimates were not statistically significant. Estimates generally classified tumors less than 20 mm as small though some defined small as less than 5 mm.

We found consistent evidence that women with high vs low grade of tumor had a 104% increase in odds of IBTR (Figure 2). Comparisons of intermediate (2) vs low (1) grade were much less consistent.

Comedo necrosis was consistently and strongly associated with increased risk of IBTR, with hazard ratios generally above 2.0 and as high as 9.3. No study reported a significant association between comedo and non-comedo DCIS and all-cause mortality, breast

cancer mortality, contralateral invasive carcinoma, or all events. The association between necrosis and IBTR differed depending on the treatments women had (Figure 3). The association was not significant after mastectomy or skin-sparing mastectomy and inconsistent in direction and significance after lumpectomy plus radiation and in studies that combined all treatment together in analysis. The risk of IBTR in women after lumpectomy was increased by 116%.

Studies of estrogen receptor status and DCIS outcomes are generally limited to small studies, often including approximately 100 cases. Generally, all are consistent in their findings that positive estrogen receptor status is associated with a reduced likelihood of local DCIS or invasive recurrence, although few of the associations are statistically significant. Whether the association was independent of tamoxifen treatment is unclear because adjustment for treatments was not consistent across the studies. The studies investigating the association between progesterone receptor status and patient outcomes showed a tendency toward less IBTR in progesterone receptor-positive women.

The relationship between HER2 positivity and recurrence was only studied in relatively small DCIS studies of 129 patients or less. Consistently, investigators have found that women with HER2-positive DCIS were at higher risk of recurrence. HER3 and HER4 have only been evaluated in a single study (120). Women with DCIS and HER4-positive or HER3-negative status had a lower risk of recurrence.

Overall Predicted Risk of Local Recurrence

Women at higher risk had worse outcomes (18,22,34,36–38, 45,63,89,96–99,106,109). The studies applied the exact Van Nuys criteria (nine scores for grade, size, and margin) (22,34,36,45,62, 63,89,97–99,106,110) or the USC/Van Nuys Prognostic Index adding age (38,63,89,98).

Despite differences in definitions of total score, women in higher risk categories had higher rates of IBTR (Figure 4) (34,36,38,45,63,89,97,99). Women with a maximal score of 12 had a 274% greater risk of IBTR. The association between total score and risk of IBTR was not linear dose response. Maximal increase in relative risk by 740% was observed in women with a score of 5–7 compared with a score of 3–4.

Women with scores of 10–12, using the USC/Van Nuys Prognostic Index scoring system, had 224% greater odds of mortality compared with women with a 4–6 risk category (89). Breast cancer mortality was examined in four studies (34,36,38,89); one found a significant positive association with greater predicted risk (OR = 8.61, 95% CI = 1.06 to 70.17) in women with scores of 10–12 in the Van Nuys index compared with those with scores of 4–6 (89). The odds of any event were 509% higher (OR = 6.09, 95% CI = 2.40 to 15.50) in women at the highest Van Nuys index scores category compared with the lowest score (89).

Discussion

Synthesis of evidence of the association between women's characteristics and patient outcomes was hampered by different definitions of the outcomes and predictor categories, low statistical power to detect differences in outcomes in predictor categories, and inconsistent adjustment for treatment and tumor characteristics across the studies.

Why outcomes varied among women's subgroups was not clear. Adjustment for tumor size, grade, or necrosis attenuated racial differences in IBTR in the studies that we identified for this review. Only one SEER analysis examined access to treatment and overall mortality in racial subgroups with DCIS and found that African American women were less likely to receive follow-up radiotherapy and had a significantly increased risk of death (17). Neither comorbidity status nor surgical margin status was included in the analysis because this information is not available in the registries (17). A recently published case series from the Johns Hopkins Medical Institutions (125) found no differences in breast cancer mortality and histology of DCIS in African American women when compared with Caucasians. However, overall mortality, mostly from cardiovascular diseases, was greater in African American women. Difference in screening patterns and access or quality of overall and breast cancer care can contribute to the observed race differences in incident second breast cancer in the United States.

Based on a comprehensive literature review, we recommend that future research should evaluate risk of patient outcomes over time to help develop postdiagnostic surveillance policies. Additional work improving the DCIS prognostic index using additive scores or interaction is needed. A prognostic index should be developed for all outcomes, should include women's race, and should be based

on multivariate-adjusted regression coefficients. Future research should assess the association between health-care structure and quality, process variables, and patient outcomes.

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Affiliations of authors: Division of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis, MN (TS, S-YW, BV, RLK); Minnesota Evidence-based Practice Center, Minneapolis, MN (TS, RLK); Department of Surgery, University of Minnesota Medical School, Minneapolis, MN (TT).