EPIDEMIOLOGY

Time-varying risks of second events following a DCIS diagnosis in the population-based Vermont DCIS cohort

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Abstract

Purpose Long-term disease-free survival patterns following surgical, radiation, and endocrine therapy treatments for ductal carcinoma in situ (DCIS) are not well characterized in general US practice.

Methods We identified 1252 women diagnosed with DCIS in Vermont during 1994–2012 using data from the Vermont Breast Cancer Surveillance System, a statewide registry of breast imaging and pathology records. Poisson regression and Cox regression with time-varying hazards were used to evaluate disease-free survival among self-selected treatment groups.

Results With 7.8 years median follow-up, 192 cases experienced a second breast cancer diagnosis. For women treated with breast-conserving surgery (BCS) alone, the annual rate of second events decreased from 3.1% (95% CI 2.2–4.2%) during follow-up years 1–5 to 1.7% (95% CI 0.7–3.5%) after 10 years. In contrast, the annual rate of second events among women treated with BCS plus adjuvant radiation therapy increased from 1.8% (95% CI 1.1–2.6%) during years 1–5 to 2.8% (95% CI 1.6–4.7%) after 10 years ($P < 0.05$ for difference in trend compared to BCS alone). Annual rates of second events also increased over time among women treated with BCS plus adjuvant radiation and endocrine therapy ($P = 0.01$ for difference in trend compared to BCS alone). The rate of contralateral events increased after 10 years for all groups with adjuvant treatments. The rate of second events did not vary over time among women who underwent ipsilateral mastectomy ($P = 0.62$).

Conclusions Long-term risk of a second event after DCIS varies over time in a manner dependent on initial treatment.

Keywords Breast cancer · Ductal carcinoma in situ · Treatment outcome · Cohort studies · Disease-free survival

Abbreviations

BCS	Breast-conserving surgery
CI	Confidence interval
DCIS	Ductal carcinoma in situ
ER	Estrogen receptor
ET	Endocrine therapy
RT	Radiation therapy
VBCSS	Vermont Breast Cancer Surveillance System
VCR	Vermont Cancer Registry

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Introduction

Approximately 20% of breast cancers diagnosed in the United States are ductal carcinoma in situ (DCIS), a non-invasive form of breast cancer [1]. There are several treatment approaches for DCIS, including combinations of surgical management and adjuvant therapies [2]. While no studies have demonstrated mortality differences between treatments, observational studies have demonstrated lower risk of recurrence with mastectomy compared to breast-conserving surgery (BCS) alone [3–5] and randomized trials have demonstrated that adjuvant radiation therapy (RT) or endocrine therapy (ET) after BCS reduces risk of recurrence [6–8].

Outside of clinical trials, treatments are guided by patient preferences and values related to side effects and perceptions of protection against recurrence, in addition to DCIS characteristics including grade, size, and estrogen receptor (ER) status [2, 9–11]. Uncertainty remains regarding long-term outcomes following each DCIS management strategy as it is used in general US practice. In particular, long-term data on rates of ipsilateral and contralateral events, type of recurrence (DCIS vs. invasive breast cancer), and timing of recurrence from population-based cohorts are limited. There is particular uncertainty regarding the long-term duration of effectiveness for both RT and ET, with some studies suggesting that RT reduces risk of recurrence only within the first 5 years after treatment [12, 13].

We sought to provide evidence regarding long-term DCIS outcomes among a population-based cohort of women diagnosed in the state of Vermont. Women in our observational study self-selected into treatment groups and thus there are inherent biases when attempting to compare the effectiveness of one treatment group to another. Instead, we sought to characterize patterns in disease-free survival within each treatment group. In particular, we describe how risk of second events changed during the course of long-term follow-up.

Methods

Study setting

We constructed an observational cohort of women diagnosed with DCIS in Vermont during 1994–2012 using data from the Vermont Breast Cancer Surveillance System (VBCSS), a registry of breast cancer screening and diagnostic imaging performed at radiology facilities in Vermont [14], and a founding member of the Breast Cancer Surveillance Consortium [15]. The VBCSS links patient and breast imaging data from radiology facilities to statewide breast pathology records and Vermont Cancer Registry (VCR) data. This study was approved by the University of Vermont Institutional Review Board with a waiver of consent and all study procedures were compliant with the Health Insurance Portability and Accountability Act.

Study population

Women aged 18 years and older diagnosed with DCIS as a first primary breast cancer in the VBCSS with at least 6 months of follow-up were eligible for inclusion in the cohort. Women with a previous breast cancer diagnosis or a concurrent invasive breast cancer diagnosis (within 6 months of DCIS diagnosis) and those who opted out of participation in VBCSS research (10% of women) were excluded. A total of 1376 potentially eligible DCIS cases were identified. Pathology slides and/or blocks were available for 1154 cases and a centralized review was conducted by four breast pathology experts. The DCIS diagnosis was confirmed in 95.7% of cases (38 cases were downgraded to benign disease; 12 cases were upgraded to invasive disease); the 38 downgraded cases were excluded, leaving 1326 DCIS cases in the study cohort. For statistical analyses, we excluded bilateral DCIS ($N = 5$), cases with missing treatment data ($N = 49$), and cases treated by bilateral mastectomy ($N = 20$), leaving a final sample size of 1252 DCIS cases.

Available data

Women undergoing breast imaging at radiology facilities in the state of Vermont are asked to complete a clinical questionnaire at each visit that collects data on demographics, height, weight, family history of breast cancer, reproductive/menstrual characteristics, and use of postmenopausal hormones. Women also report whether they have previously undergone needle biopsy, excisional biopsy, lumpectomy, mastectomy, or RT on each breast, and whether they have ever used ET (tamoxifen or aromatase inhibitors).

Radiology facilities provided data on all breast imaging exams, including indication for exam (i.e., screening vs. diagnostic) and assessment category. Assessments were classified as positive or negative according to the Breast Imaging Reporting and Data System [16].

The VBCSS obtains copies of pathology reports for all breast specimens evaluated at pathology facilities in Vermont. A trained abstractor recorded standardized data on all malignant and benign diagnoses, including specimen type (e.g., core needle biopsy, lumpectomy, mastectomy), histology, grade, size, and results of hormone receptor testing. The VCR provided consolidated breast cancer diagnosis data to the VBCSS, including date of diagnosis, histological

subtype, stage at diagnosis, hormone receptor status, and treatment information.

Measures and definitions

Treatment

Type of surgery was defined as BCS, ipsilateral mastectomy, or bilateral mastectomy based on VCR data, pathology records, and clinical questionnaires. If disagreements between sources could not be resolved, surgery type was set to unknown. Women who met either of the following criteria were considered to have received RT: (1) VCR indicated receipt of RT; or (2) self-reported RT on a clinical questionnaire after the date of DCIS diagnosis but before any recurrence. The same algorithm was used to define receipt of ET based on self-report and VCR data.

Second events

Data from pathology reports and VCR records were used to identify second breast cancer diagnoses occurring at least 6 months after the index DCIS diagnosis. Second events were categorized as ipsilateral or contralateral relative to the index diagnosis and classified as either invasive breast cancer or DCIS.

Covariates

Tumor characteristics for the index DCIS diagnosis, including grade, size, and ER status, were determined from VCR records and pathology records. Mode of detection was considered screening if the index DCIS was diagnosed within 1 year following a positive screening exam; symptom detected if diagnosed within 6 months of diagnostic imaging in the absence of a recent positive screening exam; and missing if no breast imaging records were available within 6 months prior to the date of diagnosis.

Statistical analyses

Differences in the characteristics of women undergoing different treatments were assessed with χ^2 tests, using the method described by Fleiss to adjust for multiple pair-wise comparisons [17]. Follow-up time began at the date of diagnosis and continued until the earliest of (1) a new breast cancer diagnosis or (2) the last VBCSS clinical questionnaire, radiology record, or pathology record. Patients were considered censored at the date of the last VBCSS record as they may have left the VBCSS catchment area. For certain analyses, follow-up time was categorized as 0–5 years, more than 5–10 years, and more than 10 years. Incidence of second breast cancer for differing time intervals during follow-up was computed by dividing the number of events by the number of person-years occurring during that time period, and 95% confidence intervals (CI) were based on the Poisson distribution. Poisson regression was used to compare differences in incidence between groups of women receiving different treatments and across time within treatment group. Differences in temporal patterns of risk during follow-up among treatment groups were assessed by including an interaction term in the Poisson regression model. Cumulative risk was estimated by fitting Cox regression models with time-varying hazard ratios. For BCS treatment groups, Cox regression with competing risks and time-varying hazard ratios was used to estimate probabilities of differing types of second events (ipsilateral invasive, ipsilateral DCIS, and contralateral) during differing periods of follow-up. Women undergoing mastectomy were not included in the competing risk analysis because the nature of their treatment and the lack of surveillance mammography on the ipsilateral side resulted in few ipsilateral invasive events and no ipsilateral DCIS events. All analyses were performed in SAS Version 9.4 (SAS Institute Inc., Cary, NC) and P values ≤ 0.05 were considered statistically significant.

Results

Among the cohort of 1252 DCIS cases, 1051 (83.9%) underwent BCS and 201 (16.1%) underwent mastectomy. As expected, type of treatment was related to the year of DCIS diagnosis; as adjuvant ET became available, fewer women underwent mastectomy or BCS alone (Table 1). Women who underwent mastectomy were more likely to have DCIS that was high grade, larger size, and ER negative compared to women who underwent BCS (either with or without adjuvant therapy; $P < 0.05$). Among women undergoing BCS, women who underwent adjuvant RT (with or without adjuvant ET) were more likely to have higher grade and larger DCIS than women in the groups that did not receive radiation. Nearly all women who received adjuvant ET and a large majority (88.5%) of the women who underwent BCS alone had ER-positive DCIS. A significantly smaller proportion (65.6%) of women who underwent adjuvant RT without ET had ER-positive DCIS.

During a median 7.8 years of follow-up, 192 cases experienced a second breast cancer diagnosis for an overall rate of 1.8 per 100 person-years (Table 2). Compared to women treated with BCS alone (3.0, 95% CI 2.3–3.7), rates of second events were lower among women who underwent mastectomy (1.4, 95% CI 0.9–2.0; $P = 0.001$), BCS plus adjuvant RT (2.0, 95% CI 1.5–2.6; $P = 0.04$), BCS plus adjuvant RT and ET (1.0, 95% CI 0.7–1.5; $P < 0.001$), and BCS plus adjuvant ET (1.2, 95% CI 0.6–2.1; $P = 0.004$).

Table 1 Characteristics of 1252 DCIS cases from the Vermont Breast Cancer Surveillance System

	All (N=1252)		Mastectomy (N=201)		BCS alone (N=327)		BCS+RT (N=318)		BCS+RT and ET (N=276)		BCS+ET (N=130)	
	N	%	N	%	N	%	N	%	N	%	N	%
Age at diagnosis												
< 40	27	2.2	7	3.5	7	2.1	5	1.6	8	2.9	0	0.0
40–49	300	24.0	53	26.4	78	23.8	73	23.0	72	26.1	24	18.5
50–59	379	30.3	48	23.9	79	24.2	104	32.7	107	38.8	41	31.5
60–69	277	22.1	53	26.4	52	15.9	82	25.8	56	20.3	34	26.2
70–79	194	15.5	35	17.4	62	19.0	42	13.2	30	10.9	25	19.2
80+	75	6.0	5	2.5	49	15.0	12	3.8	3	1.1	6	4.6
Year of diagnosis												
1994–1998	218	17.4	40	19.9	85	26.0	85	26.7	3	1.1	5	3.9
1999–2003	386	30.8	74	36.8	106	32.4	56	17.6	92	33.3	58	44.6
2004–2008	378	30.3	54	26.9	88	26.9	90	28.3	110	39.9	36	27.7
2009–2012	270	21.6	33	16.4	48	14.7	87	27.4	71	25.7	31	23.9
Mode of detection												
Screen detected	948	85.3	140	80.9	234	82.7	226	85.3	239	90.2	109	86.5
Symptom detected	164	14.7	33	19.1	49	17.3	39	14.7	26	9.8	17	13.5
Missing	140		28		44		53		11		4	
Grade												
Low	162	14.8	16	9.4	58	21.6	22	8.2	32	12.0	34	27.9
Intermediate	544	49.7	75	44.1	147	54.9	120	44.9	133	49.8	69	56.6
High	388	35.5	79	46.5	63	23.5	125	46.8	102	38.2	19	15.6
Missing	158		31		59		51		9		8	
Size												
≤ 1 cm	492	57.6	52	39.7	151	73.3	119	51.3	102	50.7	68	80.9
1.1–2 cm	206	24.1	31	23.7	33	16.0	69	29.7	62	30.8	11	13.1
>2 cm	156	18.3	48	36.6	22	10.7	44	19.0	37	18.4	5	6.0
Missing	398		70		121		86		75		46	
ER status												
Negative	102	17.7	29	34.5	13	11.5	53	34.4	6	3.8	1	1.5
Positive	474	82.3	55	65.5	100	88.5	101	65.6	151	96.2	67	98.5
Missing	676		117		214		164		119		62	

BCS breast-conserving surgery, *ER* estrogen receptor, *ET* endocrine therapy, *RT* radiation therapy

Examination of second breast cancer events during 5-year intervals following the index DCIS diagnosis indicated that temporal changes in the event rates varied among treatment groups (Table 3). Women who underwent BCS with no adjuvant therapy experienced higher rates of second events during the first 10 years of follow-up, after which the annual incidence of second events decreased. In contrast, rates of second events increased slightly over time in women who underwent BCS plus adjuvant RT and increased more markedly among women who underwent BCS plus adjuvant RT and ET. The trend in each of the groups receiving radiation differed significantly from the trend observed among women who underwent BCS alone (Table 3). As a consequence, differences in the cumulative risk of second events among women who underwent BCS alone compared to those who underwent BCS with adjuvant RT diminished with increasing duration of follow-up, as illustrated by the cumulative incidence estimates (Fig. 1). Women who underwent mastectomy or BCS with adjuvant ET but no RT experienced relatively constant and low rates of second events throughout the duration of follow-up (Table 3; Fig. 1).

In a competing risks analysis of ipsilateral invasive, ipsilateral DCIS, and contralateral second events in the BCS treatment groups, the hazard ratios varied significantly over time ($P < 0.001$) for each type of event, indicating that temporal changes in the risk of that event differed among women undergoing differing treatments. These temporal effects were not the same for all three types of event and 5-year interval risk estimates derived from this analysis indicate that the differences in temporal trends observed in the rates of any

Table 2 Second breast cancer events according to initial treatment among 1252 DCIS cases from the Vermont Breast Cancer Surveillance System

	All ($N=1252$)	Mastectomy ($N=201$)	BCS alone ($N=327$)	BCS+RT ($N=318$)	BCS+RT and ET ($N=276$)	BCS+ET ($N=130$)
Median follow-up (years)	7.8	8.1	6.2	7.8	8.5	7.9
Any second event, N (rate per 100 person-years)	192 (2.0)	24 (1.5)	72 (3.6)	57 (2.3)	26 (1.1)	13 (1.3)
Ipsilateral event, N	114	6	55	29	14	10
Contralateral event, N	69	17	15	25	10	2
Bilateral event, N	7	0	2	2	2	1
Distant events, N	2	1	0	1	0	0
Invasive event, N	126	16	45	40	15	10
DCIS event, N	66	8	27	17	11	3
Ipsilateral invasive, N	74	6	33	19	9	7
Ipsilateral DCIS, N	40	0	22	10	5	3
Contralateral Invasive, N	45	9	11	18	5	2
Contralateral DCIS, N	24	8	4	7	5	0
Bilateral invasive, N[a]	5	0	1	2	1	1
Bilateral DCIS, N[a]	2	0	1	0	1	0

BCS breast-conserving surgery, *DCIS* ductal carcinoma in situ, *ET* endocrine therapy, *RT* radiation therapy

[a]A bilateral diagnosis was counted as invasive if either or both breasts had an invasive second event and as DCIS if both breasts had DCIS

Table 3 Incidence of a second event by treatment group and time since diagnosis among 1252 DCIS cases from the Vermont Breast Cancer Surveillance System

	Time since diagnosis							
	0–5 years		5–10 years		> 10 years			
	Annual Incidence (%)	95% CI	Annual Incidence (%)	95% CI	Annual Incidence (%)	95% CI	P_{trend}[a]	$P_{interaction}$[b]
BCS alone	3.1	2.2–4.2	3.3	2.1–4.9	1.7	0.7–3.5	0.11	Ref
BCS+RT	1.8	1.1–2.6	2.0	1.2–3.2	2.8	1.6–4.7	0.20	0.04
BCS+RT and ET	0.7	0.3–1.3	1.2	0.6–4.4	2.1	0.8–4.4	0.03	0.01
BCS+ET	1.4	0.6–2.8	0.9	0.2–2.6	1.2	0.2–4.4	0.97	0.57
Ipsilateral mastectomy	1.4	0.7–2.4	1.9	0.8–3.4	0.6	0.1–2.2	0.41	0.93

BCS breast-conserving surgery, *DCIS* ductal carcinoma in situ, *ET* endocrine therapy, *RT* radiation therapy

[a]Test for trend in annual incidence across three categories of follow-up time intervals

[b]Test for treatment by time since DCIS diagnosis interaction to assess differences in trend compared to BCS alone as reference group

second breast cancer event were largely due to contralateral events (Table 4). Among women who underwent BCS without any adjuvant therapy, the probability of a contralateral second event was similar during the three time periods. In contrast, the risk of contralateral events increased over time among women receiving BCS plus adjuvant RT and/or ET.

Corresponding estimates of cumulative incidence illustrate the differing patterns in types of recurrence among the treatment groups. Similar patterns were observed for women undergoing BCS alone (Fig. 2a) and BCS plus ET (Fig. 2d), with ipsilateral invasive second events being the most likely. In both of these treatment groups, the

cumulative incidence of ipsilateral DCIS leveled off with increasing time since DCIS diagnosis, as the risk of this type of second event decreased. Among women undergoing BCS with adjuvant radiation, the cumulative incidence throughout follow-up was higher for contralateral events than either an ipsilateral DCIS or ipsilateral invasive event (Fig. 2b). For women undergoing BCS plus adjuvant RT and ET, cumulative incidence was very low for both contralateral and ipsilateral DCIS second events during the first 5 years of follow-up but then increased for contralateral events (Fig. 2c).
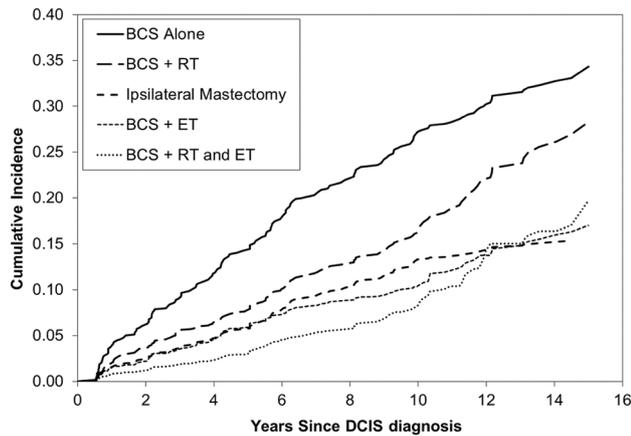
Fig. 1 Cumulative incidence of second events according to self-selected treatment group among 1252 DCIS cases treated with breast-conserving surgery, from the Vermont Breast Cancer Surveillance System. *BCS* breast-conserving surgery, *ET* endocrine therapy, *RT* radiation therapy

Table 4 Probability of first recurrence during 5-year intervals after diagnosis, conditional on no recurrence of any type in previous intervals, among 1051 DCIS cases treated with breast-conserving surgery from the Vermont Breast Cancer Surveillance System

	BCS alone (N=327)	BCS+RT (N=318)	BCS+RT and ET (N=276)	BCS+ET (N=130)
Any event				
0–5 years	0.143	0.076	0.029	0.058
6–10 years	0.129	0.086	0.052	0.045
11–15 years	0.071	0.121	0.116	0.066
Ipsilateral invasive				
0–5 years	0.060	0.026	0.018	0.042
6–10 years	0.077	0.032	0.023	0.017
11–15 years	0.032	0.038	0.005	0.036
Ipsilateral DCIS				
0–5 years	0.059	0.016	0.007	0.016
6–10 years	0.022	0.020	0.001	0.014
11–15 years	0.013	0.013	0.056	0.003
Any contralateral				
0–5 years	0.024	0.034	0.004	0.000
6–10 years	0.030	0.034	0.028	0.014
11–15 years	0.026	0.070	0.055	0.027

BCS breast-conserving surgery, *DCIS* ductal carcinoma in sit, *ET* endocrine therapy, *RT* radiation therapy

Discussion

Our results indicate that the risk of a second event after DCIS varies during follow-up time in a treatment-dependent manner. Women treated with BCS alone experienced a declining rate of second events over time following their diagnosis. In contrast, women treated with BCS and adjuvant RT (with or without ET) experienced increasing rates of second events during the course of follow-up.

The observed differences in disease-free survival likely reflect differences in the biological types of DCIS represented in each self-selected treatment group and differences in patients' intrinsic breast cancer risk (e.g., for new primary breast cancers), in addition to the effects of the received treatments. For example, women undergoing BCS with adjuvant RT were more likely to be younger and to have high-grade, large, ER-negative DCIS lesions than women undergoing BCS alone. Consequently, these DCIS lesions may be expected to have a higher risk of disease progression. In our data it appeared that RT was effective in suppressing risk of ipsilateral second events for up to 10 years, after which the incidence of second events (conditional on no previous event) exceeds that of women who underwent BCS alone.

Women treated with BCS and adjuvant ET (no radiation) were more likely to have low-grade, small, ER-positive DCIS lesions than women who received adjuvant RT. They may therefore be expected to have lower risk, and indeed the overall rate of second events remained low throughout the duration of the follow-up period. However, there was some suggestion that the rate of contralateral second events increased over time. The standard recommendation for the duration of adjuvant ET for DCIS during our study period was 5 years of treatment [2] and thus our results likely reflect the temporary suppression of contralateral events during the active treatment period, followed by gradually increasing rates after cessation of ET.

Our findings are consistent with some but not all findings from randomized trials and prior observational studies. The NASBP-B17 [7], EORTC 10,853 [12], and SweDCIS [18] trials of breast-conserving surgery with vs. without radiation observed that the risk of local recurrence for women treated with BCS alone is highest during the first 5 years and declines thereafter, as observed in our study. This pattern was also observed in a large observational study of women diagnosed with DCIS in the Netherlands [13]. The NSABP-B17, SweDCIS, and Netherlands studies also reported constant rates of contralateral events over the duration of follow-up for women with BCS alone [7, 13, 18], consistent with the pattern observed in our study.

For women treated with BCS plus radiation, the NASBP-B17, EORTC 10,853, and SweDCIS trials observed that the rate of ipsilateral DCIS recurrence declined after 5 years but the rate of local invasive recurrence was constant over time [7, 12, 18]. The EORTC and SweDCIS trials reported that the protective effect of radiation against invasive ipsilateral recurrence was restricted to the first 5 and 10 years after treatment, respectively [12]. The Netherlands observational study observed an increasing rate of ipsilateral invasive recurrences over time among women treated with BCS plus
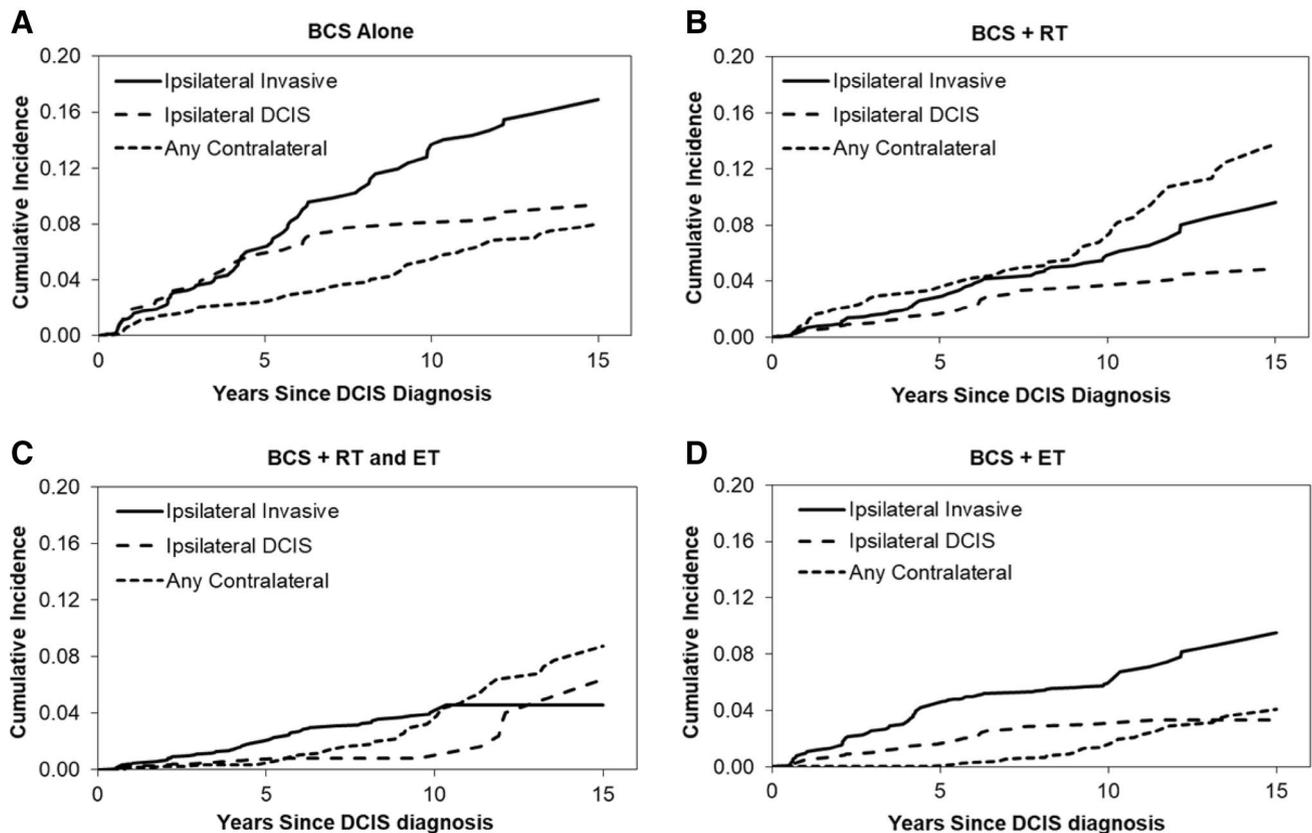
Fig. 2 Cumulative incidence of specific types of second events by treatment group among 1051 DCIS cases treated with breast-conserving surgery, from the Vermont Breast Cancer Surveillance System. *BCS* breast-conserving surgery, *ET* endocrine therapy, *RT* radiation therapy

radiation and reported that the reduction in ipsilateral invasive recurrence associated with RT declines over time since diagnosis [13]. Our results are also consistent with these prior findings, with a stable or increasing rate of ipsilateral invasive events among women treated with BCS plus radiation, though we observed a relatively constant rate of ipsilateral DCIS events. Interestingly, the SweDCIS trial observed an increasing rate of contralateral events over the course of follow-up [18], similar to that observed in our study, though this was not observed in the NSABP-B17 trial [7].

In our study, women who underwent BCS with adjuvant RT and ET experienced an increasing rate of second events over time, with specific increases in ipsilateral DCIS events and contralateral events after 10 years of follow-up. These results contrast with the NASBP-B24 trial, which observed a constant rate of ipsilateral invasive and contralateral events over time among women randomized to 5 years of tamoxifen [7]. The UK/ANZ randomized trial observed a declining rate of second events over time among women who were randomized to 5 years of tamoxifen [8], though this included a mix of women who did or did not receive adjuvant RT. The reasons for these differences are not entirely clear, but likely stem from the critical difference that in our observational

study patients self-selected into treatment groups based on clinical factors and personal preferences. Additionally, the randomized trials included women diagnosed in the 1980s and 1990s prior to the recognition that ET is effective only in women with hormone receptor positive disease [19]. The vast majority of women in our study who received ET were diagnosed after 1999 and had ER-positive DCIS.

Our population-based cohort of women with DCIS included women treated in diverse clinical settings across Vermont. Other strengths include the long duration of follow-up and the identification of second events from pathology reports and the statewide cancer registry, rather than reliance on self-report. Although Vermont is socioeconomically diverse, limitations include the lack of racial and ethnic diversity (more than 90% of women were non-Hispanic whites) and the relatively small sample size for investigating specific types of second events within treatment groups, particularly among women treated with ipsilateral mastectomy and BCS plus adjuvant ET without radiation, or among patient subgroups defined by age or other characteristics.

Our results have a number of important implications. The observed time-dependent variation in incidence of second events during the course of follow-up indicates that recurrence

rates based on short-term data should not be used to predict recurrence risk in women who are disease-free at 5 or 10 years following their initial DCIS diagnosis. Doing so would overestimate the cumulative risk over extended periods of follow-up for women treated with BCS alone, while underestimating risk for women treated with adjuvant therapies. Our results also demonstrate that women receiving adjuvant ET have very low rates of second events for up to 10 years following diagnosis, with apparent protection against both ipsilateral and contralateral events. However, the increasing risk of contralateral events over time among women undergoing adjuvant ET supports current guideline recommendations and suggests that women may wish to consider continued ET beyond 5 years to lengthen protection against second events [20].

Compliance with ethical standards

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