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Radiotherapy for ductal carcinoma in situ and risk of second non-breast cancers

Diana R. Withrow, PhD*, Lindsay M. Morton, PhD, Rochelle E. Curtis, MA, Sara J. Schonfeld, PhD, Amy Berrington de González, DPhil

Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Abstract

Purpose: Radiotherapy for ductal carcinoma (DCIS) is increasing, but the risks and benefits of the treatment remain uncertain. We aimed to investigate the relationship between radiotherapy for DCIS and risk of second non-breast cancers in a large US cohort.

Methods: We conducted a retrospective cohort study of 52,556 women in 12 U.S. population-based cancer registries diagnosed with first primary DCIS during 1992–2008 at age 25–79 years. We estimated relative risks (RRs), attributable risks (AR) and excess absolute risks (AER) of second non-breast cancers associated with radiotherapy using Poisson regression adjusted for age at and year of diagnosis, grade, hormonal therapy (yes/no or unknown), and time since diagnosis.

Results: Approximately half of the women (46.3%) received radiotherapy. Radiotherapy was associated with an increased risk of all second non-breast cancers combined (RR=1.17, 95% Confidence Interval [CI] 1.08–1.28) and all in-field, radiation-related second cancers combined (RR=1.37, 95% CI: 1.15–1.63), driven by second lung cancers (RR=1.33, 95% CI: 1.10–1.60) and non-CLL leukemia (RR=1.71, 95% CI: 1.02–2.86). The estimated cumulative excess risk of all second non-breast cancers was 0.8% by 15 years after DCIS diagnosis.

Conclusions: Radiotherapy was associated with an increased risk of second non-breast cancers. The specific excess of cancers at sites likely in/near the radiotherapy field suggests the findings are unlikely due exclusively to confounding, but further research into factors related to receipt of radiotherapy is needed. Our risk estimates can be used to help assess the balance of the risks and benefits of radiotherapy for DCIS and to inform clinical practice.

Keywords

Ductal Carcinoma in Situ; Radiotherapy; Breast neoplasms; Second cancers

*CORRESPONDING AUTHOR: Diana Withrow, PhD, Postdoctoral Fellow, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 7E514, Bethesda MD 20892-9778 (For USPS only), Rockville MD 20850 (For FedEx, UPS, courier services and map searches only), diana.withrow@nih.gov / phone: +1.240.276.7869 / fax: +1.240.276.7840.

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INTRODUCTION

The reported incidence of ductal carcinoma in situ (DCIS) has increased nearly 6-fold since 1975[1], largely attributable to increases in breast cancer screening and use of digital mammography[2]. Currently, about one quarter of all neoplastic breast lesions are DCIS, amounting to 51,000 new cases annually in the U.S[3]. The high survival rate of DCIS – breast cancer-specific survival exceeds 95% after 15 years – and the increasing incidence have resulted in a large and growing population of DCIS survivors[1, 4].

The current standard of care for DCIS is breast-conserving surgery with whole breast irradiation, and hormonal therapy if appropriate[5]. In the context of invasive breast cancer, radiotherapy has been associated with significantly increased risk of cancers within the radiation field, but the absolute risks are small compared to the absolute benefits in terms of reduction in breast cancer mortality[6, 7].

Meta-analyses of four randomized clinical trials of radiotherapy for DCIS demonstrated that radiotherapy halves the risk of ipsilateral invasive disease[8], but with fewer than 4000 patients combined, the trials lack sufficient statistical power to assess the risks of second non-breast cancers. A recent observational study reported that despite reducing the risk of invasive disease, radiotherapy for DCIS did not lead to decreased breast cancer-specific mortality 10 years post-diagnosis, contributing to an ongoing discussion regarding the magnitude of the benefit of radiotherapy for DCIS[9–13]. Two small studies have reported the patterns of second non-breast cancers after breast carcinoma in situ (BCIS), but they did not evaluate the effect of radiotherapy[14, 15].

In this study, we use data from the Surveillance, Epidemiology and End Results (SEER) registries, a large set of US population-based registries with long-term follow-up to estimate the absolute and relative risks of second non-breast cancers associated with radiotherapy for DCIS.

METHODS

Population and follow-up

Women diagnosed with first primary DCIS between 1992 and 2008 were identified using 12 U.S. National Cancer Institute SEER registries (SEER 13 excluding Alaska) [16]. DCIS was defined as female breast cancer with in situ behavior and one of the following International Classification of Disease for Oncology (ICD-O-3) histology codes: 8201, 8500, 8501, 8503, 8507, and 8523. Because under-reporting of second cancers occurs among elderly patients with more co-morbid conditions, DCIS cases were limited to those diagnosed prior to age 79 years and follow-up was censored at age 85[17]. The cohort was restricted to women who survived at least five years to allow for the minimum latency for subsequent radiation-induced cancers[18]. Accordingly, follow-up began on the 5-year anniversary of diagnosis and continued until the first of a second malignancy, age 85 years, death, or December 31st, 2012. To ensure censoring for invasive breast cancer did not alter the estimated risks of non-breast second cancers, we conducted a sensitivity analysis where women were still

considered at risk after an invasive breast cancer had been diagnosed. In a subset of analyses (described below), the cohort was expanded to include one-year survivors.

Exposure, Outcome, and Covariates

Radiotherapy received as part of the first course of treatment is recorded in the SEER registries and was dichotomized into known receipt (yes) and unknown or no receipt (no). The primary outcome of interest was diagnosis with a second invasive non-breast cancer. Second cancers were coded according to ICD-O-3 site and histology groupings used in SEER[19]. Here, we report on all second non-breast cancers combined and the ten most commonly diagnosed non-breast cancers among DCIS survivors. Due to uncertainty about the radiogenicity of chronic lymphocytic leukemia (CLL) compared to other leukemias[20], a sub-group analysis for leukemia was conducted restricted to non-CLL leukemia. Radiation-related cancers considered more likely to be within the radiation field were also aggregated for subgroup analyses and included lung cancer, non-CLL leukemia, soft tissue cancers of the thorax, upper limb and shoulder and cancer of the esophagus. Calendar year of diagnosis, age at DCIS diagnosis, DCIS grade and hormonal therapy (yes vs. no/unknown) were all ascertained from the SEER databases. Estrogen receptor status of the DCIS was largely incomplete in SEER during our study period and was accordingly not considered in our analyses. Most DCIS cases are estrogen receptor positive[21].

Statistical methods

Standardized incidence ratios (SIRs) were calculated to compare the observed number of cancers among DCIS survivors to that expected in the general population. The expected number of cancers was estimated based on age-, sex-, race and calendar time-specific incidence rates among the general population residing in SEER cancer registry catchment areas, taking into account the number of person-years within each of these strata in the survivor cohort. SIRs and their 95% confidence intervals were estimated using SEER*Stat software (version 8.3.2).

To estimate the relative risks (RRs) of second non-breast cancers associated with radiotherapy, we used multivariate Poisson regression. The models incorporate the expected number of second cancers as an offset, indirectly accounting for attained age and attained calendar period[22]. RRs were adjusted for age and decade of DCIS diagnosis, grade and hormonal therapy (yes vs. no/unknown) through stratification. Statistical interaction was assessed using likelihood ratio tests to compare models with and without an interaction term between radiotherapy and each of the covariates. Tests of statistical significance were two-sided and based on Poisson exact methods[23]. Models were fitted using the Amfit module of the Epicure software[22].

We also used Poisson regression to model the absolute risks of second non-breast cancers after DCIS. The excess number of cancer cases among irradiated women attributable to radiotherapy was estimated as the difference between the observed number of cancers and the expected number in the absence of radiotherapy; the latter estimated using the parameters from the Poisson regression models described above among 5-year survivors. The attributable risk (AR) was estimated by dividing the number of excess second cancers

attributable to radiotherapy by the total number of incident second cancers among irradiated women. The excess absolute risk (EAR) is the rate complement to the number of excess cancers –the number of excess cases per 10,000 person years. We estimated AR and EAR among both one- and five-year survivors to extend generalizability to DCIS survivors overall. As we do not expect any excess cancers attributable to radiotherapy to occur less than five years after DCIS diagnosis, the excess number estimated from the model of 5-year survivors is used when estimating AR and EAR among 1-year survivors. To estimate the cumulative excess risk 15 years after diagnosis, we multiplied the annual excess absolute risk among 1-year survivors by 14 years.

RESULTS

Select demographics and treatment information for the cohort are described in Table 1. The cohort included 52,556 five-year survivors of DCIS followed for a mean of 11 years (range: 5–21 years). Of those, just under half ($n=24,353$, 46.3%) underwent radiotherapy as part of their initial course of treatment. Over two thirds (70.0%) of the women were diagnosed between the ages of 50 and 79. Younger women (25–49 years of age) had a similar likelihood of undergoing radiotherapy as older women. Radiotherapy uptake increased over time (34.1% of patients in 1992–1996 vs. 54.0% in 2007–2008) and there was a modestly increased likelihood of radiotherapy with increasing grade of breast cancer (p -trend<0.001 for known grades). Nearly 30% of the cohort had unknown grade and these women were significantly less likely to be categorized as having undergone radiotherapy than those with known grade ($p<0.001$). On average, one-fifth ($n=10,449$, 19.9%) of women in the cohort were recorded as having received hormonal therapy. Uptake of hormonal therapy increased over the study period however, and in 2007 to 2008, at least 40% of women had received hormonal therapy (not shown).

Among 5-year survivors, 2,319 non-breast second invasive cancers were diagnosed (Table 2). The five most common non-breast second cancers were lung, endometrial (corpus uteri), colon, non-Hodgkin lymphoma and melanoma. Together these five sites accounted for just over half of all non-breast second cancers.

Compared to the general population, DCIS survivors were at decreased risk of all non-breast cancers combined (SIR:0.89, 95%CI:0.85–0.92). Specifically, DCIS survivors were at significantly decreased risk of lung (SIR: 0.79, 95%CI:0.72–0.86) and colon cancers (SIR: 0.71, 95%CI: 0.62–0.82). The only cancer for which DCIS survivors had a significantly increased risk relative to the general population was endometrial cancer (SIR: 1.30, 95%CI: 1.16–1.46). The SIR for endometrial cancer among women who received hormonal therapy was higher than that among those who were not recorded as having received it (SIR: 1.60, 95%CI: 1.22–2.06 for hormonal therapy vs. SIR: 1.25, 95%CI: 1.10–1.41 for no/unknown hormonal therapy; data not shown).

After adjustment for covariates, radiotherapy was associated with a significantly increased relative risk of all non-breast second cancers combined (RR: 1.17, 95%CI: 1.08–1.28), lung cancer (RR:1.33, 95%CI:1.10–1.60), melanoma (RR:1.52, 95%CI: 1.04–2.22), non-CLL leukemias (RR: 1.71, 95% CI: 1.02–2.86) and in-field/radiation-related cancers combined

(RR:1.37, 95%CI: 1.15–1.63). Of the 539 incident cancers categorized as in-field/radiation-related, 451 (78.2%) were lung cancers. The relative risk associated with radiotherapy was higher for the ipsilateral lung (RR: 1.43, 95% CI: 1.08–1.90) than for the contralateral lung (RR: 1.28, 95% CI: 0.98–1.67) and higher in the 5 to 10 years following DCIS diagnosis (RR: 1.52, 95% CI: 1.18–1.95) than more than 10 years post DCIS diagnosis (RR: 1.10, 95% CI: 0.81–1.48; data not shown). For melanoma, which is not considered radiation-related, the proportion of cancers that arose within the potential radiation field (i.e., trunk, upper limb and shoulder) did not differ significantly between irradiated and non-irradiated women (60.3% among women who received radiotherapy vs. 62.0% among women with no or unknown radiotherapy, not shown).

We estimated that 160 (95%CI: 74–246) non-breast second cancer cases were possibly related to radiotherapy, equivalent to 9% (95%CI: 4–13) of all non-breast second cancers among 1-year survivors of DCIS who received radiotherapy (Table 3). Just under half of these (n=74) occurred at sites that were categorized as within the radiation field or radiation-related (i.e. esophagus; soft tissue of the thorax, upper limb and shoulder; lung and bronchus; non-CLL leukemia). The excess absolute risk of non-breast cancers associated with radiotherapy among 1-year survivors was 6/10,000 person-years (95%CI: 3–10), which is equivalent to a cumulative excess risk of 0.8% within 15 years from diagnosis. Attributable risks among 5-year survivors ranged from 15% (95%CI: 7–22) of all non-breast cancers, to 27% (95%CI: 12–42) of in-field/radiation-related cancers. Allowing women to stay in the risk set after a diagnosis of invasive breast cancer as per our sensitivity analyses did not meaningfully alter the results.

DISCUSSION

To our knowledge, this is the largest study to characterize non-breast cancer risks after DCIS and the first to estimate the effect of radiotherapy on the absolute and relative risks of non-breast cancer among DCIS survivors. Overall, the risk of non-breast second cancers among women with a history of DCIS tended to be lower than that in the general population. Among DCIS survivors, radiotherapy was associated with an increased risk of all non-breast second cancers, and in particular a significantly increased risk of lung cancer, melanoma, and in aggregate, second cancers within the radiation field. It was estimated that approximately 9% (95%CI: 4–13) of non-breast cancers and 18% (95%CI: 8–28) of cancers at sites within the radiation field could be attributable to radiotherapy among 1-year DCIS survivors, and that the cumulative excess risk was 0.8% by fifteen years after diagnosis.

Previous smaller studies have estimated cancer risk among in situ breast cancer survivors compared to that in the general population. A Dutch study of 1402 BCIS cases diagnosed between 1972 and 2002 found that among 5-year survivors, the SIR for all non-breast cancers combined was 1.2[14]. Given the small number of events (n=21), our estimate of the confidence interval around the SIR is wide (0.7–1.8) and overlaps with our SIR of 0.89 (95% CI: 0.85–0.92). A larger, UK-based study of 12,836 survivors of BCIS diagnosed between 1971 and 2003 reported SIRs for 9 of the 10 cancers included in our analyses; despite small numbers of many second cancers, estimates were compatible with those reported here and

similarly showed that BCIS survivors tended to be at decreased risk of non-breast cancers compared to members of the general population[15].

In our study, lower overall incidence of non-breast cancers overall among DCIS survivors was driven by decreased risks of lung and colorectal cancers. The screening behaviors of DCIS survivors is a possible explanation for this finding. In the contemporary setting, nearly 90% of DCIS cases are initially detected through breast cancer screening[24]. Women who participate in breast cancer screening tend to have higher socioeconomic status and are less likely to smoke and more likely to attend other cancer screening programs, such as colorectal cancer screening than the general population[25]. These attributes would contribute to lower rates of lung and colorectal cancers among survivors[26].

This is the only observational study we are aware of that has estimated relative risks of non-breast cancers associated with radiotherapy for DCIS. While the comparison between risk after invasive breast cancers and DCIS is complicated by the range of treatment fields used to treat invasive disease, the relative risks we have reported for DCIS are compatible with the results of similar studies of invasive breast cancer survivors[6, 27]. Specifically, a SEER-based study of breast cancer survivors reported a RR of 1.11 (95%CI: 1.06–1.16) for all non-breast cancers combined associated with radiotherapy, and RRs of lung cancer and in-field cancers more generally of 1.39 (95%CI: 1.26–1.51) and 1.45 (95%CI: 1.33–1.58) respectively[6]. RRs for leukemia after DCIS were also consistent with estimates after invasive breast cancer[28, 29].

The significantly increased risk of melanoma after radiation was a surprising finding, as ionizing radiation is not currently understood to be a cause of melanoma[30]. Exploratory analyses did not find evidence of differences in the topography of melanomas in those who did versus did not receive radiotherapy. Sensitivity analyses taking into account geographical region-specific expected melanoma risk did not meaningfully alter the findings. There have been some previous reports of significantly increased risks of melanoma among irradiated invasive breast cancer survivors compared to members of the general population, and compared to non-irradiated women[31–33], but formal estimation of the relative risk associated with radiotherapy has either not been conducted, or not been statistically significant. A cohort study of childhood cancer survivors found no association between melanoma and radiotherapy (RR: 0.99, 95% CI: 0.53–1.84)[34]; however, that and many other studies have few incident melanoma cases and may be underpowered to detect a significant association. Future large-scale studies of radiotherapy and second cancer risk should include melanoma as an outcome to explore this question further.

The use of SEER registries for second cancers studies has advantages and disadvantages. Advantages include the large numbers of patients eligible for study and a long history allowing for several decades of potential follow-up. Limited treatment information (i.e., first course only, unknown radiotherapy fields, technique and dose, no differentiation between hormonal therapies) is one major limitation of using SEER databases in this context. The positive predictive value of the radiotherapy variable is high (98% for in situ breast cancers) but sensitivity is lower (82%)[35, 36]. Under-reporting of hormonal therapy in SEER is well established[36]. Given the association between radiotherapy and hormonal therapy, the

borderline increased risk of endometrial cancer associated with radiotherapy may be a spurious result of incomplete adjustment for hormonal therapy[29, 37–39]. Furthermore, SEER registries only capture those cancer cases diagnosed within their catchment areas. If a survivor moves out of the area, second cancers will not be ascertained. While this could result in an underestimate of risk of second cancers overall, it is unlikely to affect the estimates of relative or attributable risk associated with radiotherapy.

In this observational study, radiotherapy was not randomized and unmeasured factors associated with receipt of radiotherapy and risk of second cancers could lead to residual confounding. The primary contraindications to radiotherapy for breast cancer are prior radiotherapy, pre-existing heart conditions and genetic predispositions to cancer[40]. These factors are likely associated with a higher risk of cancer and thus uncontrolled confounding would result in underestimation of the radiotherapy-related risk. Conversely, if receipt of radiotherapy is related to increased medical surveillance and attendance at screening, this could have resulted in over-estimation of true radiotherapy-related risks. Further research into patient characteristics related to radiotherapy for DCIS, such as co-morbidities and cigarette smoking, is warranted.

We estimated that 9% of cancers among one-year survivors of DCIS were associated with radiotherapy. An attributable risk of 8% associated with radiotherapy has been found on average across a range of first cancers[41]. Attributable risks vary widely by first cancer site (i.e. 4% after cancers of the eye and orbit to 24% after testicular seminomas). This variation can likely be explained, at least in part, by average age at radiotherapy exposure, size of the treatment field and the organs located within those fields[41]. Conventional tangential fields used for DCIS can include some portion of the ipsilateral lung, where a third of our excess cancers were estimated to occur[4]. DCIS treatment fields have not changed substantially over the last decades, but improved treatment planning and increasing use of heart blocks or breath-holds over time would be expected decrease second cancer risk to some extent among current patients.

Overall, we found that 5-year survivors of DCIS are at lower risk of non-breast second cancers than women in the general population, likely attributable in large part to a healthy screener effect. However, radiotherapy was associated with an increased risk of some second cancers. The specific excess of cancers at sites likely in/near the radiotherapy field suggests the findings are unlikely to be fully explained by confounding. The estimated magnitude of absolute risk associated with radiotherapy among DCIS survivors was small (0.8% cumulative excess risk by 15 years), similar to that for other adult cancers[41].

Optimal treatment for DCIS is currently unclear. Clinical trials of radiotherapy for DCIS have not found a reduction in breast cancer mortality but have shown that radiotherapy reduces the risk of any ipsilateral breast event (i.e., either recurrent or invasive cancer) by a factor of 2[8]. A recently initiated trial is assessing the risks and benefits of active surveillance compared to guideline concordant care for low risk DCIS[42]. Our risk estimates can provide context for discussions of optimal DCIS treatment[43], and be used to help assess the balance of the risks and benefits of radiotherapy for DCIS to inform clinical practice.

ABBREVIATIONS

AR	Attributable risk
BCIS	Breast cancer in situ
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
DCIS	Ductal carcinoma in situ
EAR	Excess absolute risk
ICD-O-3	International Classification of Diseases for Oncology, 3 rd Edition
RR	Relative risk
SEER	Surveillance, Epidemiology and End Results
SIR	Standardized incidence ratio

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Table 1.

Descriptive statistics of female 5-year survivors of DCIS diagnosed between the ages of 25 and 79 (SEER9+3 Registries, diagnosed 1992 to 2008 and followed up through 2012).

	Total		Radiotherapy			
	n	Col %	n	Row %	n	Row %
TOTAL	52,556	100.0	24,353	46.3	28,203	53.7
<i>Age at DCIS diagnosis</i>						
25–49	15,763	30.0	7,045	44.7	8,718	55.3
50–79	36,793	70.0	17,308	47.0	19,485	53.0
<i>Period of diagnosis</i>						
1992–1996	10,313	19.6	3,518	34.1	6,795	65.9
1997–2001	16,182	30.8	7,159	44.2	9,023	55.8
2002–2006	18,108	34.5	9,380	51.8	8,728	48.2
2007–2008	7,953	15.1	4,296	54.0	3,657	46.0
<i>Race</i>						
White	41,036	78.1	19,007	46.3	22,029	53.7
Black	4,812	9.2	2,268	47.1	2,544	52.9
Other	6,318	12.0	2,981	47.2	3,337	52.8
Unknown	390	0.7	97	24.9	293	75.1
<i>Region</i>						
San Francisco-Oakland	6,567	12.5	2,603	39.6	3,964	60.4
Connecticut	6,317	12.0	3,317	52.5	3,000	47.5
Detroit (Metropolitan)	6,595	12.5	3,424	51.9	3,171	48.1
Hawaii	2,250	4.3	1,345	59.8	905	40.2
Iowa	3,778	7.2	1,986	52.6	1,792	47.4
New Mexico	1,754	3.3	660	37.6	1,094	62.4
Seattle (Puget Sound)	6,509	12.4	3,276	50.3	3,233	49.7
Utah	1,811	3.4	711	39.3	1,100	60.7
Atlanta (Metropolitan)	4,137	7.9	2,005	48.5	2,132	51.5
San Jose-Monterey	3,203	6.1	1,488	46.5	1,715	53.5
Los Angeles	9,503	18.1	3,490	36.7	6,013	63.3
Rural Georgia	132	0.3	48	36.4	84	63.6
<i>Grade</i>						
I	5,111	9.7	2,357	46.1	2,754	53.9
II	14,862	28.3	7,143	48.1	7,719	51.9
III	11,572	22.0	6,056	52.3	5,516	47.7
IV	6,523	12.4	3,274	50.2	3,249	49.8
Unknown	14,488	27.6	5,523	38.1	8,965	61.9
<i>Hormonal therapy</i>						
Yes	10,449	19.9	7,675	73.5	2,774	26.5
No/Unknown	42,107	80.1	16,678	39.6	25,429	60.4

^aNo evidence of radiotherapy was found in the medical records examined.

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Standardized incidence ratios for subsequent primary malignancies and relative risks (RR) associated with radiotherapy among female 5-year survivors of DCIS diagnosed between the ages of 25 and 79 years (SEER 9+3 Registries, diagnosed 1992 to 2008 and followed up through 2012).

Table 2.

Subsequent cancer	Overall			Radiation			No		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
All sites excluding breast, non-melanoma skin	2319	*0.89	(0.85–0.92)	1095	0.98	(0.92–1.04)	1224	*0.82	(0.77–0.87)
Lung and bronchus	451	*0.79	(0.72–0.86)	227	0.93	(0.81–1.05)	224	*0.68	(0.60–0.78)
Corpus uteri	305	*1.30	(1.16–1.46)	152	*1.49	(1.26–1.75)	153	1.16	(0.98–1.36)
Colon excluding rectum	202	*0.71	(0.62–0.82)	93	*0.78	(0.63–0.96)	109	*0.66	(0.54–0.80)
Non-Hodgkin lymphoma	160	1.03	(0.88–1.20)	78	1.17	(0.93–1.46)	82	0.92	(0.73–1.14)
Melanoma of the skin	115	0.98	(0.81–1.18)	61	1.20	(0.92–1.54)	54	0.81	(0.61–1.06)
Thyroid	103	1.17	(0.95–1.42)	44	1.13	(0.82–1.52)	59	1.20	(0.91–1.55)
Kidney	101	1.12	(0.91–1.36)	53	*1.35	(1.01–1.77)	48	0.94	(0.69–1.24)
Ovary	99	0.90	(0.73–1.09)	45	0.95	(0.70–1.28)	54	0.85	(0.64–1.11)
Leukemia	98	1.16	(0.94–1.42)	50	*1.39	(1.03–1.83)	48	0.99	(0.73–1.32)
Non-CLL leukemia	61	1.24	(0.95–1.59)	33	*1.57	(1.08–2.02)	28	0.99	(0.66–1.43)
Pancreas	95	0.84	(0.68–1.03)	42	0.87	(0.63–1.18)	53	0.82	(0.62–1.07)
In-field/radiation-related cancers ^b	539	*0.83	(0.77–0.91)	274	0.99	(0.88–1.12)	265	*0.72	(0.63–0.81)

O: Observed; SIR: Standardized incidence ratio; CI: Confidence interval; CLL: Chronic lymphocytic leukemia

* Indicates a statistically significant result ($P < 0.05$)

^a Adjusted for age at diagnosis, grade, year of diagnosis, hormonal therapy

^b Includes esophagus (O=19), soft tissue of the thorax, upper limb & shoulder (O=8), lung & bronchus (O=451), and non-CLL leukemia (O=61).

Table 3.

Risk of subsequent primary malignancies among female survivors of DCIS diagnosed between the ages of 25 and 79 and treated with radiotherapy (SEER9+3 Registries, diagnosed 1992 to 2008 and followed up through 2012).

Subsequent cancer	Excess cancers ^a			1-year survivors				5-year survivors			
	n	95% CI	Total second cancers	Attributable risk	%	95% CI	EAR/10,000 P-Y	Total second cancers	Attributable risk	%	95% CI
All Sites excluding breast, non-melanoma skin	160	(74–246)	1,891	9	16	(4–13)	6	1,095	15	25	(7–22)
Lung and bronchus	56	(18–94)	340	16	18	(5–28)	2	227	25	27	(8–41)
In-field/radiation-related cancers ^b	74	(33–115)	415	18		(8–28)	3	274	27		(12–42)

EAR: Excess absolute risk; CI: Confidence interval

^a Among those treated with radiotherapy, stratified by age at diagnosis, grade, year of diagnosis, hormonal therapy

^b Includes esophagus, soft tissue of the thorax, upper limb & shoulder, lung & bronchus, and non-CLL leukemia.