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Variation in the risk of radiation-related contralateral breast cancer by histology and estrogen receptor expression in SEER

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Abstract

Radiation exposure, particularly at a young age, is an established cause of breast cancer. It is not known whether radiation-related breast cancer risk varies by molecular subtype. We characterized the relative risk (RR) of contralateral breast cancer (CBC) related to radiotherapy by histology and estrogen receptor (ER) status of the CBC in five-year survivors in the Surveillance, Epidemiology, and End Results (SEER) database using Poisson regression models adjusted for attained age and calendar year, age at and year of treatment, ER status of the first breast cancer, and disease stage. 205,316 female breast cancer survivors were followed for an average of 10 years from 1973 until 2007, during which time 6924 women developed a subsequent primary invasive breast cancer in the contralateral breast. The overall RR (and 95% confidence interval (CI)) of radiotherapy-related CBC was 1.11 (1.05–1.16). There was no heterogeneity in risk according to histology of the CBC ($p>0.50$) for all ages or young age at exposure, but case numbers were small for subtypes other than ductal and lobular carcinomas. Information on ER status was available from 1990 onwards for 3546 CBC cases, of which 2597 (73%) were ER+ and 949 (27%) were ER-. RRs were 1.10 (1.02–1.19) for ER+ CBC and 1.19 (1.04–1.35) for ER- CBC ($P_{\text{difference}}=0.33$). Among women treated age <35 years, radiation-related risk of CBC was non-significantly elevated for ER- (RR=1.38, 95%CI: 0.96–1.97) but not for ER+ tumors (RR=0.80, 95%CI: 0.47–1.35) ($P_{\text{difference}}=0.09$). We did not find clear evidence that radiation-related risk varies by histology or ER status, but our findings, which were the first to examine this question, were suggestive of possible differences by ER status that may merit further investigation.

Keywords

contralateral breast cancer; radiotherapy; estrogen receptor status; histology

INTRODUCTION

Exposure to ionizing radiation is a well established risk factor for breast cancer. However, breast cancer is a highly heterogeneous disease, whose etiology appears to vary across the clinically distinct subtypes based, in part, on histology and hormone receptor expression. While increasing evidence suggests that hormonal and reproductive risk factors are associated with certain molecular subtypes and not others [1–4], it is not known whether the

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Conflict of Interest

The authors declare that they have no conflict of interest.

risk related to radiation exposure varies according to breast cancer subtypes. One reason to question whether there might be such variation is the difference in radiation-related relative risk of breast cancer in Japanese atomic bomb survivors compared to radiation-exposed Western populations [5]. Only one previous study has examined the relationship between ionizing radiation and breast cancer according to estrogen receptor (ER) status [6]. No studies have examined risk by histology. The paucity of studies is, in part, because few studies have the necessary data which include information on both radiation exposure and tumor subtypes.

Previous studies have found an increased risk of contralateral breast cancer related to radiotherapy treatment for a first primary invasive breast cancer particularly when the first cancer occurs at ages under about 40 [7–9]. The Surveillance Epidemiology and End Results (SEER) database provides a rare opportunity to investigate whether the risk of radiation-related breast cancer varies by molecular subtypes because, in addition to information on radiotherapy, data on histology of the breast cancer are available. Moreover, in 1990 the SEER database began collecting information on ER status of breast cancers. Here we evaluate the relationship between radiotherapy and contralateral breast cancer risk in this large dataset with long-term follow-up according to histology and ER status.

METHODS

Population and follow-up

For our analyses by histology, the cohort was composed of women who were diagnosed with a first primary invasive breast cancer reported to one of the nine SEER registries after 1 January 1973, and who survived for at least five years. We excluded women who did not survive for five years because it appears to take at least five years between radiation exposure and solid cancer induction [10]. The follow-up time for developing breast cancer in the contralateral breast began five years after the date of initial breast cancer diagnosis and ended at the date of diagnosis of a second invasive breast cancer in the contralateral breast, last known vital status, death, or at the end of the study (31 December 2007), whichever occurred first. We restricted follow-up to attained ages <80 years because second cancers appear to be underreported among elderly patients [11]. We restricted outcomes to breast cancer of the contralateral breast and excluded ipsilateral second breast cancers because of the difficulty in distinguishing between recurrence and subsequent primary cancer. After excluding women who did not have breast cancer surgery or with unknown surgical status (n=2,618), women who had unknown disease stage (n=4,210), and women for whom it was unknown whether they received radiotherapy (n=355) or those with bilateral or unspecified laterality of their first breast cancer (n=937), our final cohort for analyses by histology included 205,316 female breast cancer survivors.

Information on ER status was not collected in SEER until 1990. Thus, for our analyses by ER status of the CBC, we used the same inclusion and exclusion criteria to define our cohort as described above with one exception: we included only women who were diagnosed with a first primary breast cancer beginning 1 January 1985. Thus, the earliest a contralateral breast cancer diagnosis could occur in this analysis was 1 January 1990. The final cohort for analyses by ER status included 150,183 female breast cancer survivors.

For all analyses, women were classified according to whether they had received radiotherapy as part of their initial breast cancer treatment. The year of treatment was assumed to be the same as the year of diagnosis of a first primary invasive breast cancer.

Histology groupings

The following histology groupings were defined using ICD-O codes from the International Classification of Diseases for Oncology – 3rd edition (ICD-O-3): ductal carcinoma of no special type (ICD-O-3 code 8500), lobular carcinoma (ICD-O-3 code 8520–8521), mixed ductal and/or lobular carcinomas (ICD-O-3 code 8522–8524), tubular carcinoma (ICD-O-3 code 8211), medullary carcinoma (ICD-O-3 code 8510–8512), inflammatory carcinoma (ICD-O-3 code 8530), papillary carcinoma (ICD-O-3 code 8050, 8260, 8503), mucinous carcinoma (ICD-O-3 code 8480–8481), and other or unknown types including all other ICD-O-3 codes.

Statistical analysis

Poisson regression analysis was used to estimate the relative risks (RR) and 95% confidence intervals (CI) for the contralateral breast cancers according to ER status and histology after radiotherapy and surgery compared with surgery alone. The expected number of breast cancers in the general U.S. population for each type of breast cancer was used as an offset to indirectly adjust for attained age, race and attained calendar period [12]. Analyses were additionally adjusted for disease stage, age at treatment and year of first breast cancer diagnosis using stratification. Tests for heterogeneity of the RR by contralateral breast cancer histology and ER status were conducted using likelihood ratio tests. Because the relative risk for radiation-related breast cancer decreases with increasing age at exposure [5], we also conducted separate analyses for subgroups defined by age at first breast cancer diagnosis (a proxy for age at radiotherapy). Although we did not have information on adjuvant therapies, we did have information on the ER status of the first breast cancer for those diagnosed after 1990, and thus, could adjust for ER status as a proxy for adjuvant hormone therapy [13], assuming that patients diagnosed with an ER+ first primary breast cancer were treated with adjuvant hormone therapy. Moreover, adjusting for the ER status of the first primary breast cancers accounts for correlation in ER status between the first and second cancers. We did not include type of surgery (breast-conserving versus mastectomy) in the models because CBC risk estimates related to radiotherapy did not differ according to surgery type [7]. All statistical analyses were conducted using Epicure (Epicure 2008).

RESULTS

A total of 205,316 women who were diagnosed with a first primary invasive breast cancer and survived at least five years were included in this study. The women were followed up for a mean of 10 years. During the follow-up period from 1978 until 2007, 6,924 women developed a subsequent primary invasive breast cancer in the contralateral breast. Of these 3,546 were diagnosed after 1990 and had known ER status. Among the cases of contralateral breast cancer, the most common histology was ductal carcinoma (n=5233, 75.6%), followed by lobular carcinoma (n=686, 9.9%), mixed (n=590, 8.5%), mucinous (n=160, 2.3%), tubular (n=89, 1.3%), medullary (n=83, 1.2%), papillary (n=46, 0.7%), and inflammatory (n=37, 0.5%). ER positive contralateral breast cancers were more common (n=2,597, 73.2%) than ER negative cancers (n=949, 26.8%) among those cases for whom ER status was known.

Overall, 41% of women were treated for breast cancer with radiotherapy and surgery compared with 59% who were treated with surgery only (Table 1). Radiotherapy was more frequently used in women under 60 years of age compared with women diagnosed after age 60, and more frequently used in later time periods and in breast cancer cases with distant metastases than localized or regional disease. Among those women for whom ER status was known (n = 150,183), 48% received radiotherapy plus surgery as opposed to 52% who were treated with surgery only.

The relative risks related to radiotherapy by histology were identical for ductal and lobular breast carcinomas (RR=1.13, 95% CI: 1.06–1.20; and RR=1.13, 95% CI: 0.96–1.34; respectively), which were the two most common histopathologies, collectively making up 86% of all contralateral breast cancers (Table 2). RR of ductal CBC related to radiotherapy did not vary significantly by age at treatment: for women treated at younger ages (<35 years), the relative risk was 1.35 (95% CI: 1.06–1.72), and for women treated at older ages (60+ years), the relative risk was 1.18 (95% CI: 1.05–1.31) ($P_{\text{trend}} = 0.49$). The risk of radiation-related lobular CBC was significantly elevated only for women treated at age 60 or greater (RR=1.33, 95% CI: 1.01–1.75); the trend by age was not significant ($P_{\text{trend}} = 0.11$) but there were few cases diagnosed < age 45. Comparing ductal and lobular histologies only, there was no heterogeneity in risk ($p = 0.40$), even when restricting analyses to women treated at < 35 years or women treated at 60+ years ($p = 0.47$ and $p = 0.28$, respectively). There also was no heterogeneity in risk ($p > 0.50$) by histological type overall or within any age-stratum (age < 35 years or 60+ years at treatment ($p > 0.50$ and $p = 0.42$, respectively)).

There were 3,546 contralateral breast cancers with known ER status diagnosed during the follow-up period from 1990 to 2007, of which 73% were ER positive and 27% were ER negative. The relative risks (and 95% confidence intervals) related to radiotherapy were 1.10 (1.02–1.19) for ER positive contralateral breast cancer and 1.19 (1.04–1.35) for ER negative contralateral breast cancer, respectively ($p = 0.33$) (Table 3). For women treated for a first primary invasive breast cancer before the age of 35, the radiation-related relative risks (and 95% confidence intervals) were 0.80 (0.47–1.35) and 1.38 (0.96–1.97) for ER positive and ER negative breast cancers, respectively. However, case numbers were relatively small ($n = 60, 122$) and this difference was not statistically significant ($p = 0.09$). There were no clear differences in risk by ER status at older ages of treatment (Table 3).

DISCUSSION

This large study with long-term follow-up using the SEER 9 database is the first to examine whether the risk of contralateral second primary breast cancer related to radiation varies by histology or estrogen receptor status of the CBC. Given that breast cancer is a highly heterogeneous disease and that the magnitude of the relative risk of radiation-related breast cancer is higher in Japanese atomic bomb survivors than in Western populations, we hypothesized that the risk of radiation-related breast cancer varies by molecular subtypes, and specifically, by ER status or histology of the CBC. Our findings are suggestive but not statistically significant of potential variation in radiation-related breast cancer risk by ER status, particularly among women treated at younger ages. There were no clear differences in risk with respect to histology of the CBC.

Only one previous study has examined radiation-related breast cancer by molecular subtypes, specifically by ER and progesterone receptor (PR) status [6]. In a case-control study in North Carolina of 862 breast cancer cases and 790 controls, the risk of breast cancer after self-reported diagnostic and/or therapeutic medical radiation exposure to the chest (measured as a dichotomous ever/never variable) was slightly elevated but not statistically significant (OR = 1.1, 95% CI: 0.7–1.6), no substantial overall difference in risk by ER/PR status was found [6]. When analyses were restricted to pre- and peri-menopausal women at diagnosis, radiation-related breast cancer risk was higher for ER–/PR– breast cancers (RR=1.8, 95% CI: 0.5–5.9) compared with ER+/PR+ breast cancers (RR=0.6, 95% CI: 0.1–3.4), but the confidence intervals were very wide. Radiation dose to the breast varies substantially between diagnostic and therapeutic uses of medical radiation (i.e. therapeutic doses could be orders of magnitude larger than diagnostic doses), and thus, combining these exposures into a single exposure variable make the results somewhat difficult to interpret. However, our finding that radiation-related risk may be higher for ER– than for ER+ CBC

among women exposed at younger ages is consistent with the previous study. No studies have previously investigated variation in radiation-related breast cancer risks by histology.

An increased risk of CBC related to radiotherapy at older ages of treatment (60+ years) was previously identified using the SEER database [7]. Our findings indicate that this increase is present for both lobular and ductal CBC histologies. While it is generally understood that the risk of radiation-related breast cancer is very small after menopause [5], a recent pooled analysis of randomized clinical trials also found that exposure to radiotherapy for breast cancer at an older age increases the risk of radiation-related CBC [14]. This finding is worrisome given the very large number of older women who are diagnosed with breast cancer every year and treated with radiotherapy.

The SEER database of breast cancer survivors is among the largest datasets with long-term follow-up and the necessary data needed to examine variation in radiation-related cancer risk by subtypes. Nevertheless, the number of CBC cases after treatment at a young age, a time of greater radiation sensitivity [5, 15], was relatively small. Thus, our study may have lacked sufficient power to detect modest differences in risk. Our results suggest that radiation-related risk was higher for ER– breast cancers among women who were treated at less than 35 years of age, but the number of cases was small so the confidence intervals were wide and were not statistically significant. Since data on ER status have been collected only since 1990 and latency of radiation-related breast cancer is at least five years [10], continued evaluation of the SEER database may provide additional information with longer follow-up.

Another possible limitation of our study was the inability to adjust for certain potential confounders such as adjuvant chemotherapy or hormonal treatments. The use of chemotherapy decreases the risk of CBC if used pre-menopausally, and this may have led to an underestimation of radiation-related CBC risk, particularly in women treated at earlier ages [16]. However, this effect should not differ by ER status and, thus, is unlikely to have biased our results [17]. Adjuvant hormonal therapies decrease the risk of developing an ER+ CBC but have no effect on the risk of ER– breast cancer [18]. Thus, not adjusting for use of hormonal therapies could result in an underestimation of radiation-related ER+ CBC, particularly among women treated at older ages with an ER+ first breast cancer, since hormonal therapy is generally used in conjunction with radiation [13]. However, we were able to adjust for ER status of the first breast cancer as a proxy for adjuvant hormone treatment.

Other limitations of using the SEER cancer registries database for risks of CBC include potential loss to follow-up if individuals move away from the registry areas and underascertainment of radiotherapy [19], but these are unlikely to differ by histology or ER status. Another limitation is lack of individual data on radiation dose to the contralateral breast; this is likely to have reduced statistical power, but is unlikely to have biased our results. The average dose to the contralateral breast from radiotherapy to treat unilateral breast cancer is about 1 Gy, but the dose can vary from 0.1 to 8.0 Gy depending on the treatment specifications and quadrant of the breast [9]. The contralateral breast dose has not changed substantially in the calendar period covered by our ER analyses (1985 to 2007) [9], so variation in dose over time is unlikely to affect our results by ER status; furthermore, models were adjusted for calendar time.

It has long been debated why Japanese atomic bomb survivors have higher radiation-related relative risk of breast cancer than women in Western populations [5, 20]. While the difference in relative risks can be explained by differences in baseline incidence rates or radiation dose-rate effects, other factors may also contribute. For example, Japanese women have an earlier onset age-distribution of breast cancer compared with women in the U.S.

[21] and, since ER– breast cancers have a younger age distribution than ER+ breast cancers [22], the proportion of ER– breast cancers may be higher in Japanese women than in the U.S. This could potentially contribute to the population differences in radiation-related relative risks. Our findings that radiation may increase risk of ER– more than ER+ CBC among women exposed at younger ages support this hypothesis and warrant further exploration.

Few studies have the necessary information to examine radiation-related breast cancer risks by tumor types. One strength of this study is that it is the largest data set of which we are aware that has information on ER status of breast cancers as well as data on radiation exposure. Moreover, this is the first study to examine radiation-related breast cancer risk by histology. Although we did not have data on chemotherapy or hormonal therapy, we were able to adjust for other potential confounders including disease stage and ER status of the first breast cancer.

Our study provides no clear evidence that radiation-related risk of breast cancer varies by histology or estrogen receptor status. However, our findings are suggestive that radiation may increase risk of ER– but not ER+ contralateral breast cancer among women treated at younger ages (<35). Further studies are needed to better understand these findings.

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Table 1

Descriptive statistics of the women who were diagnosed with a primary invasive breast cancer before age 75 and who survived 5 years (SEER 9 registries: 1973 – 2007)

Characteristic	Surgery + radiotherapy		Surgery only		Total	
	n	%	n	%	n	%
All women	83,203	41	122,113	59	205,316	100
<i>Age at treatment (diagnosis)</i>						
20 – 34	2,479	39	3,826	61	6,305	100
35 – 44	13,239	43	17,815	57	31,054	100
45 – 59	36,402	43	48,462	57	84,864	100
60 – 74	31,083	37	52,010	63	83,093	100
<i>Year of treatment (diagnosis)</i>						
1973–1982	9,239	21	34,921	79	44,160	100
1983–1992	21,857	32	46,953	68	68,810	100
1993+	52,107	56	40,239	44	92,346	100
<i>Disease stage</i>						
Localized	54,479	40	80,755	60	135,234	100
Regional	27,400	41	40,056	59	67,456	100
Distant	1,324	50	1,302	50	2,626	100

Table 2

Risk of contralateral breast cancer by histology after invasive breast cancer in 5-year survivors (SEER 9 registries: 1973 – 2007)

Age at 1 st diagnosis	Contralateral breast cancer characteristic	Surgery + radiotherapy			Surgery only			RR ^a	(95% CI)
		Observed	Expected	SIR	Observed	Expected	SIR		
20–74	Overall	2397	803.99	2.98	4527	1632.84	2.77	1.11	(1.05, 1.16)
	<i>Histology</i>								
	Ductal	1829	599.80	3.05	3404	1234.80	2.76	1.13	(1.06, 1.20)
	Lobular	235	77.83	3.02	451	158.18	2.85	1.13	(0.96, 1.34)
	Tubular	27	13.58	1.99	62	27.48	2.26	0.93	(0.58, 1.50)
	Medullary	20	5.11	3.91	63	12.66	4.98	0.82	(0.49, 1.38)
	Inflammatory	11	5.29	2.08	26	10.96	2.37	0.94	(0.45, 1.95)
	Papillary	9	4.51	2.00	37	10.62	3.48	0.57	(0.27, 1.21)
	Mucinous	45	22.43	2.01	115	48.18	2.39	0.91	(0.63, 1.30)
20–34	Mixed	221	75.44	2.93	369	129.96	2.84	1.06	(0.89, 1.26)
	<i>P_{heterogeneity}</i>							0.40	
	Ductal	121	10.34	11.70	181	25.09	7.21	1.35	(1.06, 1.72)
35–44	Lobular	5	0.90	5.53	10	2.37	4.22	0.99	(0.33, 2.96)
	<i>P_{difference}</i>						0.04	> 0.50	
	Ductal	351	86.30	4.07	579	178.12	3.25	1.18	(1.03, 1.35)
45–59	Lobular	26	9.47	2.75	64	19.97	3.20	0.85	(0.53, 1.36)
	<i>P_{difference}</i>						0.12	0.18	
	Ductal	812	298.05	2.72	1630	617.31	2.64	1.05	(0.96, 1.15)
60–74	Lobular	112	37.70	2.97	230	78.80	2.92	1.09	(0.86, 1.39)
	<i>P_{difference}</i>						0.26	> 0.50	
	Ductal	545	205.11	2.66	1014	414.29	2.45	1.18	(1.05, 1.31)
	Lobular	92	29.75	3.09	147	57.04	2.58	1.33	(1.01, 1.75)
	<i>P_{difference}</i>						0.35	0.42	

^aRR =relative risk calculated using Poisson regression stratified by stage, age at treatment (<35, 35–44, 45–59, 60+) and year at diagnosis (<1983, 1983–1992, 1993+).

Risk of contralateral breast cancer (CBC) by ER status after invasive breast cancer in 5-year survivors (SEER 9 registries: 1990 – 2007)

Table 3

Age at 1 st diagnosis	Contralateral breast cancer characteristic	Surgery + radiotherapy			Surgery only			RR ^a	(95% CI)
		Observed	Expected	SIR	Observed	Expected	SIR		
20–74	Overall	1596	569.03	2.80	1950	770.75	2.53	1.11	(1.04, 1.18)
	ER status								
	Positive	1158	460.32	2.52	1439	624.89	2.30	1.10	(1.02, 1.19)
	Negative	438	108.72	4.03	511	145.86	3.50	1.19	(1.04, 1.35)
20–34	<i>P</i> _{heterogeneity}							0.33	
	ER status								
	Positive	22	4.70	4.68	38	6.57	5.78	0.80	(0.47, 1.35)
	Negative	61	1.91	31.86	61	2.62	23.33	1.38	(0.96, 1.97)
35–44	<i>P</i> _{heterogeneity}			< 0.001			< 0.001	0.09	
	ER status								
	Positive	169	54.24	3.12	183	72.28	2.53	1.21	(0.98, 1.50)
	Negative	120	17.62	6.81	132	23.92	5.52	1.19	(0.93, 1.53)
45–59	<i>P</i> _{heterogeneity}			< 0.001			< 0.001	> 0.50	
	ER status								
	Positive	510	218.33	2.34	662	280.93	2.36	0.99	(0.88, 1.12)
	Negative	171	54.56	3.13	202	69.31	2.91	1.11	(0.90, 1.36)
60–74	<i>P</i> _{heterogeneity}			< 0.001			< 0.001	0.37	
	ER status								
	Positive	457	183.05	2.50	556	265.11	2.10	1.21	(1.06, 1.37)
	Negative	86	34.62	2.48	116	50.01	2.32	1.10	(0.83, 1.46)
	<i>P</i> _{heterogeneity}			> 0.50			> 0.50	> 0.50	

^aRR =relative risk calculated using Poisson regression stratified by stage, age at treatment (<35, 35–44, 45–59, 60+), and ER status of the 1st breast cancer.