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Original article

A case-control study of the joint effect of reproductive factors and radiation treatment for first breast cancer and risk of contralateral breast cancer in the WECARE study

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ABSTRACT

Objective: To examined the impact of reproductive factors on the relationship between radiation treatment (RT) for a first breast cancer and risk of contralateral breast cancer (CBC).
Methods: The Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study is a multicenter, population-based case-control study where cases are women with asynchronous CBC (N = 1521) and controls are women with unilateral breast cancer (N = 2211). Rate ratios (RR) and 95% confidence intervals (CI) were estimated using conditional logistic regression to assess the independent and joint effects of RT (ever/never and location-specific stray radiation dose to the contralateral breast [0, >0-<1Gy, ≥1Gy]) and reproductive factors (e.g., parity).
Results: Nulliparous women treated with RT (≥1Gy dose) were at increased risk of CBC compared with nulliparous women not treated with RT, although this relationship did not reach statistical significance

Abbreviations: CI, Confidence interval; CBC, Contralateral breast cancer; Gy, Gray; NCI, National Cancer Institute; RT, Radiation treatment; RR, Rate ratio; SEER, Surveillance Epidemiology and End Results; UBC, Unilateral breast cancer; WECARE, Women's Environmental Cancer and Radiation Epidemiology.

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Contralateral breast cancer
WECARE Study

(RR = 1.34, 95% CI 0.87, 2.07). Women treated with RT who had an interval pregnancy (i.e., pregnancy after first diagnosis and before second diagnosis [in cases]/reference date [in controls]) had an increased risk of CBC compared with those who had an interval pregnancy with no RT (RR = 4.60, 95% CI 1.16, 18.28). This was most apparent for women with higher radiation doses to the contralateral breast.
Conclusion: Among young female survivors of breast cancer, we found some evidence suggesting that having an interval pregnancy could increase a woman's risk of CBC following RT for a first breast cancer. While sampling variability precludes strong interpretations, these findings suggest a role for pregnancy and hormonal factors in radiation-associated CBC.

1. Introduction

Exposure to ionizing radiation is an established breast cancer risk factor that is influenced by age at exposure, absorbed dose, and time since exposure [1,2]. Periods of rapid breast development (e.g., puberty) or differentiation (e.g., pregnancy) are times when the breast may be more susceptible to the carcinogenic effects of radiation [3–7], although results have been mixed [8].

Younger age at menarche and fewer full-term pregnancies are established risk factors for both first [9] and second [10] primary breast cancer. Women who have a first full-term pregnancy prior to age 30 years are at reduced risk of a first primary breast cancer compared to those who are nulliparous, and this risk is further reduced with subsequent births. There is, however, an initial transient increase in breast cancer risk for about 20 years following a pregnancy, which thereafter is followed by a lower risk when compared to nulliparous women [11].

The Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study is a multi-centered, population-based case-control study of young women (under age 55 years at first breast cancer diagnosis). We previously reported that, among women whose first breast cancer was diagnosed under age 40 years those receiving at least 1.0 Gy (Gy) of absorbed radiation dose to the contralateral breast during radiation treatment (RT) had a higher risk of developing CBC (RR = 2.5, 95% CI 1.4–4.5) than women not receiving RT [12]. We have also shown that women who were nulliparous and exposed to at least 1 Gy to the contralateral breast, or who had a full-term pregnancy after RT for a first breast cancer, were at increased risk of CBC [13]. However, the interpretation of these latter findings was limited by small numbers. The second phase of WECARE Study recruitment was recently completed, effectively doubling our sample size. Here, we present results from a combined analysis examining the joint effects of reproductive factors and RT for a first breast cancer on risk of CBC.

2. Materials and methods

2.1. Study population

The WECARE Study is a multi-center, population-based case-control study where cases are women with asynchronous CBC and controls are women with unilateral breast cancer (UBC). Case-control recruitment for the WECARE Study was conducted in two phases: WECARE I (2001–2004) and WECARE II (2009–2012). Participants were identified through eight population-based cancer registries: Los Angeles County Cancer Surveillance Program; Cancer Surveillance System of the Fred Hutchinson Cancer Research Center (Seattle, WA); State Health Registry of Iowa; The Cancer Surveillance Program of Orange County/San Diego-Imperial Organization for Cancer Control (Orange County/San Diego, CA); the Greater Bay Area Cancer Registry (San Francisco Bay Area Region and Santa Clara Region, CA); and the Sacramento and Sierra Center Registries (Sacramento Region, CA). These cancer registries all contribute to the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) program in the US. Participants were also recruited from the Ontario Cancer Registry and the Danish Breast Cancer Cooperative Group Registry, supplemented by data from the Danish Cancer Registry. All study participants provided written informed consent and the study protocol was reviewed and approved by the institutional review board at each site. Across all cancer registries, 2354 CBC cases and 3599 UBC controls were identified as eligible and were approached for the study. The number of participants who completed the interview was 1521 cases and 2212 controls. Reasons for non-participation have been described in detail [14].

Details of recruitment procedures and eligibility have been described previously, and were nearly identical for the two study phases [15,16]. Briefly, all women were diagnosed prior to age 55 years, between 1985 and 2008 with a first primary invasive breast cancer (stage I-III). Cases were diagnosed with a second primary CBC (*in situ* or invasive for WECARE I and invasive only for WECARE II) at least one year later. Controls also had no history of any second cancer diagnosis up to their reference date. The reference date for cases was the CBC diagnosis date, while for controls it was defined by adding the interval between the first breast cancer and the CBC for the matched case, to the date of breast cancer diagnosis for the control. Cases must also have been living in the same cancer ascertainment area for both diagnoses, while controls were required to be living in their matched case's cancer ascertainment area when their breast cancer was diagnosed and on their reference date. Additionally, controls must not have undergone prophylactic mastectomy of the unaffected contralateral breast. Study eligibility was restricted to women who were alive, able to be contacted, provide informed consent, complete a telephone interview, and donate a blood or saliva sample for DNA extraction.

Controls were matched to cases (2:1 for WECARE I and 1:1 for WECARE II) on year of birth in 5-year strata, year of diagnosis in 4-year strata, cancer registry region, and race/ethnicity. In WECARE I, cases and controls were further counter-matched based on cancer registry-reported RT such that two members of each case-control trio had received RT for their first breast cancer and the third member had not [15]. Counter-matching was not used in Phase II; this was taken into account in all statistical analyses, as detailed below.

2.2. Data collection

WECARE Study participants were interviewed by telephone using a structured questionnaire that was designed to obtain information about events occurring before the diagnosis of the first primary breast cancer, as well as events that occurred after the first diagnosis during the at-risk period. The at-risk period was defined as beginning at least one year after diagnosis with a first breast cancer and ending at the second diagnosis in CBC cases, or the

corresponding reference date for UBC controls. The study questionnaire included questions about personal demographics, medical history, family and reproductive history, hormone use, body size, smoking status, and alcohol intake. Additionally, medical records, pathology reports, and radiotherapy charts were used to collect detailed treatment information (i.e., chemotherapy, hormonal therapy, and radiation therapy) for the first primary breast cancer, any recurrences experienced prior to the reference date, and tumor characteristics of the first primary breast cancer. One woman (UBC control) was excluded due to missing information on RT status. Location-specific dose to the contralateral breast from stray radiation experienced during RT of a first primary breast cancer was estimated as described previously [12]. Specifically, radiation doses to the contralateral breast for each quadrant and the areolar region were estimated and the dose received in the quadrant of the breast where the case's CBC occurred was assigned to the case, and the dose received in the corresponding region of the unaffected breast of each matched control was assigned to her control(s). Dose estimates were available for 1324 cases and 1918 controls.

2.3. Statistical analysis

Rate ratios (RR) and 95% confidence intervals (CI) were estimated, fitting multivariable conditional logistic regression models, including known risk factors for CBC. The independent and joint effects of RT and reproductive factors at first diagnosis and at reference date were examined using a joint effects model [17]. We examined the joint effects of RT (ever/never and location-specific dose: 0, <1Gy and ≥1Gy) and menopausal status/age at menopause, change in menopausal status between first diagnosis and reference date, nulliparity, number of full-term pregnancies, full-term pregnancy between first diagnosis and reference date (interval pregnancy), full-term pregnancy in the two years prior to first diagnosis, and history of breastfeeding. Because treatment for a first breast cancer could induce menopause, menopausal status and age at menopause two years prior to first diagnosis were used. Analyses examining the impact of having an interval pregnancy on risk of CBC were restricted to women who were premenopausal one year after first breast cancer diagnosis. Models were adjusted for age at first diagnosis, histology, stage, first-degree family history of breast cancer, age at menarche, age at menopause, use of menopausal hormone therapy up to first diagnosis, and chemotherapy and hormonal therapy for first breast cancer. To take into account the duration of hormonal therapy, the hormonal treatment variable was coded as: no hormonal therapy, tamoxifen <5 years, tamoxifen ≥5 years, tamoxifen unknown duration, other hormonal therapy, unknown. We also examined the association between RT and risk of CBC stratified by categories of each reproductive factor, and report p-values for heterogeneity across these categories. P-values for heterogeneity were estimated using nested likelihood ratio tests. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary NC).

3. Results

Table 1 shows selected characteristics of the WECARE Study population. Cases and controls had a median age at diagnosis of 46 years, with a median time between first and second breast cancer diagnosis (first diagnosis and reference date in controls) of 6.3 years in cases and 5.6 years in controls.

Women who were postmenopausal at first diagnosis and reference date or who became postmenopausal during the at-risk period were at a higher risk of CBC than those who remained premenopausal throughout the study period. When we examined

Table 1
Characteristics of women in the WECARE study, 1985–2008.

Variable	CBC Cases (N = 1521)		UBC Controls (N = 2211)	
	Median	Range	Median	Range
Age at first diagnosis (years)	46	24–54	46	23–54
Age at reference date (years)[a]	53	27–73	52	27–71
Length of at-risk period (years)[b]	6.3	1.0–19.8	5.6	1.0–19.8
	N (%)[c]		**N (%)[c]**	
WECARE Study Phase				
WECARE I	708 (47)		1399 (63)	
WECARE II	813 (53)		812 (37)	
Study area				
California[d]	658 (43)		966 (44)	
Canada[e]	159 (10)		157 (7)	
Denmark[f]	279 (18)		457 (21)	
Iowa[g]	201 (13)		314 (14)	
Seattle[h]	224 (15)		317 (14)	
Year of first breast cancer				
1985–1988	238 (16)		467 (21)	
1989–1992	415 (27)		647 (29)	
1993–1996	427 (28)		631 (29)	
1997–2008	441 (29)		466 (21)	
Race/ethnicity				
Non-Hispanic White	1335 (88)		1977 (89)	
Hispanic White	69 (5)		93 (4)	
Black	55 (4)		76 (3)	
Asian or Other	62 (4)		65 (3)	
Histology of first breast cancer				
Ductal	1205 (79)		1772 (80)	
Lobular	179 (12)		222 (10)	
Medullary	51 (3)		65 (3)	
Tubular/mucinous	42 (3)		80 (4)	
Other	40 (3)		68 (3)	
Unknown	4 (0)		4 (0)	
Stage of first breast cancer				
Local	1061 (70)		1442 (65)	
Regional	448 (29)		758 (34)	
Unknown	12 (1)		11 (1)	
Chemotherapy for first breast cancer				
No	699 (46)		923 (42)	
Yes	822 (54)		1288 (58)	
Radiation treatment for first breast cancer[i]				
WECARE I				
No	362 (51)		266 (50)	
Yes	346 (49)		1133 (50)	
WECARE II				
No	279 (34)		256 (32)	
Yes	534 (66)		556 (68)	
Hormone treatment for first breast cancer				
No hormonal therapy	963 (63)		1270 (57)	
Tamoxifen <5 years	279 (18)		466 (21)	
Tamoxifen ≥5 years	119 (8)		184 (8)	
Tamoxifen unknown duration	69 (5)		136 (6)	
Other or unknown hormonal therapy	91 (6)		155 (7)	

Abbreviations: CBC: contralateral breast cancer; N: Number; ER: estrogen receptor; PR: progesterone receptor; UBC: unilateral breast cancer; WECARE Study: Women's Environmental Cancer and Radiation Epidemiology Study.

[a] Reference date is defined as the date of CBC diagnosis in cases and the corresponding date in matched controls. This is determined by adding the time between the two breast cancer diagnoses in the matched case to the date of the first breast cancer diagnosis in the control.

[b] The time between a case's first breast cancer and her CBC defined at-risk period. For a matched control, her case's at-risk period was added to the control's date of UBC and the date on which the at-risk period ended defined her reference date.

[c] Percentages may not sum to 100% due to rounding.

[d] Four study centers were included: 1) Los Angeles County Cancer Surveillance Program, 2) The Cancer Surveillance Program of Orange County/San Diego-Imperial Organization for Cancer Control, 3) Greater Bay Area Cancer Registry (San Francisco Bay Area Region and Santa Clara Region), and 4) Sacramento and Sierra Center Registries (Sacramento Region).

[e] The Ontario Cancer Registry.

[f] The Danish Breast Cancer Cooperative Group Database supplemented by the Danish Cancer Registry.

[g] The State Health Registry of Iowa.

[h] Cancer Surveillance System of the Fred Hutchinson Cancer Research Center.

[i] Proportion of individuals treated and not treated with radiation. In WECARE I, cases and controls were counter-matched based on cancer registry reported radiation treatment such that two members of each case-control trio had received radiation treatment for their first breast cancer diagnosis. Proportions for controls in WECARE I are weighted to reflect this selection. Proportions for cases in WECARE I (because all cases were included) and both cases and controls in WECARE II (because counter-matching was not used in WECARE II) are not weighted.

the impact of time since menopause on the relationship between RT and risk of CBC, there was some indication of an increased risk in women who received RT and had become menopausal within 5-<10 years of first diagnosis (RR = 1.69, 95% CI 0.91, 3.13) compared to premenopausal women who did not receive RT (Table 2). However, menopausal status did not modify the overall association between RT status and risk of CBC (Tables 2 and 3). Further, while the association between RT and risk of CBC was somewhat elevated in nulliparous women receiving ≥1Gy radiation dose to the contralateral breast compared to nulliparous women not treated with RT, this association was not statistically significant (RR = 1.34, 95% CI 0.87, 2.07) (Table 3).

Women who were treated with RT (ever/never) and had an interval pregnancy (i.e., pregnancy between first diagnosis and reference date) had a 4-fold higher risk of CBC (RR = 4.60, 95% CI 1.16, 18.28) compared to those who had an interval pregnancy and were not treated with RT (Table 2). When the impact of RT dose on the relationship between interval pregnancy and risk of CBC was examined, a significant positive dose-response was observed (p_{trend} across dose categories = 0.02). Compared to women who had an interval pregnancy and were not treated with RT, the risk of CBC increased non-significantly in women with >0-<1Gy dose to the contralateral breast (RR = 5.55, 95% CI 0.81, 38.10) and was significantly 12-fold higher for those with ≥1Gy dose to the contralateral breast (RR = 11.97, 95% CI 1.24, 116) (Table 3). RT-associated CBC risk was not modified by any of the other reproductive factors examined.

We also examined the timeline of diagnoses, treatments received for a first breast cancer and pregnancies for the 43 women (18 cases and 25 controls) with an interval pregnancy. The average age of diagnosis of these women was 31 years, with cases being slightly younger than controls (30 versus 32 years respectively). Cases were also younger at age at interval pregnancy (33 years for cases and 36 years for controls), with a slightly larger proportion of interval pregnancies being a first pregnancy for cases (56%) than controls (52%). We found that the average time between first breast cancer diagnosis and interval pregnancy was 2.7 years (range 0–8 years) for cases (3.5 for cases who did not receive RT and 2.3 for those that did receive RT) and 4.0 (range 0–12 years) for controls (4.7 for controls who did not receive RT and 3.6 for controls that did).

Overall, among women who had a pregnancy in the two years prior to first breast cancer diagnosis, compared to women who did not receive RT for a first breast cancer, we did not find a significant association between RT (ever/never) and risk of CBC among women (RR = 1.58, 95% CI 0.68, 3.69) (Table 2) When we looked at RT dose, compared to women with a recent pregnancy prior to diagnosis who did not receive RT, a non-statistically significant increase in risk was observed in women at both dose levels (RR = 1.31, 95% CI 0.49, 3.51 for women with >0-<1Gy dose to the contralateral breast, and RR = 2.21, 95% CI 0.77, 6.35 for women with ≥1Gy; p_{trend} across dose categories = 0.15) (Table 3).

4. Discussion

Women who were nulliparous at the time of first breast cancer diagnosis and exposed to at least 1 Gy to the contralateral breast where at an increased risk of CBC, however this finding was not statistically significant (RR = 1.34, 95% CI 0.87, 2.07). We also examined the impact of having a pregnancy around the time of RT (before or after) and risk of CBC. When we looked at women who had pregnancy following a first breast cancer diagnosis (i.e., interval pregnancy), we found an increased risk in women treated with RT compared to those that were not (RR = 4.60, 95% CI 1.16, 18.28). Overall, we did not find a significant association for pregnancy in the two years prior to first diagnosis, and while the RR increased with RT dose, the trend was not significant (p_{trend} = 0.15).

We previously reported that women who were nulliparous and exposed to at least 1 Gy to the contralateral breast had a 2-fold increased risk of CBC, and that women with an interval pregnancy treated with RT had a 6-fold higher risk of CBC (RR = 6.0 95% CI 1.3, 28.4) [13]. The current study, with nearly double the sample size, provides estimates that are somewhat attenuated with narrower (but still wide) confidence intervals. In this initial analysis we also had insufficient numbers to examine the impact of interval pregnancy by dose to the contralateral breast. In the current study with nearly doubled the sample size, interval pregnancies remained a rare occurrence (12 cases and 15 controls treated with RT and 6 cases and 10 controls not treated with RT). Still, we found a significant positive dose effect (p_{trend} = 0.02) associated with having an interval pregnancy after RT. The risk of CBC was about 12-fold higher in the highest dose group, compared to women with an interval pregnancy who did not receive RT. These risk estimates are likely to be somewhat inflated due to the small number of events and the lower risk of CBC observed in those who had an interval pregnancy who were not treated with RT (RR = 0.30, 95% CI, 0.08, 1.06). The factors driving this reduced risk are not clear. While these risk estimates must be interpreted with caution, the potential impact of having a pregnancy after treatment with RT for a first breast cancer diagnosis on risk of CBC should not be dismissed.

When we further examined the characteristics of women who had an interval pregnancy, we found that cases tended to be younger at both first breast cancer diagnosis and interval pregnancy. Further, while both cases and controls who received RT for their first breast cancer had pregnancies closer to first diagnosis than those who did not, the timing was closest for cases (2.3 years between first diagnosis and interval pregnancy for cases versus 3.6 years for controls).

Studies examining the impact of exposure to diagnostic or therapeutic radiation (e.g., treatment for tuberculosis, mastitis or Hodgkin's lymphoma) at a young age (around the time of first menses) [3,18–20], or while pregnant or lactating [3,4,21] have found an increased risk of radiation-associated breast cancer (also reviewed in Refs. [2]). The mechanism underlying this impact of interval pregnancy following RT on risk of CBC is unknown but could be related to changes in the breast that occur during and directly following pregnancy. A "dual effect" of pregnancy is observed with respect to risk of a first breast cancer. An initial increase in risk of breast cancer is seen immediately following pregnancy. This increase peaks around 5 years after childbirth and persists for about 20 years, at which point the risk becomes lower than that observed for nulliparous women [11]. It has been suggested that the increased hormone levels experienced during pregnancy could lead to the clonal expansion of previously initiated cells in the breast [22,23]. Other possible mechanisms underlying this initial increase in risk have been proposed, including a tumor promoting microenvironment associated with tissue re-modelling during post-partum involution, inflammation, and changes to the immune system following pregnancy [24]. To capture the potential impact of RT during a post-pregnancy, post-lactation, period of involutional change, we examined the relationship between having a pregnancy in the two years prior to first breast cancer diagnosis

Table 2
Joint effect of radiation treatment for first breast cancer (ever/never), reproductive factors and risk of CBC. Abbreviations: CBC: contralateral breast cancer, UBC: unilateral breast cancer, RR: rate ratio, CI: confidence interval.

	Radiation Treatment	CBC Cases N (%)[a]	UBC Controls N (%)[a]	RR (95% CI)[b,c]	RR (95% CI)[c,d]	p-het[e]
Menopausal Status						
Menopausal status/age at menopause (first diagnosis)						
Premenopausal	Never	467 (30.9)	382 (17.4)	1.00	1.00	0.92
	Ever	657 (43.4)	1293 (58.9)	1.04 (0.88–1.23)	1.04 (0.88, 1.23)	
Postmenopausal < 45 years	Never	86 (5.7)	72 (3.3)	0.96 (0.65–1.40)	1.00	
	Ever	109 (7.2)	210 (9.6)	1.09 (0.81–1.48)	1.14 (0.75, 1.74)	
Postmenopausal ≥ 45 years	Never	84 (5.6)	64 (2.9)	1.17 (0.78–1.74)	1.00	
	Ever	110 (7.3)	176 (8.0)	1.24 (0.89–1.74)	1.07 (0.70, 1.64)	
Menopausal status between first diagnosis and reference date[f]						
Premenopausal throughout	Never	79 (5.2)	73 (3.3)	1.00	1.00	0.81
	Ever	111 (7.3)	312 (14.2)	0.94 (0.62–1.41)	0.94 (0.62, 1.41)	
Pre- to post-menopausal	Never	388 (25.6)	309 (14.1)	1.56 (1.05–2.34)	1.00	
	Ever	546 (36.1)	981 (44.7)	1.70 (1.16–2.50)	1.09 (0.90, 1.31)	
Postmenopausal throughout	Never	170 (11.2)	136 (6.2)	1.63 (1.03–2.59)	1.00	
	Ever	219 (14.5)	386 (17.6)	1.75 (1.14–2.69)	1.08 (0.80, 1.45)	
Years since menopause (at first diagnosis)						
Premenopausal	Never	467 (30.9)	382 (17.4)	1.00	1.00	0.42
	Ever	657 (43.4)	1293 (58.9)	1.04 (0.88–1.22)	1.04 (0.88–1.22)	
Postmenopausal <5 years	Never	76 (5.0)	51 (2.3)	1.24 (0.80–1.88)	1.00	
	Ever	102 (6.7)	163 (7.4)	1.09 (0.78–1.52)	0.88 (0.56–1.40)	
Postmenopausal 5 - <10 years	Never	42 (2.8)	41 (1.9)	0.85 (0.50–1.43)	1.00	
	Ever	57 (3.8)	97 (4.4)	1.43 (0.95–2.16)	1.69 (0.91–3.13)	
Postmenopausal ≥ 10 years	Never	52 (3.4)	44 (2.0)	0.96 (0.60–1.52)	1.00	
	Ever	60 (4.0)	126 (5.7)	1.02 (0.70–1.50)	1.07 (0.63–1.84)	
Parity						
Nulliparity (first diagnosis)						
Yes	Never	124 (8.2)	100 (4.5)	1.00	1.00	0.50
	Ever	198 (13.1)	312 (14.1)	1.12 (0.79–1.57)	1.12 (0.79, 1.57)	
No	Never	514 (33.9)	422 (19.1)	0.96 (0.70–1.33)	1.00	
	Ever	680 (44.9)	1372 (62.2)	1.01 (0.74–1.36)	1.05 (0.89, 1.22)	
Number of full-term pregnancies (first diagnosis)						
None	Never	124 (8.2)	100 (4.5)	1.00	1.00	0.86
	Ever	198 (13.1)	312 (14.1)	1.11 (0.79–1.56)	1.11 (0.79, 1.56)	
1	Never	108 (7.1)	80 (3.6)	1.10 (0.56–2.18)	1.00	
	Ever	163 (10.8)	260 (11.8)	1.25 (0.67–2.33)	1.13 (0.78, 1.65)	
≥2	Never	406 (26.8)	342 (15.5)	1.00 (0.54–1.86)	1.00	
	Ever	517 (34.1)	1112 (50.4)	1.02 (0.55–1.89)	1.02 (0.8+, 1.22)	
Interval pregnancy (among premenopausal women at first diagnosis)[g]						
No, parous at first diagnosis	Never	180 (31.6)	115 (16.1)	1.00	1.00	0.10
	Ever	240 (42.1)	422 (59.2)	0.99 (0.65–1.50)	0.99 (0.65, 1.50)	
Yes, parous or nulliparous at first diagnosis	Never	6 (1.1)	10 (1.4)	0.30 (0.08–1.06)	1.00	
	Ever	12 (2.1)	15 (2.1)	1.36 (0.49–3.82)	4.60 (1.16, 18.28)	
No, nulliparous at first diagnosis	Never	50 (8.8)	32 (4.5)	0.92 (0.38–2.21)	1.00	
	Ever	82 (14.4)	119 (16.7)	0.86 (0.45–1.66)	0.94 (0.42, 2.07)	
Pregnancy in the 2 years prior to first diagnosis						
No, parous at first diagnosis, no pregnancy 2 years prior to first diagnosis	Never	497 (32.8)	405 (18.4)	1.00	1.00	0.52
	Ever	643 (42.4)	1315 (59.6)	1.03 (0.88–1.21)	1.03 (0.88, 1.21)	
Yes, pregnancy in the 2 years prior to first diagnosis	Never	17 (1.1)	17 (0.8)	0.75 (0.36–1.56)	1.00	
	Ever	37 (2.4)	57 (2.6)	1.19 (0.72–1.97)	1.58 (0.68, 3.69)	
No, nulliparous at first diagnosis	Never	124 (8.2)	100 (4.5)	0.91 (0.64–1.29)	1.00	
	Ever	198 (13.1)	312 (14.1)	1.00 (0.76–1.33)	1.11 (0.78, 1.56)	

[a] Frequency counts for factors do not sum to totals for cases and controls due to missing data.
[b] Joint-effects models, with reference group as unexposed for both radiation treatment and the reproductive factor of interest.
[c] Adjusted for age at first diagnosis, age at menarche, age at menopause (at first diagnosis for first diagnosis variables of interest and at reference date for reference date variables of interest), histology at first diagnosis, breast cancer family history, stage at first diagnosis, chemotherapy, hormonal treatment/duration for first diagnosis, use of menopausal hormone therapy up to first diagnosis, and mutual adjustment for reproductive factors of interest. A log-weight covariate was also included in each model to account for the sampling probability of the counter-matching for radiation treatment status used in WECARE I. WECARE II participants (who were not counter-matched) were assigned an offset term of 1.
[d] Stratified analyses examining the relationship between radiation treatment and risk of CBC by category of the different reproductive factors.
[e] p-value for heterogeneity of radiation treatment effect on risk of CBC across strata of reproductive variables and were estimated using a nested likelihood ratio test.
[f] Reference date is defined as the date of CBC diagnosis in cases and the corresponding date in matched controls. This is determined by adding the time between the two breast cancer diagnoses in the matched case to the date of the first breast cancer diagnosis in the control.
[g] Restricted to women who were premenopausal 1 year after first breast cancer diagnosis (i.e., the start of the at-risk period).

and radiation-associated CBC. We found a non-significant risk increase suggesting no major impact of RT during this time period in relation to CBC risk.

Strengths of this study include the population-based design, large study population, and detailed questionnaire and medical record data. Importantly, we had location-specific estimates of RT dose (in the quadrant where the CBC occurred), allowing for the assessment of different doses of RT received by the contralateral breast during treatment for a first primary breast cancer. However, despite the large sample size and focus on young women,

Table 3
Joint effect of radiation treatment for first breast cancer (dose), reproductive factors and risk of CBC.

	Radiation Dose[a] (Gy)	CBC Cases N (%)[b]	UBC Controls N (%)[b]	RR (95% CI)[c,d]	RR (95% CI)[d,e]	p-het[f]
Menopausal Status						
Menopausal status/age at menopause (first diagnosis)						
Premenopausal	0	396 (31.6)	321 (17.2)	1.00	1.00	0.21
	>0-<1	269 (21.5)	601 (32.3)	0.96 (0.78–1.20)	0.96 (0.78–1.20)	
	≥1	252 (20.1)	494 (26.5)	1.04 (0.83–1.32)	1.04 (0.83–1.32)	
Postmenopausal < 45 years	0	78 (6.2)	66 (3.5)	0.93 (0.63–1.38)	1.00	
	>0-<1	61 (4.9)	84 (4.5)	1.51 (0.99–2.31)	1.62 (0.97–2.70)	
	≥1	37 (3.0)	85 (4.6)	0.96 (0.59–1.56)	1.03 (0.59–1.80)	
Postmenopausal ≥ 45 years	0	65 (5.2)	61 (3.3)	0.96 (0.63–1.48)	1.00	
	>0-<1	57 (4.5)	81 (4.4)	1.46 (0.93–2.29)	1.52 (0.89–2.57)	
	≥1	38 (3.0)	68 (3.7)	1.08 (0.65–1.79)	1.12 (0.63–2.01)	
Menopausal status between first diagnosis and reference date[g]						
Premenopausal throughout	0	61 (4.9)	61 (3.3)	1.00	1.00	0.15
	>0-<1	56 (4.5)	151 (8.1)	1.13 (0.69–1.84)	1.13 (0.69–1.84)	
	≥1	39 (3.1)	113 (6.1)	0.87 (0.51–1.49)	0.87 (0.51–1.49)	
Pre-to post-menopausal	0	335 (26.7)	260 (14.0)	1.68 (1.10–2.57)	1.00	
	>0-<1	213 (17.0)	450 (24.2)	1.59 (1.03–2.45)	0.95 (0.74–1.21)	
	≥1	213 (17.0)	381 (20.5)	1.86 (1.20–2.88)	1.11 (0.86–1.44)	
Postmenopausal throughout	0	143 (11.4)	127 (6.8)	1.56 (0.95–2.54)	1.00	
	>0-<1	118 (9.4)	165 (8.9)	2.38 (1.44–3.92)	1.53 (1.06–2.20)	
	≥1	75 (6.0)	153 (8.2)	1.65 (0.97–2.78)	1.06 (0.71–1.58)	
Years since menopause (at first diagnosis)						
Premenopausal	0	396 (31.6)	321 (17.2)	1.00	1.00	0.22
	>0-<1	269 (21.5)	601 (32.3)	0.96 (0.77–1.19)	0.96 (0.77–1.19)	
	≥1	252 (20.1)	494 (26.5)	1.04 (0.82–1.31)	1.04 (0.82–1.31)	
Postmenopausal <5 years	0	58 (4.6)	49 (2.6)	1.08 (0.69–1.68)	1.00	
	>0-<1	51 (4.1)	69 (3.7)	1.27 (0.80–2.03)	1.18 (0.66–2.10)	
	≥1	35 (2.8)	65 (3.5)	0.96 (0.57–1.60)	0.89 (0.48–1.63)	
Postmenopausal 5 - <10 years	0	39 (3.1)	36 (1.9)	0.87 (0.51–1.50)	1.00	
	>0-<1	36 (2.9)	47 (2.5)	2.04 (1.17–3.53)	2.34 (1.13–4.85)	
	≥1	16 (1.3)	37 (2.0)	1.00 (0.50–2.00)	1.15 (0.50–2.65)	
Postmenopausal ≥ 10 years	0	46 (3.7)	42 (2.3)	0.83 (0.52–1.33)	1.00	
	>0-<1	31 (2.5)	49 (2.6)	1.35 (0.78–2.32)	1.62 (0.84–3.14)	
	≥1	24 (1.9)	51 (2.7)	1.11 (0.60–2.02)	1.33 (0.65–2.72)	
Parity						
Nulliparity (first diagnosis)						
Yes	0	109 (8.7)	88 (4.7)	1.00	1.00	0.36
	>0-<1	88 (7.0)	154 (8.2)	1.06 (0.71–1.60)	1.06 (0.71–1.60)	
	≥1	76 (6.1)	111 (5.9)	1.34 (0.87–2.07)	1.34 (0.87–2.07)	
No	0	430 (34.3)	364 (19.5)	0.96 (0.69–1.33)	1.00	
	>0-<1	299 (23.8)	613 (32.8)	1.07 (0.77–1.49)	1.12 (0.91–1.37)	
	≥1	253 (20.2)	538 (28.8)	0.97 (0.69–1.36)	1.01 (0.81–1.27)	
Number of full-term pregnancies (first diagnosis)						
None	0	109 (8.7)	88 (4.7)	1.00	1.00	0.59
	>0-<1	88 (7.0)	154 (8.2)	1.07 (0.71–1.60)	1.07 (0.71–1.60)	
	≥1	76 (6.1)	111 (5.9)	1.33 (0.86–2.06)	1.33 (0.86–2.06)	
1	0	90 (7.2)	69 (3.7)	0.86 (0.41–1.78)	1.00	
	>0-<1	76 (6.1)	112 (6.0)	1.17 (0.57–2.42)	1.37 (0.87–2.15)	
	≥1	62 (4.9)	106 (5.7)	1.04 (0.49–2.18)	1.21 (0.75–1.94)	
≥2	0	340 (27.1)	295 (15.8)	0.85 (0.43–1.68)	1.00	
	>0-<1	223 (17.8)	501 (26.8)	0.91 (0.46–1.83)	1.07 (0.85–1.35)	
	≥1	191 (15.2)	432 (23.1)	0.82 (0.41–1.63)	0.96 (0.74–1.23)	
Interval pregnancy (among premenopausal women at first diagnosis)[h]						
No, parous at first diagnosis	0	144 (31.2)	99 (16.6)	1.00	1.00	0.11
	>0-<1	105 (22.7)	194 (32.4)	0.71 (0.41–1.24)	0.71 (0.41–1.24)	
	≥1	87 (18.8)	158 (26.4)	1.12 (0.61–2.06)	1.12 (0.61–2.06)	
Yes, parous or nulliparous at first diagnosis	0	4 (0.9)	9 (1.5)	0.19 (0.04–0.87)	1.00	
	>0-<1	6 (1.3)	8 (1.3)	1.04 (0.26–4.13)	5.55 (0.81–38.10)	
	≥1	5 (1.1)	3 (0.5)	2.24 (0.29–17.11)	11.97 (1.24–115.75)	
No, nulliparous at first diagnosis	0	45 (9.7)	27 (4.5)	0.75 (0.33–1.74)	1.00	
	>0-<1	35 (7.6)	59 (9.9)	0.98 (0.43–2.24)	1.30 (0.55–3.06)	
	≥1	31 (6.7)	41 (6.9)	0.91 (0.37–2.21)	1.21 (0.46–3.14)	
Pregnancy in the 2 years prior to first diagnosis						
No, parous at first diagnosis	0	415 (33.1)	350 (18.7)	1.00	1.00	0.34
	>0-<1	282 (22.5)	582 (31.2)	1.13 (0.92–1.38)	1.13 (0.92–1.38)	
	≥1	237 (18.9)	521 (27.9)	0.97 (0.78–1.23)	0.97 (0.78–1.23)	
Yes, pregnancy in the 2 years prior to first diagnosis	0	15 (1.2)	14 (0.7)	0.80 (0.38–1.65)	1.00	
	>0-<1	17 (1.4)	31 (1.7)	1.04 (0.51–2.10)	1.31 (0.49–3.51)	
	≥1	16 (1.3)	17 (0.9)	1.76 (0.78–3.98)	2.21 (0.77–6.35)	
No, nulliparous at first diagnosis	0	109 (8.7)	88 (4.7)	0.88 (0.62–1.27)	1.00	
	>0-<1	88 (7.0)	154 (8.2)	0.94 (0.66–1.35)	1.07 (0.71–1.60)	
	≥1	76 (6.1)	111 (5.9)	1.18 (0.79–1.75)	1.33 (0.86–2.06)	

AbbreviationsCBC: contralateral breast cancer, UBC: unilateral breast cancer, RR: rate ratio, CI: confidence interval.

[a] Location-specific radiation dose received in the quadrant of the breast where the CBC occurred for each case, and the corresponding region in the unaffected breast of her matched control.
[b] Frequency counts for factors do not sum to totals for cases and controls due to missing data.
[c] Joint-effects models, with reference group as unexposed for both radiation treatment and the reproductive factor of interest.
[d] Adjusted for age at first diagnosis, age at menarche, age at menopause (at first diagnosis for first diagnosis variables of interest and at reference date for reference date variables of interest), histology at first diagnosis, breast cancer family history, stage at first diagnosis, chemotherapy, hormonal treatment/duration for first diagnosis, use of menopausal hormone therapy up to first diagnosis, and mutual adjustment for reproductive factors of interest. A log-weight covariate was also included in each model to account for the sampling probability of the counter-matching for radiation treatment status used in WECARE I. WECARE II participants (who were not counter-matched) were assigned an offset term of 1.
[e] Stratified analyses examining the relationship between radiation treatment and risk of CBC by category of the different reproductive factors.
[f] p-value for heterogeneity of radiation treatment effect on risk of CBC across strata of reproductive variables and were estimated using a nested likelihood ratio test.
[g] Reference date is defined as the date of CBC diagnosis in cases and the corresponding date in matched controls. This is determined by adding the time between the two breast cancer diagnoses in the matched case to the date of the first breast cancer diagnosis in the control.
[h] Restricted to women who were premenopausal 1 year after first breast cancer diagnosis (i.e., the start of the at-risk period).

pregnancy following a first breast cancer diagnosis remained a relatively rare occurrence in this study population. The median age of the study population at first breast cancer diagnosis was 46 years (784 [21%] were ≤40 years of age at first diagnosis), beyond childbearing years for most women. This suggests the need to examine the impact of an interval pregnancy after RT in women with a very young age at first breast cancer diagnosis (i.e., prior to 40 years), notably cases with an interval pregnancy in this study had two breast cancer diagnoses (UBC and CBC) prior to age 40 years. Women diagnosed at a very young age are also likely to have a familial risk of breast cancer, which has been shown to further increase the risk of breast cancer immediately following pregnancy [11,25,26]. Finally, we examined the impact of multiple reproductive factors on the relationship between RT and risk of CBC. It is possible therefore that any significant findings could be due to chance.

There is increasing focus on the potential of patient-centered, personalized treatment plans for women with breast cancer. As the average five-year survival rate for a first primary breast cancer is approaches 90% [27], there is a growing population of women who have survived a first breast cancer diagnosis. This is extending the use of a personalized approach to include survivorship [28]. Further, as more women continue to delay pregnancy, the number of pregnancies that occur after a breast cancer diagnosis is likely to increase. In the context of RT, this could include the decision to use whole-breast radiation or accelerated partial breast radiation, which would reduce the stray dose to the contralateral breast.

5. Conclusion

We found that women who were nulliparous at the time of RT (≥1Gy dose to the contralateral breast) for a first breast cancer were at an elevated risk of CBC, although this finding was not statistically significant. Further, women who had a pregnancy after a first primary breast cancer diagnosis who were treated with RT, especially those with higher doses to the contralateral breast, were at a statistically significant increased risk of CBC, although again results were based on small numbers and the confidence intervals were wide. While we are not able to make a strong statement for a relationship between pregnancy around the time of RT and risk of CBC, we are also not able to rule it out. These findings support the need for continued investigation into this relationship, particularly in young women with breast cancer for whom reproductive concerns are important. National Comprehensive Cancer Network (NCCN) guidelines currently recommend that patients do not get pregnant during treatment (RT, chemotherapy, hormonal therapy) or in the 6 months following completion of treatment with trastuzumab or pertuzumab [29]. Further examination of the impact of timing of pregnancy with respect to treatment and diagnosis is needed. As the average five-year survival rate for a first primary breast cancer approaches 90% [27], there is a growing population of women at risk of CBC. Further, as more women continue to delay pregnancy, the number of pregnancies that occur after a breast cancer diagnosis is likely to increase. Understanding the risks associated with treatments received for a first breast cancer, and how these may be modified by pregnancy, will inform discussions between patients and their physicians, help guide future treatment decisions and surveillance recommendations, and strengthen evidence-based risk communication.

Ethics approval and consent to participate

All participants gave written informed consent before enrollment in the WECARE study. The study protocols were approved by the institutional review boards at the University of Iowa (IRB-01), Fred Hutchinson Cancer Research Center, Cancer Prevention Institute of California, University of Southern California, Beckman Research Institute of the City of Hope, University of California at Irvine, Mount Sinai Hospital, Danish Cancer Society and Memorial Sloan Kettering Cancer Center, and by the Committee for the Protection of Human Subjects of the State of California and the ethical committee system in Denmark.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets analyzed during the current study are not publicly available to protect individual privacy but are available from the corresponding author on reasonable request.

Authors' contributions

JDB, JLB, JDB and RES contributed to the conception and design of the study; JDB, SAS, LB, JAK, CFL, EMJ, KEM, LM, RL, XL, MW, PC, DOS contributed to data acquisition, JDB, ASR, and XL contributed to data analysis; all authors contributed to the interpretation of the results; JDB drafted the initial manuscript and all authors contributed to the intellectual content of the revisions; all authors approved the final version of the manuscript.

Data statement

The datasets analyzed during the current study are not publicly available to protect individual privacy but are available from the corresponding author on reasonable request.

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Declaration of competing interest

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