Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2012 November 15; 84(4): 917–924. doi:10.1016/j.ijrobp.2012.01.047.

Reproductive status at first diagnosis influences risk of radiation-induced second primary contralateral breast cancer in The WECARE Study

Jennifer D. Brooks, Ph.D.¹, John D. Boice Jr, Sc.D.², Marilyn Stovall, Ph.D.³, Anne S. Reiner, M.S.¹, Leslie Bernstein, Ph.D.⁴, Esther M. John, Ph.D.⁵, Charles F. Lynch, M.D., Ph.D.⁶, Lene Møller, Ph.D.⁷, Julia A. Knight, Ph.D.⁸, Duncan C. Thomas, Ph.D.⁹, Robert W. Haile, Dr.P.H.⁹, Susan A. Smith, M.P.H.³, Marinela Capanu, Ph.D.¹, The WECARE Collaborative Group, Jonine L. Bernstein, Ph.D.¹, and Roy E. Shore, Ph.D., Dr.P.H.¹⁰

¹Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

²International Epidemiology Institute, Rockville, Maryland and Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt School of Medicine, Nashville, Tennessee, USA

³Department of Radiation Physics, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

⁴Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute and City of Hope Comprehensive Cancer Center, Duarte, California, USA

⁵Cancer Prevention Institute of California, Fremont, California, USA, and Stanford University School of Medicine and Stanford Cancer Institute, Stanford, California, USA

⁶Department of Epidemiology, University of Iowa, Iowa City, Iowa, USA

⁷Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

⁸Dalla Lana School of Public Health, University of Toronto and Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada

⁹Department of Preventive Medicine, University of Southern California, Los Angeles, California, USA

¹⁰Department of Environmental Medicine, New York University, New York, New York, USA and Radiation Effects Research Foundation, Hiroshima, Japan

Abstract

Purpose—Our study examines whether reproductive and hormonal factors prior to, at the time of, or subsequent to, radiation treatment for a first primary breast cancer, modify the risk of radiation-induced second primary breast cancer.

Methods and Materials—The Women's Environmental, Cancer and Radiation Epidemiology (WECARE) Study is a multi-center, population-based study of 708 women (cases) with asynchronous contralateral breast cancer (CBC) and 1,399 women (controls) with unilateral breast cancer. Radiotherapy (RT) records, coupled with anthropomorphic phantom simulations, were

Corresponding Author: Jennifer D. Brooks, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 E 63rd Street, 3rd floor, New York, NY (brooks@mskcc.org), 646-735-8068 (tel), 646-735-0010 (fax).

Conflicts of Interest: The authors declare no conflicts of interest.

used to estimate quadrant-specific radiation dose to the contralateral breast for each patient. Rate ratios (RR) and 95% confidence intervals (CI) were computed to assess the relationship between reproductive factors and risk of CBC.

Results—Women who were nulliparous at diagnosis and exposed to 1 gray (Gy) to the contralateral breast, had a greater risk of CBC than matched unexposed nulliparous women (RR=2.2, 95% CI 1.2–4.0). No increased risk was seen in RT-exposed parous women (RR=1.1, 95% CI 0.8–1.4). Women treated with RT who later became pregnant (n=8 cases and 9 controls) had a greater risk of CBC (RR=6.0, 95% CI 1.3, 28.4) than unexposed women (n=4 cases and 7 controls) who also became pregnant. The association of radiation with risk of CBC did not vary by number of pregnancies, history of breastfeeding or menopausal status at the time of first breast cancer diagnosis.

Conclusion—Nulliparous women treated with RT were at an increased risk of CBC. Although based on small numbers, women who become pregnant after first diagnosis also appear to be at an increased risk of radiation-induced CBC.

Keywords

Reproductive factors; radiation treatment; second primary contralateral breast cancer

Introduction

Age at menarche, age at menopause, parity and age at first full-term pregnancy are well established factors affecting breast cancer risk (1). Young age at first full-term pregnancy is associated with a reduction in lifetime risk of estrogen receptor (ER) or progesterone receptor (PR) positive breast cancer (2) that is thought to be mediated through the induction of breast differentiation associated with lower rates of breast cell proliferation (3). In the approximately 10 years following a first full-term pregnancy before age 35 years, breast cancer risk is increased, then decreases relative to nulliparous women (4).

Ionizing radiation is an established breast cancer risk factor (5). Radiation-induced breast cancer risk depends on age at exposure, radiation dose and the time since exposure. Previously we reported that women under age 40 years who received >1.0 gray (Gy) of absorbed dose to the contralateral breast during radiotherapy (RT) for a first primary breast cancer, had a significantly higher risk of developing a second primary contralateral breast cancer (CBC) (RR= 2.5, 95% CI 1.4–4.5) compared with unexposed women. Women older than 40 years at the time of RT, however, were not at increased risk (6). We also reported that parity and age at menarche, but not age at first full-term pregnancy, were risk factors for CBC (7).

During puberty and pregnancy, breast cells are rapidly dividing and may be particularly susceptible to carcinogens, including radiation. Thus, the timing of radiation exposure relative to these hormonally-related events might be important determinants of radiation-induced breast cancer risk. Exposures during puberty (8–11) and pregnancy (9, 12) have been associated with an increased risk of radiation-induced breast cancer. Previous studies have suggested that parity, age at first full-term pregnancy, number of births and breastfeeding may modify the impact of radiation exposure on breast cancer risk (9, 12–14).

The Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study is a population-based case-control study of 708 cases with asynchronous CBC and 1,399 controls with unilateral breast cancer (UBC) after comparable lengths of follow-up (15). The objective of this study is to examine whether reproductive and hormonal factors prior to, at

the time of, or subsequent to, diagnosis of a first primary breast cancer, modify the risk of radiation-induced second primary CBC.

Materials and Methods

Study Population

Subjects were identified through five population-based cancer registries: Los Angeles County Cancer Surveillance Program; Cancer Surveillance System of the Fred Hutchinson Cancer Research Center (Seattle); State Health Registry of Iowa; and the Cancer Surveillance Program of Orange County/San Diego-Imperial Organization for Cancer Control (Orange County/San Diego) and the Danish Breast Cancer Cooperative Group Registry, supplemented with data from the Danish Cancer Registry (15).

Eligible cases met the following criteria: a) diagnosed between 1/1/1985 and 12/31/2000 with UBC followed by a second *in situ* or invasive primary breast cancer in the contralateral breast, diagnosed at least 1 year later; b) resided in the same study reporting area for both diagnoses; c) no previous or intervening cancer diagnosis (except for basal or squamous cell skin cancer); d) under age 55 years at the time of diagnosis of the first primary breast cancer; e) alive and granted informed consent, completed the interview and provide a blood sample. The “at-risk” period was defined as starting one year after first diagnosis and ending at reference date: i.e., the date of second breast cancer diagnosis in cases or the corresponding date in matched controls.

WECARE Study controls met the same criteria as the cases except they had not developed a second breast cancer or undergone a prophylactic mastectomy of the contralateral breast prior to the end of the at-risk interval. Two controls were individually matched to each case on year of birth (5-year strata), year of diagnosis (4-year strata), registry region and race/ethnicity. Reproductive history was not used in defining case-control eligibility.

To improve statistical efficiency, cases and controls were counter-matched on cancer registry-recorded RT so that each triplet contained two RT-treated (exposed) women and one woman not treated with RT (unexposed). For each exposed case, one exposed and one unexposed control were selected from the relevant stratum and for each unexposed case, two exposed controls were selected. This counter-matching ensured that each triplet contributed to the analysis, avoiding the situation where all members of a matched set had the same radiation status (15).

A total of 998 women with CBC and 2,112 women with UBC were identified as being eligible for the study. Of these, 708 cases (71%) and 1,399 controls (66%) were interviewed and provided a blood sample.

Data collection

The data collection protocol was approved by the institutional review board at each of the participating centers. Each woman provided written informed consent. WECARE Study participants were interviewed by telephone using a pre-tested, structured questionnaire. Medical records, radiotherapy records, pathology reports and hospital charts were used to collect information on treatment and tumor characteristics, including tumor location in the contralateral breast.

RT details were sought from the basic RT record, RT summary, RT notes, medical record notes, surgery reports (for brachytherapy) and physician correspondence. All patients in this study were treated with conventional fields, including various combinations of tangential breast, supraclavicular, axilla, direct breast, and internal mammary chain fields. The

radiation absorbed dose to the quadrant in the contralateral breast where the second cancer arose (or to the equivalent breast location for UBC controls) was estimated for each woman. Representative irradiations in tissue-equivalent anthropomorphic phantoms were performed to estimate the dose from each type of field. These measures were used to estimate the dose to the contralateral breast received by each woman, based on the treatment fields and corresponding dose received as part of her treatment for a first breast cancer. The total dose for each woman was the sum of the contribution from each field. The mean dose to the quadrant location of the contralateral breast tumor or matching location for controls was 1.2 Gy (SD=0.7). Further details can be found in Stovall *et al* (6).

Two RT variables were created for analysis: RT (ever/never) and “RT dose”. RT (ever/never) indicates whether a woman was treated with radiation. “RT dose” is the estimated absorbed dose to the contralateral breast at the quadrant-specific location of the second breast cancer in cases or corresponding location for the matched controls. Analyses using “RT dose” were restricted to women with complete RT records, including women with no RT, and to women with known location of the second primary CBC (606 cases and 1,200 controls) (Table 1).

Statistical Analysis

The influence of reproductive and hormonal factors on radiation-induced CBC risk was assessed by exploring the relationship with RT status (ever/never and dose to the contralateral breast (0, <1Gy, 1Gy)) stratified by: menopausal status, age at menopause (premenopausal, postmenopausal and age <45 years, postmenopausal and age ≥45 years), parity (nulliparous, parous), number of full-term pregnancies (nulliparous, 1, ≥2), and history of breastfeeding (yes, no). Only full-term (third-trimester) pregnancies were included in the analysis. We also explored the influence of RT by whether a pregnancy occurred between first diagnosis and reference date (nulliparous at reference date, parous at first diagnosis but no interval pregnancy, interval pregnancy), and by time between last full-term pregnancy and first breast cancer diagnosis among those who were parous at first diagnosis but had no interval pregnancy (full-term pregnancy <5 years prior to first diagnosis, full-term pregnancy 5–<10 years prior to first diagnosis and full-term pregnancy ≥10 years prior to first diagnosis).

To assess the relationship between reproductive factors and risk of radiation-induced CBC, rate ratios (RR) and 95% confidence intervals (CI) were computed, using conditional logistic regression models, adjusting for known risk factors for breast cancer: age at (first) diagnosis, menopausal status at first diagnosis/age at menopause, age at menarche (<13, ≥13 years), number of full-term pregnancies at first diagnosis, first-degree family history of breast cancer (no, yes, adopted), histology of first primary (lobular, other), stage of first primary breast cancer (local, regional), and treatment (hormonal and/or chemotherapy: yes, no). An offset term was incorporated to account for the sampling probability of the counter-matching (15). Age- and multivariate-adjusted models are presented.

Menopausal status was estimated by comparing the date or age a woman last reported menstruating with the date of her first diagnosis of breast cancer. If a woman reported that she was still menstruating within 2 years before first diagnosis, or was pregnant, she was classified as premenopausal at that time point. A lag of two years was used to ensure minimal misclassification due to rounding errors in the self-report of age at menopause with respect to age at breast cancer diagnosis.

All statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary NC).

Results

Table 1 shows the distribution of the matching factors and selected characteristics of the WECARE Study population. Cases and controls were similar for all matching characteristics. Both had a median age at first diagnosis of 46 years and the median age at reference date was 50 years for cases and 51 years for controls. The median at-risk period length was 4 years for both cases and controls. Forty-five percent of cases and 55% of controls received chemotherapy and 28% of cases and 35% of controls received hormone therapy as part of their treatment for a first primary breast cancer.

When radiation was coded as ever/never, radiation-related CBC risk did not vary by parity, number of full-term pregnancies, history of breastfeeding and menopausal status at the time of first diagnosis (Table 2). When radiation dose (0, <1, 1 Gy) to the contralateral breast was taken into account, women who were nulliparous at the time of RT and received 1 Gy to the contralateral breast had a higher risk of CBC than unexposed nulliparous women (RR=2.2, 95% CI 1.2–4.0, $p=0.01$) (Table 3). No increase in risk was seen in similarly exposed parous women (RR=1.1, 95% CI 0.9–1.4, p for heterogeneity relative to parous women = 0.08).

Women treated with RT (ever/never) who had a full-term pregnancy between first diagnosis and reference date had a greater risk of CBC compared with unexposed women who also had a pregnancy during this time period (RR=6.0, 95% CI 1.3, 28.4, $p=0.02$) (Table 2), whereas no effect was seen in the other two groups (p for heterogeneity = 0.06). We had insufficient numbers to examine RRs by dose categories in this group of women. The 12 cases and 16 controls who had an interval pregnancy were similar with respect to median age at breast cancer diagnosis (30 years in cases, 31.5 years in controls), although cases were younger at the time of interval pregnancy (33 years for cases, 36 years for controls). This interval pregnancy was the first for 33% of cases and 29% of controls. The median number of years between initial breast cancer diagnosis and pregnancy was 2 years (range of 1–4 years) for cases and 2.5 years (range of 1–7 years) for controls, and cases with an interval pregnancy had a slightly shorter median at-risk period than controls (4 years for cases, 6 years in controls). No association was seen between time since last full-term pregnancy and radiation-induced CBC risk; again we had insufficient numbers to further stratify the interval pregnancies by time since last pregnancy.

The influence of parity at the time of first diagnosis on radiation-induced CBC risk was also examined stratified by age at first diagnosis (<45 years, ≥45 years). Nulliparous women, exposed to 1 Gy who were <45 years old at first diagnosis, had a higher risk of CBC than unexposed women (RR=2.6, 95% CI 1.4–4.9). A similar increase was not seen in women who were ≥45 years (RR=1.7, 95% CI 0.8–3.5). The results of this stratified analysis were not statistically different (p for heterogeneity=0.61). No difference was seen in parous women stratified by age at first diagnosis (results not shown).

Discussion

Women who were nulliparous at the time of diagnosis with a first primary breast cancer were at an increased risk of radiation-induced CBC. This increase appeared to be limited to women with an early age at first breast cancer diagnosis. An increased risk was not seen in RT-exposed women who were parous at first diagnosis. Associations between RT and CBC risk did not vary by menopausal status, number of pregnancies, or history of breastfeeding. Among women who had a full-term pregnancy between first diagnosis and reference date, those who were treated with RT for their first breast cancer were at a significantly higher risk of CBC compared with those who did not have RT.

The epidemiology of radiation-induced breast cancer has been largely informed by studying the Japanese atomic bomb survivors and patients exposed to diagnostic or therapeutic medical radiation. Among Japanese A-bomb survivors, parity, first full-term pregnancy at a young age, multiple births and history of breastfeeding have all been shown to be associated with a lower excess risk of breast cancer after radiation exposure (13). A recent study of Japanese atomic bomb survivors, however, found that once the baseline breast cancer risk was taken into account, radiation-induced breast cancer risk did not vary appreciably by whether exposure occurred before menarche, between menarche and first pregnancy, or after first pregnancy, i.e., radiation-associated breast cancer risk did not vary by reproductive status at the time of exposure (16).

Women exposed to diagnostic or therapeutic radiation (i.e., RT for Hodgkin lymphoma, fluoroscopic chest x-rays for monitoring lung-collapse treatment of tuberculosis, RT for acute postpartum mastitis or diagnostic x-rays for monitoring scoliosis during the growth spurt) at an early age, prior to or around the time of first menses (9–11, 17), or while pregnant (9, 12) or lactating (18), have been reported to have increased risk of radiogenic breast cancer. These time periods of high breast cell proliferation may render the breast particularly susceptible to the carcinogenic effects of radiation. Further, women treated with RT for Hodgkin lymphoma, who also received radiation to their ovaries (>5 Gy) or alkylating agents (leading to ovarian dysfunction) as part of their chemotherapy, had a lower risk of developing breast cancer compared to women who received lower RT doses to the ovaries or no alkylating agents (19). These results suggest a role for hormonal stimulation of breast cells in radiation-induced breast cancer.

In studies of predominantly ER positive breast cancers, a transient increase in risk is seen in the years directly following a pregnancy (4). It has been hypothesized that this initial increase could be due to the promotion of previously initiated cellular changes occurring in the breast. The protective effect of pregnancy observed in later years is thought to be due to tissue differentiation, which reduces susceptibility to subsequent exposures (3). The results of our analysis suggest that the nulliparous, but not the parous, breast is susceptible to the carcinogenic effect of radiation exposure experienced during treatment for a first primary breast cancer. They also suggest that women who have a full-term pregnancy after RT are at an increased risk of radiation-induced CBC. We were unable to examine the impact of interval pregnancies as to whether they were the first or a subsequent pregnancy, or the impact of pregnancies by age at diagnosis, due to small sample numbers within sub-groups of RT exposure.

The relationship between parity and breast cancer risk may vary by breast cancer molecular subtype, with a protective effect of parity seen in ER or PR positive, but not triple-negative breast cancers (2). The limited data available do not indicate heterogeneity in the relationship between radiation exposure and breast cancer risk by histological subtype or ER/PR status (20, 21). We were unable to examine the impact of tumor molecular subtype on the relationship between RT, reproductive factors and CBC risk due to small numbers and incomplete information on ER status of second primary breast cancers.

Strengths of this study include the population-based design, large study population and comprehensive questionnaire and medical record data. A further strength is the availability of detailed RT information allowing for dose estimation to the quadrant in the contralateral breast of cases where the second cancer arose. Limitations include an inability to account for tumor subtype, individual patient body shapes in dose estimation, the relatively short time interval of follow-up between first and second breast cancer diagnoses, and the small number of women treated around the time of pregnancy precluding an evaluation of this important period.

Women who were nulliparous at the time of RT for a first primary breast cancer were at an increased risk of radiation-induced CBC. An increased risk was not seen in similarly exposed parous women. Further, women who became pregnant after a first primary breast cancer diagnosis may have an increased risk of CBC, suggesting that hormonal stimulation of radiation-initiated cells may promote further changes toward malignancy. If confirmed in a larger study population, these results could have clinical implications on treatment decisions for women with breast cancer who are nulliparous, or still in their child-bearing years.

Acknowledgments

This research was funded by the National Cancer Institute: R01CA114236, and U01CA083178.

References

1. Kelsey JL, Gammon MD, John EM. Reproductive Factors and Breast Cancer. *Epidemiol Rev.* 1993; 15(1):36–47. [PubMed: 8405211]
2. Yang XR, Chang-Claude J, Goode EL, et al. Associations of Breast Cancer Risk Factors With Tumor Subtypes: A Pooled Analysis From the Breast Cancer Association Consortium Studies. *Journal of the National Cancer Institute.* 2011; 103(3):250–63. [PubMed: 21191117]
3. Russo J, Moral R, Balogh G, et al. The protective role of pregnancy in breast cancer. *Breast Cancer Res.* 2005; 7(3):131–42. [PubMed: 15987443]
4. Trichopoulos D, Hsieh C-C, MacMahon B, et al. Age at any birth and breast cancer risk. *Int J Cancer.* 1983; 31:701–4. [PubMed: 6862681]
5. Boice JD Jr. Radiation and breast carcinogenesis. *Med Pediatr Oncol.* 2001; 36:508–13. [PubMed: 11340604]
6. Stovall M, Smith SA, Langholz BM, et al. Dose to the Contralateral Breast From Radiotherapy and Risk of Second Primary Breast Cancer in the WECARE Study. *Int J Radiat Oncol Biol Phys.* 2008; 72(4):1021–30. [PubMed: 18556141]
7. Largent JA, Capanu M, Bernstein L, et al. Reproductive History and Risk of Second Primary Breast Cancer: The WECARE Study. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(5):906–11. [PubMed: 17507614]
8. McGregor D, Land C, Choi K, et al. Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950–69. *J Natl Cancer Inst.* 1977; 59(3):799–811. [PubMed: 894745]
9. Boice, JD., Jr; Stone, B. Interaction between radiation and other breast cancer risk factors. Presented at International Atomic Energy Agency; Vienna. 1978.
10. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst.* 1993; 85(1):25–31. [PubMed: 8416252]
11. Hoffman DA, Lonstein JE, Morin MM, et al. Breast cancer in women with scoliosis exposed to multiple diagnostic X rays. *J Natl Cancer Inst.* 1989; 81(17):1307–12. [PubMed: 2769783]
12. Chen J, Lee RJ, Tsodikov A, et al. Does radiotherapy around the time of pregnancy for Hodgkin's disease modify the risk of breast cancer? *Int J Radiat Oncol Biol Phys.* 2004; 58(5):1474–9. [PubMed: 15050326]
13. Land C, Hayakawa N, Machado S, et al. A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose. *Cancer Causes Control.* 1994; 5:167–76. [PubMed: 8167264]
14. Shore R, Woodward E, Hempelmann L, et al. Synergism between radiation and other risk factors for breast cancer. *Prev Med.* 1980; (9):815. [PubMed: 7454704]
15. Bernstein J, Langholz B, Haile R, et al. Study design: Evaluating gene-environment interactions in the etiology of breast cancer - the WECARE study. *Breast Cancer Res.* 2004; 6(3):R199–R214. [PubMed: 15084244]
16. McDougall JA, Sakata R, Sugiyama H, et al. Timing of menarche and first birth in relation to risk of breast cancer in A-bomb survivors. *Cancer Epidemiol Biomarkers Prev.* 2010; 19(7):1746–54. [PubMed: 20570914]

17. Ronckers CM, Doody MM, Lonstein JE, et al. Multiple diagnostic X-rays for spine deformities and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(3):605–13. [PubMed: 18349278]
18. Shore R, Hildreth N, Woodard E, et al. Breast cancer among women given X-ray therapy for acute postpartum mastitis. *J Natl Cancer Inst.* 1986; 77(33):689–96. [PubMed: 3462410]
19. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA.* 2003; 290(4):465–75. [PubMed: 12876089]
20. Huang W-Y, Newman B, Millikan RC, et al. Hormone-related Factors and Risk of Breast Cancer in Relation to Estrogen Receptor and Progesterone Receptor Status. *American Journal of Epidemiology.* 2000; 151(7):703–14. [PubMed: 10752798]
21. Neta G, Anderson W, Gilbert E, et al. Variation in the risk of radiation-related contralateral breast cancer by histology and estrogen receptor expression in SEER. *Breast Cancer Research and Treatment.* 2011 Oct 21. [Epub ahead of print].

Table 1

Characteristics of 2,107 Women with Unilateral and Contralateral Breast Cancer included in the WECARE Study

	CBC Cases (n=708)	UBC Controls (n=1,399)
<i>Race (N and %)*</i>		
Non-Hispanic white	649 (92%)	1288 (92%)
Hispanic white	24 (3%)	48 (3%)
Black	21 (3%)	39 (3%)
Asian (Chinese, Japanese, Filipino and other Asian)	13 (2%)	22 (2%)
<i>Diagnosis year of first breast cancer (N and %)</i>		
1985–1988	238 (34%)	467 (33%)
1989–1992	241 (34%)	478 (34%)
1993–1996	183 (26%)	362 (26%)
After 1997	46 (7%)	92 (7%)
Subject's age (years) at first breast cancer diagnosis (<i>median and range</i>)	46 (24, 55)	46 (23, 55)
Age (years) at reference date (<i>median and range</i>) [†]	50 (27, 71)	51 (27, 69)
At-risk period (years) (<i>median and range</i>) [‡]	4 (1, 16)	4 (1, 16)
RADIATION TREATMENT		
<i>Radiation treatment (N and %)[§]</i>		
No	362 (51%)	266 (19.0)
Yes	346 (49%)	1133 (81%)
<i>Radiation dose to the contralateral breast (N and %)</i>		
0 Gy	297 (49%)	232 (19%)
<1 Gy	169 (28%)	536 (45%)
1 Gy	140 (23%)	432 (36%)
OTHER TREATMENTS		
<i>Surgery (N and %)^{††}</i>		
Modified radical mastectomy	349 (49%)	398 (28%)
Radical mastectomy	44 (6%)	58 (4%)
Simple mastectomy	18 (3%)	19 (1%)
Lumpectomy and axillary node dissection	224 (32%)	757 (54%)
Lumpectomy	83 (12%)	182 (13%)
Axillary node dissection	6 (1%)	35 (3%)
Other	40 (6%)	97 (7%)
<i>Chemotherapy (N and %)</i>		
No	386 (55%)	629 (45%)
Yes	322 (46%)	770 (55%)
<i>Hormonal therapy (N and %)*</i>		
No	511 (72%)	909 (65%)
Yes	197 (28%)	488 (35%)
OTHER CHARACTERISTICS		

	CBC Cases (n=708)	UBC Controls (n=1,399)
<i>First-degree family history of breast cancer (N and %)</i>		
Adopted or family history unknown	11 (1%)	26 (2%)
No	472 (67%)	1088 (78%)
Yes	225 (32%)	285 (20%)
<i>ER status of first breast cancer (N and %)[¶]</i>		
Positive	338 (48%)	746 (53%)
Negative	193 (27%)	338 (24%)
Other	69 (10%)	155 (11%)
Unknown	108 (15%)	160 (11%)
<i>PR status of first breast cancer (N and %)[¶]</i>		
Positive	287 (41%)	616 (44%)
Negative	172 (24%)	318 (23%)
Other	75 (11%)	175 (13%)
Unknown	174 (25%)	290 (21%)
<i>Histology of first breast cancer (N and %)</i>		
Ductal and other	585 (82%)	1217 (87%)
Lobular	90 (13%)	131 (9%)
Medullary	33 (5%)	51 (4%)
<i>Stage of first breast cancer (N and %)</i>		
Localized	506 (71%)	916 (65%)
Regional	202 (29%)	483 (35%)

Abbreviations: CBC=asynchronous contralateral breast cancer; UBC=unilateral breast cancer only; Gy=gray; ER=estrogen receptor; PR=progesterone receptor; RT=radiotherapy

* Numbers of cases and controls due not sum to the totals due to missing data.

[†] Reference date is date of contralateral breast cancer diagnosis for cases and corresponding date for controls.

[‡] Beginning one year after first diagnosis extending to reference date (date of second diagnosis in cases).

[§] Because of counter-matching the proportion of controls undergoing RT is determined by the RT status of the matched case. See Methods section for a detailed explanation. Women received some combination of external beam radiation with or without brachytherapy. Few women underwent brachytherapy; 18 cases and 83 controls received both external beam radiation and brachytherapy and no women received brachytherapy alone.

[¶] The number of women who received RT (346 cases and 1,133 controls) and those with RT dose estimates (606 cases and 1,200 controls) differ because dose estimates include many unexposed women with a zero dose to the contralateral breast. A small number of women (n=11) did not receive breast radiation (i.e., coded as RT never) but have a location specific dose because they underwent RT as a secondary treatment (e.g., for metastases, pelvic radiation). To estimate the location specific dose, both detailed RT records and the location of the second primary breast cancer in the contralateral breast of cases was needed (available for 606 cases and 1,200 controls).

^{††} Percentages sum to more than 100% because women were asked to list all surgeries included as part of their treatment for a first primary breast cancer; thus these surgeries were not mutually exclusive.

^{¶¶} Refers to receptor status of the first primary breast cancer. The 'Other' category consists of women where no lab test was given, the test was given and the results are unknown or the test was given and the results were borderline

Reproductive and hormonal status at first diagnosis, radiation therapy (ever/never) and risk of radiation-induced CBC in the WECARE Study population

Table 2

		Cases (CBC) N=708		Controls (UBC) N=1,399		Age-Adjusted		Multivariate Adjusted ^f	
Radiation Therapy		N	%	N	%	RR ^b	95% CI	RR ^c	95% CI
Menopausal status/age at menopause*									
Premenopausal	Never	268	51.1	195	18.6	1.0		1.0	
	Ever	256	48.9	852	81.4	1.0	0.8–1.3	1.0	0.8–1.3
Postmenopausal age < 45 years									
Never	48	51.6	45	22.1	1.0			1.0	
Ever	45	48.4	159	77.9	1.4	0.8–2.3	1.3		0.8–2.3
Postmenopausal age ≥ 45 years									
Never	45	50.0	24	16.9	1.0			1.0	
Ever	45	50.0	118	83.1	0.9	0.5–1.7	0.9		0.5–1.7
Parity at first diagnosis*									
Nulliparous	Never	66	48.2	49	21.3	1.0		1.0	
	Ever	71	51.8	181	78.7	1.2	0.7–1.9	1.3	0.8–2.0
Parous									
Never	296	51.8	217	18.6	1.0			1.0	
Ever	275	48.2	950	81.4	1.1	0.9–1.3	1.0		0.9–1.3
Number of full-term pregnancies at first diagnosis*									
1	Never	55	43.7	37	18.0	1.0		1.0	
	Ever	71	56.3	169	82.0	1.4	0.9–2.3	1.4	0.8–2.4
2									
Never	241	54.2	180	18.7	1.0			1.0	
Ever	204	45.8	781	81.3	1.0	0.8–1.2	0.9		0.7–1.2
History of breast-feeding at first diagnosis*									
Never	Never	100	49.5	65	17.1	1.0		1.0	
	Ever	102	50.5	316	82.9	1.2	0.8–1.7	1.1	0.8–1.6
Ever									
Never	196	53.1	152	19.3	1.0			1.0	
Ever	173	46.9	634	80.7	1.0	0.8–1.3	1.0		0.8–1.3

Radiation Therapy		Cases (CBC) N=708		Controls (UBC) N=1,399		Age-Adjusted		Multivariate Adjusted [†]	
		N	%	N	%	RR ^b	95% CI	RR ^c	95% CI
Full-term pregnancy between first diagnosis and reference date [*]									
Nulliparous at reference date	Never	63	47.4	47	20.8	1.0		1.0	
	Ever	70	52.6	179	79.2	1.2	0.8–2.0	1.2	0.8–2.0
Parous at first diagnosis but no interval pregnancy	Never	295	52.4	212	18.4	1.0		1.0	
	Ever	268	47.6	943	81.6	1.0	0.8–1.3	1.0	0.8–1.2
Interval pregnancy	Never	4	33.3	7	43.8	1.0		1.0	
	Ever	8	66.7	9	56.3	4.9	1.0–23.1	6.0	1.3–28.4
Time from last full-term pregnancy to first diagnosis ^{**‡}									
<5 years before first diagnosis	Never	20	42.6	12	16.2	1.0		1.0	
	Ever	27	57.4	62	83.8	1.2	0.5–2.8	1.3	0.5–3.3
5–<10 years before first diagnosis	Never	31	59.6	30	21.1	1.0		1.0	
	Ever	21	40.4	112	78.9	0.8	0.4–1.7	0.8	0.4–1.7
10 years before first diagnosis	Never	244	52.6	170	18.1	1.0		1.0	
	Ever	220	47.4	769	81.9	1.0	0.8–1.3	1.0	0.8–1.3

Abbreviations: CBC=asynchronous contralateral breast cancer; UBC=unilateral breast cancer; RR=rate ratio; CI=confidence interval

^{*} Numbers of cases and controls due not sum to the totals due to missing data. all pregnancies are full-term (defined as a third trimester pregnancy).

[†] Adjusted for age at first diagnosis, menopausal status, number of pregnancies, histology, age at menarche, family history, stage, and chemotherapy/hormonal treatment.

[‡] Among women who were parous at first diagnosis but had no interval pregnancy

Reproductive and hormonal status at first diagnosis, radiation dose to the contralateral breast and risk of radiation-induced CBC in the WECARE Study population

Table 3

	Radiation Dose	Cases (CBC) N=606		Controls (UBC) N=1,200		Age-adjusted		Multivariate Adjusted ^a	
		N	%	N	%	RR ^b	95% CI	RR ^c	95% CI
Menopausal status/age at menopause [*]									
Premenopausal	0 Gy	221	49.8	166	18.4	1.0		1.0	
	<1 Gy	121	27.3	417	46.2	1.0	0.8–1.3	1.0	0.8–1.3
	1 Gy	102	23.0	319	35.4	1.1	0.8–1.6	1.1	0.8–1.6
Postmenopausal age <45 years	0 Gy	42	48.8	41	23.8	1.0		1.0	
	<1 Gy	24	27.9	65	37.8	1.9	1.0–3.6	1.9	1.0–3.7
	1 Gy	20	23.3	66	38.4	1.5	0.8–3.1	1.6	0.8–3.3
Postmenopausal age ≥45 years	0 Gy	34	44.7	23	18.9	1.0		1.0	
	<1 Gy	24	31.6	54	44.3	1.3	0.6–2.7	1.3	0.6–2.7
	1 Gy	18	23.7	45	36.9	1.1	0.5–2.5	1.0	0.5–2.3
Parity at first diagnosis [*]									
Nulliparous	0 Gy	55	47.4	42	21.3	1.0		1.0	
	<1 Gy	27	23.3	93	47.2	1.0	0.5–1.7	1.0	0.5–1.8
	1 Gy	34	29.3	62	31.5	2.0	1.1–3.6	2.2	1.2–4.0
Parous	0 Gy	242	49.4	190	19.0	1.0		1.0	
	<1 Gy	142	29.0	442	44.2	1.2	0.9–1.6	1.2	0.9–1.5
	1 Gy	106	21.6	369	36.9	1.1	0.8–1.5	1.1	0.8–1.4
Number of full-term pregnancies at first diagnosis [*]									
1	0 Gy	44	40.4	32	18.3	1.0		1.0	
	<1 Gy	38	34.9	75	42.9	1.8	1.0–3.3	1.9	1.0–3.6
	1 Gy	27	24.8	68	38.9	1.5	0.8–2.9	1.4	0.7–2.8
2	0 Gy	198	52.0	158	19.1	1.0		1.0	
	<1 Gy	104	27.3	367	44.4	1.1	0.8–1.5	1.1	0.8–1.4

	Radiation Dose	Cases (CBC) N=606		Controls (UBC) N=1,200		Age-adjusted		Multivariate Adjusted [†]	
		N	%	N	%	RR ^b	95% CI	RR ^c	95% CI
History of breast-feeding at first diagnosis [*]	1 Gy	79	20.7	301	36.4	1.0	0.7–1.4	1.0	0.7–1.4
	0 Gy	153	48.9	134	19.7	1.0		1.0	
	<1 Gy	95	30.4	305	44.8	1.2	0.9–1.7	1.2	0.8–1.6
	1 Gy	65	20.8	242	35.5	1.1	0.8–1.6	1.1	0.8–1.6
	0 Gy	89	50.3	56	17.5	1.0		1.0	
	<1 Gy	47	26.6	137	42.8	1.2	0.8–2.0	1.2	0.8–2.0
	1 Gy	41	23.2	127	39.7	1.0	0.6–1.7	0.9	0.6–1.6
	Full-term pregnancy between first diagnosis and reference date [*]								
	0 Gy	54	47.4	41	21.0	1.0		1.0	
	<1 Gy	27	23.7	93	47.7	1.0	0.5–1.8	1.0	0.5–1.8
Time from last full-term pregnancy to first diagnosis ^{**†}	1 Gy	33	28.9	61	31.3	2.0	1.1–3.7	2.2	1.2–4.0
	0 Gy	241	49.9	185	18.7	1.0		1.0	
	<1 Gy	139	28.8	437	44.1	1.2	0.9–1.5	1.1	0.9–1.5
	1 Gy	103	21.3	369	37.2	1.0	0.8–1.4	1.0	0.7–1.4
	0 Gy	2	22.2	6	50.0	1.0		1.0	
	<1 Gy	3	33.3	5	41.7	6.3	0.7–59.4	5.4	0.6–50.7
	1 Gy	4	44.4	1	8.3	no est.	no est.	no est.	no est.
	Time from last full-term pregnancy to first diagnosis ^{**†}								
	0 Gy	15	38.5	8	12.5	1.0		1.0	
	<1 Gy	13	33.3	39	60.9	0.7	0.2–2.1	0.9	0.3–2.7
5–<10 years before first diagnosis	1 Gy	11	28.2	17	26.6	1.3	0.4–4.4	1.5	0.4–5.1
	0 Gy	23	52.3	25	22.1	1.0		1.0	
	<1 Gy	13	29.5	50	44.2	1.0	0.4–2.4	0.8	0.3–2.1
1 Gy	8	18.2	38	33.6	1.4	0.5–3.8	1.4	0.5–3.8	

	Radiation Dose	Cases (CBC) N=606		Controls (UBC) N=1,200		Age-adjusted		Multivariate Adjusted [†]	
		N	%	N	%	RR ^b	95% CI	RR ^c	95% CI
10 years before first diagnosis	0 Gy	203	50.8	152	18.7	1.0		1.0	
	<1 Gy	113	28.3	348	42.8	1.2	0.9–1.6	1.2	0.9–1.6
	1 Gy	84	21.0	314	38.6	1.0	0.7–1.3	0.9	0.7–1.3

Abbreviations: CBC=asynchronous contralateral breast cancer; UBC=unilateral breast cancer; RR=rate ratio; CI=confidence interval; Gy=gray

* Numbers of cases and controls due not sum to the totals due to missing data, all pregnancies are full-term (defined as a third trimester pregnancy).

[†] Adjusted for age at first diagnosis, menopausal status, number of pregnancies, histology, age at menarche, family history, stage, and chemotherapy/hormonal treatment.

[‡] Among women who were parous at first diagnosis but had no interval pregnancy