Published in final edited form as:

Eur J Cancer. 2013 September ; 49(14): 2979–2985. doi:10.1016/j.ejca.2013.04.028.

Contralateral Breast Cancer after Radiotherapy among BRCA1 and BRCA2 Mutation Carriers: A WECARE Study Report

Jonine L. Bernstein¹, Duncan C. Thomas², Roy E. Shore³, Mark Robson⁴, John D. Boice Jr.⁵, Marilyn Stovall⁶, Michael Andersson⁷, Leslie Bernstein⁸, Kathleen E. Malone⁹, Anne S. Reiner¹, Charles F. Lynch¹⁰, Marinela Capanu¹, Susan A. Smith⁶, Lina Tellhed¹¹, Sharon N. Teraoka¹², Colin B. Begg¹, Jorgen H. Olsen¹³, Lene Mellemkjaer¹³, Xiaolin Liang¹, Anh T. Diep², The WECARE Study Collaborative Group, Ake Borg¹¹, Patrick Concannon¹², and Robert W. Haile²

¹Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York ²Department of Preventive Medicine, University of Southern California, Los Angeles, California ³Department of Environmental Medicine, New York University, New York, New York, and Radiation Effects Research Foundation, Hiroshima, Japan ⁴Department of Clinical Genetics, Memorial Sloan-Kettering Cancer Center, New York, New York ⁵Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee and National Council on Radiation Protection and Measurements, Bethesda, Maryland ⁶Department of Radiation Physics, University of Texas M.D. Anderson Cancer Center, Houston, Texas ⁷Department of Oncology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark ⁸Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, California ⁹Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington ¹⁰Department of Epidemiology, University of Iowa, Iowa City, Iowa ¹¹Department of Oncology, Clinical Sciences, Lund University, Sweden ¹²Department of Biochemistry and Molecular Genetics and Center for Public Health Genomics, University of Virginia, Charlottesville, Virginia ¹³Danish Cancer Society Research Center, Copenhagen, Denmark

Abstract

BACKGROUND—Women with germline *BRCA1* or *BRCA2* (*BRCA1/BRCA2*) mutations are at very high risk of developing breast cancer, including asynchronous contralateral breast cancer (CBC). *BRCA1/BRCA2* genes help maintain genome stability and assist in DNA repair. We examined whether the risk of CBC associated with radiation treatment was higher among women with germline *BRCA1/BRCA2* mutations than among non-carriers.

METHODS—A population-based, nested case-control study was conducted within a cohort of 52,536 survivors of unilateral breast cancer (UBC). Cases were 603 women with CBC and controls were 1199 women with UBC individually matched on age at diagnosis, race, year of first diagnosis and cancer registry. All women were tested for *BRCA1* and *BRCA2* mutations. Radiation absorbed dose from the initial radiotherapy (RT) to the CBC location within the contralateral breast was reconstructed from measurements in a tissue-equivalent phantom and details available in the therapy records.

FINDINGS—Among women treated with radiation, the mean radiation dose was 1.1 Gy (range=0.02-6.2 Gy). Risk of developing CBC was elevated among women who carried a

deleterious *BRCA1/BRCA2* mutation (rate ratio, RR=4.5, confidence interval, CI=3.0-6.8), and also among those treated with RT (RR=1.2, CI=1.0-1.6). However, among mutation carriers, an incremental increase in risk associated with radiation dose was not statistically significant.

INTERPRETATION—Multiplicative interaction of RT with mutation status would be reflected by a larger association of RT with CBC among carriers than among non-carriers, but this was not apparent. Accordingly, there was no clear indication that carriers of deleterious *BRCA/BRCA2* mutations were more susceptible to the carcinogenic effects of radiation than non-carriers. These findings are reassuring and have important clinical implications for treatment decisions and the clinical management of patients harboring deleterious *BRCA1/BRCA2* mutations.

FUNDING—All work associated with this study was supported by the U.S. National Cancer Institute [R01CA097397, U01CA083178].

Keywords

Contralateral Breast Cancer; Radiotherapy; *BRCA1/BRCA2*

BACKGROUND

Adjuvant radiation therapy (RT) for breast cancer reduces ipsilateral recurrence and improves survival (1-3). RT is effective, in part, because it generates a wide spectrum of damage to DNA in tumor cells, including DNA double-strand breaks (4, 5). The *BRCA1* and *BRCA2* gene products are integrally involved in the normal cellular response to DNA damage, particularly double strand breaks, and deficiencies in this response can predispose to cancer (6, 7). Among *BRCA/BRCA2* gene mutation carriers, estimates of lifetime risk of developing a first primary breast cancer range from 26%-84% (8-10) and about 22%-60% for developing asynchronous CBC (9, 11-15). During adjuvant RT, the contralateral breast is exposed to radiation at doses that may induce breast cancer in women treated at a young age (16, 17). It is plausible that women who carry *BRCA1/BRCA2* mutations may be especially susceptible to radiation-induced CBC due to deficient or error-prone repair of radiation-induced DNA lesions. If true, alternatives to treatment and diagnostic strategies involving radiation in *BRCA1/BRCA2* carriers might be considered.

Previously we reported that CBC was positively associated with dose of radiation received by the contralateral breast and inversely related to age at radiation treatment (18) and that carriers of deleterious *BRCA1/BRCA2* mutations had a high absolute risk of CBC (9). In this study of CBC, we examine whether the relative risk of developing CBC associated with RT is significantly greater for deleterious *BRCA1/BRCA2* mutation carriers than for non-carriers.

METHODS

Study Population

The WECARE Study is a multi-center, population-based, nested case-control study selected from a cohort of 52,536 women with histologically confirmed invasive breast cancer (19). The study includes 705 women with CBC (cases) and 1,398 women with unilateral breast cancer (UBC, controls), all of whom were ascertained through five population-based cancer registries covering the country of Denmark, the state of Iowa, Los Angeles County and the Orange County-San Diego regions of California, and three western Washington counties in the United States (all of the US registries participate in the Surveillance, Epidemiology, and End Results [SEER] registry system).

All cases and controls were diagnosed before age 55 years from 1985 to 2000 with a first primary invasive breast cancer that had not spread beyond regional lymph nodes. Cases were diagnosed with a second primary invasive or *in situ* CBC at least 1 year after first primary diagnosis from 1986 to 2001. Two controls were individually matched to each case on birth year (within 5-year strata), year of first primary diagnosis (within 4-year strata), registry, and race/ethnicity and were required to have an intact contralateral breast. Cases and controls were counter-matched on registry-reported radiotherapy so that each triplet included one radiation-unexposed woman and two radiation treated women (for 12 cases with one control identified, matched pairs included one radiation exposed and one unexposed woman), as described previously (19). Each control's at-risk period was the same length as the interval between her matched case's first and second cancer diagnoses. This at-risk period began on the control's date of diagnosis and ended on the reference date reflecting the end of her at-risk period. Cases and controls were required to have had no other prior/intervening cancers, to have resided in a registry catchment area at the initial diagnosis and at the CBC diagnosis/reference date, and to provide a blood sample. The study protocol was approved by the institutional review boards at each US site and by the ethical committee system in Denmark. Written informed consent was obtained from all participants.

Data Sources

A detailed questionnaire was administered during a telephone interview to each eligible participant and a blood sample was collected during an in-home visit. Treatment history and tumor characteristics were ascertained through a review of medical records, pathology reports, and radiation records. For each patient who received RT as treatment for the first primary breast cancer, estimated absorbed radiation doses to each of the four quadrants and the nipple area of the contralateral breast were reconstructed for each treatment regimen using tissue-equivalent phantoms and modeling procedures. Measurements were made on an average size female phantom with medium breasts, using orthovoltage, cobalt-60 and megavoltage (6 MV) energies. Phantoms contained lithium fluoride powder, that was calibrated and standardized using output of a cobalt-60 unit in the Accredited Dosimetry Calibration Laboratory located at MD Anderson Cancer Center, which is certified by the National Institute of Standards and Technology (19, 20). Individual dose estimates were based on each patient's tumor dose, field configurations, and energy of photon and/or electron radiation beams; these details were available for 96% of cases and 95% of controls.

Dose estimates were performed by staff who were blinded as to case-control status (19, 20). For the cases included in this study, the location of the contralateral breast tumor was known, permitting dose to be estimated for that breast location for exposed cases and matched controls (18). The average specific dose to each quadrant of the breast was used for analyses because quadrant was the most specific location available for the majority of the cases. Using average quadrant dose to represent the dose to the tumor could result in uncertainty as great as a factor of 3 for the medial quadrants where the dose gradient is large. **Laboratory Methodology.** Coding and flanking intronic regions of *BRCA1* and *BRCA2* were screened for DNA variants by denaturing high-performance liquid chromatography as previously described (9). Data analyses focused exclusively on sequence variants known to have a deleterious effect including changes known or predicted to truncate the protein, splice site mutations located within 2 base pairs of an intron/exon boundary or shown to result in aberrant splicing, and missense changes definitively demonstrated to have a deleterious effect on function. Our mutation classification strategy followed current clinical care standards and Breast Cancer Information Core (BIC) classifications (<http://research.nhgri.nih.gov/projects/bic/>).

Statistical Methodology

Of the 708 cases and 1399 controls(2107), 3 cases and 1 control were not tested for *BRCA1* or *BRCA2* mutations, 4 cases and 4 controls were missing dose, and 102 cases were missing location of the contralateral breast tumor. Therefore there were 603 cases and 1199 matched controls for whom information on RT and location of case's contralateral breast tumor were known and who had *BRCA1/BRCA2* mutation carrier status determined. Multivariable-adjusted rate ratios (RRs) with corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression modeling techniques with an "offset" term to account for the counter-matched design (19). Models were adjusted for factors that were significantly associated with CBC in univariate models, including age at first diagnosis, age at menarche, number of full-term pregnancies, age at menopause, breast cancer family history in a first-degree relative, treatment (chemotherapy and hormonal therapy), histology, and stage of the first primary. RRs assessing the effect of radiation dose were calculated by comparing, within each triplet, the dose received to the case's specific CBC location and the dose received at the same breast location for her matched controls (21). An indicator was included if covariate data were missing (22). The RRs shown in Table 2 are genotype-specific radiation effects (i.e., the RT effect within *BRCA1/BRCA2* mutation carrier/non-carrier). The inclusion of interaction terms between RT dose (or ever/never received radiation) and *BRCA1/BRCA2* indicator variables permits investigation of potential effect modification by mutation carrier status. Presence of a multiplicative interaction of RT with mutation status would be reflected by a larger association of RT with CBC among carriers than among non-carriers. Heterogeneity in the RT effect across carriers and non-carriers was evaluated using a likelihood ratio test comparing models that included main effects for *BRCA1* and/or *BRCA2* carrier status and RT dose (or ever/never) only and models that contained those effects plus their interaction terms.

All analyses were conducted using SAS TPREG (SAS Institute, Cary, NC).

Role of the Funding Source

The data collection, analysis and interpretation of the data presented, and writing of the manuscript was supported through grants awarded from the National Cancer Institute, which had no role in any of these activities. The decision to submit the work for publication was made jointly with all of the named authors; the final decision to submit was the responsibility of Dr. Jonine Bernstein who had full access to all of the data.

RESULTS

We identified 96 carriers (57 *BRCA1*, 39 *BRCA2*) of deleterious germline mutations among the 603 cases (15.9%), and 62 carriers (37 *BRCA1*, 25 *BRCA2*) among the 1399 controls (4.4%) (Table 1). Among women who received RT, the mean radiation dose was 1.1 Gy (range 0.02-6.2 Gy); the risk among those exposed to more than 1Gy was slightly elevated (RR=1.2, 95% CI=1.0-1.6).. The risk of developing CBC was four and one half-fold greater among carriers of either a *BRCA1* or *BRCA2* deleterious mutation than among non-carriers (RR=4.5, 95% CI=3.0-6.8). The prevalence of carriers was similar in controls who did versus did not receive radiation: 5.5% (53/961) versus 3.8% (9/238). In cases, the corresponding carrier frequency was modestly higher among those receiving radiation: 18.5% (56/302) versus 13.3% (40/301). The multiplicative effect of radiation in carriers was not statistically significantly elevated (RR=1.4, CI=0.6-3.3) (Table 2). Although larger in *BRCA2* than *BRCA1* carriers, this difference was also not statistically significant. The departure from an additive model was even larger, but still not statistically significant (both interaction $\chi^2 < 1$). When this analysis was examined by the dosage of radiation received, no trend was observed. Although limited by statistical power, when dose of radiation

received and *BRCA1/BRCA2* carrier status were examined by age at diagnosis of first breast cancer and time since first breast cancer, no meaningful trends were observed in the carriers (data not shown).

INTERPRETATION

This is the first population-based study designed specifically to evaluate the joint effects of *BRCA1/BRCA2* mutations, radiation exposure, and CBC risk. Breast location-specific estimates of absorbed radiation dose were utilized for evaluation of dose-response. We found that carriers of deleterious *BRCA1/BRCA2* mutations had a 4-fold greater risk of CBC than non-carriers. However, mutation carriers who were exposed to radiation from RT for primary invasive breast cancer were not at significantly higher relative risk of CBC than unexposed carriers and there was little evidence of a dose-response relationship.

Given the known roles of the breast cancer susceptibility genes *BRCA1* and *BRCA2* in biochemical pathways involved in DNA damage responses, it is frequently suggested that carriers of such mutations might be radiosensitive. If true, then among radiation-exposed women, such sensitivity could result in an even greater increased risk of breast cancer. However, the data addressing this issue at either the cellular or population levels are limited and conflicting. Nieuwenhuis et al. (23) reported no difference in the repair of DNA double strand breaks in a blind comparison of irradiated lymphocytes or fibroblasts derived from carriers or healthy controls. Micronucleus tests do reveal increased mutagen sensitivity in lymphocytes from *BRCA1* carriers relative to cells from healthy controls (24). However, when the micronucleus test was applied to irradiated cells derived from *BRCA1/BRCA2* carriers with breast cancer, non-carriers with breast cancer, healthy *BRCA1/BRCA2* carriers, and healthy non-carriers, no significant differences were observed in the radiosensitivity of cells from breast cancer patients when comparing carriers to non-carriers or among healthy controls for the same comparison (25).

Our study provides additional insights into the findings of the few published studies that have examined risk of CBC associated with RT among *BRCA1/BRCA2* carriers (12, 26-30). The multi-center follow-up study of breast cancer patients attending high risk clinics conducted by Pierce and colleagues (28, 31) compared patients treated with breast-conserving surgery and RT. All 655 *BRCA1/BRCA2* mutation carriers were followed for 15 years, and over 40% developed CBC; however, there was no statistically significant difference by use of RT indicating no additional risk from scatter RT at 10 and 15 years. Their finding of an increased risk of CBC among carriers is also consistent with ours. In a case-only study, Broeks et al. examined 247 CBC cases to identify carriers of a germline mutation in *ATM*, *BRCA1/BRCA2*, or *CHEK2* (26) and found an interaction of RT with carriers of these mutations. However, this study only examined risk by aggregating genes and the extent of interaction attributable to *BRCA1/BRCA2* carrier status was not reported.

Previous studies have also examined whether mammography-associated radiation was related to an increased risk of breast cancer (32-37). In contrast to the doses of radiation delivered to the contralateral breast during RT, the average radiation dose received during a mammogram (average 0.01 Gy) is lower by more than two orders of magnitude (2). As women with hereditary risk of breast cancer often begin annual mammographic screening at young ages, their risk of developing radiation-induced breast cancer could be increased as a result of this early exposure to radiation (2, 33). This risk might be further increased if mutation carriers are more sensitive to radiation carcinogenesis than the general population, providing the radiation dose received from mammography is sufficient to modify risk, such as that suggested by previous experimental studies (37). Two studies, Narod et al. (36) and Goldfrank et al., (34) examined whether breast cancer risk was associated with

mammography among *BRCA1/BRCA2* carriers; neither found a significant association. On the other hand, Andrieu et al. (32) observed an increase in breast cancer risk associated with self-reported numbers of chest x-rays in a retrospective cohort of *BRCA1/BRCA2* carriers recruited to the International *BRCA1/BRCA2* Carrier Cohort Study. Although their study provided no dose estimates and latency could not be established, the total radiation dose was estimated to be less than 20 mGy. Most recently, Pijpe et al. reported findings from the retrospective Gene-Rad-Risk Study, a large clinical cohort study of *BRCA1/BRCA2* conducted in France, the Netherlands and the UK (38) which demonstrated that carriers of *BRCA1/BRCA2* mutations exposed to diagnostic radiation before age 30 had an increased risk of breast cancer. However, the estimates for screening mammography alone (either defined as ever/never or as total number) were not statistically significant. Our findings of no significantly increased risk from considerably higher radiation doses (in our study, mean 1.1Gy) among *BRCA1/BRCA2* mutation carriers, suggests that exposure to such low doses as from mammography is unlikely to increase risk of radiation-induced breast cancer among carriers to a greater degree than among non-carriers.

Along with the many strengths of this unique, large-scale epidemiologic study, there are some important limitations to consider. A major strength of our study is the large, well-characterized, population-based sample of long-term breast cancer survivors with individual location-specific radiation dose estimates. Nonetheless, the number of carriers identified was somewhat limited, resulting in relatively wide confidence intervals that reflect the uncertainty in the risk estimates. The quadrant-specific dose estimates calculated for each woman individually in this study are a significant improvement over prior studies without such specificity; however, some uncertainty remains in these estimates, especially within the inner quadrants, due to occasional incomplete or imprecise information on tumor-location (20). Further, while our genotyping strategy allowed us to identify a wide range of deleterious *BRCA1/BRCA2* mutations, we recognize that large genomic deletions or duplications would be missed. Lastly, we used the published BIC classifications to classify deleterious mutations. However, if unclassified variants of unknown clinical significance in these genes (39-41) are associated with radiation-induced CBC, we may have underestimated the association.

In conclusion, the baseline risk of developing CBC among *BRCA1/BRCA2* mutation carriers is large and we did not find that carriers are proportionally more susceptible than non-carriers to the carcinogenic effects of radiation received to the contralateral breast during treatment for the first invasive breast cancer. Further, there was little evidence for a dose-response relationship between CBC risk and radiation dose among mutation carriers. At face value these results suggest that, in view of the known benefits of RT for primary breast cancer, RT remains an appropriate option for carriers of *BRCA1/BRCA2* mutations. We did not directly investigate the cumulative effect of very low dose radiation from mammography, which for some women—particularly *BRCA1/BRCA2* carriers—might begin at ages much earlier than the age at treatment for most of our radiotherapy patients. Nevertheless, our results showing little or no increased risk of CBC for an exposure of substantially greater magnitude, suggest that low-dose x-ray mammograms are unlikely to disproportionately increase CBC risk in carriers compared with non-carriers.

Acknowledgments

SOURCE OF FUNDING This work was supported by the National Cancer Institute, grants number R01CA097397 and U01CA083178.

Appendix

WECARE Study Collaborative Group Memorial Sloan Kettering Cancer Center (New York, NY): Jonine L. Bernstein Ph.D. (WECARE Study P.I.), Colin B. Begg. Ph.D., Marinela Capanu Ph.D., Xiaolin Liang M.D., Anne S. Reiner M.P.H., Tracy M. Layne M.P.H.

City of Hope (Duarte, CA) (some work performed at University of Southern California, Los Angeles CA): Leslie Bernstein Ph.D., Laura Donnelly-Allen

Danish Cancer Society (Copenhagen, Denmark): Jørgen H. Olsen M.D., D.M.Sc., Michael Andersson M.D., D.M.Sc., Lisbeth Bertelsen M.D., Ph.D., Per Guldberg Ph.D., Lene Mellemkjær Ph.D

Fred Hutchinson Cancer Research Center (Seattle, WA): Kathleen E. Malone Ph.D.

International Epidemiology Institute (Rockville, MD) and Vanderbilt University (Nashville, TN): John D. Boice Jr. Sc.D.

Lund University (Lund, Sweden): Åke Borg Ph.D., Therese Törngren M.Sc., Lina Tellhed, B.Sc.

National Cancer Institute (Bethesda, MD): Daniela Seminara Ph.D. M.P.H

New York University (New York, NY): Roy E. Shore Ph.D., Dr.PH.

Norwegian Radium Hospital (Oslo, Norway): Laila Jansen, Anne-Lise Børresen-Dale Ph.D. (also University of Oslo, Norway)

University of California at Irvine (Irvine, CA): Hoda Anton-Culver, Ph.D., Joan Largent Ph.D. M.P.H.

University of Iowa (Iowa City, IA): Charles F. Lynch M.D., Ph.D., Jeanne DeWall M.A.

University of Southern California (Los Angeles, CA): Robert W. Haile DrPH., Graham Casey, Ph.D., Bryan Langholz Ph.D., Duncan C. Thomas Ph.D., Nianmin Zhou, M.D, Anh T. Diep, Evgenia Ter-Karapetova

University of Southern Maine (Portland, ME):W. Douglas Thompson Ph.D.

University of Texas, M.D. Anderson Cancer Center (Houston, TX): Marilyn Stovall Ph.D., Susan Smith M.P.H.

University of Virginia (Charlottesville, VA) (some work performed at Benaroya Research Institute, Seattle WA): Patrick Concannon, Ph.D., Sharon N.Teraoka, Ph.D., Eric R. Olson, Nirasha Ramchurren, Ph.D.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest: None.

Disclaimers: None

CONFLICTS OF INTEREST None of the authors declare a financial or personal conflict of interest.

AUTHORS CONTRIBUTIONS Conception and Design. Jonine L. Bernstein, Duncan C. Thomas, Roy E. Shore, Mark Robson, John D. Boice, Marilyn Stovall, Michael Andersson, Leslie Bernstein, Kathleen E. Malone, Charles F. Lynch, Colin B. Begg, Jorgen H. Olsen, Lene Mellemkjaer, Ake Borg, Patrick Concannon, Robert W. Haile

Collection and Assembly of Data and Patients. Jonine L. Bernstein, Marilyn Stovall, Michael Andersson, Leslie Bernstein, Kathleen E. Malone, Charles F. Lynch, Susan A. Smith, Lina Tellhed, Sharon N. Teraoka, Jorgen H. Olsen, Lene Mellemkjaer, Xiaolin Liang, Anh T. Diep, Ake Borg, Patrick Concannon, Robert W. Haile

Data analysis and Interpretation. Jonine L. Bernstein, Duncan C. Thomas, Roy E. Shore, Mark Robson, John D. Boice, Marilyn Stovall, Michael Andersson, Leslie Bernstein, Kathleen E. Malone, Anne S. Reiner, Charles F. Lynch, Marinela Capanu, Sharon N. Teraoka, Colin B. Begg, Jorgen H. Olsen, Lene Mellemkjaer, Xiaolin Liang, Ake Borg, Patrick Concannon, Robert W. Haile

Manuscript Writing. Jonine L. Bernstein, Duncan C. Thomas, Roy E. Shore, Mark Robson, John D. Boice, Marilyn Stovall, Michael Andersson, Leslie Bernstein, Kathleen E. Malone, Charles F. Lynch, Colin B. Begg, Jorgen H. Olsen, Lene Mellemkjaer, Ake Borg, Patrick Concannon, Robert W. Haile

Final Approval of Manuscript. Jonine L. Bernstein, Duncan C. Thomas, Roy E. Shore, Mark Robson, John D. Boice, Marilyn Stovall, Michael Andersson, Leslie Bernstein, Kathleen E. Malone, Anne S. Reiner, Charles F. Lynch, Marinela Capanu, Susan A. Smith, Lina Tellhed, Sharon N. Teraoka, Colin B. Begg, Jorgen H. Olsen, Lene Mellemkjaer, Xiaolin Liang, Anh T. Diep, Ake Borg, Patrick Concannon, Robert W. Haile

REFERENCES CITED

1. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011; 378(9804):1707–16. [PubMed: 22019144]
2. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res*. 2002; 158(2):220–35. [PubMed: 12105993]
3. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. *Breast Cancer Res*. 2005; 7(1):21–32. [PubMed: 15642178]
4. Bhatti P, Struwing JP, Alexander BH, Hauptmann M, Bowen L, Mateus-Pereira LH, et al. Polymorphisms in DNA repair genes, ionizing radiation exposure and risk of breast cancer in U.S. Radiologic technologists. *Int J Cancer*. 2008; 122(1):177–82. [PubMed: 17764108]
5. Turnbull C, Miragaes N, Eeles R. Radiotherapy and genetic predisposition to breast cancer. *Clin Oncol (R Coll Radiol)*. 2006; 18(3):257–67. [PubMed: 16605057]
6. Narod SA, Foulkes WD. *BRCA1 and BRCA2*: 1994 and beyond. *Nat Rev Cancer*. 2004; 4(9):665–76. [PubMed: 15343273]
7. Venkitaraman AR. Cancer susceptibility and the functions of *BRCA1* and *BRCA2*. *Cell*. 2002; 108(2):171–82. [PubMed: 11832208]
8. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case Series unselected

- for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003; 72(5):1117–30. [PubMed: 12677558]
9. Begg CB, Haile RW, Borg A, Malone KE, Concannon P, Thomas DC, et al. Variation of breast cancer risk among *BRCA1/2* carriers. *JAMA.* 2008; 299(2):194–201. [PubMed: 18182601]
 10. Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, et al. Prevalence and predictors of *BRCA1* and *BRCA2* mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res.* 2006; 66(16):8297–308. [PubMed: 16912212]
 11. Haffty BG, Harrold E, Khan AJ, Pathare P, Smith TE, Turner BC, et al. Outcome of conservatively managed early-onset breast cancer by *BRCA1/2* status. *Lancet.* 2002; 359(9316):1471–7. [PubMed: 11988246]
 12. Metcalfe K, Gershman S, Lynch HT, Ghadirian P, Tung N, Kim-Sing C, et al. Predictors of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *Br J Cancer.* 2011; 104(9): 1384–92. [PubMed: 21487411]
 13. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, et al. Contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *J Clin Oncol.* 2004; 22(12):2328–35. [PubMed: 15197194]
 14. Robson M, Levin D, Federici M, Satagopan J, Bogolminy F, Heerdt A, et al. Breast conservation therapy for invasive breast cancer in Ashkenazi women with *BRCA* gene founder mutations. *J Natl Cancer Inst.* 1999; 91(24):2112–7. [PubMed: 10601383]
 15. Weitzel JN, Robson M, Pasini B, Manoukian S, Stoppa-Lyonnet D, Lynch HT, et al. A comparison of bilateral breast cancers in *BRCA* carriers. *Cancer Epidemiol Biomarkers Prev.* 2005; 14(6): 1534–8. [PubMed: 15941968]
 16. Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med.* 1992; 326(12):781–5. [PubMed: 1538720]
 17. Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. *Int J Radiat Oncol Biol Phys.* 2003; 56(4):1038–45. [PubMed: 12829139]
 18. Stovall M, Smith SA, Langholz BM, Boice JD Jr, Shore RE, Andersson M, 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]
 19. Bernstein JL, Langholz B, Haile RW, Bernstein L, Thomas DC, Stovall M, et al. Study design: evaluating gene-environment interactions in the etiology of breast cancer - the WECARE study. *Breast Cancer Res.* 2004; 6(3):R199–214. [PubMed: 15084244]
 20. Stovall M, Weathers R, Kasper C, Smith SA, Travis L, Ron E, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. *Radiat Res.* 2006; 166(1 Pt 2):141–57. [PubMed: 16808603]
 21. Langholz B, Thomas DC, Stovall M, Smith SA, Boice JD Jr, Shore RE, et al. Statistical methods for analysis of radiation effects with tumor and dose location-specific information with application to the WECARE study of asynchronous contralateral breast cancer. *Biometrics.* 2009; 65(2):599–608. [PubMed: 18647297]
 22. Huberman M, Langholz B. Application of the missing-indicator method in matched case-control studies with incomplete data. *Am J Epidemiol.* 1999; 150(12):1340–5. [PubMed: 10604777]
 23. Nieuwenhuis B, Van Assen-Bolt AJ, Van Waarde-Verhagen MA, Sijmons RH, Van der Hout AH, Bauch T, et al. *BRCA1* and *BRCA2* heterozygosity and repair of X-ray-induced DNA damage. *Int J Radiat Biol.* 2002; 78(4):285–95. [PubMed: 12020440]
 24. Speit G, Trenz K. Chromosomal mutagen sensitivity associated with mutations in *BRCA* genes. *Cytogenet Genome Res.* 2004; 104(1-4):325–32. [PubMed: 15162060]
 25. Baeyens A, Thierens H, Claes K, Poppe B, de Ridder L, Vral A. Chromosomal radiosensitivity in *BRCA1* and *BRCA2* mutation carriers. *Int J Radiat Biol.* 2004; 80(10):745–56. [PubMed: 15799620]
 26. Broeks A, Braaf LM, Huseinovic A, Nooijen A, Urbanus J, Hogervorst FB, et al. Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study. *Breast Cancer Res.* 2007; 9(2):R26. [PubMed: 17428320]

27. Gaffney DK, Brohet RM, Lewis CM, Holden JA, Buys SS, Neuhausen SL, et al. Response to radiation therapy and prognosis in breast cancer patients with *BRCA1* and *BRCA2* mutations. *Radiother Oncol.* 1998; 47(2):129–36. [PubMed: 9683359]
28. Pierce LJ, Levin AM, Rebbeck TR, Ben-David MA, Friedman E, Solin LJ, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in *BRCA1/2*-associated stage I/II breast cancer. *J Clin Oncol.* 2006; 24(16):2437–43. [PubMed: 16636335]
29. Shanley S, McReynolds K, Ardern-Jones A, Ahern R, Fernando I, Yarnold J, et al. Late toxicity is not increased in *BRCA1/BRCA2* mutation carriers undergoing breast radiotherapy in the United Kingdom. *Clin Cancer Res.* 2006; 12(23):7025–32. [PubMed: 17145824]
30. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002; 347(16):1227–32. [PubMed: 12393819]
31. Pierce LJ, Phillips KA, Griffith KA, Buys S, Gaffney DK, Moran MS, et al. Local therapy in *BRCA1* and *BRCA2* mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. *Breast Cancer Res Treat.* 2010; 121(2):389–98. [PubMed: 20411323]
32. Andrieu N, Easton DF, Chang-Claude J, Rookus MA, Brohet R, Cardis E, et al. Effect of chest X-rays on the risk of breast cancer among *BRCA1/2* mutation carriers in the international *BRCA1/2* carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. *J Clin Oncol.* 2006; 24(21):3361–6. [PubMed: 16801631]
33. Berrington, de Gonzalez A.; Berg, CD.; Visvanathan, K.; Robson, M. Estimated risk of radiation-induced breast cancer from mammographic screening for young *BRCA* mutation carriers. *J Natl Cancer Inst.* 2009; 101(3):205–9. [PubMed: 19176458]
34. Goldfrank D, Chuai S, Bernstein JL, Ramon YCT, Lee JB, Alonso MC, et al. Effect of mammography on breast cancer risk in women with mutations in *BRCA1* or *BRCA2*. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(11):2311–3. [PubMed: 17119064]
35. Lecarpentier J, Nogues C, Mouret-Fourme E, Stoppa-Lyonnet D, Lasset C, Caron O, et al. Variation in breast cancer risk with mutation position, smoking, alcohol, and chest X-ray history, in the French National *BRCA1/2* carrier cohort (GENEPSO). *Breast Cancer Res Treat.* 2011; 130(3):927–38. [PubMed: 21761160]
36. Narod SA, Lubinski J, Ghadirian P, Lynch HT, Moller P, Foulkes WD, et al. Screening mammography and risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers: a case-control study. *Lancet Oncol.* 2006; 7(5):402–6. [PubMed: 16648044]
37. Scully R, Livingston DM. In search of the tumour-suppressor functions of *BRCA1* and *BRCA2*. *Nature.* 2000; 408(6811):429–32. [PubMed: 11100717]
38. Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Nogues C, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of *BRCA1/2* mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ.* 2012; 345:e5660. [PubMed: 22956590]
39. Easton DF, Deffenbaugh AM, Pruss D, Frye C, Wenstrup RJ, Allen-Brady K, et al. A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the *BRCA1* and *BRCA2* breast cancer-predisposition genes. *Am J Hum Genet.* 2007; 81(5):873–83. [PubMed: 17924331]
40. Johnson N, Fletcher O, Palles C, Rudd M, Webb E, Sellick G, et al. Counting potentially functional variants in *BRCA1*, *BRCA2* and *ATM* predicts breast cancer susceptibility. *Hum Mol Genet.* 2007; 16(9):1051–7. [PubMed: 17341484]
41. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. *Nat Genet.* 2008; 40(1):17–22. [PubMed: 18163131]

Table 1

The effect of carrying BRCA1 or BRCA2 mutations on risk of developing contralateral breast cancer.

	Mutation Carrier Status	Cases (%)	Controls (%)	Rate Ratio^a	95% CI
BRCA1 or BRCA2	No	507 (84)	1137 (95)	1.0	
	Yes	96 (16)	62 (5)	4.5	3.0-6.8
BRCA1	No	546 (90)	1162 (98)	1.0	
	Yes	57 (10)	37 (2)	5.1	3.0-8.5
BRCA2	No	564 (93)	1174 (98)	1.0	
	Yes	39 (6)	25 (2)	3.9	2.2-7.0

^aRate ratios are adjusted for age at first diagnosis, age at menarche, number of full term pregnancies, age at menopause, family history, treatment (chemotherapy and hormonal therapy), histology, and stage of the first primary. Please note that RRs can only be calculated after appropriately adjusting for counter-matching and cannot be calculated based on the raw frequencies alone. The proportions are weighted by the counter-matching (Bernstein et al, Br Ca Res 2004; 6(3):R199-214)

Table 2
Effect of radiation exposure on risk of developing contralateral breast cancer by BRCA1 or BRCA2 carrier status.

Radiation Exposure	<u>No BRCA1/BRCA2 mutation</u>				<u>BRCA1</u>				<u>BRCA2</u>				<u>BRCA1 or BRCA2</u>						
	Case n (%)	Control n (%)	RR ^a	95%CI	Case n (%)	Control n (%)	RR ^a	95%CI	P ^b	Case n (%)	Control n (%)	RR ^a	95%CI	P ^c	Case n (%)	Control n (%)	RR ^a	95%CI	P ^d
No	261 (51)	229 (50)	1.0		23 (40)	3 (38)	1.0			17 (44)	6 (42)	1.0			40 (42)	9 (41)	1.0		
Yes	246 (49)	908 (50)	1.1	0.9-1.4	34 (60)	34 (62)	0.8	0.2-3.2	0.8	22 (56)	19 (58)	2.2	0.7-7.3	0.2	56 (58)	53 (59)	1.4	0.6-3.3	0.7
<i>Estimated dose to contralateral breast</i>																			
No	261 (52)	229 (50)	1.0		23 (40)	3 (38)	1.0			17 (44)	6 (42)	1.0			40 (42)	9 (41.0)	1.0		
0<1.0Gy	128 (25)	502 (27)	1.0	0.8-1.3	18 (32)	15 (22)	1.1	0.2-4.8		17 (44)	12 (38)	2.9	0.8-10.3		35 (36)	27 (30.0)	1.9	0.7-4.8	
1.0Gy	118 (23)	406 (23)	1.2	1.0-1.6	16 (28)	19 (40)	0.6	0.1-2.6	0.5	5 (12)	7 (20)	1.5	0.3-7.0	0.3	21 (22)	26 (29.0)	1.0	0.4-2.8	0.2

^aRate ratios are adjusted for age at first diagnosis, age at menarche, number of full term pregnancies, age at menopause, family history, treatment (chemotherapy and hormonal therapy), histology, and stage of the first primary. Please note that RRs can only be calculated after appropriately adjusting for counter-matching and cannot be calculated based on the raw frequencies alone, the proportions presented are weighted by the counter-matching (Bernstein et al, Br Ca Res 2004; 6(3):R199-214).

^bP value for heterogeneity of effect of radiation exposure in *BRCA1* carriers versus non-carriers.

^cP value for heterogeneity of effect of radiation exposure in *BRCA2* carriers versus non-carriers.

^dP value for heterogeneity of effect of radiation exposure in *BRCA1* and *BRCA2* carriers combined versus non-carriers.