Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Diagnostic Chest X-Rays and Breast Cancer Risk before Age 50 Years for *BRCA1* and *BRCA2* Mutation Carriers

Esther M. John[1,2], Valerie McGuire[2], Duncan Thomas[4], Robert Haile[3], Hilmi Ozcelik[5,7†], Roger L. Milne[10,11], Anna Felberg[2], Dee W. West[2], Alexander Miron[15], Julia A. Knight[6,9], Mary Beth Terry[16], Mary Daly[17], Saundra S. Buys[18], Irene L. Andrulis[5,8], John L. Hopper[11], Melissa C. Southey[12], Graham G. Giles[11,13], Carmel Apicella[11], Heather Thorne[14], for the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab), and Alice S. Whittemore[2]

Abstract

Background: The effects of low-dose medical radiation on breast cancer risk are uncertain, and few studies have included genetically susceptible women, such as those who carry germline *BRCA1* and *BRCA2* mutations.

Methods: We studied 454 *BRCA1* and 273 *BRCA2* mutation carriers ages younger than 50 years from three breast cancer family registries in the United States, Canada, and Australia/New Zealand. We estimated breast cancer risk associated with diagnostic chest X-rays by comparing mutation carriers with breast cancer (cases) with those without breast cancer (controls). Exposure to chest X-rays was self-reported. Mammograms were not considered in the analysis.

Results: After adjusting for known risk factors for breast cancer, the ORs for a history of diagnostic chest X-rays, excluding those for tuberculosis or pneumonia, were 1.16 [95% confidence interval (CI), 0.64–2.11] for *BRCA1* mutations carriers and 1.22 (95% CI, 0.62–2.42) for *BRCA2* mutations carriers. The OR was statistically elevated for *BRCA2* mutation carriers with three to five diagnostic chest X-rays ($P = 0.01$) but not for those with six or more chest X-rays. Few women reported chest fluoroscopy for tuberculosis or chest X-rays for pneumonia; the OR estimates were elevated, but not statistically significant, for *BRCA1* mutation carriers.

Conclusions: Our findings do not support a positive association between diagnostic chest X-rays and breast cancer risk before the ages of 50 years for *BRCA1* or *BRCA2* mutation carriers.

Impact: Given the increasing use of diagnostic imaging involving higher ionizing radiation doses, further studies of genetically predisposed women are warranted. *Cancer Epidemiol Biomarkers Prev; 22(9); 1547–56. ©2013 AACR.*

Authors' Affiliations: [1]Cancer Prevention Institute of California, Fremont; [2]Division of Epidemiology, Department of Health Research and Policy, [3]Division of Oncology, Department of Medicine, Stanford University School of Medicine, Stanford; [4]Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California; [5]Fred A. Litwin Centre for Cancer Genetics, [6]Prosserman Centre for Health Research, Samuel Lunenfeld Research Institute, Mount Sinai Hospital; [7]Department of Laboratory Medicine and Pathobiology, [8]Department of Molecular Genetics, [9]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; [10]Genetic & Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain; [11]Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, [12]Department of Pathology, The University of Melbourne; [13]Cancer Epidemiology Centre, Cancer Council Victoria; [14]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [15]Dana-Farber Cancer Institute, Boston, Massachusetts; [16]Department of Epidemiology, Mailman School of Public Health, Columbia University, and the Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, New York; [17]Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, Pennsylvania; and [18]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah

†Deceased.

Corresponding Author: Esther M. John, Cancer Prevention Institute of California, 2201 Walnut Avenue, Suite 300, Fremont, CA 94538-2334. Phone: 510-608-5007; Fax: 510-608-5085; E-mail: esther.john@cpic.org

doi: 10.1158/1055-9965.EPI-13-0189

Introduction

There is extensive epidemiologic evidence that exposure to moderate- and high-dose ionizing radiation, particularly at young ages, is associated with an increase in a woman's risk of developing breast cancer (1, 2). In contrast, relatively few studies have evaluated the association between low-dose diagnostic chest X-rays and breast cancer risk. Positive associations have been reported for patients with tuberculosis monitored with frequent fluoroscopy (3, 4), patients with scoliosis evaluated with repeated X-rays of the spine (5), and women with frequent diagnostic chest X-rays before the age of 20 years (6, 7) or 30 years (8), or diagnostic chest X-rays administered before 1960 (8), when radiation doses were likely to be higher than current levels.

There is evidence from some (5–7), but not all (8), studies that breast cancer risk associated with diagnostic chest X-rays is greater for women with a family history of breast cancer. Positive associations with diagnostic chest radiation have also been reported for women carrying a mutation in *BRCA1* or *BRCA2* (9–12), suggesting that genetically predisposed women could be sensitive to

Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

low-dose diagnostic radiation exposure. For mammography, a common source of low-dose radiation, 3 studies found no significant associations with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers (12–14).

As *BRCA1* and *BRCA2* are involved in the detection and cellular repair of DNA double-strand breaks induced by ionizing radiation (15), it is plausible that *BRCA1* and *BRCA2* mutation carriers may have reduced ability to repair radiation-induced DNA damage and, therefore, be at increased risk of radiation-induced breast cancer. Women who receive therapeutic radiotherapy for their first breast cancer have an elevated risk for contralateral breast cancer (16) which could be even further increased for those who carry a germline mutation in a gene involved in DNA-damage repair (e.g., *ATM*, *CHEK2*, *BRCA1*, *BRCA2*; refs. 17–19).

To further study the possible association of low-dose radiation from medical diagnostic procedures, we examined breast cancer risk and diagnostic chest X-rays using self-reported data on exposure from 454 *BRCA1* and 273 *BRCA2* mutation carriers identified by 3 large family registries of breast cancer in the United States, Canada, and Australia. Because the established association between radiation and breast cancer risk is observed primarily for women exposed to radiation at a young age, we analyzed only mutation carriers ages younger than 50 years.

Materials and Methods

Study sample

A detailed description of the study design and analytic methods has been provided elsewhere (20). Briefly, women carrying a deleterious mutation in *BRCA1* or *BRCA2* (see below) were identified from the Breast Cancer Family Registry (BCFR) composed of 6 registries in the United States, Canada, and Australia (21); the Ontario Cancer Genetics Network (OCGN) in Canada; and the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) in Australia and New Zealand (22). Three registries of the BCFR ascertained families through probands with incident breast cancer who were sampled from population-based cancer registries. All other families were identified through cancer clinics or community outreach efforts. Probands were either affected or unaffected with breast or ovarian cancer and included those with multiple or early-onset cases of breast or ovarian cancer among first- and second-degree relatives or relatives known to carry a mutation in *BRCA1* or *BRCA2*.

In this case–control analysis of mutation carriers, we defined cases as women carrying a deleterious mutation in *BRCA1* or *BRCA2* who had been diagnosed with a first primary invasive breast cancer and controls as mutation carriers without a history of breast cancer. We assigned each carrier a reference age, defined for cases as the age at breast cancer diagnosis, and for controls as the age at the earliest of the following events: questionnaire completion, bilateral mastectomy, bilateral oophorectomy, or diagnosis of *in situ* breast cancer. We restricted the analysis to carriers with a reference age <50 years. To minimize survival bias, we further restricted the analysis to carriers who completed the questionnaire no more than 5 years after their reference age. Approximately 82% of carriers completed the questionnaire within 3 years of their reference age. We excluded from the analysis a small number of *BRCA1* mutation carriers (2 cases and 1 control) and *BRCA2* mutation carriers (3 cases and 2 controls) who reported therapeutic radiation exposures to the chest before breast cancer diagnosis (cases) or interview (controls). The final analysis was based on 454 non-Hispanic white *BRCA1* mutation carriers (167 cases and 287 controls) and 273 non-Hispanic white *BRCA2* mutation carriers (104 cases and 169 controls).

All participants in the BCFR, OCGN, and kConFab provided written informed consent to participate in research programs that were approved by the Institutional Review Board of each center participating in the BCFR, OCGN, and kConFab. This study was approved by the Institutional Review Board of the Stanford University School of Medicine (Stanford, CA).

Data collection

All study sites used the same structured questionnaire, completed by interview or mail. Information was collected on established and suspected breast cancer risk factors, including chest X-ray examinations (other than mammograms) and radiation treatment to the chest area before breast cancer diagnosis for cases or interview for controls. The questionnaire asked about treatment with radiation for selected conditions (i.e., tuberculosis, cancer, acne, mastitis, enlarged thymus, or hemangioma), and other conditions in the chest area, as well as diagnostic X-ray examinations for heart catheterization or scoliosis, or other intensive X-ray examinations of the chest area. When a participant reported "therapeutic chest X-rays for other conditions" or "other intensive X-ray examinations of the chest area," information was requested on the type of condition. The term "other intensive chest X-rays" was not further defined in the questionnaire. Although the questionnaire listed tuberculosis as a condition for treatment with radiation, we recognize that fluoroscopy was used to follow the progress of lung inflation to normal after induced pneumothorax treatment for tuberculosis; radiation was not used as a treatment for tuberculosis per se. For both therapeutic and diagnostic radiation exposure, information was collected on age at first exposure and total number of exposures. As we previously found positive associations between breast cancer risk and chest fluoroscopy for tuberculosis and chest X-rays for pneumonia (8), we examined associations with these 2 exposure categories separately. All other diagnostic chest X-rays (e.g., back or shoulder examinations, upper body bone fractures, routine chest X-rays, and chest X-rays for unspecified indications) were pooled together for the analysis. X-rays from mammograms were not considered,

Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

as the questionnaire did not assess a lifetime mammography history.

BRCA1 and *BRCA2* mutation testing

BRCA1 and *BRCA2* mutation testing was conducted for incident breast cancer cases recruited from the 3 population-based BCFR registries and the youngest breast cancer case for families from clinics. Women of Ashkenazi Jewish ancestry were tested for the 3 founder mutations. Testing was conducted either by complete gene sequencing at Myriad Genetics, Inc. or by one of several other methods: enzymatic mutation detection, 2-dimensional gene scanning, chemical cleavage of mismatch, the protein truncation test, single-strand conformation polymorphism analysis, heteroduplex analysis, and denaturing high-conductance liquid chromatography (DHPLC; refs. 23–25). Mutations considered included small insertions and deletions, nonsense mutations, and splice site variants that all resulted in truncated and dysfunctional BRCA1 and BRCA2 proteins. All mutations were confirmed by sequencing. The analysis for this study was restricted to carriers of mutations that were classified as deleterious by applying the criteria used by the Breast Information Core and Myriad Genetics Inc., as described elsewhere (24). When a deleterious mutation was identified, all relatives of the carrier who had provided a DNA sample were subsequently tested for the same mutation.

Statistical analysis

We used unconditional logistic regression implemented in SAS version 9.1 to estimate ORs and 95% confidence intervals (CI). A robust variance estimator was used to account for possible correlation in covariates between family members (26). This approach accommodates the possibility that some carriers were ascertained because of their breast cancer status. Valid inferences for association parameters can be obtained by ignoring other ascertainment issues provided that the exposure–disease OR for ascertained carriers is equal to the corresponding OR for unascertained carriers having the same family history (26). This condition would be violated only if ascertainment modified the association between exposure and breast cancer. All regression models included reference age as a categorical (<40 and 40–49 years) variable and as a continuous variable, dummy variables for country/region (Canada, Australia, Utah, other U.S. sites), family history of breast or ovarian cancer in first-degree relatives (yes, no), and number of full-term pregnancies (0, 1–2, $\geq$3). On the basis of our previous finding of increased breast cancer risk associated with chest fluoroscopy for tuberculosis and chest X-rays for pneumonia (8), we estimated breast cancer risk in relation to 3 categories of diagnostic X-ray exposure: chest fluoroscopy for tuberculosis, chest X-rays for pneumonia, and chest X-rays for other reasons. Women in these exposure categories were compared with a single referent category that included women without a history of therapeutic and diagnostic chest X-rays.

Results

Characteristics of cases and controls are shown in Table 1. Cases were older than controls and fewer cases than controls had a college or university degree. More controls than cases were ascertained from clinic-based sources and had a family history of breast or ovarian cancer which is the result of the ascertainment and *BRCA1* and *BRCA2* mutation testing protocols (20).

For *BRCA1* mutation carriers, a history of diagnostic chest X-rays was not associated with breast cancer risk (OR, 1.31; 95% CI, 0.75–2.30; Table 2). There was no evidence of increased risk associated with diagnostic chest X-rays (OR, 1.16; 95% CI, 0.64–2.11), excluding those for pneumonia or chest fluoroscopy. Elevated, but statistically not significant, ORs were associated with a history of chest fluoroscopy for tuberculosis (OR, 2.58; 95% CI, 0.22–30) and chest X-rays for pneumonia (OR, 4.54; 95% CI, 0.53–30). For other chest X-rays (excluding those for pneumonia or chest fluoroscopy), risk did not vary by age or year at first chest X-ray or total number of chest X-rays.

Similarly, for *BRCA2* mutation carriers, there was no evidence of increased breast cancer risk associated with a history of diagnostic chest X-rays (OR, 1.13; 95% CI, 0.59–2.18; Table 2). Subgroup analyses showed an elevated risk only for carriers with 3 to 5 chest X-rays (OR, 10.6; 95% CI, 1.93–58), excluding those for pneumonia or chest fluoroscopy.

Discussion

The results from the present study suggest that for *BRCA1* and *BRCA2* mutation carriers ages younger than 50 years, there is no association between diagnostic chest X-rays and breast cancer risk, neither for exposure at any age nor for exposure before age 20 years when radiosensitivity is highest. For *BRCA2* mutation carriers, our finding of a large OR estimate associated with 3 to 5 diagnostic X-rays, bounded by a wide CI, is likely due to chance, given the lack of association with $\geq$6 X-rays.

Few prior studies have examined diagnostic X-ray exposure and breast cancer risk for *BRCA1* and *BRCA2* mutation carriers and, in contrast to our findings, strong associations have been reported by some of the European studies (refs. 9, 11, 12; Table 3). There was, however, some overlap in mutation carriers between the 3 European studies (9, 11, 12); the analysis by Andrieu and colleagues (9) included 319 French mutation carriers from the study by Lecarpentier and colleagues (11), and 21% of mutation carriers included in the analysis by Pijpe and colleagues (12) were also included in the study by Andrieu and colleagues (9). In the incident cohort analysis by Andrieu and colleagues (9) of 969 mostly European *BRCA1* and *BRCA2* mutation carriers, a history of diagnostic chest X-rays (excluding mammograms) was associated with increased breast cancer risk (HR, 1.75; 95% CI, 1.1–2.8). For women ages 40 years or younger, risk was increased more than 2-fold (HR, 2.75; 95% CI, 1.4–5.3). Similarly, in

Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

Table 1. Characteristics of non-Hispanic white *BRCA1* and *BRCA2* mutation carriers, by case–control status

	BRCA1 mutation carriers		*BRCA2* mutation carriers	
	Cases ($n = 167$)	Controls ($n = 287$)	Cases ($n = 104$)	Controls ($n = 169$)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Reference age, year				
<30	18 (11)	77 (27)	8 (8)	34 (20)
30–39	73 (44)	104 (36)	51 (49)	57 (34)
40–49	76 (45)	106 (37)	45 (43)	78 (46)
Study site				
Australia	75 (45)	117 (41)	50 (48)	84 (50)
Canada	39 (23)	11 (4)	27 (26)	12 (7)
United States	53 (32)	159 (55)	27 (26)	73 (43)
Ascertainment				
Clinic	99 (59)	271 (94)	59 (57)	148 (88)
Population	68 (41)	16 (6)	45 (43)	21 (12)
Education				
Less than college or university	45 (27)	51 (18)	18 (17)	39 (23)
Some college or university	67 (40)	124 (43)	52 (50)	66 (39)
College or university degree	54 (33)	112 (39)	31 (30)	64 (38)
Unknown	0 (0)	0 (0)	3 (3)	0 (0)
Family history of breast or ovarian cancer[a]				
Yes	102 (61)	218 (76)	56 (54)	119 (70)
No	65 (39)	69 (24)	48 (46)	50 (30)
Full-term pregnancies				
0	45 (27)	97 (34)	22 (21)	37 (22)
1–2	85 (51)	111 (39)	48 (46)	78 (46)
≥3	37 (22)	78 (27)	34 (33)	54 (32)

[a]In first-degree relatives.

the French study of 990 *BRCA1* and *BRCA2* mutation carriers, breast cancer risk associated with a history of diagnostic chest X-rays (excluding mammograms) was increased both for *BRCA1* (HR, 4.12; 95% CI, 1.82–9.35) and *BRCA2* (HR, 5.43; 95% CI, 1.36–21.7) mutation carriers (11). The largest study to date by Pijpe and colleagues (12) assessed associations with several categories of diagnostic radiation exposure, including fluoroscopy, conventional radiography (X-rays) of chest or shoulders, mammography, computed tomography of chest or shoulders, and other diagnostic procedures (e.g., bone scans). Consistent with our findings, there were no statistically significant associations with a history of diagnostic chest X-rays (HR, 1.38; 95% CI, 0.87–2.20) or chest X-rays before the age of 20 years (HR, 1.29; 95% CI, 0.84–1.98) for *BRCA1* and *BRCA2* mutation carriers combined. In that study, significant associations with diagnostic radiation exposure emerged only when all types of exposures (fluoroscopy, X-rays, mammography, other diagnostic procedures) before the age of 30 years were considered jointly (HR, 1.90; 95% CI, 1.20–3.00). Finally, a Polish study of patients with breast cancer diagnosed at ages 50 years or younger compared 138 affected *BRCA1* mutation carriers with 158 affected non-carriers; affected carriers were more likely to report a history of chest X-rays before the age of 30 years than affected non-carriers (OR, 1.8; 95% CI, 1.2–2.9; ref. 10).

Our findings of a relatively large OR estimate associated with chest fluoroscopy for tuberculosis is in agreement with the study by Pijpe and colleagues (12) that found a 2-fold increased risk for exposure before the age of 20 years, but in both studies, the associations were based on small numbers of exposed mutation carriers and were not statistically significant. Chest fluoroscopy for tuberculosis has also been associated with increased breast cancer risk (3, 8) and mortality (4) in the general population. It is uncertain whether in the other European studies (9–11) reports of chest X-rays included fluoroscopy for tuberculosis. The inclusion of fluoroscopy could have contributed to the positive associations with chest X-rays, particularly for exposures before the age of 20 years. In our study, we asked about diagnostic X-ray exposure for heart catheterization and for the monitoring of scoliosis, which has been associated with increased breast cancer risk (5) and mortality (27) in the U.S. Scoliosis Cohort Study. For other intensive X-rays, we requested the reason for the diagnostic procedure. Although our questionnaire did not ask

Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

Table 2. Diagnostic chest X-rays and breast cancer risk for non-Hispanic white women, by *BRCA1* and *BRCA2* mutation status

	BRCA1 mutation carriers			*BRCA2* mutation carriers		
	Cases ($n = 167$)	Controls ($n = 287$)	Multivariate adjusted OR (95% CI)[a]	Cases ($n = 104$)	Controls ($n = 169$)	Multivariate adjusted OR (95% CI)[a]
History of diagnostic chest X-rays						
No chest X-rays	125	246	1.0	76	133	1.0
One or more chest X-rays	42	41	1.31 (0.75–2.30)	28	36	1.13 (0.59–2.18)
Chest fluoroscopy for tuberculosis	3	1	2.58 (0.22–30)	2	2	0.93 (0.11–7.89)
Chest X-rays for pneumonia	3	2	4.54 (0.53–39)	2	2	0.33 (0.02–5.63)
Other diagnostic chest X-rays	36	38	1.16 (0.64–2.11)	24	32	1.22 (0.62–2.42)
Other diagnostic chest X-rays[b]						
Age at first chest X-ray, y						
No chest X-rays	125	246	1.0	76	133	1.0
<20 y	10	22	0.57 (0.22–1.48)	9	10	1.55 (0.54–4.47)
≥20 y	21	14	1.69 (0.76–3.76)	11	17	1.06 (0.43–2.60)
Unknown	5	2	2.58 (0.42–15.8)	4	5	1.12 (0.24–5.26)
Year of first chest X-ray						
No chest X-rays	125	246	1.0	76	133	1.0
Before 1980	16	17	1.14 (0.48–2.70)	10	6	2.18 (0.69–6.88)
1980 or after	15	19	1.01 (0.44–2.29)	10	21	0.90 (0.37–2.19)
Unknown	5	2	2.62 (0.43–16.0)	4	5	1.10 (0.24–5.12)
Number of chest X-rays						
No chest X-rays	125	246	1.0	76	133	1.0
1–2	11	16	0.84 (0.33–2.13)	7	15	0.80 (0.28–2.28)
3–5	8	6	1.22 (0.35–4.21)	9	2	10.63 (1.93–58)
≥6	6	7	1.20 (0.37–3.96)	3	3	0.89 (0.15–5.49)
Unknown	11	9	1.75 (0.57–5.35)	5	12	0.62 (0.18–2.17)

[a]ORs and 95% confidence interval (CI), adjusted for age, study site, family history of breast or ovarian cancer in first-degree relatives, and number of full-term pregnancies.

[b]Excluding individuals with chest X-rays fluoroscopy for tuberculosis or chest X-rays for pneumonia.

specifically about chest fluoroscopy, some women reported such exposure under "other intensive diagnostic X-rays" or in the questionnaire section on therapeutic radiation.

The most striking difference between the European studies and ours is the prevalence of self-reported diagnostic X-rays (Table 3). For unaffected carriers, the proportion of women who reported a history of diagnostic chest X-rays ranged from 15% (not including those for pneumonia or chest fluoroscopy for tuberculosis) in our study to 45% (not including fluoroscopy) in the study by Pijpe and colleagues (12), 50% in the study by Andrieu and colleagues (9), and 76% in the study by Lecarpentier and colleagues (11). Differences in the prevalence of reported chest X-rays were particularly pronounced for exposures before the age of 20 years. For affected carriers, proportions ranged from 7% in our study to 23% in the Polish study (10), 31% in the study by Pijpe and colleagues (12), 66% in the study by Andrieu and colleagues (9), and 88% in the study by Lecarpentier and colleagues (11). Large differences were also seen in the prevalence of fluoroscopy; a positive history was reported by 2% of affected mutation carriers in our study, compared with 15% in the European study by Andrieu and colleagues (12).

Differences in the frequency of self-reported diagnostic chest radiation could be due to differences between studies in the wording of questions and/or the inclusion of specific diagnostic procedures, differences between countries in the practice of administering diagnostic X-rays or differences between studies in the age distribution, or birth cohorts, of the mutation carriers. The frequency of medical X-rays has been shown to vary between countries (28). Chest fluoroscopy, for example, has been reported to be more common in Sweden than in the United States (29), and in the Netherlands, mass population screening for tuberculosis was conducted in young people from 1940 to 1960 (12). Analytic differences between the European studies may have also contributed to differences in results. As commented by Pijpe and colleagues (12), the analysis by Andrieu and colleagues (9) assessed lifetime X-rays, including exposure after

Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

Table 3. Summary of published studies on diagnostic chest X-rays and breast cancer risk for *BRCA1* and *BRCA2* mutation carriers

	Andrieu and colleagues (9)	Lecarpentier and colleagues (11)	Pijpe and colleagues (12)	Gronwald and colleagues (10)	Current study
Study	IBCCS cohort (2/3 of carriers are from GENEPSO, EMBRACE, HEBON)	GENEPSO	GENE-RAD-RISK Cohort (carriers from GENEPSO, EMBRACE, HEBON)	Study of early-onset breast cancer	BCFR, OCGN, kConFab
Country	13 European countries;[a] Quebec, Canada	France	France, UK, Netherlands	Poland	USA, Canada, Australia, New Zealand
Ascertainment of *BRCA1* and *BRCA2* mutation carriers	Family cancer clinics or previous participation in research family studies	Family cancer clinics	Family cancer clinics and clinical genetic centers	Unselected breast cancer cases from 18 hospitals	Participation in research family studies
Number of affected/unaffected *BRCA1* and *BRCA2* mutation carriers included in analysis	295/674[b]	379/611[c]	174/948[b]	138 affected *BRCA1* carriers 158 affected non-carriers	271/456
Age, y	≥18	≥18	≥18	30–50	≤50
Birth cohort	<1940 to ≥1960	<1950 to ≥1970	<1955 to >1968	1948–1972	1940 to ≥1970
Data collection	1997–2002 Mailed questionnaire	2000–2010 Mailed questionnaire	2006–2009 Mailed questionnaire	1996–2002 Mailed questionnaire	1995–2003 Mailed questionnaire or interview
Assessment of diagnostic chest X-rays	Chest X-rays	Chest x-rays	Conventional radiography of chest or shoulders	Chest X-rays before the age of 30 y	Chest X-rays for heart catheterization, scoliosis, other intensive chest X-rays
	Excluding mammograms	Excluding mammograms	Excluding fluoroscopy or mammograms		Excluding mammograms, chest fluoroscopy for tuberculosis or chest X-rays for pneumonia
	Number of X-rays at ages <20, ≥20 y	Number of X-rays at ages <20, ≥20 y	Age at first X-rays, number of X-rays at ages <20, 20–29, 30–39 y, age at last X-rays	Age at first X-ray, total number of X-rays	Age at first X-rays, total number of X-rays

(Continued on the following page)

Table 3. Summary of published studies on diagnostic chest X-rays and breast cancer risk for *BRCA1* and *BRCA2* mutation carriers (Cont'd)

	Andrieu and colleagues (9)	Lecarpentier and colleagues (11)	Pijpe and colleagues (12)	Gronwald and colleagues (10)	Current study
Frequency of chest X-rays					
Affected carriers	70%	96%	51%[d]	53%	22%[d]
Unaffected carriers	50%	76%	45%[d]		15%[d]
Frequency of chest X-rays at age <20 y					
Affected carriers	66%	88%	31%	23%	7%
Unaffected carriers				15%[f]	7%
Association with chest X-rays (ever, never)[e]					
BRCA1 carriers	HR = 1.91 (1.1–3.3)[b]	HR = 4.12 (1.82–9.35)[c]		OR = 1.8 (1.2–2.9)[g]	OR = 1.16 (0.64–2.11)[d]
BRCA2 carriers	HR = 1.71 (0.4–8.2)[b]	HR = 5.43 (1.36–21.7)[c]			OR = 1.22 (0.62–2.42)[d]
All carriers	HR = 1.75 (1.1–2.8)[b]	HR = 4.29 (2.09–8.81)[c]	HR = 1.38 (0.87–2.20)		
Association with first chest X-rays (ever, never) at age <20 y					
BRCA1 carriers				OR = 1.7 (0.9–3.0)[g]	OR = 0.57 (0.22–1.48)[d]
BRCA2 carriers					OR = 1.55 (0.54–4.47)[d]
All carriers	HR = 5.21 (1.6–17.5)[b,h]	HR = 4.16 (2.03–8.56)[c]	HR = 1.29 (0.84–1.98)[b,d]		

[a]United Kingdom, Ireland, the Netherlands, France, Spain, Italy, Austria, Belgium, Germany, Hungary, Iceland, Denmark, and Sweden.

[b]Main analysis was based on cohort comprised of *BRCA1* and *BRCA2* mutation carriers who were diagnosed with breast cancer or who were censored within the 5 years before questionnaire completion.

[c]Main analysis was based on cohort comprised of one woman per family.

[d]Excludes chest fluoroscopy for tuberculosis.

[e]HRs and 95% CI or ORs and 95% CIs.

[f]Among affected non-carriers.

[g]Odds of having X-ray exposure for carriers versus non-carriers.

[h]Chest X-rays (ever, never) at age <20 years only.

Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

diagnosis of breast cancer, potentially biasing associations away from the null.

As the frequency and spectrum of mutations in *BRCA1* and *BRCA2* vary by race/ethnicity (30, 31), we limited our analysis to non-Hispanic white mutation carriers. Breast cancer risk in mutation carriers, however, appears to vary by mutation position (32, 33). It is not known whether radiation sensitivity varies by mutation type and position. Lecarpentier and colleagues (11) found no variation in breast cancer risk associated with chest X-rays by mutation position in *BRCA1* or *BRCA2*. Larger studies will be needed to assess whether the differences in associations between our study, and the European studies are due to differences in mutation types and radiosensitivity.

Several study limitations need to be considered when interpreting our results. As in previous studies (9–12), our exposure assessment relied on self-report. We, therefore, cannot rule out the possibility of inaccurate recall, especially of diagnostic procedures in the distant past. In the few studies conducted in the United States (29, 34) and Sweden (29, 35) that compared self-reported diagnostic X-rays and other diagnostic imaging against medical records, reporting errors tended to be nondifferential by disease status (29, 34, 36), although in one of the Swedish studies, there was evidence of differential recall bias for those ages younger than 50 years (35). A study from the Netherlands (36) that assessed the reliability of self-reported chest X-rays among *BRCA1* and *BRCA2* mutation carriers reported that the agreement between baseline and follow-up reports was nondifferential by disease status. Nondifferential exposure misclassification would bias risk estimates toward the null and might have reduced the possibility of finding a true association in our study. It is also possible that we failed to find statistically significant associations with diagnostic chest X-rays, especially for chest fluoroscopy and X-rays for pneumonia, due to insufficient power stemming from limited sample sizes. Our risk estimates have wide confidence intervals and are, therefore, imprecise. Future studies of *BRCA1* and *BRCA2* mutation carriers would benefit from improved exposure assessment, including queries about all types of diagnostic imaging procedures in the chest area, including mammograms which we did not assess in the current study.

Strengths of this study include use of the same questionnaire by the 3 family registry studies to assess therapeutic and diagnostic chest X-rays, which allowed us to identify unexposed carriers as the referent, and the focus on younger mutation carriers who need better guidelines for diagnostic procedures involving ionizing radiation at a young age. To minimize potential survival bias, we limited the affected mutation carriers to those who completed the questionnaire within 5 years of diagnosis. Our results remained unchanged when we further restricted the affected mutation carriers to those who completed the questionnaire within 3 years of diagnosis (data not shown).

Future studies should include larger numbers of *BRCA1* and *BRCA2* mutation carriers, and obtain detailed information on diagnostic imaging of the chest, including type and number of procedures, age at first exposure, and indications that required diagnostic procedures to the chest. Ideally, such reports would be verified by medical records to minimize any recall bias. However, given that ionizing radiation exposure at a young age (e.g., before the age of 20 years) is the most relevant window of susceptibility for radiation-induced breast cancer, retrospective verification may be very difficult, if not impossible. Study designs that include prospective breast cancer cases in a mutation carrier cohort providing baseline information on low-dose radiation exposure before diagnosis would avoid differential recall bias by case status.

Conclusions

Our findings do not support a positive association between diagnostic chest X-rays and breast cancer risk before the age of 50 years for *BRCA1* and *BRCA2* mutation carriers. Nevertheless, continued surveillance of the possible effects of diagnostic radiation exposure on breast cancer risk is warranted for these women, given the widespread and increasing use of diagnostic imaging involving ionizing radiation. Special attention might need to be paid to computed tomography, an imaging technology that is being used with increasing frequency both for children and adults and delivers much larger doses of ionizing radiation than conventional chest X-rays (37–39).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the BCFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government or the BCFR.

Authors' Contributions

Conception and design: E.M. John, D.C. Thomas, R. Haile, R.L. Milne, D.W. West, M. Daly, J.L. Hopper, G.G. Giles, A.S. Whittemore
Development of methodology: E.M. John, V. McGuire, D.C. Thomas, D.W. West, A. Miron, J.L. Hopper, G.G. Giles, A.S. Whittemore
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.M. John, R. Haile, D.W. West, J.A. Knight, M.B. Terry, M. Daly, S.S. Buys, I.L. Andrulis, J.L. Hopper, M.C. Southey, C. Apicella, H. Thorne
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.M. John, D.C. Thomas, H. Ozcelik, R.L. Milne, A. Felberg, D.W. West, A. Miron, J.A. Knight, M.B. Terry, J.L. Hopper, M.C. Southey, A.S. Whittemore
Writing, review and/or revision of the manuscript: E.M. John, V. McGuire, D.C. Thomas, R. Haile, H. Ozcelik, R.L. Milne, D.W. West, J.A. Knight, M.B. Terry, M. Daly, S.S. Buys, I.L. Andrulis, J.L. Hopper, M.C. Southey, G.G. Giles, C. Apicella, H. Thorne, A.S. Whittemore
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.M. John, V. McGuire, H. Ozcelik, A. Felberg, J.L. Hopper, M.C. Southey, C. Apicella, H. Thorne, A.S. Whittemore
Study supervision: E.M. John, D.W. West, J.L. Hopper

Acknowledgments

The authors thank Eveline Niedermayr, all the kConFab research nurses and staff, and the heads and staff of the Family Cancer Clinics for their contributions to this resource. The authors also thank the many families who contribute to the BCFR, kConFab, and OCGN.

Grant Support

This study was supported by the National Cancer Institute grant RO1 CA097359 (to A.S. Whittemore). The Breast Cancer Family Registry (BCFR) is supported by National Cancer Institute grant UM1 CA164920 (to I.L. Andrulis, S.S. Buys, M. Daly, J.L. Hopper, E.M. John, M.B. Terry). The Australian site of the BCFR was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation, and the Victorian Breast Cancer Research Consortium. kConFab is supported by grants from the National Breast Cancer Foundation, the National Health and Medical Research Council (NHMRC) and by the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia (to J.F. Sambrook). The Clinical Follow-Up Study is funded by NHMRC grants 145684, 288704 and 454508 (to J.F. Sambrook).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 21, 2013; revised June 7, 2013; accepted June 8, 2013; published OnlineFirst July 12, 2013.

References

1. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res 2005;7:21–32.
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;158:220–35.
3. Boice JD Jr, Preston D, Davis FG, Monson RR. Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res 1991;125:214–22.
4. Howe GR, McLaughlin J. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. Radiat Res 1996;145:694–707.
5. Ronckers CM, Doody MM, Lonstein JE, Stovall M, Land CE. Multiple diagnostic X-rays for spine deformities and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:605–13.
6. Hill DA, Preston-Martin S, Ross RK, Bernstein L. Medical radiation, family history of cancer, and benign breast disease in relation to breast cancer risk in young women, USA. Cancer Causes Control 2002; 13:711–8.
7. Ma H, Hill CK, Bernstein L, Ursin G. Low-dose medical radiation exposure and breast cancer risk in women under age 50 years overall and by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast Cancer Res Treat 2008;109:77–90.
8. John EM, Phipps AI, Knight JA, Milne RL, Dite GS, Hopper JL, et al. Medical radiation exposure and breast cancer risk: findings from the Breast Cancer Family Registry. Int J Cancer 2007;121:386–94.
9. 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;24:3361–6.
10. Gronwald J, Pijpe A, Byrski T, Huzarski T, Stawicka M, Cybulski C, et al. Early radiation exposures and BRCA1-associated breast cancer in young women from Poland. Breast Cancer Res Treat 2008;112:581–4.
11. 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;130:927–38.
12. 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.
13. 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: 402–6.
14. 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;15:2311–3.
15. Powell SN, Kachnic LA. Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation. Oncogene 2003;22:5784–91.
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;326:781–5.
17. 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:R26.
18. Mellemkjaer L, Dahl C, Olsen JH, Bertelsen L, Guldberg P, Christensen J, et al. Risk for contralateral breast cancer among carriers of the CHEK2*1100delC mutation in the WECARE Study. Br J Cancer 2008;98:728–33.
19. Bernstein JL, Haile RW, Stovall M, Boice JD Jr, Shore RE, Langholz B, et al. Radiation exposure, the ATM Gene, and contralateral breast cancer in the women's environmental cancer and radiation epidemiology study. J Natl Cancer Inst 2010;102:475–83.
20. Haile RW, Thomas DC, McGuire V, Felberg A, John EM, Milne RL, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006; 15:1863–70.
21. John EM, Hopper JL, Beck JC, Knight JA, Neuhausen SL, Senie RT, et al. The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast Cancer Res 2004;6: R375–89.
22. Osborne RH, Hopper JL, Kirk JA, Chenevix-Trench G, Thorne HJ, Sambrook JF. kConFab: a research resource of Australasian breast cancer families. Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer. Med J Aust 2000;172:463–4.
23. Andrulis IL, Anton-Culver H, Beck J, Bove B, Boyd J, Buys S, et al. Comparison of DNA- and RNA-based methods for detection of truncating BRCA1 mutations. Hum Mutat 2002;20:65–73.
24. Neuhausen SL, Ozcelik H, Southey MC, John EM, Godwin AK, Chung W, et al. BRCA1 and BRCA2 mutation carriers in the Breast Cancer Family Registry: an open resource for collaborative research. Breast Cancer Res Treat 2009;116:379–86.
25. Mann GJ, Thorne H, Balleine RL, Butow PN, Clarke CL, Edkins E, et al. Analysis of cancer risk and BRCA1 and BRCA2 mutation prevalence in the kConFab familial breast cancer resource. Breast Cancer Res 2006; 8:R12.
26. Whittemore AS, Halpern J. Multi-stage sampling in genetic epidemiology. Stat Med 1997;16:153–67.
27. Morin Doody M, Lonstein JE, Stovall M, Hacker DG, Luckyanov N, Land CE. Breast cancer mortality after diagnostic radiography: findings from the U.S. Scoliosis Cohort Study. Spine 2000;25:2052–63.
28. Regulla DF, Eder H. Patient exposure in medical X-ray imaging in Europe. Radiat Prot Dosimetry 2005;114:11–25.
29. Berrington de Gonzalez A, Ekbom A, Glass AG, Galanti MR, Grimelius L, Allison MJ, et al. Comparison of documented and recalled histories of exposure to diagnostic x-rays in case-control studies of thyroid cancer. Am J Epidemiol 2003;157:652–63.
30. John EM, Miron A, Gong G, Phipps AI, Felberg A, Li FP, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA 2007;298:2869–76.
31. Kurian AW. BRCA1 and BRCA2 mutations across race and ethnicity: distribution and clinical implications. Curr Opin Obstet Gynecol 2010; 22:72–8.

Published OnlineFirst July 12, 2013; DOI: 10.1158/1055-9965.EPI-13-0189

32. Thompson D, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 2001;68: 410–9.

33. Thompson D, Easton D. Variation in BRCA1 cancer risks by mutation position. Cancer Epidemiol Biomarkers Prev 2002;11:329–36.

34. Pogoda JM, Preston-Martin S. Radiation exposure from diagnostic imaging: agreement between self-report and medical records. Health Phys 2002;83:907–17.

35. Hallquist A, Jansson P. Self-reported diagnostic X-ray investigation and data from medical records in case-control studies on thyroid cancer: evidence of recall bias? Eur J Cancer Prev 2005;14:271–6.

36. Pijpe A, Manders P, Mulder RL, van Leeuwen FE, Rookus MA. Reliability of self-reported diagnostic radiation history in BRCA1/2 mutation carriers. Eur J Epidemiol 2010;25:103–13.

37. Brenner DJ, Hall EJ. Computed tomography–an increasing source of radiation exposure. N Engl J Med 2007;357:2277–84.

38. Pearce MS. Patterns in paediatric CT use: an international and epidemiological perspective. J Med Imaging Radiat Oncol 2011;55: 107–9.

39. Smith-Bindman R. Environmental causes of breast cancer and radiation from medical imaging: findings from the Institute of Medicine report. Arch Intern Med 2012;172:1023–7.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Diagnostic Chest X-Rays and Breast Cancer Risk before Age 50 Years for *BRCA1* and *BRCA2* Mutation Carriers

Esther M. John, Valerie McGuire, Duncan Thomas, et al.

Cancer Epidemiol Biomarkers Prev 2013;22:1547-1556. Published OnlineFirst July 12, 2013.