

Medical radiation, family history of cancer, and benign breast disease in relation to breast cancer risk in young women, USA

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Received 7 September 2001; accepted in revised form 13 April 2002

Key words: breast diseases, breast neoplasms, genetic predisposition to disease, radiography.

Abstract

Objective: In previous studies breast cancer risk has been increased among women who received high doses (above 100–200 cGy) of ionizing radiation or those exposed to lower doses prior to age 20. Some evidence suggests that such risk may be distinctly elevated among women with a family history of breast or ovarian cancer (probably only carriers of specific gene mutations) and women with benign breast disease (BBD).

Methods: A population-based case-control study in Los Angeles County obtained interview data from 744 women who were aged 40 or younger and diagnosed with breast cancer during 1983–1988, and from 744 matched controls. Women with a positive family history of breast or ovarian cancer reported cancer in a mother, sister, or grandmother. Women with BBD reported a physician diagnosis. Radiation exposure was defined as a history of either radiation therapy or moderate exposure to medical radiography.

Results: Breast cancer risk was elevated among women exposed to medical radiation prior to age 20 years (odds ratio (OR) = 1.4, 95% confidence interval (CI) = 1.2–1.8), relative to unexposed women. This increased risk was observed only among women with a history of BBD (OR = 2.4, 95% CI = 1.6–3.7). Overall, risk was not associated with exposure to medical radiation after age 20 years, although among women with a positive family history of breast or ovarian cancer, exposed women had an increased risk (OR = 1.8, 95% CI = 1.0–3.1). Breast cancer risk was not increased among women with a family history of breast/ovarian cancer exposed to medical radiation before age 20 years or those with BBD exposed to medical radiation after age 20 years.

Discussion: Study participants may have received radiation doses that are no longer common, hampering study generalizability. Although differences in recall between cases and controls cannot be completely excluded, women with BBD or a family history of breast cancer appear to have greater breast cancer risk following relatively low ionizing radiation exposure than other women in this study.

Introduction

Breast cancer risk is increased among women exposed to relatively high doses (above 100–200 cGy) [1–5] of ionizing radiation or those exposed to lower doses if exposure occurred prior to age 20 [3, 4]. Women who received high doses of ionizing radiation as treatment

for Hodgkin's disease [1], benign breast disease [2] or other medical conditions [3, 4], or who were residents of Hiroshima or Nagasaki at the time of the atomic bomb blasts [5], have an elevated breast cancer risk in comparison with unexposed women. In addition, relative risk of breast cancer is increased among women who received lower doses (20–49 cGy) if exposure occurred prior to age 20 [3, 4]. Regardless of dose, relative risk declines with increasing age, and few studies have identified an increased risk among women exposed after age 40 [5, 6]. While high radiation doses or young age at exposure may characterize women with an elevated

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breast cancer risk, recent studies suggest additional factors that may distinguish such women.

Women who inherit a BRCA1 or BRCA2 gene mutation have an increased risk of breast or ovarian cancer prior to age 40 [7, 8]. In several investigations, cell lines deficient in BRCA1 or BRCA2 have demonstrated widespread cell death and reduced capacity to repair DNA damage following high-dose radiation (100–1000 cGy) [9, 10], suggesting that women who carry mutations in these genes also may have diminished ability to repair radiation-induced DNA damage. Among young breast cancer cases, 11–29% of those with a family history of breast or ovarian cancer may be mutation carriers [7, 8].

Risk of benign breast disease (BBD) is elevated among women who have received moderate doses of radiation [11–14], and women with BBD who subsequently receive radiation exposure may have a particularly increased breast cancer risk [2]. In four large cohorts of radiation-exposed women the risk of developing BBD was 1.3–3.0 times greater than among unexposed women [11–14]. In one study the relative risk was particularly elevated for proliferative BBD and atypical hyperplasia [14], which are associated with greater breast cancer risk than nonproliferative BBD [15]. BBD risk also increased with increasing radiation dose [12, 14]. Women diagnosed with BBD who receive subsequent radiation exposure might also have a higher breast cancer risk than expected given both risk factors [16]. Among Swedish women given radiation treatment for BBD, relative risk of breast cancer remained substantially elevated among those first exposed at ages 20–39 or at age 40 or older [2], in contrast with findings from other studies. In a pooled comparison of eight radiation-exposed cohorts, breast cancer risk among Swedish women treated for BBD exceeded that of all other women except those from Hiroshima/Nagasaki, and risk was notably elevated among those exposed prior to age 20 (Preston D, personal communication).

We report results for a population-based case–control study of breast cancer risk factors in young women (aged 40 years or younger) in which we evaluated breast cancer risk in relation to medical or dental radiation, particularly among women with a family history of breast or ovarian cancer, and because of previous findings in the literature we also examined risk among those with BBD.

Materials and methods

We conducted a case–control study of breast cancer among residents of Los Angeles County, California.

Breast cancer patients were identified through the Cancer Surveillance Program, the population-based registry for Los Angeles County that provides information on all cancers newly diagnosed among County residents. Women diagnosed with *in-situ* or invasive breast cancer between 1 July 1983 and 31 December 1988 were included in the study if they were 40 years or younger, white (including Latina whites), and born in the United States, Canada, or Europe. Women previously diagnosed with breast cancer were ineligible. In all, 969 eligible patients were identified. Of these, 20 (2.1%) died prior to interview, 172 could not be interviewed due to physician refusal (5.6%) or patient (11.5%) refusal, or illness (0.7%), and 33 (3.4%) had moved outside Los Angeles County or were lost to follow-up. Interviews were conducted with 744 women (76.7%).

Control subjects were identified in the neighborhood of cases and individually matched to each interviewed case patient on birth date (within 36 months), race (white), and parity status (nulliparous or parous). Control subjects were also restricted as to birthplace (United States, Canada, or Europe); and those previously diagnosed with breast cancer were ineligible. Details regarding control recruitment have previously been described [17]. In total, 938 women who met matching criteria were identified to recruit and interview 744 controls (79.3%). Each control was assigned a reference date that was equivalent to one year prior to the date of diagnosis of the matched case patient. This date also served as the case's reference date.

We conducted in-person interviews with participants, recording reproductive and medical history up to the reference date, as well as cancer history in female relatives and demographic data. We collected information on whether participants had ever had BBD, which was defined as “breast disease, cysts, or lumps in the breast” diagnosed by a physician prior to reference date. We collected data regarding radiation exposure to the chest or neck, including radiation therapy received prior to diagnosis, and lead apron use during dental X-ray exams, including the frequency of full-mouth (14–20 X-ray films) and other dental exams (generally fewer films). We also asked about the following diagnostic procedures: upper gastrointestinal (GI) exams, computerized tomography (CT) exams of the trunk or neck, gallbladder (GB) exams, intravenous pyelograms (IVP) of the kidney, chest fluoroscopy (CF), angiograms, and arteriograms. In addition, we collected information regarding other conventional diagnostic X-rays of the trunk or neck (65% were chest X-rays), which included only those that did not involve fluoroscopy or contrast media. We obtained information on exam site, whether

it was received prior to age 20 or afterwards, and reason for exam (radiation therapy and conventional exams only). No women received radiotherapy for BBD, and mammograms were excluded. Interviewing was completed in December 1991. This study was approved by the University of Southern California Research Committee, in accord with assurances approved by the US Department of Human Services. Written informed consent was obtained from all study participants.

We classified medical radiation received prior to age 20 years as "childhood" medical radiation, and that received later as "adulthood" radiation, with most women exposed during both age periods. The seven "diagnostic procedures" (upper GI, CT, GB, IVP, CF, angiograms, and arteriograms) were grouped together as one exposure variable, and all other diagnostic radiographs of the trunk or neck were also considered together as "conventional X-ray exams". We added the questions regarding diagnostic procedures and conventional exams to the study after interviewing 199 matched pairs, who do not contribute to the analysis of these variables.

Women were considered to have a positive family history if they reported breast or ovarian cancer in their mothers, sisters, or grandmothers (information was not collected regarding aunts). To examine breast cancer risk in the relatively small family history strata it was necessary to combine exposed women. "Radiation exposure" was defined as a history of either radiation therapy, any of seven diagnostic exams, dental exams without a lead apron, or three or more conventional X-rays, prior to age 20 or at older ages. Women who received radiation were compared to unexposed women with a similar family history, so as to separate the breast cancer risk associated with radiation from the risk associated with cancer family history. For similar reasons, exposed women with BBD were compared primarily to unexposed women with BBD.

We evaluated known or suspected breast cancer risk factors as potential confounders, including pregnancy-associated factors, age at menarche, body mass index (weight (kg)/height (m²)), BBD, family history of breast or ovarian cancer, oral contraceptive use, alcohol use, and lifetime exercise history. We also assessed the education and occupation of parent or guardian when the participant was age 18, and the education and occupation of the participant at the reference date. Information on parental occupation was not collected from the first 199 case-control pairs. Multivariate conditional logistic regression methods were used to derive odds ratios (OR) and associated 95% confidence intervals (CI) for the relationship between medical radiation and breast cancer risk. Variables which altered

the OR estimates by 10% or more, and which were included in the multivariate analysis were: age at menarche (≤ 12 years, ≥ 13 years), participant's education (college graduate vs less education), and occupation of parent or guardian when participant was age 18 years (professional/administrative/clerical vs skilled/unskilled labor/machine operator). To determine whether odds ratio estimates were heterogeneous across strata defined by the presence or absence of either BBD or cancer family history, interaction was assessed in a multiplicative conditional logistic regression model that included two main effect variables and a term for their joint effects. Analyses of medical radiation received during one age period (childhood or adulthood) were adjusted for exposure during the other age period.

Results

Cases were more likely than controls to have an earlier age at menarche and to have completed less than a college education (Table 1). Women with a family history of breast cancer (adjusted OR = 2.2; 95% CI = 1.6-2.9) or ovarian cancer (OR = 3.0; 95% CI = 1.3-6.5) had increased breast cancer risk (Table 2). A greater proportion of cases than controls reported a physician diagnosis of BBD (OR = 1.9; 95% CI = 1.5-2.4).

Table 1. Description of study population

	No. of cases (%)	No. of controls (%)
	744 (100)	744 (100)
Reference age (years)		
≤ 30	107 (14.4)	121 (16.3)
31-35	260 (35.0)	266 (35.7)
≥ 36	377 (50.6)	357 (48.0)
Education		
Less than high school graduate	40 (5.4)	31 (4.2)
High school graduate	163 (21.9)	149 (20.0)
Some college	312 (41.9)	274 (36.8)
College graduate/graduate training	229 (30.8)	290 (39.0)
Age at menarche (years)		
≤ 12	423 (56.9)	384 (51.6)
> 12	321 (43.1)	360 (48.4)
Parent's occupation when participant was age 18 (Hollingshead Occupational Index)		
Executive/administrative/clerical/technician	323 (43.4)	358 (48.1)
Skilled manual labor/machine operator/unskilled labor	217 (29.2)	176 (23.7)
Not asked (matched pairs)	199 (26.7)	199 (26.7)
Unknown	5 (0.7)	11 (1.5)

Table 2. Breast cancer risk among young women, according to family history of cancer or personal history of benign breast disease

	No. of cases (%)	No. of controls (%)	Odds ratio ^b (95% CI)
	744 (100)	744 (100)	
Family history of breast cancer ^a			
No	559 (75.1)	645 (86.7)	1.0
Yes	185 (24.9)	99 (13.3)	2.2 (1.6–2.9)
Family history of ovarian cancer			
No	722 (97.0)	735 (98.8)	1.0
Yes	22 (3.0)	9 (1.2)	3.0 (1.3–6.5)
Personal history of benign breast disease			
No	475 (63.8)	564 (75.8)	1.0
Yes	269 (36.2)	180 (24.2)	1.9 (1.5–2.4)

^a History of a given cancer in first-degree female relatives or grandmothers. Fourteen women who were adopted are considered to have no family history of cancer.

^b Odds ratios were adjusted for age at menarche (≤ 12 , > 12), parent's occupation when participant was age 18 (professional/administrative/clerical, skilled/unskilled labor/machine operator), and participant's education (college graduate, less education).

Overall, medical radiation exposure prior to age 20 years was somewhat more common among women with breast cancer than among controls (Table 3). Cases and controls did not differ in reported radiation exposure at older ages. In an analysis confined to women with a family history of breast or ovarian cancer, breast cancer risk was somewhat increased if women were exposed to childhood radiation (OR = 1.5; 95% CI = 0.9–2.5), or adulthood radiation (OR = 1.8; 95% CI = 1.0–3.3), in comparison with unexposed women (Table 4).

We also examined breast cancer risk separately among women with BBD. In the strata confined to women with BBD, those who received radiation exposure during childhood had an increased breast cancer risk (OR = 2.4; 95% CI = 1.6–3.7), in comparison with unexposed women (Table 4). Among women with BBD, childhood radiation exposure was related to a somewhat greater breast cancer risk for nulliparous women (OR = 3.8; 95% CI = 1.8–7.9; 63 cases, 22 controls) than for parous women (OR = 1.9; 95% CI = 1.1–3.2; p -value for difference = 0.15), and was somewhat greater for women under age 35 years at reference date than for older women (data not shown), relative to unexposed women of similar age or parity. Women with BBD who received medical radiation during adulthood did not have an altered risk. Women without BBD or a family history of breast/ovarian cancer, who comprised the majority of the study population, did not have an increased risk of breast cancer following childhood or adulthood radiation (Table 4).

We calculated whether the effects of radiation exposure on breast cancer risk differed between women who had a family history of breast/ovarian cancer vs those who did not, and among women with BBD compared to women without BBD. Breast cancer risk of women with a family history did not differ from that of women without a family history when exposure to childhood radiation was assessed. The apparently increased risk of 1.5 (95% CI 0.9–2.5) in Table 4 was attributable entirely to women with BBD within that subgroup. However, women with a family history and radiation exposure at age 20 years or older had a greater breast cancer risk than expected from the joint multiplicative effects of each risk factor (OR = 1.8; 95% CI = 1.0–3.1), relative to those with neither risk factor, demonstrating that risk was different between the two groups. The breast cancer risk of women reporting both BBD and radiation exposure at before age 20 years also was greater than expected from the joint multiplicative effects of each risk factor (OR = 2.2; 95% CI = 1.3–3.5), relative to those who reported neither exposure, indicating that risk was also different between women with BBD and women without BBD.

Discussion

Most previous studies of breast cancer among women exposed to ionizing radiation have not evaluated the potential modifying effects of other risk factors, possibly masking heterogeneity in risk. We found that a woman's breast cancer risk may differ according to her family history of breast/ovarian cancer and personal history of BBD. In our data, only women with BBD have an increased breast cancer risk following exposure to childhood medical radiation. In contrast, only women with a positive family history of breast/ovarian cancer appear to have an elevated breast cancer risk after radiation exposure at older ages. Notably, for the majority of women exposed to low-dose radiation in this study, there was no evidence of an increased breast cancer risk. Our findings should be considered in light of other potential explanations, including the possibility that the accuracy of reports of key risk factors may differ between cases and controls. Another important consideration is the unknown temporal relationship between radiation exposure and BBD diagnosis.

Differences in recall between cases and controls could occur because cases are concerned about the origins of their illness, and thus may recall medical radiation exposures more thoroughly than controls. Women with a family history of breast or ovarian cancer or a BBD diagnosis may be somewhat more likely to recall past

Table 3. Breast cancer risk among women who received medical radiation, according to age at exposure

	Age 1–19 years			Age 20+ years		
	No. of cases (%)	No. of controls (%)	OR ^a (95% CI)	No. of cases (%)	No. of controls (%)	OR ^a (95% CI)
<i>Radiation therapy</i>						
No	719 (96.6)	722 (97.0)	1.0	736 (98.9)	734 (98.7)	1.0
Yes	25 (3.4)	22 (3.0)	1.2 (0.6–2.3)	8 (1.1)	10 (1.3)	0.6 (0.2–1.7)
<i>Diagnostic procedures^b</i>						
0	487 (65.5)	493 (66.3)	1.0	344 (46.2)	346 (46.6)	1.0
1	37 (5.0)	38 (5.1)	1.0 (0.6–1.6)	110 (14.9)	108 (14.5)	0.9 (0.7–1.3)
2+	21 (2.8)	14 (1.9)	1.6 (0.8–3.5)	91 (12.2)	91 (12.2)	1.2 (0.8–1.9)
Not asked	199 (26.7)	199 (26.7)		199 (26.7)	199 (26.7)	
<i>Conventional X-rays</i>						
0	239 (32.2)	271 (36.5)	1.0	103 (13.8)	106 (14.2)	1.0
1–2	180 (24.2)	187 (25.1)	1.1 (0.8–1.5)	155 (20.9)	170 (22.9)	0.9 (0.7–1.3)
3+	126 (16.9)	87 (11.7)	1.5 (1.1–2.1)	287 (38.6)	269 (36.2)	1.0 (0.7–1.5)
Not asked	199 (26.7)	199 (26.7)		199 (26.7)	199 (26.7)	
<i>Dental Exams: lead apron worn</i>						
Yes	412 (55.4)	461 (62.0)	1.0	543 (73.0)	583 (78.4)	1.0
No	217 (29.2)	165 (22.2)	1.5 (1.1–1.9)	178 (23.9)	149 (20.0)	1.1 (0.8–1.4)
Don't know	115 (15.4)	118 (15.8)		23 (3.1)	12 (1.6)	
<i>Full mouth exams</i>						
1	37(5.0)	31 (4.2)	1.2 (0.6–2.1)	18 (2.4)	16 (2.2)	1.3 (0.6–2.9)
2+	72(9.7)	52 (6.7)	1.4 (0.9–2.3)	92 (12.4)	77 (10.4)	1.2 (0.8–1.7)
<i>Non-full mouth exams</i>						
1–2	50 (6.7)	34 (4.6)	1.4 (0.8–2.3)	23 (3.1)	33 (4.4)	0.6 (0.3–1.0)
3–5	48 (6.5)	41 (5.5)	1.0 (0.6–1.7)	40 (5.4)	32 (4.3)	1.0 (0.6–1.7)
6+	84 (11.3)	63 (8.5)	1.4 (0.9–2.2)	71 (9.5)	45 (6.1)	1.5 (0.9–2.3)
<i>Radiation exposure^c</i>						
No	410 (55.1)	470 (63.2)	1.0	297 (39.9)	320 (43.0)	1.0
Yes	334 (44.9)	274 (36.8)	1.4 (1.2–1.8)	447 (60.1)	424 (57.0)	1.1 (0.9–1.4)

^a All odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age at menarche (≤ 12 , > 12), parent's occupation when participant was age 18 (professional/administrative/clerical, skilled/unskilled labor/machine operator), participant's education (college graduate, less education), and radiation received during the other age period.

^b Diagnostic procedures include upper gastrointestinal exams; intravenous pyelograms of the kidney; computerized tomography exams of the trunk, head, or neck; gallbladder exams; chest fluoroscopy; angiograms; and arteriograms.

^c Radiation exposure was defined as a history of either radiation therapy, any of seven diagnostic procedures; absence of a lead apron during dental exams; or three or more conventional X-rays of the trunk, head, or neck during the relevant age period.

events carefully, but differential recall between cases and controls without these characteristics would also be expected, and is not evident. Nonetheless, more extensive recall by particular subsets of cases and underreporting of radiation exposure and BBD among controls could introduce bias, and must be considered in interpreting the study results. However, some data argue against recall bias as the sole explanation for our findings. Risk estimates associated with a family history of breast or ovarian cancer or a personal history of BBD (Table 2) are comparable with those from other studies. In addition, the greater radiation-related breast cancer risk for women with BBD who were nulliparous as compared with those who are parous is consistent with

the reported decrease in radiation-related breast cancer risk with increasing parity [5, 18], while there is no reason to expect particularly differential recall among these women. The OR estimates for women with BBD are somewhat stronger than those usually attributed to recall bias. While disparate recall may have influenced some responses, the strength and specificity of the results suggest that they are not attributable entirely to recall bias.

Misclassification of genetic predisposition to cancer or of BBD diagnosis is also a concern in this study. Some women who report a clinical diagnosis of BBD may not have the disease, and others not reporting BBD may be affected [19]. Over 30% of women may develop BBD in

Table 4. Breast cancer risk among women who received medical radiation, according to age at exposure, family history of breast or ovarian cancer, and benign breast disease

Radiation exposures ^a	Age 1–19 years			Age 20+ years		
	No. of cases (%)	No. of controls (%)	Odds ratio (95% CI) ^b	No. of cases (%)	No. of controls (%)	Odds ratio (95% CI) ^b
Among women with a family history of breast or ovarian cancer						
No	111 (54.7)	71 (66.4)	1.0	77 (37.9)	53 (49.5)	1.0
Yes	92 (45.3)	36 (33.6)	1.5 (0.9–2.5)	126 (62.1)	54 (50.5)	1.8 (1.0–3.1)
Among women without a family history of breast or ovarian cancer						
No	299 (55.3)	401 (63.0)	1.0	220 (40.7)	267 (41.9)	1.0
Yes	242 (44.7)	236 (37.0)	1.4 (1.1–1.8)	321 (59.3)	370 (58.1)	0.9 (0.7–1.2)
Among women with benign breast disease						
No	128 (47.6)	121 (67.2)	1.0	94 (34.9)	67 (37.2)	1.0
Yes	141 (52.4)	59 (32.8)	2.4 (1.6–3.7)	175 (65.1)	113 (62.8)	1.0 (0.6–1.5)
Among women without benign breast disease						
No	282 (59.4)	351 (62.2)	1.0	203 (42.7)	253 (44.9)	1.0
Yes	193 (40.6)	213 (37.8)	1.1 (0.9–1.5)	272 (57.3)	311 (55.1)	1.0 (0.8–1.4)

^a Radiation exposure was defined as a history of either radiation therapy; any of seven diagnostic procedures; absence of lead apron use during dental exams; or three or more conventional X-rays of the trunk, head, or neck during the relevant age period.

^b Odds ratios were adjusted for age at menarche (≤ 12 , > 12), parent's occupation when participant was age 18 (professional/administrative/clerical, skilled/unskilled labor/machine operator), participant's education (college graduate, less education), and radiation received during the other age period.

their lifetimes [20], and those who receive a physician diagnosis may constitute the most symptomatic cases. Further misclassification would occur if only particular histopathologic type(s) of BBD are related to breast cancer risk following radiation exposure. Misclassification that is nondifferential with respect to case–control status usually would attenuate any relationship between radiation and breast cancer [21]. Misclassification of stratification variables such as BBD or family history of breast/ovarian cancer can also introduce bias in risk estimates [22], although these variables are not confounders of the exposure–disease relationship.

Although we do not know the age at which study participants developed BBD, it is likely that childhood radiation exposure preceded BBD onset, suggesting that ionizing radiation may contribute to the development of BBD. Female atomic bomb survivors exposed to a radiation dose of 1 Sievert (Sv) (~ 100 cGy) had a greater risk of BBD than unexposed women in an autopsy study [14]. Risk was highest for development of proliferative disease or atypical hyperplasia, and increased with radiation dose. Women irradiated for postpartum mastitis also had a two-fold increased risk of developing fibroadenomas and intraductal papillomas compared with unirradiated mastitis patients [13]. In addition, women treated in infancy for thymic enlargement with radiation doses of 1–49 cGy had twice the risk of subsequent BBD (fibroadenoma or intraductal papilloma) as their nonirradiated female siblings [12].

TB patients who received chest fluoroscopy appeared to have an increased BBD risk only at doses above 500 cGy, but BBD prevalence was low (15%) [11]. Also, ionizing radiation exposure is related to a dose-dependent increase in mammary fibroadenoma in rats [23].

If breast disease is a consequence of low-dose ionizing radiation exposure, then BBD is not a modifier of risk, as its use as a stratification variable suggests. BBD is not usually a direct precursor of breast cancer, and some forms of BBD may be only a marker of enhanced risk. For example, fibroadenomas arise in connective tissue which rarely undergoes further oncogenic transformation, although such diagnoses imply a higher risk of cancer development in adjacent epithelial tissue. In addition, less than 5% of all benign biopsies are classified as atypical hyperplasia [15], which may be a more direct breast cancer precursor. Furthermore, women only have a slightly greater risk of developing invasive breast cancer in the ipsilateral breast of the benign biopsy as compared with the contralateral breast [24]. Thus, BBD is not usually a histologic intermediate on the breast cancer development pathway, but an indicator of enhanced risk.

Breast cancer risk among our study participants with BBD is greater than might be expected when compared with Swedish women treated with radiotherapy for BBD (primarily fibroadenoma). These women had a 2.2-fold greater risk than unirradiated women with BBD, per 100 cGy of exposure, and those who received a dose of 20–

49 cGy had a 1.5-fold greater risk, despite a median exposure age of 43 [2]. In our study, women received radiation therapy primarily for hemangioma or an enlarged thymus, and those with similar indications received mean breast doses of 29 cGy [25], and 69 cGy [3] in previous studies. Our remaining participants are presumed to have received less than 10–20 cGy prior to age 20; however, little information is available regarding breast dose received from diagnostic radiology during the 1950s and early 1960s. Doses declined at least 2–5-fold between 1950 and 1970 in one comparison [26]. An upper GI exam (six films + fluoroscopy) involved an entrance skin dose of 3.1 cGy in 1964 [27].

What factors might account for the increased breast cancer risk observed at the lower doses in this study? A portion may be explained by young age at exposure and diagnosis (mean diagnosis age = 36). Infants treated for an enlarged thymus [3] or young women treated for scoliosis [4] (average age 12 years) had 2.7–3.4-fold increased breast cancer risks in the lower dose range of 20–49 cGy. Risk also was elevated among atomic bomb survivors exposed before age 20 and diagnosed before age 35 (excess RR per Sv = 13.5) [5], although this was not observed in another study [28]. In contrast, Swedish women with BBD, treated at a median age of 40, developed breast cancer 15–30 years later and after menopause [2], when radiation-related breast cancer rarely occurs [5, 6]. The distinctly younger age at exposure and diagnosis of our subjects may explain some differences in risk estimates between the women with BBD in our study and the Swedish BBD study.

Only a few studies have examined whether breast cancer risk differs from that expected among women who are both exposed to radiation, and who also report BBD or a family history of breast cancer. Among atomic bomb survivors, neither risk factor was related to increased breast cancer risk when women were matched on radiation dose, but the authors indicate that both factors may be poorly reported [29]. Breast cancer risk was somewhat greater than expected on an additive scale for women irradiated for mastitis who later reported BBD, but not for those who reported a family history, possibly because some controls were sisters and matched on that risk factor [16]. No interaction between BBD and radiation exposure was evident, and no interaction with family history was calculated among breast cancer cases ($n = 28$) in an early report from the TB Fluoroscopy Cohort [11].

Of women who received medical radiation during adulthood, only those with a family history of breast/ovarian cancer have an increased risk in this study. However, the latency period was relatively short. Also,

women exposed at the youngest ages had the highest breast cancer risks in previous studies [2, 5]. Yet, women with a family history (or BBD) might be expected to have increased risks in both age periods, if recall bias was a major determinant of our results. Among women who inherit a single BRCA mutation, loss of the second allele may be necessary for DNA repair to be compromised [9, 10], and the age at which this might occur is unknown. In one study the latency period for radiation-related cancer was relatively short (5% cumulative incidence at 8 years) among those who inherited a gene conferring an increased risk of radiation-induced cancer [30]. Our data provide limited evidence of the hypothesized radiation sensitivity among women with a breast/ovarian cancer family history.

If these findings can be confirmed by more recent data the interpretation of our results for young women who have BBD or a family history of breast/ovarian cancer may become much more straightforward. The radiation doses received by the women in this study, whose median birth year was 1950 and reference year was 1985, are much higher than those received by later cohorts [26]. Lead aprons subsequently have become a standard requirement during dental X-rays, and routine chest X-rays have virtually ceased. In short, the elevated risks in this study can be attributed primarily to exposures and radiation doses that are no longer routine. Thus, the results of this study are not generalizable to younger cohorts, nor to women diagnosed with breast cancer after age 40 years. There is a need for investigations that incorporate dose information from more recent, lower-dose exposures, and that directly measure genotype, to quantify the hazards of ionizing radiation for the women identified as potentially susceptible in this study.

Acknowledgements

This study was supported by National Cancer Institute grants CA44546 and CA17054, and by the California Public Health Foundation, subcontract 050-F-8709, which is supported by the California Department of Health Services as part of its statewide cancer reporting program, mandated by Health and Safety Code Sections 210 and 211.3. Dr Hill was also supported by funds provided by the California Breast Cancer Research Program of the University of California, grant 4FB-0123.

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