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Original Contribution

Evidence for Increased Susceptibility to Breast Cancer From Exposure to Ionizing Radiation Due to a Familial History of Breast Cancer: Results From the Swedish Hemangioma Cohort

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Women with a history of breast cancer among family members are at increased risk for breast cancer. However, it is unknown whether a familial breast cancer history (FBCH) also increases individual susceptibility to breast cancer from radiation exposure. In this cohort study, 17,200 female Swedish hemangioma patients with 1,079 breast cancer cases diagnosed between 1958 and 2013, exposed to ionizing radiation in infancy, were linked to their first-degree relatives. The association between FBCH and radiation-induced breast cancer risk was assessed. Further, the relevance for breast cancer radiotherapy and mammography screening was evaluated. On average, the radiation-induced excess relative risk and excess absolute risk of breast cancer at age 50 years were 0.51 Gy^{-1} (95% confidence interval (CI): 0.33, 0.71) and 10.8 cases/10,000 person-years/Gy (95% CI: 7.0, 14.6), respectively. Radiation risk was higher by a factor of 2.7 (95% CI: 1.0, 4.8; $P = 0.05$) if 1 first-degree relative was affected by breast cancer. For whole-breast standard radiotherapy at age 40 years with a contralateral breast dose of 0.72 Gy, the 20-year radiation-related excess risk of contralateral breast cancer was estimated to increase from 0.6% for women without FBCH to 1.7% for women with FBCH. In a biennial mammography screening program at ages 40–74 years, radiation risk up to age 80 years would increase from 0.11% for women without FBCH to 0.29% for women with FBCH.

breast cancer; breast cancer risk; familial breast cancer history; ionizing radiation; radiation epidemiology

Abbreviations: *BRCA*, breast cancer susceptibility gene; CI, confidence interval; EAR, excess absolute risk; FBCH, familial breast cancer history; LAR, lifetime attributable risk; PASSOS, Personalised Assessment of Late Health Risks After Exposure to Ionising Radiation and Guidance for Radiation Applications in Medicine; SHC, Swedish Hemangioma Cohort.

Breast cancer is the most frequently diagnosed cancer in women worldwide. Women with a family history of breast cancer are known to be at elevated risk. One out of 9 women who develop breast cancer have an affected mother, sister, or daughter (1). Current clinical guidelines include family history as important element for recommendations on patient treatment and care (2). Familial breast cancer is likely to be associated with a strong genetic component. The molecular landscape of breast cancer shows significant molecular heterogeneity (3–5). Within the group of familial breast cancer, only around 25% of breast cancer cases may be attributed to germline mutations in the 2 high-susceptibility genes, breast cancer type 1 (*BRCA1*) and breast cancer type 2 (*BRCA2*), and the majority of cases are attributed to moderate- and low-susceptibility genes (6).

Ionizing radiation increases the risk of female breast cancer (7–10). It is plausible that women with an inherited genetic predisposition may be more susceptible to the effects of radiation exposure. For carriers of the *BRCA* mutation, efforts have been made to assess radiation-induced risk from therapeutic and diagnostic applications (11, 12). Bernstein et al. (11) found a relative risk for contralateral breast cancer of 1.4 (95% confidence interval (CI): 0.6, 3.3) in *BRCA* carriers treated with breast radiotherapy in comparison with *BRCA*

carriers without radiotherapy. Pijpe et al. (12) reported that in *BRCA* carriers, any exposure to diagnostic radiation before 30 years of age was associated with an increased risk of breast cancer (hazard ratio = 1.90, 95% CI: 1.20, 3.00) in comparison with *BRCA* carriers without such exposure. However, the evidence for breast cancer risk from the studies on *BRCA* carriers is weak, and for the more general group of women with a familial breast cancer history (FBCH) but without information on genetic mutations, no estimate on breast cancer risk from ionizing radiation exists.

The Swedish Hemangioma Cohort (SHC) offered us a unique opportunity to address this challenge. The SHC is one of the world's most important sources for data on radiation-induced breast cancer risk (13, 14) and comprises 17,200 women. The patients were treated for skin hemangioma in infancy by means of external radiation applicators, which resulted in highly nonuniform whole-body exposures. Furthermore, the existence of cancer registers and multigenerational demographic registers in Sweden allowed linkage between records for the SHC members and records for their mothers, sisters, and daughters, including information on familial cancer occurrence.

The potential clinical relevance of FBCH is evaluated for 2 important sources of breast exposure in the population, breast cancer radiotherapy and mammography screening. In both clinical applications it may be possible to reduce breast exposures. The patients can usually expect long survival times, so late health effects become increasingly important. It has been estimated that approximately 8% of all second solid cancers combined among 1-year survivors could be related to radiotherapy (15). Therefore, we estimated the risk of second primary breast cancer after breast radiotherapy for women with and without FBCH. In addition, risk from mammography screening was assessed. The results can serve as a basis for personalized benefit-risk considerations, particularly in light of modern multifield radiotherapy techniques that might induce large doses to the contralateral breast or with regard to screening method and frequency.

Our aim in the current study was to analyze the risk of radiation-induced breast cancer in women with a FBCH and to evaluate the clinical implications.

METHODS

The SHC

During the period 1920–1965, many people in Sweden were treated for skin hemangioma by means of external radiation applicators, mainly with radium-226. The SHC includes 2 subcohorts, 1 from Stockholm and 1 from Gothenburg. In the current work, we analyzed breast cancer incidence among 17,200 women in this combined cohort. All participants were younger than 18 months of age at the time of first treatment. While most infants received 1 or 2 treatments, receipt of several treatments was not unusual. The subcohorts have been described in detail previously (16).

Doses to the breast anlage were individually calculated on the basis of measurements made with thermoluminescent dosimeters in an anthropomorphic phantom. Recently, dose estimates were improved using Monte Carlo simulations (17, 18). The mean and median breast doses in the cohort were 0.18 Gy and 0.04 Gy, respectively. Only 3% of the women had doses exceeding 1 Gy, with a maximum of 32.8 Gy.

Using the unique identification number assigned to each person in Sweden, record linkage to several Swedish national registries was performed for women in the SHC. Information about the women's mothers, sisters, and daughters was retrieved from the Swedish Multigeneration Registry. Information on breast cancer incidence during the period 1958–2013 was obtained from the Swedish Cancer Registry. Follow-up information on vital data, emigrations, and deaths was retrieved from national population registries.

Characteristics of the cohort, treatment, breast doses, and familial information are presented in Table 1. Follow-up ranged from January 1, 1958, or the date of first treatment if that was later, to the date of the first of the following events: emigration, breast cancer diagnosis, death, or December 31, 2013. There were 1,079 women with breast cancer in the SHC and 1,225, 696, and 100 breast cancers among the mothers, sisters, and daughters, respectively. There were 101 breast cancer cases among the mothers where the SHC member also had breast cancer, and similarly 89 and 15 cases for the sisters and daughters, respectively. The analysis was censored at the first diagnosis of breast cancer, and second breast cancers were not taken into account. Biological material for the SHC members is not available, so no information on mutation patterns exists.

The SHC was established and analyzed with the permission of the Swedish Data Inspection Board, which is responsible for protecting the privacy of the individuals in the database, and the Swedish Ministry of Justice. This study was also approved by the Regional Ethics Review Board in Gothenburg.

Radiation risk models

The SHC was analyzed previously without information on FBCH (14, 19). The current analysis, including an additional 4 years of follow-up time, used the same model structure that was found to best describe the radiation risk, shown in equation A1 of Web Appendix 1 (available at https://academic.oup.com/aje). However, here it is formulated in terms of an excess absolute risk (EAR) model. This allows us to clearly separate spontaneous and radiation-induced familial risk and to analyze directly the impact of FBCH on radiation risk without substantial dependence on the parameterization of familial spontaneous risk. The model is given by

$$\lambda(a, D) = \lambda_{\text{spon}}(a) \times \text{RR}_{\text{spon}}^{\text{fam}} + \text{EAR}(a) \times \text{RR}_{\text{rad}}^{\text{fam}} \times D. \quad (1)$$

Here, λ represents the breast cancer incidence rate, λ_{spon} represents the spontaneous (i.e., non–radiation-induced) rate, a is attained age, and D is total dose. EAR(a) is the EAR per dose. FBCH is represented by the familial relative risk factor for spontaneous risk, $\text{RR}_{\text{spon}}^{\text{fam}}$, and by

Table 1. Features of Treatment, Breast Cancer Incidence[a], and Follow-up (884,363 Person-Years) for the 17,200 Women in the Swedish Hemangioma Cohort and Breast Cancer Incidence Among Their Mothers, Sisters, and Daughters, 1958–2013

Characteristic	No. of Persons	%	Median (Range)
Years of treatment			
1920–1929	261	1.5	
1930–1939	1,370	8.0	
1940–1949	7,699	44.8	
1950–1959	7,797	45.3	
1960–1964	73	0.4	
Age at first treatment, months			5.1 (0–18.0)
Absorbed dose in breast[b], Gy			
Median dose[c]			0.040 (0.010–0.120)
Mean dose[d]			0.186 (0.727)
Dose category			
0	5,485	15.9	
0.001–0.099	18,264	53.1	
0.100–0.199	4,980	14.5	
0.200–0.499	3,423	10.0	
0.500–0.999	918	2.7	
1.000–4.999	1,233	3.6	
≥5.000	97	0.3	
Distribution of cohort members			
Cohort members	17,200	100.0	
Nonexposed (<0.1 Gy)	11,292	65.7	
Exposed (≥0.1 Gy)	5,908	34.3	
Cohort members with BC	1,079	6.3	
Nonexposed (<0.1 Gy)	669	3.9	
Exposed (≥0.1 Gy)	410	2.4	
Cohort members with and without an FBCH			
No FBCH	15,276	100.0	
Nonexposed (<0.1 Gy)	10,015	65.6	
Exposed (≥0.1 Gy)	5,261	34.4	
With BC	893	5.8	
Nonexposed (<0.1 Gy)	557	3.6	
Exposed (≥0.1 Gy)	336	2.2	
FBCH	1,924	100.0	
Nonexposed (<0.1 Gy)	1,277	66.4	
Exposed (≥0.1 Gy)	647	33.6	
With BC	186	9.7	
Nonexposed (<0.1 Gy)	112	5.8	
Exposed (≥0.1 Gy)	74	3.8	
Distribution of relatives			
Mothers[e]	16,128	100.0	
With BC	1,225	7.6	
With BC and related cohort member with BC	101	0.6	

Table continues

Table 1. Continued

Characteristic	No. of Persons	%	Median (Range)
Sisters	14,233	100.0	
With BC	696	4.9	
With BC and related cohort member with BC	89	0.6	
Daughters	15,630	100.0	
With BC	100	0.6	
With BC and related cohort member with BC	15	0.1	
Status at end of follow-up			
Still alive on December 31, 2013	13,415	78.0	
BC event during follow-up	1,079	6.3	
Emigrated	1,181	6.9	
Deceased	1,525	8.9	
Age at end of follow-up, years			
Age on December 31, 2013 (among survivors)			65 (49–94)
Age at BC event			55 (24–84)
Age at emigration			29 (1–69)
Age at death			59 (0–94)

Abbreviations: BC, breast cancer; FBCH, familial breast cancer history.
[a] Only the first case of breast cancer was counted.
[b] Dose is given per breast ($n = 34{,}400$).
[c] Values are presented as median (interquartile range).
[d] Values are presented as mean (standard deviation).
[e] Some mothers were born before the establishment of the Swedish Multigeneration Register in 1932.

the corresponding relative risk factor for familial radiation-induced risk, RR_{rad}^{fam}. In the absence of familial breast cancer, the relative risk factors are equal to 1.

In case-control studies, it has been found that spontaneous breast cancer risk is elevated for women with FBCH and that it increases further if more than 1 relative has been affected by breast cancer (1). Consistently, in this analysis the relative risk factors were allowed to increase with the number of familial breast cancers. For spontaneous risk, the best description was achieved by using separate familial relative risk factors, and this was used for the main analysis. As a consistency check, additional analyses were performed with a joint spontaneous risk factor for mothers, sisters, and daughters. To enhance statistical power, we performed the main analysis of familial radiation risk with a common factor for all relatives together:

$$RR_{rad}^{fam} = e^{\beta_{rad} \times n_{fam}}, \quad (2)$$

where n_{fam} represents the total number of familial first-degree breast cancers and β_{rad} is a fit parameter. In addition, separate risk values for the relatives were estimated (see equation A2 in Web Appendix 1). Model-fitting was performed using individual likelihood methods (19). Parameter selection and confidence intervals were based on likelihood ratio tests and evaluation of the profile likelihood.

Long-term risk from breast cancer radiotherapy and mammography screening

To evaluate the relevance of FBCH for medical applications, we estimated the radiation-induced long-term risk from breast cancer radiotherapy and mammography screening. In both applications, a typical exposure scenario was chosen and evaluated for persons with and without FBCH. Long-term risk can be assessed by means of the lifetime attributable risk (LAR), defined as the accumulated probability that an individual will develop radiation-associated cancer up to a certain age (7, 8), as presented in equation A3 (Web Appendix 1). We provide estimates of risk within 20 years after exposure and up to age 80 years.

For contralateral breast cancer risk after adjuvant breast cancer radiotherapy, the results from the PASSOS Study (Personalised Assessment of Late Health Risks After Exposure to Ionising Radiation and Guidance for Radiation Applications in Medicine) were used. In that study, organ doses from 128 contemporary patients were analyzed for different radiotherapy techniques (20, 21). For whole-breast radiotherapy with standard tangential 3-dimensional conformal radiotherapy without compensatory wedges, the mean dose to the contralateral breast was 0.72 Gy. The use of wedges increased the mean breast dose by about 50% due to increased scatter radiation. Application of flattening filter-free techniques led to a dose reduction of about 25%. Multifield techniques depend strongly on planning, and

Table 2. Excess Relative Risk and Excess Absolute Risk of Breast Cancer Among Women Without Information on Familial History of Breast Cancer at Different Attained Ages, Swedish Hemangioma Cohort, 1958–2013

Age, years	ERR		EAR	
	Estimate, Gy^{-1}	95% CI	Estimate, no. of cases/10,000 PY/Gy[a]	95% CI
40	0.51	0.33, 0.71	3.9	2.5, 5.4
50	0.51	0.33, 0.71	10.8	7.0, 14.6
60	0.51	0.33, 0.71	17.5	11.4, 23.6
70	0.51	0.33, 0.71	20.5	13.3, 28.2
80	0.51	0.33, 0.71	19.9	12.4, 29.0

Abbreviations: CI, confidence interval; EAR, excess absolute risk; ERR, excess relative risk; PY, person-years.
[a] EAR estimates were calculated for women with 2 children, representing the cohort average. Absolute risk was higher by 34% for women without children.

for intensity-modulated radiotherapy a substantially higher mean breast dose of 2.56 Gy was induced.

Mammography risk with and without FBCH was calculated for a population-based screening program as implemented in Sweden. In Sweden, the invitation to undergo screening starts at age 40 years and continues every 2 years until age 74 years. Typical screening doses are 2 mGy, which accumulate to a total dose of 36 mGy. In previous Swedish trials, the benefit from the mammography screening program has been estimated to be a relative reduction of breast cancer mortality of about 15%–21% (22, 23).

RESULTS

Breast cancer risk without information on FBCH

Spontaneous breast cancer risk increased with age and was lower for women with a greater number of children; details and parameter values are presented in Web Appendix 2 and Web Table 1. Radiation-induced breast cancer risk increased linearly with dose, and no indication of a quadratic or nonlinear dose response was found. The relative risk was independent of attained age. Radiation risk was still substantially elevated even 60 or 70 years after exposure, and the absolute risk actually increased with increasing age. This observation is consistent with the previous analysis (14), now including 4 more years of follow-up and increased statistical power. With exposure in infancy, the SHC represents one of the strongest sources of evidence for lifelong increased radiation risk. Relative and absolute risk values are shown in Table 2. The interaction of FBCH and radiation risk was calculated relative to these estimates.

Breast cancer risk including FBCH

Spontaneous breast cancer risk was higher for women with breast cancer among first-degree relatives. The familial risk parameters RR_{spon}^{fam} were all separately found to be statistically significant for cancer among mothers, sisters, and daughters (Web Appendix 3 and Web Table 2). For the joint analysis, the common familial relative risk was 1.75 and was highly significant.

The influence of FBCH on radiation risk is shown in Table 3, which presents the best parameter estimates together with the uncertainty range. As the main result, EAR was higher by a factor of 2.7 (95% CI: 1.0, 4.8) if cancer had been diagnosed in a first-degree relative. The result was significant at the 95% level ($P = 0.05$). The analyses for cancer among mothers, sisters, and daughters separately demonstrated remarkable consistency. Even though the single parameter values were not statistically significant, all parameters supported an increase in radiation risk of a factor of 2.3–3.0 (P for heterogeneity = 0.90).

Since the risk values might have depended on the chosen model for spontaneous familial risk, an alternative implementation of RR_{spon}^{fam} was analyzed as well. The range of risk

Table 3. Familial Relative Risk of Radiation-Induced Breast Cancer Among All Relatives (Main Model With 1 Breast Cancer) and Separate Estimates of Risk in the Presence of 1 Breast Cancer Among Mothers, Sisters, and Daughters (P = 0.90 for Heterogeneity)[a], Swedish Hemangioma Cohort, 1958–2013

Group	RR_{rad}^{fam}	95% CI	*P* Value
All relatives	2.7	1.0, 4.8	0.05
Mothers	3.0	0.8, 6.9	0.078
Sisters	2.3	0, 5.0	0.29
Daughters	3.0	0, 11.9	0.37

Abbreviations: CI, confidence interval; RR, relative risk.
[a] Example: Using the results from Table 2 for an exposure of 1 Gy and an age of 60 years, the expected number of radiation-induced cases of breast cancer per 10,000 person-years would increase from 17.5 cases by a factor of 2.7 to a total of 47.2 cases in the presence of 1 familial breast cancer. The excess relative risk would increase from 0.51 to 1.38 in comparison with the risk without familial cancer.

values was very consistent (see Web Appendix 4 and Web Table 3) and provided additional evidence for the validity of the results on familial radiation risk. Nevertheless, the difference between the spontaneous and radiation-induced relative risk factors for women with FBCH was not statistically significant. In comparison with the assumption of equal familial risk factors for spontaneous and radiation-induced risk, the deviance was improved by 1 point ($P = 0.32$). Furthermore, we investigated whether cancer at a young age among family members increased radiation risk. However, the statistical power in the cohort was low, and the parameter estimates had a large amount of uncertainty. For example, for women with breast cancer among relatives before the age of 45 years, the relative spontaneous risk was 1.18 (95% CI: 0.74, 1.89) and the relative radiation-induced risk was 0.83 (95% CI: 0.11, 6.3).

Both spontaneous and radiation-induced risk were increased further if more than 1 relative had been affected by breast cancer. Based on equations 2 and A2 (Web Appendix 1), the exponent of the relative risk depended linearly on the number of familial cancers. Consequently, relative risk for spontaneous cancer increased from 1.75 for a woman with 1 familial cancer to 3.0 for a woman with 2 familial cancers, and from 2.7 to 7.1 for radiation-induced cancer. Allowing the exponents to vary with the number of cancers in a power form with 1 additional parameter each for spontaneous and radiation risk indicated an even larger dependence, with power of 1.6 and 1.25 for spontaneous and radiation risk, respectively. However, statistical support for such a larger increase than the linear one was small for the spontaneous risk ($P = 0.21$), and even less for the radiation relative risk alone ($P > 0.5$).

Risk from medical applications

Figure 1 shows the cumulative risk of cancer in the contralateral breast after breast cancer radiotherapy for the 20 years following exposure and up to age 80 years (LAR-80) for a standard 3-dimensional conformal radiotherapy technique without compensatory wedges and a mean breast dose of 0.72 Gy. For spontaneous familial risk, the common relative risk factor of 1.75 was applied.

Radiation-induced risk for women with FBCH is 2.7 times higher than that for women without FBCH. For comparison, the risks of spontaneous contralateral breast cancer with and without FBCH are also presented. The 20-year risk reaches its maximum at around ages 50–60 years at exposure. Below this age range, breast cancer rates for the following 20 years are lower than those for exposure at older ages. For ages at exposure above 60 years, overall survival for the next 20 years is reduced. For LAR-80, the radiation risk accumulates with time and is therefore higher for young ages at exposure.

The estimated risk of radiation-induced breast cancer from mammography screening is presented in Table 4. Because of the protracted exposure, the 20-year risk is less informative and only LAR-80 is shown. Radiation risk increases from 0.11% for women without FBCH to 0.29% for women with FBCH.

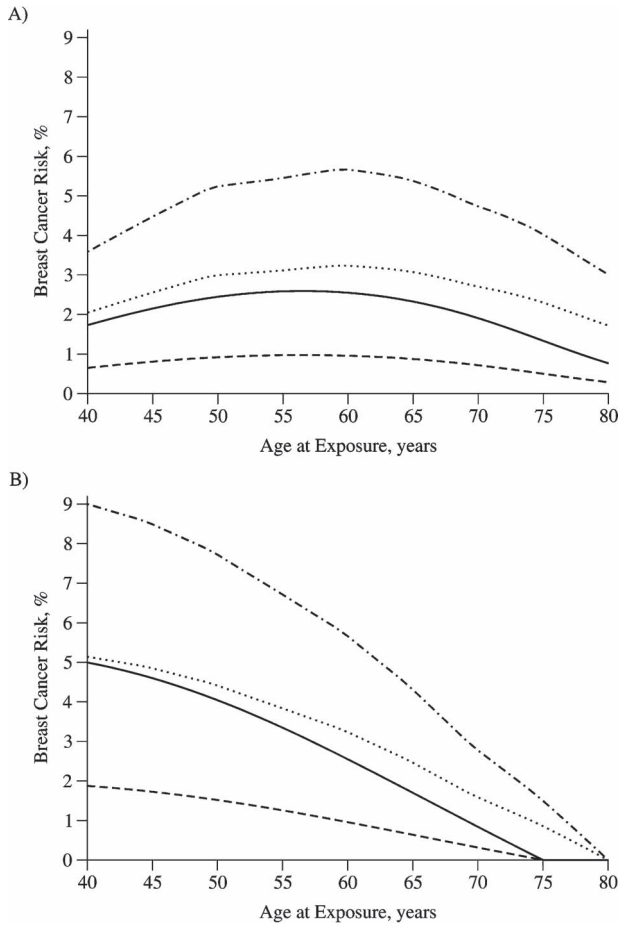

Figure 1. Cumulative risk of cancer in the contralateral breast (%) after breast radiotherapy as a function of age at exposure (projections based on results from the Swedish Hemangioma Cohort, 1958–2013). A) Risk for the 20 years following exposure; B) risk up to age 80 years. The solid and dashed lines represent the radiation-induced risks with and without a familial breast cancer history (FBCH), respectively. For comparison, the spontaneous risks with and without FBCH are depicted as dashed-dotted and dotted lines. The mean dose to the contralateral breast was 0.72 Gy. A time lag of 5 years was assumed, and risk up to age 80 years vanishes for exposures above age 75 years.

DISCUSSION

In this study, spontaneous breast cancer risk was found to be 1.75 times higher for women with 1 breast cancer among first-degree relatives and to increase further in the presence of several such breast cancers. These results are consistent with population studies which observed an increase by a factor of about 1.8 for women with FBCH (1, 24, 25). Since familial risk is probably related to a genetic component, it is plausible that women with FBCH are also at increased risk for radiation-induced breast cancer; the SHC provides a unique opportunity to study this hypothesis.

Figure 2 illustrates the findings in a schematic way. Using the spontaneous breast cancer risk for women without FBCH as the reference value of 1, these women have an additional

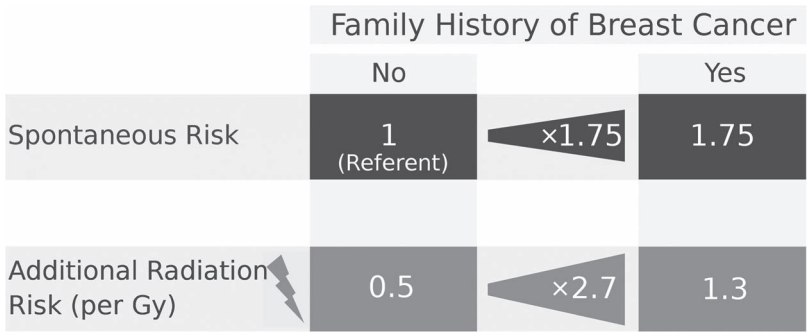

Figure 2. Susceptibility to breast cancer among women with a family history of breast cancer, Swedish Hemangioma Cohort, 1958–2013. Using the spontaneous breast cancer risk for women without a familial breast cancer history (FBCH) as the reference value of 1, these women have an additional 50% risk after exposure of 1 gray (Gy). The risk scales linearly with dose. Women with FBCH have higher individual susceptibility to breast cancer. In the presence of 1 case of familial breast cancer, the spontaneous breast cancer risk is 1.75 times higher. The best estimate of individual susceptibility for radiation-induced risk is even higher, and the risk increases by a factor of 2.7.

50% risk after exposure of 1 Gy; the absolute values can be obtained from Table 2. The risk scales linearly with dose. If 1 breast cancer has occurred in a first-degree relative, the radiation risk for these women is higher by a factor of 2.7. The increase in radiation risk was significant ($P = 0.05$). This best estimate indicates an even higher individual susceptibility for radiation risk than for the increase in spontaneous risk by a factor of 1.75. However, the difference between both susceptibility factors was not statistically significant, and similar factors are compatible with the data.

The results imply increased contralateral breast cancer risk after breast radiotherapy for women with FBCH. For example, assuming whole breast treatment at age 40 years with standard 3-dimensional conformal radiotherapy without wedges and contralateral breast doses of 0.72 Gy, the 20-year excess risk would increase from 0.6% for a woman without FBCH to 1.7% for a woman with FBCH, and the risk to age 80 would increase from 1.9% to 5.0%. Based on the PASSOS results, use of wedges would increase risk until age 80 to 7.5% for a woman with FBCH, whereas flattening filter-free techniques would reduce the risk to 3.8%. The significantly higher doses from intensity-modulated radiotherapy would induce a risk of 17.8%. Modern techniques like intensity-modulated radiotherapy or volumetric-modulated arc therapy can reduce high-dose peaks through the use of multifield configurations. However, potential direct beam traversal of the contralateral breast can increase the radiation burden and risk substantially.

Table 4. Risk of Breast Cancer From Mammography Screening as Performed in Sweden for Women With and Without a Familial History of Breast Cancer[a]

Type of Risk	LAR-80, %[b]	
	Without FBCH	With FBCH
Spontaneous risk	10.3	18.0
Radiation risk	0.11	0.29

Abbreviations: FBCH, familial breast cancer history; LAR, lifetime attributable risk.

[a] Projections based on results from the Swedish Hemangioma Cohort, 1958–2013.

[b] LAR-80 gives the cumulative probability of contracting breast cancer from the start of screening at age 40 years to age 80 years. The cumulative risk of contracting spontaneous cancer was calculated for the same age interval.

For biennial mammography screening, the radiation-induced risk up to age 80 years was estimated to be about 0.11% for women without FBCH. For women with 1 familial breast cancer, this risk would increase to 0.29%. While these values appear small in comparison with the spontaneous risks of 10.3% and 18.0%, respectively, it should be considered that only for a small portion of the spontaneous cases will screening present a benefit in terms of earlier detection and improved treatment. Nevertheless, considering that screening was shown to reduce the mortality rate by 15%–21% (22, 23), there is still a clear benefit of screening compared with the radiation-induced risk, even for women with FBCH. Notwithstanding, a sizeable contribution of screening risk is present that might be reduced or avoided if, for instance, magnetic resonance imaging were to replace mammography for women with FBCH.

The SHC is one of the most important sources of data on breast cancer risk after exposure to ionizing radiation. It is a large cohort with high-quality follow-up and dosimetry. Use of the unique Swedish identification number allowed us to link data on the SHC patients to data on their relatives, including vital status and cancer incidence information. Because of the high statistical power of the cohort data, with sufficient numbers of cancer cases in both the hemangioma patients and their relatives, together with the large range of doses, it was possible to analyze radiation-induced risk among women with FBCH.

Breast cancer is a multifactorial disease that is associated with hormonal, environmental, lifestyle, and genetic factors. Radiation may interact with these factors (9, 10). Only a limited number of factors are known for the SHC, including

number of children and age at first childbirth. However, it is unlikely that these factors induced significant bias in the risk estimates. Doses were determined basically by the distance between the location of the radiation applicator and the breast anlage and were therefore uncorrelated with other breast cancer risk factors.

We provided the risk estimates for medical procedures to assess the relevance of FBCH, and they should be interpreted with caution. They are based on several assumptions concerning risk transfer between populations, dose response, and age dependencies. EAR values from the SHC were used for lifetime risk estimates, albeit exposures were at young ages. Nevertheless, they are compatible with recommendations from international organizations like the United Nations Scientific Committee on the Effects of Atomic Radiation and the International Commission on Radiological Protection (7, 8, 26), which are strongly based on the Japanese atomic bomb survivors (the Life Span Study cohort), and give preference to an additive transfer of risk between populations for breast cancer. Several high-dose studies on secondary breast cancer risk after radiotherapy have shown substantially smaller relative risk coefficients, albeit at higher doses (>4 Gy) (27). In the Life Span Study, the preferred excess relative risk model depended on attained age but was independent of age at exposure (10), whereas the absolute rates depended on age at exposure due to the increase of background rates with year of birth. Assuming multiplicative interaction between radiation and other breast cancer risk factors, lifetime risks were calculated assuming independence of age at exposure. For less-than-multiplicative interaction, the Life Span Study data would point to decreasing radiation risk with increasing age at exposure, and the lifetime risk estimates would probably be an overestimate. These issues are discussed in greater detail in Web Appendix 5.

Furthermore, individual doses from a specific medical application can be very different from the generic doses chosen here. However, since the risk scales linearly with dose, for risk-benefit estimates it is easily possible to adjust the given risk estimates. In addition, for breast radiotherapy the contralateral breast cancer risk depends on a number of individual risk factors, such as chemotherapy, hormone therapy, or estrogen level. Risk is substantially higher for carriers of the *BRCA1* or *BRCA2* mutation (28). Information about genetic mutations allows much more precise treatment and care in comparison with just the information about FBCH. Furthermore, women with known genetic mutations or women with FBCH who are established noncarriers of *BRCA* mutations might have different radiation-related risks. In the Women's Environment, Cancer, and Radiation Epidemiology (WECARE) Study, no increased risk of contralateral breast cancer after breast radiotherapy was observed in women aged 40 years or more at exposure, but there was a significant excess relative risk for women under age 40 years (29). Hooning et al. (30) studied the interaction between radiation dose and FBCH in the risk of contralateral breast cancer. They found that the joint effect of radiotherapy and strong FBCH (3 or more relatives with breast cancer) on risk was greater than when the individual risks were summed.

In conclusion, in this study we assessed risk of breast cancer after radiation exposure for women with FBCH. We found that breast cancer among first-degree relatives increases the risk associated with radiation almost 3-fold. Breast cancer radiotherapy and mammography are among the most significant sources of breast radiation exposure in the population, and for typical exposures in both clinical applications the potential long-term risk for women with FBCH was estimated. While individual risks will have substantial variations, depending on the specific exposure and other personal risk factors, the results show that the risk of contralateral breast cancer after breast radiotherapy can be substantial, especially for modern multifield radiotherapy techniques. In particular, for women with FBCH we suggest avoiding direct beam exposure of the contralateral breast as much as possible.

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