

# Evidence for Increased Susceptibility for Breast Cancer from Exposure to Ionizing Radiation due to Familial Breast Cancer History: Results from the Swedish Hemangioma Cohort

## Web Material

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<sup>†</sup> Marie Lundell passed away prior to manuscript submission.

## Web Appendix 1. Radiation risk models

### 1.1 Risk model in the absence of information on familial cancer

The analysis uses the same model structure that was found to best describe radiation risk in previous analyses of this cohort (1, 2). The dose response was linear with no indication of a quadratic dose component, and the excess relative risk (ERR) was independent of attained age. In addition, spontaneous breast cancer risk was lower for women with a higher number of children. The current analysis, including additional 4 years of follow-up time, is formulated in terms of an excess absolute risk (EAR) model:

$$\begin{aligned}\lambda(a, D) &= \lambda_{spon}(a) + \text{EAR}(a) \cdot D = e^{\psi_0 + \psi_a} + \beta_{50} \cdot e^{\psi_a} \cdot D, \\ \psi_a(a) &= \psi_1 \cdot \ln(a/50) + \psi_2 \cdot \ln^2(a/50) + \psi_{ch} \cdot n_{ch}(a),\end{aligned}\quad (\text{A1})$$

where  $\lambda$  is the breast cancer incidence rate in cases per person year (PYR).  $\lambda_{spon}$  is the spontaneous, i.e. non-radiation-induced, rate,  $a$  is attained age,  $D$  is total dose, and  $n_{ch}$  is the number of children.  $\psi_{0,1,2,ch}$  and  $\beta_{50}$  are fit parameters, where  $\beta_{50}$  is the excess absolute risk per dose at age 50 for women without children. Since the ERR is independent of attained age, the EAR has the same age dependence as the background,  $\propto e^{\psi_a}$ .

### 1.2 Risk model including familial cancer history

Familial breast cancer history (FBCH) can increase spontaneous and radiation-induced risk:

$$\begin{aligned}\lambda(a, D) &= \lambda_{spon}(a) \cdot RR_{spon}^{fam} + \text{EAR}(a) \cdot RR_{rad}^{fam} \cdot D, \\ \text{All:} \quad RR_{spon,rad}^{fam} &= e^{\beta^{all} \cdot n_{fam}}, \\ \text{Separate:} \quad RR_{spon,rad}^{fam} &= e^{(\beta^{mo} \cdot n_{mo} + \beta^{si} \cdot n_{si} + \beta^{dau} \cdot n_{dau})}.\end{aligned}\quad (\text{A2})$$

The familial relative factors for spontaneous and radiation-induced risk are given by  $RR_{spon}^{fam}$  and  $RR_{rad}^{fam}$ , respectively. In the first model relative risk depends on the total number of breast cancers among all first-degree relatives,  $n_{fam}$ . In the second model the risk is estimated separately for the relatives, depending on the number of breast cancers among mothers, sisters and daughters,  $n_{mo,si,dau}$ . For the mother,  $n_{mo}$  can only take values of 0 or 1 since second cancers are ignored. All  $\beta$ 's are fit parameters and can be determined independently for spontaneous and radiation risk. In the absence of familial breast cancer the relative risk factors are equal to 1.  $\lambda_{spon}$  and EAR are parameterized as in equation A1. The formulation in terms of the EAR model allows a clear separation of familial spontaneous and familial radiation-induced risk. In addition, it was investigated whether cancer at young ages among family members was associated with increased radiation risk. Fits were performed jointly for all parameters with individual likelihood methods (1).

### 1.3 Lifetime attributable risk

The lifetime attributable risk (LAR) estimates the accumulated probability that an individual will develop cancer associated with the radiation exposure until a certain age (3–5). With multiple exposures at ages  $e_i$  and doses  $d_i$ , the LAR is defined as

$$\text{LAR}(a_f, e_i, d_i) = \sum_i \int_{e_i+5}^{a_f} \text{EAR}(a, d_i) \frac{S(a)}{S(e_i)} da. \quad (\text{A3})$$

EAR and  $S(a)$  are the excess absolute risk and the population survival of the target population. A time lag of 5 years is assumed between exposure and breast cancer induction. Depending on the final age  $a_f$ , different risk measures can be calculated. For  $a_f = 80$  years, the LAR represents the risk to develop radiation-induced breast cancer until age 80. For a single exposure, or exposures within a short time interval such as for breast radiotherapy,  $a_f = e + 20$  gives the risk of developing cancer within 20 years after exposure.  $\text{EAR}(a, d_i)$  was taken from

the current analysis of the Swedish hemangioma cohort; other major radioepidemiological cohorts such as the cohort of the Japanese atomic bomb survivors (LSS) have compatible absolute risk values. For  $S(a)$ , national population survival rates were used. For comparison, also the lifetime spontaneous risk was calculated similar to equation A3, but substituting EAR by the population breast cancer incidence rate, and without time lag.

## Web Appendix 2. Breast cancer risk without information on FBCH

Without information on familial cancer cases, spontaneous and radiation risk can be determined from the parameters of equation A1 which are presented in Web Table 1.  $\beta_{50}$  is the excess absolute rate per dose at age 50 for women without children. Spontaneous breast cancer risk is lower for women with more children, for each additional child the risk decreases by 14%. It was investigated whether also radiation risk depends on the number of children. The best fit estimate decreased EAR by 21% for each child ( $p = 0.11$ ) similar, albeit somewhat stronger, to the decrease in spontaneous risk. Since the difference to spontaneous risk is of low statistical power ( $p > 0.5$ ), in this work the same dependence on the number of children is assumed, as implemented in equation A1. In addition to the number of children, no significant effect of the age at first childbirth on risk was seen.

Parameter	Value
$\psi_0$	$-5.89 \pm 0.063$
$\psi_1$	$3.51 \pm 0.17$
$\psi_2$	$-4.70 \pm 0.58$
$\psi_{ch}$	$-0.15 \pm 0.03$
$\beta_{50}$	$14.2 \pm 2.6 (10^4 \text{ PYR Gy})^{-1}$

**Web Table 1.** Parameter values of equation A1 with  $1\sigma$  uncertainty range.

## Web Appendix 3. Spontaneous breast cancer risk including FBCH

Web Table 2 shows the familial relative risk for spontaneous breast cancer in the presence of FBCH. If one cancer occurred among any relative, the risk is 1.75 times higher and highly significant. Separate risk values for mothers, sisters and daughters are also significant ( $p = 0.013$  for heterogeneity). It was checked whether cancer at young age among relatives was correlated with higher risk for the SHC members. Although such an effect has been observed in population studies (6), no such effect could be identified in the SHC, likely because of low statistical power.

Person Group	$RR_{spon}^{fam}$	95% CI	$p$ Value
All	1.75	(1.50; 2.02)	$< 10^{-5}$
Mothers	1.41	(1.12; 1.75)	0.0038
Sisters	2.20	(1.76; 2.70)	$< 10^{-5}$
Daughters	2.14	(1.15; 3.59)	0.017

**Web Table 2.** Familial relative risk for spontaneous breast cancer with one breast cancer among all relatives, and separate risk estimates in the presence of one breast cancer among the mother, sisters or daughters ( $p = 0.013$  for heterogeneity).

#### Web Appendix 4. Radiation-induced breast cancer risk including FBCH for alternative parametrisation of spontaneous risk

As a consistency check, familial radiation risk was estimated similar to Table 3, but with a parametrization for spontaneous risk that uses a common factor  $RR_{spon}^{fam}$  for all relatives. The results are presented in Web Table 3. The overall risk  $RR_{rad}^{fam} = 2.6$  is very similar to the previous estimate of 2.7, and also the error bounds are almost identical. While there is a shift in the individual risk values, the range of values between 2.2 and 3.3 is very consistent with Table 3. This confirms that the results for radiation risk in the presence of FBCH are largely independent of the specific functional form for the familial spontaneous risk.

Person Group	$RR_{rad}^{fam}$	95% CI	<i>p</i> Value
All	2.6	(0.9; 4.8)	0.06
Mothers	2.2	(0; 5.4)	0.25
Sisters	2.9	(0; 5.6)	0.12
Daughters	3.3	(0; 11.7)	0.27

**Web Table 3.** Familial relative risk for radiation-induced breast cancer with one breast cancer among all relatives, and separate risk estimates in the presence of one breast cancer among the mother, sisters or daughters ( $p = 0.86$  for heterogeneity). Spontaneous risk is given by a common familial risk factor.

#### Web Appendix 5. Risk extrapolation and dose response relationship of breast cancer risk

The lifetime risk calculations involve an integration of the excess absolute risk with and without FBCH over a certain age range (equation A3). For consistency, both the familial relative risk factor and the spontaneous absolute risk were taken from the SHC. The latter may appear problematic since exposure was at infant age, but the considered medical exposures are typically at middle and older ages. Nevertheless, the EAR values from Table 2 are very much compatible with the recommendations by international organizations like ICRP, UNSCEAR and BEIR VII (4, 5, 7), which are based on the Japanese atomic bomb survivors (Life Span Study (LSS)) and several other breast cancer studies, and give preference to an additive transfer of risk between populations for breast cancer. A pooled study of several breast cancer cohorts by Preston et al. found the best common description by excess absolute rates (8). These studies have high statistical significance for the low- and medium-dose range until about 1–2 Gy, and the applied risk values in this study are consistent with these recommendations.

On the other hand, high-dose radiotherapy studies for (secondary) breast cancer often find smaller relative risk coefficients, however, usually at higher doses above 4 Gy (9, 10). Together the results from the low/medium- and high-dose studies might indicate that in some intermediate dose range of about 1–4 Gy the slope of the dose response function becomes smaller. For estimates of the potential relevance of FBCH in the manuscript the results from the low- and medium-dose studies was used because they were applied to low doses and to doses until about 1 Gy.

Another unresolved problem relates to a potential dependence of breast cancer risk on age at exposure. In several studies of the LSS, which is the largest cohort on radiation-induced breast cancer risk including also women exposed at older ages, the data were best described by an ERR model that depends on attained age, but is independent on age at exposure (11–13). For example, in the study by Brenner et al. (13) with an ERR of  $1.12 \text{ Gy}^{-1}$  at age 70, a nonsignificant decrease in the ERR of  $-5\%$  per decade increase in age at exposure (95% CI:  $-23\%$ ;  $15\%$ ,  $p = 0.58$ ) was found.

In the LSS, for a given attained age the background rates significantly increased with increasing year of birth by  $36\%$  per decade (13). Therefore, since in the LSS increasing year of birth corresponds to younger age at exposure, the excess absolute rates depend in a similar way on age at exposure as the background rates,

indicating a multiplicative interaction between radiation and other breast cancer risk factors, as discussed in more detail in Preston et al. (11). Using this assumption, the best ERR values from the LSS and SHC, and the difference in age-standardized background rates which are about two times higher in Sweden than in the LSS (11), the excess absolute rates from the SHC used in this work and from the LSS are similar. Nevertheless, it should be noted that several radiotherapy studies found a substantially smaller or vanishing risk for older ages at exposure compared to younger ages (e.g., 14, 15). Also, assuming a less than multiplicative interaction between radiation and other breast cancer risk factors, the LSS data would point to a decreasing radiation risk with increasing age at exposure. In this case the lifetime risk estimates in this work would likely be an overestimate and the estimates on the increase in risk for women with familial breast cancer history would reduce accordingly.

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