Estimated Risk of Radiation-Induced Breast Cancer From Mammographic Screening for Young *BRCA* Mutation Carriers

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BRCA mutation carriers are recommended to start mammographic screening for breast cancer as early as age 25–30 years. We used an excess relative risk model (based on a pooled analysis of three cohorts with 7600 subjects who received radiation exposure) to estimate the lifetime risk of radiation-induced breast cancer from five annual mammographic screenings in young (<40 years) BRCA mutation carriers. We then estimated the reduction in breast cancer mortality required to outweigh the radiation risk. Breast cancer rates for mutation carriers were based on a pooled analysis of 22 pedigree studies with 8139 subjects. For BRCA1 mutation carriers, the estimated lifetime risk of radiation-induced breast cancer mortality per 10 000 women resulting from annual mammography was 26 (95% confidence interval [CI] = 14 to 49) for screening at age 25–29 years, 20 (95% CI = 11 to 39) for screening at age 30–34 years, and 13 (95% CI = 7 to 23) for screening at age 35–39 years. To outweigh these risks, screening would have to reduce breast cancer mortality by 51% (95% CI = 27% to 96%) at age 25–29 years, by 12% (95% CI = 6% to 23%) at age 30–34 years, and by 4% (95% CI = 2% to 7%) at age 35–39 years; estimates were similar for BRCA2 mutation carriers. If we assume that the mortality reduction from mammography is 15%–25% or less for young women, these results suggest that there would be no net benefit from annual mammographic screening of BRCA mutation carriers at age 25–29 years; the net benefit would be zero or small at age 30–34 years, but there should be some net benefit at age 35 or older. These results depend on a number of assumptions due to the absence of empiric data. The impact of varying these assumptions was therefore examined.

BRCA mutation carriers are recommended to start mammographic screening for breast cancer as young as age 25–30 years (1,2). However, the safety and efficacy of mammographic screening before age 40 years has not been demonstrated directly. Exposure to ionizing radiation from repeated diagnostic X-rays is an established cause of breast cancer (3,4), and after exposure, a woman's risk remains elevated for her entire lifetime (5). The lifetime risk of radiation-induced breast cancer will be higher for women who start mammography at younger ages because of the longer time available to accumulate risk. In contrast, the absolute benefit from mammography screening will be lower for women at younger than at older ages because, in

younger women, screening efficacy and breast cancer incidence rates are lower (6). We suggested previously that the benefit from mammographic screening before age 40 years may not outweigh the radiation risk for women with a family history of breast cancer (7). This question has not been investigated for *BRCA* mutation carriers.

It is not feasible to quantify the risk of radiation-induced breast cancer from mammography screening by studying the risks directly because a study of thousands of women who were followed up for their entire lifetimes would be required (8). However, it is possible to estimate the risk indirectly by extrapolating results from studies of other radiation-exposed populations.

In this analysis, we used this indirect approach to estimate the risk of radiation-induced breast cancer mortality from five annual mammographic screenings in *BRCA* mutation carriers before age 40 years and calculated the mortality reduction from screening that would be required to outweigh the radiation risk.

An outline of the methods is presented here, and additional details are available in a previous publication (7). To estimate the risk of radiation-induced breast cancer, we used an excess relative risk model (per gray) that was based on a pooled analysis of two cohorts of women who were exposed to multiple fluoroscopies and a cohort of children who received thymic irradiation (n = 7600) (5). The radiation exposures in those studies were from high-dose-rate X-rays similar to those that are used for mammography screening. The assumption underlying the excess relative risk model is that the magnitude of the radiation-induced cancer risk is proportional to the baseline cancer rate in the exposed population. Estimates of the baseline breast cancer incidence rates for *BRCA1* and *BRCA2* mutation carriers were taken from a pooled analysis of 22 studies of pedigree data (n = 8139) (9). The mean radiation dose to the glandular breast tissue (which is the most radiosensitive tissue in the breast) per two-view mammographic screen was estimated to be 3.85 mGy (10,11). We assumed that for these low-dose exposures delivered at a high dose rate, the risk increases linearly with dose and there is no threshold below which there is no risk (5).

CONTEXT AND CAVEATS

Prior knowledge

Women with *BRCA* mutations are encouraged to start mammographic screening at age 25–30 years because of their higher risk of breast cancer. Among average-risk women, mammography reduces breast cancer mortality by 15%–25% (approximately one in 1000 or less).

Study design

A model to estimate the lifetime risk of death from radiation-induced breast cancer from five annual mammograms among young *BRCA* mutation carriers age 40 years and younger was developed and the estimates were used to determine in what age group screening would be beneficial to these women, assuming a 25% or less reduction in mortality from mammography.

Contribution

The risk of radiation-induced breast cancer deaths decreased with increasing age at screening, such that screening at age 35–39 years would have a net benefit.

Implications

Based on this model, the reduction in breast cancer mortality from screening among women with *BRCA* mutations is not substantially greater than the risk of radiation-induced breast cancer mortality when screening before age 34 years.

Limitations

It is unknown how much mammography reduces breast cancer mortality in this population (ie, whether it is by 25% or less).

From the Editors

An example of the risk calculation for annual mammographic screening from age 35–39 years is described below. In the pooled risk model from the three cohorts, the risk was found to decrease with attained age, but there was no additional improvement in model fit if an age at exposure effect was also included. Therefore, the risk of radiation-induced breast cancer incidence (R_j) at attained age j was calculated for $j > 45$ years (to allow for the 10-year lag period for the induction of cancer) as

$$R_j = \lambda_j 0.74 \left(\frac{j}{50}\right)^{-2} \sum_{k=35}^{j-10} d_k,$$

where λ_j is the baseline breast cancer incidence rate for *BRCA* mutation carriers (9) at the attained age j, 0.74 is the radiation coefficient per Gy for attained age 50 years (5),

and d_k is the radiation dose to the glandular breast tissue from a two-view mammographic screen (10,11) at age k, with $d_k = 0.00385$ Gy for $k = 35–39$ years, and $d_k = 0$ otherwise. For each attained age j, the relevant exposures are the sum of the doses from age 35 years through ($j − 10$) years to allow for the lag period.

Radiation-induced breast cancer mortality was estimated by multiplying the incidence risk calculated above by 1.0 minus the current age-specific breast cancer survival probability (assumed to be equal to the current 10-year survival probability in the United States) (12). Preston et al. (5) found that breast cancer rates remained elevated for at least 60 years after radiation exposure. Hence, the total absolute risk of radiation-induced breast cancer mortality was estimated as the cumulative risk from 10 years after exposure (the assumed lag period) to age 84 years, with adjustment for competing causes of death that included the higher mortality rates from ovarian and breast cancer in *BRCA* mutation carriers (9,13).

Breast cancer mortality without screening was estimated for each of the screening periods by using cumulative incidence–based mortality rates. A 2-year lead time was assumed for each screening period (14); for example, for screening from age 35 through 39 years, the cumulative incidence rate that could be affected by screening was calculated to be the cumulative incidence rate from age 35 through 41 years. These cumulative incidence rates were then multiplied by 1.0 minus the age-specific breast cancer survival probability [as described above (12)] to estimate mortality.

The percentage mortality reduction required by screening to outweigh the radiation risk was calculated for each screening period by dividing the risk by the cumulative incidence–based mortality rate. We estimated 95% confidence intervals (CIs) for the results using Monte Carlo simulation methods (15), which took account of the statistical uncertainties in the model parameters (5,9).

For *BRCA1* mutation carriers, the estimated lifetime risk of radiation-induced breast cancer mortality per 10 000 women from annual mammography decreased with increasing age at screening from 26 (95% CI = 14 to 49) at age 25–29 years to 13

(95% CI = 7 to 23) at age 35–39 years (Table 1). The estimated cumulative breast cancer mortality without screening increased with increasing age at screening. Therefore, the estimated reduction in breast cancer mortality from screening required to outweigh this radiation risk decreased with increasing age at screening from 51% (95% CI = 27% to 96%) at age 25–29 years to 4% (95% CI = 2% to 7%) at age 35–39 years (Table 1). Because baseline breast cancer rates for *BRCA2* mutation carriers are lower than those for *BRCA1* mutation carriers, the absolute radiation risks and the absolute cumulative mortality in the absence of screening for *BRCA2* carriers were lower, but the estimates of the mortality reduction required to outweigh the radiation risk were similar for both groups (Table 1).

Results from randomized controlled screening trials suggest that the reduction in breast cancer mortality from mammographic screening for average-risk women age 40–49 years is 15%–25% (5). The efficacy of screening for younger high-risk women is uncertain because there have not been any trials that have had mortality as an endpoint, but it is probably lower because mammography sensitivity is lower (16). Therefore, assuming that screening efficacy would be 15%–25% or lower, our results suggest that there may be no net benefit from annual mammographic screening of *BRCA* mutation carriers age 25–29 years, the net benefit may be zero or small for screening of those age 30–34 years, but some net benefit from screening should exist for those age 35 years or older.

These calculations were based on several assumptions and so we examined the impact of varying the following key assumptions: 1) the joint effect of *BRCA* and radiation exposure, 2) the lead time for breast cancer, 3) the linear no-threshold assumption for radiation-induced cancer, and 4) the breast cancer survival probability in *BRCA* mutation carriers.

Because *BRCA* mutations are associated with a reduction in DNA repair efficiency, it has been hypothesized that there could be a gene–radiation interaction that would result in a supra-additive or supramultiplicative joint effect of these two exposures (17,18). Epidemiological studies (19–23) that have examined whether there is a supramultiplicative joint effect have yielded

Table 1. Estimated lifetime risk of radiation-induced breast cancer mortality from annual mammographic screening per 10 000 women, mortality without screening† per 10 000 women, and % reduction in breast cancer mortality from screening needed to outweigh radiation risk by screening period

Mutation carrier status and screening period	Cumulative lifetime risk* of radiation-induced breast cancer mortality per 10 000 (95% CI)	Cumulative breast cancer mortality without screening† per 10 000	Mortality reduction needed to outweigh radiation risk, % (95% CI)
BRCA1			
Age 25–29 y	26 (14 to 49)	51	>51 (27 to 96)
Age 30–34 y	20 (11 to 39)	172	>12 (6 to 23)
Age 35–39 y	13 (7 to 23)	345	>4 (2 to 7)
BRCA2			
Age 25–29 y	15 (8 to 28)	33	>45 (24 to 85)
Age 30–34 y	12 (6 to 23)	84	>14 (7 to 27)
Age 35–39 y	10 (5 to 21)	143	>7 (3 to 15)

* Cumulative risk to age 84 years. CI = confidence interval.

† Due to breast cancers arising during the screening period.

inconsistent results. One recent study (19) estimated that the risk of radiation-induced breast cancer in *BRCA* mutation carriers was approximately 1.5 times higher than the risk in noncarriers (ie, a supramultiplicative interaction of 1.5); if this were true, then the reduction in breast cancer mortality from screening required to outweigh the radiation risk would be increased by a factor of 1.5 (Table 2).

A previous study (24) assumed that the joint effect of radiation exposure and a family history of breast cancer was additive and concluded that for women with a family history of breast cancer, the benefit from mammography screening would outweigh the radiation risk in women age 30 years or older. The additive assumption was used because a study that compared the risk of radiation-induced breast cancer among Japanese atomic bomb survivors and those of US women who were exposed to multiple fluoroscopies found that the patterns of risk were more consistent across studies for the additive model than for the multiplicative risk model (5). This result has been interpreted as meaning that the joint effect of radiation and other breast cancer risk factors is additive. If this were true for the joint effect of *BRCA* mutations and radiation, then the estimated reduction in breast cancer mortality that is required to outweigh the radiation risk would be up to sixfold lower for *BRCA1* and threefold lower for *BRCA2* mutation carriers than those estimated with the multiplicative model, resulting in a potential net benefit from screening for women age 30 years or older (Table 2).

Because no direct estimates of the lead time are currently available for young *BRCA* mutation carriers, we used an estimate from a study of screening of average-risk women age 40–49 years (14). Tumors in young *BRCA* mutation carriers may grow faster than breast cancers in the general population (25) and so the lead time may be shorter. If the lead time was 1 year rather than 2 years, the required mortality reduction would increase by approximately 25%; however, if the lead time were longer, for example, 3 years, the required mortality reduction would decrease by approximately 25% (Table 2).

We assumed that the risk of radiation-induced breast cancer is linear in dose and there is no threshold below which there is no risk. These assumptions are supported for breast cancer by the results from the pooled analysis of breast cancer cohorts (n = 7600) by Preston et al. (5) and also by experimental results (26). However, if the dose–response curve at

Table 2. Estimated reduction in breast cancer mortality from screening (%) needed to outweigh the risk of radiation-induced breast cancer under the original and alternative assumptions for the joint effect of radiation and *BRCA* mutation status and breast cancer lead time

Mutation carrier status and screening period	Original assumptions,* % mortality reduction needed to outweigh radiation risk	Alternative assumptions			
		Radiation risk model, %		Lead time for breast cancer <age 40 y, %	
		Additive	Supramultiplicative†	3 y	1 y
BRCA1					
Age 25–29 y	>51	>8	>77	>38	>64
Age 30–34 y	>12	>2	>17	>9	>15
Age 35–39 y	>4	>1	>6	>3	>5
BRCA2					
Age 25–29 y	>45	>15	>64	>33	>58
Age 30–34 y	>14	>5	>21	>12	>19
Age 35–39 y	>7	>2	>10	>6	>8

* The original assumptions included a multiplicative risk model and a lead time of 2 years.

† For this model, we assumed an interaction effect of 1.5 (19).

low doses of radiation (<100 mGy) was not linear but curved either upward or downward, this would result in lower or higher risk estimates for mammographic screening, respectively. Some experimental research suggests that the risks per unit dose are halved at low doses (27), which at low doses would halve the estimated required reduction in mortality for the benefit to outweigh the risk. Similarly, if the risk per unit dose was doubled at low doses, this would double the required mortality reduction.

We assumed that the average breast cancer survival probability for *BRCA* mutation carriers was the same as the average survival probability in the general population (28). Varying this probability would have little impact on the estimated mortality reduction required to outweigh the risk because it would change the radiation risk and the benefit approximately proportionally if we assume that the survival probability for radiation-induced breast cancers does not differ from nonradiation-induced cancers. Because it is not currently possible to distinguish breast cancers caused by radiation from breast cancers caused by other factors, it is not possible to test this assumption.

An additional factor that could alter the balance of the risks and benefits from mammographic screening is oophorectomy, which is now commonly recommended for *BRCA* mutation carriers who are no longer at child-bearing age, because it has been shown to effectively lower the rates of breast and gynecologic cancers (29). This surgical removal of the ovaries should theoretically reduce the risk of radiation-induced breast cancer from mammographic screening because it would reduce the baseline rate of breast cancer, although the benefit from screening before the oophorectomy would not be changed.

This example for oophorectomy highlights the fact that the benefits and risks associated with radiation from screening mammography occur at different points in time. The benefits (deaths prevented) occur close to the screening period, whereas the radiation-induced breast cancer deaths occur later in life; in these calculations, about half of the radiation-induced breast cancer deaths were estimated to occur after age 50 years (data not shown). We have assumed that proximate and distant deaths carry equal weighting, but women who are more con-

cerned about proximate events may apply different weightings, which would also alter the risk–benefit assessment.

Although the results depend on a number of assumptions, we have based the assumptions on the currently available data and have also illustrated the impact of varying the assumptions. In the absence of direct empiric data, our estimates can be used by those involved in the decision-making process for *BRCA* mutation carriers to assess whether the benefits from early mammographic screening are likely to outweigh the radiation risks.

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