Risk of Radiation-induced Breast Cancer from Mammographic Screening

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Purpose:
To assess a schema for estimating the risk of radiation-induced breast cancer following exposure of the breast to ionizing radiation as would occur with mammography and to provide data that can be used to estimate the potential number of breast cancers, cancer deaths, and woman-years of life lost attributable to radiation exposure delivered according to a variety of screening scenarios.

Materials and Methods:
An excess absolute risk model was used to predict the number of radiation-induced breast cancers attributable to the radiation dose received for a single typical digital mammography examination. The algorithm was then extended to consider the consequences of various scenarios for routine screening beginning and ending at different ages, with examinations taking place at 1- or 2-year intervals. A life-table correction was applied to consider reductions of the cohort size over time owing to nonradiation-related causes of death. Finally, the numbers of breast cancer deaths and woman-years of life lost that might be attributable to the radiation exposure were calculated. Cancer incidence and cancer deaths were estimated for individual attained ages following the onset of screening, and lifetime risks were also calculated.

Results:
For a cohort of 100,000 women each receiving a dose of 3.7 mGy to both breasts and who were screened annually from age 40 to 55 years and biennially thereafter to age 74 years, it is predicted that there will be 86 cancers induced and 11 deaths due to radiation-induced breast cancer.

Conclusion:
For the mammographic screening regimens considered that begin at age 40 years, this risk is small compared with the expected mortality reduction achievable through screening. The risk of radiation-induced breast cancer should not be a deterrent from mammographic screening of women over the age of 40 years.

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The per capita dose of ionizing radiation used for medical imaging procedures has increased sixfold between the 1980s and the present (1). This has come about in part through the introduction of powerful new imaging techniques that have come to be an indispensable part of routine diagnostic or interventional procedures. While the absorbed dose received by the breast during mammography represents a relatively small component of the lifetime accumulated dose from medical imaging and other sources, both the popular press and, frequently, the general medical literature tend to focus on the potential radiation risk from mammography, particularly as used for periodic screening. Although risk is mentioned frequently, this is usually done in non-specific and qualitative terms.

There has been enormous effort expended on the study of radiation risk and, in particular, the correlation of radiation-induced cancer to dose and other factors, such as dose rate, age at exposure, and time since exposure. For obvious ethical reasons, randomized controlled trials cannot be conducted in humans to answer these questions, and human data come almost exclusively from retrospective observational studies. Data derived from human exposure studies are always complicated by factors associated with lack of availability or imprecision of certain information, such as the dose received, comorbid conditions, and the actual cause of death.

Nevertheless, enormous effort has been expended in analyzing available data from groups of patients who have received radiation exposure from the nuclear weapons used in Japan or through the use of radiation in medicine. Preston et al (2) evaluated eight cohorts who received exposure to the breast and used the most consistent data to develop a risk model for radiation-induced breast cancer. An adapted version of this excess absolute risk model was selected as the preferred model of the National Academy of Sciences Committee on the Biologic Effects of Ionizing Radiation (3).

Our purpose was to present a schema for estimating the risk of radiation-induced breast cancer following exposure of the breast to ionizing radiation as would occur in mammography and to provide data that can be used to estimate the potential number of breast cancers, cancer deaths, and woman-years of life lost that are attributable to radiation exposure delivered according to a variety of screening scenarios.

Materials and Methods

Number of Radiation-induced Breast Cancers

The excess absolute risk of developing a radiation-induced breast cancer at a given age after the breast is exposed to a single dose of ionizing radiation corresponding to a single mammographic examination at another given age can be estimated by using the preferred model developed by Preston et al (2). This model was adopted in the Committee on the Biologic Effects of Ionizing Radiation VII report (3) for the calculation of breast cancer risk; however, because of discrepancies in the equation as published in that report, we used the original equations from Preston et al. The equation for this model, as well as the other risk calculations discussed in this section, are described in Appendix E1 (online).

Following the recommendations of the Committee on the Biologic Effects of Ionizing Radiation VII, the absolute rather than relative risk estimate was used because this is considered to be more stable when applied to populations other than those from which the model was developed.

It has been suggested (3) that, for low doses or low dose rates, a “dose and dose-rate effectiveness factor” should be applied to reduce the risk. Typically, its value would be about 1.5, which would reduce the risk estimate to about 66% of its original value. Preston et al (2) did not observe this effect in cohorts of women who received dose rates similar to those used in mammography, and Heyes et al (4) and the U.S. Environmental Protection Agency (5) have argued that a reduction factor does not apply in cases where fractionated high-dose-rate radiation is received, as in mammography. Therefore, we did not apply a dose and dose-rate effectiveness factor. The Committee on the Biologic Effects of Ionizing Radiation VII used a reduction factor of 1.5. As a consequence, the cancer risk results we present here will be 1.5 times higher.

To model the screening process and calculate the number of radiation-induced...
cancers that would appear at a given age of interest, we considered a cohort of 100000 women and calculated the excess absolute risk for each age of exposure from the age at which screening began until it was terminated. The appearance of radiation-induced cancer is known to have a latency of at least 10 years following exposure (6). Therefore, an excess absolute risk of zero is assigned until the latency period has been exceeded. The model also includes a life-table correction to account for deaths of some women from causes other than radiation-induced breast cancer between the age at which screening began and the age of interest. We used the life tables for Canadian women in 2002 (7).

The lifetime risk of radiation-induced breast cancer expressed as the number of such cancers that would appear in this cohort was then obtained by summing the number of radiation-induced cancers that would appear each year between the age at which the first breast cancer could conceivably appear (the age when screening began plus the latency) and the maximum age of interest, which we chose to be 109 years. The adoption of digital mammography has resulted in the possibility of a reduced dose compared with that required for screen-film mammography. Hendrick et al (8) reviewed doses delivered in the Digital Mammography Imaging Screening Trial, or DMIST, and demonstrated that the average dose fell from 4.7 mGy for screen-film mammography to 3.7 mGy for digital mammography for a standard examination with two views per breast. We have calculated risks for the doses typical with digital mammography.

Deaths due to Radiation-induced Breast Cancer

The number of deaths that might result at an age of interest from these radiation-induced cancers was calculated by considering the number of such cancers that might appear at an earlier age and the probability that a woman would die at that age of interest due to the cancer, not having previously died of some other cause or having had successful treatment of the radiation-induced cancer. The probability of death at a given time after diagnosis was obtained from the survival curve. Survival curves differ between women who are part of a screened population and those who are not (9–12). For women who receive regular screening, the survival curves were based on the data of Coldman et al (11). These curves extend to 8 years but were extrapolated based on the data of Tabar et al (9) in a Swedish population, for which 20-year survival information was available. Curves were further extended to 50 years by using a linear model. For an unscreened population, survival data from Coldman et al (10) were used. These data reflect women whose cancers were diagnosed fairly recently (1988–2003), with curves available out to a maximum of 10 years. Again, these were extrapolated to 20 years based on the shape of the curves for the unscreened Swedish population of Tabar et al (9) and then linearly to 50 years.

Deaths were calculated for each possible age at which the cancer could surface, beginning after the latency period, up to the age at death, and these values were summed to obtain the total number of deaths occurring at the age of interest. Again, a life-table correction was used to account for other causes of death.

Finally, the total number of deaths potentially caused by radiation-induced cancer was estimated by adding the deaths that occurred in all years after exposure. Details of these calculations are provided in Appendix E1 (online).

Woman-Years of Life Lost

It is possibly more useful to consider the number of woman-years of life potentially lost due to radiation-induced cancer, especially since the diagnosis of disease and the risk of death would occur many years after the exposure. This was compared with the gain attributable to earlier detection of breast cancer with mammographic screening, as was done by Berrington de González and Reeves (12).

The number of woman-years of life potentially available, WY, was obtained by considering a cohort of 100000 women at the initial screening age and then multiplying by the average number of expected years of life remaining at that age, which was obtained from a life table (7).

The number of woman-years of life lost owing to death from radiation-induced breast cancer, YL, was estimated by multiplying the number of deaths in the cohort that would occur in each year by the average remaining years of life and summing over all ages at death, as shown in Appendix E1 (online). The average loss of life expectancy in years was YL/100000, and the relative number of woman-years of life lost was (YL/WY) · 100%.

Background Breast Cancer Incidence and Mortality

It is useful to compare the estimated number of radiation-induced cancers and the deaths arising from these cancers (ie, a harm of screening) to the background number of expected breast cancers and the resulting deaths in the population. The benefit of screening would come from averting some of these deaths. Table 1 gives the age-specific incidence and mortality of breast cancer in 100000 Canadian women (13). As an example, we can consider 100000 women at age 40 years. The number of cancers that will appear in the next 10 years is calculated by multiplying the incidence from Table 1 at each age (obtained by interpolation) by the life-table correction from age 40 years to each attained age (to correct for deaths) and summing the numbers that arise each year in that decade. The mortality due to these cancers is obtained in the same fashion used to calculate deaths from radiation-induced cancers described in Appendix E1 (online), except that survival curves for an unscreened population are applied.

Benefit and Risk

The extensive comparison of the benefits and risks of screening is beyond the scope of our article; however, it is worth noting that Feig and Hendrick (14) estimated that, for a cohort of 100000 women screened annually with mammography beginning at age 40 years, the number of lives predicted to be saved as a result of screening was 292, while Berrington de González and Reeves (12) estimated this number to be 96. The difference likely comes from use of different survival statistics for breast cancer and...
different assumed mortality reduction factors attributable to screening (ie, 36% by Feig and Hendrick and 20% by Berrington de González and Reeves). The results of other studies (11,15) suggest that the actual mortality reduction achievable with modern mammography is about 24%. By using the calculated number of deaths expected in the background population, the number of lives saved was calculated.

The benefit of earlier detection can also be quantified in terms of the number of woman-years of life saved with screening, and a benefit-to-risk ratio can be calculated on that basis. The method for calculating the woman-years potentially saved is given in Appendix E1 (online).

Sensitivity Analysis

For any risk estimation from a population model, there are a number of sources of uncertainty. These uncertainties arise from the choice of model, the confidence interval on fitted parameters in the model, and the assumptions used in the model. All parameters were obtained from Preston et al (2). The uncertainty in risk prediction in the pooled excess absolute risk model by Preston et al is about 40%; therefore, uncertainties on that order should be applied when considering our results. The correlation between uncertainties in each parameter is unknown. Thus, all parameters are assumed to be uncorrelated.

To obtain an estimate of the variation in results, either the upper or lower 95% confidence bound was substituted for each parameter, and the combination of parameters was selected to yield the minimum and maximum risk values to specify a bound on the risk calculation. The following three conditions were investigated: using a relative risk model instead of an absolute risk model, reducing the latency to 0 years, and considering the survival rates to be those of an unscreened population.

Results

Number of Radiation-Induced Breast Cancers

The predictions provided by the model for a single exposure are illustrated in Figure 1 for a dose of 3.7 mGy to both breasts. As an example, if 100 000 women received a dose to both breasts at age 45 years, then 25 years later, when these women reached 70 years, the probability of a radiation-induced cancer in this cohort would be about 0.19 cancers per 100 000 woman-years, or the risk to an individual would be 1.9 × 10⁻⁴.

Figure 2a illustrates the predictions of the risk model for two routine annual screening strategies, with and without life-table correction. In Figure 2b, the incidence of radiation-induced cancers is modeled, with life-table correction, for additional scenarios where we consider annual screening in the 40s, as well as the possibility of biennial screening after age 50 years. We have also modeled the cancer risk for annual screening up to age 55 years as a possible surrogate for menopause, followed by biennial screening to age 74 years.

Lifetime risks of cancer induction following a single screening examination with digital mammography are given in Table 2, while those for different screening regimens are provided in Table 3. In both tables, results are also given for a 1-mGy dose so that they can be applied to a particular application by multiplying by the actual per-examination dose in milligrams and by scaling to the number of women actually screened.
The percentage of life expectancy lost is also given. The life expectancy of a woman at age 40 years is an additional 43.63 years, so for the cohort of 100,000, there are 4,363,000 woman-years of life lost for the same screening scenarios set out for Figure 2b. In Table 3, the predicted total number of deaths in the cohort due to radiation-induced breast cancer (for a dose typical of digital mammography and for 1 mGy) is given for various screening strategies.

**Deaths due to Radiation-induced Breast Cancer**

Data extracted from the survival curves for screened and unscreened populations are given in Figure 3. Linear extrapolation resulted in a net change in survival of −0.14% per year and −0.088% per year beyond year 20 for the unscreened and screened populations, respectively. Figure 4 illustrates the results of the model for a cohort of 100,000 women.

**Woman-Years of Life Lost**

Estimates of the number of woman-years lost owing to radiation-induced cancer for a cohort of 100,000 women at the onset of screening are given in Table 4. In the regimen with annual screening from ages 40 to 55 years and biennial screening until 74 years, life expectancy was shortened by 0.0014 years or 12.7 hours! The percentage of life expectancy lost is also given. The life expectancy of a woman at age 40 years is an additional 43.63 years, so for the cohort of 100,000, there are 4,363,000 woman-years of life lost for the same screening scenarios set out for Figure 2b. In Table 3, the predicted total number of deaths in the cohort due to radiation-induced breast cancer (for a dose typical of digital mammography and for 1 mGy) is given for various screening strategies.
Background Breast Cancer Incidence and Mortality

The numbers of cancers expected to arise in the absence of radiation (ie, the background incidence) during the periods considered for the different screening regimens for a cohort of 100,000 women at the beginning of the screening period are shown in Table 5. For example, the total number of cancers arising in women between the ages of 40 and 49 years would be 1316. Assuming the survival life expectancy (6). For women at age 50 years, the life expectancy is an additional 34.172 years, with 3,417,200 woman-years in the cohort. Data are also provided for a dose of 1 mGy to facilitate scaling to other doses received per examination.

Figure 3: Survival curves from Coldman et al (10, 11) (Coldman) in British Columbia and Tabar et al (9) (Tabar) in Sweden. Curves from Coldman et al were extrapolated by matching the curvature of the curves from Tabar et al and then extrapolated linearly from 20 to 50 years.

Figure 4: Graph of deaths per year that are potentially attributable to radiation-induced cancer at various attained ages (in years) following various screening regimens (3.7 mGy breast dose per examination). 50–59 = annual screening from ages 50 to 59 years, 50–59 (2yr) = biennial screening from ages 50 to 59 years, 40–49 = annual screening from ages 40 to 49 years, 40–59 = annual screening from ages 40 to 59 years, 40–59 (2yr > 50) = annual screening from ages 40 to 50 years and biennial screening to age 59 years, 40–74 (2yr > 55) = annual screening from ages 40 to 55 years and biennial screening to age 74 years.
annually from 40 to 55 years, biennially to 74 years 136.4 (0.0031) 36.9 (0.00084)

Table 4

<table>
<thead>
<tr>
<th>Screening Regimen</th>
<th>Total* Per Milligray Per Examination</th>
</tr>
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<tbody>
<tr>
<td>Annually from 40 to 49 years</td>
<td>105.4 (0.0024) 28.5 (0.00065)</td>
</tr>
<tr>
<td>Annually from 50 to 59 years</td>
<td>32.3 (0.00094) 8.7 (0.00026)</td>
</tr>
<tr>
<td>Biennially from 50 to 59 years</td>
<td>17.2 (0.0005) 4.6 (0.00014)</td>
</tr>
<tr>
<td>Annually from 40 to 49 years</td>
<td>137.2 (0.0031) 37.1 (0.00085)</td>
</tr>
<tr>
<td>Annually from 40 to 49 years, biennially to 59 years</td>
<td>122.4 (0.0028) 33.1 (0.00076)</td>
</tr>
<tr>
<td>Annually from 40 to 49 years, biennially to 74 years</td>
<td>136.4 (0.0031) 36.9 (0.00084)</td>
</tr>
</tbody>
</table>

Table 5

<table>
<thead>
<tr>
<th>Screening Age Range (y)</th>
<th>Background Breast Cancer</th>
<th>Screening Mammography*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>No. of Deaths</td>
</tr>
<tr>
<td>40–49</td>
<td>1316</td>
<td>363</td>
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<tr>
<td>50–59</td>
<td>2440</td>
<td>645</td>
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<tr>
<td>50–59</td>
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<td>1000</td>
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<tr>
<td>40–74</td>
<td>8175</td>
<td>2070</td>
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</table>

* Assuming 24% mortality reduction attributable to screening regardless of screening regimen.

Discussion

In the analysis by Berrington de González and Reeves (12), a much higher radiation-induced mortality rate was calculated (50 deaths per 100 000 women beginning at 40 years vs 7.6 deaths in our analysis). This is attributable to three factors. First, in their work, the dose per examination was higher, reflecting that of screen-film mammography as used in the United Kingdom (4.5 mGy) (16). Second, they used an excess relative risk model from Preston et al (2). Third, in their analysis, survival for breast cancer was lower than that now being observed in North American women. They used a 10-year mortality rate of 35% for women aged 45–59 years compared with the 15% mortality extrapolated from the screened survival reported by Coldman et al (10). This difference in survival may be related to differences in the size and stage of cancers detected: In the United Kingdom, a screening interval of 3 years is often used, while in North America, women are typically screened annually in their 40s and either annually or biennially thereafter.

These three factors account for much of the 6.5-fold higher estimated mortality
due to radiation-induced breast cancer seen in the predictions by Berrington de González and Reeves (12). The increase is 1.2-fold for higher dose, 2.3-fold for use of the relative risk model, and 2.3-fold owing to a lower survival, for a combined 6.3-fold increase. Slight differences are also incurred owing to the difference in the maximum age used in calculations (85 years vs 109 years), different populations (British vs Canadian), and the use of age-specific survival for British women. Use of the relative risk model in our calculations would still have yielded mortality estimates that was lower by a factor of 2.6. This would result in a benefit-to-risk ratio of 4.5:1 for lives saved and 9.5:1 for woman-years saved.

We also note that our calculations are based on a dose reduction from 4.5 mGy to 3.7 mGy per examination due to a shift from screen-film to digital mammography. There is some variability in the dose efficiency of the technologies used for digital mammography. Actual doses will also depend on how the equipment is operated. Representative doses are normally measured as part of a quality assurance program, and data in our tables allow the calculation of risk to be adjusted to the applicable dose.

The predicted risk of radiation-induced breast cancer from mammographic screening is low in terms of the number of cancers induced, the number of potential deaths, and the number of woman-years of life lost. For women 40 years of age and older, the expected benefit of reduction in premature mortality afforded by routine mammographic screening in terms of either lives saved or woman-years of life saved greatly exceeds this risk.

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