Mammography, Breast Tomosynthesis, and Risk of Radiation-Induced Breast Cancer

James G. Mainprize

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25.1 Introduction
The best evidence to date suggests that low radiation doses from X-ray imaging procedures may carry a small risk of causing a radiation-induced cancer (National Research Council 2006). Both mammography (see Chapter 19 of this book) and breast tomosynthesis (see Chapter 20) typically have higher radiation doses than simple chest radiography, but lower than most CT procedures (see Chapter 29 for more on radiation dose in mammography and tomosynthesis). In a breast cancer screening program, in which most women are expected to never develop the disease, the risk of inducing a cancer is a small, but important concern. In this chapter, the biological effects of ionizing radiation are introduced, as well as the concepts of excess risk and the benefits of breast cancer screening. Several groups have attempted to establish an estimate of radiation risk in a modern screening program, and a comparison of their approaches is presented. Finally, recent trends in radiation dose levels in screening mammography and breast tomosynthesis are described.

25.2 Radiation Doses
For radiation measurement, the “absorbed dose” is measured in grays (Gy), which is a unit of energy deposited per unit of irradiated mass (J/kg). Typically, diagnostic radiology procedures are on the order of 0.1 to 10 milligray (mGy). The “effective dose” is measured in Sieverts (Sv), which is adjusted to account for the differing radiosensitivities of organs in the body. See Table 25.1 for a comparison of typical radiology procedures. The weighting factor to convert the absorbed dose in the breast to an effective dose is 0.12 (Wrixon 2008).

25.3 A Brief Overview of Radiation Biology
The seventh report from the National Research Council on the Biological Effects of Ionizing Radiation (BEIR VII Phase 2) is a consensus report from a large committee of experts across several fields of study, on the “Health Risks from Exposure to Low Levels of Ionizing Radiation” (National Research Council 2006). The first chapters from that report are on the observed radiation biology effects at the molecular, genomic, and cellular levels. Later chapters deal with the current epidemiological understanding of radiation effects in human populations and risk assessment for low levels of radiation. An overview of the findings reported by BEIR VII is presented here, with a focus on radiation-induced breast cancer.*

X-rays are ionizing radiation, meaning that X-ray interactions with matter can knock electrons from atoms, resulting in an ion or the breaking of chemical bonds. When X-rays interact in matter, the X-ray energy is transferred as kinetic energy to bound electrons which, in turn, can interact with other electrons, possibly causing additional bond breaks. These secondary electrons can produce “clusters of ionizations” that can cause clustered-damage or “locally multiply damaged sites” in the DNA (BEIR,

* Page numbers indicated throughout this section refer to BEIR VII Phase 2 Report (National Research Council 2006).
TABLE 25.1

<table>
<thead>
<tr>
<th>Medical Procedure</th>
<th>Average Effective Doses (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Radiography</td>
<td>0.07</td>
</tr>
<tr>
<td>Mammography</td>
<td>0.26 (2.2 mGy)</td>
</tr>
<tr>
<td>CT Scan</td>
<td>7.4</td>
</tr>
<tr>
<td>Angiography</td>
<td>9.3</td>
</tr>
</tbody>
</table>


National Research Council 2006, p. 26). The energy range of X-ray photons used for mammography and tomosynthesis imaging is roughly 15 to 40 keV. This is sufficient energy for each X-ray photon interacting in tissue to be potentially responsible for hundreds or even thousands of chemical bond breaks.

If these bond breaks occur in the DNA of the cell, single or double strand breaks or cross-linking may occur directly in the DNA. More likely, the X-ray interaction liberates “free radicals” (e.g., hydroxyl radicals) from nearby molecules. Free radicals are highly reactive chemical groups with unpaired electrons that can cause oxidative reactions that can result in additional DNA damage and damage to other cellular structures (BEIR, National Research Council 2006, pp. 29–31).

Generally, normal cellular repair mechanisms can repair DNA damage. These mechanisms deal with the inherent instability of the DNA molecule. In a typical cell, DNA may undergo several thousand damage events per day, which generally corrected by DNA repair mechanisms (BEIR, National Research Council 2006, pp. 30, 33–39) (Saul and Ames 1986). However, an ionizing radiation event may cause many localized simultaneous breaks and, if there are enough events, the repair mechanisms may fail to correct the damage. If the radiation dose is high enough in the cell, the DNA damage may be so severe that it causes the cell to die. However, at sub-lethal doses, the DNA may be incorrectly repaired, resulting in a cell transformation. A transformed cell with a mutation in a tumor suppressor gene or a proto-oncogene will pass this on to progeny cells, and may ultimately lead to malignancy.

One intriguing line of investigation regarding radiation effects is the so-called “bystander effect” (BEIR, National Research Council 2006, pp. 45, 53–55) (Morgan 2003), which suggests that even cells that are not directly hit by radiation may become affected. This is presumably because of cell–cell signaling between a damaged cell and the surrounding cells. Some studies (Dent et al. 1999; Lorimore et al. 2001) have indicated that this may decrease cancer risk by causing the affected cell to be eliminated, whereas others have suggested that this might actually increase the risk as this cell signaling adversely affects the normal cells nearby (Belyakov et al. 2001). It is possible both positive and negative bystander effects may play a role in humans, but their effects at low doses have been limited to laboratory studies, and have not been observable in a human population (BEIR, National Research Council 2006, p. 55).

A number of studies have attempted to measure the “dose response” relationship between radiation dose and the number of chromosomal damage, mutations, or malignant transformations of a cell, and determine its functional shape (Grosovsky and Little 1985; Ullrich et al. 1987; Lloyd et al. 1992; Schiéstl et al. 1994). Most studies, across a number of cell types, have demonstrated a linear response down to ~50 mGy, and a few as low as ~20 mGy. Most of these studies are “consistent with a linear no-threshold model” (LNT), suggesting that there is a linear risk increase extrapolated down to 0 dose (BEIR, National Research Council 2006, pp. 9–11, 57–59).

At a human population level, much of our understanding of radiation dose effects are from the Life Span Study (LSS) on Japanese A-bomb survivors of Hiroshima and Nagasaki, and a number of much smaller cohorts that were exposed to various levels of radiation either acutely or over a protracted period of time (Preston et al. 2002b, 2007; Land et al. 2003). These cohorts have been studied extensively, with attempts to establish a model relationship between radiation dose and excess cancers seen in these cohorts compared to an unexposed population. At high doses (>100 mSv), there is strong evidence of a linear dose response model for solid tumors. Leukemia is a notable exception, which appears to have a linear-quadratic dose response (BEIR, National Research Council 2006, pp. 15, 43, 144). The BEIR VII committee reviewed the “available biological and biophysical data” to determine the most likely cancer risk model for low doses (<100 mGy). Their conclusion was that there was an increased risk in humans, and that the LNT model was the best estimate to date (BEIR, National Research Council 2006, p. 15).

One of the factors that may also affect the risk associated with low dose radiation is the dose rate. Studies have shown that acute doses have a greater effect than a slower dose rate, with a “dose and dose rate effectiveness factor” (DDREF) of approximately 1.5 for radiation doses below 2 Gy. It is believed that cellular “adaptation” (stress response that protects DNA or enhances DNA repair) and/or bystander effects may be responsible for the reduced risk at lower dose rates. The DDREF may be tissue type specific with a DDREF of 2 to 6 for leukemia and lymphoma, ~3 for lung adenocarcinoma, and ~1 for mammary tumor for radiation doses below 2 Gy (BEIR, National Research Council 2006, pp. 78, 246–50).

At-risk populations (those that carry a gene mutation pre-disposing them to cancer) may be at increased risk of developing radiation-induced cancer. This hypothesis appears to be supported by experiments and mechanistic models developed from animal studies for several mutations, including Atm, Rad51 and p53 (BEIR, National Research Council 2006, pp. 79–83, 85–6), Gene mutations of BRCA1 and BRCA2, which are involved in repair of DNA double strand breaks, are of particular interest for breast cancer. Women who are BRCA1/BRCA2 gene mutation carriers are at significantly increased risk of developing breast cancer (Pijpe et al. 2012). Intuitively, one might conclude that this population of women would be at increased risk of radiation-induced cancer. However, it was several years before such a link could be established. Several small studies of BRCA1/BRCA2 gene mutation carriers have shown inconsistent results (Andrieu et al. 2006; Narod et al. 2006), and only recently was the GENE-RAD-RISK study (Pijpe et al. 2012) able to conclude that there is a 90% increased risk for women with BRCA1 or BRCA2 mutations for any radiation (mammography or otherwise) for women under 30. Somewhat surprisingly, no increased risk was observed for women exposed at ages 30 to 39. The study included \( n = 1993 \) women currently in cohort studies in the UK, The Netherlands,
and France, and used a detailed questionnaire to establish their exposure history (e.g., fluoroscopy, radiography, mammography) before the age of 40. Despite the potential for memory recall bias in self-reported studies and a relatively crude estimate of radiation dose (based on typical historical exams), the researchers were able to demonstrate increased risk at all dose levels. The researchers attempted to minimize “survival bias” by analyzing a sub-cohort of women who were diagnosed with cancer within 5 years of the study date, and showed largely similar risks as the larger population. The researchers did not establish a dose–response relationship, but demonstrated that, with the increasing number of ionizing radiation procedures, the hazard ratios increased.

In addition to cancer, radiation exposure has been demonstrated to increase the risk of other diseases, particularly cardiovascular disease, in persons exposed to high therapeutic doses, and also in A-bomb survivors exposed to more modest doses. However, there is no direct evidence to date of increased risk of non-cancer diseases at low doses, and data are inadequate to quantify this risk if it exists (BEIR, National Research Council 2006, p. 153). Radiation exposure has also been shown to increase risks of some benign tumors, but data are inadequate to quantify this risk.

### 25.4 Excess Risk Due to Radiation Exposure

When more disease is observed in a sub-population compared to the expected (background) rate, that increase may be expressed as an excess risk. This excess risk may be modeled as additive or multiplicative risk. An additive excess risk is called an Excess Absolute Risk (EAR), as added to the background rates of disease. Alternatively, a multiplicative risk is the Excess Relative Risk (ERR), in which the increased rate of disease is the product of the ERR and the background rate. Within that sub-population, the ERR and EAR should yield the same numbers of new disease. The EAR or ERR model may be more appropriate when describing the excess risk in a different population than the original cohort(s) modeled. Care must be taken when risk models are transported to a different population where the background cancer rates are different (BEIR, National Research Council 2006, pp. 240–3; Walsh and Schneider 2013). Often neither model is completely satisfactory at explaining the excess risk observed in different populations, and, in some cases, hybrid EAR/ERR models have been suggested (Walsh and Schneider 2013).

#### 25.4.1 Dose/Risk Models for Radiation-Induced Breast Cancer

BEIR VII recommends the EAR model developed by Preston et al. (2002a,b) that fits incidence rates of breast cancer seen in four separate cohorts. The committee noted that Preston et al. also examined four other cohorts for which the model did not fit well, possibly because of low dose rates (two skin hemangioma cohorts), or the existence of breast disease (post-partum mastitis and benign breast disease cohorts). Preston et al. examined whether an ERR model would successfully describe the behavior of excess cancers in these cohorts, especially knowing that the background risk for breast cancer in the eight cohorts were different (e.g., the LSS have particularly low breast cancer rates, and the acute post-partum mastitis cohort have significantly increased background cancer rates). However, no single model could explain the behavior seen in each cohort. Attempts to use the Preston ERR model by Pijpe et al. (2012) did not explain the observed hazard ratios seen in the GENE-RAD-RISK study in groups with increased background risk.

There are a number of factors that can potentially modify the dose response for an individual, especially sex, age of exposure (fetal, childhood, and pubescent exposures are at significantly increased risk, whereas ages >50 show little increased risk), and attained age (how old they are at present). Often corrections are made for a “birth year effect”, which acts as a surrogate for changing societal, lifestyle, and environmental factors that affect cancer rates in populations. As described above, genetic mutation carriers and family history of breast cancer appears to increase the risk of radiation-induced cancer.

#### 25.4.2 Average Radiation Risk Model

From Preston et al. (2002b), the EAR model of radiation risk is,

\[
EAR = \beta D \cdot \exp(-\theta \cdot (a_x - 25)) \left(\frac{a}{50}\right)_{\gamma(a)},
\]

where \(a_x\) is the age of exposure, \(a\) is the attained age, \(\beta = 9.9 \times 10^{-2}\) women-years/mGy, \(D\) is the dose in milligray, \(\theta = 0.05\) year\(^{-1}\), and \(\gamma(a) = 3.5\) for \(a < 50\) (“pre-menopausal attained-age effect”) and \(\gamma(a) = 1\) for \(a \geq 50\) (“post-menopausal attained-age effect”). Table 25.2 summarizes the model parameters and their 95% confidence intervals, which are large. Preston et al. (2002b) postulate that uncertainties on the risk estimates from the model should be of the order of 40%. Note that many radiation risk models employ the effective dose (in mSv), whereas breast risk models largely use the absorbed dose (in mGy) to the fibroglandular tissue in the breast.

The effect of age of exposure in the EAR model is strong, as illustrated in Figure 25.1 for ages 40 and 50. For comparison, the Preston ERR model is also shown, using the background breast cancer rates of the UK (Office for National Statistics 2003), similar to data used by Berrington de González and Reeves (2005). The ERR model lacks an age of exposure component, and the increased risk at any attained age is, therefore, the same, regardless of the age of exposure. Lifetable corrections are applied (dotted lines) to indicate the expected rates for 100,000 women at the age of exposure and surviving until the attained ages shown. At younger ages, the ERR and EAR models for a UK population are dramatically different, although they converge to similar results at 70+ years.

Preston et al. (2002b) note that their models largely do not predict the excess risk in the earliest years following exposure.

### TABLE 25.2

<table>
<thead>
<tr>
<th>(\beta)</th>
<th>(\theta)</th>
<th>(\gamma(a &lt; 50))</th>
<th>(\gamma(a \geq 50))</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.9 (7.1,14)</td>
<td>0.05 (0.033,0.071)</td>
<td>3.5 (2.4,4.9)</td>
<td>1.1 (−0.4,2.4)</td>
</tr>
</tbody>
</table>
postulating that a latency period, in which the lesions are not clinically detectable, is required to complete the model. Latencies of 0 to 10 years with zero excess risk have been used by various groups to model this sub-clinical period of tumor development. Note that latency is not included in Figure 25.1.

As mentioned above (see Section 25.4), neither model (EAR or ERR) may be entirely acceptable. For example, the best fit model may not accommodate an observable age of exposure term, or it does not account for an observable birth year effect. In such cases, a hybrid ERR/EAR model may yield better results (Walsh and Schneider 2013). Largely, these hybrid models are based on ad hoc weighting factors. Walsh and Schneider have suggested a more algorithmic approach to selecting appropriate weights based on “information scoring” that essentially weights the models towards the one with the least deviance and the fewest model parameters. Using this approach, they have suggested weighting factors for several cancers based on the analysis of LSS data by Preston et al. (2002b). In their analysis, they show that the optimum weighting for breast cancer risk for the Japanese population is the 100%/0% ERR/EAR model, unless the EAR model includes the pre/post-menopausal attained age scaling factor (i.e., including a model term like \( \gamma(a) \) in Equation 25.1) in which case the best fit is the 70/30 ERR/EAR model.

Ideally, we would like to use the risk models determined from one population to predict the risk for a different population. The populations may have different geo-ethnicity, health, genetic, environmental, or age distribution. If the populations can be shown to be relatively similar (e.g., similar background rates of cancer, similar competing risk factors, or similar cancer sub-type distribution), then transport of the ERR (or EAR) model might work. However, if the populations are different, then the epidemiological models are likely to fail unless significant correction factors are used. For example, the baseline rates of breast cancer in Japanese women in the LSS study are dramatically lower than their contemporary western counterparts, and even more so when looking at a modern population, say in the US or Europe. Preston et al. (2002b) suggest that, if their ERR model fitted to the LSS data was to be applied to a US cohort, then the ERR should be scaled down by roughly the ratio of the background rates of the Japanese to US population: 1.8 ERR/Gy (at age 50) scaled by the ratio of the background rates at age 50 (0.3) to yield 0.5 ERR/Gy, which is reasonably close to the 0.74 ERR/Gy (95% CI = 0.4–1.2) developed in a pooled model of three western cohorts.

Hybrid models may help reduce bias when transporting to a new population, or mechanistic models that model cancer growth may be more robust in new populations (Bijwaard et al. 2010). Regardless of the methodology used in transport to the new population, it pre-supposes that at least some measure of the excess risk is known in the new population against which the model can be evaluated. Without that knowledge, any transported model predictions cannot be expected to be reliable.

### TABLE 25.3
Selected Incidence and Mortality Risks Reported by Four Different Models for Several Screening Regime and Radiation Doses per 100,000 Women

<table>
<thead>
<tr>
<th>Reference</th>
<th>Screening Years</th>
<th>Average Glandular Dose/Exam (mGy)</th>
<th>Number of Exams</th>
<th>Incidence (/100,000)</th>
<th>Mortality (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEND</td>
<td>40–80</td>
<td>3.7</td>
<td>41</td>
<td>72</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>50–80</td>
<td>3.7</td>
<td>31</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>BERR</td>
<td>40–49</td>
<td>4.5</td>
<td>10</td>
<td>–</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>4.5</td>
<td>4</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>4.5</td>
<td>4</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>YAFF</td>
<td>40–49</td>
<td>3.7</td>
<td>10</td>
<td>59</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>3.7</td>
<td>10</td>
<td>26</td>
<td>3.1</td>
</tr>
<tr>
<td>MIGL</td>
<td>40–74</td>
<td>4.8</td>
<td>35</td>
<td>125</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>50–74</td>
<td>4.8</td>
<td>25</td>
<td>49</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 12D-1 and Table 12D-2 in BEIR VII (National Research Council 2006). Note that, in the BEIR VII, tables of LAR were reduced by a DDREF of 1.5 included in the HEND model.

Berrington de González and Reeves (2005) (BERR) used a more sophisticated model based on the ERR model from Preston et al. (2002b). For BERR, the mortality was calculated summing the expected mortality resulting from a cancer induced at the attained age, \( a_j \). The “cumulative risk of radiation-induced breast cancer mortality,” (CLR) is

\[
CLR = \sum_{j=1}^{a} R_j M_j S_j
\]

where \( R_j \) is the incidence, \( M_j \) is the age-specific mortality from cancers, and \( S_j \) is the all-cause survival to adjust the number of women dying due to competing causes. The incidence was calculated from the Preston ERR model as

\[
R_j = \lambda_j \left( \frac{\alpha_j}{50} \right) \sum_{k=0}^{\gamma_j - 10} D(k)
\]

where \( \lambda \) is the background rate at \( \alpha_j \), \( \beta = 0.74 \) is the ERR at age 50, \( \gamma_j = -2 \) is the attained age risk reduction exponent, and \( D(k) \) is the screening dose at age \( k \) from the start of screening up to 10 years (the latency period) prior to age \( \alpha_j \). The BERR model used age-specific mortality rates, an all-cause survival (i.e., dying due to non-breast cancer effects) correction, and background breast cancer rates for the UK that was reported in years 2001 to 2005. They also calculated the expected increase in radiation-induced cancer mortality for women with family history of breast cancer by adjusting the background incidence and mortality terms, based on data from the Collaborative Group on Hormonal Factors in Breast Cancer (2001).

Yaffe and Mainprize (2011) (YAFF) used a similar approach to the BERR model, but elected to use the Preston EAR (Equation 25.1) model preferred by BEIR VII, and applied the all-cause survival and mortality rates observed in Canada. They did not use an age-specific survival, but instead calculated the number of women surviving to each year, \( a_x \), following a cancer incident in each previous year, based on the average breast cancer survival curve reported by Coldman et al. (2007) for women in British Columbia (a province in Canada). See the Supplement in Yaffe and Mainprize (2011) for the complete description of the calculation.

More recently, Miglioretti et al. (2016) (MIGL) described a twin model incorporating a validated mechanistic tumor growth model called the MISCAN-Fadia model, as well as a second model similar in principle to that of the YAFF model, but incorporating age-specific mortalities extracted from the MISCAN-Fadia model. The MISCAN-Fadia model simulates the natural lifespan of a woman, and uses a continuous growth tumor model with a “fatal diameter” acting as a surrogate for the lethality of the cancer (i.e., if detected before the tumor achieves the fatal diameter, the cancer is curable and, if detected after, then the cancer is fatal). The MISCAN-Fadia model shows a good match to the Swedish Two Country Screening trial and to US breast cancer statistics (Tan et al. 2006). Like the YAFF model, the MIGL models used the Preston EAR model for estimated excess radiation risk. The second MIGL model was more complex than the YAFF model, in that it allowed for variation of the number of views per exam (because of re-takes, “tiling,” and/or uncommon views), breast size and breast density, and age-related changes in density, as well as incorporating an estimate of extra imaging due to recalled exams. In their modeling, the average radiation dose was 4.3 mGy for the screening exam alone, which increased to an average of 4.8 mGy, when the extra dose included for all recalled workup and diagnostic imaging was included. Both of the models were consistent in predicting cancer incidence and mortality for the average breast dose and were shown to be reasonably consistent with HEND and YAFF models. The second model showed that, because of variability in radiation dose due to breast size, density, and extra views, a small percentage of women (<5%) received doses of 21 mGy compared to the 4.8 mGy average. The LAR predicted for an annual screening program was six per 100,000 women for an annual screening program between ages 50 and 74 for women with small breasts compared to 14 per 100,000 for women with large breasts, and as high as 25 per 100,000 for women in the 95th percentile of the large breast group.

Because of the differences in the approaches from each of these four studies and different choices made in comparing the screening regimen, it is somewhat difficult to compare the results in a straightforward manner (Table 25.3). To facilitate this here, the approaches of the first three studies are re-calculated, matching the algorithms as closely as possible to the original references, at a standardized breast dose of 1 mGy per exam. The radiation-induced cancer incidence and mortality are tabulated in Tables 25.4 and 25.5 for annual and biennial screening, either from ages 40 or 50 to age 74. For the MIGL study, the data were already presented for these screening regimens, and are simply rescaled to 1 mGy for the average woman.

Three of the studies that used the Preston EAR model present remarkably similar incidence rates, despite different methodologies. Mortalities for the YAFF and MIGL models are much lower than HEND, because HEND used the total population mortality rate (a mix of screened and unscreened women), and the YAFF and MIGL models both used survival data for screened populations. The BERR model shows much higher incidence and mortality rates (∼2.5× and 3.3×, respectively). This is primarily due to the discrepancy seen between the Preston ERR model and the Preston EAR model over the age ranges of interest, and a secondary effect due to the greater mortality rate used in the BERR model, reflecting statistics seen in the UK over the study period.

It should be noted that the uncertainties in a radiation risk model are large. In Table 25.2, the 95% confidence intervals are provided for each parameter of the EAR (Equation 25.1). Ideally, to estimate the uncertainties on the final risk model, these uncertainties could be propagated through the complete model. However, Equation 25.1 is non-linear, and the cross-correlations of the terms are not stated in Preston et al. (2002b). To create a conservative estimate of uncertainty, the parameters for the EAR in the YAFF model were sequentially changed for their lower and upper bounds and the minimum and maximum risk (incidence or mortality) were recorded for each screening strategy. These “extreme bounds” (EB) are listed in Tables 25.4 and 25.5.
for the YAFF model, in brackets, and should not be confused with the true 95% confidence interval for incidence and mortality. In reality, the true confidence interval is likely much narrower than the bounds listed. Nevertheless, these extreme bounds show the remarkable range of risk estimates that range roughly $0.25 \times$ to $4 \times$ the mean estimate of the risk model. Preston et al. (2002b) suggest a smaller uncertainty on the EAR model of 40%. The MIGL model is largely a mechanistic model, and a more complete uncertainty analysis can be performed because the variabilities of the biological, epidemiological, and screening parameters for the MISCAN-Fadia cancer growth model were evaluated. They demonstrate approximately 40% to 50% variability in risk estimates. It is unclear if MIGL incorporated the uncertainty of the Preston EAR model as well.

### 25.5.1 Benefit and Risk of Mammography

No risk analysis for a medical test is complete without assessing the benefits of that exam. Screening mammography has been shown to reduce mortality and morbidity by earlier detection of breast cancer. Finding cancers earlier allows for treatments that are more localized, and with fewer side-effects than for treatments for late stage cancers. The mortality reduction has been observed to be between 10% and 40% (Blanks et al. 2000; Humphrey et al. 2002; Tabar et al. 2003; Coldman et al. 2007), with many studies having at least 10 years, and some with more than 20 years of follow-up.

Breast cancer is very common, with roughly a 1:10 risk of developing breast cancer for women in developed nations, or approximately 10,000 (fewer if all-cause survival corrections are included) women from a group of 100,000 women could develop cancer in their lifetime. In Yaffe and Mainprize (2011), it was estimated that the number of background breast cancers developing over a screening period of 40 to 74 years of age was 8175 (out of 100,000 women) for a Canadian population, and that 2070 women would die of the disease.

If a woman dies prematurely due to cancer, the number of years of life lost can be estimated by comparing the age of death to the expected age of death for that woman. Yaffe and Mainprize (2011) estimated for the 2070 premature deaths, 44,470 years of life lost.

### TABLE 25.4

<table>
<thead>
<tr>
<th>Screening Years</th>
<th>Number of Exams</th>
<th>HEND</th>
<th>BERR</th>
<th>YAFF</th>
<th>MIGL</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–74 B</td>
<td>18</td>
<td>14</td>
<td>34 (243%)</td>
<td>14 (100%) [3.5–52 EB]</td>
<td>–</td>
</tr>
<tr>
<td>50–74 B</td>
<td>13</td>
<td>6.1</td>
<td>16 (262%)</td>
<td>5.4 (89%) [1–25 EB]</td>
<td>5.6 (92%)</td>
</tr>
<tr>
<td>40–74 A</td>
<td>35</td>
<td>28</td>
<td>65 (232%)</td>
<td>26 (93%) [7–100 EB]</td>
<td>26 (93%)</td>
</tr>
<tr>
<td>50–74 A</td>
<td>25</td>
<td>12</td>
<td>31 (258%)</td>
<td>10 (83%) [2–48 EB]</td>
<td>10 (83%)</td>
</tr>
</tbody>
</table>

*The DDREF = 1.5 reduction used in HEND was removed for comparison.*

### TABLE 25.5

<table>
<thead>
<tr>
<th>Screening Years</th>
<th>Number of Exams</th>
<th>HEND</th>
<th>BERR</th>
<th>YAFF</th>
<th>MIGL</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–74 B</td>
<td>18</td>
<td>3.9</td>
<td>13 (333%)</td>
<td>1.6 (41%) [0.5–5.7 EB]</td>
<td>2.5 (64%)</td>
</tr>
<tr>
<td>50–74 B</td>
<td>13</td>
<td>1.8</td>
<td>6 (350%)</td>
<td>0.6 (33%) [0.1–2.6 EB]</td>
<td>0.8 (46%)</td>
</tr>
<tr>
<td>40–74 A</td>
<td>35</td>
<td>7.5</td>
<td>24 (333%)</td>
<td>3.1 (41%) [0.8–11 EB]</td>
<td>3.3 (44%)</td>
</tr>
<tr>
<td>50–74 A</td>
<td>25</td>
<td>3.4</td>
<td>12 (353%)</td>
<td>1.1 (32%) [0.2–4.8 EB]</td>
<td>1.5 (44%)</td>
</tr>
</tbody>
</table>

*DDREF = 1.5 reduction removed for comparison.*

### TABLE 25.6

<table>
<thead>
<tr>
<th>Model</th>
<th>Screening Years</th>
<th>Lives Saved</th>
<th>Lives Lost</th>
<th>Benefit:Risk</th>
<th>WY Saved</th>
<th>WY Lost</th>
<th>Benefit:Risk (Life Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YAFF</td>
<td>40–74</td>
<td>497</td>
<td>11.6</td>
<td>43:1</td>
<td>10,673</td>
<td>145</td>
<td>74:1</td>
</tr>
<tr>
<td>YAFF</td>
<td>50–74</td>
<td>416</td>
<td>4.1</td>
<td>102:1</td>
<td>7957</td>
<td>40</td>
<td>199:1</td>
</tr>
<tr>
<td>MIGL</td>
<td>40–74</td>
<td>968</td>
<td>15</td>
<td>59:1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MIGL</td>
<td>50–74</td>
<td>819</td>
<td>6</td>
<td>123:1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>


*Note: In the YAFF model, a 24% reduction in mortality due to screening was used for a cohort of 100,000 women at the beginning of screening for an average dose of 3.7 mGy. The MIGL model has approximately a 15% mortality reduction for screening and average dose of 4.8 mGy.*
life would be lost for women with cancer developing between ages 40 and 74. If screening mammography has a mortality reduction of 24% (Coldman et al. 2007), Yaffe and Mainprize (2011) estimated 497 lives would be saved, and 10,670 years of life would be saved.

The benefit to risk for women saved by screening versus women lost to radiation-induced cancer and the years of life saved are summarized in Table 25.6 for the YAFF model. The benefit-to-risk ratios for annual screening from ages 40 or 50 to age 74 are largely in favor of screening, despite radiation risk. It is noted that earlier screening reduces the benefit-to-risk ratio by more than a factor of 2, but increases the net number of women saved by \( \sim70 \) (18% increase in net lives saved). Also shown are the lives saved and lost from the MIGL model, which had higher background incidence rates, better cancer survival rates (10–19% mortality), a more sophisticated mammography screening sensitivity model, and higher radiation doses, but showed similar trends to the YAFF model for the average woman.

Miglioretti et al. (2016) identified sub-groups of women who received notably more radiation than the average woman. For example, they calculate that the benefit to risk for women with large breasts may drop to as low as 28 (95% CI = 20–40) deaths averted for every radiation-induced cancer death for annual screening from ages 40 to 74. Identifying groups like this can help inform strategies for reducing risk and for monitoring possibly unnecessary radiation doses.

Note, however, Miglioretti et al. (2016) appear to have assumed the same benefit (breast cancer deaths averted by screening strategy) and underlying radiation risk (based on the EAR model) for all sub-groups. Ideally, calculating the benefit and risks to a specific sub-group of women should be adjusted to account for the differences in that population compared to the average population. As a theoretical example, suppose a study was performed to estimate the benefit-to-risk ratio for women with dense breasts. These women are known to be at increased risk of developing breast cancer (i.e., increased background rate over the average population), but mammography is less sensitive for dense breasts. Combining just these two effects yields a different benefit than the average population. Following the reasoning of Miglioretti et al. (2016), it is likely that these women may be subject to more recall imaging than the average population, and that will yield an increased radiation risk. Finally, and perhaps more fundamentally, can excess risk models be successfully transported from the average population to the dense breast population? Until such risk estimates can be observed for a particular sub-group (either extracted from an existing risk cohort or in new cohorts), risk estimation for these sub-groups should always be considered to be approximations with weak statistical certainty.

### 25.5.2 Recent Radiation Dose Trends

The radiation risk estimates in the above models largely rely on established data prior to 2005. Certainly, the results of the Digital Mammography Imaging Screening Trial (DMIST) (Pisano et al. 2005) were used for doses in three of the studies, and two of those studies used the extra view information reported in that study. DMIST was conducted on a number of prototype digital mammography machines that were very quickly replaced with more robust systems, better quality detectors, and, importantly, larger detectors, reducing the need for additional views.

In DMIST, nearly 20% of women imaged required extra views, yielding a mean glandular dose of 4.3 mGy (2.2–8.3 mGy for 5%/95% percentile). As digital mammography has matured, there has been a reasonably steady drop in exam doses in modern digital mammography. Young and Oduko (2016) analyzed data from 99 breast screening centers in the UK for 2010 to 2012, and found that only 2% of a two-view screening mammography exam resulted in extra views (1.4%). The average patient dose fell to 3.03 mGy, compared to 4.3 mGy for film mammography, in 2001 to 2002. A small group of women received larger doses (generally related to larger compressed breast thicknesses > 90 mm). This corresponds to \( \sim1.8\% \) of women who received \( \sim4.95 \) mGy per examination, with 0.05% of women receiving a maximum dose of greater than 9.8 mGy per examination.

It appears that doses have dropped significantly since the introduction of digital mammography, and the risks estimated in the literature should be adjusted accordingly for women currently being screened. Improvements in technology (larger detectors), quality control, and training have reduced the need for extra views, and risks for new screening women will likely be lower than reported by Miglioretti et al. (2016), even for individuals who are prone to additional views and recall imaging.

#### 25.6 Radiation Risk in Tomosynthesis

Digital breast tomosynthesis (DBT) (Chapter 20) has been proposed as an alternative to digital mammography that reduces the impact of tissue superposition by imaging the breast at different angles and reconstructing a series of planes through the breast.

One study suggested that two-view DBT has better diagnostic accuracy than two-view mammography and that one view DBT (mediolateral oblique (MLO) only) is not significantly different than two-view mammography (Wallis et al. 2012). Another small study demonstrated that one view DBT (MLO) + one view mammography (craniocaudal, CC) had a better detection rate and non-inferior malignant lesion characterization than two-view mammography (Gennaro et al. 2013). In a comparison of DBT, CC, and MLO views, it was found that 8% of lesions were only detectable on the CC view. A study by Rafferty et al. (2014) showed that that the addition of 1- or 2-view DBT to 2-view mammography improved detection and reduced the recall rate.

Bouwman et al. (2015a) examined the doses to phantoms and patients from DBT and mammography views for five systems. The doses delivered were system specific. For example, System I delivered 2.29 and 2.28 mGy in DM and DBT, respectively, for compressed breast thicknesses of 50 to 59 mm. A summary of doses is provided in Table 25.7. Assuming equal use of all five systems, the average dose to a 50 to 59 mm breast would be roughly 1.5 mGy for DM and 1.9 mGy for DBT. Please see Chapter 29 for more detail on radiation doses in DM and DBT.

From these studies, there are several possible screening regimens that could, therefore, be used. The combinations of one- and two-view DBT, with or without mammography views, are summarized in Table 25.8. Here, the dose for MLO and CC views were assumed to be the same, and the radiation doses from each view can be simply summed to estimate the total dose to the breast.
TABLE 25.7
Summary of Patient Doses (in mGy) for Compressed Breast Thicknesses of 50 to 59 mm Collected by Bouwman et al. (2015a,b)

<table>
<thead>
<tr>
<th>System</th>
<th>DM</th>
<th>DBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.29 ± 0.56</td>
<td>2.28 ± 0.25</td>
</tr>
<tr>
<td>II</td>
<td>1.47 ± 0.27</td>
<td>1.95 ± 0.42</td>
</tr>
<tr>
<td>III</td>
<td>1.32 ± 0.4</td>
<td>2.34 ± 0.64</td>
</tr>
<tr>
<td>IV</td>
<td>1.04 ± 0.26</td>
<td>1.67 ± 0.32</td>
</tr>
<tr>
<td>V</td>
<td>1.44 ± 0.35</td>
<td>1.4 ± 0.24</td>
</tr>
<tr>
<td>Simple average</td>
<td>1.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

TABLE 25.8
Possible Combinations of Views of DBT and Mammography That Could Be Used in a Screening Exam for Each Breast

<table>
<thead>
<tr>
<th>View (DBT)</th>
<th>Views (DM)</th>
<th>Radiation Dose (Compared to 2-View DM at 3 mGy)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>1.9</td>
<td>0.63</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3.4</td>
<td>1.13</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>3.8</td>
<td>1.27</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5.3</td>
<td>1.77</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6.8</td>
<td>2.27</td>
</tr>
</tbody>
</table>

As radiation risk is generally assumed to be linear, DBT screening can potentially change radiation risk by a factor of 0.63 to 2.27 depending on the number of views that become acceptable for a screening exam. Because the addition of a mammographic view is seen to increase the risk, synthesized mammograms extracted from the DBT dataset are being considered as an alternative. Although image quality is inferior to a real mammogram (Nelson et al., 2016), the results for diagnostic accuracy with a synthesized mammogram are promising (Gilbert et al., 2015). If the additional mammography views can be eliminated, then DBT screening radiation doses drop to a factor of 0.63 to 1.27 of that of a two-view mammography exam.

25.7 Summary
X-rays are ionizing radiation that carries a health risk. For medical imaging, the principle health risks are primarily radiation-induced cancers which manifest 5 to 15 years after an exposure event. At low radiation doses, the best evidence to date is that there is an elevated risk, and that risk is linear with the radiation dose. Great effort has been applied to develop models, based on several cohorts of women exposed to various levels and types of radiation to help predict radiation risk in other populations. Care must be taken when applying epidemiological models from one group to another group if there are believed to be differences in radiation sensitivity that have not been accounted for in the original models. Nevertheless, several groups have attempted to estimate the benefits and risks for screening mammography.

Digital mammography is an evolving platform that has generally seen a drop in average dose per exam from 4.3 mGy in 2002 to about 3 mGy in 2012, although these doses vary by system and by jurisdiction. From various models, the risk for screening from age 40 to 74 (if the LNT proposal is assumed) is estimated at approximately 2 to 13 additional deaths per 100,000 women per mGy for biennial screening, and twice that for annual screening. Changing the screening age to 50 drops the risk of radiation-induced cancer death to approximately 0.5 to 6 per 100,000 per mGy. This is compared to an expected benefit of 400 to 800 deaths averted by screening mammography and early treatment. Models suggest that screening beginning at age 40 will have an additional 18% cancer deaths averted. These values are for the average woman, and sub-categories of women (e.g., those with large breasts) may receive significantly higher radiation doses and corresponding radiation risk. Furthermore, women who have a genetic mutation for breast cancer may be at significantly elevated risk (e.g., young women who are BRCA1/2 carriers) compared to the average population. More work is needed to identify and predict risks (and benefits) in these subgroups of women.

Breast tomosynthesis may increase the radiation risk if it is determined that additional 2D mammographic views are necessary. However, if synthesized mammograms provide sufficient information, then radiation doses may be roughly the same as screening mammography or drop further still.

REFERENCES
Mammography, Breast Tomosynthesis, and Risk of Radiation-Induced Breast Cancer


