Radiology

Benefit to Radiation Risk of Breast-specific Gamma Imaging Compared with Mammography in Screening Asymptomatic Women with Dense Breasts[1]

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Purpose: The benefit-to–radiation risk ratios of mammography alone, breast-specific gamma imaging (BSGI) alone, and mammography plus BSGI are estimated in women with dense breasts who were asymptomatic and examined in the 2015 study by Rhodes et al.

Materials and Methods: This study uses previously published breast cancer detection rates and estimates of radiation dose and radiation risk and is, therefore, exempt from institutional review board approval. By using breast cancer detection rates for mammography alone, BSGI alone, and mammography plus BSGI from the study by Rhodes et al, as well as lifetime estimates of radiation-induced cancer mortality for mammography and BSGI on the basis of the Biologic Effects of Ionizing Radiation VII report, the benefit-to–radiation risk ratios of mammography alone, BSGI alone, and mammography plus BSGI performed annually over 10-year age intervals from ages 40 to 79 years are estimated.

Results: The benefit-to–radiation risk ratio is estimated to be 13 for women who are 40–49 years old and are screened with mammography, a figure that approximately doubles for each subsequent 10-year age interval up to 70–79 years old. For low-dose BSGI, annual screening benefit–to–radiation risk ratios are estimated to be 5 for women 40–49 years old and to double by age 70–79 years, while mammography plus BSGI has benefit-to–radiation risk ratios similar to those of BSGI alone. There are wide ranges for all of these estimates.

Conclusion: While lower dose (300 MBq) BSGI has estimated benefit-to–radiation risk ratios well in excess of 1 for screening of asymptomatic women with dense breasts who are 40 years old and older, it does not match the benefit-to–radiation risk ratio of screening mammography.

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Breast cancer detection with technetium 99m (^{99m}Tc)-sestamibi has rapidly evolved over the past decade. In the mid 2000s, whole-body gamma cameras, which have limited capabilities of depicting smaller breast cancers because of their low spatial resolution, began to be replaced by dedicated breast-specific gamma imaging (BSGI) devices (1). The Dilon 6800 system (Dilon Technologies, Newport News, Va) uses a single 15 × 20-cm detector plate composed of an array of 3 × 3-mm sodium iodide crystals. The dedicated breast design enables compression of the breast between the detector plate and a compression paddle to obtain view projections similar to those of mammography. Initial clinical studies compared BSGI to mammography in small groups of women who had an elevated likelihood of breast cancer (2–4). Those studies used label-recommended doses for breast imaging of 740–1100 MBq (20–30 mCi) of ^{99m}Tc-sestamibi. Clinical results were promising and suggested that BSGI may be suitable for breast cancer screening. Unlike mammography, which has lower sensitivity in dense breasts, BSGI has been shown to be unaffected by breast density (4).

In 2010, concerns were raised about radiation dose and cancer risks of BSGI (5,6). Because BSGI involves injecting ^{99m}Tc-sestamibi, organs involved in radionuclide clearance—such as the large and small intestines, kidneys, bladder, and gallbladder—are exposed to 10–25 times the radiation dose of fibroglandular breast tissue (5). Hendrick (6) pointed out that the cancer risk from a single BSGI study was comparable to that from a lifetime of annual screening mammography starting at the age of 40. O'Connor et al (7) estimated that doses of ^{99m}Tc-sestamibi needed to be in the range of 75–150 MBq (2–4 mCi) to obtain benefit-to–radiation risk ratios comparable to those of mammography.

In the late 2000s, BSGI was improved by the use of dedicated dual-head breast imaging devices with cadmium zinc telluride (CZT) detectors, which are also referred to as "molecular breast imaging" devices. CZT-based detectors have smaller individual detector elements (1.6 × 1.6 mm), with higher energy resolution (3%–4%) than that of sodium iodide crystals (12%–15%).

In 2011, Rhodes et al (8) used a dual-head CZT detector system to compare gamma imaging to mammography in a population of asymptomatic women with dense breasts and an increased risk for breast cancer with drawn doses of 740 MBq (20 mCi) of ^{99m}Tc-sestamibi. That study demonstrated that BSGI had a breast cancer detection rate three times that of mammography (9.6 per 1000 vs 3.2 per 1000, respectively). In light of concerns about radiation risk from BSGI, a 2015 study by Rhodes et al (9) used a dual-head CZT detector system to compare BSGI with drawn doses of 300 MBq (8 mCi) of ^{99m}Tc-sestamibi to mammography. The lower dose study also found that BSGI had a substantially higher cancer detection

Advances in Knowledge

- On the basis of risk estimates from the Biologic Effects of Ionizing Radiation VII report, the lifetime risk for radiation-induced cancer death per 100 000 women who are screened annually for 10 years with mammography ranges from 10 for those who are 40–49 years old to 1 for those who are 70–79 years old, and the risk for women who are screened with lower dose breast-specific gamma imaging (BSGI; 300 MBq of technetium 99m-sestamibi) ranges from 82 for those who are 40–49 years old to 37 for those who are 70–79 years old.
- On the basis of the assumption that 20% of women with breast cancer die from the disease in the absence of screening and that earlier detection of breast cancer with either screening mammography or lower dose BSGI has a 20% probability of averting a breast cancer death, screening mammography has a benefit-to–radiation risk ratio of 13 in asymptomatic women with dense breasts who are 40–49 years old and screened annually for 10 years and a ratio of about 90 in 70–79-year-old women, while BSGI has a benefit-to–radiation risk ratio of 5 in the same cohort of 40–49-year-old women and a ratio of 10 in 70–79-year-old women.
- Assuming the same mortality reduction for both screening mammography and lower dose BSGI in asymptomatic women with dense breasts and on the basis of recent cancer detection rates, mammography has a benefit-to–radiation risk ratio approximately two and one-half times higher than that of lower-dose BSGI in 40–49-year-old women and approximately nine times higher in 70–79-year-old women.

Implications for Patient Care

- BSGI has high breast cancer detection rates in asymptomatic women with dense breasts who are undergoing mammography and may benefit from additional screening.
- Benefit to radiation risk should be considered in the decision to add reduced-dose BSGI to mammography in screening this group of women.

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Abbreviations:
BSGI = breast-specific gamma imaging
CZT = cadmium zinc telluride

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Conflicts of interest are listed at the end of this article.

rate (10.7 per 1000) than did mammography alone (3.2 per 1000). The cancer detection rate for mammography plus BSGI was 12.0 per 1000. This study proposed that reduced-dose BSGI may be a suitable supplemental breast cancer screening tool in women with dense breasts. Comparing the expected benefit-to-estimated-radiation risk is a useful way to make that assessment. This can be done by comparing estimated breast cancer deaths averted by earlier detection through screening to estimated radiation-induced cancer deaths due to screening with a given modality in a given population. This study estimates the benefit-to–radiation risk ratios of mammography alone, BSGI alone, and mammography plus BSGI in asymptomatic women with dense breasts who were examined in the 2015 study by Rhodes et al (9).

Materials and Methods

This study uses previously acquired and published breast cancer detection rates and published estimates of dose and radiation risk; therefore, it is exempt from institutional review board approval. For each modality, benefit, risk, and benefit-to–radiation risk ratios are estimated for annual screening over 10-year intervals, starting at ages 40, 50, 60, and 70 years old. Because there is substantial uncertainty on the assumed central values going into these estimates, a sensitivity analysis based on the ranges of each variable was performed to determine the range of estimated benefit (deaths averted by early detection), risk (deaths caused by radiation-induced cancers), and benefit-to–radiation risk ratios.

In terms of breast cancer deaths averted (DA) by screening, the benefit over each 10-year interval is found by summing, over each year of screening, the product of the breast cancer detection rate per 1000 women screened (DR) for a given modality; the probability that a woman with breast cancer will die from that breast cancer in the absence of screening (P_{das}); and the probability that, once detected, earlier detection will avert a breast cancer death (P_{ls}):

$$\mathrm{DA}(b \rightarrow b+9) = 100 \cdot \Sigma_e \mathrm{DR} \cdot P_{das} \cdot P_{is} \cdot S(e)/S(b), \quad (1)$$

where the summation over e is from $e = b$, the beginning age of screening, to $e = b + 9$, with $b = 40$, 50, 60, or 70 years of age. *S(e)* is the number of women surviving at age e, and the factor *S(e)/S(b)* is the fraction of the 100 000 women who were alive at age b and are still alive at age e. Survival at each age is determined on the basis of life tables for women who are currently eligible for screening (eg, for those who are 40–49 years old, the year-by-year survival table for women born in 1970–1979, and for women who are 50–59 years old, the survival table for women born in 1960–1969, etc) (10).

We used the cancer detection rates from the 2015 Rhodes et al study (as was stated in the introduction) for mammography, BSGI, and mammography plus BSGI in asymptomatic women with dense breasts, 9% of whom had scattered fibroglandular densities (Breast Imaging and Reporting Data System [BI-RADS] density category B], 77% had heterogeneously dense breasts (BI-RADS category C), and 14% had extremely dense breasts (BI-RADS category D) (9). Because *DR* is the cancer detection rate per 1000 women screened, it was multiplied by 100 to get the cancer detection rate per 100 000 women, and Equation (1) was multiplied by 100 to estimate the deaths averted per 100 000 women.

In 2009, the Cancer Intervention- and Surveillance Modeling Network (CISNET) estimated that, in the absence of screening, a woman with a normal risk who develops breast cancer has a median lifetime probability of dying from that breast cancer of 24.4% (11). In 2016, updated CISNET modeling estimated that same probability at 19.4% (12). On the basis of these findings, our central estimate for the probability that, in the absence of screening, a woman with breast cancer will die from that breast cancer is 20%, with a range of 15%–25%. On the basis of collective randomized controlled trial results of screening mammography in women who were 39–74 years old, our central estimate for the probability that early detection through screening will avert a breast cancer death is 20%, with a range 15%–40% (13–16).

For each modality, the risk for radiation-caused mortality in terms of lives lost to screening (LLS) due to 10 years of annual screening per 100 000 women is found by summing, over all exposed organs, the organ-specific estimates of radiation dose multiplied by the organ- and age-specific lifetime attributable risks for cancer mortality ($\mathrm{LAR}_i[e]$, where i refers to the organ, and e refers to the age at exposure):

$$\mathrm{LLS}(b \rightarrow b+9) = 100\,000 \cdot \Sigma_e \Sigma_i (\mathrm{D}_i) \cdot \mathrm{LAR}_i(e) \cdot S(e)/S(b), \quad (2)$$

where the summation over the age at exposure is from $e = b$ (the beginning year of exposure) to $e = b + 9$ and $b = 40$, 50, 60, or 70 years, and the summation over i includes all organs receiving a nonnegligible radiation dose.

For mammography, the only organ exposed to a substantial amount of ionizing radiation is fibroglandular breast tissue; thus, the summation over organs is unnecessary (17). Mammography radiation doses are estimated for two-view digital mammography on the basis of mean glandular doses reported from digital screening studies on 4366 subjects in the American College of Radiology Imaging Network Digital Mammographic Screening Trial, which averaged 3.72 mGy (18). Recent articles have suggested that, because of technology improvements and breast heterogeneity, current mammography screening doses may be lower than this (19,20). Others have suggested that screening doses may be higher than the Digital Mammographic Screening Trial estimate because breast density may be lower than the 50% fibroglandular and 50% fat composition that is normally assumed for mean glandular dose estimates and because of the need for additional screening views (21–23). Therefore, our central estimate for

Table 1

Estimated Mortality Benefit and Mortality Risk from Annual Screening over 10-year Age Ranges with Mammography Alone, BSGI Alone, and Mammography Plus BSGI

Measure	40–49 Years Old	50–59 Years Old	60–69 Years Old	70–79 Years Old
Benefit (cancer deaths averted)				
Mammography only	127 (71–316)	124 (70–311)	119 (67–297)	102 (58–256)
BSGI only	423 (238–1058)	415 (234–1039)	397 (224–993)	342 (193–856)
Mammography plus BSGI	474 (267–1186)	466 (262–1165)	446 (251–1114)	384 (216–960)
Risk (cancer deaths caused)				
Mammography only	10 (4–18)	5 (2–9)	2.5 (1.0–4.5)	1.1 (0.4–2.0)
BSGI only	82 (37–136)	73 (33–120)	58 (26–96)	37 (17–61)
Mammography plus BSGI	92 (41–153)	78 (35–129)	61 (27–101)	38 (17–63)

Note.—Data are mean estimates, and data in parentheses are range estimated on the basis of ranges described in Materials and Methods. Estimated mortality benefit is breast cancer deaths averted per 100 000 women screened, and mortality risk is cancer deaths caused per 100 000 women screened. Figures are based on a mean glandular dose of 3.72 mGy per round for mammography, a drawn dose of 300 MBq (8 mCi) of ^{99m}Tc-sestamibi, and an administered dose of 240 MBq (6.4 mCi) of ^{99m}Tc-sestamibi.

mammography screening dose is 3.72 mGy, with a range of 3.0 to 4.5 mGy (0.8−1.2 times the Digital Mammographic Screening Trial estimate).

In the 2015 Rhodes et al study (9), BSGI was performed with a drawn dose of 300 MBq (8 mCi) of ^{99m}Tc-sestamibi (9). A 2013 study by Swanson et al (24) found that, for drawn doses of 150–300 MBq of ^{99m}Tc-sestamibi, 20.1% ± 8.0 was retained by the syringe and tubing. For BSGI radiation risk estimates, we assumed that the administered dose was 80% of the drawn dose, or 240 MBq (6.4 mCi) of ^{99m}Tc-sestamibi, with a range of 216–264 MBq (plus or minus 10% of the administered dose). For BSGI, the summation over *i* included all internal organs stated to receive a radiation dose in sestamibi labeling; dose values were taken from that labeling and scaled to the administered doses stated previously (5).

Lifetime radiation risk estimates for both mammography and BSGI were based on the United States National Academy of Sciences Biologic Effects of Ionizing Radiation (BEIR) VII report, which estimated age-dependent cancer incidence and mortality risks for women in the United States on the basis of high-level ionizing radiation exposure (25). Extrapolation to lower organ doses that occur in mammography and BSGI assumed a linear, no-threshold model typically used for radiation protection. Organ-specific and exposure age–dependent lifetime attributable risks for cancer mortality are from Table 12D-2 of the BEIR VII report (25). Because of substantial uncertainties in lifetime attributable risk values, we include a range of 0.5 to 1.5 times the values in the BEIR VII report.

Benefit-to–radiation risk estimates are the ratios of estimated breast cancer deaths averted by early detection to radiation-caused cancer deaths, each per 100 000 women screened, for mammography alone, BSGI alone, and mammography plus BSGI. Benefit, risk, and benefit-to–radiation risk ratios are estimated for annual screening over 10-year intervals, starting at age 40, 50, 60, and 70 years.

Results

Table 1 shows estimated benefits in terms of breast cancer deaths averted and risks in terms of radiation-caused cancer deaths, both per 100 000 women screened, as a result of bilateral screening mammography, low-dose BSGI, and combined mammography plus BSGI performed annually for 10 rounds by age range at the time of examination. Lifetime radiation-caused mortality risks from mammography and BSGI decrease with age, with mammography risk decreasing by one-half for each decade and BSGI risk decreasing to about one-half over 4 decades. This difference is a result of the faster decrease in the risk for radiation-induced cancer deaths in the breast than in other body organs that are exposed during clearance of ^{99m}Tc-sestamibi.

Table 2 shows benefit-to–radiation risk ratios for mammography, BSGI, and mammography plus BSGI by age range at the time of imaging on the basis of breast cancer detection rates presented in the 2015 study by Rhodes et al (9). Benefit-to–radiation risk ratios increase with screening age for both mammography and BSGI, with benefit-to–radiation risk ratios for mammography doubling with each increasing decade and those for BSGI approximately doubling over 4 decades. Range estimates are wide for both modalities. Table 2 also shows that benefit-to-risk ratios for mammography plus BSGI are dominated by those for BSGI alone.

The last row of Table 2 shows the required administered ^{99m}Tc-sestamibi dose to achieve the same benefit-to-risk ratio for BSGI as that for mammography, assuming the same cancer detection rate as reported by Rhodes et al (9). For women 40–49 years old, 40% of the 240-MBq administered dose would yield the same benefit-to–radiation risk ratio as mammography, while for women 70–79 years old, 10% of the dose reported by Rhodes et al would yield the same benefit-to-risk ratio as mammography. Drawn doses are approximately 20% higher than the stated administered

Table 2

Estimated Benefit-to–Radiation Risk Ratios for Mammography, BSGI, and Mammography Plus BSGI Performed Annually over 10-year Age Ranges

Modality	40–49 Years Old	50–59 Years Old	60–69 Years Old	70–79 Years Old
Mammography only	13 (4–80)	24 (8–153)	47 (15–296)	92 (29–573)
BSGI only	5 (2–29)	6 (2–32)	7 (2–38)	9 (3–52)
Mammography plus BSGI	5 (2–29)	6 (2–33)	7 (2–41)	10 (3–56)
BSGI dose*	96 (2.6)	56 (1.5)	35 (0.9)	24 (0.6)

Note.—Data are mean estimates, and data in parentheses are ranges of benefit-to-risk ratios estimated on the basis of ranges described in Materials and Methods.

* Estimated dose required for the same benefit-to–radiation risk ratio as for mammography alone. Data are the dose in megabecquerels, and data in parentheses are the dose in millicuries.

doses because 20% of the radionuclide is retained in the syringe and tubing (24). These data indicate that the administered dose needed for BSGI to equal the benefit-to-risk ratio of mammography is strongly age dependent.

Rhodes et al (9) suggested that BSGI be used either as a biennial supplement to mammography or biennially alternated with mammography in women with dense breasts. Alternating biennial screening would halve the risk of radiation-induced cancer deaths. If each round of BSGI and mammography had the same breast cancer detection rate as annual screening, the benefit also would be halved, and the overall benefit-to-risk ratio would be the same as for the annual use of each. If alternating biennial screening increased the combined 2-year breast cancer detection rate, the benefit-to–radiation risk ratio would roughly increase in proportion to the ratio of the combined-modality biennial screening detection rate to the combined-modality annual detection rate. Similarly, annual mammography combined with biennial BSGI would cut the BSGI radiation risk in half, whereas the benefit would depend on the combined 2-year cancer detection rate from this approach.

Discussion

The 2015 study by Rhodes et al (9) reported that, in asymptomatic women with dense breasts, BSGI had a breast cancer detection rate that was 3.3 times that of mammography. On the basis of these results, the authors suggested that supplemental screening with low-dose BSGI may offer benefit as a screening tool in asymptomatic women with dense breasts. Our findings show that reduced-dose BSGI performed with a drawn dose of 300 MBq and an administered dose of 240 MBq confers an age-dependent lifetime mortality risk from ionizing radiation that is about eight times that of mammography in 40–49-year-old women and increases to about 30 times that of mammography in 70–79-year-old women. Benefit-to–radiation risk ratios are about 2.5 times higher for mammography than BSGI in 40–49-year-old women and about 10 times higher for mammography in 70–79-year-old women, assuming the cancer detection rate for each modality is constant as a function of age. Note that ranges of these estimates are wide.

Limitations of this study include the assumption that cancer detection rates observed by Rhodes et al for both mammography and BSGI in women with dense breasts are constant with age, that incident BSGI screens maintain the same cancer detection rate as prevalent screens, and that the probability that early detection will avert a breast cancer death is 20% because of screening with each modality (mammography, BSGI, and mammography plus BSGI). While this last assumption is guided by results from randomized control trial meta-analysis, they apply to a general population of asymptomatic women, not specifically asymptomatic women with dense breasts (13). The mortality reduction from mammography to the subgroup of asymptomatic women with dense breasts is likely to be less than that to the general population of asymptomatic women because of the lower sensitivity of mammography in this subgroup; however, the specific mortality benefit in this subgroup is unknown. The mortality benefit of BSGI among asymptomatic women with dense breasts may be greater or less than the assumed 20% mortality benefit. However, unlike mammography, the sensitivity of BSGI does not appear to be substantially influenced by breast density (4).

Known risks of breast cancer screening include false-positive results, which lead to recall and possibly biopsy when cancer is not present. Hypothetical risks include overdiagnosis of cancers that would not become evident or require treatment in the absence of screening. The radiation risk of cancer induction from mammography is also hypothetical in that no large-scale epidemiologic studies have demonstrated an increase in cancer risk from exposure to the low diagnostic levels of ionizing radiation in mammography. This study compares the known benefits of screening with the hypothetical risks of cancer induction from radiation, assuming a linear, no threshold relationship between organ radiation doses and cancer risk. Recall and biopsy risks, along with possible radiation risks, should be considered when choosing supplemental screening approaches in subgroups of women, such as those with dense breasts. While lower dose (300 MBq) BSGI has significantly improved cancer detection rates compared with screening mammography and has a benefit-to–radiation risk ratio well in excess of 1 for women with dense breasts who are over 40 years old, it does not match the benefit-to–radiation risk ratio of screening mammography.

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