nursing home patients are dual eligible, can incentivize these transfers.[5] Evidence[6] has shown that reducing these potentially preventable visits has the potential to generate significant savings for public insurance programs.

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Risk and Risk Reduction of Major Coronary Events Associated With Contemporary Breast Radiotherapy

Long-term breast cancer survival rates have improved markedly over recent decades, so minimization of long-term treatment-related complications is increasingly important. Several reports have suggested links between breast cancer radiotherapy and long-term cardiovascular mortality.[1] A recent analysis by Darby et al[2] of patients treated with breast radiotherapy between 1958 and 2001 revealed a statistically significant linear dependence of the risk of major coronary events on mean cardiac dose. We use these historical data to estimate risks of major coronary events induced by modern breast radiotherapy. Our motivation is to quantify contemporary risks and also to guide efforts to minimize radiotherapy-induced cardiovascular risks.

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Methods | The risk estimates derived here were based on contemporary patient-specific radiation doses averaged over the cardiac volume (hereafter, mean cardiac dose). These were derived from breast radiotherapy treatment plans for 48 patients with stage 0 through IIA breast cancer who were treated after 2005 at New York University Department of Radiation Oncology.[3] Two treatment plans, for supine and for prone treatment positions, were generated for each patient. This was a prospective trial and received institutional review board approval. Informed consent was obtained from all participants.

Excess absolute risks (R) of radiotherapy-induced major coronary events (defined, as in Darby et al,[2] as myocardial infarction, coronary revascularization, or death from ischemic heart disease) were calculated for each patient, on the basis of patient-specific mean cardiac doses and using the dose-response relationship reported by Darby et al for these end points:

$$R = 0.074 \times D \times B.$$

Here, D is the mean cardiac dose (in grays) and B is the baseline risk for a major coronary event, as defined in the previous paragraph. Because the radiation-associated risk depends on the baseline risk, we report risk estimates for typical low-risk, medium-risk, and high-risk patients, with baseline risks (B) estimated (**Table**) on the basis of the standard Reynolds algorithm.[4] Cardiac risks were calculated over 20 years after radiotherapy, the approximate mean life expectancy after early-stage breast cancer.

Results | For standard supine-positioned radiotherapy, the patient-averaged mean cardiac dose was 1.37 (95% CI, 1.12-1.61) Gy (to convert to rad, multiply by 100), less than one-third of the average mean cardiac dose reported[2] for breast radiotherapy from 1958 to 2001. As expected,[3] mean cardiac doses were significantly lower for right-sided than for left-sided breast radiotherapy (2-tailed P = .001 for supine positioning and <.001 for prone positioning). For left-sided (but not right-sided) radiotherapy, treating in a prone position resulted in a halving of the mean cardiac dose.

Table. Patient-Averaged Mean Cardiac Doses and Estimated Patient-Averaged Lifetime Excess Risks of Major Coronary Events Associated With Contemporary Breast Cancer Radiotherapy

Treatment Side	Radiotherapy Position	Cardiac Dose, Mean (95% CI), Gy[a]	Excess Risk (95% CI), %[b]		
			Low Baseline Risk Patients[c]	Medium Baseline Risk Patients[c]	High Baseline Risk Patients[c]
Left	Supine	2.17 (1.36-2.98)	0.22 (0.08-0.36)	0.42 (0.14-0.70)	3.52 (1.47-5.85)
	Prone	1.03 (0.87-1.19)	0.09 (0.05-0.13)	0.17 (0.09-0.25)	1.31 (0.86-1.86)
Right	Supine	0.62 (0.54-0.71)	0.05 (0.03-0.07)	0.10 (0.06-0.14)	0.79 (0.57-1.06)
	Prone	0.64 (0.56-0.72)	0.06 (0.03-0.08)	0.11 (0.05-0.16)	0.84 (0.57-1.18)

SI conversion factor: To convert grays to rad, multiply by 100.

[a] Mean cardiac doses averaged over 48 patients who received radiotherapy, mean (range) age, 58 (31-87) years. To convert grays to rad, multiply by 100.

[b] Lifetime radiation-associated risks of a major cardiac event (myocardial infarction, coronary revascularization, or death from ischemic heart disease), estimated for each patient using patient-specific mean cardiac doses, for 3 different baseline cardiac risk scenarios. The risk estimates for each scenario were then averaged over all patients. Lifetime risks were calculated over a 20-year period after radiotherapy, which is the approximate mean life expectancy after early-stage breast cancer.

[c] Radiation-associated risks of a major coronary event for different categories of baseline risks. Age-dependent baseline risks, *B*, were estimated for low, medium, and high cardiac risk patients using the standard Reynolds algorithm,[4] on the basis of a large cohort of contemporary US women, for myocardial infarction, coronary revascularization, ischemic stroke, or death from ischemic heart disease, and then the estimated risk[5] for ischemic stroke was subtracted. On the basis of quartiles of the population studied in developing the Reynolds risk score,[4] age-dependent baseline risks were estimated for low risk (serum total cholesterol level, 183 mg/dL [to convert to millimoles per liter, multiply by 0.0259]; high-density lipoprotein [HDL], 62 mg/dL; systolic blood pressure [SBP], 115 mm Hg; serum C-reactive protein [CRP] level, 0.8 mg/L [to convert to nanomoles per liter, multiply by 9.524]; nonsmoker), for medium risk (serum total cholesterol level, 208 mg/dL; HDL, 52 mg/dL; SBP, 125 mm Hg; CRP level, 2.0 mg/L; nonsmoker), and for high risk (serum total cholesterol level, 235 mg/dL; HDL, 43 mg/dL; SBP, 135 mm/Hg; CRP level, 4.3 mg/L; smoker; treated with antihypertensive medication; with family history of myocardial infarction before age 60 years). To calculate 20-year baseline risks from the (10-year) Reynolds baseline data,[4] age-dependent survival probabilities from 2008 US life tables (www.cdc.gov/nchs/products/life_tables.htm) were additionally applied, corrected for breast cancer–specific relative survival (from www.seer.cancer.gov).

Shown in the Table are the predicted lifetime risks of major coronary events induced by contemporary breast cancer radiotherapy, stratified by left vs right side radiotherapy, by supine vs prone treatment position, and by low, medium, or high baseline cardiac disease risk. The highest estimated radiotherapy-induced risks were for left-sided radiotherapy in high-cardiac risk women treated in the supine position (3.52% [95% CI, 1.47%-5.85%]), whereas the lowest risks were for right-sided radiotherapy in low-cardiac risk women (<0.1%).

Discussion | Cardiac doses from breast radiotherapy have generally decreased during recent decades (although not for all modern treatment techniques), so typical risks of major cardiac events associated with contemporary radiotherapy are lower than in earlier eras.[2] Estimated lifetime risks of major coronary events for patients who receive radiotherapy for breast cancer are now in the range from 0.05% to 3.5%, with a typical value of 0.3% for a typical scenario. The highest cardiac doses and excess cardiac risks result from supine positioning during left-sided radiotherapy; for left-sided radiotherapy, prone positioning significantly reduces cardiac doses and risks.[3] For right-sided radiotherapy, where the heart is always out of field, cardiac doses and risks are smaller, and prone vs supine positioning has little effect, although prone position radiotherapy does reduce ipsilateral lung doses and thus reduces potential second lung cancer risks.[6]

Because the effects of radiation exposure on cardiac disease risk seem to be multiplicative,[2] the highest absolute radiation exposure risks correspond to the highest baseline cardiac risk. Consequently, radiotherapy-induced risks of major coronary events are likely to be reduced in these patients by targeting baseline cardiac risk factors (cholesterol, smoking, hypertension), by lifestyle modification, and/or by pharmacological treatment.

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Invited Commentary

Ischemic Heart Disease and Breast Cancer Radiotherapy: The Way Forward

Long-term follow-up of randomized trials has demonstrated that incidental exposure of the heart during radiotherapy for breast cancer can increase the subsequent risk of heart disease.[1] Radiation-related increases in heart disease risk have subsequently been confirmed,[2] and a dose-response relationship for ischemic heart disease based on individual patient information has been developed.[3]

Radiotherapy has improved progressively over the years, but the heart still usually receives some incidental exposure during radiotherapy for cancer of the left breast. Estimates of the absolute magnitude of the resulting cardiac risk are therefore needed to help oncologists compare the likely benefits and risks from radiotherapy as they plan each individual woman's treatment. The tools to do this also need to include estimates of the absolute benefit from radiotherapy and estimates of the other risks of radiotherapy such as radiotherapy-related second cancer, and these are given elsewhere.[1,4]

Estimation of the absolute risk of radiation-related ischemic heart disease for an individual woman requires (1) her estimated cardiac radiation dose for the radiotherapy treatment plan under consideration, (2) the percentage increase in ischemic heart disease risk per unit cardiac radiation dose, and (3) the woman's risk of ischemic heart disease in the absence of radiotherapy.

Cardiac Dose | Over the past few decades, improvements in radiotherapy planning have reduced cardiac radiation exposures. In this issue of *JAMA Internal Medicine*, Brenner et al[5] report mean heart doses, averaged over 48 women in their radiotherapy center, of 0.6 Gy (to convert to rad, multiply by 100) in right-sided disease and 1 or 2 Gy in left-sided disease, depending on whether the woman was prone or supine, respectively, when treated. Some other studies have reported similar levels of cardiac dose.[6] However, many women receive higher mean cardiac doses, especially in radiotherapy for cancer of the left breast. This can occur because the woman's heart is close to the chest wall or because she receives internal mammary radiotherapy or advanced radiotherapy techniques such as helical tomotherapy, which can deliver approximately 2 to 5 Gy to much of the heart volume.[7]

Risk per Unit Dose | The recently developed dose-response relationship[3] suggests that the risk of ischemic heart disease increases by approximately 7% (95% CI, 3%-14%) for each 1-Gy increase in the mean dose of radiation to the heart. The study found no evidence of a threshold dose below which no risk occurs, but risks following cardiac doses below approximately 2 Gy could not be estimated precisely, so the possibility of a threshold cannot be excluded. Importantly, it was found that the radiation-related risk approximately multiplied a woman's preexisting ischemic heart disease risk, implying that women with preexisting heart disease or major cardiac risk factors will have much higher absolute risks than other women.

Risk of Ischemic Heart Disease in the Absence of Radiotherapy | Detailed predictions of the risk of an acute coronary event, subdivided according to mean heart dose, presence or absence of preexisting cardiac risk factors, and age at irradiation (which determines a woman's life expectancy assuming that she survives her breast cancer) using baseline rates from western Europe—which do not differ substantially from those for the United States—are available in the online supplementary material of the paper presenting the dose-response relationship.[3] In this issue of *JAMA Internal Medicine*, Brenner et al[5] indicate how the factors included in the Reynolds risk score (age, smoking status, systolic blood pressure, serum cholesterol levels, family history) might influence the radiation-related risk for a woman who is free of cardiovascular disease when her breast cancer is diagnosed and who has a life expectancy of 20 years, for mean cardiac doses of 0.6, 1.0, and 2.2 Gy.

Relevance for Today | In breast cancer radiotherapy today, there is considerable variability in the dose received by the heart and in the extent of preexisting risk of ischemic heart disease. Thus, there is likely to be considerable variability in the cardiac risks of radiotherapy. Our dose-response relationship[3] can be used to provide reassurance for the majority of women that their absolute risk of ischemic heart disease from breast cancer radiotherapy is likely to be small compared with the likely absolute benefit from radiotherapy.[4] It can also be used to identify the minority of women for whom the benefits of radiotherapy do not clearly outweigh the risks, including those for whom adequate coverage of the target tissue cannot be achieved without a high heart dose.

Further Work | In the future, studies based on radiation dosimetry that is able to take account of the distribution of dose within the heart (rather than just the mean heart dose) may provide further insight into which parts of the heart are damaged in breast cancer radiotherapy. Studies are also needed to quantify the risks of other types of heart disease such as valvular heart disease and heart failure and the risks of breast cancer radiotherapy in women who also receive chemotherapy, which can itself be cardiotoxic.

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