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Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

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ABSTRACT

BACKGROUND

Radiotherapy for breast cancer often involves some incidental exposure of the heart to ionizing radiation. The effect of this exposure on the subsequent risk of ischemic heart disease is uncertain.

METHODS

We conducted a population-based case–control study of major coronary events (i.e., myocardial infarction, coronary revascularization, or death from ischemic heart disease) in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark; the study included 963 women with major coronary events and 1205 controls. Individual patient information was obtained from hospital records. For each woman, the mean radiation doses to the whole heart and to the left anterior descending coronary artery were estimated from her radiotherapy chart.

RESULTS

The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72). Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9 to 14.5; P<0.001), with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. The proportional increase in the rate of major coronary events per gray was similar in women with and women without cardiac risk factors at the time of radiotherapy.

CONCLUSIONS

Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose to the heart, begins within a few years after exposure, and continues for at least 20 years. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. (Funded by Cancer Research UK and others.)

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Randomized trials have shown that radiotherapy for early-stage breast cancer can reduce the rates of recurrence and of death from breast cancer.[1,2] However, long-term follow-up in some trials has shown that radiotherapy can also increase the risk of ischemic heart disease, presumably through incidental irradiation of the heart.[1,3]

Radiotherapy regimens for breast cancer have changed since the women in these trials were irradiated, and the doses of radiation to which the heart is exposed are now generally lower.[4] Nevertheless, in most women, the heart still receives doses of 1 to 5 Gy.[5-11] Several studies have suggested that exposures at this level can cause ischemic heart disease,[12-14] but the magnitude of the risk after any given dose to the heart is uncertain, as are the time to the development of any radiation-related disease and the influence of other cardiac risk factors. We therefore conducted a study relating the risk of ischemic heart disease after radiotherapy to each woman's radiation dose to the heart and to any cardiac risk factors she had at the time of radiotherapy.

Methods

Study Population

A population-based case–control study of major coronary events was conducted in women in Sweden and Denmark who received external-beam radiotherapy for invasive breast cancer. Major coronary events were defined as a diagnosis of myocardial infarction (*International Classification of Diseases, 10th Revision* [ICD-10] codes I21–I24), coronary revascularization, or death from ischemic heart disease (ICD-10 codes I20–I25). Patients with a diagnosis of angina alone were not included, because pilot studies showed that we could not reliably identify angina. Patient records from hospital oncology departments were used to obtain data on each woman's medical history before her diagnosis of breast cancer, tumor characteristics, and radiotherapy.

Eligibility Criteria

A single study protocol was used, but the selection of case patients and controls varied slightly between the two countries. In Sweden, all women living in Stockholm for whom data were recorded in the Swedish National Cancer Register[15] were considered for the study if they received a diagnosis of breast cancer between 1958 and 2001, were younger than 70 years of age at the time of diagnosis, and had received radiotherapy. Because information on radiotherapy is not kept by the Swedish Register, hospital records were used to determine which women had received radiotherapy. In Denmark, all women for whom data were recorded in the register held by the Danish Breast Cancer Cooperative Group[16] were considered for the study if they received the diagnosis of breast cancer between 1977 and 2000, were younger than 75 years at the time of diagnosis, and received radiotherapy. The study was approved by the Danish Data Protection Agency and by the ethics review board of the Karolinska Institutet in Stockholm. The requirement for informed consent was waived because of the nature of the study.

In both countries, women without histopathological confirmation of breast cancer, with bilateral or metastatic disease at the time of diagnosis, or with a history of cancer (excluding nonmelanoma skin cancer) or previous radiotherapy to the thoracic area were excluded. All other women who received radiotherapy were cross-matched with nationwide registers of diagnosis at the time of hospital discharge and cause of death (up to 2002 in Sweden and 2007 in Denmark).[17] Women whose primary diagnosis was a major coronary event that occurred after a diagnosis of breast cancer but before any recurrence or diagnosis of a second cancer were classified as case patients. Whenever possible, hospital cardiology or autopsy records were reviewed, and if the case-defining event was refuted, the woman was excluded from the study. For each remaining case patient, we defined "time period" as the time from breast-cancer diagnosis to the time of first major coronary event. Controls (one per case patient in Sweden and two per case patient in Denmark) were selected at random from all eligible women in the study population. Eligibility criteria for controls included fulfillment of the matching criteria (country of residence, age at the time of breast-cancer diagnosis, and year of diagnosis, with both age and year matched within 5 years); receipt of radiotherapy; and no recurrence of breast cancer, no diagnosis with another cancer, and no major coronary event before the index date (defined as the date of breast-cancer diagnosis plus the time period of the matched case).

RADIATION DOSIMETRY

Individual radiotherapy charts, including a diagram or photograph of the treatment fields and a dose plan (where available) were copied. Virtual simulation and planning based on computed tomography (CT) (or, for a few regimens, manual planning) were used to reconstruct each radiotherapy regimen on the CT scan of a woman with typical anatomy. Virtual simulation and CT planning involved the reconstruction of radiotherapy fields on a CT scan. Radiation doses to the structures of interest were then estimated with the use of the treatment-planning system Helax–TMS, version 6.1B (Nucletron). In manual planning, the doses were estimated on the basis of charts on which isodose curves (i.e., lines delimiting areas receiving the same radiation dose) had been drawn. As previously described,[18,19] dose-volume histograms for the whole heart and for the left anterior descending coronary artery (which often receives the highest dose of radiation from radiotherapy for cancer of the left breast) were obtained for the regimens used, and the mean doses received by these two structures were calculated. Equivalent doses delivered in 2-Gy fractions (EQD2)[20] were calculated from the dose-volume histograms as $nd[(d+\alpha/\beta)\div(2+\alpha/\beta)]$, where n was the number of fractions, d was the dose to the heart per fraction (in Gy), and α/β was 2 Gy.[21]

STATISTICAL ANALYSIS

Rate ratios were estimated with the use of conditional logistic regression after stratification according to country and to age at the time of cancer diagnosis, year of cancer diagnosis, and years from cancer diagnosis to first subsequent major coronary event (for case patients) or the index date (for controls) (all in 5-year categories).[22,23] To estimate the proportional increase in the rate of major coronary events per gray of radiation, the data were also stratified according to presence or absence of a cardiac risk factor. The rate of major coronary events was modeled as $B_s(1+KX)$, where B_s was the stratum-specific rate of major coronary events in the absence of radiotherapy, X was the dose (or EQD2) of cardiac radiation (in Gy), and K was the percentage increase in the rate of major coronary events per gray. The form 1+KX was chosen for the dose–response relationship because a wide variety of functions are approximately linear for small values of X. The adequacy of 1+KX for summarizing the dose–response relationship was examined by carrying out analyses based on categories of radiation dose. In these analyses and in tests for interactions between radiation dose and other factors, models similar to the model described above were used. Significance tests were two-sided, and both significance tests and confidence intervals were based on the likelihood ratio. For analyses in which the explanatory variable was categorical, the confidence intervals for every category, including the reference category, were estimated from the amount of information in that category.[24] Calculations were performed with the use of Stata Statistical Software, release 12 (StataCorp),[25] and EpiWin, release 1.8 (Hirosoft International).[26]

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 963 women with major coronary events and 1205 controls were included in the study. Among the case-defining major coronary events (i.e., the event resulting in inclusion in the study), 44% occurred less than 10 years after breast cancer was diagnosed, 33% occurred 10 to 19 years afterward, and 23% occurred 20 or more years afterward. Hospital cardiology or autopsy records confirmed the case-defining major coronary event in 65% of case patients and were consistent with the event in 9% of case patients; for the remaining 26% of case patients, no relevant record could be found. A total of 54% of case patients were known to have died from ischemic heart disease, either at the time of their case-defining event or subsequently. (For further information, see Tables S1, S2, and S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

RISK FACTORS FOR A MAJOR CORONARY EVENT

Women irradiated for cancer of the left breast had higher rates of major coronary events than women irradiated for cancer of the right breast ($P=0.002$), but there were no other strong associations between the rate of major coronary events and tumor characteristics or the cancer treatments administered in addition to radiotherapy (rate ratio, 1.20; $P=0.06$ for nodal status and $P\geq0.10$ for all other tumor or treatment characteristics) (Table 1). In contrast, the overall rate ratio for a major coronary event among women with a history of ischemic heart disease as com-

Table 1. Characteristics of the Women in the Study at the Time of Breast-Cancer Diagnosis and Association between the Characteristics and the Subsequent Rate of Major Coronary Events.*

Characteristic	No. of Case Patients (N=963)	No. of Controls (N=1205)	Rate Ratio	P Value†
Tumor characteristics				
Nodal status				0.06
Negative	482	610	1.00	
Positive	463	579	1.20	
Unknown	18	16	0.96	
Size				0.97
<2 cm	331	449	1.00	
2–5 cm	494	604	1.00	
Other or unknown	138	152	1.08	
Location				0.22
Outer quadrants	350	572	1.00	
Inner quadrants	114	204	0.84	
Other or unknown	499	429	0.82	
Laterality of breast cancer				0.002
Right	420	604	1.00	
Left	543	601	1.32	
Cancer treatment				
Surgery				0.22
Mastectomy	748	860	1.00	
Breast-conserving surgery	212	337	0.86	
None	3	8	0.39	
Adjuvant hormonal therapy‡				0.10
No	732	892	1.00	
Yes	229	311	1.23	
Unknown	2	2	0.80	
Adjuvant chemotherapy§				0.13
No	889	1057	1.00	
Yes	74	148	0.73	
Ovarian ablation¶				0.54
No	774	1027	1.00	
Yes	70	89	0.89	
Unknown	119	89	1.54	
Factors associated with subsequent coronary event				<0.001
No known cardiac risk factors	353	600	1.00	
History of ischemic heart disease‖	109	38	6.67**	
Risk factors other than ischemic heart disease††	458	527	1.96**	
Unknown	43	40	1.23	
History of circulatory disease other than ischemic heart disease‡‡				<0.001
No	536	845	1.00	
Yes	265	269	1.88	
Unknown	53	53	1.04	
History of diabetes§§				<0.001
No	704	1056	1.00	
Yes	55	29	3.23	
Unknown	95	82	1.19	
History of COPD§§				<0.001
No	736	1076	1.00	
Yes	15	6	6.33	
Unknown	103	85	1.24	

Table 1. (Continued.)

Characteristic	No. of Case Patients (N=963)	No. of Controls (N=1205)	Rate Ratio	P Value†
Current smoker§§				<0.001
No	160	344	1.00	
Yes	167	195	1.87	
Unknown	527	628	1.39	
BMI§§				0.002
<30	321	574	1.00	
≥30	139	165	1.57	
Unknown	394	428	1.00	
Analgesic medication§§				0.02
No	509	836	1.00	
Yes	50	54	1.65	
Unknown	295	277	1.01	
Other medications				
Hormone-replacement therapy				0.006
No	495	731	1.00	
Yes	79	178	0.66	
Unknown	389	296	1.70	
Thyroid medication				0.60
No	635	888	1.00	
Yes	26	37	0.87	
Unknown	302	280	0.90	
Other medications¶¶				0.08
No	740	958	1.00	
Yes	38	70	0.69	
Unknown	185	177	0.84	

* The category listed first is the baseline category. Rate ratios were estimated after stratification according to country and age at breast-cancer diagnosis, year of breast-cancer diagnosis, and years from breast-cancer diagnosis to first subsequent major coronary event (for case patients) or index date (for controls) (all in 5-year categories). BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

† The test for heterogeneity between categories did not include the categories of "unknown" or "other or unknown."

‡ Adjuvant hormonal therapy consisted of tamoxifen in 197 case patients and 258 controls, an aromatase inhibitor in 6 case patients and 16 controls, and another medication in 26 case patients and 37 controls.

§ Chemotherapy consisted of cyclophosphamide, methotrexate, and fluorouracil in 44 case patients and 105 controls; an anthracycline-based regimen in 8 case patients and 9 controls; and other chemotherapy (but without an anthracycline) in 22 case patients and 34 controls.

¶ For 34 case patients and 55 controls, ovarian ablation consisted of oophorectomy before the diagnosis of breast cancer.

‖ Women with a history of ischemic heart disease were defined as those for whom myocardial infarction or angina had been cited in their oncology record at the time of breast-cancer diagnosis or for whom ischemic heart disease had been recorded as a primary diagnosis in the hospital discharge register before the breast-cancer diagnosis.

** These rate ratios can be subdivided according to the time since breast-cancer diagnosis. Rate ratios for major coronary events in women with a history of ischemic heart disease up to 10 years and 10 or more years after breast-cancer diagnosis were 13.43 (95% confidence interval [CI], 7.65 to 23.58) and 2.09 (95% CI, 1.05 to 4.13), respectively (P<0.001). Rate ratios for major coronary events in women without a history of ischemic heart disease but with other cardiac risk factors for up to 10 years and for 10 years or more after the breast-cancer diagnosis were 2.60 (95% CI, 1.89 to 3.57) and 1.63 (95% CI, 1.24 to 2.15), respectively (P=0.03). See Table S4 in the Supplementary Appendix for further details.

†† The factors associated with a subsequent risk of heart disease in women without a history of ischemic heart disease included factors for which the association was likely to be causal (e.g., current smoker) and factors for which the association was indirect (e.g., history of chronic obstructive pulmonary disease).

‡‡ This category excludes 109 case patients and 38 controls who had a history of ischemic heart disease (as defined above) and indicates which of the remaining women who, before their diagnosis of breast cancer, had received a primary diagnosis of circulatory disease (*International Classification of Diseases, 10th Revision*, codes I-00 to I-15 or I-26 to I-99), according to the hospital discharge register, or had received medication for cardiac disease or hypertension according to their oncology record.

§§ This category excludes 109 case patients and 38 controls who had a history of ischemic heart disease (as defined above) and indicates which of the remaining women appeared in the hospital discharge register with this condition as a primary diagnosis before breast-cancer diagnosis or had an oncology record in which this factor was cited.

¶¶ This category excludes women who at the time of their diagnosis were receiving medication for cardiac disease or hypertension or an analgesic medication, according to the oncology record.

pared with women with no such history was 6.67 (95% confidence interval [CI], 4.37 to 10.18). The rate ratio was 13.43 (95% CI, 7.65 to 23.58) during the first 10 years after the cancer diagnosis as compared with 2.09 (95% CI, 1.05 to 4.13) during later years (P<0.001) (Table S4 in the Supplementary Appendix). Rates of major coronary events were also elevated among women with a history of other circulatory diseases, diabetes, or chronic obstructive pulmonary disease; among women who smoked; and among women with a high body-mass index or a history of regular analgesic use. The rate ratio for the presence of one or more of these factors but no ischemic heart disease was 1.96 overall (95% CI, 1.60 to 2.40); during the first 10 years after the cancer diagnosis, the rate ratio was 2.60 (95% CI, 1.89 to 3.57) as compared with 1.63 (95% CI, 1.24 to 2.15) during later years (P=0.03).

EFFECT OF RADIOTHERAPY

The overall average of the estimated mean doses of radiation to the heart was 6.6 Gy for women with tumors in the left breast, 2.9 Gy for those with tumors in the right breast, and 4.9 Gy overall (range, 0.03 to 27.72). The rate of major coronary events increased by 7.4% for each increase of 1 Gy in the mean radiation dose delivered to the heart (95% CI, 2.9 to 14.5; P<0.001) (Fig. 1). When women were grouped according to whether the mean radiation dose to the heart was less than 2 Gy, 2 to 4 Gy, 5 to 9 Gy, or 10 or more Gy, the percentage increases in the rate of major coronary events in these four categories, as compared with the estimated rate if the cardiac dose had been zero, were 10% (95% CI, −9 to 33), 30% (95% CI, 14 to 49), 40% (95% CI, 15 to 72), and 116% (95% CI, 59 to 195), respectively. The percentage increase per gray did not differ significantly according to any of the matching factors used in the selection of controls, tumor characteristics (including whether the tumor was in the left or right breast), or cancer treatments in addition to radiotherapy. Despite the fact that the rate of major coronary events was higher among women with cardiac risk factors than among those without such risk factors, the percentage increase in the rate of major coronary events per gray was similar for women with and those without a cardiac risk factor at the time of breast-cancer diagnosis (Table 2).

VARIATION WITH TIME SINCE EXPOSURE

The percentage increases in the rate of major coronary events per gray of radiation according to the number of years since radiation exposure were as follows: 0 to 4 years, 16.3% (95% CI, 3.0 to 64.3); 5 to 9 years, 15.5% (95% CI, 2.5 to 63.3); 10 to 19 years, 1.2% (95% CI, −2.2 to 8.5); and 20 or more years, 8.2% (95% CI, 0.4 to 26.6) (Table 3). The variation among these values was consistent with random variation (P=0.16 for heterogeneity; P=0.26 for trend). Findings were similar when the analysis was repeated separately according to age at the time of the breast-cancer diagnosis, the presence or absence of preexisting cardiac risk factors, whether the case patient had died from ischemic heart disease, and whether the case patient's hospital cardiology record or autopsy record had been reviewed (Tables S5 through S8 in the Supplementary Appendix).

OTHER MEASURES OF DOSE

The overall average of the mean EQD2 doses to the heart was 3.9 Gy (range, 0.1 to 30.4). The mean doses and the EQD2 doses to the heart were highly correlated (correlation coefficient, 0.98). The results of analyses based on dose and EQD2 dose were therefore similar (Fig. S1 in the Supplementary Appendix). Estimated mean doses to the left anterior descending coronary artery and to the heart were also correlated (correlation coefficient, 0.76) (Table S9 in the Supplementary Appendix). The mean dose of radiation to the heart was a better predictor of the rate of major coronary events than the mean dose to the left anterior descending coronary artery (P<0.001 for mean dose to the heart; P=0.001 for mean dose to the left anterior descending coronary artery). The mean dose of radiation to the heart remained significantly associated with the rate of major coronary events after the mean dose to the left anterior descending coronary artery was taken into account (P=0.04). However, the converse did not apply: the mean dose to the left anterior descending coronary artery was not significantly associated with the rate of major coronary events after the mean dose to the heart was taken into account (P=0.62).

DISCUSSION

Breast cancer is the most common cancer in women worldwide, with more than 1 million new

diagnoses each year.[27] Moreover, every year, tens of thousands of women worldwide receive a diagnosis of ductal carcinoma in situ. The overall 5-year survival rate for these two diagnostic groups combined is approximately 90%, and in both groups many of the survivors will have received radiotherapy.[28] Current mean doses of radiation to the heart from radiotherapy for breast cancer are typically about 1 or 2 Gy for disease of the right breast. For disease of the left breast, the doses are usually higher but vary widely, and for some women, including those in whom the distance of the heart to the thoracic wall is small and those who require internal mammary irradiation, the mean dose may be around 10 Gy.[5-11]

Among the 2168 women in this study, the mean dose to the heart ranged from 0.03 Gy to 27.72 Gy, with an overall average of the mean doses of 4.9 Gy. The risk of a major coronary event increased linearly with the mean dose to the heart. The magnitude of the risk was 7.4% per gray, with no apparent threshold below which there was no risk. The risk started to increase within the first 5 years after exposure and continued for at least 20 years. The percentage increase in risk per gray was similar for women with and those without cardiac risk factors at the time of radiotherapy.

A strength of this study is that it relates the risk of ischemic heart disease among women who have received radiotherapy for breast cancer to individual doses of cardiac radiation and individual cardiac risk factors at the time of their cancer diagnosis. Other strengths of the study are that it was carried out in women with cancer that had not recurred (thus avoiding confusion with the influence of further treatment); that it was population-based, including all women recorded as receiving radiotherapy for breast cancer in Denmark or Stockholm during the period of interest (thus avoiding the tendency in randomized trials to omit patients in poor health); and that the majority of cardiac events were confirmed by a review of cardiology or autopsy records. Because health status may play a role in the selection of women for radiotherapy, we included in the study only women who had received radiotherapy; nonrandomized comparisons of women who underwent irradiation with those who did not could produce misleading estimates of risk.[29]

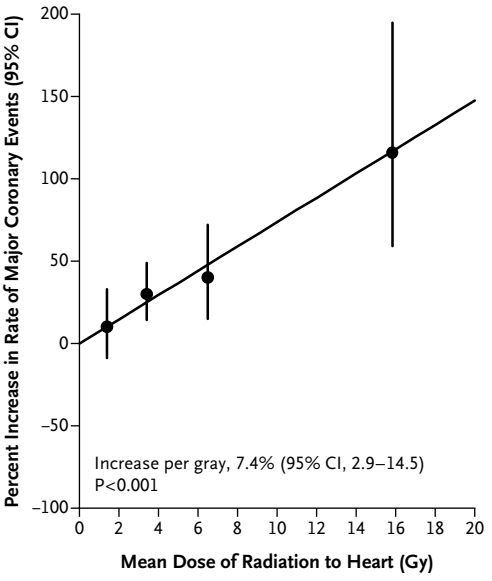

Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Major coronary events included myocardial infarction, coronary revascularization, and death from ischemic heart disease. The values for the solid line were calculated with the use of dose estimates for individual women. The circles show values for groups of women, classified according to dose categories; the associated vertical lines represent 95% confidence intervals. All estimates were calculated after stratification for country and for age at breast-cancer diagnosis, year of breast-cancer diagnosis, interval between breast-cancer diagnosis and first major coronary event for case patients or index date for controls (all in 5-year categories), and presence or absence of a cardiac risk factor. The radiation categories were less than 2, 2 to 4, 5 to 9, and 10 Gy or more, and the overall averages of the mean doses to the heart of women in these categories were 1.4, 3.4, 6.5, and 15.8 Gy, respectively.

A limitation of our study was that individual CT-based information on radiotherapy was unavailable for the women studied, because they were treated before the era of three-dimensional CT-based planning. However, we have used 20 consecutive individual CT-based, three-dimensional planning scans to show that for left and right tangential radiotherapy and for left and right direct internal mammary fields, the patient-to-patient variation in mean radiation dose to the heart is small (coefficients of variation, 30%, 11%, 11%, and 21%, respectively).[4] We have also confirmed that the patient with typical anatomy who

was used to calculate the dose estimates in this study was average in terms of the radiation dose to her heart. Consideration of irradiated structures within the heart[30,31] may prove fruitful in the future, but in the present study, inclusion of the estimated mean dose to the left anterior descending coronary artery did not improve prediction of the rate of major coronary events.

Since our study included few women who were younger than 40 years of age at the time of radiotherapy, caution is needed in applying our results to women in this age group, and the possibility of larger increases in the rate of major coronary events per gray of radiation for this group cannot be ruled out. Few women in this study were treated with anthracyclines, and none with taxanes or trastuzumab, all of which are known to affect the heart, even in the absence of radiotherapy.[32]

Table 2. Radiation Dose to the Heart and Percentage Increase in the Rate of Major Coronary Events per Gray, According to Risk Factors and Other Characteristics.*

Characteristic	Radiation Dose to Heart	Increase in Rate of Major Coronary Events (95% CI)†	P Value for Heterogeneity‡
	Gy	*% increase/Gy*	
Characteristics used for selection of matched controls§			
Country			0.38
Sweden	5.4±5.7	5.7 (1.2 to 13.7)	
Denmark	4.4±2.7	11.2 (2.5 to 30.7)	
Age at diagnosis of breast cancer (yr)			0.99
20–39	4.7±4.8	–1.5 (<–25.3 to 616)	
40–49	4.9±4.8	6.3 (–2.0 to 41.3)	
50–59	5.1±4.8	7.1 (0.4 to 22.2)	
60–69	4.8±4.2	7.8 (1.7 to 19.7)	
70–74	4.9±3.1	9.7 (–2.9 to 116)	
Year of breast-cancer diagnosis			0.13
1958–1969	3.7±4.1	6.6 (–0.2 to 20.7)	
1970–1979	7.3±6.3	20.4 (5.4 to 79.2)	
1980–1989	4.9±3.6	0.8 (–2.8 to 8.7)	
1990–2001	4.2±2.7	11.8 (–0.1 to 56.2)	
Tumor characteristics			
Nodal status			0.26
Negative	4.8±4.4	4.0 (–1.0 to 14.1)	
Positive	5.0±4.3	11.8 (2.7 to 33.6)	
Size			0.24
<2 cm	4.9±4.2	20.4 (3.6 to 98.3)	
2–5 cm	4.9±4.5	6.9 (1.1 to 18.0)	
Location			0.17
Outer quadrants	4.4±2.8	10.0 (1.1 to 32.8)	
Inner quadrants	4.8±3.5	–2.1 (<–6.9 to 21.2)	
Laterality of breast cancer			0.88
Right	2.9±2.5	5.0 (–2.2 to 22.5)	
Left	6.6±4.9	4.1 (–0.4 to 13.8)	

Table 2. (Continued.)

Characteristic	Radiation Dose to Heart	Increase in Rate of Major Coronary Events (95% CI)†	P Value for Heterogeneity‡
	Gy	*% increase/Gy*	
Cancer treatment			
Surgery			0.59
Mastectomy	5.1±4.7	8.7 (3.2 to 18.0)	
Breast-conserving surgery	4.3±3.1	14.9 (–0.1 to 77.6)	
Adjuvant hormonal therapy			0.55
No	5.0±4.7	10.0 (3.9 to 20.4)	
Yes	4.7±3.4	5.2 (–2.1 to 29.0)	
Adjuvant chemotherapy			0.47
No	5.0±4.5	7.6 (2.9 to 15.2)	
Yes	4.6±3.3	–0.4 (<–6.7 to 70.2)	
Ovarian ablation			0.94
No	4.9±4.2	5.5 (1.1 to 12.9)	
Yes	4.3±4.2	6.5 (<–3.6 to 77.7)	
Factors associated with subsequent major coronary event¶			0.99
No	5.1±4.7	7.4 (1.8 to 17.8)	
Yes	4.9±4.1	7.4 (1.1 to 19.5)	
Other medications‖			0.58
No	4.8±4.1	8.4 (1.9 to 21.3)	
Yes	4.7±3.6	2.8 (–4.3 to 47.3)	
Death of case patient from ischemic heart disease**			0.81
No	4.9±4.2	8.0 (2.3 to 17.2)	
Yes	4.9±4.5	7.2 (2.4 to 14.9)	
Cardiology record of case patient reviewed††			0.60
No	4.5±3.1	9.2 (1.8 to 21.7)	
Yes	5.1±4.8	7.0 (2.5 to 14.2)	
All women	4.9±4.4	7.4 (2.9 to 14.5)	

* Radiation doses to the heart are arithmetic averages of mean doses to the whole heart for cases and controls combined, with standard deviations.

† Rates were estimated after stratification according to country, age at breast-cancer diagnosis, year of breast-cancer diagnosis, and years from breast-cancer diagnosis to first major coronary event (for case patients) or index date (for controls) (in 5-year categories), the presence or absence of a cardiac risk factor, and the characteristic under examination.

‡ P values are based on tests for heterogeneity between the percentage increases in the rate of major coronary events per gray of radiation for the categories listed for each characteristic.

§ The numbers of women in each category for the variables used as the basis of selection are listed in Table S2 in the Supplementary Appendix.

¶ Women for whom information about cardiac risk factors was unavailable were classified as not having the risk factors.

‖ This category includes medications other than those prescribed for cardiac disease or hypertension and analgesic medications.

** "Yes" indicates case patients for whom ischemic heart disease was known to be the underlying cause of death and their matched controls. "No" indicates case patients for whom it was not the underlying cause of death and their matched controls.

†† "Yes" indicates case patients for whom a hospital cardiology or autopsy record was reviewed and was found to confirm or to be consistent with the case-defining event and their matched controls. "No" indicates case patients for whom no information was available for cardiology review and their matched controls.

Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (–2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

* The values shown are the numbers of years since the breast-cancer diagnosis. The median time from the breast-cancer diagnosis to the start of radiotherapy was 42 days.

† The percentage increase was estimated after stratification according to country, age at breast-cancer diagnosis, year of breast-cancer diagnosis, years from breast-cancer diagnosis to first major coronary event (for case patients) or index date (for controls), and the presence or absence of a cardiac risk factor. Chi-square for heterogeneity=5.2 with 3 df, P=0.16; chi-square for trend=1.2 with 1 df, P=0.26.

Studies comparing rates of cardiac disease among women who received radiotherapy for cancer of the left breast and women who received radiotherapy for cancer of the right breast have been reviewed elsewhere.[33-35] Such studies are likely to underestimate the extent of any radiation-related risk because they rely on any difference in cardiac dose between women irradiated for tumors in the left breast and those irradiated for tumors in the right breast. In addition, these studies have generally not had information on whether a woman had prior heart disease, and thus could not account for any tendency to avoid irradiation in women with preexisting cardiac risk factors and cancer of the left breast or for the exclusion of women whose only diagnosis was angina (which may be unreliably recorded in routine records). In our study, the radiation-related increase in the risk of major coronary events began within the first 5 years after exposure. Early increases in risk have been reported in studies of patients with Hodgkin's lymphoma who received radiotherapy.[36-38] The effect of preexisting cardiac risk factors on the risk of radiation-related ischemic heart disease has not been well studied, but one report on patients with breast cancer indicated that the absolute effect of radiotherapy was greater in smokers than in nonsmokers.[39] Several studies have empirically investigated the relationship between cardiac radiation dose and risk of heart disease (Table S10 in the Supplementary Appendix). The estimates vary considerably, but this is to be expected, since both the populations studied and the end points reported were diverse.

The relevance of our findings to a woman receiving radiotherapy for breast cancer today is that they make it possible to estimate her absolute risk of radiation-related ischemic heart disease. This absolute risk can be weighed against the probable absolute reduction in her risk of recurrence or death from breast cancer that would be achieved with radiotherapy.[2] The percentage increases in risk per unit increase in the mean dose of radiation to the heart are similar for women with and women without preexisting cardiac risk factors. Therefore, absolute radiation-related risks are greater for women with preexisting cardiac risk factors than for other women.

Data from a case–control study do not by themselves permit estimation of absolute risks. Therefore, we have illustrated our results on the risk of fatal ischemic heart disease by combining them with recent data on rates of death from ischemic heart disease for the 15 westernmost countries of the European Union combined (Table S11 in the Supplementary Appendix). We have also illustrated the effect of radiotherapy for breast cancer on the risk of an acute coronary event (i.e., a major coronary event or unstable angina) by assuming that for women younger than 50 years of age, those 50 to 59 years of age, those 60 to 69 years of age, and those 70 to 79 years of age, the rates of acute coronary events are 6 times, 5 times, 3 times, and 2 times the rates of death from ischemic heart disease, respectively.[40] The resulting baseline lifetime risk estimates are similar to recent estimates for the United States.[41]

For a 50-year-old woman with no preexisting cardiac risk factors, radiotherapy involving a mean dose to the heart of 3 Gy would increase her risk of death from ischemic heart disease before the age of 80 years from 1.9% to 2.4% (i.e., an absolute increase of about 0.5 percentage points), and it would increase her risk of having at least one acute coronary event from 4.5% to 5.4% (i.e., an absolute increase of about 0.9 percentage points) (Fig. 2). If her mean cardiac dose were 10 Gy, her absolute risk of death from ischemic heart disease would increase from 1.9% to 3.4% (1.5 percentage points), and her absolute risk of having at least one acute coronary event would increase from 4.5% to 7.7% (3.2 percentage points).

For women with one or more preexisting car-

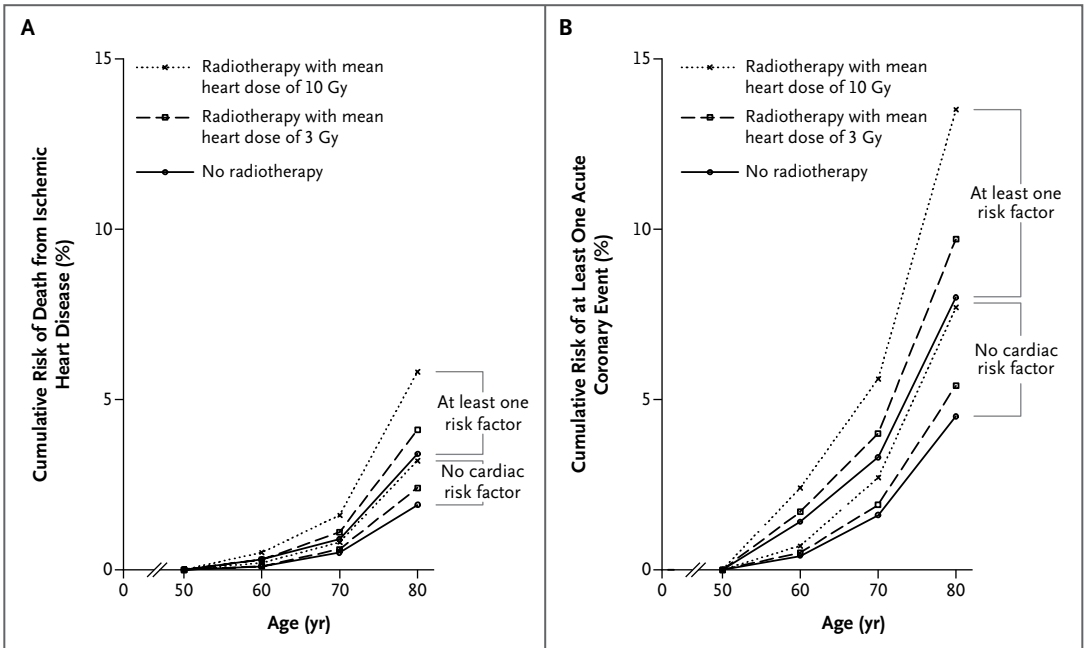

Figure 2. Cumulative Risks of Death from Ischemic Heart Disease and of at Least One Acute Coronary Event.

In Panel A, rates of death from ischemic heart disease and from all causes in the underlying population were assumed to be equal to the most recent values available (mostly for the year 2010) for the 15 westernmost countries of the European Union (Table S11 in the Supplementary Appendix). In Panel B, the rates of acute coronary events in women in the underlying population who were younger than 50, 50 to 59, 60 to 69, and 70 to 79 years of age were assumed to be 6 times, 5 times, 3 times, and 2 times the rate of death from ischemic heart disease, respectively. In both panels, results are shown for a woman who was 50 years old at the time of breast-cancer diagnosis who received either no radiotherapy or radiotherapy with a mean dose to the heart of 3 Gy or 10 Gy. Results are shown for women with no cardiac risk factors and for those with one or more cardiac risk factors. In both panels, the distribution of cardiac risk factors in the population was assumed to be equal to that in the present study. Cumulative risks for other mean doses of radiation to the heart and for different ages at irradiation are provided in Tables S12 and S13 in the Supplementary Appendix. Acute coronary events are nonfatal or fatal major coronary events or unstable angina.

diac risk factors, both the baseline risks and the absolute increases in risk are higher. For example, radiotherapy involving a mean dose of radiation to the heart of 3 Gy in a 50-year-old woman with one or more cardiac risk factors would increase her risk of death from ischemic heart disease before the age of 80 years from 3.4% to 4.1% (an absolute increase of 0.7 percentage points), and it would increase her absolute risk of having an acute coronary event by the age of 80 years by 1.7 percentage points. A mean dose of 10 Gy to her heart would result in radiation-related risks that were considerably higher.

In conclusion, we found that incidental exposure of the heart to radiotherapy for breast cancer increased the rate of major coronary events by 7.4% per gray, with no apparent threshold. The percentage increase per unit increase in the mean dose of radiation to the heart was similar for women with and women without preexisting cardiac risk factors, which indicates that the absolute increases in risk for a given dose to the heart were larger for women with preexisting cardiac risk factors. Therefore, clinicians may wish to consider cardiac dose and cardiac risk factors as well as tumor control when making decisions about the use of radiotherapy for breast cancer.

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