Long-Term Risk of Cardiovascular Disease in 10-Year Survivors of Breast Cancer

Maartje J. Hooning, Akke Botma, Berthe M. P. Aleman, Margreet H. A. Baaijens, Harry Bartelink, Jan G. M. Klijn, Carolyn W. Taylor, Flora E. van Leeuwen

Background Radiotherapy for breast cancer as delivered in the 1970s has been associated with increased risk of cardiovascular disease, but recent studies of associations with modern regimens have been inconclusive. Few data on long-term cardiovascular disease risk according to specific radiation fields are available, and interaction with known cardiovascular risk factors has not been examined.

Methods We studied treatment-specific incidence of cardiovascular disease in 4414 10-year survivors of breast cancer who were treated from 1970 through 1986. Risk of cardiovascular disease in these patients was compared with general population rates and evaluated in Cox proportional hazards regression models. All statistical tests were two-sided.

Results After a median follow-up of 18 years, 942 cardiovascular events were observed (standardized incidence ratio = 1.30, 95% confidence interval [CI] = 1.22 to 1.38; corresponding to 62.9 excess cases per 10 000 patient-years). Breast irradiation only was not associated with increased risk of cardiovascular disease. However, radiotherapy to either the left or right side of the internal mammary chain was associated with increased cardiovascular disease risk for the treatment period 1970–1979 (for myocardial infarction, hazard ratio [HR] = 2.55, 95% CI = 1.55 to 4.19; $P<.001$; for congestive heart failure, HR = 1.72, 95% CI = 1.22 to 2.41; $P = .002$) compared with no radiotherapy. Among patients who received internal mammary chain radiotherapy after 1979, risk of myocardial infarction declined over time toward unity, whereas the risks of congestive heart failure (HR = 2.66, 95% CI = 1.27 to 5.61; $P = .01$) and valvular dysfunction (HR = 3.17, 95% CI = 1.90 to 5.29; $P<.001$) remained increased. Patients who underwent radiotherapy plus adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil) after 1979 had a higher risk of congestive heart failure than patients who were treated with radiotherapy only (HR = 1.85, 95% CI = 1.25 to 2.73; $P = .002$). Smoking and radiotherapy together were associated with a more than additive effect on risk of myocardial infarction (HR = 3.04, 95% CI = 2.03 to 4.55; P for departure from additivity = .039).

Conclusions Radiotherapy as administered from the 1980s onward is associated with an increased risk of cardiovascular disease. Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease.

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During the past 30 years, survival of breast cancer patients has improved substantially due to earlier diagnosis, introduction of combination chemotherapy and hormonal treatment, and refinement of radiation techniques (1). However, several studies have demonstrated that breast cancer patients who were treated with adjuvant radiation have an increased risk of mortality from ischemic heart disease (2–5). Most of these studies are of patients who were treated with radiotherapy during the 1960s and 1970s, when radiation therapy used techniques that are now considered suboptimal. Studies of more modern regimens administered during the 1980s show inconclusive results for both postmastectomy radiotherapy and breast-conserving therapy (6–11). Few long-term data are available, but previous studies (2,3,12) have shown that radiotherapy-related cardiac risk may become manifest only after 10 or more years since first treatment. To date, there have been no reports of the associations of specific radiotherapy fields in relation to cardiac disease, and differences in fields might partly explain the different results between studies. Furthermore, only cardiac mortality, not

Affiliations of authors: Departments of Epidemiology (MJH, AB, FEVL) and Radiation Oncology (BMPA, HB), Netherlands Cancer Institute, Amsterdam, The Netherlands; Departments of Radiation Oncology (MHAB) and Medical Oncology (JGMK), Erasmus Medical Center, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands; Clinical Trial Service Unit, University of Oxford, Oxford, UK (CWT).

Correspondence to: Flora E. van Leeuwen, PhD, Department of Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands (e-mail: f.v.leeuwen@nki.nl).

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CONTEXT AND CAVEATS

Prior knowledge

Radiation treatment for breast cancer received in the 1970s has been associated with increased risk of cardiovascular disease, but studies of modern regimens have been inconclusive.

Study design

Ten-year breast cancer survivors who were treated from 1970 through 1986 were followed for treatment-specific incidence of cardiovascular disease. Rates were compared with rates in the general population.

Contribution

Radiotherapy to the internal mammary chain was associated with increased risk of cardiovascular disease among women who were treated from 1970 through 1979. Among women who received internal mammary chain irradiation from 1980 through 1986, the risk of myocardial infarction declined with time, but risks of valvular dysfunction and congestive heart failure remained increased. Radiation with adjuvant chemotherapy from 1980 through 1986 was associated with higher risk of congestive heart failure than radiotherapy alone. Smoking was associated with a more than additive increased risk for myocardial infarction over radiotherapy alone.

Implications

Radiotherapy for breast cancer administered from 1980 may be associated with an increased risk of cardiovascular disease; smoking may be associated with additional risk.

Limitations

The study group and the referent population may have different baseline risks for cardiovascular disease due to behavior and socioeconomic status; differences may also exist between the surgery-only referent group and the study groups. The dose of radiation to the heart could not be determined from the data available.

morbidity, has been investigated in most studies, although cardiac morbidity has a serious impact on the life expectancy and quality of life of long-term survivors.

We report here on the incidence of cardiac disease in the Dutch Late Effects Breast Cancer Cohort of 4414 10-year survivors who were treated between 1970 and 1986. Unique features of this study include long-term and near-complete follow-up, the assessment of cardiac risk according to radiation field, and the incorporation of cardiac risk factors into analyses.

Patients and Methods

Data Collection Procedures

The Late Effects Breast Cancer Cohort consists of 7425 1-year female breast cancer survivors, younger than age 71 years at diagnosis, treated for stages I, II, and IIIA from 1970 through 1986 at the Netherlands Cancer Institute (NKI) or the Erasmus Medical Center, Daniel den Hoed Cancer Center (DDHK). A detailed description of data collection procedures has been published previously (12). In brief, all patients were identified through the hospital-based cancer registries of the two centers. From the registries and the patient records, we collected date of breast cancer diagnosis, tumor histology, axillary lymph node involvement, dates and treatment modalities of primary breast cancer and of recurrent disease (type of surgery, radiation fields, chemotherapy, hormonal treatment), history of cardiac disease before diagnosis of breast cancer, dates of diagnoses of cardiac events, cardiovascular risk factors, date of most recent medical information or date of death, and primary cause of death according to International Classification of Diseases, 9th Revision (13). Risk factors (smoking, hypertension, diabetes mellitus, and hypercholesterolemia) were recorded both at the date of diagnosis of breast cancer and at the end of follow-up. Patients were considered as smokers if they were smokers at the end of follow-up or had stopped smoking less than 1 year before the end of follow-up. Patients were scored positive for hypertension if they had received treatment for high blood pressure or had a diastolic blood pressure that exceeded the limit of 95 mmHg on two occasions. Patients who had been treated for diabetes mellitus or hypercholesterolemia were scored as positive for these conditions.

We restricted this study to all 10-year survivors (n = 4414) because we have shown in a previous report on mortality in the Late Effects Breast Cancer Cohort (12) that the increase in cardiac risk associated with radiotherapy does not emerge until 10 years after treatment. Data regarding specific cardiac diagnoses and risk factors for all patients were updated through January 1, 2000, or later by questionnaire to the patients' general practitioners. In The Netherlands, nearly all residents have a general practitioner who receives all medical correspondence from attending physicians. Forty-six patients were excluded from the 10-year survivors' cohort because their records did not contain information after 10 years since diagnosis of breast cancer and no additional information could be obtained from their general practitioners. For the remaining 4368 patients, we collected cardiac data for 83% of the patients from both the patient record and the general practitioner and for the other 17% from the patient records only. Complete follow-up information through at least January 1, 2000, was eventually available for 4259 (96%) of all 10-year survivors. For patients who died from an acute cardiac event and had no prior evidence of cardiac disease, the date of death was recorded as date of diagnosis of the cardiac event.

Treatment

During the early 1970s, standard treatment for stages I, II, and IIIA breast cancers consisted of modified or radical mastectomy, with or without radiotherapy. In 1975, adjuvant systemic treatment was introduced for lymph node–positive patients, combination chemotherapy for premenopausal patients, and, gradually, from 1980 onward, tamoxifen for postmenopausal patients. Standard adjuvant chemotherapy consisted of CMF (cyclophosphamide, methotrexate, and fluorouracil) during the entire study period; until 1980, 12 cycles were administered, afterward only six. In 1980, both hospitals introduced breast-conserving therapy that consisted of wide local excision and axillary lymph node dissection, followed by whole-breast irradiation (14).

The radiotherapy regimen depended on type of surgery and stage of disease, with some differences between the two cancer centers. In the NKI, irradiation of the ipsilateral internal mammary chain field was common during the entire study period (1970–1986) for patients who had centrally or medially located tumors and/or axillary lymph node metastases. Patients who had

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extensive axillary nodal metastases also had irradiation to the axilla and supraclavicular nodes. Chest wall irradiation was given to patients with incomplete resection or extensive primary tumors. After breast-conserving therapy, the breast was always irradiated postoperatively. In the DDHK, 60% of patients with centrally or medially located tumors and/or axillary lymph node metastases were treated with radiation to the internal mammary chain field. Indications for irradiation of the axilla, supraclavicular nodes, chest wall, or breast were comparable to the indications used in the NKI. The dose to the internal mammary chain field varied from 40 Gy in 15 fractions to 50 Gy in 25 fractions, using either photon beams or a mixture of photons and electrons; the chest wall received doses between 35 and 45 Gy in 15–20 fractions, using electrons. Breast irradiation consisted of a dose of 50 Gy in 25 fractions using two tangential photon beams (4–8 MV or cobalt-60), followed by a boost of 15–25 Gy to the tumor bed, using an iridium implant.

Dosimetry for Estimation of Radiation Dose to the Heart

Radiation equipment and techniques changed considerably over the years. Although the regions irradiated were known for every patient, the individual cardiac radiation doses could not be calculated because we had no information on the specific regimens used. However, based on the distribution of these different techniques for the years 1970–1986 in a random sample of 160 patients, we could roughly estimate the mean cardiac doses received by patients in our study who were irradiated at specific regions.

Heart dose estimations were performed by one of the authors (C. W. Taylor) in Oxford, U.K., at the Clinical Trial Service Unit of Oxford University. For each specific radiotherapy regimen, we determined the technique, typical dose, the beam energy involved, and field borders. The estimated dose of radiation to the heart was based on virtual simulation (15,16) and computed tomography planning (Helax TMS version 6.1B, Nucletron Ltd, Veenendaal, The Netherlands). The computed tomography planning scans were of patients set up with a T-bar arm rest, similar to that of immobilization techniques used in breast treatments in previous decades. A series of approximately 40 scans were reviewed, and one patient of average weight and build was selected as a representative patient for whom all dose estimations were performed. The three-dimensional patient surface and lung contours were defined by automated density gradient tracking. The heart and coronary arteries were contoured by a radiation oncologist and reviewed by a radiologist. Virtual simulation software was used to identify relevant skin and bony landmarks. For each radiotherapy technique, beam arrangements were set up and exported to a computed tomography planning computer. Dose plans were evaluated, dose volume histograms were generated, and mean heart dose was calculated.

Statistical Analysis

We compared the incidence of cardiovascular diseases in the study population with the incidence in the Dutch female population, taking into account the person-years of observation in the cohort (by age, calendar period, and follow-up interval). Incidence data of the Continuous Morbidity Registration Nijmegen (CMRN) (17), which are derived from several general practitioners' practices from representative regions in The Netherlands, were used as reference rates. This registry has collected data on the incidence of myocardial infarction, angina pectoris, and congestive heart failure for the period 1972–2000, allowing for multiple separate diagnoses per person but recording only the first of a specific diagnosis per person (18). Comparison of recent incidence rates of myocardial infarction and angina pectoris from the CMRN with those of several new registries in The Netherlands, including only short-term incidence rates, showed similar rates for CMRN and for the other registries combined, indicating that the CMRN is representative of The Netherlands (19).

To assess treatment effects on risk of cardiovascular disease, we distinguished five mutually exclusive treatment categories that were defined by all treatments received up to 1 year before end of follow-up: 1) surgery only, 2) radiotherapy with or without surgery, 3) radiotherapy and chemotherapy with or without surgery, 4) radiotherapy and hormone therapy with or without surgery, and 5) radiotherapy, chemotherapy, and hormone therapy with or without surgery. Treatments given in the last year of follow-up were excluded from the analysis because the period following salvage treatment was too short for long-term effects of treatment to emerge. Time at risk began 10 years after the start of first treatment and ended at the date of diagnosis of a specific cardiac event, date of death, or date of most recent medical information, whichever came first. In the analysis by laterality, time at risk would end at date of a contralateral breast cancer, but only if the patient had received radiotherapy to the contralateral side. Observed numbers of a cardiovascular diagnosis were based on all first events of a specific cardiovascular diagnosis occurring after 10 years of follow-up time because the expected numbers of events were recorded correspondingly; patients who were diagnosed with a specific cardiovascular event before breast cancer diagnosis or within 10 years since first treatment were excluded from the analysis. The standardized incidence ratios (SIRs) of the observed and expected numbers of myocardial infarction, angina pectoris, and congestive heart failure in the study population were determined, and the confidence limits of the standardized incidence ratios were calculated using exact Poisson probabilities of observed numbers (20). *P* values for tests for trend were two-sided and were calculated using chi-square test statistics. $P<.05$ was considered statistically significant. Absolute excess risk was calculated by subtracting the expected number of cardiovascular disease events in our cohort from the number observed and dividing by person-years at risk (expressed per 10 000 person-years).

The Cox proportional hazards model (21) was used to quantify the effects of different treatments on cardiovascular disease risk taking into account several covariates (age at treatment, cardiovascular risk factors). The assumptions of proportionality were verified by comparing log–log survival curves. To evaluate the independent effects of primary treatment, we did a separate analysis in which time at risk ended at date of treatment for recurrent disease. Cox models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL).

Biologic interaction was evaluated as departure from additivity of the effect of two risk factors, for which the interaction risk is the risk that cannot be explained by the joint exposure to both risk factors, as expressed in the following formula (22): $R_{INT} = R_{A+B} - (R_A + R_B - R_U)$, for which A and B are risk factors, R_{INT} is interaction risk, and R_U is background risk. We performed statistical

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analysis to determine whether the joint effect was different from that of a single factor. For this test, we used EPICURE software (23). The test was based on the null hypothesis $\gamma = 0$ in $R_{A+B} = (R_A + R_B - R_U + \gamma)$, i.e., allowing for an additive departure (γ) from an additive joint effect. The test was a two-sided likelihood ratio test.

Results

Patient Characteristics

Approximately half of all patients were treated in the period of 1970–1980 and the other half between 1981 and 1986 (Supplementary Table 1, available online). Overall, median age at breast cancer diagnosis was 49 years. Median follow-up time was 17.7 years, and 31% of the patients were followed for more than 20 years. More than half (54%) of the study population was treated with surgery plus radiotherapy; 12% with surgery, radiotherapy, and chemotherapy; and 12% with surgery only. More than half (58%) of the patients received internal mammary chain irradiation, 30% received breast irradiation, and 20% received chest wall irradiation.

Information on smoking habits was available for 88% of the patients: 49% had never smoked, 32% smoked at the time of breast cancer diagnosis, and 10% still smoked at the end of follow-up (Supplementary Table 2, available online). Hypertension was reported in 26% of the patients during any time from breast cancer diagnosis until the end of follow-up, diabetes mellitus in 9%, and hypercholesterolemia in 10%.

Risk of Cardiovascular Disease by Age and Follow-up Interval

Incidence of cardiovascular disease was recorded (Table 1). After a median follow-up of 18 years, 942 cardiovascular events were observed (SIR = 1.30, 95% confidence interval [CI] = 1.22 to 1.38; 62.9 excess cases per 10 000 patient-years). Heart failure was the most frequently observed cardiovascular event (n = 382 out of 942 diagnoses). The study population experienced moderately but statistically significantly increased risks of myocardial infarction (SIR = 1.23, 95% CI = 1.08 to 1.39), angina pectoris (SIR = 1.30, 95% CI = 1.16 to 1.45), and congestive heart failure (SIR = 1.35, 95% CI = 1.22 to 1.49) compared with the general female population, with absolute excess risks of 13.5, 20.6, and 28.7 per 10 000 patient-years, respectively (Table 1). The standardized incidence ratio for angina pectoris increased with follow-up duration (Table 2), from 1.09 for 10–14 years since first treatment to 1.70 at 20 years and later, corresponding to absolute excess risks of 5.5 and 59.9 per 10 000 patient-years, respectively. For myocardial infarction and congestive heart failure, there was no trend over time. The risk of congestive heart failure was highest among patients who were youngest at first treatment (for the age-group of 35–44 years, SIR = 3.64; for those younger than 35 years, SIR = 6.54). The same pattern was seen with attained age (for developing congestive heart failure before age 55, SIR = 4.25), with declining risks as attained age increased (P_{trend}<.001). Analyses by laterality showed slightly but statistically nonsignificantly higher standardized incidence ratios of cardiovascular disease for patients with left-sided breast cancer than for those with right-sided breast cancer (Table 2). In total, 167 patients died from cardiovascular disease, mostly from acute myocardial infarction or congestive heart failure.

Risk of Cardiovascular Disease in Relation to Treatment

Risks of myocardial infarction, angina pectoris, and congestive heart failure were statistically significantly increased in irradiated patients compared with the rates in general female population (SIR = 1.33, 95% CI = 1.14 to 1.55; SIR = 1.42, 95% CI = 1.23 to 1.63; and SIR = 1.23, 95% CI = 1.07 to 1.40; Table 2). Conversely, patients who were treated with surgery only experienced a lower risk of myocardial infarction than the general population (SIR = 0.68, 95% CI = 0.43 to 1.03). With regard to congestive heart failure, the risk was strongly associated with chemotherapy (for radiotherapy plus chemotherapy treatment versus radiotherapy only, SIR = 3.48 versus SIR = 1.23; relative risk [RR] = 2.84; 95% CI = 1.96 to 4.00).

Comparisons Within the Cohort

Overall, radiotherapy (compared with surgery only) was associated with an increased risk of cardiovascular disease (hazard ratio [HR] = 1.41, 95% CI = 1.14 to 1.74). To determine whether changes in treatment during the study period influenced risk of cardiovascular disease, we divided the cohort according to period

Table 1. Standardized incidence ratios for cardiovascular diseases in 10-year survivors of breast cancer*

Diagnosis	ICD-9 code	Obs	Exp	SIR (95% CI)	AER
Ischemic heart disease	410–414				
Acute myocardial infarction	410	254	206.6	1.23 (1.08 to 1.39)	13.5
Angina pectoris	411–414	306	235.9	1.30 (1.16 to 1.45)	20.6
Other heart diseases	420–429				
Pericarditis	420, 423	22	–	–	–
Valvular dysfunction	424	186	–	–	–
Cardiomyopathy	425	56	–	–	–
Dysrhythmias	427	333	–	–	–
Congestive heart failure	428	382	282.6	1.35 (1.22 to 1.49)	28.7
Cardiovascular disease†	410–414, 428	942	725.1	1.30 (1.22 to 1.38)	62.9

* ICD-9 = International Classification of Diseases, 9th Revision; Obs = observed number of events; Exp = expected number of events; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk per 10 000 patients per year; – = no reference rates available for pericarditis, valvular dysfunction, cardiomyopathy, or dysrhythmias.

† Combined group, allowing more than one event per person: both myocardial infarction and angina pectoris were reported in 70 patients; both myocardial infarction and congestive heart failure were reported in 40 patients; both angina pectoris and congestive heart failure were reported in 66 patients; and myocardial infarction, angina pectoris, and congestive heart failure were reported in 34 patients.

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Table 2. Risks of myocardial infarction, angina pectoris, and congestive heart failure by follow-up interval, age at start of treatment, attained age, treatment category, and laterality*

Characteristic	Myocardial infarction			Angina pectoris			Congestive heart failure		
	Obs	SIR (95% CI)	AER	Obs	SIR (95% CI)	AER	Obs	SIR (95% CI)	AER
Follow-up interval, y									
10–14	128	1.35 (1.13 to 1.61)	17.4	129	1.09 (0.91 to 1.29)	5.5	149	1.27 (1.08 to 1.50)	16.8
15–19	85	1.19 (0.95 to 1.47)	12.2	111	1.42 (1.17 to 1.71)	30.6	146	1.49 (1.26 to 1.76)	44.0
≥20	41	1.02 (0.73 to 1.38)	1.4	66	1.70 (1.31 to 2.16)	59.9	87	1.28 (1.03 to 1.59)	41.8
P_{trend}		.1			.002			.8	
Age at start of treatment, y									
<45	32	1.11 (0.76 to 1.57)	2.8	63	1.67 (1.28 to 2.14)	22.5	67	3.87 (3.00 to 4.92)	43.6
45–54	104	1.40 (1.14 to 1.69)	21.3	137	1.38 (1.16 to 1.63)	27.6	131	1.81 (1.51 to 2.15)	42.5
≥55	118	1.14 (0.94 to 1.37)	15.0	106	1.07 (0.88 to 1.30)	8.0	184	0.95 (0.82 to 1.10)	−9.6
P_{trend}		.6			.004			<.001	
Attained age, y									
<55	11	1.25 (0.63 to 2.24)	3.5	17	1.40 (0.82 to 2.24)	7.9	24	4.25 (2.72 to 6.32)	29.7
55–64	65	1.46 (1.12 to 1.86)	16.5	94	1.39 (1.13 to 1.71)	22.0	78	2.85 (2.26 to 3.56)	41.4
≥65	178	1.16 (1.00 to 1.35)	15.0	195	1.25 (1.08 to 1.44)	24.7	280	1.12 (0.99 to 1.26)	18.8
P_{trend}		.2			.4			<.001	
Treatment									
Surgery only	23	0.68 (0.43 to 1.03)	−21.5	37	1.01 (0.71 to 1.39)	0.9	44	0.85 (0.61 to 1.14)	−16.7
RT (±surgery)	167	1.33 (1.14 to 1.55)	20.1	204	1.42 (1.23 to 1.63)	29.9	215	1.23 (1.07 to 1.40)	19.4
RT + CT (±surgery)	20	1.36 (0.83 to 2.10)	14.3	29	1.66 (1.12 to 2.40)	31.7	39	3.48 (2.48 to 4.76)	75.3
RT + HT (±surgery)	27	1.38 (0.91 to 2.02)	25.2	23	1.05 (0.66 to 1.57)	3.5	54	1.86 (1.40 to 2.43)	83.9
RT + CT + HT (±surgery)	12	1.19 (0.61 to 2.08)	8.6	13	0.99 (0.53 to 1.70)	−0.4	26	2.66 (1.74 to 3.90)	72.8
Laterality									
Left	122	1.22 (1.01 to 1.45)	12.8	149	1.31 (1.11 to 1.54)	21.5	184	1.37 (1.18 to 1.58)	29.8
Right	117	1.19 (0.98 to 1.43)	11.2	138	1.22 (1.03 to 1.44)	15.6	167	1.25 (1.07 to 1.46)	21.0

* Obs = observed number of events; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk per 10000 patients per year; RT = radiotherapy; CT = chemotherapy; HT = hormonal therapy.

of treatment (Fig. 1). Because breast-conserving therapy was introduced at our institutions in 1980, we used this year as cutoff point for stratification. For the period 1970–1979, irradiated patients experienced a 1.49-fold higher risk of cardiovascular disease than nonirradiated patients, whereas for the period 1980–1986, the risk declined to 1.35 (and was not statistically significant). Only adjustment for age was needed—smoking, hypertension, diabetes mellitus, and hypercholesterolemia were independent risk factors and did not influence the risk estimates for radiotherapy. Any radiotherapy was associated with increased risks of both myocardial infarction (HR = 2.77, 95% CI = 1.62 to 4.75; P<.001) and congestive heart failure (HR = 1.47, 95% CI = 1.04 to 2.08; P = .03) compared with no radiotherapy for the treatment period 1970–1979, whereas these risks declined and were no longer different from unity for the period 1980–1986 (Table 3). Furthermore, chemotherapy was associated with an increased risk of congestive heart failure for the treatment period 1980–1986 (HR = 1.85, 95% CI = 1.25 to 2.73; P = .002, Table 3, Fig. 2). In a separate analysis that was restricted to primary treatment, risk of congestive heart failure remained increased for patients who received adjuvant chemotherapy during 1980–1986 (HR = 2.30, 95% CI = 1.44 to 3.67; data not shown in Table).

Risks of myocardial infarction and congestive heart failure were also analyzed by region of irradiation (Table 4; Supplementary Figs. 1 and 2, available online). For the period 1970–1979, radiotherapy to the internal mammary chain was associated with

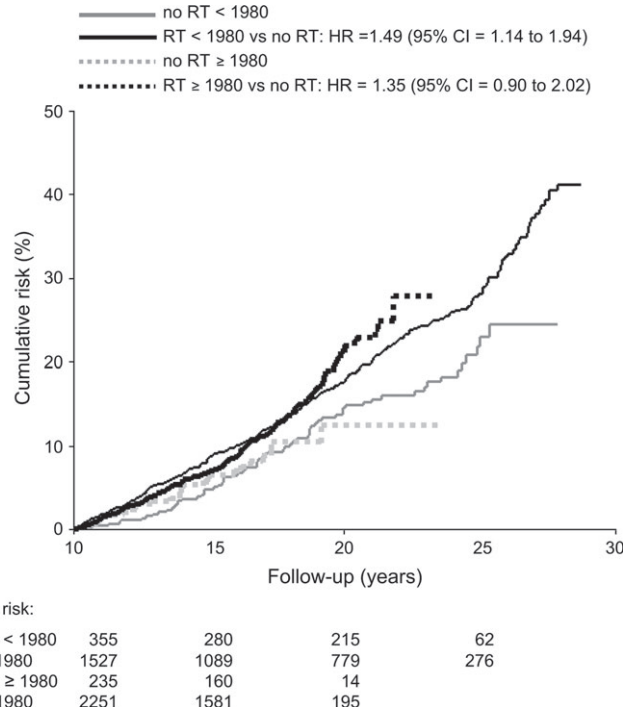

Fig. 1. Risk of cardiovascular disease by radiotherapy (RT) and treatment period (Cox model), adjusted for age. HR = hazard ratio; CI = confidence interval.

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Table 3. Multivariable Cox regression analyses* of potential risk factors for myocardial infarction and congestive heart failure by treatment period

	Risk of myocardial infarction†				Risk of congestive heart failure†			
	1970–1979		1980–1986		1970–1979		1980–1986	
Risk factor	HR (95% CI)	P‡	HR (95% CI)	P‡	HR (95% CI)	P‡	HR (95% CI)	P‡
Treatment								
RT vs no RT	2.77 (1.62 to 4.75)	<.001	0.87 (0.47 to 1.59)	.64	1.47 (1.04 to 2.08)	.03	1.39 (0.69 to 2.80)	.35
CT vs no CT	0.64 (0.29 to 1.41)	.27	1.22 (0.74 to 2.00)	.43	0.78 (0.45 to 1.37)	.39	1.85 (1.25 to 2.73)	.002
HT vs no HT	1.09 (0.70 to 1.71)	.70	1.16 (0.68 to 1.95)	.59	1.60 (1.16 to 2.20)	.004	1.23 (0.80 to 1.91)	.35
Smoking ever vs never								
Through the end of follow-up	2.00 (1.42 to 2.83)	<.001	2.63 (1.51 to 4.59)	.001	1.39 (1.05 to 1.84)	.02	1.30 (0.75 to 2.25)	.35
Ex-smoker	1.34 (0.79 to 2.29)	.28	1.35 (0.80 to 2.25)	.26	1.01 (0.66 to 1.57)	.96	1.04 (0.66 to 1.63)	.88
Hypertension, yes vs no/unknown	1.90 (1.35 to 2.66)	<.001	1.97 (1.29 to 3.01)	.002	1.35 (1.03 to 1.76)	.03	1.41 (0.96 to 2.05)	.08
Diabetes mellitus, yes vs no/unknown	1.20 (0.78 to 1.84)	.40	1.31 (0.78 to 2.21)	.31	1.13 (0.78 to 1.63)	.53	1.30 (0.80 to 2.11)	.29
Hypercholesterolemia, yes vs no/unknown	2.90 (1.96 to 4.28)	<.001	2.79 (1.81 to 4.32)	<.001	1.09 (0.72 to 1.65)	.68	2.30 (1.55 to 3.41)	<.001

* Results from four Cox analyses: two separate models were used both for myocardial infarction and for congestive heart failure, with patients stratified by treatment period (1970–1979 and 1980–1986, respectively). HR = hazard ratio; CI = confidence interval; RT = radiotherapy; CT = chemotherapy; HT = hormonal therapy.

† Adjusted for age at breast cancer diagnosis; all presented variables were included in the model, although the cardiovascular risk factors did not influence the risk estimates for RT, CT, or HT.

‡ *P* value from Wald test statistic.

an increased risk of myocardial infarction irrespective of tumor laterality (HR = 2.55, 95% CI = 1.55 to 4.19) as compared with the referent group (patients treated without radiotherapy or with fields giving a negligible dose to the heart). For the treatment period 1980–1986, these risks were close to unity. Compared with the referent group, patients who received radiotherapy to the left chest wall alone in the period 1970–1979 experienced an increased risk of myocardial infarction (HR = 2.72, 95% CI = 1.38 to 5.38), whereas radiotherapy to the right chest wall showed a statistically nonsignificantly 1.76-fold increased risk. For the period 1980–1986, risk of myocardial infarction was not increased after chest wall or breast irradiation (Table 3). However, analysis using another Cox model specifically for radiotherapy to left chest wall alone in this period, showed increased risk of myocardial infarction (HR = 3.54, 95% CI = 1.13 to 11.1) versus the referent group (receiving no radiotherapy, or negligible dose to the heart). Risk of angina pectoris showed similar, although less pronounced, associations with the various radiotherapy fields.

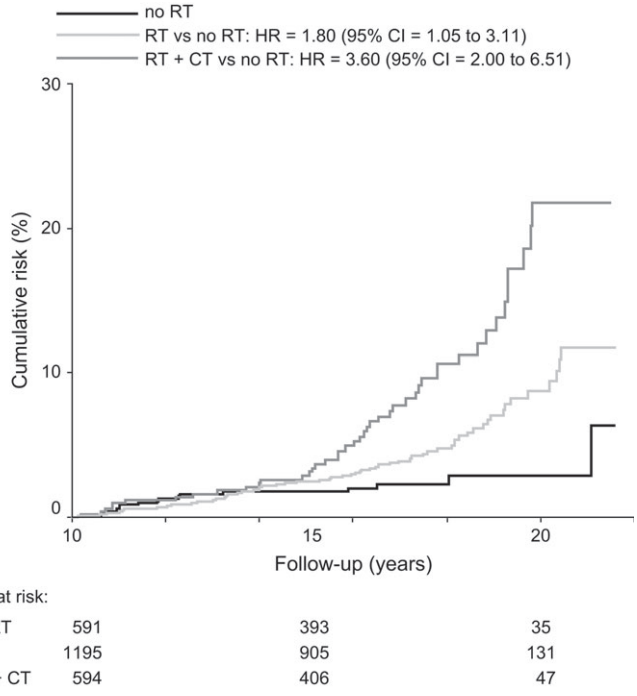

Fig. 2. Risk of congestive heart failure by treatment group (Cox model), adjusted for age and for patients treated since 1980. RT = radiotherapy; CT = chemotherapy; HR = hazard ratio; CI = confidence interval.

We next examined risk of congestive heart failure by irradiated region. Radiotherapy to the internal mammary chain plus chest wall in the period 1970–1979 was also associated with an increased risk of congestive heart failure for both left- and right-sided tumors (Table 4; HR = 2.29, 95% CI = 1.44 to 3.65 and HR = 2.15, 95% CI = 1.28 to 3.60, respectively), whereas radiotherapy to the internal mammary chain only was associated with marginally statistically significantly increased risks. For those treated in the period 1980–1986, the risk of congestive heart failure remained increased after irradiation of the internal mammary chain plus breast (irrespective of laterality, HR = 2.66, 95% CI = 1.27 to 5.61). We calculated rough estimates of mean cardiac dose for each region and the range in doses using various techniques (Table 4). In general, risk of congestive heart failure increased with higher mean dose of radiation to the heart. As for risk of myocardial infarction, the same trend with dose was observed in patients who were treated during 1970–1979 but not in patients from the later period of 1980–1986. Comparison of risks for patients treated with left- versus right-sided radiation fields (Table 5) only showed a statistically nonsignificant increase in left/right ratio of risk of

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Table 4. Multivariable Cox regression analyses for myocardial infarction and congestive heart failure by radiotherapy (RT) field and estimated mean radiation dose to the heart by treatment period*

Treatment period	No. of patients	Estimated mean heart dose, Gy	Dose range, Gy	Myocardial infarction HR (95% CI)†	Myocardial infarction *P*‡	Congestive heart failure HR† (95% CI)	Congestive heart failure *P*‡
1970–1979							
RT fields							
No RT/fields not including heart§	431	≈0	≈0	1.0 (referent)		1.0 (referent)	
Chest wall/breast: right-sided	179	≈3	1.2–3.8	1.76 (0.88 to 3.51)	.11	0.96 (0.57 to 1.63)	.89
Chest wall/breast: left-sided	168	≈7	2.5– 9.0	2.72 (1.38 to 5.38)	.004	1.10 (0.64 to 1.92)	.73
IMC only: right-sided	348	≈7	0.5–11.6	2.59 (1.46 to 4.61)‖	.001	1.44 (0.94 to 2.20)¶	.10
IMC only: left-sided	386	≈9	0.7–15.6	2.00 (1.12 to 3.58)‖	.02	1.61 (1.08 to 2.41)¶	.02
IMC + chest wall/breast: right-sided	158	≈11	2.7–15.4	4.77 (2.43 to 9.35)‖	<.001	2.15 (1.28 to 3.60)¶	.004
IMC + chest wall/breast: left-sided	166	≈15	4.7–18.3	2.59 (1.29 to 5.18)‖	.007	2.29 (1.44 to 3.65)¶	<.001
1980–1986							
RT fields							
No RT/fields not including heart§	261	≈0	≈0	1.0 (referent)		1.0 (referent)	
Breast/chest wall: right-sided	316	≈1.5	1.2–1.6	0.71 (0.29 to 1.74)	.46	0.80 (0.28 to 2.29)	.68
Breast/chest wall: left-sided	395	≈5	2.5–5.3	0.79 (0.36 to 1.72)#	.55	1.16 (0.48 to 2.79)	.75
IMC only: right-sided	359	≈6	0.5–11.6	0.95 (0.46 to 1.93)	.88	1.43 (0.65 to 3.16)	.38
IMC only: left-sided	346	≈7	0.7–15.6	0.94 (0.46 to 1.91)	.86	1.81 (0.84 to 3.92)	.13
IMC + breast/chest wall: right-sided	365	≈9	2.5–14.0	0.80 (0.36 to 1.78)	.58	2.82 (1.27 to 6.29)**	.01
IMC + breast/chest wall: left-sided	376	≈13	4.0–19.9	0.67 (0.30 to 1.52)	.34	2.52 (1.13 to 5.62)**	.02

* Results from four Cox analyses: two separate models were run both for myocardial infarction and for congestive heart failure, with patients stratified by treatment period (1970–1979 and 1980–1986, respectively). HR = hazard ratio; CI = confidence interval; IMC = internal mammary chain.

† Adjusted for age at breast cancer diagnosis, chemotherapy, hormonal therapy, and the cardiovascular risk factors.

‡ *P* value from Wald test statistic.

§ Fields not including heart: no IMC, chest wall, or breast.

‖ Risk of myocardial infarction: for any IMC RT given between 1970 and 1979, irrespective of laterality, HR = 2.55; 95% CI = 1.55 to 4.19 (*P*<.001).

¶ Risk of congestive heart failure: for any IMC RT given between 1970 and 1979, irrespective of laterality, HR = 1.72; 95% CI = 1.22 to 2.41 (*P* = .002).

Risk of myocardial infarction: for left-sided chest wall RT given between 1980 and 1986, HR = 3.54; 95% CI = 1.13 to 11.1 (*P* = .03).

** Risk of congestive heart failure: for IMC + breast RT given between 1980 and 1986, irrespective of laterality, HR = 2.66; 95% CI = 1.27 to 5.61 (*P* = .01).

myocardial infarction (HR = 1.77, 95% CI = 0.91 to 3.43) and congestive heart failure (HR = 1.41, 95% CI = 0.76 to 2.61) after chest wall field irradiation.

We also examined the association of radiotherapy on risk of valvular dysfunction. Irrespective of the treatment period, patients who had radiotherapy to the internal mammary chain for both left- and right-sided tumors experienced an increased risk of valvular dysfunction, (HR = 3.17, 95% CI = 1.90 to 5.29). Risk of dysrhythmias was not associated with any radiotherapy field.

Analyses stratified by follow-up time showed that the radiotherapy-associated risk of cardiovascular disease increased with longer follow-up (for myocardial infarction during the 10- to 20-year and >20-year follow-up intervals, HR = 1.5 and HR = 1.8, respectively, P_{trend} = .03 and for congestive heart failure, HR = 1.6 and HR = 2.1, respectively, P_{trend}<.001).

Analysis of the combined effects of radiotherapy and various cardiac risk factors (Table 6) revealed a more than additive effect of the combination of radiotherapy and smoking on myocardial infarction risk (HR = 3.04, 95% CI = 2.03 to 4.55; $P_{departure\ from\ additivity}$ = .039).

Discussion

After a median follow-up of almost 18 years, we found an association between increased risk of cardiovascular disease and internal mammary chain irradiation for both left- and right-sided breast cancers in the period 1970–1979. For those treated during 1980–1986, the risk of myocardial infarction after internal mammary chain (plus breast) irradiation declined toward unity, but the risk of congestive heart failure remained increased. Internal mammary chain radiotherapy was also associated with an increased risk of valvular dysfunction. Irradiation of the left but not the right chest wall was associated with an increased risk of myocardial infarction for the entire treatment period 1970–1986. After a median follow-up of more than 16 years, the risks of myocardial infarction and congestive heart failure were not increased in patients who received radiotherapy to the breast only. Surprisingly, patients who were treated with radiotherapy plus adjuvant CMF experienced a statistically significantly increased risk of congestive heart failure compared with those treated with radiotherapy alone. Remarkably, the combined effects of radiotherapy and smoking on myocardial infarction risk were more than additive. To our knowledge, our study is the first to examine the effects of combined exposure to radiotherapy and cardiovascular risk factors.

To date, most studies have focused on cardiac mortality, and only a few have reported on morbidity (8,9,11,24). Few risk estimates for cardiac disease after radiation to specific fields have been published, and radiation doses to the heart were not estimated in previous reports. Therefore, our results may explain some of the inconsistencies raised by previous studies. There is little debate regarding the radiotherapy-related risk of cardiac disease imposed by the older radiotherapy regimens from the 1960s and 1970s (2–5). In the last update of the Early Breast Cancer Trialists'

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Table 5. Risks of myocardial infarction and congestive heart failure by radiotherapy (RT) field from multivariable Cox regression analysis*

	Myocardial infarction		Congestive heart failure	
RT fields	**HR (95% CI)**	***P*†**	**HR (95% CI)**	***P*†**
IMC, left vs right	0.87 (0.59 to 1.29)	.49	1.16 (0.84 to 1.60)	.37
Chest wall, left vs right	1.77 (0.91 to 3.43)	.09	1.41 (0.76 to 2.61)	.28
Breast, left vs right	0.74 (0.31 to 1.79)	.51	1.01 (0.40 to 2.55)	.99

* HR = hazard ratio; CI = confidence interval; IMC = internal mammary chain.

† *P* value from Wald test statistic.

Collaborative Group (EBCTCG) meta-analysis on local therapy, comparison of cardiovascular mortality between patients treated with and without radiotherapy yielded a statistically significant rate ratio of 1.27 (4). Studies on cardiovascular risk following more modern regimens from the 1980s, however, have had inconclusive results, possibly because of differences in the types of radiotherapy fields used, the methodology used to compare left- versus right-side–associated risks, the size of the studies, the duration of follow-up, and the definition of endpoints. In many studies of radiotherapy-related cardiovascular mortality, risk is compared between left- and right-sided tumors, as a surrogate for cardiac exposure to radiation (6–10,24–26). Patients who have left-sided breast cancer and are treated with radiation to the chest wall generally receive a higher dose of radiation to a larger volume of cardiac tissue than patients with right-sided disease. However, the left–right difference in cardiac exposure to radiation can be less evident in case of internal mammary chain irradiation through a separate anterior field (27). Estimation of mean radiation dose to the heart in our study indeed showed that the difference between left- and right-sided irradiation was relatively small for internal mammary chain irradiation (Table 4). Consequently, information on the regimens used is required to decide whether a left–right comparison is meaningful.

In our study, many patients received internal mammary chain radiation using an anterior field, and we only found a slightly statistically nonsignificantly increased risk of cardiovascular disease (HR = 1.1, 95% CI = 0.9 to 1.2) for left- versus right-sided tumors. This left- versus right-sided comparison did not reveal that the true risk increase due to radiotherapy was higher (HR = 1.4, 95% CI = 1.1 to 1.7) when compared with surgery only. Likewise, Vallis et al. (9), Rutqvist et al. (8), and Nixon et al. (6) did not find excess risks of cardiovascular disease among patients who received irradiation of the left breast, with regional nodal areas irradiated in less than 6%, 12%, and 80% of the patients, respectively. Interpretation of these results is difficult, however, because the studies analyzed only few cardiac events. Furthermore, follow-up time was fairly short for an increase of cardiovascular disease risk to become manifest. This was also the case in the study by Højris et al. (11), which compared patients in Denmark who were treated during 1982–1990 with or without postmastectomy radiation (including the ipsilateral internal mammary chain field) and found no increased risk of cardiovascular disease among the irradiated patients. Conversely, in two large population-based studies (7,10), statistically significantly increased risks of cardiac death were associated with left-sided tumors (2.1 and 1.1, respectively). Based on the 1973–2000 dataset from the Surveillance, Epidemiology, and End Results (SEER) cancer registries, Giordano et al. (25) also found a statistically significant increase of cardiac mortality among patients with left-sided tumors who were treated with radiation therapy in

Table 6. Multivariable Cox regression analysis: combined effects of radiotherapy (RT) and cardiovascular risk factors on myocardial infarction*

	No RT			RT			
Risk factor	**No. of patients at risk**	**No. of events**	**HR† (95% CI)**	**No. of patients at risk**	**No. of events**	**HR† (95% CI)**	***P*‡**
Smoking§							
No	797	43	1.00 (ref.)	2072	113	1.34 (0.94 to 1.91)	
Yes	231	11	1.36 (0.69 to 2.68)	737	61	3.04 (2.03 to 4.55)	.039
Hypercholesterolemia							
No	1127	45	1.00 (ref.)	2780	134	1.59 (1.13 to 2.24)	
Yes	120	18	3.11 (1.78 to 5.42)	315	57	4.62 (3.06 to 6.98)	.36
Hypertension							
No	894	24	1.00 (ref.)	2302	95	1.92 (1.22 to 3.01)	
Yes	353	39	2.49 (1.49 to 4.16)	793	96	3.31 (2.09 to 5.24)	>.50
Diabetes mellitus							
No	1123	45	1.00 (ref.)	2843	160	1.81 (1.29 to 2.53)	
Yes	124	18	2.01 (1.15 to 3.53)	252	31	1.87 (1.17 to 3.00)	.12
History of IHD							
No	1222	59	1.00 (ref.)	3044	181	1.56 (1.16 to 2.11)	
Yes	25	4	1.53 (0.54 to 4.32)	51	10	2.31 (1.15 to 4.65)	>.50

* Biologic interaction was evaluated as departure from additivity of the effect of two risk factors, where the "interaction risk" is the risk that cannot be explained by the joint exposure to both risk factors, as expressed in the formula $R_{INT} = R_{A+B} - (R_A + R_B - R_U)$. For example, R_A = risk of myocardial infarction (MI) from smoking, R_B = risk of MI from RT, R_{A+B} = risk of MI from smoking and RT together, and R_U = background risk of MI = 1.0. In the formula, $R_{INT} = 3.04 - (1.36 + 1.34 - 1.0) = 1.34$. HR = hazard ratio; CI = confidence interval; ref. = reference group = 1.0, for background risk; IHD = ischemic heart disease.

† Hazard ratio adjusted for age at breast cancer diagnosis, treatment period, smoking, hypercholesterolemia, hypertension, and diabetes mellitus.

‡ *P* value for departure from additivity, derived from likelihood ratio test statistic.

§ Total of 505 patients with unknown smoking status excluded from analysis.

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the period 1973–1979 (for 1979, HR = 1.5), whereas after 1979, the difference in risk between patients with left- and right-sided tumors declined to unity. Also based on the SEER dataset but with longer follow-up, a recent study by Darby et al. (26) showed increased cardiac mortality ratios (left- versus right-sided tumors) for patients who were treated with radiation therapy during 1973–1982 and decreasing ratios for patients treated from 1983 onward. In the last four studies (7,10,24,25), no information was available on the proportion of patients who received radiation treatment to the regional lymph nodes.

Most previous studies of cardiovascular disease risk after breast cancer treatment evaluated risk of ischemic heart disease, except for that of Patt et al. (24), who also reported on risk of valvular heart disease, congestive heart failure, and conduction abnormalities. They found no statistically significant differences in cardiac morbidity after radiation for left- versus right-sided breast cancer among patients who were treated between 1986 and 1993. However, mean follow-up was only 9.5 years. Among Hodgkin lymphoma survivors who were treated with radiotherapy, valvular dysfunction at a median of 22 years after first treatment has been described (28). Our study showed associations not only between radiation therapy and increased risks of ischemic heart disease but also between radiation treatment and valvular dysfunction and congestive heart failure. Thus, many cardiac events may be missed by restricting study outcome to ischemic heart disease.

A remarkable finding in our study was that chemotherapy was associated with increased risk of congestive heart failure. The risk associated with chemotherapy was increased even more in the analysis that was restricted to primary treatment only, indicating an association with CMF, the standard adjuvant chemotherapy regimen during the study period. We can only speculate on the mechanisms involved, assuming the association is causal. Treatment with high doses of cyclophosphamide has been associated with increased risk of congestive heart failure. An increased risk could also be mediated through preliminary menopause from CMF, resulting in lower estrogen levels. However, we cannot rule out chance or undetected confounding as an explanation. Nor can we exclude a residual effect of radiotherapy that cannot be controlled for effectively because all patients who are treated with chemotherapy also received radiotherapy.

To date, no study of radiation therapy for breast cancer and cardiovascular disease has incorporated cardiovascular risk factors into its analysis. A recent study of coronary heart disease after radiotherapy for peptic ulcer disease (29) found that radiotherapy and smoking were independently associated with cardiovascular disease risk. In a study of Hodgkin lymphoma patients (30), no differences were found in radiotherapy-associated risk of myocardial infarction by history of smoking. Information on smoking was incomplete, however, which may have impaired the interaction analysis. We found that the joint associations between radiotherapy and smoking and myocardial infarction risk were greater than expected when individual risks were summed. Consequently, the advice to stop smoking appears to be even more important for irradiated patients and should be given at the time of treatment.

When interpreting our results, the strengths and limitations of our study should be considered. Unlike most studies, we collected information on all primary and follow-up treatments, including radiation fields and cardiovascular disease risk factors. Follow-up was nearly complete and very long, with more than 30% of patients followed for more than 20 years.

A potential limitation of our study is the assumption that the population-based incidence rates for cardiac disease are an appropriate comparison group in the person-years analysis. In this analysis, we accounted for age and calendar year during follow-up, but we cannot exclude potential differences in cardiac risk profiles between the study group and the reference population. It is possible that patients included in our study may have begun a healthier lifestyle after breast cancer diagnosis. Also, in this hospital-based study population, we may have selected breast cancer patients with higher socioeconomic status than the general population. Nevertheless, these differences would result in an underestimation of the true cardiac risk as compared with a general population sample with similar characteristics. This potential limitation relates only to our general population comparisons and not to the Cox model analyses.

Surveillance bias is highly unlikely in our patient population because the majority of patients were discharged from routine follow-up in the cancer center 10 years after breast cancer diagnosis. Also, although radiotherapy-related risk of cardiovascular disease has been known for a long time, we know from the medical records of patients in the study that irradiated patients were not routinely screened for cardiac symptoms. This lack of screening was also confirmed in a pilot study showing that 20% of the cardiovascular events reported by the general practitioners were not registered in our oncologic records. Furthermore, as we reported earlier in an analysis of cause-specific mortality in this cohort (12), we also found increased mortality of cardiovascular disease in irradiated patients (standardized mortality ratio [SMR] = 1.12; 95% CI = 0.95 to 1.30) compared with patients who were treated with surgery only (SMR = 0.54; 95% CI = 0.35 to 0.80; for irradiated versus nonirradiated patients, RR = 2.07; 95% CI = 1.35 to 3.29). Finally, the reference rates used to generate population-expected values as well as the observed events were both obtained from general practitioners. Therefore, confounding from using different sources to obtain observed and expected rates is highly unlikely.

Our choice for the surgery-only group as a reference group in the Cox regression analysis is a possible limitation if patients who were treated with surgery alone had a different cardiovascular risk profile than that of other treatment groups. This seemed to be the case in several population-based studies (7,10,24–26) and was a motivation for comparison of cardiac risks between irradiated patients with left- and right-sided tumors in those studies, excluding patients who were treated with surgery only. We believe that confounding by contraindication in general occurs only in older patients who have comorbid conditions (31,32). In our study, patients who were older than 70 years were excluded, and we did not observe patient selection for treatment. In both cancer centers, treatment decisions regarding radiotherapy were not affected by either socioeconomic status, distance to the cancer center (data not shown), or the presence of cardiac disease. Even among patients who had a history of cardiovascular disease or hypertension at the time of breast cancer diagnosis (n = 528), 95.0% of patients for whom radiotherapy (axillary node involvement and/or medially located tumor) was prescribed were indeed treated, compared with 95.1% of patients without these risk factors.

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Possible relationships between cardiovascular disease risk and irradiated volume of the heart or dose per fraction as assessed by others (7,33) could not be evaluated in our cohort because not all required data were collected. We could, however, roughly estimate the mean cardiac doses received in various periods from different fields and techniques. The range of doses per field was wide, and, thus, the increased risk of cardiovascular disease observed in a category with estimated low mean cardiac dose may reflect a subgroup of patients who received relatively high cardiac doses. Furthermore, the clear reduction in myocardial infarction risk for patients treated in 1980–1986, with mean cardiac radiation doses that were only slightly lower than in the earlier period, could arise if the relevant exposure parameter is radiation dose to the left anterior descending coronary artery or the percentage of the heart exposed to 5 Gy or more.

Overall, however, the risk of cardiovascular disease increased with increasing mean cardiac dose. The decline in risk observed for the more recent treatment period is consistent with recently published studies. Whether the excess risk has disappeared completely remains to be determined. During the 1990s, the use of internal mammary chain irradiation was drastically reduced, but it may still be used in patients with positive internal mammary chain nodes as diagnosed by the sentinel node procedure or in patients with a high number of tumor-positive axillary nodes. As a consequence, a sizable and growing patient population is at increased risk of cardiovascular disease. Yet, we should remember the rationale for administering adjuvant radiotherapy in the first place: the last meta-analysis of the EBCTCG on the reduced risk of local recurrence after radiotherapy (4) concluded that, in the hypothetical absence of other causes of death, approximately one breast cancer death during the next 15 years would be avoided for every four local recurrences avoided.

In conclusion, apart from the clear benefits of adjuvant radiotherapy, physicians should be still aware of the potentially increased risk of cardiovascular disease following specific radiotherapy regimens in long-term breast cancer survivors. Radiotherapy to the left and right internal mammary chains was associated with equally increased risks of congestive heart failure, whereas irradiation of the left chest wall was associated with increased risk of myocardial infarction. Irradiation of the breast only, with the heart receiving minimal exposure, was not associated with an increased risk of cardiovascular disease. Apart from radiotherapy, adjuvant CMF was also associated with increased risk of congestive heart failure. To our knowledge, this late adverse effect from non–anthracycline-containing chemotherapy has not been reported before and warrants further research. The greater than additive magnitude of smoking and radiotherapy on risk of myocardial infarction stresses the need to advise irradiated patients even more urgently to refrain from smoking. Clearly, more prolonged follow-up of large cohorts will be needed to further evaluate the long-term risks and benefits of modern adjuvant radiotherapy and chemotherapy for early breast cancer (1,3,4).

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Notes

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