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ARTICLE

Cardiovascular Morbidity and Mortality After Treatment for Ductal Carcinoma In Situ of the Breast

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Background Recent concerns about potential overdiagnosis and overtreatment of ductal carcinoma in situ of the breast (DCIS) render evaluation of late effects of treatment, such as cardiovascular disease (CVD), of great importance. We studied cardiovascular morbidity and mortality in a large population-based cohort of DCIS patients.

Methods Data on all incident DCIS case patients in the Netherlands between 1989 and 2004 who were diagnosed before the age of 75 years were obtained (n = 10 468). CVD data was acquired through linkage with population-based registries. Standardized mortality ratios were calculated by comparing mortality in our cohort with that in the Dutch female population, taking into account person-years of observation. Within-cohort comparisons were based on multivariable competing-risk regression.

Results Compared with the general population, 5-year survivors of DCIS had a similar risk of dying due to any cause (standardized mortality ratio [SMR] = 1.04; 95% confidence interval [CI] = 0.97 to 1.11) but a lower risk of dying of CVD (SMR = 0.77; 95% CI = 0.67 to 0.89). No difference in CVD risk was found when comparing 5-year survivors treated with radiotherapy with those treated with surgery only. Left-sided vs right-sided radiotherapy also did not increase this risk (hazard ratio [HR] = 0.94; 95% CI = 0.67 to 1.32). In a subgroup analysis of all DCIS patients diagnosed between 1997 and 2005, we were able to account for history of CVD and did not observe a risk difference between treatment groups (left-sided vs right-sided radiotherapy: HR = 0.94; 95% CI = 0.68 to 1.29).

Conclusions After a median follow-up of 10 years, we did not find an increased risk for cardiovascular morbidity or mortality after radiotherapy for DCIS when comparing surgery and radiotherapy vs surgery only, nor when comparing radiotherapy for left-sided vs right-sided DCIS. Compared with the general population, DCIS patients have a decreased risk of cardiovascular death, independent of treatment.

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Since the introduction of breast cancer (BC) screening programs, the number of noninvasive BC diagnoses has increased substantially, mainly because of increased incidence of ductal carcinoma in situ of the breast (DCIS) (1–4). Although DCIS is generally thought to be a precursor of invasive BC, it remains unclear what proportion would progress into invasive BC if left untreated (5). Nevertheless, current practice is to treat all DCIS patients. Consequently, an unknown but substantial proportion of these patients may be overtreated, rendering knowledge about late adverse effects after DCIS treatment of great importance.

Treatment of DCIS typically consists of surgery, and in the case of wide local excision, this is often followed by radiation using tangential breast fields. Previous research has shown that radiation exposure of the heart, for instance in patients treated for Hodgkin lymphoma (6–8) and invasive BC (9, 10), can increase the long-term risk of cardiovascular disease (CVD). Exposures to lower doses (<2 Gy) have also been shown to increase the risk of CVD, although this concerned whole body irradiation with potential vascular damage to other organs (eg, kidneys) (11,12). Recently, a dose–effect relationship for ischemic heart disease (IHD) was shown in BC patients treated with radiotherapy (13). Radiation in DCIS treatment will result in exposure of the heart, but with relatively low doses (estimated mean heart dose during study period is approximately 6 Gy for left-sided disease and 2 Gy for right-sided) (14) compared with, for example, exposure from treatment for invasive BC that also included nodal fields. Yet, until now, only three studies have examined treatment-related CVD in DCIS patients (15–17), and the results were inconsistent. Because these studies examined cardiovascular mortality rather than morbidity (15,16) or included rather few patients (17), it remains unclear whether patients treated with radiotherapy for DCIS are at increased risk for CVDs. We therefore studied the risk of cardiovascular morbidity and mortality in a large population-based cohort of patients treated for DCIS.

Methods

Data Collection Procedures

The Dutch population-based DCIS cohort consists of 10468 female patients diagnosed with DCIS as their first neoplasia before the age of 75 years between 1989 and 2004. Patient selection was performed by the Netherlands Cancer Registry (NCR). The NCR has a coverage of at least 96% of invasive malignant neoplasms and selected noninvasive cancers, including DCIS, occurring in the Netherlands since 1989 (18). The NCR performs an annual linkage with the population-based municipal personal records database for date of death. For both initial DCIS and subsequent neoplasia, the NCR provided date of birth, diagnosis, and death; topography; morphology; differentiation; stage; type of surgery; whether chemotherapy was administered; and whether radiotherapy was administered.

Linkages with two different population-based registries were performed for CVD information (see Supplementary Methods, available online, for linkage details). First linkage was with the Cardiac Intervention Registry maintained by the Steering Committee Heart Interventions Netherlands (BHN). This population-based registry collects data on all heart interventions (including open heart surgery and percutaneous coronary interventions) performed in the Netherlands since 1995 (19).

After linkage with BHN, the cohort was sent to Statistics Netherlands, where linkages were performed for cause of death and with the second registry with information on CVD, the Dutch Hospital Data (DHD). This registry provides data on all hospital discharges. Diagnoses are coded by local hospital staff according to the International Classification of Diseases, Ninth Revision (20). Because the DHD does not contain a unique personal identifier or patient names, linkage with the DHD could be performed only for patients who were uniquely identifiable using the variables available in the registry (ie, birth date, sex, and four-digit postal code; 90.7% of the cohort) (see Supplementary Methods and Supplementary Figure 1, available online).

Lack of histological confirmation (n = 9) or treatment including chemotherapy (n = 15) were reasons for exclusion. The analytical cohort was comprised of 10444 DCIS patients.

A cardiovascular event was defined as cardiovascular-related hospital admission/surgical intervention/death. The first hospitalization of each specific CVD was used in the analyses. Follow-up on second neoplasia, vital status, cardiovascular interventions, and hospital admissions were complete until at least January 1, 2010. The study was approved by the review boards of the NCR, BHN, and Statistics Netherlands.

Treatment

DCIS was treated with surgery (either mastectomy or wide local excision), and, in case of wide local excision, this was, especially in the later years, frequently followed by tangential breast field irradiation to a prescribed dose equivalent of 50 Gy in 25 fractions. (Dose equivalent refers to a measure of biological effectiveness of an absorbed dose.) The percentage of DCIS patients treated with radiotherapy changed considerably during the study period, from 20% in 1989 to 46% in 2004.

Statistical Analysis

Because of the anatomical position of the heart, the radiation dose to the heart is higher after radiotherapy of the left breast than the right breast. Based on primary treatment, we therefore defined three mutually exclusive treatment categories: surgery only, radiotherapy for right-sided DCIS, and radiotherapy for left-sided DCIS.

We compared cardiovascular mortality in the study population with that in the Dutch female population, taking into account person-years of observation in the cohort (by age, calendar period, and follow-up interval). From the results of the person-years analysis, we calculated standardized mortality ratios (SMRs) as ratios of observed and expected numbers of cardiovascular deaths, and we calculated absolute excess risk (AER) as observed minus expected, divided by the number of person-years at risk, multiplied by 10000. To quantify the effects of different treatments on CVD risk, within-cohort comparisons were performed using competing-risk regression models (21) with death due to other causes than the event of interest as a competing risk and including age at DCIS treatment (continuous) and year of DCIS treatment in the model as covariables. The assumptions of proportionality were verified by comparing log-log survival curves. Competing-risk regression models were fitted with the use of Stata/SE 11.0 (StataCorp LP, College Station, TX), and a P value less than .05 was considered statistically significant.

To examine whether patients with a history of CVD are at increased risk for developing radiation-induced CVD, as well as to rule out confounding by indication, we aimed to take into account history of CVD. However, because CVD incidence information was available from 1995 onwards only, history of CVD before BC diagnosis was not available for all patients and the number of years with information on history of CVD increased with year of diagnosis after 1995; therefore, a subgroup analysis for patients diagnosed between 1997 and 2005 was performed.

Because CVD incidence data in the first 5 years after treatment were not available for the entire cohort and because most studies did not find an increased risk in these first years after radiotherapy (9,22–24) time at risk of all patients started 5 years after DCIS diagnosis in the overall analyses (6 years for patients diagnosed with DCIS in 1989) and directly after DCIS diagnosis in the subgroup analyses. Events before start of time at risk were ignored unless stated differently. Time at risk ended at date of diagnosis of the event of interest, date of death, date of diagnosis of a second (breast) neoplasia if this neoplasia was treated with chemotherapy or radiotherapy above the diaphragm, emigration, or date of most recent medical information, whichever came first. Moreover, when DHD data were used in analysis, only the first period in time during which a person was uniquely identifiable was taken into account because linkage with the DHD is not possible for admissions during nonunique periods in time.

Results

Patient Characteristics

Nearly 54% of the patients were diagnosed with left-sided DCIS (Table 1). Patient characteristics did not differ between left- and right-sided DCIS. Median follow-up time was 10 years (8 years when restricting to patients treated with radiotherapy). Almost 28% of the cohort was irradiated, mostly after wide local excision. During follow-up, 1319 patients died and 2124 were diagnosed with a second neoplasia. Few patients (1.7%) had a history of CVD before their DCIS diagnosis.

Table 1. Characteristics of the population-based cohort of patients with ductal carcinoma in situ of the breast*

Characteristic	All patients No.† (%)	Left-sided DCIS No. (%)	Right-sided DCIS No. (%)
No. of patients	10444 (100.0)	5613 (53.9)	4825 (46.1)
Age at DCIS diagnosis, y			
<49	2090 (20.0)	1122 (20.0)	967 (20.0)
49–59	4242 (40.6)	2258 (40.2)	1982 (41.1)
60–69	3073 (29.4)	1687 (30.1)	1385 (28.7)
70–74	1039 (9.9)	546 (9.7)	491 (10.2)
Attained age at end of follow-up, y			
<50	586 (5.6)	309 (5.5)	277 (5.7)
50–59	1923 (18.4)	998 (17.8)	924 (19.2)
60–69	3567 (34.2)	1919 (34.2)	1648 (34.2)
70–79	3180 (30.4)	1758 (31.3)	1419 (29.4)
≥80	1188 (11.4)	629 (11.2)	557 (11.5)
Treatment period DCIS			
1989–1992	1382 (13.2)	757 (13.5)	625 (13.0)
1993–1996	2373 (22.7)	1268 (22.6)	1102 (22.8)
1997–2000	3096 (29.6)	1702 (30.3)	1394 (28.9)
2001–2004	3590 (34.4)	1886 (33.6)	1704 (35.3)
Follow-up time, median, y	10	10	10
Patients treated with radiotherapy, median, y	8	8	8
Follow-up interval, y			
0	7 (0.1)	3 (0.1)	4 (0.1)
<5	481 (4.6)	251 (4.5)	230 (4.8)
5–9	4653 (44.6)	2487 (44.3)	2165 (44.9)
10–14	3366 (32.2)	1834 (32.7)	1528 (31.7)
≥15	1937 (18.5)	1038 (18.5)	898 (18.6)
Primary DCIS treatment			
Surgery only	7466 (71.5)	3985 (71.0)	3476 (72.0)
Mastectomy	4434 (42.5)	2318 (41.3)	2113 (43.8)
Lumpectomy	2014 (19.3)	1113 (19.8)	900 (18.7)
Type of surgery unknown‡	1018 (9.7)	554 (9.9)	463 (9.6)
Surgery and radiotherapy	2899 (27.8)	1584 (28.2)	1314 (27.2)
Mastectomy and radiotherapy	111 (1.1)	63 (1.1)	48 (1.0)
Lumpectomy and radiotherapy	2543 (24.3)	1393 (24.8)	1149 (23.8)
Type of surgery unknown‡ and radiotherapy	236 (2.3)	126 (2.2)	110 (2.3)
Untreated§	79 (0.8)	44 (0.8)	35 (0.7)
Vital status			
Alive	8916 (85.4)	4775 (85.1)	4135 (85.7)
Dead	1319 (12.6)	724 (12.9)	595 (12.3)
Emigrated	209 (2.0)	114 (2.0)	95 (2.0)
Patients ever uniquely identifiable during follow-up‖	9470 (90.7)	5081 (90.5)	4389 (91.0)
Laterality			
Left	5613 (53.7)		
Right	4825 (46.2)		
Unknown	6 (0.1)		
Differentiation DCIS			
Well-differentiated	968 (9.3)	537 (9.6)	430 (8.9)
Moderately differentiated	1715 (16.4)	909 (16.2)	805 (16.7)
Poorly differentiated	2788 (26.7)	1462 (26.0)	1326 (27.5)
Unknown¶	4973 (47.6)	2705 (48.2)	2264 (46.9)
History of cardiovascular disease#	182 (1.7)	97 (1.7)	84 (1.7)
DCIS diagnosis 1989–1992**	NA	NA	NA
DCIS diagnosis 1993–1996**	9 (0.1)	4 (0.1)	5 (0.1)
DCIS diagnosis 1997–2000	58 (0.6)	33 (0.6)	25 (0.5)
DCIS diagnosis 2001–2004	114 (1.1)	60 (1.1)	54 (1.1)
Second primary neoplasia	2124 (20.3)	1188 (21.2)	936 (19.4)

* DCIS = ductal carcinoma in situ of the breast; NA = not available.

† The numbers of left-sided and right-sided DCIS do not add up to the total because of six patients with missing laterality.

‡ Type of surgery was not registered in every region during the first years of the registry.

§ Excluded from analyses.

‖ Linkage with the Hospital Discharge Registry is only possible for patients who were ever unique based on postal code, date of birth, and sex.

¶ Time dependent, with "unknown" coded more often during older years of diagnoses.

History of cardiovascular disease defined as a hospital admission for cardiovascular disease or cardiovascular before the DCIS diagnosis.

** Data on cardiovascular disease is available since 1995.

In total, 950 patients experienced a cardiovascular event, of whom 814 were admitted to the hospital, 255 underwent a cardiovascular intervention, and 282 died due to CVD (Table 2). Considering events occurring 5 or more years after DCIS diagnosis only, 684 events remained for analyses, of which 574 were hospital admissions, 170 were cardiovascular interventions, and 204 were cardiovascular deaths.

Comparison With the General Population

Compared with the general population, 5-year survivors of DCIS had a similar risk of dying from any cause (SMR = 1.04; 95% confidence interval [CI] = 0.97 to 1.11). However, cardiovascular mortality, including both cardiovascular and cerebrovascular diseases, was lower for DCIS patients, with a standardized mortality ratio of 0.77 (95% CI = 0.67 to 0.89) (Table 3). Standardized mortality ratios did not vary by age at diagnosis, treatment period, follow-up interval, or treatment, or for all cardiovascular deaths combined or death due to myocardial infarction, other IHD, or other heart disease separately (Table 4).

Within-Cohort Comparison

When comparing patients treated with radiotherapy to patients treated with surgery only and patients treated with left-sided vs right-sided radiotherapy, no statistically significantly increased risks were found for the combined group of any cardiovascular event (hazard ratio [HR] = 0.94; 95% CI = 0.67 to 1.32), or for

Table 2. Cardiovascular events in the population-based ductal carcinoma in situ of the breast cohort*

Cardiovascular event	ICD-10	Total, No.	5-year survivors,† No.
Any cardiovascular event‡		950	684
Cardiovascular death	I00-99	282	204
Myocardial infarction	I21-22	76	48
Other ischemic heart disease	I20, 23–25	25	15
Other heart disease	I30-52	78	63
Pericarditis	I30-32	0	0
Valvular dysfunction	I34-38	17	15
Cardiomyopathy	I42	2	2
Arrhythmia	I47-49	10	6
Congestive heart failure	I50	23	18
Cerebrovascular disease	I60-69	68	55
Hospital admission for cardiovascular disease§	I20-25, 30-52	814	574
Ischemic heart disease	I20-25	411	268
Acute myocardial infarction	I21-22	137	83
Angina pectoris	I20	146	88
Valvular dysfunction	I34-38	52	39
Arrhythmia	I47-49	308	215
Congestive heart failure	I50	154	120
Surgical intervention for cardiovascular disease‖		255	170
Percutaneous coronary intervention		158	101
Coronary artery bypass surgery		56	36
Valvular dysfunction		53	41
Arrhythmia		4	3

* ICD-10 = International Classification of Diseases, 10th Revision.

† Time at risk started 5 years after DCIS diagnosis.

‡ Cardiovascular death, hospital admission for cardiovascular disease, or surgical intervention for cardiovascular disease.

§ Data available since 1995 for patients who were unique based on date of birth, sex, and postal code at time of the hospital discharge.

‖ Data available since 1995.

Table 3. Standardized mortality ratios in population-based cohort of 5-year survivors of ductal carcinoma in situ of the breast*

Cause	ICD-10	Observed	SMR (95% CI)	AER
All causes†	A00-Y89	941	1.04 (0.97 to 1.11)	5.7
Unknown cause		6		
Circulatory system	I00-99	195	0.77 (0.67 to 0.89)	−10.2
Myocardial infarction	I21-22	43	0.83 (0.60 to 1.11)	−1.6
Other ischemic heart disease	I20, 23-25	15	0.78 (0.44 to 1.29)	−0.7
Other heart disease	I30-33, 39-52	47	0.69 (0.50 to 0.91)	−3.8
Cerebrovascular disease	I60-69	52	0.77 (0.58 to 1.01)	−2.7
Other cardiovascular disease	I00-15, 26-28, 34-52, 70-99	38	0.83 (0.59 to 1.14)	−1.4

* Time at risk started 5 years after ductal carcinoma in situ diagnosis. Patients were censored at diagnosis of a second neoplasia treated with chemotherapy or radiotherapy above the diaphragm or date of emigration. AER = absolute excess risk per 10,000 patients per year; CI = confidence interval; ICD-10 = International Classification of Diseases, 10th Revision; SMR = standardized mortality ratio.

† Without taking censoring for second neoplasia into account.

Table 4. Risks of different cardiovascular diseases in 5-year survivors of ductal carcinoma in situ by age, follow-up interval, treatment, and laterality*

	Circulatory system†			Myocardial infarction‡			Other ischemic heart disease§			Other heart disease‖		
Patient characteristics	**O**	**SMR (95% CI)**	**AER**	**O**	**SMR (95% CI)**	**AER**	**O**	**SMR (95% CI)**	**AER**	**O**	**SMR (95% CI)**	**AER**
Age at DCIS diagnosis, y												
<49	0	0.0 (0.00 to 0.56)	−5.0	0	0.0 (0.00 to 2.19)	−1.3	0	0.0 (0.00 to 10.12)	−0.3	0	0.0 (0.00 to 2.30)	−1.2
50–59	23	0.6 (0.38 to 0.91)	−6.5	8	0.9 (0.37 to 1.69)	−0.6	2	0.7 (0.08 to 2.44)	−0.4	6	0.7 (0.24 to 1.41)	−1.4
60–69	97	0.7 (0.58 to 0.87)	−23.0	17	0.6 (0.35 to 0.97)	−6.5	6	0.6 (0.21 to 1.24)	−2.7	22	0.6 (0.38 to 0.92)	−8.3
70–74	75	1.0 (0.82 to 1.30)	7.3	18	1.4 (0.83 to 2.20)	13.8	7	1.3 (0.54 to 2.75)	4.8	23	0.9 (0.55 to 1.31)	−8.2
Treatment period DCIS												
1989–1992	66	0.7 (0.56 to 0.91)	−17.4	13	0.7 (0.37 to 1.17)	−4.0	5	0.7 (0.24 to 1.69)	−1.3	32	0.9 (0.58 to 1.20)	−3.7
1993–1996	69	0.8 (0.63 to 1.03)	−7.9	16	0.9 (0.52 to 1.48)	−0.8	5	0.8 (0.25 to 1.82)	−0.7	26	0.7 (0.45 to 1.01)	−5.7
1997–2000	36	0.8 (0.56 to 1.10)	−7.5	8	0.9 (0.38 to 1.72)	−0.9	4	1.2 (0.32 to 2.99)	0.5	20	0.9 (0.52 to 1.32)	−2.5
2001–2004	24	0.8 (0.49 to 1.14)	−7.5	6	0.9 (0.34 to 2.03)	−0.5	1	0.4 (0.01 to 2.33)	−1.4	14	0.9 (0.53 to 1.55)	−0.9
Follow-up interval, y												
5–9	96	0.8 (0.63 to 0.96)	−7.4	28	1.0 (0.67 to 1.46)	0.1	7	0.7 (0.30 to 1.51)	−0.7	23	0.8 (0.48 to 1.13)	−2.1
10–15	75	0.8 (0.66 to 1.04)	−9.1	14	0.8 (0.44 to 1.34)	−2.1	4	0.6 (0.16 to 1.52)	−1.6	16	0.6 (0.36 to 1.03)	−5.6
>15	24	0.6 (0.39 to 0.90)	−37.3	1	0.1 (0.00 to 0.83)	−13.8	4	1.4 (0.39 to 3.66)	2.9	8	0.6 (0.28 to 1.27)	−10.6
DCIS treatment												
Surgery only	159	0.8 (0.65 to 0.89)	−10.8	35	0.8 (0.57 to 1.14)	−1.2	13	0.8 (0.44 to 1.42)	−0.6	82	0.8 (0.66 to 1.02)	−3.7
Radiotherapy	36	0.8 (0.55 to 1.10)	−8.0	8	0.8 (0.37 to 1.67)	−0.6	2	0.6 (0.07 to 2.09)	−1.2	11	0.7 (0.36 to 1.29)	−3.5
Right-sided radiotherapy	19	0.9 (0.55 to 1.43)	−3.4	2	0.5 (0.06 to 1.67)	−4.3	2	1.3 (0.15 to 4.56)	0.8	7	1.0 (0.39 to 2.01)	−0.3
Left-sided radiotherapy	17	0.7 (0.40 to 1.10)	−11.8	6	1.2 (0.43 to 2.54)	1.3	0	0.0 (0.00 to 1.97)	−2.9	4	0.5 (0.14 to 1.27)	−6.1
Surgery only, right-sided	82	0.7 (0.59 to 0.92)	−11.9	17	0.7 (0.43 to 1.19)	−2.4	2	0.2 (0.03 to 0.86)	−2.6	43	0.8 (0.57 to 1.07)	−4.4
Surgery only, left-sided	77	0.8 (0.63 to 1.00)	−9.4	18	0.9 (0.51 to 1.44)	−0.8	11	1.5 (0.76 to 2.71)	1.8	39	0.9 (0.62 to 1.18)	−2.8

* Time at risk started 5 years after ductal carcinoma in situ diagnosis. Patients were censored at diagnosis of a second neoplasia treated with chemotherapy or radiotherapy above the diaphragm or date of emigration. AER = absolute excess risk per 10 000 patients per year; CI = confidence interval; DCIS = ductal carcinoma in situ; O = observed; SMR = standardized mortality ratio.

† I00-99 International Classification of Diseases, 10th Revision.

‡ I21-22 International Classification of Diseases, 10th Revision.

§ I20, 23-25 International Classification of Diseases, 10th Revision.

‖ I30-33, 39-52 International Classification of Diseases, 10th Revision.

cardiovascular death, cardiovascular surgical intervention, hospital discharge diagnoses of CVD, myocardial infarction, other heart disease, valvular dysfunction, arrhythmia, or congestive heart failure separately (Table 5). Risks of hospital discharge diagnoses for IHD and angina pectoris were increased for patients treated with right-sided radiotherapy compared with surgery only (HR = 1.47, 95% CI = 1.01 to 2.13; HR = 2.53; 95% CI = 1.46 to 4.41, respectively). However, no statistically significant differences were seen comparing left-sided vs right-sided radiotherapy (HR = 0.78, 95% CI = 0.48 to 1.27 for IHD; HR = 0.57, 95% CI = 0.27 to 1.23 for angina pectoris). Although non-statistically significant, risks of cardiovascular mortality, IHD, congestive heart failure, and cardiovascular surgical interventions tended to be lower for patients treated with radiotherapy to the left breast than for patients irradiated to the right breast. Conversely, risks of valvular dysfunction and arrhythmia were somewhat higher, although not statistically significantly, for left-sided vs right-sided radiotherapy.

In a subgroup analysis of patients diagnosed with DCIS between 1997 and 2005, with time at risk starting directly after DCIS diagnosis and taking into account history of CVD, we did not observe a risk difference between treatment groups (adjusted estimate for left-sided vs right-sided radiotherapy: HR = 0.94, 95% CI = 0.68 to 1.29) (Table 6). Additionally, the risk in the first 5 years after treatment did not differ from the risk more than 5 years after treatment (HR = 0.63; 95% CI = 0.42 to 0.94). In stratified analyses, similar risks were found for patients with and without a history of CVD (HR = 0.88, 95% CI = 0.37 to 2.06; HR = 0.94, 95% CI = 0.67 to 1.33, respectively). When taking into account history of CVD within 2 years before DCIS diagnosis only, thus equaling the number of years with information on history of CVD for all patients, a non-statistically significant risk increase of 1.85 was seen for patients with a history of CVD (95% CI = 0.50 to 6.82), whereas no increased risk was seen for patients without a history of CVD (HR = 0.95; 95% CI = 0.68 to 1.33). However, the number of patients available for this analysis was small.

Discussion

In this large population-based cohort study, we observed that, compared with the general population, 5-year survivors of DCIS had a decreased risk of cardiovascular death, independent of treatment. After a median follow-up of 10 years, we did not find an increased risk for cardiovascular morbidity or mortality after radiotherapy treatment for DCIS. We compared patients treated with radiotherapy vs those treated with surgery only, as well as patients treated with radiotherapy for left-sided vs right-sided DCIS. Overall, history of CVD before DCIS diagnosis did not seem to increase the risk of radiation-associated CVD. When taking into account cardiovascular events that occurred 2 years before DCIS diagnosis only, however, a non-statistically significantly increased risk was seen for patients with a history of CVD. Because of the low number of patients with a history of CVD in this analysis, this may be a chance finding.

Contrary to our expectations, we did not find a risk increase of IHD incidence or mortality after radiotherapy for DCIS, possibly because of the relatively short follow-up duration. Excess risks for valvular dysfunction, arrhythmia, and congestive heart failure were not expected because of the expected low mean heart dose.

Although we did not collect information on radiation fields, it is plausible to assume that patients treated with radiotherapy were irradiated using tangential breast fields only. In the Netherlands, DCIS and invasive BC are treated with similar tangential fields (provided internal mammary nodes are not included); therefore our results also apply to invasive BC patients. The Early BC Trialists' Collaborative Group (15) compared DCIS patients (n = 3729) treated with radiotherapy to patients treated with surgery only and found a slight but non-statistically significant risk increase in cardiovascular mortality. Although we had a comparable follow-up duration, we were not able to confirm this finding. Our results are, however, in line with the two other CVD studies in DCIS patients (16,17). Ernster et al. (16) found a similarly decreased standardized mortality ratio for CVD using the Surveillance, Epidemiology and End Results database (n = 7072). However, they were not able to make any further distinctions based on laterality or treatment. Also in invasive BC patients, lower standardized mortality ratios were found (22,24). Possible explanations for lower standardized mortality ratios for CVD are differences in CVD risk factors between DCIS patients and the general population (eg, higher socioeconomic status, later age at menopause, or being more health-conscious or adopting a healthier lifestyle after DCIS diagnosis).

Park et al. (17) compared cardiovascular morbidity and mortality in a small patient group (n = 129) treated with radiotherapy for left-sided vs right-sided DCIS and did not find a difference. Studies looking at the effect of tangential breast field irradiation for invasive BC showed mixed results (25,26). Our results are in contrast with Darby et al.'s (13) recently published increase of IHD risk of 7.4% per Gy mean heart dose. We have no clear explanation why the results of our study do not point to an increased risk after left-sided RT, but possible explanations include a much narrower mean heart radiation dose range in our study and differences between the two studies with regard to the calendar periods in which the patients were treated in combination with changes in cardiovascular risk management in these calendar periods.

We used two treatment groups as internal reference groups: right-sided radiotherapy and surgery only. It has been discussed whether the latter group is an appropriate comparison group. Some researchers argue that patients treated with surgery only might differ from patients treated with radiotherapy on CVD risk factors (10). However, because of the excellent Dutch health insurance system and the small distances to radiation facilities, only comorbidity could have influenced the treatment choice, next to DCIS disease characteristics and patient preferences. If comorbidity had an influence, the effect was probably small because the prevalence of a history of CVD before DCIS diagnosis was low (1.7%) in our patient population aged 75 years or younger at DCIS diagnosis. Moreover, patients with a history of CVD did not receive radiotherapy less often than patients without a history of CVD, and estimates comparing radiotherapy vs surgery only did not materially differ from those of left-sided vs right-sided radiotherapy comparisons.

Our study had several strengths and limitations. Unique features of our population-based study include taking into account both cardiovascular morbidity and mortality, performing linkage with two population-based registries with CVD information, and examining the effect of a history of CVD.

There is no reason to assume either confounding by indication or surveillance bias in our study population. There was no difference in use of radiotherapy between left-sided and right-sided

Table 5. Competing risk regression analyses for different cardiovascular events in 5-year survivors of ductal carcinoma in situ*

Risk factor	ICD-10	No. of events	HR (95% CI)
Any cardiovascular event†,‡		613	
Surgery only		475	1.00 (Referent)
Right-sided radiotherapy		65	1.08 (0.83 to 1.41)
Left-sided radiotherapy		73	1.01 (0.79 to 1.30)
Left- vs right-sided radiotherapy		138	0.94 (0.67 to 1.32)
Cardiovascular death§	I20-25, 30-52	125	
Surgery only		101	1.00 (Referent)
Right-sided radiotherapy		13	1.29 (0.72 to 2.31)
Left-sided radiotherapy		11	0.89 (0.48 t0 1.66)
Left- vs right-sided radiotherapy		24	0.70 (0.31 to 1.56)
Hospital discharge diagnosis of cardiovascular disease‡	I20-25, 30-52	542	
Surgery only		416	1.00 (Referent)
Right-sided radiotherapy		59	1.12 (0.85 to 1.48)
Left-sided radiotherapy		67	1.07 (0.82 to 1.38)
Left- vs right-sided radiotherapy		126	0.95 (0.67 to 1.36)
Hospital discharge diagnosis of ischemic heart disease‡	I20-25	253	
Surgery only		189	1.00 (Referent)
Right-sided radiotherapy		33	1.47 (1.01 to 2.13)
Left-sided radiotherapy		31	1.15 (0.78 to 1.68)
Left- vs right-sided radiotherapy		64	0.78 (0.48 to 1.27)
Hospital discharge diagnosis of acute myocardial infarction‡	I21	75	
Surgery only		62	1.00 (Referent)
Right-sided radiotherapy		8	1.13 (0.54 to 2.40)
Left-sided radiotherapy		5	0.59 (0.24 to 1.48)
Left- vs right-sided radiotherapy		13	0.52 (0.17 to 1.63)
Hospital discharge diagnosis of angina pectoris‡	I20	82	
Surgery only		55	1.00 (Referent)
Right-sided radiotherapy		16	2.53 (1.46 to 4.41)
Left-sided radiotherapy		11	1.43 (0.76 to 2.71)
Left- vs right-sided radiotherapy		27	0.57 (0.27 to 1.23)
Hospital discharge diagnosis of other heart disease†	I30-52	340	
Surgery only		266	1.00 (Referent)
Right-sided radiotherapy		31	0.89 (0.61 to 1.31)
Left-sided radiotherapy		43	1.05 (0.76 to 1.46)
Left- vs right-sided radiotherapy		74	1.19 (0.75 to 1.91)
Hospital discharge diagnosis of valvular dysfunction‡	I34-38	37	
Surgery only		29	1.00 (Referent)
Right-sided radiotherapy		3	0.83 (0.25 to 2.71)
Left-sided radiotherapy		5	1.18 (0.47 to 2.94)
Left- vs right-sided radiotherapy		8	1.51 (0.36 to 6.28)
Hospital discharge diagnosis of arrhythmia‡	I47-49	205	
Surgery only		157	1.00 (Referent)
Right-sided radiotherapy		20	0.91 (0.57 to 1.48)
Left-sided radiotherapy		28	1.09 (0.73 to 1.64)
Left- vs right-sided radiotherapy		48	1.20 (0.67 to 2.15)
Hospital discharge diagnosis of congestive heart failure‡	I50	107	
Surgery only		87	1.00 (Referent)
Right-sided radiotherapy		10	1.04 (0.53 to 2.03)
Left-sided radiotherapy		10	0.87 (0.45 to 1.67)
Left- vs right-sided radiotherapy		20	0.83 (0.34 to 2.03)
Cardiovascular surgical intervention§		164	
Surgery only		125	1.00 (Referent)
Right-sided radiotherapy		20	1.44 (0.89 to 2.36)
Left-sided radiotherapy		19	1.12 (0.69 to 1.82)
Left- vs right-sided radiotherapy		39	0.78 (0.41 to 1.46)

* With death treated as a competing risk. Adjusted for age at ductal carcinoma in situ (DCIS) diagnosis and year of DCIS diagnosis. Patients were censored at diagnosis of a second neoplasia treated with chemotherapy or radiotherapy above the diaphragm or date of emigration. Multiple cardiovascular events per person possible. CI = confidence interval; HR = hazard ratio; ICD-10 = International Classification of Diseases, 10th Revision.

† Cardiovascular death, hospital admission for cardiovascular disease, or surgical intervention for cardiovascular disease.

‡ Time at risk started at the first moment of becoming uniquely identifiable, with a minimum of 5 years after DCIS diagnosis.

§ Time at risk started 5 years after DCIS diagnosis.

Table 6. Risk of any cardiovascular event in subgroup analysis for all patients with ductal carcinoma in situ diagnosed between 1997 and 2005 taking into account history of cardiovascular disease*

Risk factor	No. of patients	No. of events	HR (95% CI)
1997–2005, total	6676	477	
Surgery only	4352	324	1.00 (Referent)
Right-sided radiotherapy	1061	71	1.02 (0.78 to 1.33)
Left-sided radiotherapy	1263	82	0.96 (0.75 to 1.23)
Left- vs right-sided radiotherapy	2324	153	0.94 (0.68 to 1.29)
1997–2005, without history of cardiovascular disease	6504	413	
Surgery only	4240	281	1.00 (Referent)
Right-sided radiotherapy	1034	61	1.02 (0.77 to 1.36)
Left-sided radiotherapy	1230	71	0.97 (0.74 to 1.26)
Left- vs right-sided radiotherapy	2264	132	0.94 (0.67 to 1.33)
1997–2005, with history of cardiovascular disease	172	64	
Surgery only	112	43	1.00 (Referent)
Right-sided radiotherapy	27	10	1.06 (0.53 to 2.13)
Left-sided radiotherapy	33	11	0.98 (0.51 to 1.91)
Left- vs right-sided radiotherapy	60	21	0.88 (0.37 to 2.06)

* Time at risk started at the first moment of becoming unique. Death was treated as a competing risk. Adjusted for age at ductal carcinoma in situ (DCIS) diagnosis, year of DCIS diagnosis, and history of hospital admission for cardiovascular disease. Patients were censored at diagnosis of a second neoplasia treated with chemotherapy or radiotherapy above the diaphragm or date of emigration. Cardiovascular events were defined as cardiovascular death, hospital admission for cardiovascular disease, or surgical intervention for cardiovascular disease. History of cardiovascular disease was defined as a hospital admission for cardiovascular disease before the DCIS diagnosis. CI = confidence interval; HR = hazard ratio.

DCIS, history of CVD incidence did not differ by laterality, and DCIS patients irradiated to the breast are not routinely screened for cardiac symptoms in routine clinical care.

A limitation of our study is that we missed less-severe cases of CVD that did not require hospitalization or cardiac intervention and did not lead to death. Furthermore, we were unable to perform linkage with the DHD for 9.7% of our cohort because these patients were not uniquely identifiable. There is, however, no reason to assume difference in CVD incidence between identified and nonidentified patients because no differences in patient characteristics or frequency of cardiovascular surgical interventions between the two groups were found.

Cardiovascular surgical interventions always include a hospital admission of at least 1 day. Therefore, in theory, all interventions provided by BHN should be present in the DHD database. Contrary to BHN, which is nearly complete since 2001, the completeness of the DHD has declined since 2003 from 99.4% to 87.3% in 2009. This decreased completeness is caused by a decline in participation in the DHD registry among hospitals. Yet, because hospital admissions for general CVDs are indiscriminately distributed among hospitals, the effect of the incompleteness for general CVDs is thought to be random. Only serious cardiovascular surgical interventions are limited to certain hospitals in the Netherlands. Such interventions are registered by BHN. Therefore, linkage with both population-based registries ensured a high coverage of CVD with only some random incompleteness of the less severe CVDs.

Because the DHD and the BHN registries were digitalized/initiated in 1995, CVD incidence before 1995 was unavailable for our cohort. Therefore, we included only 5-year survivors in our overall analyses. Because earlier research has frequently shown that radiotherapy-related CVD risk did not become clinically manifest until after 5 to 10 years (9,22–24), no effect of radiotherapy was expected in the first 5 years after irradiation. In our analyses in patients diagnosed in 1997 or later, we did not observe risk increases in the first 5 years after treatment.

Unfortunately, we did not have information on CVD risk factors. However, it is unlikely that any possible risk factor would differ by laterality.

Especially because radiation effects on CVD have a long induction period, it is unfortunate that the follow-up in our study was relatively short, with a median of 10 years in the total cohort and 8 years for patients treated with radiotherapy. Although restriction of the analyses to patients with a follow-up of 10 years or more did not change our results, power was limited in these analyses.

The results of our study are important for the debate with regard to screening for BC and the possibility of overtreating the increasing number of patients diagnosed with DCIS. Possible benefits and risks of BC screening and radiotherapy after breast-conserving surgery for DCIS should be weighed carefully. Importantly, radiotherapy after breast-conserving surgery for DCIS approximately halves the rate of ipsilateral breast events during the subsequent decade with little effect on contralateral or distant events (15). Although our results are reassuring, studies with longer follow-up after breast irradiation are needed before definitive conclusions regarding CVD risk can be drawn.

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