Risk of pacemaker or implantable cardioverter defibrillator after radiotherapy for early-stage breast cancer in Denmark, 1982-2005

Rehammar, Jens Christian; Johansen, Jens Brock; Jensen, Maj-Britt; Videbæk, Lars; Jørgensen, Ole Dan; Laugaard Lorenzen, Ebbe; Ewertz, Marianne

Published in:
Radiotherapy & Oncology

DOI:
10.1016/j.radonc.2016.08.024

Publication date:
2017

Document version
Final published version

Radiotherapy and Oncology 122 (2017) 60–65

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast radiotherapy

Risk of pacemaker or implantable cardioverter defibrillator after radiotherapy for early-stage breast cancer in Denmark, 1982–2005

Jens Christian Rehammar [a,b,*], Jens Brock Johansen [c,e], Maj-Britt Jensen [d], Lars Videbæk [c], Ole Dan Jørgensen [e,f], Ebbe Lorenzen [a,b], Marianne Ewertz [a,b]

[a] Department of Oncology, Odense University Hospital; [b] Institute of Clinical Research, University of Southern Denmark; [c] Department of Cardiology, Odense University Hospital; [d] Danish Breast Cancer Cooperative Group Secretariat, Copenhagen University Hospital, Rigshospitalet; [e] Danish Pacemaker and ICR Registry Secretariat; and [f] Department of Thoracic Surgery, Odense University Hospital, Denmark

ARTICLE INFO

Article history:
Received 1 May 2016
Received in revised form 2 July 2016
Accepted 29 August 2016
Available online 15 September 2016

Keywords:
Breast cancer
Radiotherapy
Heart disease
Arrhythmia
Cardiac conduction abnormality
Pacemaker

ABSTRACT

Background and purpose: To examine the risk of cardiac conduction abnormalities or severe ventricular arrhythmias requiring implantation of a cardiac implantable electronic device (CIED), either a pacemaker or an implantable cardioverter-defibrillator, subsequent to breast cancer (BC) radiotherapy (RT).
Material and methods: All women treated for early-stage BC in Denmark from 1982 to 2005 were identified from the Danish Breast Cancer Cooperative Group. By record linkage to the Danish Pacemaker and ICD Registry information was retrieved on CIED implants subsequent to RT. Standardized incidence ratios (SIR) of CIED implantation were estimated for women receiving RT and compared to women not receiving RT for BC. Uni- and multivariate Poisson regression models were used to estimate incidence rate ratios (IRR) among irradiated women compared to non-irradiated.
Results: Of 44,423 BC patients, 179 had a CIED implanted among 18,251 women who received RT, and 401 had a CIED in 26,172 who did not receive RT. The unadjusted IRR was 1.09 (0.91–1.30 95% CI) for CIED implants among women receiving RT compared to non-irradiated women and the IRR was 1.13 (0.93–1.38 95% CI) when adjustments were made.
Conclusions: BC RT as practiced in Denmark in 1982–2005 did not increase the risk of CIED implants. This indicates that RT for BC does not increase the risk of severe ventricular arrhythmias or cardiac conduction abnormalities.

Breast cancer (BC) after non-melanoma skin cancer is the most frequent malignant disease among women in Denmark as well as in the world [1]. Treatment modalities for early stage BC include surgery, radiotherapy (RT), and systemic medical treatment.

The benefits of postoperative RT in early stage BC have been documented in randomized clinical trials and include moderate reductions in BC mortality and substantial reductions in local recurrence, resulting in considerable improvements in BC survival [2–4].

However, one of the main concerns regarding RT is the radiation dose to the heart. Data from Denmark and Sweden suggest a linear relationship between an increasing risk of ischemic heart disease and an increasing dose to the heart [5]. Though doses to the heart have been reduced in modern RT regimens, the mean heart dose is around 3.3 Gy for right-sided and 5.4 Gy for left-sided BC but with a wide variation between regimens and countries [6].

The first report of electrocardiogram (ECG) changes after mediastinal radiation was published in 1925 [7]. Since then, ECG changes have been documented after mediastinal RT for Hodgkin's lymphoma (HL) [8–14]. Evidence is more sparse after RT for BC. A study of 69 Swedish BC patients comparing ECG before and after RT showed that there was a high incidence of T-wave changes 6 months after RT for left-sided BC but the ECG changes were reversible. The perimyocardial damage was functionally insignificant at long-term follow-up [15].

ECG changes constitute a quite heterogeneous pattern. They range from transient and harmless (single supra ventricular premature complexes, T-wave inversion) without a need for treatment, to severe and life-threatening (high degree AV-block, sinus node dysfunction and ventricular tachyarrhythmias) with an indication for either a pacemaker or an implantable cardioverter defibrillator [16]. The aim of this study was to examine if BC RT was associated with a risk of so severe arrhythmias and conduction abnormalities that implantation of a cardiovascular implantable electronic device (CIED), was needed.

* Corresponding author at: Sdr. Boulevard 29, 5000 Odense C, Denmark.
E-mail address: christian@rehammar.se (J.C. Rehammar).

http://dx.doi.org/10.1016/j.radonc.2016.08.024
0167-8140/

Methods

Study design and subject selection

This is a register based cohort study. Data were ascertained through three Danish national registries; The Danish Breast Cancer Cooperative Group Registry (DBCG), The Danish Pacemaker and ICD Registry (DPIR), and the Danish National Patient Register (LPR).

DBCG has registered all women with primary, early-stage BC in Denmark since 1977. More than 80,000 women are registered and the registry has been validated to have close to complete ascertainment [17]. The DBCG registry includes individual patient information on demographic and histopathological variables, treatment modalities (surgery, medical treatment and RT) and follow-up for recurrence and death. All Danish hospitals involved in diagnosis and treatment of BC patients (breast surgeons, pathologists and oncologists) are reporting to this registry.

We identified 64,071 women diagnosed with histologically verified, early-stage (stage I-IIIC/non-metastatic) BC in Denmark from 1st January 1982 to 31st December 2005 and without prior malignancies (Fig. 1). A total of 2099 women were excluded since they only had a breast biopsy, 1311 patients because of bilateral BC, 2024 women due to unknown BC laterality, 2768 patients because of old age (more than 80 years at the time of the diagnosis) and 322 with a follow-up of less than 6 months. Additionally, 8492 patients were excluded due to lack of valid information on RT. Patients were selected for RT according to the guidelines from the DBCG [18]. RT was not recommended as a standard treatment for patients over the age of 70 years after a mastectomy but for all patients after breast conserving surgery. From 1982 to 1989, there were three regimens after mastectomy, 50 Gy in 25 fractions over 5 weeks, 48 Gy in 24 fractions over 5 weeks, and 36 Gy in 20 fractions over 4 weeks, the latter with orthovoltage. After breast conserving surgery 50 Gy was given in 25 fractions over 5 weeks some with an additional boost of 10–24 Gy. From 1989 to 2005 after breast conserving surgery, all patients were given 48 Gy in 24 fractions over 4.5 weeks with boost doses of 10–16 Gy in 5–8 fractions to the tumor bed. Endocrine therapy included tamoxifen only, initially for 1–2 years, later for 5 years, from 1977 to 2007 [17].

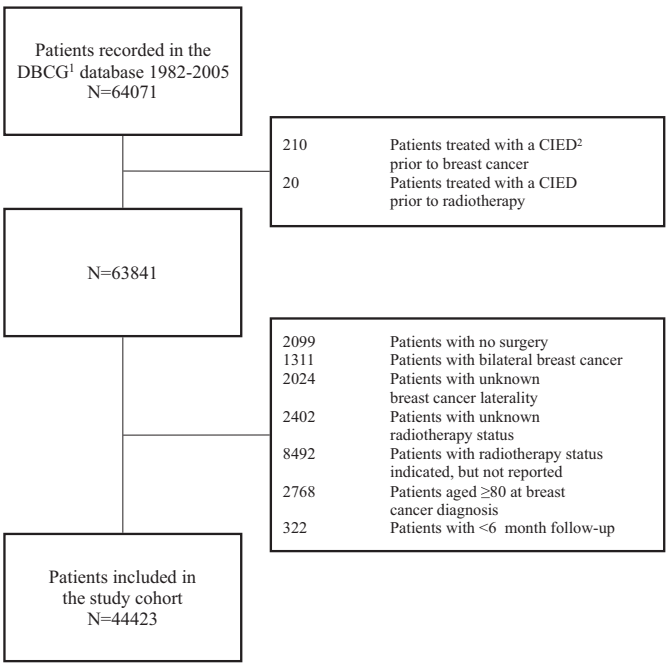

Fig. 1. Inclusion and exclusion flowchart. [1]The Danish Breast Cancer Cooperative Group. [2]Cardiovascular Implantable Electronic Device.

DPIR started in 1982 and has registered all CIEDs including permanent pacemakers (PMs), implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy devices with defibrillators (CRT-Ds) or without (CRT-Ps). More than 30,000 Danish women are registered in the DPIR, which includes individual patient information of new implants, re-implants, indication for the implant, and clinical symptoms of the patient [19].

The Danish personal identification number enabled a linkage between DBCG and DPIR. Hereby, information on CIED among women treated with radiation for BC were retrieved [20]. We identified 210 patients with a CIED implanted prior to the BC diagnosis and 20 patients who had a CIED implanted within 6 months post diagnosis. These were excluded.

LPR was established in 1977, and the register has been expanded over the years, from originally covering only somatic inpatients to covering somatic as well as psychiatric in- and outpatients in all hospitals in Denmark today. The registry has been maintained by a public enterprise under the Danish Ministry of Health [21]. Information about prior cardiac disease was identified from the LPR and was defined as having any of the following ICD-codes at least 30 days before the BC diagnosis; conduction abnormality/arrhythmia, ICD8 427.90–427.98/ICD10 I44, 45, I47-49, other cardiac diseases, ICD8 390.00–429.99/ICD10 I00-I52 (ICD-codes for conduction abnormality/arrhythmia not included).

The Danish Health and Medicines Authority and the Danish Data Protection Agency approved the study.

Statistical methods

Differences in patient characteristics between BC patients who had received RT and BC patients who had not received RT were tested using the χ^2-test. Level of significance was set to 5%. Crude standardized incidence ratios (SIR) were estimated for CIED implants as the observed numbers of CIED implants divided by the expected number of CIED implants. The expected number of implants was estimated from accumulated person-year at risk and CIED implant rates of the general Danish female population in five-year calendar-time and age groups. Ninety-five percent confidence intervals (CI) were formed assuming the expected numbers to be Poisson-distributed. Time at risk started 6 months after BC diagnosis, to avoid inclusion of CIED implants during RT for arrhythmias and conduction abnormalities prevalent prior to RT. Time at risk ended at death, emigration, CIED implant or at last date of follow-up (1st July 2014), whichever occurred first. Poisson regression models were applied to assess the incidence rate ratio (IRR) and standard likelihood ratio tests comparing Poisson's regression models were used to test for heterogeneity across subgroups. Univariate analysis of the parameters included follow-up time. The multivariate model further included RT, calendar year of diagnosis, age at diagnosis, time since diagnosis, axillary lymph nodal status, estrogen receptor status, laterality of BC, adjuvant medical treatment and prior cardiac disease.

The calendar years of BC diagnosis were divided into three groups according to different treatment strategies. The first group covers the period 1982–1989, when anthracyclines were not used in standard chemotherapy. The second group covers the period 1990–2002. As anthracyclines were used in a trial study by the end of 1989, and became standard as of 1999 onward. The third group covers the period 2003–2005, when it was decided that the internal mammary nodes should be irradiated only for women with right-sided BC, in order to reduce the radiation dose to the heart for left-sided BC.

Analyses were made with STATA 14 [22].

Results

After the exclusions the final study population included 44,423 patients with early-stage BC (Fig. 1). The median age at BC diagnosis was 57 years (range 21–79). Median follow-up time was 11.7 years (interquartile range, 6.1–16.3) with 30% having more than 15 years of follow-up. Table 1 shows that the use of RT increased with calendar time from 26% of patients diagnosed in 1982–1989 to 74% of patients diagnosed in 2003–2005 ($p < 0.01$). RT was more frequent in younger patients, among axillary lymph node positive patients and among patients receiving chemotherapy with anthracyclines ($p < 0.01$ for all). Chemotherapy with anthracyclines was used in 20% of patients receiving RT compared to 4% in non-irradiated patients. Prior cardiac disease was equally present in patients with and without RT (7% and 8%, respectively).

Among the 18,251 women receiving RT, 179 (1.0%) had a CIED implanted subsequent to RT compared to 401 (1.5%) among the 26,172 women who did not receive RT (Table 1). Table 2 shows the distribution of the 580 implanted CIEDs distributed according to indication. The majority (91%) of the CIEDs was PMs. The indications, irrespective of device, were sinus node dysfunction (N = 266, 46%), AV block (N = 206, 36%), and ventricular tachyarrhythmias (N = 30, 5%). Fig. 2 illustrates the location of the sinoatrial (SA) and atrioventricular (AV) nodes in relation to tangential RT for a left-sided BC.

The study cohort accrued close to half a million person-years (521,574) in whom 573.2 CIED were expected compared with 580 observed, yielding a crude SIR of 1.01 (95% CI 0.93–1.10) (Table 3). In the univariate analysis, there was a statistically significant increase in CIED implants with an increase in years since BC diagnosis ($p = 0.02$) and a presence of prior cardiac disease ($p < 0.01$), and also a statistically significant decrease in CIED implants among estrogen receptor negative patients ($p = 0.02$). The multivariate analysis did not reveal statistically significant associations with RT. There was a reduced risk of CIED implants among patients with negative axillary lymph mode status ($p = 0.01$) and negative estrogen receptor status ($p < 0.01$). Notably, chemotherapy with anthracyclines did not increase the risk of having a CIED. In the multivariate model, there were no statistically significant interactions between RT and; time since diagnosis, age at BC diagnosis, axillary lymph node status, laterality of BC or prior cardiac disease.

Among 18,251 women treated with radiation, 9282 had left-sided and 8969 right-sided BC. IRR for implants of CIED

Table 1
Characteristics of the 44,423 women in the study population by radiotherapy status and number of Cardiovascular Implantable Electronic Devices.

	Numbers of patients			Numbers of CIED[a]		
	RT (%)[b]	No RT(%)[b]	Total	RT (%)[c]	No RT (%)[d]	Total
Year of breast cancer diagnosis						
1982–1989	2520 (26)	7330 (74)	9850	33 (1.3)	138 (1.9)	171
1990–2002	10,229 (38)	16,864 (62)	27,093	115 (1.1)	249 (1.5)	364
2003–2005	5502 (74)	1978 (26)	7480	31 (0.6)	14 (0.7)	45
Age at breast cancer diagnosis (yrs)						
<50	6406 (52)	5887 (48)	12,293	21 (0.3)	37 (0.6)	58
50–59	5980 (45)	7231 (55)	13,211	59 (1.0)	74 (1.0)	133
60–69	4709 (38)	7832 (62)	12,541	70 (1.5)	171 (2.2)	241
70–79	1156 (18)	5222 (82)	6378	29 (2.5)	119 (2.3)	148
Axillary lymph node status						
Positive	11194 (57)	8606 (43)	19800	100 (0.9)	106 (1.2)	206
Negative	7002 (29)	17046 (71)	24048	78 (1.1)	284 (1.7)	362
Unknown	55 (10)	520 (90)	575	1 (1.8)	11 (2.1)	12
Estrogen receptor status						
Positive (⩾10%)	12674 (45)	15277 (55)	27951	129 (1.0)	248 (1.6)	377
Negative (0–9%)	3656 (42)	5007 (58)	8663	19 (0.5)	43 (0.9)	62
Unknown	1921 (25)	5888 (75)	7809	31 (1.6)	110 (1.9)	141
Laterality of breast cancer						
Left	9282 (41)	13485 (59)	22767	90 (1.0)	211 (1.6)	301
Right	8969 (41)	12687 (59)	21656	89 (1.0)	190 (1.5)	279
Adjuvant medical treatment						
Anthracyclines	3564 (76)	1132 (24)	4696	14 (0.4)	0 (0.0)	14
Other chemotherapy	3191 (49)	3369 (51)	6560	16 (0.5)	27 (0.8)	43
Endocrine therapy[e] (alone)	5877 (53)	5280 (47)	11,157	76 (1.3)	77 (1.5)	153
None	4639 (28)	12220 (72)	16859	65 (1.4)	231 (1.9)	296
Unknown/indicated but not reported	980 (19)	4171 (81)	5151	8 (0.8)	66 (1.6)	74
Prior cardiac disease[f]						
Conduction disorders & arrhythmias[g]	341 (37)	571 (63)	912	13 (3.8)	30 (5.3)	43
Other cardiac diseases[h]	932 (36)	1653 (64)	2585	20 (2.1)	49 (3.0)	69
No/Unknown	16,978 (41)	23,948 (59)	40,926	146 (0.9)	322 (1.3)	468
All women	18,251 (41)	26,172 (59)	44,423	179 (1.0)	401 (1.5)	580

[a] Cardiovascular implantable electronic device.
[b] Row percentages.
[c] Percentages of implants among irradiated women.
[d] Percentages of implants among non-irradiated women.
[e] Endocrine therapy included tamoxifen only, initially for 1–2 years, later for 5 years, from 1977 to 2007. Since 2007 aromatase inhibitors for 5 years were recommended to postmenopausal women while premenopausal women continued to receive tamoxifen for 5 years [17].
[f] Defined as having any of the following ICD-codes at least 30 days before cancer diagnosis.
[g] ICD10 I44 (atrioventricular block & left bundle-branch block), I45 (right bundle-branch block, sinus arrest, conduction disorder unspecified), I47–49 (supra ventricular & ventricular tachycardia, atrial fibrillation/flutter, ventricular fibrillation/flutter, sick sinus syndrome) & ICD8 427.90–427.98 (corresponding to ICD10-codes).
[h] ICD10 I00-I52 (acute rheumatic fever, chronic rheumatic heart diseases, hypertensive diseases, ischemic heart diseases, pulmonary heart disease and diseases of pulmonary circulation, other forms of heart disease) & ICD8 390.00–429.99 (corresponding to ICD10-codes) (ICD-codes for conduction abnormality/arrhythmia not included).

Table 2
Overview of implanted devices by indication by type of implant among 44,423 women with breast cancer, diagnosed in 1982–2005.

Implantation indication	CRT[a]	ICD[b]	PM[c]	Total
Sinus node dysfunction				
Sinus node dysfunction with pause	1		117	118
Sinus node dysfunction without pause			24	24
Sinus node dysfunction unspecified			27	27
Bradycardia – Tachycardia syndrome			97	97
Atrioventricular block				
AV block – 1°			1	1
AV block – 2° type I			8	8
AV block – 2° type II			27	27
AV block – 2:1			6	6
AV block – 3°	1		129	130
AV conduction impaired – status unknown			4	4
Left bundle branch block	11		3	14
Right bundle branch block			2	2
Bundle branch block, unspecified	1		6	7
Chronic atrial fibrillation & AV block	1		6	7
Tachyarrhythmia				
Ventricular Fibrillation	1	10		11
VT – monomorphic Non-sustained	1	6		7
Wide complex tachycardia unspecified		1		1
Syncope with inducible VT or VF	1			1
Prophylactic (none documented)	5	5		10
Others				
Chronic atrial fibrillation & bradycardia			59	59
Polymorphic VT/Torsades des pointes			1	1
Arrhythmia not documented	2		5	7
Unknown	2	1	8	11
Any	27	23	530	580

[a] Cardiac Resynchronization Therapy.
[b] Implantable Cardioverter Defibrillator.
[c] Pacemaker.

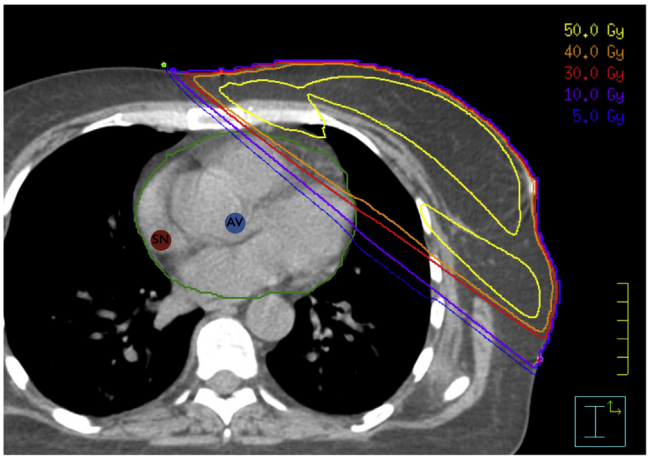

Fig. 2. Left-sided breast cancer radiotherapy CT-plan. Illustration of the dose distribution form left-sided tangential radiotherapy. The mean heart dose is 8.4 Gy. SN: Sinoatrial node. AV: Atrioventricular node.

comparing left- with right-sided RT was 0.96 (95% CI 0.72–1.29, $p = 0.78$), and this estimate remained virtually the same (0.97, 95% CI 0.72–1.30, $p = 0.84$) after adjustment for calendar year of diagnosis, age at diagnosis, time since diagnosis, axillary lymph node status, estrogen receptor status, adjuvant medical treatment and prior cardiac disease.

Discussion

Based on more than 40,000 patients with early-stage BC followed for up to 32 years, this nationwide registry-based cohort study failed to detect a statistically significant association between incidence of implantation of a CIED and RT. This suggests that BC RT does not seem to increase the risk of so severe cardiac arrhythmias or conductions abnormalities that implantation of a CIED is needed.

Our results may appear to be at variance with those of another Danish study of 5731 one-year survivors of BC in adolescence and adulthood reporting an increased risk of hospitalization for conduction disorders (ICD-codes I44-I45) (RR = 1.17, 95% CI 0.79–1.73) and disturbances of heart rhythm (ICD-codes I47-I49) (RR = 1.26, 95% CI 1.09–1.45) [23]. However, the patients in that study were less than 40 years old at diagnosis compared with our mean age of 57 years, no information was available on RT, and the arrhythmias may not have been so severe as to indicate a CIED. Other studies of BC are based on a much smaller number of patients, 69 in the study of Strender et al. [15] and two in a case report from 1977 [24].

Most studies observing arrhythmias and conduction abnormalities after RT are based on HL patients treated with mantle field irradiation [10–13], with typical mean heart doses around 20 Gy [25]. All RT given to patients aged less than 70 years at BC diagnosis, has followed the DBCG guidelines of that particular time period. The heart doses from these techniques have been estimated previously to be lower with mean heart doses around 1–5 Gy for right-sided and 1–10 Gy for left-sided RT respectively [26–28]. Moreover, the SA and the AV nodes are located relatively far from the radiation field for BC as illustrated in Fig. 2, while the mantle field may cover the entire mediastinum. It is also difficult to compare patients with BC and HL due to the different age distributions with a median age at diagnosis for HL being 38 years of age compared with 61 years of age for BC (valid in 2012)[29].

Comparing left- versus right-sided RT can be used when mean heart dose is considered the exposure variable of interest [26]. However, most PMs are implanted due to dysfunction of the SA

Table 3
Observed and expected numbers of CIED with corresponding univariate (crude) and multivariate standardized incidence ratios (SIR) among breast cancer patients in Denmark diagnosed in 1982–2005.

	Numbers of CIED[a]				Univariate[b]			Multivariate[c]		
	Observed	Expected	SIR[d]	95% CI	IRR[e]	95% CI	*p*	IRR	95% CI	*p*
All	580	573.2	1.01	(0.93–1.10)						
Radiotherapy							0.37			0.22
Yes	179	170.4	1.05	(0.91–1.22)	1.09	(0.91-1.30)		1.13	(0.93–1.38)	
No	401	402.7	1.00	(0.90–1.10)	1			1		
Years since breast cancer diagnosis[f]							0.02			0.06
0–4	105	118.9	0.88	(0.73–1.07)	1			1		
5–9	143	161.7	0.88	(0.75–1.04)	1.00	(0.78–1.29)		1.02	(0.79-1.31)	
10–14	158	133.6	1.18	(1.01–1.38)	1.34	(1.05–1.71)		1.28	(0.98–1.66)	
15–19	99	88.2	1.12	(0.92–1.37)	1.27	(0.97–1.67)		1.15	(0.85–1.56)	
20–24	60	49.9	1.20	(0.93–1.55)	1.36	(0.99–1.87)		1.09	(0.76–1.58)	
25+	15	20.9	0.72	(0.43–1.19)	0.81	(0.47–1.40)		0.61	(0.34–1.10)	
Age at breast cancer diagnosis (yrs)							0.75			0.78
<50	58	52.4	1.11	(0.86–1.43)		1		1		
50–59	133	126.4	1.05	(0.89–1.25)	0.94	(0.69–1.29)		0.94	(0.68–1.30)	
60–69	241	230.0	1.05	(0.92–1.19)	0.95	(0.70–1.28)		0.89	(0.65–1.22)	
70–79	148	164.4	0.90	(0.77–1.06)	0.86	(0.62–1.19)		0.83	(0.57–1.21)	
Axillary lymph node status							0.29			0.01
Node positive	206	190.6	1.08	(0.94–1.24)	1			1		
Node negative	362	372.2	0.97	(0.88–1.08)	0.88	(0.74–1.05)	0.69	(0.53–0.90)		
Unknown	12	10.3	1.16	(0.66–2.05)	1.13	(0.63–2.03)	1.13	(0.61–2.12)		
Estrogen receptor status							<0.01			0.04
Positive (⩾10%)	377	374.5	1.01	(0.91–1.11)		1		1		
Negative (0–9%)	62	83.4	0.74	(0.59–0.95)	0.73	(0.56–0.96)		0.73	(0.55–0.97)	
Unknown	141	115.3	1.22	(1.04–1.44)	1.19	(0.97–1.46)		1.07	(0.86–1.34)	
Laterality of breast cancer							0.92			0.96
Left	301	298.6	1.01	(0.90–1.13)	1			1		
Right	279	274.6	1.02	(0.90–1.14)	1.01	(0.86–1.19)		1.00	(0.85–1.18)	
Adjuvant medical treatment							0.78			0.11
Anthracyclines	14	16.2	0.86	(0.51–1.46)	0.84	(0.49–1.45)		0.83	(0.46–1.51)	
Other chemotherapy	43	44.6	0.96	(0.71–1.30)	0.89	(0.65–1.23)		0.68	(0.46–1.00)	
Endocrine therapy (alone)	153	155.6	0.98	(0.84–1.15)	0.94	(0.77–1.16)		0.71	(0.53-0.95)	
None	296	272.5	1.09	(0.97–1.21)		1		1		
Unknown/Indicated. but not reported	74	84.2	0.88	(0.70–1.10)	0.86	(0.66–1.12)		0.74	(0.53–1.02)	
Prior cardiac disease[g]							<0.01			<0.01
Conduction disorders & arrhythmias[h]	43	12.5	3.43	(2.54–4.63)	4.27	(3.11–5.86)		4.85	(3.51–6.68)	
Other cardiac diseases[i]	69	37.2	1.86	(1.47–2.35)	2.27	(1.76–2.94)		2.51	(1.94–3.26)	
No/Unknown	468	523.5	0.89	(0.82–0.99)		1		1		

[a] Cardiovascular Implantable Electronic Devices.
[b] Adjusted for time at risk (started 6 month after breast cancer diagnosis).
[c] Adjusted for year of breast cancer diagnosis, time at risk (started 6 month after breast cancer diagnosis), age at breast cancer diagnosis, axillary lymph node status, estrogen receptor status, laterality of breast cancer, adjuvant medical treatment and prior cardiac disease.
[d] Standardize incidence ratio.
[e] Incidence rate ratio.
[f] Time at risk started 6 month after breast cancer diagnosis.
[g] Defined as having any of the following ICD-codes at least 30 days before cancer diagnosis.
[h] ICD10 I44, I45, I47–49 & ICD8 427.90–427.98.
[i] ICD10 I00-I52 & ICD8 390.00–429.99 (ICD-codes for conduction abnormality/arrhythmia not included).

node and/or the AV node which are located in the right side of the heart, and more or less placed in the midline of the mediastinum. It was therefore not surprising that a risk estimate close to unity was obtained comparing left- with right-sided RT in this study.

Larsen et al. [30] investigated ECG changes and arrhythmias after cancer therapy in children and young adults. They included 134 patients with different types of malignancies (non-breast cancer) treated with RT. The authors found an increase in ventricular and supra-ventricular premature complexes. These were transient, and not found at later follow-ups. The authors, however, furthermore found an increase in prolonged QT interval among young patients who received anthracyclines, RT or both. This prolonged QT interval was not transient and could increase the risk of severe conditions (ventricular tachycardia, Torsades des pointes ventricular tachycardia) even for normally quite harmless ventricular premature complexes. It has been suggested that radiation induced fibrosis in the heart is associated with increases in ventricular ectopic activity [12]. In healthy hearts, ectopic activity occurrence is usually associated with no clinical significance, but can be a life threatening condition, if the patient is known to have other cardiac diseases [31]. Among patients at high-risk for ventricular tachycardia, this is an indication for implantation of an ICD.

We found an increased risk of CIED among patients with cardiac disease prior to BC. This was expected, as preexisting cardiac disease is a strong risk factor for having another (more severe) cardiac disease, as well as developing cardiac conduction abnormalities, i.e. the reason for having a CIED implant. Previous studies have shown that RT increases the risk of ischemic heart disease[5], possibly by acceleration of coronary arteriosclerosis [32,33]. However, it was surprising that the multivariate analysis showed a significant association between CIED implantation and axillary lymph nodal status and estrogen receptor status. We have no obvious explanation for this finding other than possibly residual confounding by factors which were not included in the present analysis.

A strength of the present study is that it is based on an entire population of women treated for BC in Denmark between 1982 and 2005. Follow-up was complete through register-data provided by the DBCG and the DPIR. All patients had valid information on RT

since patients with unknown RT status were excluded. In this study we used information from the general female population on rates of CIED implants. This information was ascertained independently of RT status, and only first-time implants were included.

However, there are limitations too. In some situations, comparisons of BC patients who received RT with BC patients who did not can be biased, because BC patients selected for RT may have a lower baseline risk of cardiovascular disease than BC patients who did not receive RT [34]. Our study population may have had a lower baseline risk for cardiac disease compared to the background population due to higher socioeconomic status, resulting in a selection bias [35,36]. This could mask a real increased risk for CIED implants after RT, i.e. our estimates could be underestimated. In addition, we do not have any information on known risk factors for the development of heart disease, such as smoking status, diabetes, obesity or cholesterol status.

There is a possibility of surveillance bias when SIRs are used, since BC patients are followed more closely in the healthcare system compared to the general population. However, if a patient suffers from cardiac disease which indicates a CIED, anyone in the general population would have been identified, especially as the healthcare services in Denmark are free of charge. Finally, we excluded about 31% (10,894 women) of potentially eligible patients with no certain information on RT status in the DBCG database. Unfortunately, this was the price for obtaining a high degree of certainty in the estimates of the effect of RT.

Conclusion

Adjuvant RT as practiced in Denmark for early stage BC did not increase the risk of so severe ventricular arrhythmias or cardiac conduction abnormalities in the heart that CIEDs were needed. This is reassuring for women receiving RT for BC.

Conflict of interest statement

None of the authors disclose any financial or personal relationships with other persons or organizations that could inappropriately influence their work.

Acknowledgement

We thank The Danish Breast Cooperative Cancer Group and The Danish Pacemaker and ICD Registry for providing data. Financial support for this study was provided by the Clinical Trial Service Unit and Epidemiological Studies Unit, Oxford, England.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–386.
[2] Clarke M, Collins R, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087–106.
[3] Darby S, McGale P, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707–16.
[4] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35.
[5] Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987–98.
[6] Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses published during 2003 to 2013. Int J Radiat Oncol Biol Phys 2015;93(845–853):b0035.
[7] Emery ESJ, Gordon B. The effect of roentgenotherapy on the human heart. Am J Med Sci 1925;170:884–7.
[8] Cohen SI, Bharati S, Glass J, Lev M. Radiotherapy as a cause of complete atrioventricular block in hodgkin's disease: an electrophysiological-pathological correlation. Arch Intern Med 1981;141:676–9.
[9] Kereiakes DJ, Morady F, Ports TA. High-degree atrioventricular block after radiation therapy. AJC 1983;51:1233–4.
[10] Pohjola-Sintonen S, Tötterman KJ, Salmo M, Siltanen P. Late cardiac effects of mediastinal radiotherapy in patients with Hodgkin's disease. Cancer 1987;60:31–7.
[11] Pohjola-Sintonen S, Tötterman KJ, Kupari M. Sick sinus syndrome as a complication of mediastinal radiation therapy. Cancer 1990;65:2494–6.
[12] Slama MS, Le Guludec D, Sebag C, et al. Complete atrioventricular block following mediastinal irradiation: a report of six cases. PACE 1991;14:1112–8.
[13] Orzan F, Brusca A, Gaita F, Giustetto C, Figliomeni MC, Libero L. Associated cardiac lesions in patients with radiation-induced complete heart block. Int J Cardiol 1993;39:151–6.
[14] Galper SL, Yu JB, Mauch PM, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. Blood 2011;117:412–8.
[15] Strender LE, Lindahl J, Larsson LE. Incidence of heart disease and functional significance of changes in the electrocardiogram 10 years after radiotherapy for breast cancer. Cancer 1986;57:929–34.
[16] Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2013;34:2281–329.
[17] Möller S, Jensen MB, Ejlertsen B, et al. The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. Acta Oncol 2008;47:506–24.
[18] Overgaard M, Juul Christensen J. Postoperative radiotherapy in DBCG during 30 years. Techniques, indications and clinical radiobiological experience. Acta Oncol 2008;47:639–53.
[19] Johansen JB, Jörgensen OD, Möller M, et al. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011;32:991–8.
[20] Pedersen CB. The Danish civil registration system. Scand J Public Health 2011;39:22–5.
[21] Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39:30–3.
[22] Release 14 College Station S TX: StataCorp LP. Stata Statistical Software; 2015.
[23] Rugbjerg K, Mellemkjaer L, Boice JD, Köber L, Ewertz M, Olsen JH. Cardiovascular disease in survivors of adolescent and young adult cancer: a danish cohort study, 1943–2009. J Natl Cancer Inst 2014;106(dju110):b0120.
[24] Tzivoni D, Ratzkowski E, Biran S, Brook JG, Stern S. Complete heart block following therapeutic irradiation of the left side of the chest. Chest. 1977;71:231–4.
[25] Nimwegen FAV, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2016;34:235–43.
[26] Taylor CW, Brönnum D, Darby SC, et al. Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977–2001. Radiother Oncol. 2011;100:176–83.
[27] Thorsen LBJ, Thomsen MS, Overgaard M, Overgaard J, Offersen BV. Quality assurance of conventional non-CT-based internal mammary lymph node irradiation in a prospective Danish Breast Cancer Cooperative Group trial: The DBCG-IMN study. Acta Oncol 2013;52:1526–34.
[28] Lorenzen EL, Brink C, Taylor CW, Darby SC, Ewertz M. Uncertainties in estimating heart doses from 2D-tangential breast cancer radiotherapy. Radiother Oncol 2016;119:71–6.
[29] Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2013, National Cancer Institute. Bethesda, MD, based on November 2015 SEER data submission, posted to the SEER web site; 2016. Available from: http://seer.cancer.gov/csr/19752013/.
[30] Larsen RL, Jakacki RI, Vetter VL, Meadows AT, Silber JH, Barber G. Electrocardiographic changes and arrhythmias after cancer therapy in children and young adults. AJC 1992;70:73–7.
[31] Ng GA. Treating patients with ventricular ectopic beats. Heart 2006;92:1707–12.
[32] Cohn KE, Stewart JR, Fajardo LF, Hancock EW. Heart disease following radiation. Medicine 1967;46:281–98.
[33] Gottdiener JS, Katin MJ, Borer JS, Bacharach SL, Green MV. Late cardiac effects of therapeutic mediastinal irradiation. N Engl J Med 1983;308:569–72.
[34] Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005;6:557–65.
[35] Heck KE, Pamuk ER. Explaining the relation between education and postmenopausal breast cancer. Am J Epidemiol 1997;145:366–72.
[36] Luepker RV, Rosamond WD, Murphy R, et al. Socioeconomic status and coronary heart disease risk factor trends. The Minnesota Heart Survey. Circulation 1993;88:2172–9.