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Long-Term Cardiovascular Risk After Radiotherapy in Women With Breast Cancer

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***Background*—**Radiotherapy for breast cancer often involves some incidental exposure of the heart to ionizing radiation. The effect of this exposure on the subsequent risk of heart disease is uncertain. We performed a meta-analysis to investigate the link between radiotherapy and long-term cardiovascular morbidity and mortality in patients with breast cancer.

***Methods and Results*—**We performed a literature search using MEDLINE (January 1966 to January 2015) and EMBASE (January 1980 to January 2015) with no restrictions. Studies that reported relative risk (RR) estimates with 95%CIs for the associations of interest were included. Pooled effect estimates were obtained by using random-effects meta-analysis. Thirty-nine studies involving 1 191 371 participants were identified. Patients who received left-sided radiotherapy, as compared with those receiving right-sided radiotherapy, experienced increased risks of developing coronary heart disease (RR 1.29, 95%CI 1.13-1.48), cardiac death (RR 1.22, 95%CI 1.08-1.37) and death from any cause (RR 1.05, 95%CI 1.01-1.10). In a comparison of patients with radiotherapy and without radiotherapy, the RRs were 1.30 (95%CI 1.13-1.49) for coronary heart disease and 1.38 (95%CI 1.18-1.62) for cardiac mortality. Radiotherapy for breast cancer was associated with an absolute risk increase of 76.4 (95%CI 36.8-130.5) cases of coronary heart disease and 125.5 (95%CI 98.8-157.9) cases of cardiac death per 100 000 person-years. The risk started to increase within the first decade for coronary heart disease and from the second decade for cardiac mortality.

***Conclusions*—**Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent risk of coronary heart disease and cardiac mortality. **(*J Am Heart Assoc*. 2017;6:e005633. DOI: 10.1161/JAHA.117.005633.)**

Key Words: cardiotoxicity • cardiovascular complications • cardiovascular disease • cardiovascular disease prevention • cardiovascular disease risk factors

Breast cancer is the most common cancer in women, with over a million new cases diagnosed each year worldwide. During the past 30 years, prognosis of breast cancer patients has improved substantially, with 5-year survival now around 90% in many countries, due partly to earlier diagnosis and greater use of adjuvant therapies.[1] Although radiotherapy for early breast cancer can reduce the risk of death from the disease several years later, it usually involves some irradiation of the heart, and therefore, much uncertainty still remains regarding the long-term cardiac effect from breast cancer radiotherapy.[2]

The US SEER (Surveillance Epidemiology and End Results) cancer registries have reported increased risk of cardiovascular death after radiotherapy for breast cancer during the first 2 decades.[3] A population-based case-control study by Darby et al suggested that exposure of the heart to ionizing radiation during breast cancer radiotherapy increased the subsequent rate of ischemic heart disease in a dose-response relationship.[4] In contrast, a population-based cohort study by Boekel et al did not find an increased risk of cardiovascular disease after radiotherapy for ductal carcinoma in situ.[5] The discordant findings may be explained, in part, by differences in the duration of follow-up, disease outcomes (eg, coronary heart disease or cardiac death), radiation schemes (eg, older or modern radiotherapy techniques), and radiotherapy fields.

If the relationship between cardiac radiation exposure and the long-term risk of heart disease were known, then physicians should weigh the likely long-term benefit of radiotherapy on the breast cancer and the likely long-term

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Accompanying Tables S1 through S4 and Figures S1 through S7 are available at http://jaha.ahajournals.org/content/6/5/e005633/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- The association between radiotherapy for breast cancer and long-term cardiovascular risk remains unclear.
- The meta-analysis found that, in women diagnosed with breast cancer, risks of coronary heart disease and cardiac mortality were increased in patients with left-sided radiotherapy compared with those with right-sided radiotherapy, as well as in the comparison of patients with radiotherapy and those without radiotherapy.

What Are the Clinical Implications?

- The meta-analysis found that, in women diagnosed with breast cancer, radiotherapy increased the risks of coronary heart disease and cardiac mortality.
- Contemporary radiotherapy techniques have likely reduced the risk, but they may not have eliminated cardiotoxicity, and therefore the long-term hazards in the general population still need to be monitored directly.
- The association between radiotherapy and cardiovascular risk has clinical relevance with respect to individual screening, risk factor modification, and the primary and secondary prevention of heart disease.

risk of radiation-induced heart disease and tailor the treatment accordingly. Therefore, we conducted a meta-analysis with the following aims: (1) to investigate cardiovascular risk in breast cancer patients with left-sided irradiation or with right-sided irradiation; (2) to investigate cardiovascular risk in breast cancer patients with or without radiotherapy; (3) to measure the relationship between breast cancer radiotherapy and cardiovascular risk according to different characteristics of the study populations, study designs, follow-up duration, and treatment eras; and (4) to estimate absolute risk of cardiovascular disease associated with breast cancer radiotherapy in the studies included in the meta-analysis.

Methods

Search Strategy

We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses.[6] We searched the publications listed in the electronic databases MEDLINE (source PubMed, January 1, 1966 to January 31, 2014) and EMBASE (January 1, 1980 to January 31, 2014) using the following text and key words in combination both as MeSH terms and text word "radiotherapy OR irradiation OR radiation" AND "breast cancer OR breast tumor" AND "cardiac OR cardiovascular OR heart OR coronary OR toxicity OR morbidity OR mortality OR death." We searched articles published in any language and scrutinized references from these studies to identify other relevant studies. Ethical approval was not needed.

Outcomes

The primary study end points were coronary heart disease (defined as diagnosis of ischemic heart disease, acute coronary syndrome, acute myocardial infarction, or death from ischemic heart disease) and cardiac mortality identified using the death registry or validated with medical records. In addition, we included an analysis of death from any cause to examine whether the risk for cardiac death would offset the survival benefit by radiotherapy. We also analyzed the end point of heart failure, arrhythmia, and valvular heart disease that may be associated with cardiovascular toxicity by radiotherapy.

Study Selection

To minimize differences between studies, we imposed the following methodological restrictions for the inclusion criteria. (1) We used studies that contained the minimum information necessary to estimate the relative risk (RR) associated with radiotherapy and a corresponding measure of uncertainty (ie, 95%CI, standard error, variance, or *P* value of the significance of the estimate). (2) We included cohort studies, case-control studies, and randomized controlled trials published as original articles; case reports, ecological, and prevalence studies were excluded. (3) We considered studies that were independent. Once full articles were retrieved, studies were further excluded if there was an overlap in patients with another study within the same analysis (in which case, the larger sample size of the 2 studies was selected). If some patients had been included in another study with different analysis (eg, coronary heart disease and cardiac mortality), they would be included once in 1 given analysis. Consequently, there was no overlap in patients included in our meta-analyses.

Data Abstraction and Quality Assessment

Two authors (Y.-J.C. and X.-Y.N.) extracted the data, and 1 author (C.-C.J.) independently double-checked the available data. The following data were extracted from each study: first author's name, publication year, geographical location, mean age, sample size, study design, sampling framework, study population, study end points, number of events, duration of follow-up, treatment era, and the relative risks and associated measure of variance for all categories of outcomes. When available, we used the most comprehensively adjusted risk estimates. Percentage agreement between the 2 authors on

the quality review ranged from 90% to 100%. Any disagreements were resolved by consensus.

To determine the quality of the included studies, we used the Modified Jadad Score for the randomized control trials and the Newcastle-Ottawa scale for the observational studies. Y.-J.C. and X.-Y.N. developed the evaluation criteria (Tables S1 through S3). The score ranged from 0 to 9 points for cohort and case-control studies and from 0 to 5 points for randomized controlled studies, with a higher score indicating higher study quality.

Statistical Analysis

The RR was used as a measure of the association between breast cancer radiotherapy and cardiovascular risk. For case-control studies, the odds ratio was used as an estimate of the RR because cardiovascular events are sufficiently rare.[7]

We assessed the heterogeneity across studies by the Cochran test and by calculating the I^2 statistic (describing the percentage of total variation across trials that was due to heterogeneity rather than chance), applying the following interpretation for I^2: <50%=low heterogeneity; 50% to 75% =moderate heterogeneity; >75%=high heterogeneity.[8,9] We pooled RRs from individual trials according to the method of DerSimonian and Laird for random effects. Subgroup analyses and meta-regression models were carried out to investigate potential sources of between-study heterogeneity. We calculated absolute difference in event rate with radiotherapy as $\{(RR-1)\times I_0\}$, where RR indicates pooled RRs and I_0 was the cumulative event rate per 100 000 patient-years of follow-up for the reference population. On the basis of population-based cohort studies, I_0 was estimated by weighting by the sample size of each study.

Small study bias, consistent with publication bias, was assessed with funnel plot, by the Begg adjusted rank correlation test and by the Egger regression asymmetry test.[8,9] We also performed the Duval and Tweedie nonparametric "trim and fill" procedure to further assess the possible effect of publication bias in our meta-analysis.[10] All *P* values are 2-sided. Results were considered to be statistically significant at a *P* value of less than 0.05. Statistical analysis was performed with the use of Stata software, version 12.0 (StataCorp, College Station, TX).

Results

Study Selection

Our literature search identified 2523 potentially relevant studies as shown in the flow diagram. Of these, 281 articles were considered of interest, and full text was retrieved for detailed evaluation. An additional 242 studies were excluded due to overlap of patients or no relevant outcomes, and finally, 39 studies were included in the meta-analysis (Figure S1).

Study Characteristics

A total of 1 191 371 individuals were enrolled in 39 eligible studies, including 11 randomized controlled trials,[11-21] 13 cancer registry database studies,[5,22-33] and 15 single- and multi-institutional trials.[34-48] Twenty-two studies were based in Europe, 13 in North America, 1 in Australia and 3 were multinational; 16 studies recruited participants from population registers, and 23 were hospital based (Table S1). The years of patient irradiation ranged from 1949 to 2008, with the study results typically published between 1985 and 2014 and a median follow-up of 1 to 28 years. Ten trials compared patients who had received radiation therapy with those who had not received radiation therapy; 14 trials compared left-sided breast cancer radiation therapy and right-sided breast cancer radiation therapy, and 15 trials compared both. The sizes of the studies ranged from 41 to 558 871, with the 9 largest studies recruiting over 10 000 patients. Of the 28 observational studies, the scores of the Newcastle-Ottawa scale quality assessment ranged from 5 to 9, and 14 studies had scores of 7 or higher. The methodological quality of the 11 randomized controlled trials was generally good, with Modified Jadad Score of 3 or higher in all the studies (Tables S2 through S4).

Cardiovascular Morbidity and Mortality in Patients With Left-Sided Radiotherapy or With Right-Sided Radiotherapy

Coronary Heart Disease

Twenty studies were included for the outcome of coronary heart disease, involving 233 761 participants and 2723 events. In a comparison of women receiving left-sided radiotherapy with those receiving right-sided radiotherapy, the overall RR of coronary heart disease was 1.29 (95%CI 1.13-1.48; *P*<0.001), with low between-study heterogeneity (I^2 42.87%, 95%CI 3.01-66.35%, *P*=0.02) (Figure 1). Visual inspection of the Begg funnel plot did not identify substantial asymmetry, and the Begg rank correlation test was not statistically significant (*P*=0.23) (Figure S2). However, the Egger linear regression test indicated a possibility of publication bias (*P*=0.02). With the trim-and-fill approach, the imputed estimate (RR 1.26, 95%CI 1.09-1.46, *P*=0.002) was similar to that in the main analysis, indicating that results are unlikely to be explained by publication bias. In a sensitivity analysis that included only the 11 studies that used myocardial infarction or death due to coronary heart disease as the outcome of interest, the pooled RR was 1.34 (95%CI 1.20-

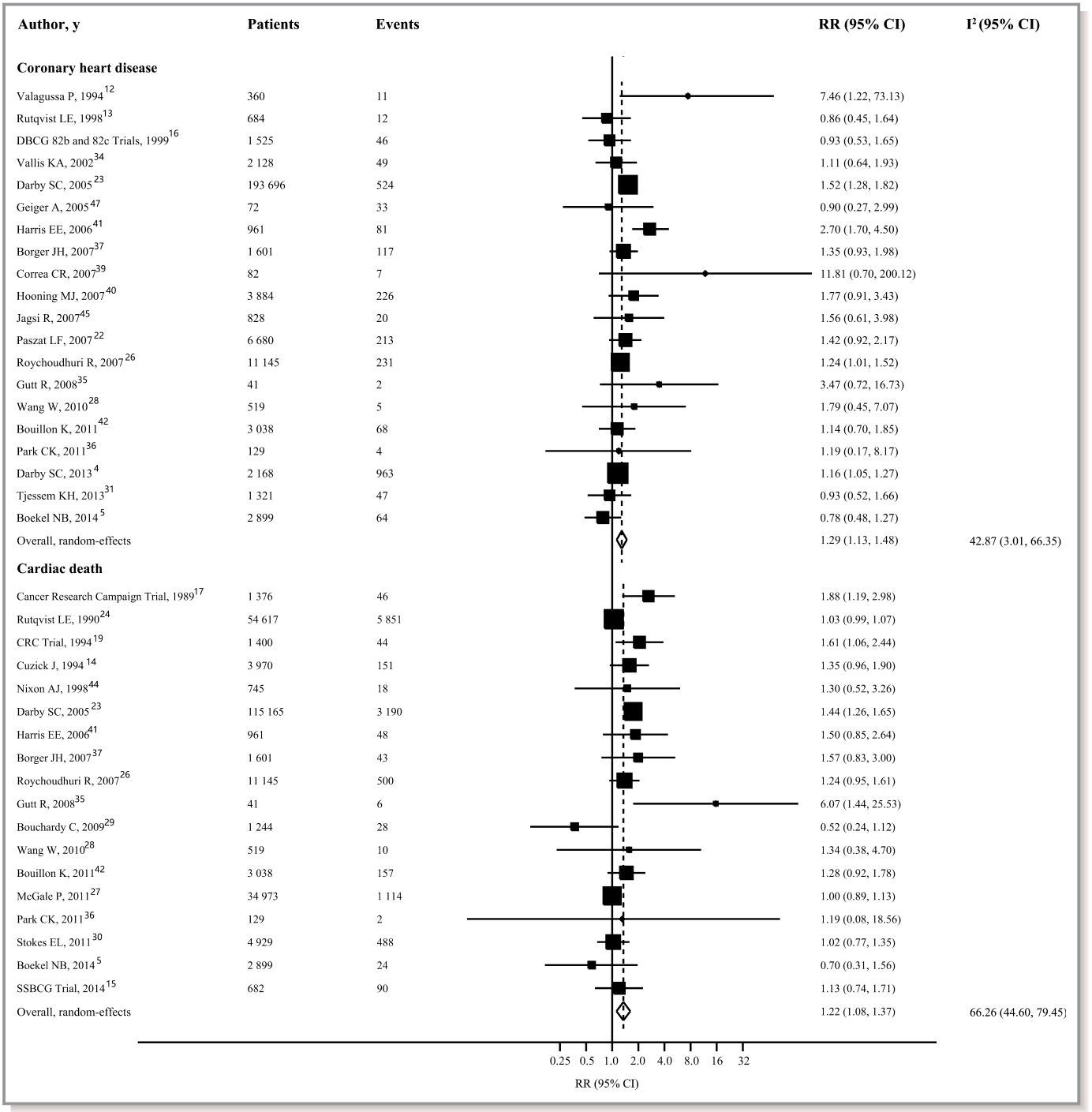

Figure 1. Forest plot for risk of coronary heart disease and cardiac mortality in patients with left-sided radiotherapy vs those with right-sided radiotherapy. The size of each square is proportional to the study's weight (inverse of variance). I^2 indicates variation in RR attributable to heterogeneity; RR, relative risk.

1.50), with no evidence of significant heterogeneity (I^2 0%, 95%CI 0-60.23%, *P*=0.49) (Figure S3).

In the stratified analyses little of the heterogeneity was explained by study type (*P*=0.65), breast cancer staging (*P*=0.69), follow-up duration (*P*=1.00), age at breast cancer diagnosis (*P*=0.11), number of patients (*P*=0.47), source of patients (*P*=0.83), whether risk profiles were adjusted (*P*=0.83), or whether adjuvant chemotherapy was administered (*P*=0.38). Significant heterogeneity between pooled analyses was noted for studies published before 2010 compared with those published after 2010 (RR 1.42, 95%CI 1.19-1.69 versus 1.14, 95%CI 1.04-1.25, *P*=0.03), studies in which cases were validated with medical record compared with studies in which they were not (RR 1.66, 95%CI 1.09-

2.54 versus 1.26, 95%CI 1.10-1.44, *P*=0.03), and breast cancer diagnosed before 1980 compared with breast cancer diagnosed after 1980 (RR 1.32, 95%CI 1.09-1.44 versus 1.16, 95%CI 1.01-1.33, *P*=0.04). The RRs for coronary heart disease in women with left-sided versus right-sided radiotherapy, according to the number of years since diagnosis of breast cancer, were as follows: 0 to 4 years, 1.14 (95%CI 0.95-1.36); 5 to 9 years, 1.17 (95%CI 1.04-1.32); 10 to 14 years, 1.93 (95%CI 1.13-3.30); 15 to 20 years, 1.39 (95%CI 1.08-1.79) (Table 1).

In a sensitivity analysis of women who had not been irradiated, the relative risk of coronary heart disease, left versus right tumor laterality, was close to 1 (1.02, 95%CI 0.95-1.10, *P*=0.60) (Figure S4). Using the average event rate in women receiving right-sided radiotherapy from included studies and the summary estimates obtained from all studies combined, left-sided breast cancer radiotherapy was associated with an absolute risk increase of 66.8 (95%CI 37.6-102.5) cases of coronary heart disease per 100 000 person-years.

Cardiac Mortality

Eighteen studies with data of 239 434 individuals and at least 11 810 events reported risk estimates for cardiac mortality. Overall, compared with women who had received radiotherapy for a right-sided tumor, women who had received radiotherapy for a left-sided breast cancer experienced a significantly increased risk for cardiac mortality (RR 1.22, 95%CI 1.08-1.37, *P*=0.002). There was evidence of moderate heterogeneity of RRs across these studies (I^2 66.26%, 95%CI 44.60% to 79.45%, *P*<0.001) (Figure 1). Neither funnel plots nor Egger and Begg tests showed evidence of publication bias (Egger, *P*=0.88; Begg, *P*=0.47) (Figure S2).

To explore the study heterogeneity, we performed analyses subdivided by a number of key study characteristics and clinical factors. Study type, geographical area, surgery type, publication year, follow-up duration, age at breast cancer diagnosis, number of patients, source of patients, whether risk profiles were adjusted, or whether adjuvant chemotherapy was administered were not significant sources of heterogeneity. However, we found higher risks in studies in which cases were validated with medical records than in studies in which they were not (RR 1.56, 95%CI 1.28-1.91 versus 1.12, 95%CI 1.00-1.27, *P*=0.01). In addition, breast cancer diagnosis period also seemed to be associated with the results (RR 1.45, 95%CI 1.14-1.89 for women diagnosed before 1980 and irradiated versus 1.15, 95%CI 0.92-1.44 for women diagnosed after 1980 and irradiated; *P*=0.04). The RRs for cardiac mortality, left versus right tumor laterality, increased steeply with time since diagnosis of breast cancer: 0 to 4 years, 1.02 (95%CI 0.96-1.08); 5 to 9 years, 1.05 (95% CI 0.97-1.14); 10 to 14 years, 1.26 (95%CI 1.11-1.44); 15 to 20 years, 1.44 (95%CI 1.14-1.82) (Table 1).

For women not given radiotherapy, there was little evidence of an association between breast cancer laterality and subsequent cardiac mortality (1.02, 95%CI 0.98-1.06, *P*=0.28) (Figure S5). Compared with women receiving right-sided radiotherapy, women with left-sided radiotherapy experienced an absolute risk increase of 73.9 (95%CI 41.6-113.9) cases of cardiac death per 100 000 person-years.

Secondary End Points

For death from any cause, 13 studies were included, reporting 96 725 events among 534 419 participants. Left-sided radiotherapy was associated with a significantly increased risk of death from any cause compared with right-sided radiotherapy (RR 1.05, 95%CI 1.01-1.10, *P*=0.02) (Figure S6). We also had additional analysis of other end points in relation to coronary heart disease. Similarly, women with left-sided radiotherapy, as compared with the reference group, appeared to experience increased risk of death from coronary heart disease (RR 1.23, 95%CI 1.07-1.41, *P*=0.004), death from myocardial infarction (RR 1.35, 95%CI 1.12-1.63, *P*=0.002), and myocardial infarction (RR 1.21, 95%CI 1.05-1.39, *P*=0.007) (Table 2). However, left-sided radiotherapy did not seem to be associated with risks of heart failure, arrhythmia, and valvular heart disease (Table 2).

Cardiovascular Morbidity and Mortality in Patients With Radiotherapy or Without Radiotherapy

Coronary Heart Disease

From 17 studies analyzed, there were 10 640 cases of coronary heart disease among 155 236 participants. In a comparison of women who received radiotherapy with those who received no radiotherapy, the RR for coronary heart disease was 1.30 (95% CI 1.13-1.49, *P*<0.001), with moderate heterogeneity (I^2 72.89%, 95%CI 56.06% to 83.28%, *P*<0.001) (Figure 2). Visual inspection of the Begg funnel plot revealed asymmetry (*P*<0.001). This raises the possibility of publication bias, although neither the Begg nor the Egger test was statistically significant (Begg, *P*=0.48; Egger, *P*=0.22) (Figure S2). Because of this, we undertook a sensitivity analysis using the trim-and-fill method, and the pooled analysis incorporating the hypothetical studies continued to show a statistically significant association between radiotherapy and risk of coronary heart disease (RR 1.18, 95%CI 1.03-1.36, *P*=0.01). Further analysis of 9 studies that used myocardial infarction or death from coronary heart disease as the end point yielded similar results (RR 1.39, 95%CI 1.10-1.76, *P*=0.01) (Figure S7).

Table 1. Stratified Analysis and Heterogeneity Analysis of Relative Risks of Coronary Heart Disease and Cardiac Mortality in Left-Sided Versus Right-Sided Radiotherapy

	Coronary Heart Disease				Cardiac Mortality			
Factors Stratified	Patients	Events	RR (95%CI)	*P* Value*	Patients	Events	RR (95%CI)	*P* Value*
All studies	233 761	2723	1.29 (1.13-1.48)		239 434	11 810	1.22 (1.08-1.37)	
Types of studies								
Observational studies	231 876	2666	1.30 (1.13-1.48)	0.65	232 006	11 479	1.16 (1.01-1.32)	0.10
RCT	1885	57	2.07 (0.28-15.05)		7428	331	1.44 (1.18-1.76)	
Location								
Europe	27 024	1668	1.14 (1.01-1.29)	0.01	115 344	8005	1.14 (1.01-1.29)	0.65
North America	10 921	409	1.65 (1.16-2.34)		6805	562	1.37 (0.88-2.13)	
Publication year								
<2010	223 687	1572	1.42 (1.19-1.69)	0.03	192 265	9925	1.34 (1.11-1.62)	0.08
≧2010	10 074	1151	1.14 (1.04-1.25)		47 169	1885	1.03 (0.93-1.14)	
Breast cancer staging								
0 to II	7143	300	1.38 (0.90-2.11)	0.69	36 152	866	1.40 (1.22-1.61)	<0.001
I to IV	226 618	2423	1.27 (1.12-1.43)		131 838	8648	1.07 (0.97-1.17)	
Surgery								
Breast-conserving	6130	291	1.80 (1.21-2.66)	0. 02	98 148	7921	1.12 (1.00-1.25)	0.58
Mastectomy	7414	331	1.05 (0.77-1.43)		68 621	2922	1.30 (1.03-1.64)	
Breast-conserving or mastectomy	220 217	2101	1.24 (1.09-1.42)		23 774	1207	1.08 (0.88-1.33)	
Follow-up, y								
<20	15 797	483	1.35 (0.93-1.94)	1.00	47 169	1885	1.18 (0.93-1.52)	0.52
≧20	217 892	2207	1.28 (1.14-1.44)		192 265	9925	1.25 (1.08-1.45)	
Adjusted for risk profiles								
Yes	221 489	1440	1.30 (1.12-1.53)	0.83	232 387	11 485	1.35 (1.08-1.69)	0.33
No	12 272	1283	1.36 (1.03-1.78)		7047	325	1.18 (1.03-1.35)	
Adjuvant chemotherapy								
Yes	214 908	2237	1.35 (1.12-1.63)	0.38	159 218	4986	1.13 (0.92-1.39)	0.30
No	18 853	486	1.20 (1.01-1.42)		80 216	6824	1.32 (1.08-1.60)	
Patients, n								
<2000	8123	385	1.42 (1.02-1.97)	0.47	8698	335	1.41 (1.08-1.84)	0.11
≧2000	225 638	2338	1.25 (1.10-1.43)		230 736	11 475	1.15 (1.01-1.30)	
Age, y								
<55	9659	498	1.23 (1.09-1.38)	0.11	3307	109	1.49 (1.01-2.19)	0.21
≧55	224 102	2225	1.60 (1.10-2.34)		229 381	11 460	1.13 (0.99-1.28)	
Source of patients								
Population based	227 067	2467	1.28 (1.09-1.50)	0.83	176 405	5621	1.26 (1.07-1.48)	0.49
Hospital based	6694	256	1.33 (0.97-1.83)		63 029	6189	1.16 (0.92-1.48)	
Case validation								
Yes	6640	1166	1.66 (1.09-2.54)	0.03	9012	323	1.56 (1.28-1.91)	0.01
No	227 121	1557	1.26 (1.10-1.44)		230 422	11 487	1.12 (1.00-1.27)	

Continued

Table 1. Continued

Factors Stratified	Coronary Heart Disease				Cardiac Mortality			
	Patients	Events	RR (95%CI)	*P* Value*	Patients	Events	RR (95%CI)	*P* Value*
Period of breast cancer diagnosis								
<1980	84 335	5046	1.32 (1.21-1.44)	0.04	81 730	10 855	1.45 (1.14-1.89)	0.04
≧1980	88 680	3455	1.16 (1.01-1.33)		143 606	6680	1.15 (0.92-1.44)	
Years since breast cancer diagnosis								
1 to 4	308 190	1534	1.14 (0.95-1.36)	NA	173 683	4794	1.02 (0.96-1.08)	NA
5 to 9	303 821	1445	1.17 (1.04-1.32)		166 014	2801	1.05 (0.97-1.14)	
10 to 14	302 376	1250	1.93 (1.13-3.30)		164 387	1125	1.26 (1.11-1.44)	
15 to 20	285 165	736	1.39 (1.08-1.79)		124 462	929	1.44 (1.14-1.82)	

RCT indicates randomized controlled trial; RR, relative risk.
**P*-values test homogeneity between strata.

The finding of increased risk of coronary heart disease in patients who received radiotherapy was consistently found in all of the stratified analyses. Study quality characteristics did not seem to markedly influence the results, although a stronger association was observed for studies in which cases of coronary heart disease were confirmed by laboratory examination or medical record (*P*=0.004). Notably, although treatment era seemed to be associated with the results, patients diagnosed after 1980 with modern radiotherapy techniques still experienced increased risk of coronary heart disease compared with those without radiotherapy (RR 1.21, 95%CI 1.01-1.37, *P*=0.04). The risk increase started within the first 5 years and continued into the third decade after radiotherapy: the RRs were 1.40 (95%CI 1.12-1.74) for 0 to 4 years, 1.70 (95%CI 1.18-2.45) for 5 to 9 years, 1.79 (95%CI 1.08-2.97) for 10 to 14 years, 1.23 (95%CI 1.02-1.48) for 15 to 19 years, and 1.88 (95%CI 1.08-3.27) for 20 years or more (Table 3). From studies that reported information on person-years in patients with radiotherapy and without radiotherapy, we could calculate that women with radiotherapy experienced an absolute risk increase of 76.4 (95%CI 36.8-130.5) cases of coronary heart disease per 100 000 person-years.

Table 2. Summary Estimates of Relative Risks of Other Cardiovascular Outcomes Associated With Radiotherapy for Breast Cancer

End Points	No. of Studies	No. of Participants	No. of Events	RR (95%CI)	I^2 (95%CI) *	*P* Value†
Left-sided radiotherapy vs right-sided radiotherapy						
Death from any cause	13	534 419	96 725	1.05 (1.01-1.10)	57.23 (20.69-76.94)	0.01
Death from coronary heart disease	13	252 654	5103	1.23 (1.07-1.41)	54.41 (14.75-75.62)	0.01
Death from myocardial infarction	10	221 515	4476	1.35 (1.12-1.63)	49.61 (0-75.59)	0.04
Myocardial infarction	14	126 998	5337	1.21 (1.05-1.39)	47.75 (2.93-71.87)	0.02
Heart failure	7	59 157	2570	1.00 (0.91-1.12)	7.69 (0-73.05)	0.37
Arrhythmia	7	58 630	2645	1.00 (0.92-1.07)	0 (0-70.81)	0.68
Valvular heart disease	4	57 699	640	1.22 (0.91-1.66)	35.79 (0-75.96)	0.18
Radiotherapy vs no radiotherapy						
Death from any cause	8	50 346	8388	1.01 (0.85-1.20)	90.33 (83.35-94.38)	<0.001
Death from coronary heart disease	8	34 083	1152	1.40 (1.12-1.75)	60.47 (14.16-81.80)	0.01
Death from myocardial infarction	4	5628	53	1.84 (0.56-6.04)	78.93 (43.61-92.13)	0.003
Myocardial infarction	9	69 358	3278	1.33 (1.002-1.77)	77.95 (58.27-88.35)	<0.001
Heart failure	9	70 354	11 235	1.17 (0.90-1.51)	74.55 (50.71-86.86)	<0.001
Arrhythmia	3	15 749	252	1.04 (0.69-1.58)	30.80 (0-92.80)	0.24
Valvular heart disease	4	20 580	239	1.97 (0.84-4.62)	61.04 (0-86.96)	0.05

RR indicates relative risk.
*I^2 is a measure of the variation in RR attributable to heterogeneity.
†*P* value for I^2.

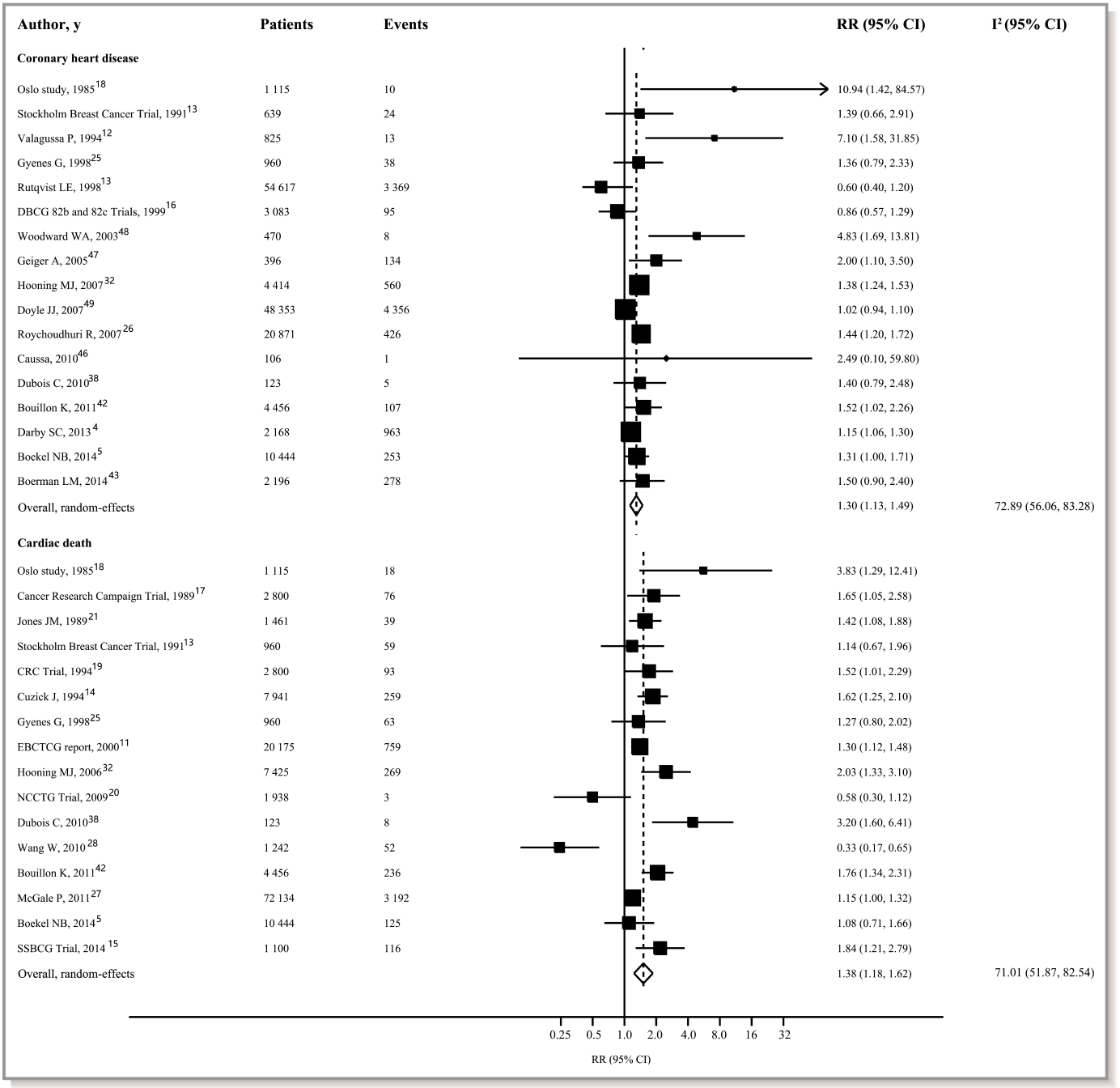

Figure 2. Forest plot for risk of coronary heart disease and cardiac mortality in patients with radiotherapy vs those without radiotherapy. The size of each square is proportional to the study's weight (inverse of variance). I^2 indicates variation in RR attributable to heterogeneity; RR, relative risk.

Cardiac Mortality

For the end point of cardiac mortality in women with radiotherapy versus no radiotherapy, 16 studies involving 137 074 patients and 5367 events were included. Compared with women who had not received radiotherapy, those who had received radiotherapy had a 1.38-fold (95%CI 1.18-1.62, $P<0.001$) higher risk of cardiac mortality (Figure 2). Although there was moderate heterogeneity among the available studies (I^2 71.01%, 95%CI 51.87% to 82.54%, $P<0.001$), the Begg and Egger tests indicated no evidence of publication bias (Begg, $P=0.96$; Egger, $P=0.12$) (Figure S2).

When we evaluated prespecified potential sources of heterogeneity, the major sources were follow-up duration, case validation, and breast cancer diagnosis period. The RRs were higher in studies with follow-up duration of more than 20 years than in those with follow-up duration of less than 20 years (RR 1.51, 95%CI 1.29-1.77, versus 1.01, 95%CI

Table 3. Stratified Analysis and Heterogeneity Analysis of Relative Risks of Cardiac Death and Coronary Heart Disease in Radiotherapy Versus No Radiotherapy

	Coronary Heart Disease				Cardiac Mortality			
Factors Stratified	Patients	Events	RR (95%CI)	*P* Value*	Patients	Events	RR (95%CI)	*P* Value*
All studies	155 236	10 640	1.30 (1.13-1.49)		137 074	5367	1.38 (1.18-1.62)	
Types of studies								
Observational studies	149 104	10 490	1.26 (1.11-1.44)	0.31	98 245	3948	1.33 (1.01-1.75)	0.74
RCT	6132	150	2.63 (1.05-6.58)		38 829	1383	1.43 (1.17-1.75)	
Location								
Europe	106 017	6142	1.29 (1.13-1.17)	0.02	113 719	4553	1.53 (1.31-1.79)	0.01
North America	866	142	2.78 (1.20-6.40)		3180	55	0.44 (0.25-0.76)	
Publication year								
<2010	135 743	9033	1.32 (1.06-1.63)	0.86	47 575	1638	1.43 (1.22-1.67)	0.68
≧2010	19 493	1607	1.20 (1.10-1.31)		89 499	3929	1.30 (0.89-1.88)	
Breast cancer staging								
0 to II	67 136	3670	1.21 (0.69-2.11)	0.43	41 332	1253	1.36 (1.01-1.67)	0.95
I to IV	88 100	6970	1.32 (1.14-1.53)		95 742	4114	1.39 (1.07-1.82)	
Surgery								
Breast-conserving	54 617	3369	0.60 (0.35-1.04)	0.20	…	…	…	
Mastectomy	10 681	735	1.47 (1.02-2.12)		11 319	472	1.59 (1.31-1.94)	0.10
Breast-conserving or mastectomy	89 938	6536	1.31 (1.13-1.52)		125 755	4895	1.21 (0.97-1.52)	
Follow-up, year								
<20	72 870	4071	1.20 (0.88-1.63)	0.43	21 144	471	1.01 (0.71-1.45)	0.02
≧20	81 847	6430	1.32 (1.11-1.57)		115 807	4888	1.51 (1.29-1.77)	
Adjusted for risk profiles								
Yes	148 875	10 484	1.26 (1.10-1.44)	0.31	110 750	4688	1.43 (1.22-1.66)	0.50
No	6361	156	2.10 (1.12-3.95)		26 324	679	1.28 (0.91-1.80)	
Adjuvant chemotherapy								
Yes	116 751	9782	1.23 (1.03-1.46)	0.17	104 137	4399	1.25 (0.93-1.68)	0.40
No	38 485	858	1.42 (1.24-1.62)		32 937	968	1.50 (1.33-1.71)	
Patients, n								
<2000	4634	233	2.04 (1.36-3.07)	0.10	8899	358	1.26 (0.83-1.92)	0.47
≧2000	150 602	10 407	1.20 (1.05-1.37)		128 175	5009	1.43 (1.24-1.66)	
Age, y								
<55	8011	860	2.00 (1.21-3.30)	0.06	9363	272	1.11 (0.33-3.80)	0.81
≧55	144 511	9708	1.19 (1.03-1.37)		110 634	4551	1.31 (1.04-1.64)	
Source of patients								
Population based	147 915	10 446	1.25 (1.09-1.44)	0.34	108 451	4364	1.14 (0.88-1.48)	0.09
Hospital based	7321	194	1.83 (1.12-3.06)		28 623	1003	1.56 (1.29-1.89)	
Case validation								
Yes	5231	449	2.26 (1.43-3.57)	0.004	24 142	726	1.68 (1.23-2.27)	0.03
No	150 005	10 191	1.20 (1.05-1.36)		122 932	4641	1.25 (1.05-1.50)	

Continued

Table 3. Continued

	Coronary Heart Disease				Cardiac Mortality			
Factors Stratified	Patients	Events	RR (95%CI)	*P* Value*	Patients	Events	RR (95%CI)	*P* Value*
Period of breast cancer diagnosis								
<1980	9913	882	1.52 (1.29-1.79)	0.02	22 493	843	1.58 (1.39-1.80)	0.04
≧1980	70 699	6053	1.21 (1.01-1.37)		33 084	1060	1.27 (0.82-1.97)	
Years since breast cancer diagnosis								
1 to 4	15 944	537	1.40 (1.12-1.74)	NA	22 211	212	1.04 (0.51-2.12)	NA
5 to 9	7596	408	1.70 (1.18-2.45)		11 672	149	1.17 (0.55-2.48)	
10 to 14	9066	614	1.79 (1.08-2.97)		10 332	210	1.41 (1.04-1.92)	
15 to 19	26 800	844	1.23 (1.02-1.48)		14 578	375	1.63 (1.21-2.21)	
>20	4612	259	1.88 (1.08-3.27)		13 324	1128	1.59 (1.33-1.91)	

RCT indicates randomized controlled trial; RR, relative risk.
**P*-Values test homogeneity between strata.

0.71-1.45, *P*=0.02), studies with case validation than those without case validation (RR 1.68, 95%CI 1.23-2.27, versus 1.25, 95%CI 1.05-1.50, *P*=0.03), and breast cancer diagnosed before 1980 than that diagnosed after 1980 (RR 1.58, 95%CI 1.39-1.80, versus 1.27, 95%CI 0.82-1.97, *P*=0.04). The RRs of cardiac mortality were 1.04 (95%CI 0.51-2.12) during 0 to 4 years after primary diagnosis, 1.17 (95%CI 0.55-2.48) during 5 to 9 years, 1.41 (95%CI 1.04-1.92) during 10 to 14 years, 1.63 (95%CI 1.21-2.21) during 15 to 19 years, and 1.59 (95%CI 1.33-1.91) after 20 years (Table 3). The absolute excess risk of cardiac mortality for patients receiving radiotherapy, as compared with those who received no radiotherapy, was 125.5 (95%CI 98.8-157.9) cases per 100 000 person-years.

Secondary End Points

For the end points associated with coronary heart disease, elevated RRs were observed for death from coronary heart disease (RR 1.40, 95%CI 1.12-1.75, *P*=0.003) and myocardial infarction (RR 1.33, 95%CI 1.002-1.77, *P*=0.049). Analysis of 4 studies involving 5628 patients and 53 events showed a statistically nonsignificant 1.84-fold increased risk for death from myocardial infarction. In addition, we found no significant association between radiotherapy and risk of death from any cause, heart failure, arrhythmia, and valvular heart disease (Table 2).

Discussion

The present meta-analysis, involving 1 191 371 patients from 39 studies, has assessed the strength and consistency of associations between breast cancer radiotherapy and subsequent risk of cardiovascular disease. We have shown that in women diagnosed with breast cancer, coronary heart disease and cardiac mortality were increased in the comparison of patients with left-sided radiotherapy and those with right-sided radiotherapy, as well as in the comparison of patients with radiotherapy and those without radiotherapy. In subgroup analyses the increase in risk with radiotherapy seemed to be driven by a stronger association among studies in which the cases were validated with medical records and breast cancer was diagnosed before 1980. The increase of risk started within the first decade for coronary heart disease and from the second decade for cardiac mortality and continued into the third decade after radiotherapy.

Previous studies have identified that atomic bomb survivors and patients given radiotherapy for peptic ulcer disease had dose-related increases in late cardiac morbidity and mortality, whereas conflicting results were reported for patients receiving radiotherapy for breast cancer.[50,51] Results from our analysis suggest that breast cancer radiotherapy is independently associated with risk of coronary heart disease and cardiac mortality. The risk magnitude appears to be less robust than those reported for well-established major risk factors such as smoking, hypertension, diabetes mellitus, or hyperlipidemia. It is of note that lack of case validation tends to deflate the pooled risk estimate, indicating that the true magnitude of association between breast cancer radiotherapy and cardiovascular risk may be greater. In absolute terms, 76.4 excess cases of coronary heart disease and 125.5 excess cases of cardiac death occurred per 100 000 person-years associated with radiotherapy. The absolute risk is not small, and given that postoperative radiotherapy is one of the most commonly used adjuvant therapies and that over a million women develop breast cancer annually, the total number of excess cases of coronary heart disease and cardiac death may not be negligible. In addition, our results showed that radiotherapy did not provide improvement in the overall

survival, and even left-sided radiotherapy could increase risk of death from any cause, indicating that absolute cardiovascular risk can be weighed against the probable absolute reduction in the risk of recurrence or death from breast cancer that would be achieved with radiotherapy. In spite of the clear association between radiotherapy and cardiovascular risk in breast cancer patients, the American College of Cardiology/American Heart Association guidelines do not provide specific recommendations regarding radiation-induced coronary heart disease or cardiovascular disease.[52]

There is 1 factor that may confound the interpretation of cardiovascular risk associated with radiotherapy in breast cancer patients. Outside the context of randomized trials, patients may have been selected for radiotherapy according to age, nature of breast cancer, and factors associated with the prognosis, and these factors can potentially produce selection biases.[27] Therefore, simple comparisons of subsequent mortality of irradiated and unirradiated patients might not reliably reflect the real benefit and hazard of treatments. It seems unlikely, however, that the effect can be attributed completely to selection bias because some effect remains even when only coronary heart disease and cardiac mortality are considered, and the effect for heart disease is strong even during the period over 10 years after breast cancer diagnosis. Furthermore, in the randomized trials that involved less selection bias, both risks for coronary heart disease and cardiac mortality were increased in irradiated versus unirradiated patients. But outside the randomized trials, comparisons that avoid selection biases could also be performed, as breast cancer laterality plays little part in determining who should be given radiotherapy, and the cardiac radiation dose is generally greater in left-sided than in right-sided breast cancer.[53,54] Therefore, comparisons of cardiovascular morbidity and mortality in irradiated women with left-sided versus right-sided breast cancer can give a valid indication of the extent of any radiation-related cardiac effect even though the magnitude of risk is likely to be underestimated. The consistency of the findings of increased risk of coronary heart disease and cardiac mortality in patients with left-sided radiotherapy versus right-sided radiotherapy as well as in patients with radiotherapy versus those without radiotherapy suggests a causal effect of radiotherapy on heart disease.

Although previous studies have indicated that radiation-associated cardiovascular complications involved injury of pericardium, myocardium, valves, and conduction systems, our results suggest that radiation-induced heart disease might be mainly mediated by radiation damage to the coronary arteries leading to myocardial ischemia and myocardial infarction.[55] First, our study identified that radiotherapy was associated with an increased risk for coronary heart disease but not for heart failure, arrhythmia, and valvular heart disease. The association persists and remains statistically significant across a number of stratified analyses exploring clinical and study quality factors and also persists in the analyses of the outcomes that are less likely to be misclassified such as myocardial infarction and death from coronary heart disease. And death from coronary heart disease may account for the largest number of deaths from cardiac cause, of which the risk is also increased in association with radiotherapy. Second, there is an appropriate temporal relationship: radiotherapy preceded incidence of coronary heart disease in all studies. The risk for coronary heart disease started within the first decade, whereas risk for cardiac death started from the second decade after radiation exposure. This is consistent with existing knowledge that it may take a patient with coronary heart disease a certain period of time to develop into cardiac death. Third, contemporary radiotherapy techniques can involve substantially lower cardiac exposures than those used previously, and therefore, the decline in risk observed for the more recent treatment period provides indirect evidence of a dose-response relationship for radiation-induced coronary heart disease. Fourth, there is biological plausibility for causality in that radiation may lead to oxidative stress, inflammatory cell infiltration, endothelial injury, fibrosis of the intima, a prothrombotic state, and atherosclerosis in the coronary arteries and thus may contribute to an increased risk of ischemic heart disease.[55]

Over the past few decades, improvements in radiotherapy planning have reduced cardiac radiation exposures. This situation has been achieved partly by omitting irradiation of the internal mammary chain of lymph nodes, switching from orthovoltage to megavoltage, use of respiratory gating, or blocking the heart in tangential fields.[56] However, dosimetric studies have demonstrated that modern techniques could not eliminate cardiac exposure, and for approximately half of left-sided patients, part of the heart still received more than 20 Gy, probably including part of the left anterior descending coronary artery.[57] This suggests that contemporary radiotherapy techniques may still increase the risk of ischemic heart disease in a proportion of patients, consistent with our findings that risk for coronary heart disease still slightly increased for patients irradiated after 1980. Hardenberg et al also indentified that modern radiotherapy techniques were associated with defects in myocardial perfusion, abnormalities in wall motion, and declines in ejection fraction of the heart.[58] Notably, the excess risk of cardiac death associated with breast cancer did not become clear until more than 10 years after exposure. Thus, a possible explanation for the lack of any definite hazard of cardiac death from our analysis of a subgroup of patients diagnosed after 1980 is that the follow-up is not long enough. Therefore, care should continue to be taken to minimize cardiac exposure as much as is practical in patients undergoing radiotherapy for breast cancer.

Strengths of this meta-analysis include the strict inclusion criteria, the large number of patients analyzed, the robustness of the findings in sensitivity analyses, and the fact that all subgroup analyses were prespecified a priori. There are several limitations to this study. First, there is heterogeneity of RRs among studies in the primary analysis. However, stratified analyses showed pooled RRs consistently greater than 1 across a number of clinical factors. Second, the funnel plot analysis showed some asymmetry, suggesting the possibility of publication bias for coronary heart disease. The trim-and-fill sensitivity analysis did not change the general result, suggesting that the association is not an artifact of unpublished negative studies. Third, lack of individual participant data may preclude determining the independent associations of individual variables with study outcomes. Instead, we used between-study meta-regressions when possible. Fourth, because radiation doses to the whole heart and to the left anterior descending coronary artery could not be obtained, direct assessment of a dose-response relationship for radiation-induced heart disease was not available. We therefore compared cardiovascular risk between different treatment eras as a surrogate, which might to some extent reflect the difference in the dose of radiation to the heart. Fifth, because the individual participant data were not available, we could not calculate the risk for every subcategory of coronary heart disease. We therefore used the composite end point of coronary heart disease instead, which might not be optimal but could be appropriate in assessing the cardiovascular risk associated with breast cancer radiotherapy.[59-62] Sixth, given that there are no best tools available for the evaluation of the methodologic quality of randomized controlled trials, we used the most widely used Jadad scoring system as a surrogate.[63-65]

In conclusion, the results from this meta-analysis suggest that radiotherapy for breast cancer might increase the risk of coronary heart disease as well as cardiac mortality. The increase of risk started within the first decade for coronary heart disease and from the second decade for cardiac mortality. Contemporary radiotherapy techniques have likely reduced the risk, but they may not have eliminated cardiotoxicity, and therefore, the long-term hazards in the general population still need to be monitored directly. The association between radiotherapy and cardiovascular risk has clinical relevance with respect to individual screening, risk factor modification, and the primary and secondary prevention of heart disease.

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Disclosures

None.

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Supplemental Material

Table S1. Studies included in the meta-analysis that assessed cardiac morbidity and mortality associated with breast cancer radiotherapy.

Study	Country	Treatment period	Study type	Study design	End points	Source of participants
Prospective randomized controlled trial						
EBCTCG report[1]	Multi-national	1985-2000	Randomized controlled trial	Radiotherapy vs. without radiotherapy	Death from any cause; cardiac mortality	Population-based
Valagussa P[2]	Italy	1980-1990	Randomized controlled trial	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Coronary heart disease; arrhythmia	Hospital-based
Woodward WA[3]	USA	1975-1994	Randomized controlled trials	Radiotherapy vs. without radiotherapy	Death from myocardial infarction	Hospital-based
Stockholm Breast Cancer Trial[4]	Sweden	1971-1976	Randomized controlled trial	Radiotherapy vs. without radiotherapy	Death from any cause; cardiac death; death from coronary heart disease	Hospital-based
Cuzick J[5]	UK	1949-1974	Randomized controlled trial	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Cardiac mortality	Hospital-based
SSBCG Trial[6]	Sweden	1978-1985	Randomized controlled trial	Left-sided vs. right-sided radiotherapy; Radiotherapy vs. without radiotherapy	Cardiac mortality	Hospital-based
DBCG 82b and 82c	Denmark	1982-1990	Randomized controlled	Left-sided vs. right-sided	Death from any cause;	Hospital-based

Trials[7]			trial	radiotherapy; radiotherapy vs. without radiotherapy	death from coronary heart disease; death from myocardial infarction; coronary heart disease; myocardial infarction	
Cancer Research Campaign Trial[8]	UK	1970-1980	Randomized controlled trial	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Death from any cause; cardiac mortality	Hospital-based
Oslo study[9]	Norway	1964-1972	Randomized controlled trial	Radiotherapy vs. without radiotherapy	Cardiac mortality; death form myocardial infarction	Hospital-based
CRC Trial[10]	UK	1970-1975	Randomized controlled trial	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Death from any cause; cardiac mortality	Hospital-based
Jones JM[11]	UK	1949-1955	Prospective cohort	Radiotherapy vs. without radiotherapy	Cardiac mortality	Hospital-based
NCCTG Trial[12]	USA	2000-2005	Randomized controlled trial	Radiotherapy vs. without radiotherapy	Cardiac mortality; chronic heart failure	Hospital-based
Population-based tumor registry/database reviews						
Ontario cancer registry						
Paszat LF[13]	Canada	1973-1992	Prospective cohort	Left-sided vs. right-sided	Death from	Population-based

				radiotherapy	myocardial infarction	
SEER database cohort study						
Patt DA[14]	Multi-national	1986-1993	Prospective cohort	Left-sided vs. right-sided radiotherapy	Coronary heart disease; chronic heart failure; valvular heart disease; arrhythmia	Population-based
Pinder MC[15]	Multi-national	1992-2002	Prospective cohort	Left-sided vs. right-sided radiotherapy; Radiotherapy vs. without radiotherapy	Chronic heart failure	Population-based
Harlan LC[16]	USA	1996-1999	Prospective cohort	Radiotherapy vs. without radiotherapy	Chronic heart failure; myocardial infarction	Population-based
Darby SC[17]	Multi-national	1973-2001	Prospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; cardiac mortality; death from coronary heart disease; death from myocardial infarction	Population-based
Henson KE[18]	Multi-national	1973-2008	Prospective cohort	Left-sided vs. right-sided radiotherapy	Cardiac mortality	Population-based
Jacobson JS[19]	Multi-national	1982-1990	Prospective cohort	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Coronary heart disease; myocardial infarction	Population-based
Giordano SH[20]	USA	1973-2000	Prospective cohort	Left-sided vs. right-sided radiotherapy	Death from coronary heart disease	Population-based
Swedish Cancer						

Registry						
Rutqvist LE[21]	Sweden	1970-1986	Prospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; cardiac mortality; death from myocardial infarction	Population-based
Stockholm Breast Cancer Study Group						
Gyenes G[22]	Sweden	1971-1976	Prospective cohort	Radiotherapy vs. without radiotherapy	Cardiac mortality; death from coronary heart disease; death from myocardial infarction; myocardial infarction	Hospital-based
Rutqvist LE[23]	Sweden	1976-1987	Prospective cohort	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Myocardial infarction; death from myocardial infarction	Population-based
Thames Cancer Registry						
Roychoudhuri R[24]	UK	1971-1998	Prospective cohort	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Death from any cause; cardiac mortality; death from coronary heart disease	Population-based
Swedish National Cancer Registry and DBCCG						
McGale P[25]	Denmark and	1976-2006	Prospective cohort	Left-sided vs. right-sided	Cardiac mortality;	Population-based

	Sweden			radiotherapy	death from coronary heart disease; death from myocardial infarction; coronary heart disease; myocardial infarction; chronic heart failure; valvular heart disease; arrhythmia	
Darby SC[26]	Denmark and Sweden	1958-2001	Case-control	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Coronary heart disease; death from coronary heart disease	Population-based
NSW Central Cancer Registry						
Wang W[27]	Australia	1995	Prospective cohort	Left-sided vs. right-sided vs. without radiotherapy	Death from any cause; cardiac mortality; death from coronary heart disease; death from valvular heart disease; death from chronic heart failure	Hospital-based
Geneva Cancer Registry						
Bouchardy C[28]	Switzerland	1980-2004	Prospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; cardiac mortality	Population-based
BCCA study						

Stokes EL[29]	Canada	1990-1996	Retrospective cohort	Left-sided vs. right-sided radiotherapy	Cardiac mortality	Population-based
NRH radiation therapy registry						
Tjessem KH[30]	Norway	1975-1991	Prospective cohort	Left-sided vs. right-sided radiotherapy	Death from coronary heart disease	Population-based
Dutch Late Effects Breast Cancer Cohort						
Hooning MJ[31]	Netherlands	1970-1986	Prospective cohort	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Coronary heart disease; myocardial infarction; chronic heart failure; valvular heart disease	Population-based
Dutch population-based DCIS cohort						
Boekel NB[32]	Netherlands	1989-2004	Prospective cohort	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Cardiac mortality; coronary heart disease; myocardial infarction; chronic heart failure arrhythmia; valvular heart disease	Population-based
National Cancer Database						
Rutter CE[33]	USA	1998-2006	Prospective cohort	Left-sided vs. right-sided	Death from any cause	Population-based

				radiotherapy		
Single and Multi-institutional reviews						
Vallis KA[34]	USA	1982-1988	Retrospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; death from myocardial infarction; myocardial infarction	Hospital-based
Gutt R[35]	USA	1980-1994	Retrospective cohort	Left-sided vs. right-sided radiotherapy	Cardiac mortality; death from coronary heart disease; death from chronic heart failure	Hospital-based
Park CK[36]	USA	1986-1992	Retrospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; cardiac mortality; Coronary heart disease; chronic heart failure; arrhythmia	Hospital-based
Borger JH[37]	Multi-national	1980-1993	Prospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; cardiac mortality; death from coronary heart disease; death from myocardial infarction; coronary heart disease	Hospital-based
Dubois C[38]	Belgium	1998-2005	Case-control	Radiotherapy vs. without	Cardiac mortality;	Hospital-based

				radiotherapy	myocardial infarction	
Correa CR[39]	USA	1977-1995	Prospective cohort	Left-sided vs. right-sided radiotherapy	Coronary heart disease	Hospital-based
Hooning MJ[40]	Netherlands	1970-1975	Prospective cohort	Radiotherapy vs. without radiotherapy	Cardiac mortality	Hospital-based
Harris EE[41]	USA	1997-1994	Retrospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; cardiac mortality; death from myocardial infarction; death from chronic heart failure; coronary heart disease; myocardial infarction; chronic heart failure; valvular heart disease; arrhythmia	Population-based
Bouillon K[42]	Sweden	1954-1984	Retrospective cohort	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Cardiac mortality; death from coronary heart disease; death from chronic heart failure; death from valvular heart disease; arrhythmia	Population-based
Boerman LM[43]	Netherlands	1970-2006	Case-control	Radiotherapy vs. without radiotherapy	Coronary heart disease	Population-based
Nixon AJ [44]	USA	1968-1986	Prospective cohort	Left-sided vs. right-sided radiotherapy	Death from any cause; cardiac mortality	Hospital-based

Jagsi R[45]	USA	1984-2000	Prospective cohort	Left-sided vs. right-sided radiotherapy	Coronary heart disease; myocardial infarction	Hospital-based
Caussa L[46]	France	2003-2007	Prospective cohort	Radiotherapy vs. without radiotherapy	Coronary heart disease	Hospital-based
Geiger A[47]	USA	1980-2000	Case-control	Left-sided vs. right-sided radiotherapy; radiotherapy vs. without radiotherapy	Myocardial infarction	Population-based

Table S2. The quality assessment of included cohort studies using the Newcastle-Ottawa scale.

	Selection				**Comparability**		**Outcome**			
Author	Representativeness of Exposed Cohort	Selection of Non-Exposed Cohort	Ascertainment Of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Adjust for age	Adjust for other factors such as tumor size, tumor grade, type of surgery	Assessment of outcome	Follow-up length	Loss to follow-up rate	Total Quality Score
Wang W, 2011[27]	1	1	1	1	0	0	1	1	0	6
Vallis KA, 2002[34]	0	1	1	0	0	0	1	1	1	5
Rutter CE, 2014[33]	1	1	1	1	1	1	1	1	0	8
Gutt R, 2008[35]	0	1	1	1	0	0	1	1	0	5
Park CK,2011[36]	0	1	1	1	0	0	0	1	1	5
Darby SC, 2005[17]	1	1	1	1	0	0	1	1	1	7
Borger JH, 2007[37]	0	1	1	0	0	0	1	1	1	5
Correa CR,	0	1	1	1	0	0	1	1	1	6

2007[39]										
Hooning MJ, 2006[40]	0	1	1	0	1	0	1	1	1	6
Boekel NB, 2014[32]	1	1	1	1	1	0	1	1	1	8
Bouchardy C, 2008[28]	1	1	1	1	1	1	1	1	0	8
Stokes EL, 2011[29]	1	1	1	1	1	1	1	1	0	8
McGale P, 2011[25]	1	1	1	1	0	0	1	1	0	6
Roychoudhuri R, 2007[24]	1	1	1	1	1	0	1	1	1	8
Harris EE, 2006[41]	1	1	1	1	1	1	1	1	1	9
Gyenes G, 1998[22]	0	1	1	1	1	0	1	1	1	8
Tjessem KH, 2013[30]	1	1	1	1	0	0	1	1	0	6
Bouillon K, 2011[42]	1	1	1	1	1	1	1	1	0	8
Hooning MJ, 2007[31]	0	1	1	0	1	0	1	1	1	6
Rutqvist LE, 1990[21]	1	1	1	1	0	0	1	1	1	7

Paszat LF, 1999[13]	1	1	1	1	1	1	1	1	0	8
Nixon AJ, 1998[44]	0	1	1	1	1	1	1	1	1	9
Jagsi R, 2006[45]	0	1	1	0	1	0	1	1	1	7
Woodward WA, 2003[3]	0	1	1	0	0	0	1	1	1	5
Caussa L, 2010[46]	0	1	1	1	0	0	1	1	1	6

The quality of included studies was assessed by the Newcastle Ottawa scale. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories and a maximum of two stars for Comparability.

Selection: 1) Representativeness of exposed cohort: 1, study population truly or somewhat representative of a community/ population based study; 0, study population was sampled from a special population, ie. population from a company, hospital patients, data from the health insurance company or health examination organization, nurses, Adventist group.

2) Selection of non-exposed cohort: 1, drawn from the same community as the exposed cohort.

3) Ascertainment of exposure: 1, specific dietary assessment method of radiotherapy with validation; 0, no specific dietary assessment method or specific radiotherapy assessment method without validation

4) Demonstration that outcome was not present at start of study: 1, yes; 0, no.

Comparability: 1) 1, whether a study adjusted for age deliberately; 1, whether a study adjusted for other factors such as tumor size, tumor grade, type of surgery

Outcome: 1) Assessment of outcome:1, cases were confirmed by medical records or record linkage; 0, self-reported.

2) Was follow-up long enough for outcomes to occur: 1, duration of follow-up >= 5 year; 0, if duration of follow-up < 5 year.

3) Loss to follow-up rate: 1, complete follow-up or loss to follow up rate <=20 %; 0, follow-up rate < 80% or no description of those lost.

Table S3. The quality assessment of included case-control studies using the Newcastle-Ottawa scale.

	Selection				Comparability		Outcome			
Author	Adequacy of case definition	Representativeness of the cases	Selection of Controls	Definition of Controls	Adjust for age	Adjust for other factors such as tumor size, tumor grade, type of surgery	Assessment of outcome	Same method of ascertainment for cases and controls	Non-Response rate	Total Quality Score
Dubois C, 2010[38]	1	1	0	1	0	0	1	1	0	5
Boerman LM, 2014[43]	1	1	1	1	1	1	1	1	0	8
Geiger A, 2005[47]	1	1	1	1	1	1	1	1	0	8

The quality of included studies was assessed by the Newcastle Ottawa scale. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories and a maximum of two stars for Comparability.

Selection: 1) Adequacy of case definition: 1, cases were confirmed by medical records or record linkage; 0, self-reported.

2) Representativeness of the cases: 1, consecutive or obviously representative series of cases; 0, potential for selection biases or not stated.

3) Selection of Controls: 1, community controls; 0, hospital controls or no description.

4) Definition of Controls: 1, no history of cardiovascular events; 0, no description of source.

Comparability: 1) 1, whether a study adjusted for age deliberately; 1, whether a study adjusted for other factors such as tumor size, tumor grade, type of surgery.

Outcome: 1) Assessment of outcome: 1, cardiovascular events were confirmed by medical records or record linkage; 0, self-reported.

2) Same method of ascertainment for cases and controls: 1, yes; 0, no.

3) Non-Response rate: 1, same rate for both groups; 0, non respondents described rate different and no designation.

Table S4. The quality assessment of included randomized controlled studies using the Modified Jadad Scores.

Author	Randomization	Concealment of allocation	Withdrawals and dropouts	Total
EBCTCG report[1]	2	2	1	5
Valagussa P[2]	1	2	1	4
Stockholm Breast Cancer Trial[4]	1	2	0	3
Cuzick J[5]	1	1	1	3
SSBCG Trial[6]	2	1	1	4
DBCG 82b and 82c Trials[7]	2	2	1	5
Cancer Research Campaign Trial[8]	1	1	1	3
Oslo study[9]	2	1	1	4
CRC Trial[10]	1	1	1	3
NCCTG Trial[12]	1	2	1	4
Jones JM[11]	1	1	1	3

Randomization: 0, not randomized or inappropriate method of randomization; 1, the study was described as randomized; 2, the method of randomization was described and it was appropriate.

Concealment of allocation: 0, not describe the method of allocation concealment; 1, the study was described as using allocation concealment method; 2, the method of allocation concealment was described appropriately.

Double blinding: 0, no blind or inappropriate method of blinding; 1, the study was described as double blind; 2, the method of double blinding was described and it was appropriate.

Withdrawals and dropouts: 0, not describe the follow-up; 1, a description of withdrawals and dropouts.

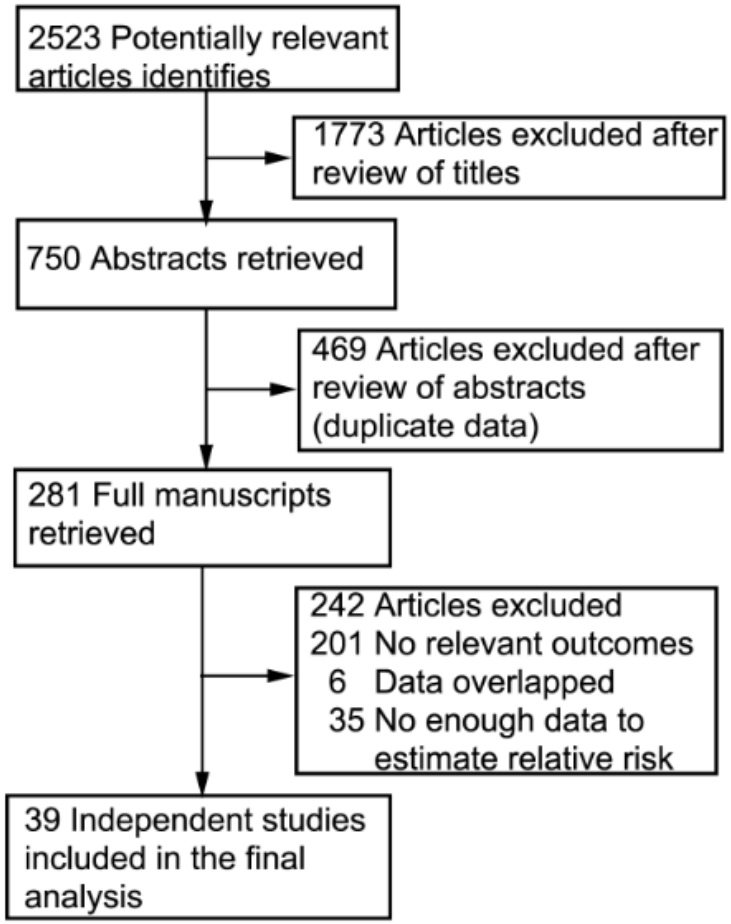

Figure S1. Flowchart of the selection of studies included in meta-analysis.

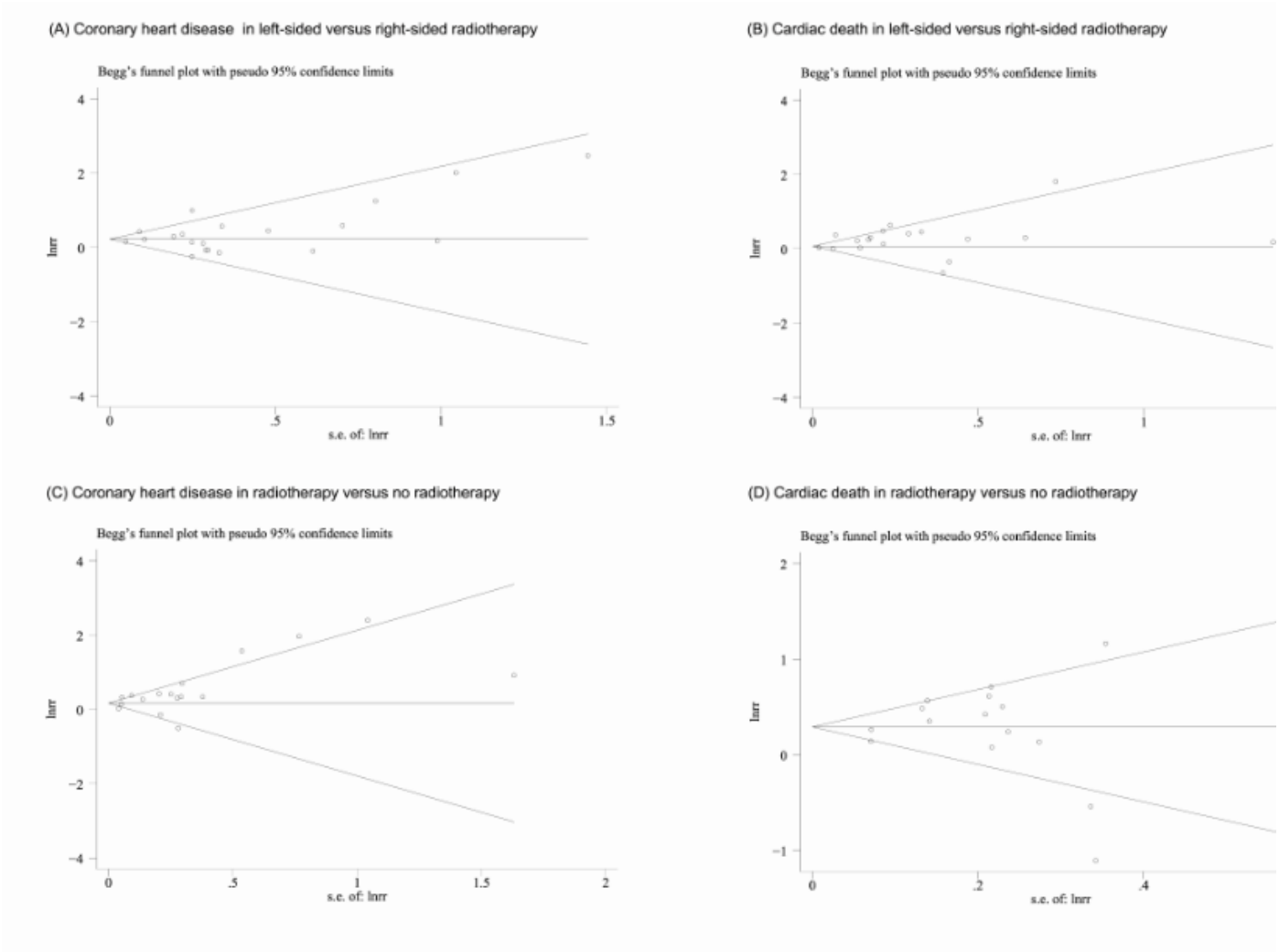

Figure S2. Funnel plots showing association of coronary heart disease and cardiac death with radiotherapy.

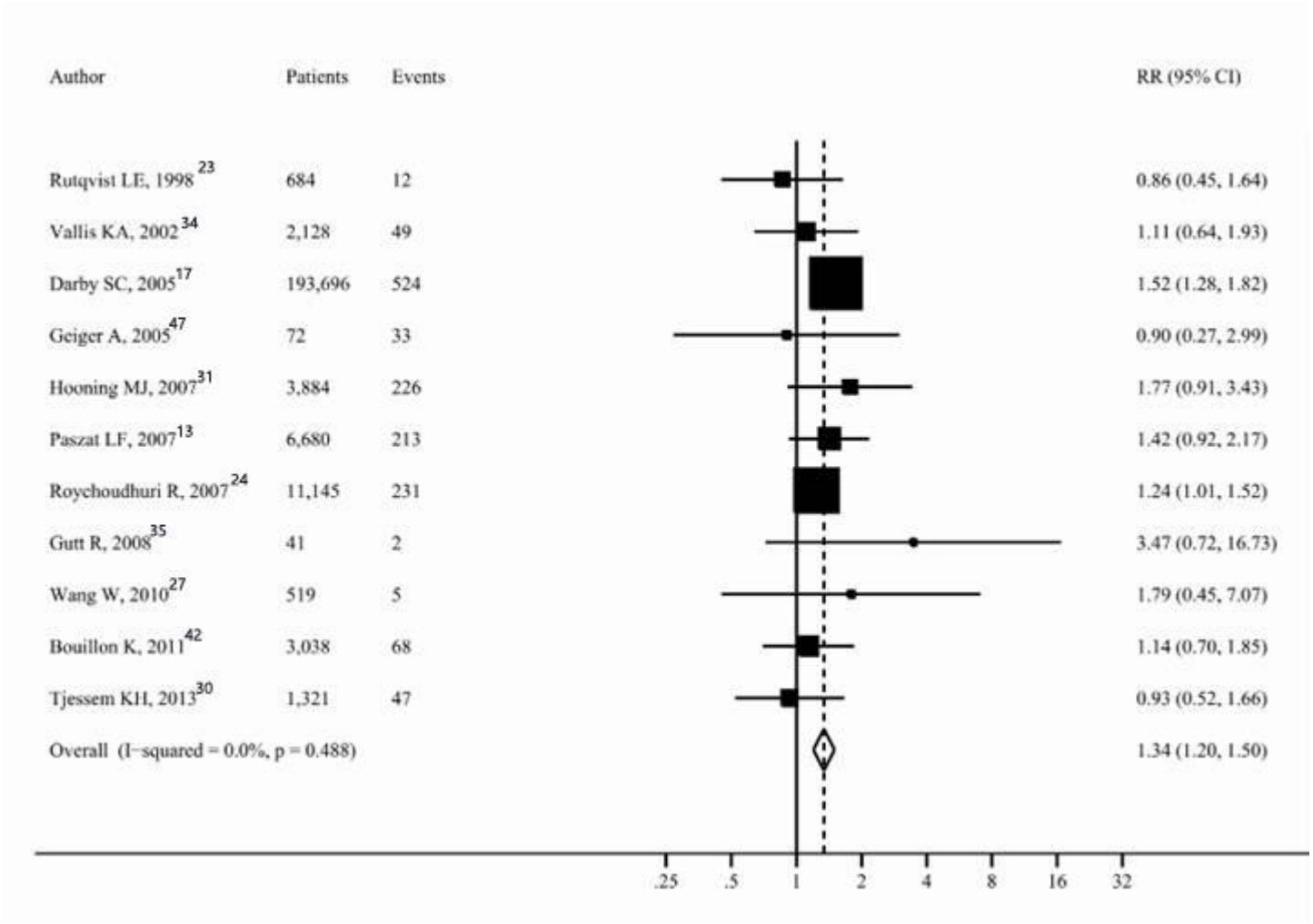

Figure S3. Forest plot for risk of myocardial infarction and death from coronary heart disease in patients with left-sided radiotherapy versus right-sided radiotherapy.

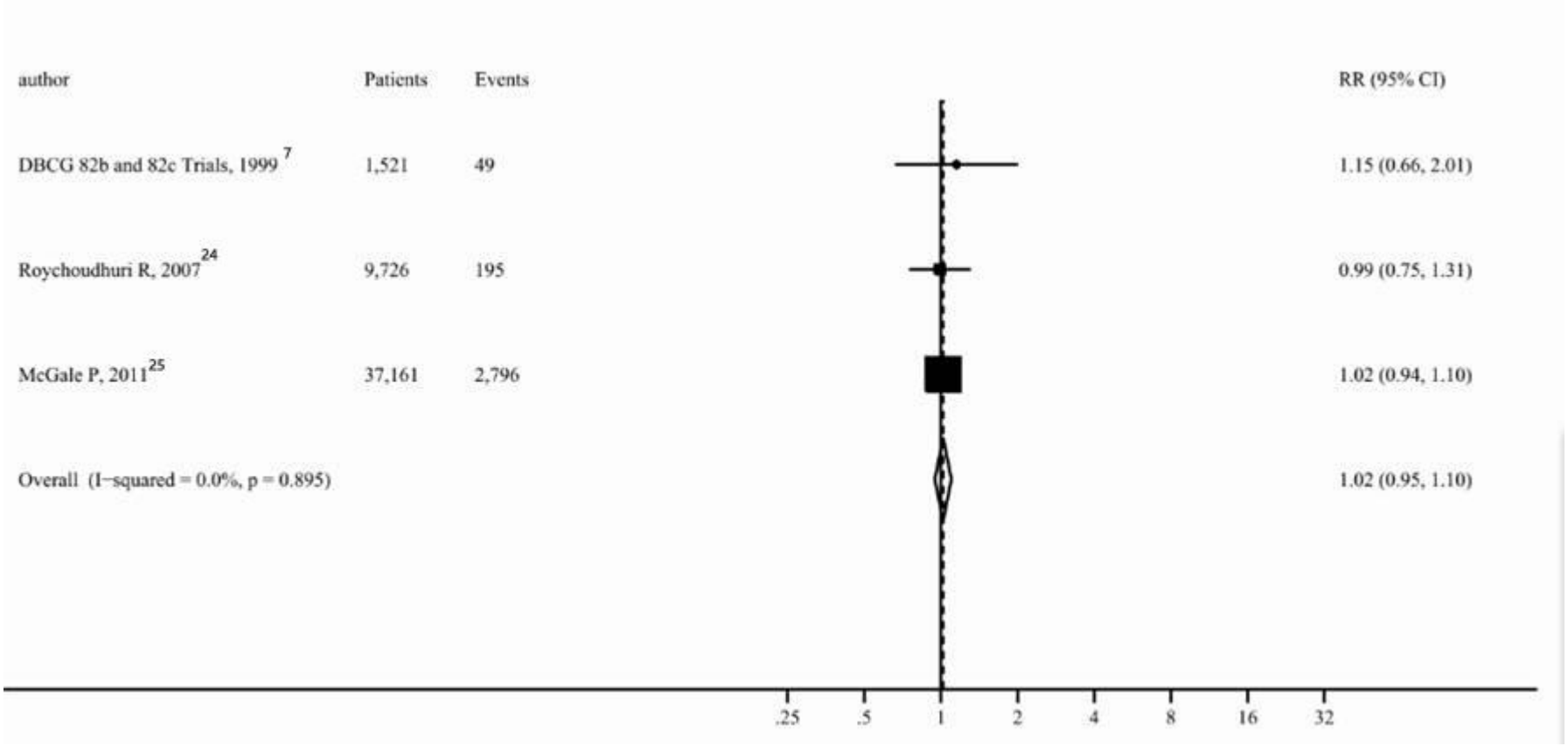

Figure S4. Forest plot for risk of coronary heart disease in unirradiated patients with left-sided versus right-sided breast cancer.

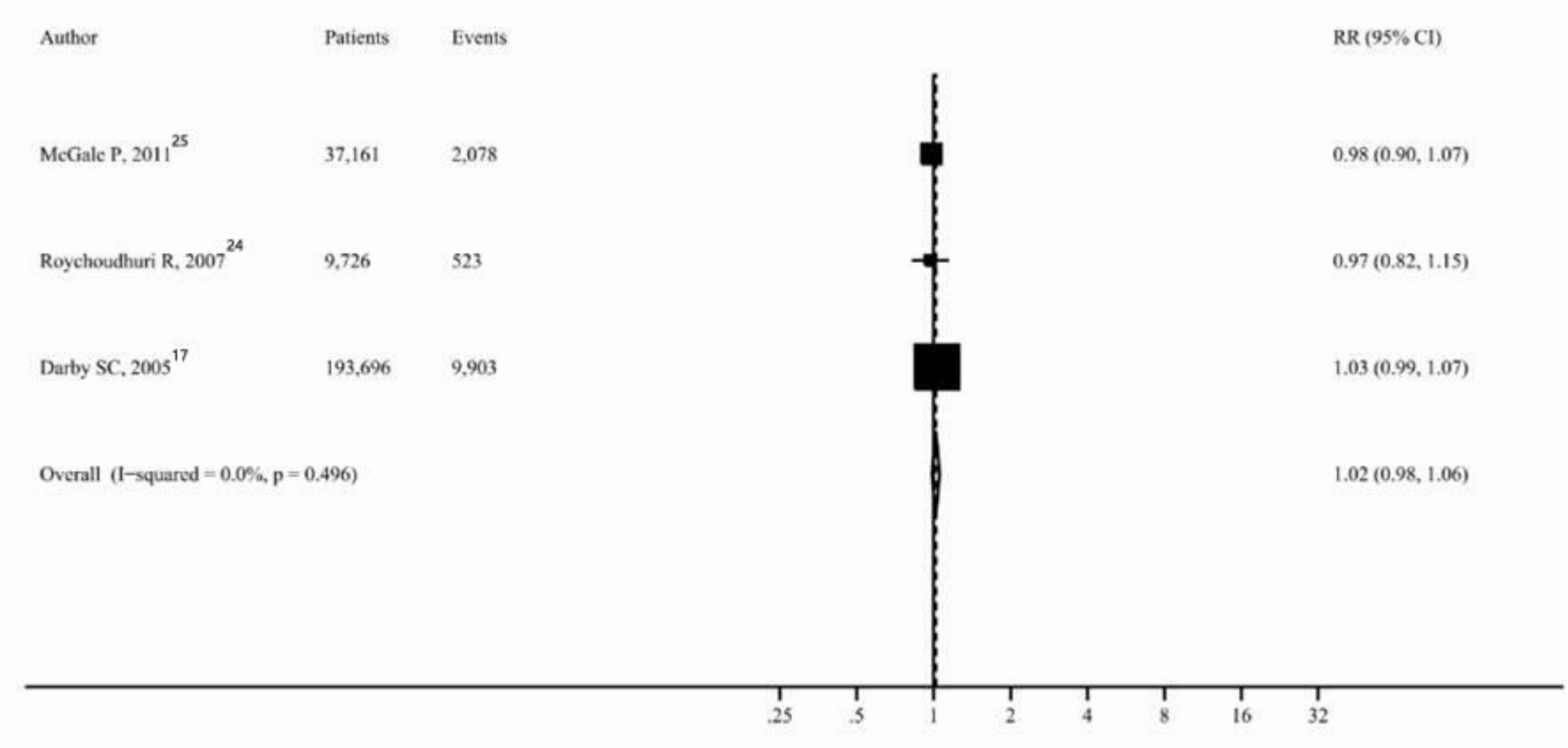

Figure S5. Forest plot for risk of cardiac death in unirradiated patients with left-sided versus right-sided breast cancer.

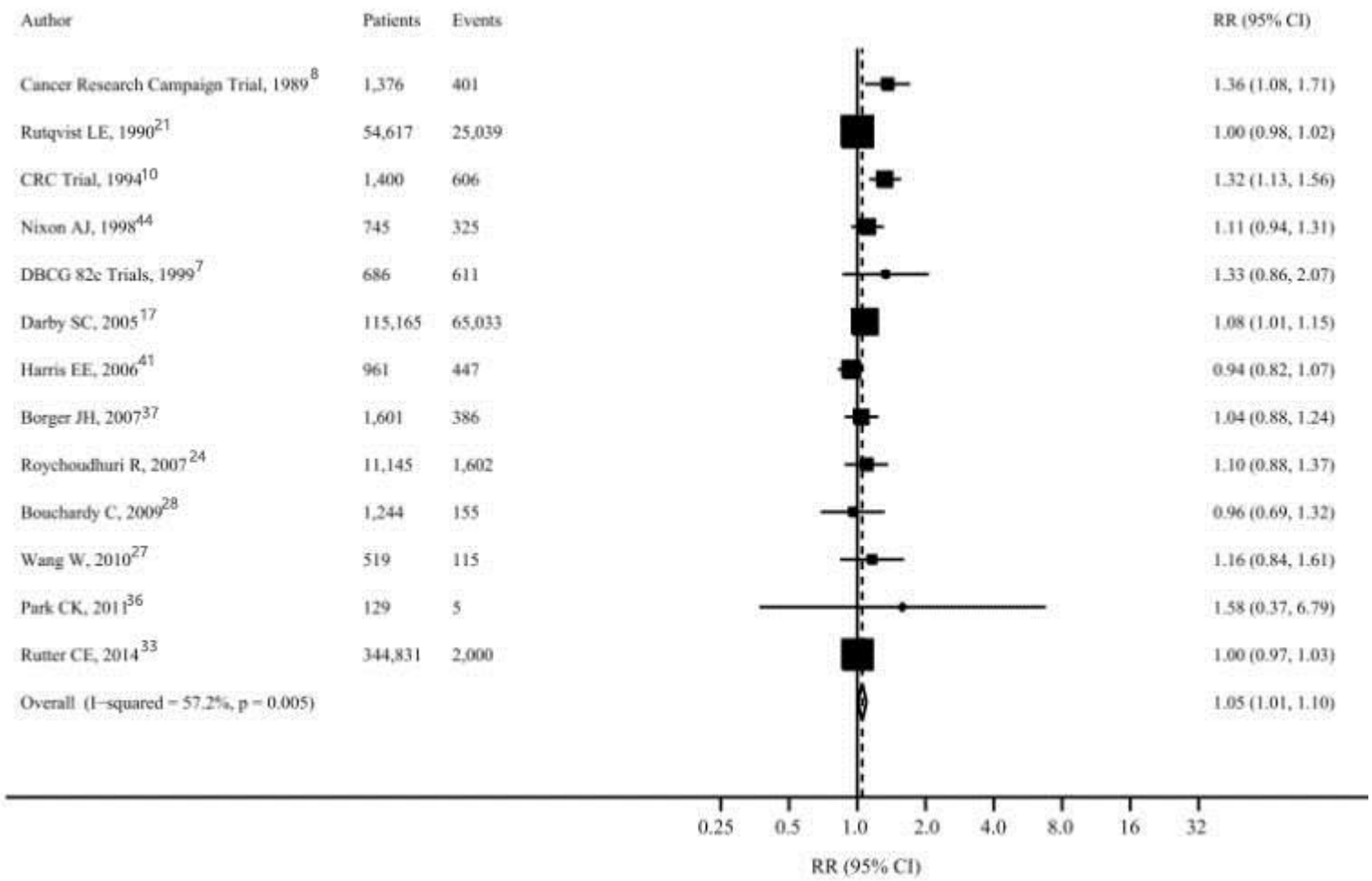

Figure S6. Forest plot for risk of death from any cause in patients with left-sided radiotherapy versus right-sided radiotherapy.

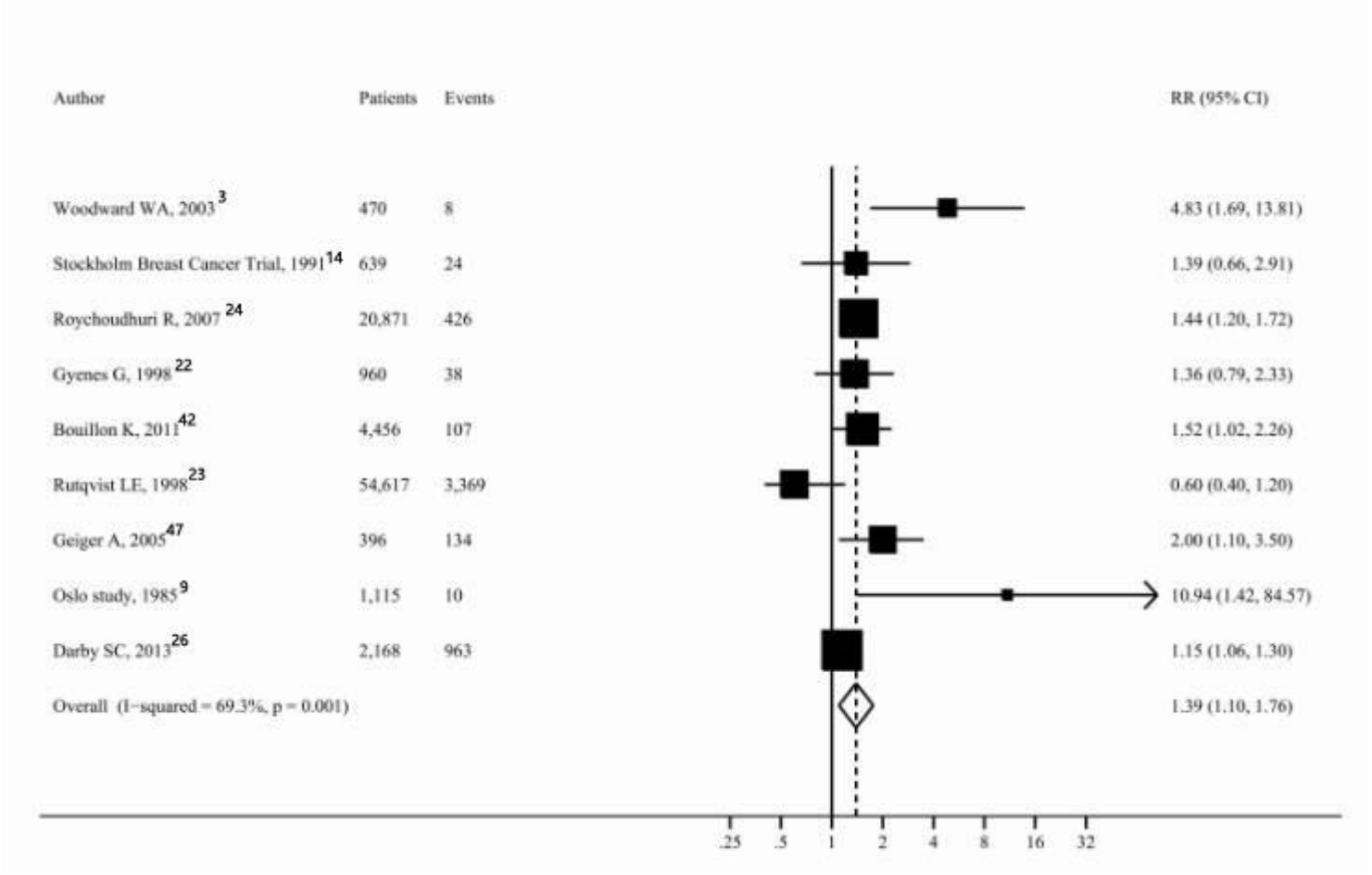

Figure S7. Forest plot for risk of myocardial infarction and death from coronary heart disease in patients with radiotherapy versus without radiotherapy.

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