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.

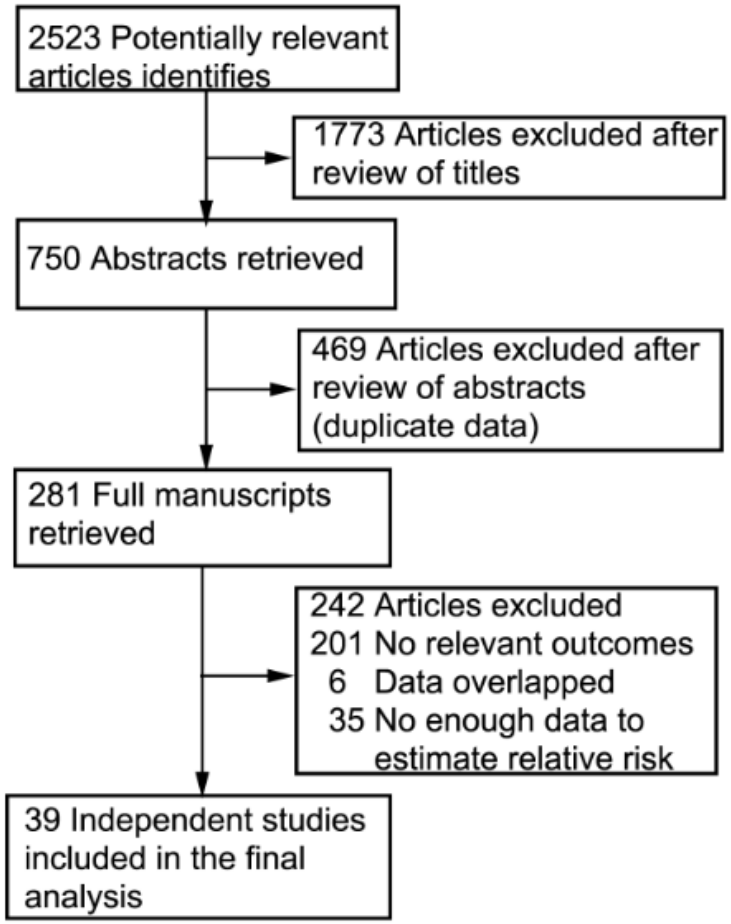

Figure S1. Flowchart of the selection of studies included in meta-analysis.

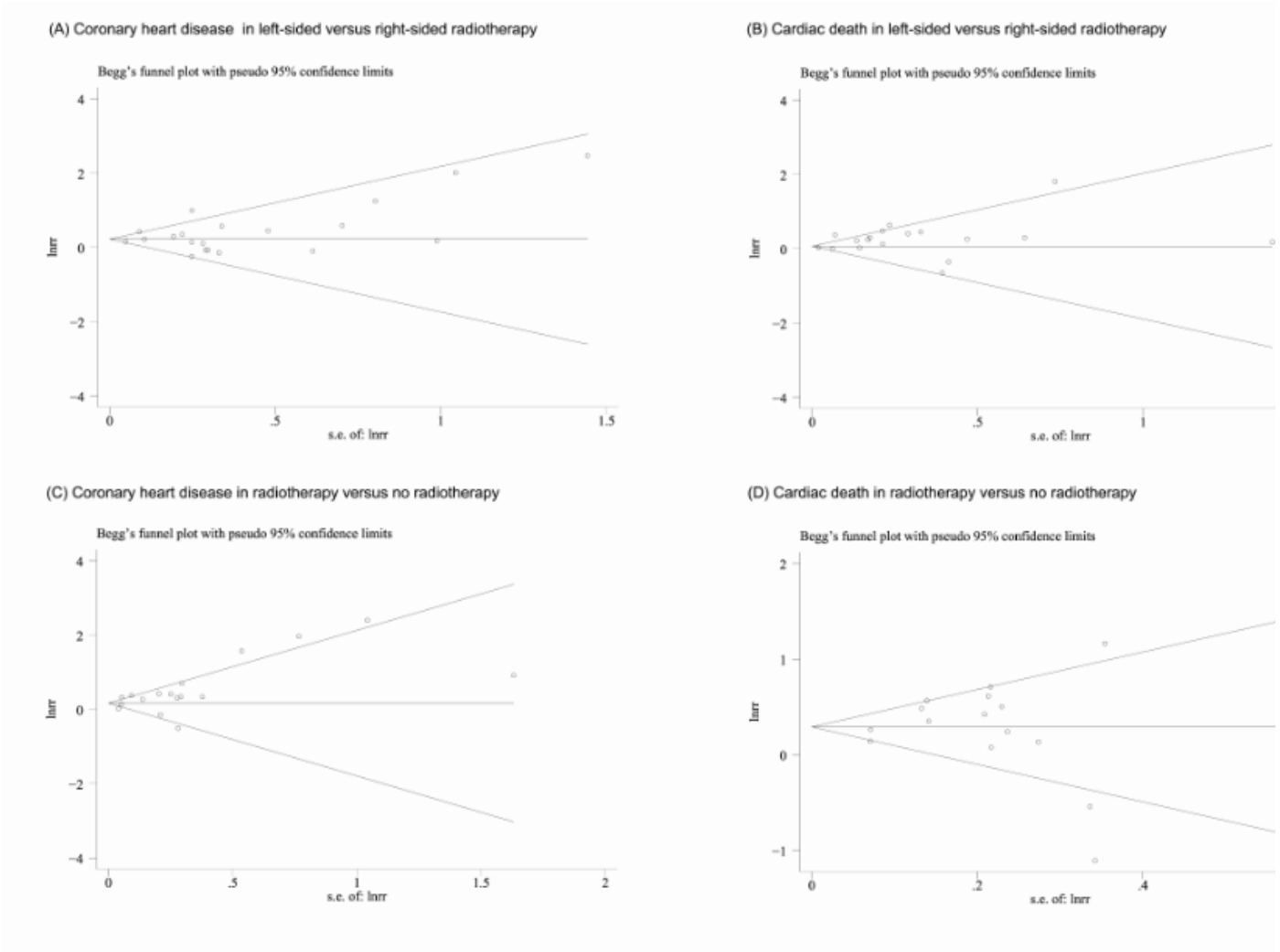

Figure S2. Funnel plots showing association of coronary heart disease and cardiac death with radiotherapy.

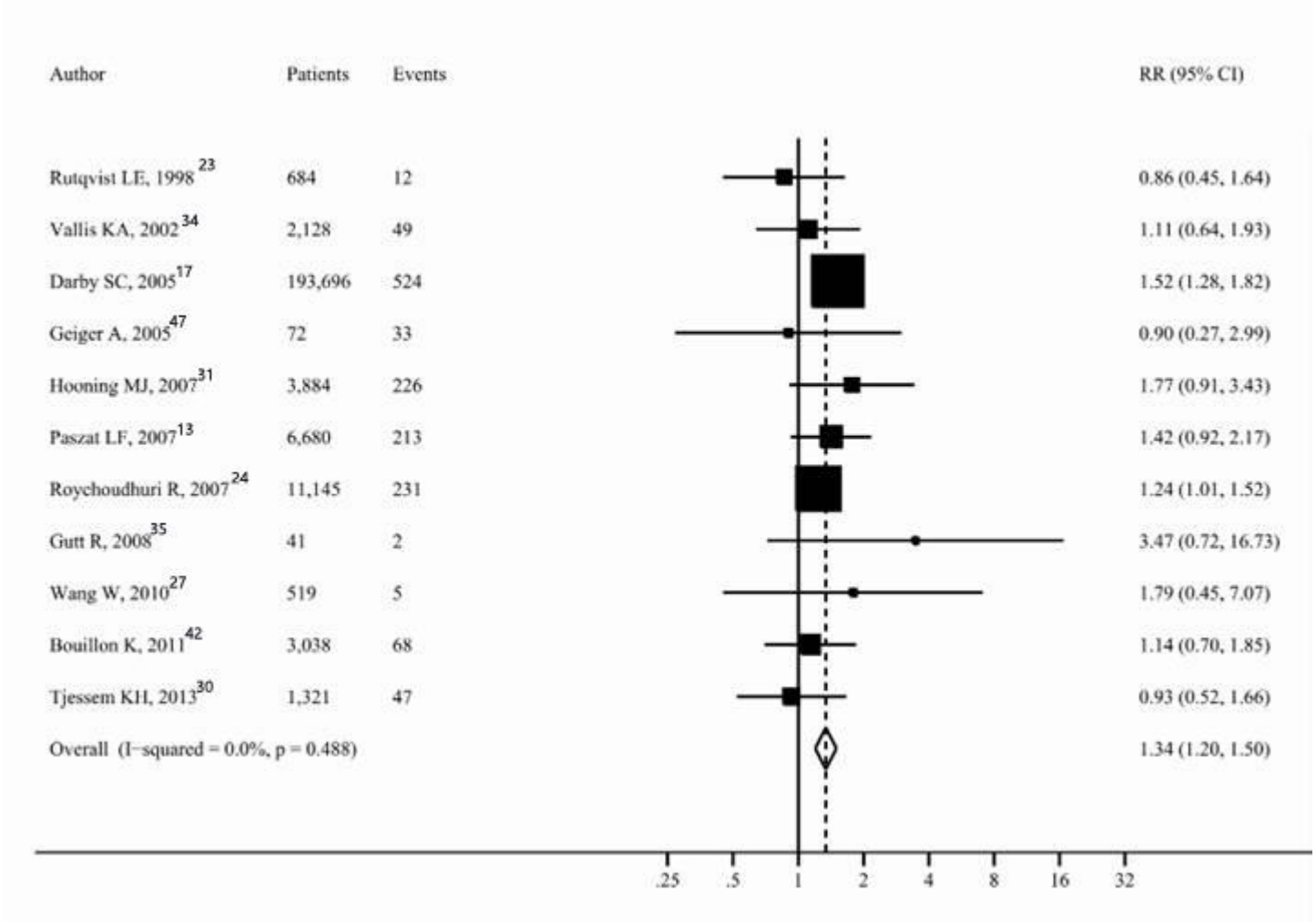

Figure S3. Forest plot for risk of myocardial infarction and death from coronary heart disease in patients with left-sided radiotherapy versus right-sided radiotherapy.

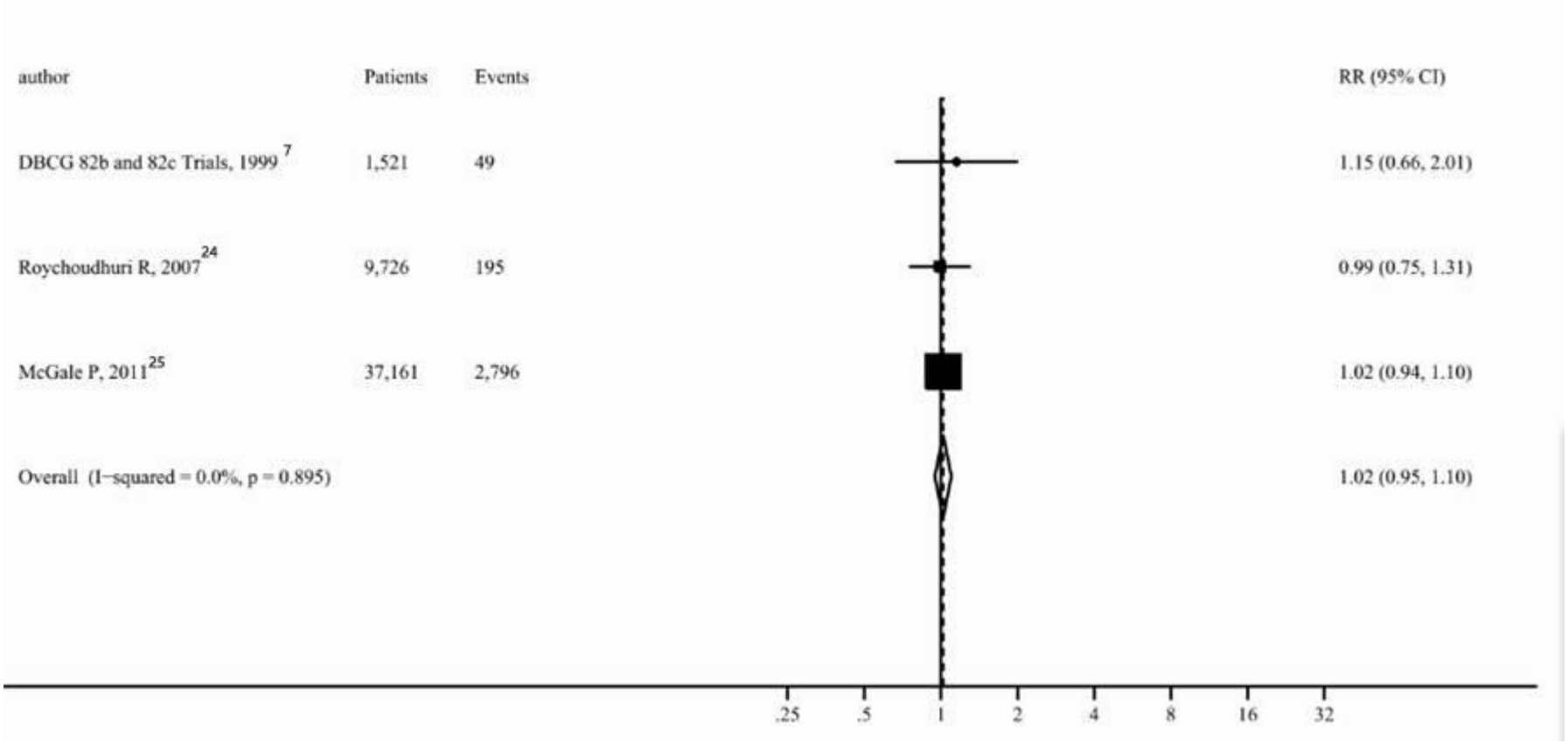

Figure S4. Forest plot for risk of coronary heart disease in unirradiated patients with left-sided versus right-sided breast cancer.

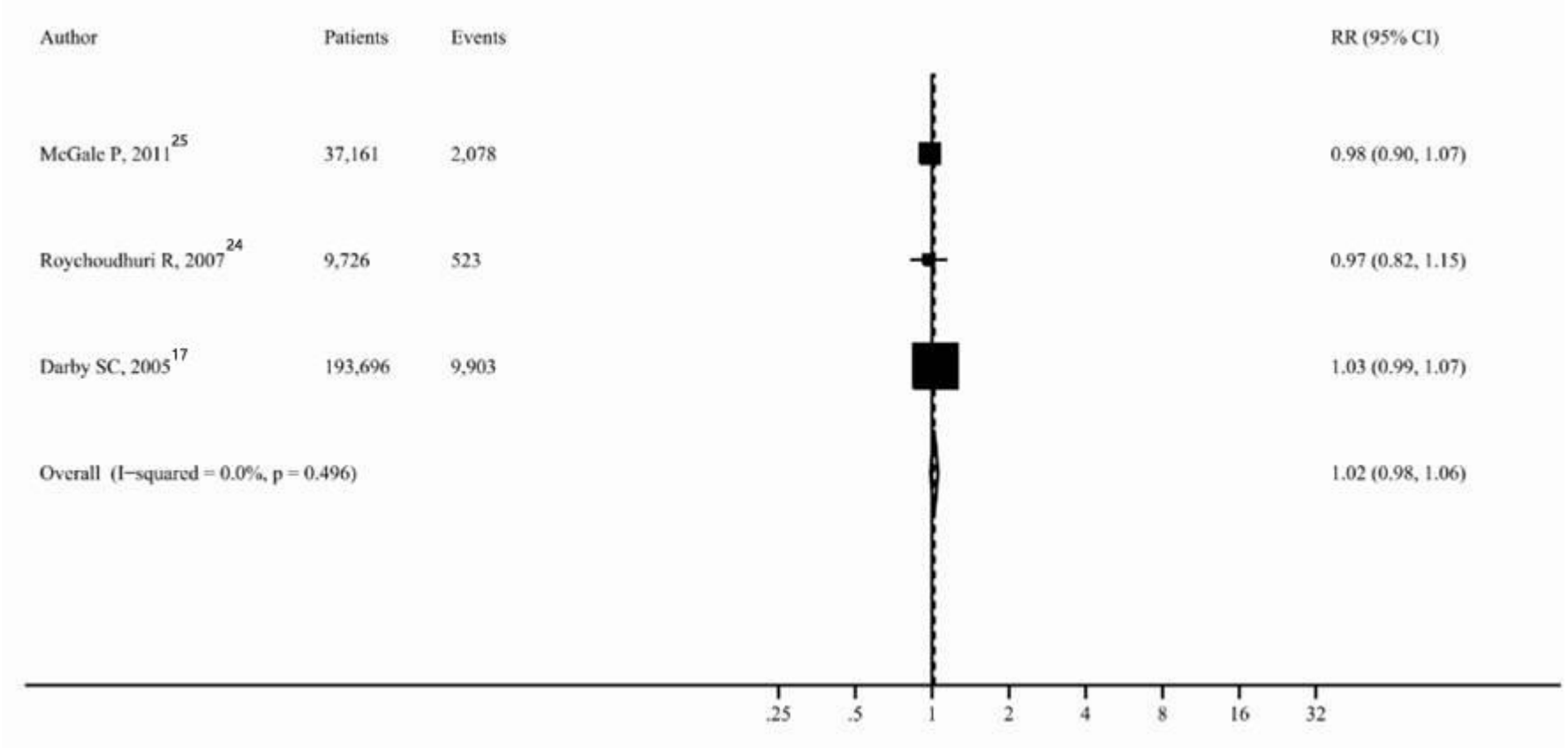

Figure S5. Forest plot for risk of cardiac death in unirradiated patients with left-sided versus right-sided breast cancer.

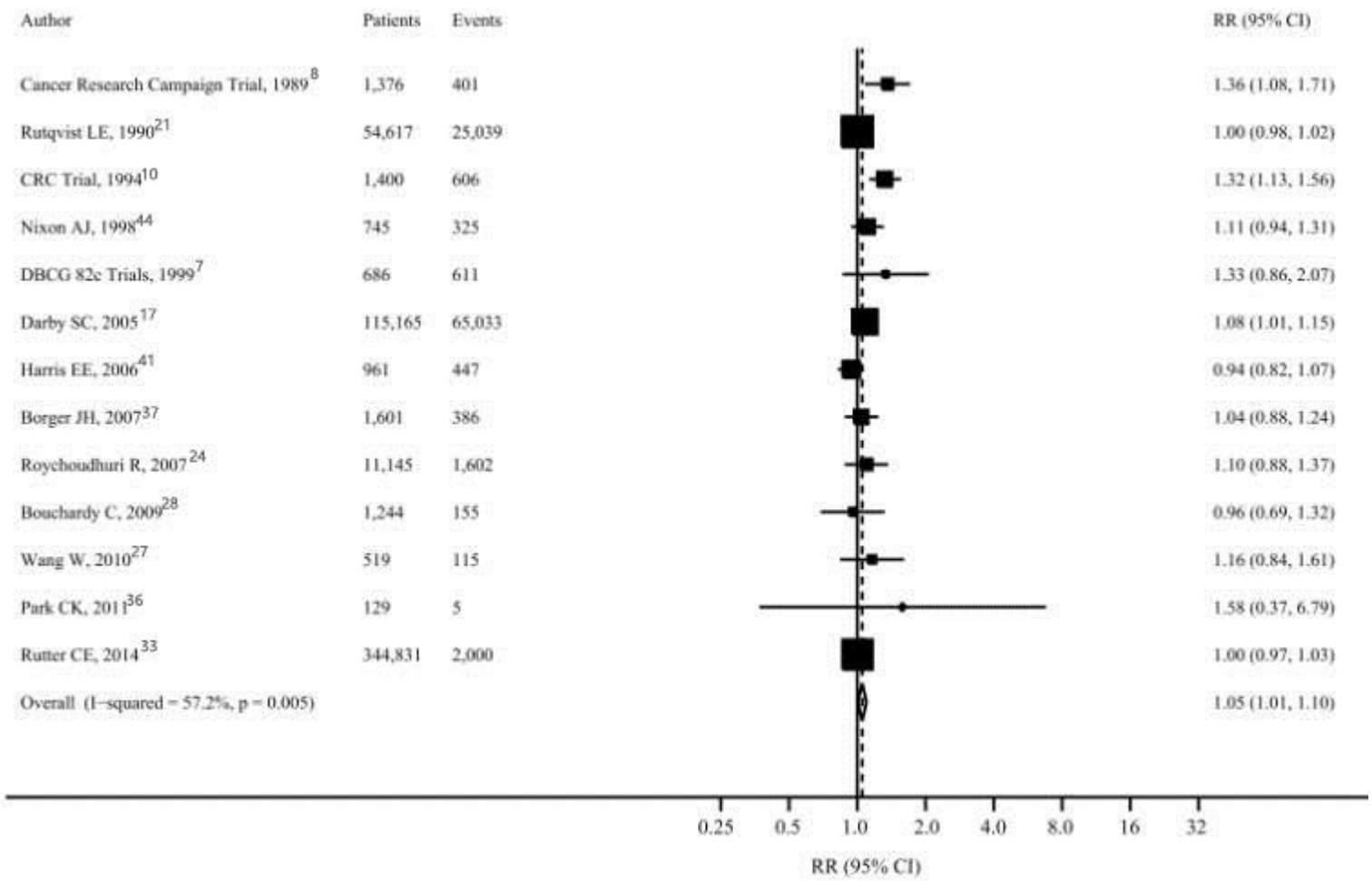

Figure S6. Forest plot for risk of death from any cause in patients with left-sided radiotherapy versus right-sided radiotherapy.

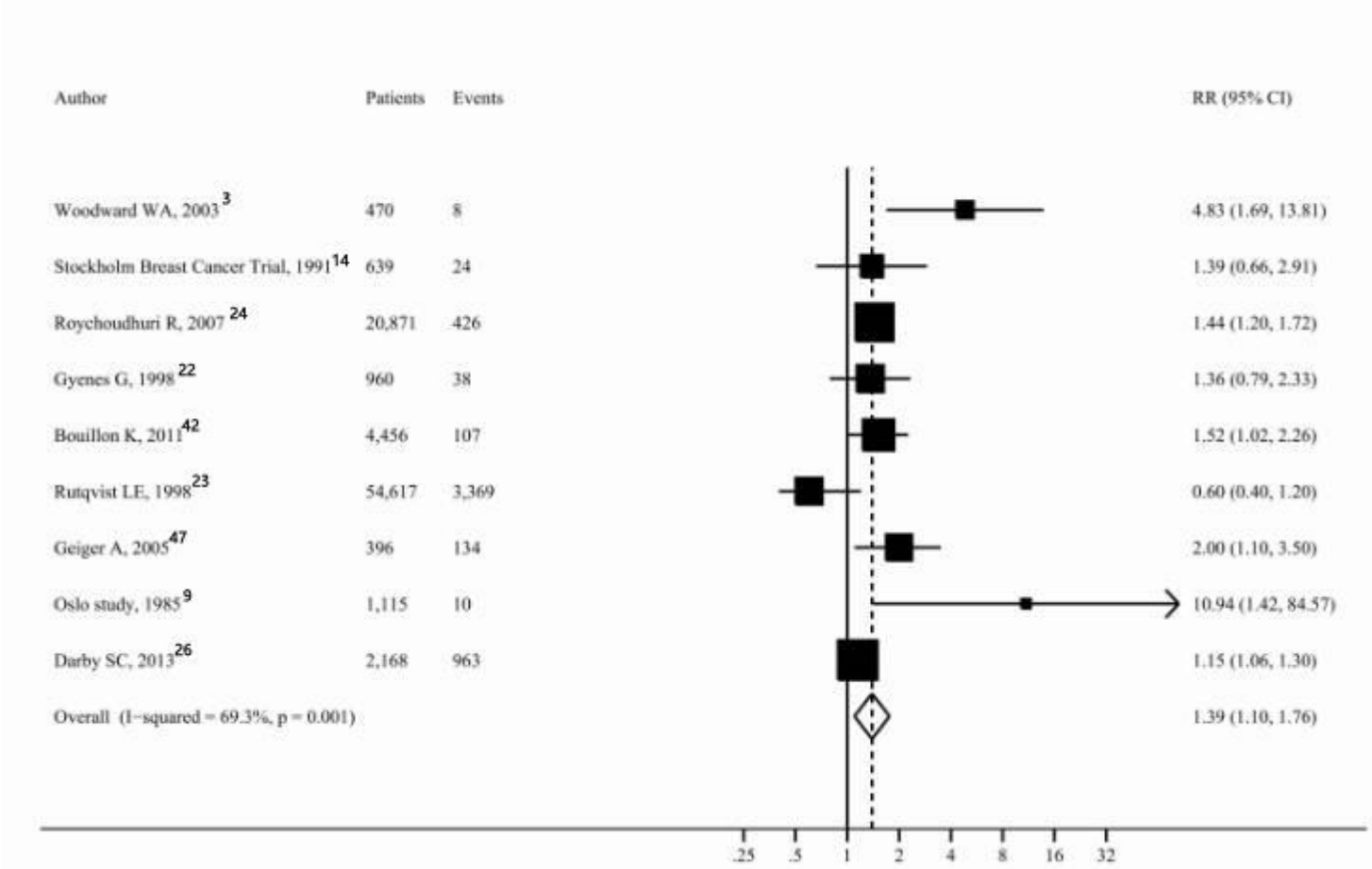

Figure S7. Forest plot for risk of myocardial infarction and death from coronary heart disease in patients with radiotherapy versus without radiotherapy.

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