Supplement to: Cardiac Mortality after Radiotherapy, Chemotherapy and Endocrine Therapy for Breast Cancer: Cohort Study of 2 Million Women from 57 Cancer Registries in 22 Countries

KE Henson, P McGale, SC Darby, DM Parkin, Y Wang, CW Taylor (Study conducted in collaboration with the International Association of Cancer Registries)

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Table S1. Registries and other organisations contributing data to the study and individuals who worked on the preparation of the data or who attended the Study Meeting

Country	Organisation	Individuals who worked on the Preparation of the Dat or attended the Study Meeting				
Europe: Bri	tain and Ireland					
UK	*Eastern Cancer Registration & Information Centre (Cambridge)	David Greenberg, Clement Brown, Karen Wright				
	*Northern and Yorkshire Cancer Registry and Information Service	David Forman, Phillip Deer, Michael Walkley				
	Scottish Cancer Registry	David Brewster, Catherine Storey				
	*Thames Cancer Registry	Henrik Møller, Karen Linklater				
	*West Midlands Cancer Intelligence Unit	Stacey Croft, Rosie Day				
	*Currently part of Public Health England					
Ireland	Ireland National Cancer Registry	Harry Comber				
Europe: No	rdic counties					
Denmark	Danish Breast Cancer Cooperative Group	Maj-Britt Jensen; Marianne Ewertz				
	Danish Cancer Society - Danish Cancer Registry	Georg Paludan Müller, Gerda Engholm, Hans cynthia				
Finland	Finnish Cancer Registry	Eero Pukkala				
Norway	Cancer Registry of Norway	Steinar Tretli				
Sweden	Gothenburg Regional Cancer Registry	Nils Conradi, Ingmarie Johanson				
	Regional Tumour Registry, Linköping	Bo Nordenskjöld, Helena Fohlin, Johan Rosell				
	The Swedish Cancer Registry (Stockholm & Umea)	Jan Adolfsson, Nils Olof Bengtsson, Per Hall, Anna Bennet				
Europe: Oth	ner countries					
Austria	Cancer Registry of Salzburg	Richard Greil, Johann Lettner				
	Cancer Registry of Tyrol	Wilhelm Oberaigner				
	Cancer Registry of Voralberg	Hans Concin, Hanno Ulmer				

Table S1 continued overleaf

Table S1 continued

Country	Organisation	Individuals who worked on the Preparation of the Data
Country	Organisation	or attended the Study Meeting
Estonia	Estonian Cancer Registry	Margit Mägi, Mare Tekkel, Kaja Rahu
France	Institut Gustave Roussy	Carole Rubino
Germany	Population Based Cancer Registry Bavaria	Gabriele Schubert-Fritschle, Martin Meyer
	Gemeinsames Krebsregister (Berlin)	Bettina Eisinger, Roland Stabenow
	Bremen Cancer Registry	Klaus Giersiepen
	Cancer Registry of Schleswig-Holstein Registerstelle	Alexander Katalinic
Italy	Friuli Venezia Giulia Cancer Registry	Luigino Dal Maso, Lorenzo Simonato, Loris Zanier, Diego Serraino, Margherita de Dottori, Massimo Rugge
	Latina Cancer Registry	Fabio Pannozzo, Antonella Fontana
	Lombardy Cancer Registry	Giovanna Tagliabue, Paolo Contiero, Sabrina Fabiano, Paolo Crosignani
	Modena Cancer Registry	Massimo Federico, Monica Pirani
	National Tumour Institute (Milan)	Russo Antonio
	Parma Province Cancer Registry	Vincenzo De Lisi, Paolo Sgargi
	Piedmont Cancer Registry	Roberto Zanetti, Stefano Rosso
	Ragusa Cancer Registry	Rosario Tumino, Aurora Sigona
	Sondrio Cancer Registry	Roberto Tessandori
	Tuscany Cancer Registry	Lorenzo Livi, Emanuelle Crocetti
	Umbria Cancer Registry	Cynthia Aristei, Francesco La Rosa, Fabrizio Stracci
	Venetian Tumour Registry	Paola Zambon
Lithuania	Lithuanian Cancer Registry	Juozas Kurtinaitis, Simona Letautiene
Netherlands	Eindhoven Cancer Registry	Isabelle Soerjomataram
	Netherlands Cancer Institute	Flora van Leeuwen, Berthe Aleman, Willem Klokman
Slovakia	National Cancer Registry of Slovak Republic	Martina Ondrusova

Table S1 continued overleaf

Table S1 continued

Country	Organisation	Individuals who worked on the Preparation of the Data or attended the Study Meeting
Slovenia	Cancer Registry of Slovenia	Maja Primic Zakelj
Spain	Catalan Institute of Oncology (Barcelona)	Josepa Ribes Puig
	Epidemiology Unit and Girona Cancer Registry	Rafael Marcos-Gragera
	Navarra Cancer Registry	Maria Eva Ardanaz Aicua
Switzerland	Geneva Cancer Registry	Christine Bouchardy, Massimo Usel
	Grisons Cancer Registry	Bertrand Camey, Harald Frick
	Cancer Registry of St. Gall-Appenzell	Silvia Ess
	Ticino Cancer Registry	Andrea Bordoni, Alessandra Spitale
North Ameri	ca	
Canada	Alberta Cancer Registry	Heather Bryant
	British Columbia Cancer Registry	Ivo Olivotto, Caroline Speers
	Ontario Cancer Registry	Laurence Paszat
USA	Connecticut Tumour Registry	Anthony Polednak
	Puerto Rico Central Cancer Registry	Mariela Torres Cintron
	Surveillance Epidemiology and End Results Program	Brenda Edwards
Other region	S	
Australia	New South Wales Central Cancer Registry	Paul Jelfs, Elizabeth Tracey, Helen Barraclough
Israel	Israel National Cancer Registry	Micha Barchana
Japan	Tumour & Tissue Registry Office (Hiroshima)	Nobue Nishi, Ritsu Sakata
•	Kanagawa Cancer Centre	Naoyuke Okamoto
	Nagasaki Prefectural Cancer Registry	Midori Soda

Note: Several other organisations provided preliminary data for the study, but did not have information on all the variables necessary for inclusion in the final analysis.

Text S1. Summary of Data Requested from Individual Cancer Registries

Cancer registries and other appropriate organisations in high income countries worldwide were invited to contribute to the study. Appropriate contacts were identified through the International Association of Cancer Registries and personal knowledge. A Data Sheet was made available to each organisation detailing the eligibility and exclusion criteria and the variables requested (see next page). Each contributing organisation assembled a patient-level data file locally including follow-up information. The file was then depersonalised before being transferred to Oxford, alongside the coding sheet used for any local variables. The data files were then collated and combined by the analysis team in Oxford.

Eligibility criteria:

- 1. Women diagnosed with carcinoma in situ in the breast, who received radiotherapy.
- 2. Women diagnosed with invasive breast cancer (regardless of whether they received radiotherapy) and who were not already in 1.

The term "index breast cancer" denoted the first event (either carcinoma in situ or invasive cancer) after the start of the registry that qualified the woman for entry to the study.

Exclusion criteria:

- Male sex
- Bilateral breast cancer or carcinoma in situ
- Previous invasive cancer (apart from non-melanoma skin cancer) on or before the date of diagnosis of the index breast cancer. A previous diagnosis of cancer in situ of a site other than the breast (e.g. carcinoma in situ of cervix uteri) was allowed
- Emigration at any time prior to date of diagnosis of the index breast cancer (even if subsequently reimmigrated)
- Immigration at any time (before or after date of index breast cancer diagnosis)
- Death on recorded date of diagnosis of the index breast cancer, or cancer diagnosed at autopsy
- Previous treatment with thoracic radiotherapy

Text S1 (continued)

Variable	Values recorded
Essential variables	
ID number	(depersonalised)
Date of birth (or age at diagnosis of index breast cancer)	DD/MM/YYYY
Date of diagnosis of index breast cancer	DD/MM/YYYY
Laterality of index breast cancer	Left / Right / Unknown / Bilateral*
Behaviour of index breast cancer	Malignant / In situ
Radiotherapy for index breast cancer ⁺	Yes / No / Unknown
Date of death or emigration or last known to be alive, or date	DD/MM/YYYY or Unknown
lost to follow-up	
Status on date above	Dead / Emigrated / Alive / Unknown
Underlying cause of death	Code ‡
Desirable variables	
Region/hospital	Country specific
Ethnic group	Codes used by cancer registry
Topography of breast cancer	Code ¶
Morphology of breast cancer	Code ¶
ER-status	Codes used by cancer registry
PR-status	Codes used by cancer registry
Stage of breast cancer	CIS § / Local ** / Regional ++ / Advanced ++ /
	Unknown
Type of surgery to breast	Breast Conserving Surgery / Mastectomy /
	Other / None / Unknown
Type of surgery to the axilla	Axillary node clearance / Axillary node
	sampling / Other / None / Unknown
Chemotherapy	Yes / No / Unknown
Endocrine therapy	Yes / No / Unknown
Ovarian ablation or suppression	Yes / No / Unknown
Dates of diagnosis of any subsequent invasive cancers	DD/MM/YYYY
(including invasive breast cancer, if recorded)	
Site of any subsequent invasive cancers	Code ‡
Laterality of any subsequent invasive lung or breast cancer	Left / Right / Unknown / Not applicable ¶ ¶ / Bilateral *
Morphology of any subsequent invasive cancer	Code ¶
Basis of diagnosis of any subsequent invasive cancer	Codes used by cancer registry
Contributory causes of death (all known)	Code(s) ‡

* Diagnosed in both breasts simultaneously (or within 4 months)

⁺ If possible, distinguishing between women who received radiotherapy and those for whom it was indicated but not necessarily received

‡ Coding schedule requested (for example ICD 7/8/9/10 or registry-specific code)

¶ Coding schedule requested (for example ICD-0 code, edition 1, 2, or 3, or registry-specific code)

§ Carcinoma in situ

- ** Node-negative
- ++ Node-positive or locally advanced
- ‡‡ Distant metastases
- $\P~\P$ If diagnosed in the trachea

Table S2. Tenth Revision International Classification of Diseases (ICD-10) codes used to define the categories of cardiac disease used in the analysis.

Cause of Death	ICD-10 codes
Ischaemic heart disease	120-125
Arrhythmia	144-49
Heart failure	101.2, 109.0, 111.0, 113.0, 113.2, 140-143, 150, 151.4-5, 151.7
Non-rheumatic valvular	134-139
Rheumatic valvular	101.1, 105-108, 109.1
Pericarditis	101.0, 109.2, 130-132
Other cardiac disease	101.8-9, 102.0, 109.8-9, 111.9, 113.1, 113.9, 127.1-9, 133, 151.0-3, 151.6, 151.8-9, 152
All cardiac disease	101, 102.0, 105-109, 111, 113, 120-125, 127.1-9, 130-152

Table S3. Data included in analyses.

	Organisation	Dates of breast cancer diagnosis	Period of follow-up	Number of women	Number given RT	% RT	Cardiac disease deaths
Europe: Brit	ain and Ireland						
UK	Eastern Cancer Registration & Information Centre (Cambridge)	1941 to 2006	1969 to 2007	43,544	23,266	53	628
	Northern and Yorkshire Cancer Registry and Information Service	1980 to 2004	1991 to 2006	51,701	29,723	57	597
	Scottish Cancer Registry	1996 to 2004	1997 to 2006	22,486	13,373	59	389
	Thames Cancer Registry	1960 to 2006	1960 to 2006	160,472	81,370	51	2,642
	West Midlands Cancer Intelligence Unit	1977 to 2004	1977 to 2007	65,781	39,470	60	1,929
Ireland	Ireland National Cancer Registry	1994 to 2004	1994 to 2006	13,594	6,117	45	114
Europe: Nor	rdic counties						
Denmark	Danish Breast Cancer Cooperative Group	1977 to 2005	1978 to 2011	57,663	28,529	49	2,046
	Danish Cancer Registry	1943 to 1977	1943 to 2001	44,217	30,923	70	3,632
Finland	Finnish Cancer Registry	1953 to 2006	1969 to 2006	76,194	45,850	60	5,310
Norway	Cancer Registry of Norway	1986 to 2004	1986 to 2006	20,310	9,644	47	187
Sweden	Gothenburg Regional Cancer Registry	1989 to 2006	1989 to 2007	12,651	6,925	55	279
	Regional Tumour Registry, Linköping	1986 to 2003	1986 to 2004	7,077	5,209	74	212
	The Swedish Cancer Registry (Stockholm & Umea)	1976 to 2006	1976 to 2006	28,332	16,414	58	1,262

Table S3 continued overleaf

Table S3 continued

	Organisation	Dates of breast cancer diagnosis	Period of follow-up	Number of women	Number given RT	% RT	Cardiac disease deaths
Europe: Oth	er countries						
Austria	Cancer Registry of Salzburg	1962 to 2007	1979 to 2007	6,011	3,556	59	91
	Cancer Registry of Tyrol	1988 to 2003	1988 to 2005	4,138	1,812	44	114
	Cancer Registry of Voralberg	1985 to 2003	1985 to 2007	1,459	1,320	90	18
Estonia	Estonian Cancer Registry	1968 to 2000	1968 to 2005	11,043	4,959	45	722
France	Institut Gustave Roussy	1954 to 1984	1954 to 2005	6,017	4,472	74	192
Germany	Population Based Cancer Registry Bavaria	1998 to 2007	1998 to 2007	30,954	23,545	76	55
	Gemeinsames Krebsregister (Berlin)	1961 to 2005	1961 to 2007	194,532	101,509	52	2,170
	Bremen Cancer Registry	1988 to 2005	1999 to 2007	1,935	1,884	97	5
	Cancer Registry of Schleswig-Holstein Registerstelle	1997 to 2004	1999 to 2007	9,425	7,508	80	53
Italy	Friuli Venezia Giulia Cancer Registry	1995 to 2003	1995 to 2005	516	516	100*	2
	Latina Cancer Registry	2002 to 2007	2004 to 2007	489	487	100*	0
	Lombardy Cancer Registry	1980 to 2000	1980 to 2005	3,015	533	18	38
	Modena Cancer Registry	1988 to 2005	1989 to 2007	5,074	2,494	49	48
	National Tumour Institute (Milan)	1999 to 2002	1999 to 2006	4,306	2,924	68	44
	Parma Province Cancer Registry	1994 to 2004	1994 to 2006	1,993	1,767	89	19
	Piedmont Cancer Registry	2000 to 2003	2000 to 2007	2,701	1,828	68	6
	Ragusa Cancer Registry	1990 to 2003	1990 to 2006	830	542	65	15
	Sondrio Cancer Registry	1997 to 2006	1998 to 2007	994	565	57	7
	Tuscany Cancer Registry	1985 to 2004	1985 to 2005	13,758	5,761	42	291
	Umbria Cancer Registry	1968 to 2004	1994 to 2006	3,721	2,040	55	52
	Venetian Tumour Registry	1987 to 2001	1987 to 2007	2,307	1,485	64	33

Table S3 continued overleaf

Table S3 continued

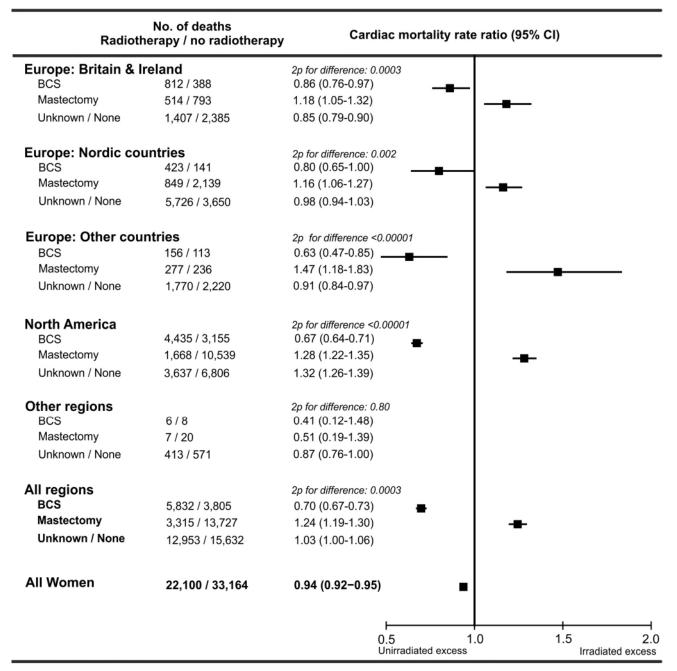
	Organisation	Dates of breast cancer diagnosis	Period of follow-up	Number of women	Number given RT	% RT	Cardiac disease deaths
Lithuania	Lithuanian Cancer Registry	1993 to 2005	1993 to 2007	10,812	4,765	44	192
Netherlands	Eindhoven Cancer Registry	1964 to 2004	1971 to 2004	18,319	11,840	65	0
	Netherlands Cancer Institute	1970 to 1987	1971 to 2004	7,101	6,217	88	235
Slovakia	National Cancer Registry of Slovak Republic	1978 to 2003	1978 to 2006	28,139	18,314	65	73
Slovenia	Cancer Registry of Slovenia	1971 to 2004	1988 to 2007	8,863	3,754	42	135
Spain	Institute Catalá d'Oncolgía (Barcelona)	1991 to 1997	1991 to 2005	850	646	76	15
	Cancer Registry of Girona	1963 to 2005	1978 to 2006	1,818	1,722	95	18
	Navarra Cancer Registry	1990 to 2002	1990 to 2007	3,187	2,332	73	24
Switzerland	Geneva Cancer Registry	1970 to 2004	1975 to 2005	802	630	79	15
	Grisons Cancer Registry	1989 to 2005	1989 to 2007	1,524	591	39	30
	Cancer Registry of St. Gall-Appenzell	1940 to 2005	1980 to 2007	2,689	1,076	40	53
	Ticino Cancer Registry	1995 to 2004	1996 to 2007	1,961	1,178	60	7
North Americ	a						
Canada	Alberta Cancer Registry	1989 to 2004	1989 to 2007	20,911	10,533	50	411
	British Columbia Cancer Registry	1985 to 2004	1985 to 2007	29,723	19,115	64	606
	Ontario Cancer Registry	1982 to 1997	1984 to 2007	55,477	55,477	100*	1,294
USA	Connecticut Tumour Registry	1935 to 1972	1935 to 2007	26,640	7,852	29	3,379
	Puerto Rico Central Cancer Registry	1987 to 2003	1987 to 2008	13,263	6,982	53	137
	Surveillance Epidemiology and End Results Program	1973 to 2008	1973 to 2008	738,145	327,521	44	24,413

Table S3 continued overleaf

Table S3 continued

	Organisation	Dates of breast cancer diagnosis	Period of follow-up	Number of women	Number given RT	% RT	Cardiac disease deaths
Other regions Australia	New South Wales Central Cancer Registry	1972 to 2004	1972 to 2004	46,993	27,023	58	845
Israel	Israel National Cancer Registry	1960 to 2000	1961 to 2006	4,827	1,503	31	108
Japan	Tumour & Tissue Registry Office (Hiroshima) Kanagawa Cancer Centre Nagasaki Prefectural Cancer Registry	1957 to 2001 1941 to 1989 1956 to 2005	1957 to 2007 1971 to 2007 1961 to 2005	695 1,631 638	104 372 638	15 23 100*	48 19 5

*Registry provided information only on women who were given radiotherapy.



BCS: Breast-conserving surgery 2p is for difference between BCS and mastectomy

Figure S1. Irradiated versus unirradiated women: Cardiac mortality rate ratios by geographic region and type of surgery.

Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country.

Table S4. Treated versus untreated women: Cardiac mortality rate ratios with and without adjustment for the effect of the other treatments in women aged 60+ years when diagnosed with cancer.

Treatment	Cardiac mortality rate ratio, treatment versus no treatment (95% CI)								
meatment	Unadjusted	Adjusted for other treatments							
Radiotherapy	0.87 (0.85-0.89)	0.88 (0.86-0.90)							
Chemotherapy	0.86 (0.80-0.92)	0.87 (0.81-0.94)							
Endocrine therapy	0.92 (0.88-0.95)	0.93 (0.89-0.97)							

Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country.

Calendry var of diagnosis Calendry Cale					All women					Women diagnosed <1990					Women diagnosed 1990+					
Calendary year of disgrosis Calendary (1970) 46,011 Calendary (1970) 46,011 Calendary (1970) 46,713 86,773 80,733 50.15 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 50.16 50.56 10.16 <th></th> <th></th> <th>Num</th> <th>ber</th> <th>Pe</th> <th>rcentage ir</th> <th>radiated</th> <th></th> <th>Num</th> <th>ber</th> <th>Pe</th> <th colspan="2">Percentage irradiated</th> <th>4</th> <th colspan="2">Number</th> <th colspan="2">Percentage irradiated</th> <th></th>			Num	ber	Pe	rcentage ir	radiated		Num	ber	Pe	Percentage irradiated		4	Number		Percentage irradiated			
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1970 1979 88,78 80,73 50.13 60.21 0.01 995 1.0.1 0.00 955 1.0.1 0.00 955 1.0.1 0.00 955 1.0.1 0.00 1.0.1 <td>,</td> <td></td>	,																			
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000 967,30 967,30 967,90 95.0 95.0 95.0 95.00 9			,						176,543	164,497	46.71	46.77	-0.06	0.72			-	-	-	-
Age at career Other With the second of the sec			,	,											,	,				0.37
adig cond cond <th< td=""><td></td><td>2000+</td><td>367,307</td><td>349,909</td><td>55.09</td><td>55.50</td><td>-0.42</td><td><0.001</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>367,30</td><td>7 349,909</td><td>55.09</td><td>55.50</td><td>-0.42</td><td><0.001</td></th<>		2000+	367,307	349,909	55.09	55.50	-0.42	<0.001	-	-	-	-	-	-	367,30	7 349,909	55.09	55.50	-0.42	<0.001
40-9 20,149 195,363 55.9 55.0 0.09 0.57 62,804 51.38 52.26 52.27 0.10 11,125 12,125 0.10 14,145 15,124 55.57 55.66 0.02 60.69 21,607 24,036 53.39 53.32 0.22 0.11 77,05 0.30 0.29 12,260 123,257 44.84 45.00 0.07 Race/ethnicity White 46,60 44,645 47,63 47,90 0.27 0.01 122,957 38.23 7.88 0.30 0.29 123,80 13.33 5.77 0.42 43,89 0.20 23,852 6.69 45.93 45.97 0.42 43,89 0.20 23,852 6.69 45.93 45.97 0.42 45.99 45.97 0.42 43,89 0.20 23,852 6.69 5.45 0.43 0.55 5.42 0.41 0.5 26.97 7.91 13.8 7.7 0.42 43 45.57 6.42	Age at cancer																			
sps sps< sps sps< sps< sps< sps sps sps< sps sps sps sps sps sps sps sps sps sp	diagnosis (years)		67,579	66,078					,	23,421	53.38				43,47	1 42,657				0.61
66-69 76-79 <th< td=""><td></td><td>40-49</td><td>204,149</td><td>195,363</td><td>55.59</td><td>55.50</td><td>0.09</td><td>0.57</td><td>62,804</td><td>59,169</td><td>53.38</td><td>52.86</td><td>0.52</td><td>0.07</td><td>141,34</td><td>5 136,194</td><td>56.57</td><td>56.64</td><td>-0.07</td><td>0.70</td></th<>		40-49	204,149	195,363	55.59	55.50	0.09	0.57	62,804	59,169	53.38	52.86	0.52	0.07	141,34	5 136,194	56.57	56.64	-0.07	0.70
Recent mark Resent mark		50-59	267,959	252,010	56.03	56.25	-0.22	0.11	77,296	71,682	52.62	52.72	-0.10	0.71	190,663	3 180,328	57.41	57.65	-0.24	0.14
Bace/ethnicity White 466,65 47.68 -0.27 0.01 132,602 12.38 37.89 0.31 0.00 28.352 26.695 45.99 45.57 0.42 Black 34,502 32,348 42.99 42.89 0.10 0.80 6.150 5.653 29.15 30.23 -1.08 0.20 28.352 26.695 45.99 45.57 0.42 Other/unknown 141.446 131.814 52.11 52.29 -0.41 0.56 53.514 52.66 52.31 -0.66 0.52 26.477 25.14 44.04 48.65 -0.44 Other/unknown 141.46 131.814 52.12 52.00 111.128 103.318 62.00 62.91 -0.41 0.6 52.39 -0.47 63.62 63.81 43.83 70.77 71.14 -0.8 62.074 58.404 40.45 60.46 -0.22 10.4778 97.64 63.68 63.63 63.07 50.40 50.12 0.41 65.66 <		60-69	261,607		53.09	53.32		0.12	85,023	78,650	49.06	48.89			176,584	4 165,386	55.04	55.42	-0.38	0.02
white 466,630 446,365 47.6 47.90 0.27 0.01 132,602 123,353 38.23 38.23 37.80 0.34 0.07 37.028 322,430 51.38		70-79	194,991	180,476	42.97	43.26	-0.29	0.07	62,131	56,949	38.98	39.28	-0.30	0.29	132,860	0 123,527	44.83	45.10	-0.27	0.18
Index 34,502 32,348 42.99 42.99 64.29 <	Race/ethnicity																			
Alan/pacific 29.90 28.28 45.27 45.91 0.10 0.12 3.569 3.511 2.561 2.57 0.56 0.52 2.57.47 2.51.11 48.01 48.65 0.64 0.01 Stage at career 0000 200.01 208.08 51.21 52.29 0.01 111.285 53.451 52.09 0.41 0.05 83.780 78.363 52.16 5.040 0.01 0.01 61.01 52.03 0.01		White	469,630	446,365	47.63	47.90	-0.27	0.01	132,602	123,935	38.23	37.89	0.34	0.07	337,028	8 322,430	51.33	51.75	-0.42	<0.001
Other/unknown 141,446 131,846 52,12 52,29 0.17 0.38 57,666 53,315 52,06 52,31 0.06 0.33 83,780 78,363 52,16 52,39 0.24 Stage at cancer		Black	34,502	32,348	42.99	42.89	0.10	0.80	6,150	5,653	29.15	30.23	-1.08	0.20	28,352	2 26,695	45.99	45.57	0.42	0.32
Not recorded 320,801 298,008 61.66 61.98 -0.32 0.01 111,285 103,318 62.50 62.91 -0.41 0.05 209,516 195,400 61.21 61.48 -0.27 Stage at career diagnosis 015 67,950 63,824 30.12 0.26 13.56 14.70 -1.14 0.08 62,074 58,404 40.45		Asian/pacific	29,906	28,628	45.27	45.91	-0.64	0.12	3,659	3,514	25.61	26.27	-0.66	0.52	26,24	7 25,114	48.01	48.65	-0.64	0.14
Stage at cancer diagnosis Cols G7,950 G8,824 Superimentary Bagional 244,231 229,963 54.55 54.65 0.10 0.51 67,504 63,827 54.83 0.15 0.50 289,745 276,958 54.49 55.37 0.04 <0 Regional 244,231 229,963 54.55 54.65 0.10 0.51 67,504 63,057 50.40 50.22 0.28 0.32 176,727 166,906 56.46 46.70 0.00 0.01 0.51 0.50 52.43 0.29 51,599 48,18 73.96 74.36 -0.40 0.01 0.07 52,806 48,999 67.66 67.97 -0.31 0.29 51,599 48,18 73.96 74.36 -0.40 -0.41 -0.48 -0.11 0.38 27.87 26,435 70.95 70.13 0.29 51,599 48,18 73.97 73.28 -0.21 0.01 244,952 225,806 49,915 10.38 27.87 74,43 32.46 0.02		Other/unknown	141,446	131,814	52.12	52.29	-0.17	0.38	57,666	53,451	52.06	52.13	-0.06	0.83	83,780	D 78,363	52.16	52.39	-0.24	0.34
diagnosis DCS 67,950 63,824 38,12 38,26 -0.14 0.60 58,76 5,420 13,56 14,70 -1.14 0.08 62,074 58,404 40,45 40,45 0.00 -0.44 40 Local 378,26 360,074 229,965 54,55 54,65 -0.10 0.51 67,504 63,57 54,35 0.02 229,745 276,956 56,14 56,36 -0.42 -0.44 -0.44 -0.44 -0.44 -0.44 -0.44 -0.44 -0.44 -0.22 -0.23 -0.24 -0.44		Not recorded	320,801	298,808	61.66	61.98	-0.32	0.01	111,285	103,318	62.50	62.91	-0.41	0.05	209,51	5 195,490	61.21	61.48	-0.27	0.08
Local 378,266 360,074 50.04 50.41 -0.37 0.002 88,521 83,116 34.03 33.87 0.15 0.50 289,745 276,958 54,93 55.37 -0.44 < Regional 244,213 229,963 54.55 54.56 -0.10 0.51 67,504 63,057 50.40 50.28 0.23 176,727 166,906 56.14 56.36 -0.22 Not recorded 104,405 97,183 70.77 71.14 -0.36 0.07 52,806 48,999 67.66 67.97 -0.31 0.29 51,599 48,184 73.96 74.36 -0.40 Surgery BCS 26,2831 252,280 72.85 72.95 -0.11 0.38 27,879 24,433 32.44 32.46 -0.02 170,248 161,879 24.28 24.57 -0.29 170,248 161,879 24.28 24.57 -0.29 170,248 161,879 24.28 24.57 -0.29 170,248 161,879 24.	Stage at cancer																			
Regional Metastatic/unknown Norecorded 244,231 229,963 54,55 54,65 -0.10 0.51 67,504 63,057 54,15 54,23 0.22 176,727 166,906 56,14 56,36 -0.22 Surgery 104,05 97,133 126,913 70,77 71,14 0.30 0,76 67,07 0.31 0.23 176,727 169,006 46,68 46,70 0.01 Surgery 8 6 77,77 71,14 0.38 70,48 70,45 70,97 0.31 0.22 10,47,78 74,30 74,36 0.40 Surgery 4 74,477 72,85 0.11 51,28 0.15 70,95 70,13 0.82 0.02 102,2 170,48 73,07 73,28 -0.29 None/unknown 399,406 370,468 51,13 51,28 0.15 10,19 162,05 141,49 20,21 0,01 70,01 70,30 63,23 40,10 10,00 10,00 10,00 10,00	diagnosis	DCIS	67,950	63,824	38.12	38.26	-0.14	0.60	5,876	5,420	13.56	14.70	-1.14	0.08	62,074	4 58,404	40.45	40.45	0.00	0.99
Metastatic/unknown Not recorded 201,433 186,919 50.27 50.39 -0.13 0.43 96,655 89,279 54.15 54.43 -0.28 0.23 104,778 97,640 46.68 46.70 -0.02 Surgery Mastetomy 97,183 72.85 72.95 0.11 0.38 27,879 26,435 70.95 70.13 0.82 0.04 234,952 225,845 73.07 73.28 -0.21 Mastetomy 249,487 236,322 26.87 72.95 0.11 0.38 27,879 74.43 32.44 32.46 -0.02 0.92 170,248 161,879 24.28 24.57 -0.29 None/unknown 84,561 78,993 71.97 72.22 -0.25 0.26 41,639 38,792 74.00 74.21 -0.21 0.50 24,502 24,010 70.00 236,501 220,267 53.84 54.57 -0.29 Radiotherapy Yes 52,570 494,935 100.00 100.00 0.00 <td></td> <td>Local</td> <td>378,266</td> <td>360,074</td> <td>50.04</td> <td>50.41</td> <td>-0.37</td> <td>0.002</td> <td>88,521</td> <td>83,116</td> <td>34.03</td> <td>33.87</td> <td>0.15</td> <td>0.50</td> <td>289,74</td> <td>5 276,958</td> <td>54.93</td> <td>55.37</td> <td>-0.44</td> <td><0.001</td>		Local	378,266	360,074	50.04	50.41	-0.37	0.002	88,521	83,116	34.03	33.87	0.15	0.50	289,74	5 276,958	54.93	55.37	-0.44	<0.001
Not recorded 104,405 97,183 70.7 71.14 -0.36 0.07 52,806 48,999 67.66 67.97 -0.31 0.29 51,599 48,184 73.96 74.36 -0.40 Surgery CS 262,831 252,280 72.85 72.95 -0.11 0.38 27,879 26,435 70.95 70.13 0.82 0.04 234,952 225,845 73.07 73.28 -0.29 Not recorded 399,406 370,468 51.13 51.28 -0.15 0.19 162,605 150,201 47.18 47.24 -0.07 0.70 236,802 20,267 53.44 54.03 -0.19 Not recorded 84,561 78,99 71.97 72.22 -0.5 153,004 150,001 47.18 47.21 -0.21 0.50 42,922 40,101 70.01 70.01 70.01 70.01 70.05 314,357 95,609 50.01 50.01 14.2452 100.00 100.00 100.00 100.00 100.01		Regional	244,231	229,963	54.55	54.65	-0.10	0.51	67,504	63,057	50.40	50.12	0.28	0.32	176,72	7 166,906	56.14	56.36	-0.22	0.20
Surgery BCS 262,831 252,280 72.95 72.95 0.01 0.38 27,879 26,435 70.95 70.14 0.02 0.92 170,248 54.95 72.95 0.29 None/unknown 399,406 370,468 51.13 51.28 -0.15 0.19 162,605 150,201 47.18 47.24 -0.07 0.70 236,801 220,267 53.84 54.33 -0.19 None/unknown 399,406 370,468 51.13 51.28 -0.15 0.19 162,605 150,201 47.18 47.24 -0.07 0.70 236,801 220,267 53.84 54.03 -0.19 Radiotherapy Yes 523,570 494,935 100.00 100.00 -0.00 -153,004 142,452 100.00 100.00 -0.00 -370,566 352,483 100.00 100.00 0.00 -0.00 -314,357 295,609 0.00 100.00 0.00 -0.153,838 147,419 0.00 0.00 -314,357 295,609 0.00 0.00 0.00 0.00 -0.33 0.08 205,299 191,125 50.97 51.40 -0.42		Metastatic/unknown	201,433	186,919	50.27	50.39	-0.13	0.43	96,655	89,279	54.15	54.43	-0.28	0.23	104,77	8 97,640	46.68	46.70	-0.02	0.93
BCS 262,831 252,280 72.85 72.95 -0.11 0.38 27,879 26,435 70.95 70.13 0.82 0.04 234,952 225,845 73.07 73.28 -0.21 Mastectomy 249,487 236,322 26.87 27.05 -0.18 0.15 79,239 74,443 32.44 32.46 -0.02 0.92 170,248 161,879 24.28 24.27 -0.29 0.29 Not recorded 399,406 370,468 51.13 51.28 -0.15 0.19 162,605 150,201 47.18 47.24 -0.07 0.70 236,922 20,01 70.01 70.00 -0.29 Radiotherapy versorded 84,561 78,935 100.00 100.00 0.00 -0 -0 153,004 142,452 100.00 100.00 -0 314,357 256,69 0.00 100.00 0.00 -0 314,357 256,69 0.01 100.00 0.00 -0 314,357 256,69 0.01 100,00 0.00 0.00 0.00 -0.01 314,357 256,91 55,		Not recorded	104,405	97,183	70.77	71.14	-0.36	0.07	52,806	48,999	67.66	67.97	-0.31	0.29	51,599	9 48,184	73.96	74.36	-0.40	0.15
BCS 262,831 252,280 72.85 72.95 -0.11 0.38 27,879 26,435 70.95 70.13 0.82 0.04 234,952 225,845 73.07 73.28 -0.21 Mastectomy 249,487 236,322 26.87 27.05 -0.18 0.15 79,239 74,443 32.44 32.46 -0.02 0.92 170,248 161,879 24.28 24.27 -0.29 0.29 Not recorded 399,406 370,468 51.13 51.28 -0.15 0.19 162,605 150,201 47.18 47.24 -0.07 0.70 236,922 20,01 70.01 70.00 -0.29 Radiotherapy versorded 84,561 78,935 100.00 100.00 0.00 -0 -0 153,004 142,452 100.00 100.00 -0 314,357 256,69 0.00 100.00 0.00 -0 314,357 256,69 0.01 100.00 0.00 -0 314,357 256,69 0.01 100,00 0.00 0.00 0.00 -0.01 314,357 256,91 55,	Surgery																			
None/unknown 399,406 370,468 51.13 51.28 -0.15 0.19 162,605 150,201 47.18 47.24 -0.07 0.70 236,801 220,267 53.84 54.03 -0.19 Radiotherapy Yes 523,577 494,935 100.00 100.00 0.00 - 153,004 142,452 100.00 100.00 0.00 - 314,357 295,609 100.00 0.00 0.00 - 314,357 295,609 0.00 0.00 0.00 0.00 - 314,357 295,609 0.00	•	BCS	262,831	252,280	72.85	72.95	-0.11	0.38	27,879	26,435	70.95	70.13	0.82	0.04	234,952	2 225,845	73.07	73.28	-0.21	0.10
Not recorded 84,561 78,893 71.97 72.22 -0.25 0.26 41,639 38,792 74.00 74.21 -0.21 0.50 42,922 40,101 70.01 70.00 -0.29 Radiotherapy Yes 523,570 494,935 100.00 0.00 - 153,004 142,452 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 - 370,566 352,483 <		Mastectomy	249,487	236,322	26.87	27.05	-0.18	0.15	79,239	74,443	32.44	32.46	-0.02	0.92	170,248	8 161,879	24.28	24.57	-0.29	0.05
Radiotherapy Yes 523,570 494,935 100.00 100.00 0.00 - 153,004 142,452 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00		None/unknown	399,406	370,468	51.13	51.28	-0.15	0.19	162,605	150,201	47.18	47.24	-0.07	0.70	236,80	1 220,267	53.84	54.03	-0.19	0.21
Yes 523,570 494,935 100.00 100.00 0.00 - 153,004 142,452 100.00 100.00 0.00 - 370,566 352,483 100.00 100.00 0.00 Chemotherapy Ves 115,195 107,882 63.84 63.87 -0.02 0.91 16,717 15,800 58.41 59.09 -0.68 0.21 98,478 92,082 64.77 64.69 0.08 -0.42 -0.44 -0.03 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.42 -0.41 -0.42 -0.41 -0.41 -0.42 -0.41 -0.41 </td <td></td> <td>Not recorded</td> <td></td> <td></td> <td>71.97</td> <td>72.22</td> <td>-0.25</td> <td>0.26</td> <td>41,639</td> <td></td> <td>74.00</td> <td>74.21</td> <td>-0.21</td> <td>0.50</td> <td></td> <td>-</td> <td>70.01</td> <td>70.30</td> <td>-0.29</td> <td>0.35</td>		Not recorded			71.97	72.22	-0.25	0.26	41,639		74.00	74.21	-0.21	0.50		-	70.01	70.30	-0.29	0.35
No 472,715 443,028 0.00 0.00 - 158,358 147,419 0.00 0.00 - 314,357 295,609 0.00 0.00 0.00 Chemotherapy Yes 115,195 107,882 63.84 63.87 -0.02 0.91 16,717 15,800 58.41 59.09 -0.68 0.21 98,478 92,082 64.77 64.69 0.08 No 355,681 329,821 52.72 53.09 -0.37 0.002 150,382 138,696 55.09 55.42 -0.33 0.08 205,299 191,125 50.97 51.40 -0.42 Unknown 16,193 15,260 72.16 71.97 0.19 0.70 3,504 3,204 63.98 62.64 1.34 0.25 12,689 12,056 74.42 74.44 -0.03 Endocrine therapy Vis Vis 140,759 132,171 41.31 41.04 0.25 12,689 12,050 52.03 52.63 -0.34 0.0 </td <td>Radiotherapy</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>,</td> <td>,</td> <td></td> <td></td> <td></td> <td></td> <td>,</td> <td>,</td> <td></td> <td></td> <td></td> <td></td>	Radiotherapy								,	,					,	,				
No 472,715 443,028 0.00 0.00 - 158,358 147,419 0.00 0.00 - 314,357 295,609 0.00 0.00 0.00 Chemotherapy Yes 115,195 107,882 63.84 63.87 -0.02 0.91 16,717 15,800 58.41 59.09 -0.68 0.21 98,478 92,082 64.77 64.69 0.08 No 355,681 329,821 52.72 53.09 -0.37 0.002 150,382 138,696 55.09 55.42 -0.33 0.08 205,299 191,125 50.97 51.40 -0.42 Unknown 16,193 15,260 72.16 71.97 0.19 0.70 3,504 3,204 63.98 62.64 1.34 0.25 12,689 12,056 74.42 74.44 -0.03 Endocrine therapy Vis Vis 140,759 132,171 41.31 41.04 0.25 12,689 12,050 52.03 52.63 -0.34 0.0 </td <td>.,</td> <td>Yes</td> <td>523.570</td> <td>494.935</td> <td>100.00</td> <td>100.00</td> <td>0.00</td> <td>-</td> <td>153.004</td> <td>142.452</td> <td>100.00</td> <td>100.00</td> <td>0.00</td> <td>-</td> <td>370.56</td> <td>5 352.483</td> <td>100.00</td> <td>100.00</td> <td>0.00</td> <td>-</td>	.,	Yes	523.570	494.935	100.00	100.00	0.00	-	153.004	142.452	100.00	100.00	0.00	-	370.56	5 352.483	100.00	100.00	0.00	-
Chemotherapy Yes 115,195 107,882 63.84 63.87 -0.02 0.91 16,717 15,800 58.41 59.09 -0.68 0.21 98,478 92,082 64.77 64.69 0.08 No 355,681 329,821 52.72 53.09 -0.37 0.002 150,382 138,696 55.09 55.42 -0.33 0.08 205,299 191,125 50.97 51.40 -0.42 Unknown 16,193 15,260 72.16 71.97 0.19 0.70 3,504 3,204 63.98 62.64 1.34 0.25 12,689 12,056 74.42 74.44 -0.03 Endocrine therapy Vir recorded 509,216 485,000 49.26 49.47 -0.21 0.03 140,759 132,171 41.31 41.04 0.27 0.15 368,457 352,829 52.30 52.63 -0.34 -0.34 0.25 12,689 12,056 74.42 74.44 -0.03 Endocrine therapy Yes 164,624 152,995 62.80 63.15 -0.36 0.04 31,797 </td <td></td> <td></td> <td>,</td> <td>,</td> <td></td> <td></td> <td></td> <td>-</td> <td>,</td> <td></td> <td>-</td>			,	,				-	,											-
No 355,681 329,821 52.72 53.09 -0.37 0.002 150,382 138,696 55.09 55.42 -0.33 0.08 205,299 191,125 50.97 51.40 -0.42 Unknown 16,193 15,260 72.16 71.97 0.19 0.70 3,504 3,204 63.98 62.64 1.34 0.25 12,689 12,056 74.42 74.44 -0.03 Endocrine therapy Yes 164,624 152,995 62.80 63.15 -0.36 0.04 31,797 29,199 60.86 61.26 -0.40 0.31 132,827 123,796 63.26 63.60 -0.34 0.09 152,985 144,69 -0.33 0.09 152,985 144,69 -0.33 0.08 61.26 -0.40 0.31 132,827 123,796 63.26 63.60 -0.34 -0.33 0.09 152,986 142,909 47.77 48.16 -0.39 No 289,196 268,949 50.73 51.07	Chemotherapy								,	,					,	,				
No 355,681 329,821 52.72 53.09 -0.37 0.002 150,382 138,696 55.09 55.42 -0.33 0.08 205,299 191,125 50.97 51.40 -0.42 Unknown 16,193 15,260 72.16 71.97 0.19 0.70 3,504 3,204 63.98 62.64 1.34 0.25 12,689 12,056 74.42 74.44 -0.03 Endocrine therapy Yes 164,624 152,995 62.80 63.15 -0.36 0.04 31,797 29,199 60.86 61.26 -0.40 0.31 132,827 123,796 63.26 63.60 -0.34 0.09 152,986 142,909 47.77 48.16 -0.39 Endocrine therapy Yes 164,624 152,995 62.80 63.15 -0.35 0.01 136,210 126,040 54.37 -0.33 0.09 152,986 142,909 47.77 48.16 -0.39 Unknown 8,175 7,307 69.50 <td></td> <td>Yes</td> <td>115.195</td> <td>107.882</td> <td>63.84</td> <td>63.87</td> <td>-0.02</td> <td>0.91</td> <td>16.717</td> <td>15.800</td> <td>58.41</td> <td>59.09</td> <td>-0.68</td> <td>0.21</td> <td>98.47</td> <td>8 92.082</td> <td>64.77</td> <td>64.69</td> <td>0.08</td> <td>0.72</td>		Yes	115.195	107.882	63.84	63.87	-0.02	0.91	16.717	15.800	58.41	59.09	-0.68	0.21	98.47	8 92.082	64.77	64.69	0.08	0.72
Unknown Not recorded 16,193 15,260 72.16 71.97 0.19 0.70 3,504 3,204 63.98 62.64 1.34 0.25 12,689 12,056 74.42 74.44 -0.03 Endocrine therapy Endocrine therapy Unknown 164,624 152,995 62.80 63.15 -0.36 0.04 31,797 29,199 60.86 61.26 -0.40 0.31 132,827 123,796 63.26 63.60 -0.34 -0.34 -0.31 No 289,196 268,949 50.73 51.07 -0.35 0.01 136,210 126,040 54.37 -0.33 0.09 152,986 142,909 47.77 48.16 -0.39 Unknown 8,175 7,307 69.50 69.39 0.12 0.87 2,147 1,953 58.64 56.53 2.11 0.17 6,028 5,354 73.37 74.08 -0.31			,	,		53.09	-0.37		150.382	,	55.09	55.42			,	,	50.97	51.40		0.01
Not recorded 509,216 485,000 49.26 49.47 -0.21 0.03 140,759 132,171 41.31 41.04 0.27 0.15 368,457 352,829 52.30 52.63 -0.34 -0.34 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.34 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34 -0.31 132,827 123,796 63.26 63.60 -0.34									-											0.96
Endocrine therapy Yes 164,624 152,995 62.80 63.15 -0.36 0.04 31,797 29,199 60.86 61.26 -0.40 0.31 132,827 123,796 63.26 63.60 -0.34 No 289,196 268,949 50.73 51.07 -0.35 0.01 136,210 126,040 54.05 54.37 -0.33 0.09 152,986 142,909 47.77 48.16 -0.39 Unknown 8,175 7,307 69.50 69.39 0.12 0.87 2,147 1,953 58.64 56.53 2.11 0.17 6,028 5,354 73.37 74.08 -0.70			,	,					,											0.004
Yes164,624152,99562.8063.15-0.360.0431,79729,19960.8661.26-0.400.31132,827123,79663.2663.60-0.34No289,196268,94950.7351.07-0.350.01136,210126,04054.0554.37-0.330.09152,986142,90947.7748.16-0.39Unknown8,1757,30769.5069.390.120.872,1471,95358.6456.532.110.176,0285,35473.3774.08-0.70	Endocrine therapy		,	,					,	/_			•		,	,				
No 289,196 268,949 50.73 51.07 -0.35 0.01 136,210 126,040 54.05 54.37 -0.33 0.09 152,986 142,909 47.77 48.16 -0.39 Unknown 8,175 7,307 69.50 69.39 0.12 0.87 2,147 1,953 58.64 56.53 2.11 0.17 6,028 5,354 73.37 74.08 -0.70			164.624	152.995	62.80	63.15	-0.36	0.04	31.797	29,199	60.86	61.26	-0.40	0.31	132.82	7 123,796	63.26	63.60	-0.34	0.08
Unknown 8,175 7,307 69.50 69.39 0.12 0.87 2,147 1,953 58.64 56.53 2.11 0.17 6,028 5,354 73.37 74.08 -0.70									,	-										0.03
			,	,					,	,						,				0.40
			,	,					,	,						,				0.02
Total 996,285 937,963 52.55 52.77 -0.21 0.003 311,362 289,871 49.14 49.14 <0.01 0.98 684,923 648,092 54.10 54.39 -0.28	Tatal		000 285	027.002	52.55	F2 77	0.24	0.002	211 202	200 071	40.14	40.14	-0.01	0.00	604.00	2 6 4 8 0 0 2	F4 40	F 4 20	0.20	0.001

Table S5. Numbers of women with left-sided and right-sided breast cancer, numbers of women and percentages irradiated by patient and tumour factors.

* Difference between percentage irradiated left and right

	er of deaths ed / right-sided	Cardiac mortality rate ratio (95% CI)
Calendar year of diagnosis <1970 1970–79 1980–89 1990–99 2000+	s 1,864 / 1,573 2,629 / 2,111 3,319 / 2,850 2,945 / 2,857 1,006 / 946	2p for trend <0.0001 1.11 (1.04-1.19) 1.18 (1.11-1.25) 1.10 (1.05-1.16) 0.96 (0.91-1.01) 1.02 (0.93-1.12)
Age at cancer diagnosis <40 40-49 50-59 60-69 70-79	201 / 139 1,012 / 850 2,265 / 1,775 4,091 / 3,668 4,194 / 3,905	2p for trend <0.0001 1.39 (1.11−1.73) 1.15 (1.05−1.26) 1.20 (1.13−1.28) 1.05 (1.00−1.10) 1.01 (0.97−1.05)
Time since diagnosis (yea 0-4 5-14 15-24 25+	rs) 3,370 / 3,144 5,141 / 4,582 2,219 / 1,784 1,033 / 827	2p for trend <0.0001 1.00 (0.96−1.05) 1.05 (1.01−1.10) 1.18 (1.11−1.26) 1.21 (1.10−1.33)
Race/Ethnicity White Black Asian/Pacific Other/unknown Not recorded	6,036 / 5,376 435 / 371 165 / 152 1,176 / 949 3,951 / 3,489	2p for heterogeneity: 0.74 1.06 (1.03−1.10) 1.12 (0.98−1.29) 1.10 (0.88−1.38) 1.13 (1.04−1.23) 1.06 (1.01−1.11)
Stage DCIS Local Regional Metastatic/unknown Not recorded	245 / 195 4,202 / 3,764 3,118 / 2,684 1,650 / 1,475 2,548 / 2,219	2p for heterogeneity: 0.07 1.16 (0.96-1.41) 1.05 (1.01-1.10) 1.12 (1.06-1.18) 1.05 (0.98-1.13) 1.06 (1.00-1.12)
Surgery BCS Mastectomy None/unknown Not recorded	2,998 / 2,834 1,766 / 1,549 4,619 / 3,845 2,380 / 2,109	2p for difference: 0.14 1.01 (0.96−1.06) 1.07 (1.00−1.15) 1.13 (1.08−1.18) 1.06 (1.00−1.12)
Chemotherapy Yes No Unknown Not recorded	413 / 352 4,475 / 3,951 113 / 87 6,762 / 5,947	2p for difference: 0.25 1.17 (1.00–1.35) 1.06 (1.02–1.11) 1.18 (0.89–1.58) 1.07 (1.03–1.11)
Endocrine therapy Yes No Unknown Not recorded	1,384 / 1,266 3,473 / 3,020 73 / 51 6,833 / 6,000	2p for difference: 0.14 1.02 (0.94–1.10) 1.09 (1.04–1.14) 1.23 (0.85–1.78) 1.07 (1.04–1.11)
Region Europe: Britain & Ireland Europe: Nordic countries Europe: Other countries North America Other regions	1,494 / 1,239 3,711 / 3,287 1,170 / 1,033 5,155 / 4,585 233 / 193	2p for heterogeneity: 0.86 1.11 (1.03−1.20) 1.06 (1.01−1.11) 1.08 (0.99−1.18) 1.06 (1.02−1.11) 1.06 (0.87−1.29)
All women	11,763 / 10,337	1.07 (1.04–1.10)
		0.5 1 1.5 2 Right-sided excess Left-sided excess

DCIS: Ductal carcinoma in situ.

BCS: Breast-conserving surgery. p-values are for tests of trend or heterogeneity between categories with known values

(i.e. excluding Other/unknown, Not recorded, Metastatic/unknown, None/unknown)

Figure S2. Irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer: Cardiac mortality rate ratios by patient, tumour and treatment characteristics, and geographic region.

Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country. See Fig. 3 in the main text for separate analyses of women irradiated <1990 and 1990+. Separate results for individual countries are given in Fig. S3.

	Number of deaths left-sided / right-sided Cardiac mortality rate ratio (95% CI)						
Europe: British Isles UK Ireland All British Isles	2p for difference: 0.1 1,481 / 1,220 13 / 19 1,494 / 1,239	15 1.12 (1.04-1.21) 0.67 (0.33-1.36) 1.11 (1.03-1.20)	← ●				
Europe: Nordic countries Denmark Finland Norway Sweden All Nordic countries	2p for heterogeneity: 1,775 / 1,585 1,623 / 1,403 17 / 15 296 / 284 3,711 / 3,287	: 0.76 1.05 (0.98-1.12) 1.09 (1.01-1.17) 1.06 (0.53-2.13) 1.00 (0.85-1.18) 1.06 (1.01-1.11)		>			
Europe: Other countries Austria Estonia France Germany Italy Lithuania Netherlands Slovakia Slovenia Spain Switzerland All other European countries	2p for heterogeneity: 48 / 30 189 / 180 75 / 62 592 / 506 72 / 58 22 / 26 101 / 100 25 / 21 13 / 10 17 / 24 16 / 16 1,170 / 1,033	1.65 (1.04-2.64) 1.06 (0.86-1.31) 1.20 (0.85-1.69) 1.08 (0.96-1.22) 1.22 (0.86-1.73) 0.80 (0.45-1.41) 0.96 (0.73-1.27) 1.02 (0.57-1.82) 1.44 (0.60-3.44) 0.75 (0.39-1.43) 0.82 (0.39-1.74) 1.08 (0.99-1.18)		→			
North America USA Canada All North America	2p for difference: 0.1 4,271 / 3,755 884 / 830 5,155 / 4,585	1.08 (1.03-1.13) 1.00 (0.91-1.10) 1.06 (1.02-1.11)	- -				
Other regions Australia Israel Japan All other regions	2p for heterogeneity: 202 / 176 19 / 10 12 / 7 233 / 193	0.37 1.03 (0.84-1.26) 1.23 (0.51-2.99) 2.64 (0.66-10.54) 1.06 (0.87-1.29)) 	→			
All women 2p for heterogeneity between 2p for heterogeneity between		1.07 (1.04-1.10)	-				
			0.5 1.0 1.5 2 Right-sided excess Left-sided exc	 2.0 ∞ess			

Figure S3. Irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer: Cardiac mortality rate ratios, by country.

Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country. See Figure S4 for separate analyses for women diagnosed before 1990 and diagnosed 1990+

	Diagno	sed before 1990			Diagnosed 1990+				
	umber of deaths -sided / right-sided	Cardiac mortality rate ration	o (95% CI)		umber of deaths -sided / right-sided	Cardiac mortality i	rate ratio (95% C		
				Europe Dittels & Lot		0- 6			
Europe: Britain & Irela		1 17 (1 00 1 00)	_	Europe: Britain & Irela		2p for different	ce: 0.21		
UK	880 / 696	1.17 (1.06-1.29)	1	Ireland	13/19	0.67 (0.33-1.36)			
All Britain & Ireland	880 / 696	1.17 (1.06-1.29)	-	UK All Britain & Ireland	601 / 524 614 / 543	1.06 (0.94-1.19) 1.05 (0.93-1.17)	Ŧ		
Europe: Nordic countr	ies	2p for heterogeneity: 0.85		Europe: Nordic countr	ies	2p for heterogenei	ity: 0.94		
Denmark	1.662 / 1.467	1.06 (0.99-1.14)	•	Denmark	113 / 118	0.87 (0.67-1.13)			
Finland	1,446 / 1,224	1.11 (1.03-1.20)	-	Finland	177 / 179	0.93 (0.75-1.14)	-		
Norway	5/5	0.92 (0.26-3.20)		Norway	12/10	1.14 (0.49-2.63)			
Sweden	168 / 156	1.08 (0.87–1.35)		Sweden	128 / 128	0.91 (0.71-1.16)	_		
All Nordic countries	3,281 / 2,852	1.09 (1.03–1.14)	-	All Nordic countries	430 / 435	0.91 (0.80-1.04)	-		
Europe: Other countrie	a c	2p for heterogeneity: 0.92		Europe: Other countrie	es	2p for heterogenei	ity: 0.38		
Austria	15 / 12	1.67 (0.75-3.72)		Austria	33 / 18	1.65 (0.92-2.93)			
Estonia	182 / 169	1.09 (0.88-1.35)		Estonia	7/11	0.63 (0.24-1.67)			
France	75/62	1.20 (0.85-1.69)		Germany	226 / 208	0.98 (0.81-1.18)	-		
				Italy	65 / 51	1.24 (0.86-1.79)			
Germany	366 / 298	1.16 (1.00-1.35)		Lithuania	22 / 26	0.80 (0.45-1.41)	_		
Italy	7/7	1.08 (0.37-3.17)	· · ·	Netherlands	0/0	0.00 (0.45-1.41)			
Netherlands	101 / 100	0.96 (0.73-1.27) -		Slovakia	1/2	0.47 (0.04-5.18)	_		
Slovakia	24 / 19	1.07 (0.59-1.96)	<u> </u>	Slovenia	10/6	1.64 (0.59-4.52)	-		
Slovenia	3/4	0.97 (0.16-5.68))	Spain	15 /22	0.70 (0.36-1.36)			
Spain	2/2				14 / 14				
Switzerland	2/2			Switzerland		0.75 (0.35-1.61)	<u> </u>		
All other European	777 / 675	1.12 (1.01–1.25)	-	All other European	393 / 358	1.01 (0.87–1.16)	Ť		
North America		2p for difference: 0.06		North America		2p for differenc	ce: 0.50		
Canada	559 / 495	1.05 (0.93-1.18)	+	Canada	325 / 335	0.92 (0.79-1.08)	-		
USA	2,238 / 1,767	1.19 (1.12-1.27)	•	USA	2,033 / 1,988	0.98 (0.92-1.04)	1		
All North America	2,797 / 2,262	1.16 (1.10-1.23)	·	All North America	2358/2323	0.97 (0.92-1.03)	1		
Other regions		2p for heterogeneity: 0.46		Other regions		2p for heterogeneit	ty: 0.60		
Australia	50 / 34	1.39 (0.90-2.16)	↓	Australia	152 / 142	0.95 (0.76-1.19)	-		
Israel	16/9	1.00 (0.38-2.68)	+ ──→	Israel	3/1	3.05 (0.31-29.81)			
Japan	11 / 6	3.34 (0.66-16.91)		Japan	1/1	1.11 (0.06-21.82)			
All other regions	77 / 49	1.40 (0.95-2.07)	⊢ •→	All other regions	156 / 144	0.96 (0.77-1.21)	+		
All women	7,812 / 6,534	1.13 (1.09–1.17)	-	All women	3,951 / 3,803	0.98 (0.93-1.02)	4		
2p for heterogeneity bei	ween regions: 0.30			2p for heterogeneity be	tween regions: 0.62				
2p for heterogneity betw	U	F	+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$	2p for heterogeneity be					
		0.5					0.5 1 1.5		
		Right-sided	excess Left-sided excess			Right-sided	excess Left-sided exce		

Figure S4. Irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer: Cardiac mortality rate ratios, by diagnosis period and country.

Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country.

Diagnosed 1990+ and aged < 60 years

Diagnosed 1990+ and aged 60+ years

L	Number of deat eft-sided / right-		y rate ratio (95% CI)		per of deaths ed / right-sided	Cardiac morta	ity rate ratio (95% CI)
Calendar year of diag 1990–99 2000+	nosis 476/ 4 01 181 / 153	2p for difference: 0.90 1.13 (0.99–1.29) 1.15 (0.93–1.42)	.	Calendar year of diagnos 1990–99 2000+	sis 2,469 / 2,456 825 / 793	2p for difference: 0.94 (0.89–0.99) 1.00 (0.90–1.10)	0.28
Time since diagnosis 0−4 5−14 15−24	(years) 307 / 277 335 / 269 15 / 8	2p for trend: 0.22 1.07 (0.91-1.25) 1.19 (1.01-1.39) 1.78 (0.75-4.20)	-	Time since diagnosis (y e 0-4 5-14 15-24	ears) 1,587 / 1,544 1,658 / 1,656 49 / 49	2p for trend: 0.97 (0.90-1.04) 0.94 (0.87-1.00) 0.91 (0.61-1.36)	0.49
Race/Ethnicity White Black Asian/Pacific Is Other/unknown Not recorded	324 / 280 79 / 71 23 / 24 66 / 67 165 / 112	2p for heterogeneity: 0.80 1.12 (0.96-1.32) 1.05 (0.76-1.44) 0.93 (0.53-1.66) - 0.93 (0.66-1.31) - 1.39 (1.09-1.77)		Race/Ethnicity White Black Asian/Pacific Is Other/unknown Not recorded	24 1,738 / 1,748 183 / 163 66 / 76 379 / 312 928 / 950	o for heterogeneity: 0.95 (0.89-1.01) 1.07 (0.86-1.32) 0.86 (0.62-1.20) 1.08 (0.93-1.25) 0.90 (0.82-0.99)	0.46
Stage DCIS Local Regional Metastatic/unknown Not recorded	28 / 21 288 / 242 196 / 194 88 / 53 57 / 44	2p for heterogeneity: 0.36 1.32 (0.74–2.33) 1.14 (0.96–1.36) 0.97 (0.79–1.18) 1.54 (1.09–2.16) 1.22 (0.82–1.81)		Stage DCIS Local Regional Metastatic/unknown Not recorded	24 175 / 139 1,626 / 1,593 739 / 772 413 / 411 341 / 334	o for heterogeneity: 1.16 (0.92-1.44) 0.96 (0.90-1.03) 0.91 (0.82-1.01) 0.93 (0.81-1.06) 0.93 (0.80-1.08)	0.16
Surgery BCS Mastectomy None/unknown Not recorded	322 / 294 120 / 113 176 / 115 39 / 32	2p for difference: 0.97 1.06 (0.90–1.24) 1.05 (0.81–1.36) 1.45 (1.15–1.84) 1.14 (0.71–1.82)	* *	Surgery BCS Mastectomy None/unknown Not recorded	1,743 / 1,712 397 / 384 907 / 907 247 / 246	2p for difference: 0.96 (0.90-1.03) 0.97 (0.84-1.12) 0.93 (0.85-1.02) 0.93 (0.78-1.11)	0.93
Chemotherapy Yes No Unknown Not recorded	81 / 60 150 / 109 9 / 8 417 / 377	2p for difference: 0.93 1.32 (0.94–1.84) 1.29 (1.01–1.65) 1.04 (0.38–2.80) 1.07 (0.93–1.23)	=	Chemotherapy Yes No Unknown Not recorded	117 / 128 1,093 / 1,072 40 / 30 2,044 / 2,019	2p for difference: 0.84 (0.65-1.08) 0.94 (0.87-1.03) 1.32 (0.82-2.13) 0.96 (0.90-1.02)	0.40
Endocrine therapy Yes No Not recorded Unknown	111 / 95 110 / 71 434 / 388 2 / 0	2p for difference: 0.18 1.10 (0.83-1.44) 1.45 (1.07-1.95) 1.08 (0.94-1.24)	- <u>-</u>	Endocrine therapy Yes No Unknown Not recorded	729 / 679 463 / 507 16 / 14 2,086 / 2,049	2p for difference: 1.00 (0.90-1.11) 0.84 (0.74-0.96) 1.07 (0.51-2.24) 0.96 (0.91-1.02)	0.04
Region Europe: Britain & Irelar Europe: Nordic countrie Europe: Other countrie North America Other regions	es 72/55	2p for heterogeneity: 0.08 1.14 (0.85–1.52) 1.22 (0.86–1.73) 2.15 (1.33–3.48) 1.06 (0.92–1.22) 1.11 (0.61–2.02)		Region Europe: Britain & Ireland Europe: Nordic countries Europe: Other countries North America Other regions	2p 513 / 459 358 / 380 338 / 334 1,953 / 1,952 132 / 124	o for heterogeneity: 1.03 (0.91–1.17) 0.87 (0.75–1.00) 0.92 (0.79–1.08) 0.95 (0.90–1.02) 0.94 (0.74–1.20)	0.52
All women aged <60	657 / 554	1.14 (1.01–1.27)	•	All women aged 60+	3,294 / 3,249	0.95 (0.91–1.00)	•
			1 1.5 2 ess Left-sided excess			Right-si	0.5 1 1.5 2 ded excess Left-sided excess

DCIS: Ductal carcinoma in situ. BCS: Breast-conserving surgery. p-values are for tests of trend or heterogeneity between categories with known values (i.e. excluding Other/unknown, Not recorded, Metastatic/unknown, None/unknown)

Figure S5. Irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer: Cardiac mortality rate ratios in women who were diagnosed with breast cancer in or after 1990, by age at diagnosis of breast cancer and other factors. Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country. [p value for difference in RR for all women aged <60 vs 60+: 0.005]

	ber of deaths ded / right-side	d Cardiac morta	ortality rate ratio (95% CI)		
Diagnosed before 1990					
Ischaemic heart disease	5,441 / 4,558	1.12 (1.08-1.17)			
Other types of cardiac disease	1,908 / 1,617	1.12 (1.05-1.20)	-		
Arrhythmia	291 / 222	1.24 (1.04-1.48)	 -		
Heart failure	760 / 644	1.12 (1.01-1.24)	-		
Non-rheumatic valvular disease	233 / 182	1.22 (1.00-1.48)	⊢ ∎		
Rheumatic valvular disease	87 / 73	1.13 (0.83-1.55)	_ ⊨		
Pericardial disease	19 / 13	1.33 (0.65-2.71)	_ →		
Other cardiac disease	433 / 388	1.07 (0.93-1.23)			
All cardiac disease	7,812 / 6,534	1.13 (1.09–1.17)	•		
Diagnosed 1990+					
Ischaemic heart disease	1,640 / 1,536	0.99 (0.92-1.06)	•		
Other types of cardiac disease	758 / 763	0.92 (0.84-1.02)	-		
Arrhythmia	152 / 162	0.88 (0.70-1.09)	-=		
Heart failure	331 / 327	0.94 (0.81-1.10)	-		
Non-rheumatic valvular disease	78 / 66	1.10 (0.79-1.53)	_		
Rheumatic valvular disease	26 / 33	0.72 (0.43-1.21)	-∎-		
Pericardial disease	6/6	0.88 (0.28-2.74)	 ,		
Other cardiac disease	116 / 125	0.87 (0.68-1.13)	- e -		
All cardiac disease	3,951 / 3,803	0.98 (0.93-1.02)	•		
		Rig	0.5 1 1.5 2 ht-sided excess Left-sided exce		

Figure S6. Irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer: Cardiac mortality rate ratios, by calendar year of breast cancer diagnosis and certified cause of death.

See Table S2 for definitions of categories. Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country. Numbers of deaths from individual disease categories do not sum to totals as information on type of heart disease was unavailable from Surveillance, Epidemiology and End Results (SEER) for years 2000-2008, and was available only as two categories (ischaemic heart disease and other types of cardiac disease) from Ontario cancer registry.

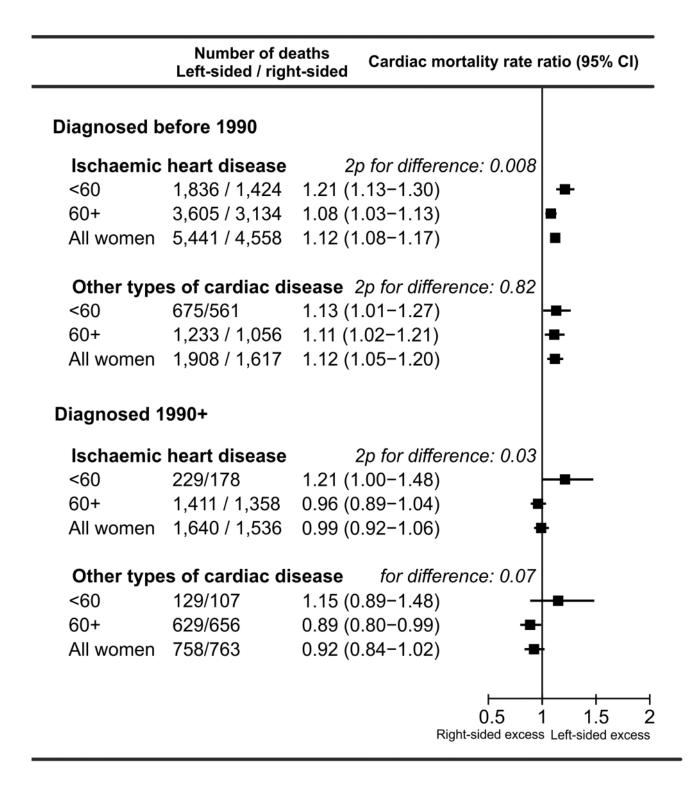


Figure S7. Irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer: Cardiac mortality rate ratios, by age at diagnosis and whether the women were diagnosed with ischaemic heart disease.

Rate ratios estimated by Poisson regression with stratification by time since breast cancer diagnosis, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, and country. Information on type of heart disease was unavailable from Surveillance, Epidemiology and End Results (SEER) for years 2000-2008.

	Median age at	Design	None	No. cardiac events after RT		Results according to age			
	RT (yr)			All	Age <40	Cardiac risk	Heart dose (Gy		
Present study	57	Cohort Left vs right		22,100 All time periods	340	Cardiac mortality RR L vs R <1990	NS		
Darby 2005	NS	Cohort Left vs right	None	894	231	Heart disease mortality ratio LvRAge 20-491.54 (1.08-2.19)Age 50-591.53 (1.19-2.16)Age 60-691.40 (1.15-1.70)Age 70-791.28 (0.87-1.90)2p trend 0.40	NS		
McGale 2011	NS	Cohort Left vs right	None	4291	104	Heart disease incidence ratio LvR Age <60	NS		
Darby 2013	55	Case control	Individual	963	20	Increase major coronary event rate per Gy Age 20-39 -1.5 (<25.3-616) Age 40-49 6.3 (-2.0-41.3) Age 50-59 7.1 (0.4-22.2) Age 60-69 7.8 (1.7-19.7) Age 70-74 9.7 (-2.9-116) p heterogeneity 0.99	Age 20-39 4.7 Age 40-49 4.9 Age 50-59 5.1 Age 60-69 4.8 Age 70-74 4.9		
EBCTCG 2017	56	Meta- analysis randomised trials	Trial-based	1253	14	Cardiac mortality RR RT vs not Age <50	Age <50: 6.4 Age 50-59 6.2 Age 60+ 6.3		
Jacobse 2019	50	Case control	Individual	183	9	Age <45 24.2 (4.4-82.3) Age 45-49 11.1(1.2-40.1) Age 50-70 2.5 (-1.4-11.9) p trend 0.07 2.5	NS		
Paszat 1998	~60	Cohort Left vs right	None	703	NS	Myocardial infarction death RRLvRAge <60	NS		

Table S6. Breast cancer radiotherapy: Studies reporting cardiac risk according to age irradiated*

*Studies are ordered according to the number of cardiac events in women irradiated when aged <40 years Abbreviations; vs=versus; RR=rate ratio; RT=radiotherapy; NS=Not specified; yr=years;Gy=gray

References for Table S6

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Table S7. Hodgkin lymphoma radiotherapy: Studies reporting cardiac risk according to age irradiated*

	Median Design Dosime age at		Dosimetry	No. cardiac events after RT		Results according to age			
	RT (yr)	RT (yr) All Age <40		Cardiac risk		Heart dose (Gy)			
Van Nimwegen 2016	32	Case control study	Individual	325	251	coronary hea Age <27.5 Age 27.5-36.4	4.2% (0.6-11.1)	NS	
Hancock 1993	29	Cohort	Individual mediastinal dose (not heart)	49	28	Myocardial ir Age <20 Age 20-29 Age 30-39 Age 40-49 Age ≥50 p trend <0.00	3.0 (1.4-5.5) 1.8 (1.0-3.0)	Mediastina Age <10 Age 10-19 Age 20-29 Age 30-39 Age 40-49 Age ≥50	21.5 37.3 40.5 38.8
Boivin 1992	NS	Case control	None	124	23	Relative risk of infarction dea Age 0-39 Age 40-59 Age 60+ P heterogene	1.95 (0.25-15.35) 1.44 (0.49-4.25) 3.78 (1.12-12.80)	NS	

*Studies are ordered according to the number of cardiac events in women irradiated when aged <40 years Abbreviations; RR=rate ratio; RT=radiotherapy; NS=Not specified; yr: years; Gy: gray

References for Table S7

Van Nimwegen FA, 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.

Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol 1993; 11: 1208-15.

Boivin J-F, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treatment for Hodgkins disease. Cancer 1992; 69: 1241-7.