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
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| Country                      | Organisation                                                                 | Individuals who worked on the Preparation of the Data or attended the Study Meeting |
|------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| **Europe: Britain 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: Nordic 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: Other 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*
| Country   | Organisation                                                                 | Individuals who worked on the Preparation of the Data 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                                         | Luigiino Dal Maso, Lorenzo Simonato, Loris Zanier, Diego                            |
|           | Latina Cancer Registry                                                        | Serraino, Margherita de Dottori, Massimo Rugge                                     |
|           | Lombardy Cancer Registry                                                      | Fabio Pannozzo, Antonella Fontana                                                 |
|           | Modena Cancer Registry                                                        | Giovanna Tagliabue, Paolo Contiero, Sabrina Fabiano, Paolo                         |
|           | National Tumour Institute (Milan)                                             | Crosignani                                                                         |
|           | Parma Province Cancer Registry                                                | Massimo Federico, Monica Pirani                                                    |
|           | Piedmont Cancer Registry                                                      | Russo Antonio                                                                      |
|           | Ragusa Cancer Registry                                                        | Vincenzo De Lisi, Paolo Sgargi                                                     |
|           | Sondrio Cancer Registry                                                       | Roberto Zanetti, Stefano Rosso                                                     |
|           | Tuscany Cancer Registry                                                       | Rosario Tumino, Aurora Sigona                                                      |
|           | Umbria Cancer Registry                                                        | Roberto Tessandori                                                                 |
|           | Venetian Tumour Registry                                                      | Lorenzo Livi, Emanuelle Crocetti                                                   |
|           |                                                                               | Cynthia Aristei, Francesco La Rosa, Fabrizio Stracci                               |
|           |                                                                               | 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

| 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-Gragerera                                                            |
|             | 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 America |                                                                                           |
| 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 regions |                                                                                        |
| 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 re-immigrated)
- 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
| 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 lost to follow-up | DD/MM/YYYY or Unknown |
| 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 (including invasive breast cancer, if recorded) | DD/MM/YYYY |
| 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
¶ ¶ 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          | I20-I25                                                                     |
| Arrhythmia                       | I44-49                                                                      |
| Heart failure                    | I01.2, I09.0, I11.0, I13.0, I13.2, I40-I43, I50, I51.4-5, I51.7              |
| Non-rheumatic valvular           | I34-I39                                                                     |
| Rheumatic valvular               | I01.1, I05-I08, I09.1                                                      |
| Pericarditis                     | I01.0, I09.2, I30-I32                                                      |
| Other cardiac disease            | I01.8-9, I02.0, 109.8-9, I11.9, I13.1, I13.9, I27.1-9, I33, I51.0-3, I51.6, I51.8-9, I52 |
| All cardiac disease              | I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-9, I30-I52                   |
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: Britain 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: Nordic 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
| Organisation | Dates of breast cancer diagnosis | Period of follow-up | Number of women | Number given RT | % RT | Cardiac disease deaths |
|--------------|----------------------------------|---------------------|----------------|----------------|------|----------------------|
| **Europe: Other 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 Vorarlberg | 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*
| 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        | 10,812          | 4,765          | 44   | 192                  |
|              |                                  | 1993 to 2007        |                 |                |      |                      |
| Netherlands  | Eindhoven Cancer Registry        | 1964 to 2004        | 18,319          | 11,840         | 65   | 0                    |
|              | Netherlands Cancer Institute     | 1970 to 1987        | 7,101           | 6,217          | 88   | 235                  |
| Slovakia     | National Cancer Registry of Slovak Republic | 1978 to 2003 | 28,139          | 18,314         | 65   | 73                   |
| Slovenia     | Cancer Registry of Slovenia      | 1971 to 2004        | 8,863           | 3,754          | 42   | 135                  |
| Spain        | Institute Catalá d’Oncolgía (Barcelona) | 1991 to 1997 | 850             | 646            | 76   | 15                   |
|              | Cancer Registry of Girona        | 1963 to 2005        | 1,818           | 1,722          | 95   | 18                   |
|              | Navarra Cancer Registry         | 1990 to 2002        | 3,187           | 2,332          | 73   | 24                   |
| Switzerland  | Geneva Cancer Registry          | 1970 to 2004        | 802             | 630            | 79   | 15                   |
|              | Grisons Cancer Registry         | 1989 to 2005        | 1,524           | 591            | 39   | 30                   |
|              | Cancer Registry of St. Gall-Appenzell | 1940 to 2005 | 2,689           | 1,076          | 40   | 53                   |
|              | Ticino Cancer Registry          | 1995 to 2004        | 1,961           | 1,178          | 60   | 7                    |
| North America| Canada                           | Alberta Cancer Registry | 1989 to 2004  | 20,911         | 10,533 | 50                  | 411 |
|              | British Columbia Cancer Registry | 1985 to 2004        | 29,723          | 19,115         | 64   | 606                  |
|              | Ontario Cancer Registry         | 1982 to 1997        | 55,477          | 55,477         | 100* | 1,294                |
| USA          | Connecticut Tumour Registry     | 1935 to 1972        | 26,640          | 7,852          | 29   | 3,379                |
|              | Puerto Rico Central Cancer Registry | 1987 to 2003 | 13,263          | 6,982          | 53   | 137                  |
|              | Surveillance Epidemiology and End Results Program | 1973 to 2008 | 738,145         | 327,521        | 44   | 24,413               |

*1,294 includes deaths due to other causes.
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) | 1957 to 2001       | 1957 to 2007    | 695            | 104    | 15                     | 48  |
|              | Kanagawa Cancer Centre           | 1941 to 1989        | 1971 to 2007    | 1,631          | 372    | 23                     | 19  |
|              | Nagasaki Prefectural Cancer Registry | 1956 to 2005       | 1961 to 2005    | 638            | 638    | 100*                   | 5   |

*Registry provided information only on women who were given radiotherapy.
| Region                      | No. of deaths Radiotherapy / no radiotherapy | Cardiac mortality rate ratio (95% CI) |
|-----------------------------|---------------------------------------------|--------------------------------------|
| **Europe: Britain & Ireland** | 2p for difference: 0.0003                  |                                      |
| BCS                         | 812 / 388                                  | 0.86 (0.76-0.97)                     |
| Mastectomy                  | 514 / 793                                  | 1.18 (1.05-1.32)                     |
| Unknown / None              | 1,407 / 2,385                              | 0.85 (0.79-0.90)                     |
| **Europe: Nordic countries** | 2p for difference: 0.002                   |                                      |
| BCS                         | 423 / 141                                  | 0.80 (0.65-1.00)                     |
| Mastectomy                  | 849 / 2,139                                | 1.16 (1.06-1.27)                     |
| Unknown / None              | 5,726 / 3,650                              | 0.98 (0.94-1.03)                     |
| **Europe: Other countries** | 2p for difference <0.00001                  |                                      |
| BCS                         | 156 / 113                                  | 0.63 (0.47-0.85)                     |
| Mastectomy                  | 277 / 236                                  | 1.47 (1.18-1.83)                     |
| Unknown / None              | 1,770 / 2,220                              | 0.91 (0.84-0.97)                     |
| **North America**           | 2p for difference <0.00001                  |                                      |
| BCS                         | 4,435 / 3,155                              | 0.67 (0.64-0.71)                     |
| Mastectomy                  | 1,668 / 10,539                             | 1.28 (1.22-1.35)                     |
| Unknown / None              | 3,637 / 6,806                              | 1.32 (1.26-1.39)                     |
| **Other regions**           | 2p for difference: 0.80                    |                                      |
| BCS                         | 6 / 8                                      | 0.41 (0.12-1.48)                     |
| Mastectomy                  | 7 / 20                                     | 0.51 (0.19-1.39)                     |
| Unknown / None              | 413 / 571                                  | 0.87 (0.76-1.00)                     |
| **All regions**             | 2p for difference: 0.0003                  |                                      |
| BCS                         | 5,832 / 3,805                              | 0.70 (0.67-0.73)                     |
| Mastectomy                  | 3,315 / 13,727                             | 1.24 (1.19-1.30)                     |
| Unknown / None              | 12,653 / 15,632                            | 1.03 (1.00-1.06)                     |
| **All Women**               | 22,100 / 33,164                            | 0.94 (0.92-0.95)                     |

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

| Calendar year of diagnosis | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|----------------------------|-----------|-----------------------|-----------------------|
|                             | Number    | Percentage irradiated | Number               | Percentage irradiated |
|                             | Left      | Right                | Left                 | Right                |
| 1970-1979                   | 48,041    | 44,621               | 56.16                | 55.96                |
|                             | 0.21      | 0.53                 | 56.16                | 55.96                |
| 1980-1989                   | 86,778    | 80,753               | 50.19                | 50.21                |
|                             | -0.01     | 0.95                 | 50.19                | 50.21                |
| 1990-1999                   | 176,543   | 164,497              | 46.71                | 46.77                |
|                             | -0.06     | 0.72                 | 46.71                | 46.77                |
| 2000+                       | 317,616   | 298,183              | 52.96                | 53.08                |
|                             | -0.11     | 0.37                 | 52.96                | 53.08                |

### Race/ethnicity

| Race/ethnicity | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|----------------|-----------|-----------------------|-----------------------|
|                | Number    | Percentage irradiated | Number               | Percentage irradiated |
|                | Left      | Right                | Left                 | Right                |
| White          | 469,630   | 446,365              | 47.63                | 47.90                |
|                | -0.27     | 0.01                 | 47.63                | 47.90                |
| Black          | 34,502    | 32,348               | 42.99                | 42.89                |
|                | 0.10      | 0.80                 | 42.99                | 42.89                |
| Asian/pacific  | 29,906    | 28,628               | 45.27                | 45.91                |
|                | -0.64     | 0.12                 | 45.27                | 45.91                |
| Other/unknown  | 141,666   | 131,814              | 52.12                | 52.29                |
|                | -0.17     | 0.38                 | 52.12                | 52.29                |
| Not recorded   | 320,801   | 298,808              | 61.66                | 61.98                |
|                | -0.32     | 0.01                 | 61.66                | 61.98                |

### Stage at cancer diagnosis

| Stage at cancer diagnosis | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|---------------------------|-----------|-----------------------|-----------------------|
|                           | Number    | Percentage irradiated | Number               | Percentage irradiated |
|                           | Left      | Right                | Left                 | Right                |
| DCIS                      | 67,950    | 63,824               | 38.12                | 38.26                |
|                           | -0.14     | 0.60                 | 38.12                | 38.26                |
| Local                     | 378,266   | 360,074              | 50.04                | 50.41                |
|                           | -0.37     | 0.02                 | 50.04                | 50.41                |
| Regional                  | 244,231   | 229,963              | 54.55                | 54.65                |
|                           | -0.10     | 0.51                 | 54.55                | 54.65                |
| Metastatic/unknown        | 201,433   | 186,919              | 50.27                | 50.39                |
|                           | -0.13     | 0.43                 | 50.27                | 50.39                |
| Not recorded              | 104,405   | 97,183               | 70.77                | 71.14                |
|                           | -0.36     | 0.07                 | 70.77                | 71.14                |

### Surgery

| Surgery | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|---------|-----------|-----------------------|-----------------------|
|         | Number    | Percentage irradiated | Number               | Percentage irradiated |
|         | Left      | Right                | Left                 | Right                |
| BCS     | 262,831   | 252,280              | 72.85                | 72.95                |
|         | -0.11     | 0.38                 | 72.85                | 72.95                |
| Mastectomy | 249,487   | 236,322              | 26.87                | 27.05                |
|         | -0.18     | 0.15                 | 26.87                | 27.05                |
| None/unknown | 399,406   | 370,468              | 51.13                | 51.28                |
|         | -0.15     | 0.19                 | 51.13                | 51.28                |
| Not recorded | 84,561    | 78,893               | 71.97                | 72.22                |
|         | -0.25     | 0.26                 | 71.97                | 72.22                |

### Radiotherapy

| Radiotherapy | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|--------------|-----------|-----------------------|-----------------------|
|              | Number    | Percentage irradiated | Number               | Percentage irradiated |
|              | Left      | Right                | Left                 | Right                |
| Yes          | 523,570   | 494,935              | 100.00               | 100.00               |
|              | -0.00     | 0.00                 | 100.00               | 100.00               |
| No           | 472,715   | 443,028              | 100.00               | 100.00               |
|              | -0.00     | 0.00                 | 100.00               | 100.00               |

### Chemotherapy

| Chemotherapy | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|--------------|-----------|-----------------------|-----------------------|
|              | Number    | Percentage irradiated | Number               | Percentage irradiated |
|              | Left      | Right                | Left                 | Right                |
| Yes          | 115,195   | 107,882              | 63.84                | 63.87                |
|              | -0.02     | 0.91                 | 63.84                | 63.87                |
| No           | 355,681   | 329,821              | 52.72                | 53.09                |
|              | -0.07     | 0.00                 | 52.72                | 53.09                |

### Endocrine therapy

| Endocrine therapy | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|-------------------|-----------|-----------------------|-----------------------|
|                   | Number    | Percentage irradiated | Number               | Percentage irradiated |
|                   | Left      | Right                | Left                 | Right                |
| Yes               | 164,624   | 152,995              | 62.80                | 63.15                |
|                   | -0.36     | 0.04                 | 62.80                | 63.15                |
| No                | 289,196   | 268,949              | 50.73                | 51.07                |
|                   | -0.35     | 0.01                 | 50.73                | 51.07                |

### Total

|                  | All women | Women diagnosed <1990 | Women diagnosed 1990+ |
|------------------|-----------|-----------------------|-----------------------|
|                  | Number    | Percentage irradiated | Number               | Percentage irradiated |
|                  | Left      | Right                | Left                 | Right                |
| Total            | 996,285   | 937,963              | 52.55                | 52.77                |
|                  | -0.21     | 0.0003               | 52.55                | 52.77                |

* Difference between percentage irradiated left and right
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.
### 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+.
**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.
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]
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.
|                                | Number of deaths (Left-sided / right-sided) | Cardiac mortality rate ratio (95% CI) |
|--------------------------------|--------------------------------------------|-------------------------------------|
| **Diagnosed before 1990**     |                                            |                                     |
| **Ischaemic heart disease**    |                                            |                                     |
| <60                            | 1,836 / 1,424                              | 1.21 (1.13–1.30)                    |
| 60+                            | 3,605 / 3,134                              | 1.08 (1.03–1.13)                    |
| All women                      | 5,441 / 4,558                              | 1.12 (1.08–1.17)                    |
|                                |                                            |                                     |
| **Other types of cardiac disease** |                                            |                                     |
| <60                            | 675/561                                    | 1.13 (1.01–1.27)                    |
| 60+                            | 1,233 / 1,056                              | 1.11 (1.02–1.21)                    |
| All women                      | 1,908 / 1,617                              | 1.12 (1.05–1.20)                    |
|                                |                                            |                                     |
| **Diagnosed 1990+**            |                                            |                                     |
| **Ischaemic heart disease**    |                                            |                                     |
| <60                            | 229/178                                    | 1.21 (1.00–1.48)                    |
| 60+                            | 1,411 / 1,358                              | 0.96 (0.89–1.04)                    |
| All women                      | 1,640 / 1,536                              | 0.99 (0.92–1.06)                    |
|                                |                                            |                                     |
| **Other types of cardiac disease** |                                            |                                     |
| <60                            | 129/107                                    | 1.15 (0.89–1.48)                    |
| 60+                            | 629/656                                    | 0.89 (0.80–0.99)                    |
| All women                      | 758/763                                    | 0.92 (0.84–1.02)                    |

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.
| Table S6. Breast cancer radiotherapy: Studies reporting cardiac risk according to age irradiated* |
|---------------------------------|-----------------|-----------------|-----------------------------------|
| Median age at RT (yr) | Design | Dosimetry | No. cardiac events after RT | Results according to age |
|---------------------|--------|-----------|-----------------------------|-------------------------|
| Present study       | 57     | Cohort    | None                         | Cardiac mortality RR L vs R <1990 |
|                     |        | Left vs right |                | Age <40 1.46 (1.15-1.86)  | NS |
|                     |        |            |                              | Age 40-49 1.19 (1.07-1.31) |    |
|                     |        |            |                              | Age 50-59 1.20 (1.12-1.28) |    |
|                     |        |            |                              | Age 60-69 1.09 (1.03-1.15) |    |
|                     |        |            |                              | Age 70-79 1.08 (1.02-1.15) |    |
|                     |        |            |                              | *p trend 0.003            |    |
| Darby 2005          | NS     | Cohort    | None                         | Heart disease mortality ratio LvR |
|                     |        | Left vs right |                | Age 20-49 1.54 (1.08-2.19)  | NS |
|                     |        |            |                              | Age 50-59 1.53 (1.19-2.16)  |    |
|                     |        |            |                              | Age 60-69 1.40 (1.15-1.70)  |    |
|                     |        |            |                              | Age 70-79 1.28 (0.87-1.90)  |    |
|                     |        |            |                              | *2p trend 0.40             |    |
| McGale 2011         | NS     | Cohort    | None                         | Heart disease incidence ratio LvR |
|                     |        | Left vs right |                | Age <60 1.12 (1.01-1.24)    | NS |
|                     |        |            |                              | Age 60-79 1.06 (0.98-1.15)  |    |
|                     |        |            |                              | *p difference 0.4          |    |
| Darby 2013          | 55     | Case control | Individual | Increase major coronary event rate per Gy |
|                     |        |            | 963                          | 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      |    |
| EBCTCG 2017         | 56     | Meta-analysis | Trial-based | Cardiac mortality RR RT vs not |
|                     |        | randomised trials | 1253         | Age <50 1.53 (1.07-2.19)    |    |
|                     |        |            |                              | Age 50-59 1.27 (1.00-1.61) |    |
|                     |        |            |                              | Age 60+ 1.28 (1.10-1.48)   |    |
|                     |        |            |                              | *p trend 0.5               |    |
| Jacobse 2019        | 50     | Case control | Individual | Excess rate ratio per Gy |
|                     |        |            | 183                          | 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              |    |
| Paszat 1998         | ~60    | Cohort    | None                         | Myocardial infarction death RRLvR |
|                     |        | Left vs right |                | Age <60 1.98 (1.31-2.97)    | NS |
|                     |        |            |                              | Age ≥60 1.17 (0.95-1.44)   |    |
|                     |        |            |                              | *P not specified           |    |

*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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Paszat LF, Mackillop WJ, Groome PA, Boyd C, Schulze K, Holowaty E. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the Surveillance Epidemiology and End-Results Cancer Registries. J Clin Oncol 1998; 16: 2625-31.
### Table S7. Hodgkin lymphoma radiotherapy: Studies reporting cardiac risk according to age irradiated*

| Design          | Dosimetry                      | Median age at RT (yr) | No. cardiac events after RT | Results according to age |
|-----------------|--------------------------------|-----------------------|-----------------------------|--------------------------|
|                 |                                |                       |                             |                          |
|                 |                                |                       | All | Age <40                     |                          |
| Van Nimwegen    | Case control study             | 32                    | Individual                   |                           |
| 2016            |                                |                       | 325 | 251                        |                           |
| Hancock         | Cohort                         | 29                    | Individual                   |                           |
| 1993            |                                |                       | 49  | 28                         |                           |
| Boivin          | Case control                   | NS                    | None                         |                           |
| 1992            |                                |                       | 124 | 23                         |                           |

**Notes:**
- **Cardiac risk:**
  - Excess relative risk incident coronary heart disease per Gy
    - Age <27.5: 20% (5.4-70.5)
    - Age 27.5-36.4: 8.8% (2.6-22.9)
    - Age 36.5-50.9: 4.2% (0.6-11.1)
  - *p interaction 0.15*
- **Myocardial infarction death RR**
  - Age <20: 44.1 (17.8-91.0)
  - Age 20-29: 7.3 (3.4-13.8)
  - Age 30-39: 5.1 (2.9-7.4)
  - Age 40-49: 3.0 (1.4-5.5)
  - Age ≥50: 1.8 (1.0-3.0)
  - *p trend <0.0001*
- **Mediastinal dose**
  - Age <10: 21.5
  - Age 10-19: 37.3
  - Age 20-29: 40.5
  - Age 30-39: 38.8
  - Age 40-49: 36.7
  - Age ≥50: 28.7
- **Relative risk of acute myocardial infarction death**
  - Age 0-39: 1.95 (0.25-15.35)
  - Age 40-59: 1.44 (0.49-4.25)
  - Age 60+: 3.78 (1.12-12.80)
  - *P heterogeneity 0.64*

*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**

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