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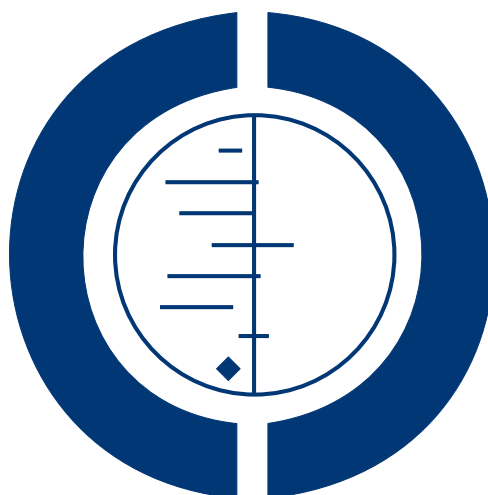
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Breast cancer in female survivors of childhood, adolescent or young adult cancer after radiotherapy involving the chest for their primary malignancy (Protocol)

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Breast cancer in female survivors of childhood, adolescent or young adult cancer after radiotherapy involving the chest for their primary malignancy (Protocol)

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[Intervention Protocol]

Breast cancer in female survivors of childhood, adolescent or young adult cancer after radiotherapy involving the chest for their primary malignancy

Irma WEM van Dijk¹, Leontien CM Kremer², Raoul C Reulen³, Tara O Henderson⁴, Claudia E Kuehni⁵, Mike M Hawkins³, Kevin C Oeffinger⁶, Flora E van Leeuwen⁷, Cecile M Ronckers⁸

¹Department of Radiotherapy, Academic Medical Center, Amsterdam, Netherlands. ²Department of Paediatric Oncology, Emma Children's Hospital / Academic Medical Center, Amsterdam, Netherlands. ³Centre for Childhood Cancer Survivor Studies, School of Health and Population Sciences/University of Birmingham, Birmingham, UK. ⁴University of Chicago Medical Center, Chicago, IL, USA. ⁵Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. ⁶Pediatrics and Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. ⁷Netherlands Cancer Institute, Amsterdam, Netherlands. ⁸Dutch Childhood Oncology Group, The Hague, Netherlands

Contact address: Cecile M Ronckers, Dutch Childhood Oncology Group, The Hague, Netherlands. c.m.ronckers@amc.nl.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To summarise the existing evidence regarding the effects of radiotherapy involving the chest for childhood, adolescent and young adult cancer on breast cancer risk in female cancer survivors. Firstly we will describe the overall breast cancer risk, as reported in all eligible studies. Secondly, we will summarise the breast cancer risk associated with (a) characteristics of treatment for a previous cancer, (b) survivor characteristics, and (c) modifying traditional predictors for breast cancer.

BACKGROUND

Due to therapeutic improvements over the last few decades, the survival rate for childhood and young adult cancer has increased remarkably. Simultaneously, late treatment-related effects have become more evident in long-term cancer survivors, as described in [Oeffinger 2006](#) and [Geenen 2007](#).

Second cancers are among the most devastating late effects of prior treatment for cancer in childhood and young adulthood. Breast cancer contributes a substantial proportion of excess tumours among female cancer survivors, with most strong evidence from female survivors of Hodgkin's lymphoma (HL) ([Bhatia 2003](#); [Kenney 2004](#); [Friedman 2010](#); [Reulen 2011](#)). Reported absolute excess risks of breast cancer in HL survivors vary from 7.8 to 57 per 10,000 person years ([De Bruin 2009](#); [Reulen 2011](#)). [Travis 2005](#) estimated cumulative absolute breast cancer risks of 11% and 29% by age 45 and 55 years respectively, for a female HL survivor treated at age 25 years with 40 Grays (Gy) chest radiation and without alkylating agents. [Franklin 2005](#) conducted an extensive meta-analysis of HL trials to contrast treatment success with risk of second cancers for various treatment protocols. However, there is also accumulating evidence among survivors of other types of cancer who were treated with radiotherapy ([Inskip 2009](#)). In general, these studies use many different study designs and risk measures.

Ionising radiation is carcinogenic, and radiation exposure of the chest can induce breast cancer. Radiation exposure of the chest includes radiotherapy directed to any part of the chest, axilla, and/or upper abdomen, including total body irradiation (TBI). The risk of breast cancer is particularly increased in female survivors who have been exposed at young age to such radiation fields ([Hill 2005](#); [Ronckers 2005](#); [Travis 2005](#); [De Bruin 2009](#); [Inskip 2009](#)). The risk of breast cancer after radiotherapy also varies by longer follow-up duration, attained age at end of follow-up, and radiation dose ([Travis 2005](#)). Treatment with chest radiotherapy in combination with gonadotoxic alkylating agents or pelvic radiotherapy reduces the risk of breast cancer compared to treatment with chest radiotherapy only ([Travis 2003](#); [Van Leeuwen 2003](#); [Inskip 2009](#)). Also, reduction of radiation volume appears to reduce the risk of breast cancer ([De Bruin 2009](#)). Other predictors that may influence the occurrence of breast cancer are attained age, sex, genetic predisposition (e.g. family history of breast and/or ovarian cancer, and BRCA1/2 status), various reproductive risk factors (e.g. age at menarche, number of children, maternal age at birth of first live-born child, markers of endogenous oestrogen exposure (e.g. age at menopause, premature menopause, including that caused by pelvic radiotherapy or possibly chemotherapy, and years of intact ovarian function after radiotherapy), and markers of exogenous sex hormone exposure (e.g. treatment with hormonal replacement therapy (HRT), duration of HRT use, oral contraceptive (OC) use, or duration of OC use), and physical activity ([Ronckers 2005](#); [Veronesi 2005](#)). However, the interaction of treatment-related risk factors and traditional predictors for breast cancer is not well un-

derstood ([Van Leeuwen 2003](#); [Hill 2005](#)). An important question still remains unanswered, i.e. whether HRT, after radiation-induced premature menopause, neutralises the protecting effect of premature menopause.

Information on risk groups and on the amount of absolute excess risk of breast cancer after treatment for childhood cancer is urgently needed to inform early detection programmes for breast cancer among childhood cancer survivors.

OBJECTIVES

To summarise the existing evidence regarding the effects of radiotherapy involving the chest for childhood, adolescent and young adult cancer on breast cancer risk in female cancer survivors. Firstly we will describe the overall breast cancer risk, as reported in all eligible studies. Secondly, we will summarise the breast cancer risk associated with (a) characteristics of treatment for a previous cancer, (b) survivor characteristics, and (c) modifying traditional predictors for breast cancer.

METHODS

Criteria for considering studies for this review

Types of studies

All study designs, (except case reports and case series), examining the effect of radiotherapy as part of treatment for a primary malignancy in female children, adolescents, and young adults (< 30 years of age) on breast cancer risk later in life. We will exclude studies in which the study population consists solely of breast cancer survivors. We will include studies with at least 50 survivors treated with radiotherapy involving the chest, or studies with at least 100 survivors treated with any radiotherapy. We will exclude studies that do not mention the number of survivors treated with radiotherapy, or that do not report any information on radiotherapy.

Types of participants

Female cancer survivors treated for a primary malignancy in childhood, adolescence, or young adulthood (< 30 years of age). We will only include studies involving survivors with a larger age range if separate data are available (either in the publication or separately, from the authors) for survivors younger than 30 years. If no follow-up time after end of treatment is stated, more than 95% of the study group should be off treatment.

Types of interventions

Treatment with radiotherapy for a primary malignancy. Since radiotherapy involving the chest is the main risk factor that we focus on, at least 50 survivors of the study population have to have been treated with radiotherapy involving the chest, defined as radiotherapy directed to any part of the chest, axilla, and/or abdomen, including TBI. Furthermore, pelvic radiotherapy and treatment with alkylating agents are also of interest, because they have the potential to modify the risk of secondary breast cancer and therefore we will include these interventions.

Characteristics of treatment for a previous cancer have to be available directly from medical records or from standardised treatment registration systems, such as nation-wide or regional cancer registries. We will exclude studies using self-reported information on treatment for a previous cancer from this review. We will include traditional predictors for breast cancer if available, and we will accept both self-reported information as well as information extracted from medical records for any traditional predictor.

Types of outcome measures

The outcome measure is invasive or in situ female breast cancer as a new primary malignancy, confirmed by pathology or medical record information. We will exclude studies relying solely on self-reported second malignancies (i.e. self-reported information without medical confirmation) and studies relying solely on cause of death information.

Search methods for identification of studies

See: Cochrane Childhood Cancer Group methods used in reviews ([Module CCG](#)).

We will not impose any language restrictions.

Electronic searches

We will search the following electronic databases.

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue), MEDLINE/PubMed (from 1945 to present), and EMBASE/Ovid (from 1980 to present). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are stated in the appendices ([Appendix 1](#), [Appendix 2](#), and [Appendix 3](#)).

Searching other resources

We will locate information about trials not registered in CENTRAL, MEDLINE, or EMBASE (either published or unpublished), by searching the reference lists of relevant articles and reviews. We will also scan (electronically or by handsearching) the Proceedings abstracts of the International Society for Paediatric

Oncology (SIOP) (2000 to 2011), the European Symposium on Late Complications of Childhood Cancer (ESLCCC) (2009 to 2011), and the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (1999 to 2011).

We will search for ongoing trials in the International Standard Randomised Controlled Trial Number (ISRCTN) register and the register of the National Institute of Health (both using <http://www.controlled-trials.com>).

Data collection and analysis

Selection of studies

After performing the search strategy described previously, two reviewers will independently select studies meeting the inclusion criteria. We will resolve discrepancies between reviewers by consensus. In cases of no consensus, we will achieve final resolution by a third-party arbitrator. We will obtain in full any study which seems to meet the inclusion criteria based on title, or abstract, or both, for closer inspection. We will clearly state details of reasons for exclusion of any study considered for this review.

Data extraction and management

Four reviewers will independently extract data using standardised forms. The primary reviewer will extract information from all articles. In parallel, three independent secondary reviewers will each extract information from one third of all selected studies. In case of disagreement, we will re-examine the articles and we will discuss the data extraction items until consensus is reached. If this is impossible, we will achieve final resolution by a third-party arbitrator. We will extract data on the following items.

1. Study characteristics, including:

- study design;
- number of patients of the original cohort (i.e. the source population of cancer survivors; for cohort, randomised controlled trials or controlled clinical trials (RCTs/CCTs) as well as for case-control studies);
- eligible study population (i.e. the cancer survivors who meet the inclusion criteria of this review);
- eligible study population for whom follow-up regarding the occurrence of subsequent primary malignancies was conducted;
- number of radiotherapy exposed and non-exposed (for cohort studies, and RCTs/CCTs);
- number of breast cancer cases and controls (for (nested) case-control studies); and
- are cases and controls matched, and if yes, what the matching factors are (for case-control studies).

2. Participants, including:

- age at cancer treatment (i.e. median/mean, minimum, maximum);
 - attained age during study follow-up (i.e. median/mean, minimum, maximum);
 - sex;
 - type of first primary tumour (based on the International Classification of Childhood Cancer, third edition (ICCC-3) (Steliarova-Foucher 2005);
 - calendar years of diagnosis (range, categories);
 - minimum survival (e.g. all, one-year survivors, three-year survivors);
 - definition of original source population (i.e. cancer registry, single-centre, multi-centre, nation-wide, international);
 - potential exposure to population-based breast cancer screening efforts (i.e. not mentioned, no, yes);
 - potential exposure to active screening programme for subsequent primary (breast) cancer or late effects in general targeted towards (childhood) cancer survivors (i.e. not mentioned, no, yes); and
 - type of control group (i.e. none, non-irradiated cancer survivors, high-dose versus low-dose survivors, cancer survivors who had no radiotherapy directed to any part of the chest, axilla, and/or upper part of the abdomen, siblings, general population-based reference rates).
3. Interventions, including:
- number (percentage) of survivors who had no chemotherapy and/or no radiotherapy;
 - number (percentage) of survivors who had chemotherapy only;
 - number (percentage) of survivors who had radiotherapy only;
 - number (percentage) of survivors who had radiotherapy and/or chemotherapy;
 - number (percentage) of survivors who had specific gonadotoxic chemotherapy (alkylating agents, other potentially gonadotoxic agents);
 - number (percentage) of survivors who had radiotherapy directed to any part of the chest, axilla, and/or abdomen;
 - number (percentage) of survivors who had gonadotoxic radiotherapy (pelvic radiotherapy);
 - average (minimum-maximum) tumour dose of any radiotherapy;
 - average (minimum-maximum) tumour dose of radiotherapy directed to any part of the chest, axilla, and/or upper part of the abdomen;
 - proportion of survivors who had radiotherapy directed to the chest for whom estimated absorbed breast doses are available;
 - estimated radiation volume of the breast;
 - estimated radiation dose to the breast (average or median, minimum, maximum); and
 - method of radiation dosimetry (categories defined as: precise (exact estimation of dose at second tumour site); other;

none).

4. Outcome: breast cancer as a subsequent primary malignancy, including:
- definition of outcome measure (i.e. invasive, in situ, both);
 - number (percentage) pathologically confirmed as breast cancer;
 - number (percentage) of second tumours and/or number (percentage) of breast cancers as second, third or fourth tumours;
 - attained age at breast cancer diagnosis; and
 - percentage of breast cancer cases with HL as primary cancer.
5. Follow-up, including:
- calendar period of follow-up;
 - length of follow-up (median, minimum, maximum, percentage > 20 years, percentage > 30 years); and
 - method of follow-up (i.e. active clinical, questionnaire followed by medical confirmation, cancer registry, passive clinical, combined methods, other).
6. Risk factors, including:
- any information on underlying (nontreatment-related) predictors for breast cancer available (yes/no); and
 - if yes, list the factors for which information was available (e.g. Body Mass Index (BMI), postmenopausal status, parity, family history).

Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias in included studies. In case of disagreement, we will re-examine the abstracts and articles and we will discuss the assessment items until consensus is reached. If this is impossible, we will achieve final resolution by a third-party arbitrator. For the risk of bias assessment for observational studies we will use a modified checklist, based on the STROBE recommendations for reporting observational studies, and on earlier described checklists for observational studies according to evidence-based medicine criteria (Laupacis 1994; Vandembroucke 2007; Von Elm 2007). Table 1 shows the risk of bias assessment criteria for observational studies. For case-control studies we will slightly adapt the criteria depending on how the cases were ascertained, how the controls were selected, and if applicable, what were the matching criteria (i.e. gender, age at diagnosis, type of first cancer), and what the number of controls were per case. For RCTs/CCTs we will use the risk of bias items as described in the module of the Childhood Cancer Group (Module CCG), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

Prevalence, cumulative incidence, mean difference (MD), risk ratio (RR), rate ratio, excess relative risk (ERR), odds ratio (OR), excess absolute risk (EAR), attributable risk (AR), standardised incidence ratio (SIR), and observed-to-expected ratio (OER).

Dealing with missing data

We will contact authors of individual studies for clarification of unspecified or unclear data, or to obtain missing data regarding selection of studies, the risk of bias assessment, and data extraction. In particular, we expect this to be necessary for details on radiotherapy fields or body part irradiated, and/or to obtain diagnosis and treatment characteristics of the female subcohort among a total cohort of survivors, including males and females. In observational studies we will perform best-case/worst-case analyses wherever feasible.

Assessment of heterogeneity

We anticipate finding mainly observational studies. In observational studies, heterogeneity is expected to be an issue, due to differences in design, population, difference in measuring exposure and outcome, and differences in correction for confounding. We will assess heterogeneity by visual inspection of the forest plots and we will quantify heterogeneity by one of the formal statistical tests for heterogeneity, i.e. the I^2 statistic.

Assessment of reporting biases

We will use a funnel plot to quantify the potential presence of publication bias.

Data synthesis

We expect to have three types of studies in terms of summary estimates.

1. Studies reporting standardised incidence ratios (SIRs) or observed-to-expected ratios (OERs); we will summarise such studies using the Peto method (Yusuf 1985).
2. Studies reporting rate ratios or risk ratios (RRs) from time-to-event analyses; we will summarise such studies using the Peto method (Yusuf 1985).
3. Studies reporting the risk of breast cancer by estimated radiation dose to the breast (Gy); we will report such studies as excess relative risk as per Gy (ERR/Gy).

Depending on the choice of analysis method, we will use the RevMan 2011 software or SPSS. A priori we expect the results of studies mentioned in point 3 (above) to be too heterogeneous for a meaningful pooling without individual patient data. Consequently, we will not pool these studies, but will summarise them in a descriptive way.

Subgroup analysis and investigation of heterogeneity

The outcome of the test for heterogeneity (the I^2 statistic) and the software used for analysis will play a decisive role on whether and how the study results can be pooled. When no substantial heterogeneity is identified (i.e. $I^2 \leq 50\%$) (Higgins 2011), we will pool the study results using the fixed-effect model. In case of substantial heterogeneity (i.e. $I^2 > 50\%$), we will pool the results using the random-effects model. If pooling of study results is not possible with either of the mentioned models, we will attempt to explain the sources of heterogeneity as described in Assessment of heterogeneity, and we will summarise the study results descriptively and/or we will perform subgroup analyses or stratified analyses.

Sensitivity analysis

To assess the robustness of the results, we will perform a sensitivity analysis for each risk of bias item separately. Sensitivity analyses consist of 1) repeating analysis, taking study risk of bias into account, and 2) repeating analysis, excluding very large studies to explore whether and how they influence the results.

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* Indicates the major publication for the study

ADDITIONAL TABLES**Table 1. Risk of bias assessment criteria for observational studies**

<p>Study group</p> <p>Reporting bias (well-defined: yes/no)</p> <ul style="list-style-type: none"> • If the radiotherapy field/location was mentioned • If chemotherapy regimens or specific drugs were mentioned • <i>And</i> if potential for exposure to breast cancer screening was mentioned <p>Selection bias (representative: yes/no)</p> <ul style="list-style-type: none"> • If the study population consisted of more than 90% of the original cohort of cancer survivors (= source population) • <i>Or</i> if the study population was a random sample with respect to treatment of the original cohort of cancer survivors (= source population)
<p>Follow-up</p> <p>Reporting bias (well defined: yes/no)</p> <ul style="list-style-type: none"> • If the length of follow-up was mentioned • <i>And</i> if the method of follow-up was mentioned <p>Attrition bias (yes/no)</p> <ul style="list-style-type: none"> • If the outcome was assessed at the end date of the study follow-up for 80% or more of the study population • <i>Or</i> if the outcome was assessed for more than 90% of the study group for studies with an unknown official end of follow-up date
<p>Outcome</p> <p>Reporting bias (well-defined: yes/no)</p> <ul style="list-style-type: none"> • If the outcome definition was objective (i.e. confirmed by pathology or medical record information) and precise <p>Detection bias (blind: yes/no)</p> <ul style="list-style-type: none"> • If the outcome assessors were blinded to the investigated determinant, in other words, can we assess whether the probability of being screened, or the chance of breast cancer being detected depends on the use of specific chemotherapy drugs or chest radiotherapy exposure (this is among others, the case if patients are enrolled in active risk-based surveillance programmes for cancer survivors)
<p>Risk estimation</p> <p>Analysis (well-defined: yes/no)</p> <ul style="list-style-type: none"> • If one of the following items were calculated: prevalence, cumulative incidence, mean difference (MD), risk ratio (RR), rate

Table 1. Risk of bias assessment criteria for observational studies (Continued)

ratio, excess relative risk (ERR), odds ratio (OR), excess absolute risk (EAR), attributable risk (AR), standardised incidence ratio (SIR), observed to expected ratio (OER) or χ^2 , using analysis methods such as linear, logistic, Cox Regression, or Poisson regression model

Confounding (adjustment for other factors yes/no)

- If important prognostic factors (e.g. reproductive risk factors, treatment with hormonal replacement therapy (HRT), premature menopause age, sex, co-treatment, family history of breast cancer, being a BRCA1-2 carrier) were available
- *And* if adjustment for the increasing background risk of breast cancer with increasing attained age was taken into account (i.e. analyses based on OER, or Cox regression with attained age as time scale)
- *And* if other important prognostic factors (see examples above) for breast cancer were taken into account adequately (defined as: correction for confounding was done in multivariate or stratified analyse)

APPENDICES

Appendix I. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **Breast cancer** the following text words will be used:

breast cancer OR breast cancers OR breast neoplasm OR breast neoplasms OR breast neoplasm* OR mamma carcinoma OR mamma carcinomas OR mammary gland carcinoma or mammary gland carcinomas OR Neoplasm, Breast OR Neoplasms, Breast OR Tumors, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Mammary Carcinoma, Human OR Carcinoma, Human Mammary OR Carcinomas, Human Mammary OR Human Mammary Carcinomas OR Mammary Carcinomas, Human OR Human Mammary Carcinoma OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Cancer, Breast OR Cancer of the Breast OR Cancer of Breast

2. For **Second tumor** the following text words will be used:

Neoplasms, Radiation-Induced OR Neoplasms, Radiation Induced OR Radiation-Induced Neoplasms OR Neoplasm, Radiation-Induced OR Radiation Induced Neoplasms OR Radiation-Induced Neoplasm OR Radiation-Induced Cancer OR Cancers, Radiation-Induced OR Radiation Induced Cancer OR Radiation-Induced Cancers OR Cancer, Radiation-Induced OR Cancer, Radiation Induced OR Neoplasms, Second Primary OR Neoplasm, Second Primary OR Second Primary Neoplasm OR Metachronous Second Primary Neoplasms OR Neoplasms, Metachronous OR Second Primary Neoplasms, Metachronous OR Second Malignancy OR Malignancies, Second OR Malignancy, Second OR Second Malignancies OR Second Neoplasm OR Neoplasm, Second OR Neoplasms, Second OR Second Neoplasms OR Second Primary Neoplasms OR Metachronous Neoplasms OR Metachronous Neoplasm OR Neoplasm, Metachronous OR Neoplasms, Metachronous Second Primary OR Neoplasms, Therapy-Associated OR Neoplasm, Therapy-Associated OR Neoplasms, Therapy Associated OR Therapy-Associated Neoplasm OR Neoplasms, Treatment-Associated OR Neoplasm, Treatment-Associated OR Neoplasms, Treatment Associated OR Treatment-Associated Neoplasm OR Neoplasms, Treatment-Related OR Neoplasm, Treatment-Related OR Neoplasms, Treatment Related OR Treatment-Related Neoplasm OR Therapy-Related Neoplasms OR Therapy Related Neoplasms OR Treatment-Associated Neoplasms OR Treatment Associated Neoplasms OR Treatment-Related Neoplasms OR Treatment Related Neoplasms OR Neoplasms, Therapy-Related OR Neoplasm, Therapy-Related OR Neoplasms, Therapy Related OR Therapy-Related Neoplasm OR Therapy-Associated Neoplasms OR Therapy Associated Neoplasms OR Therapy-Associated Cancer OR Cancer, Therapy-Associated OR Cancers, Therapy-Associated OR Therapy Associated Cancer OR Therapy-Associated Cancers OR Therapy-Related Cancer OR Cancer, Therapy-Related OR Cancers, Therapy-Related OR Therapy Related Cancer OR Therapy-Related Cancers OR Treatment-Related Cancer OR Cancer, Treatment-Related OR Cancers, Treatment-Related OR Treatment Related Cancer OR Treatment-Related Cancers OR Treatment-Associated Cancer OR Cancer, Treatment-Associated OR Cancers, Treatment-Associated OR Treatment Associated Cancer OR Treatment-Associated Cancers OR Cancer, Second Primary OR Cancers, Second Primary OR Second Primary Cancer OR Second Primary Cancers OR Second Cancer

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OR Cancer, Second OR Cancers, Second OR Second Cancers OR Neoplasms, Radiation-Induced/etiology OR Neoplasms, Radiation-Induced/epidemiology OR Neoplasms, Radiation effects OR Neoplasms, Second Primary/epidemiology OR Neoplasms, Second Primary/etiology OR Radiotherapy/adverse effects OR Radiotherapy/complications OR second primary malignancy OR second primary malignancies OR second malignant neoplasm OR second malignant neoplasms OR SMN OR second neoplasm OR second neoplasms OR secondary breast cancer OR subsequent malignant neoplasm OR subsequent malignant neoplasms OR subsequent neoplasm OR subsequent neoplasms OR second malignancy OR new malignancy OR new malignancies

3. For **Survivors** the following text words will be used:

Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR survivo* OR surviving

Final search 1 AND 2 AND 3

The search will be performed in title, abstract or keywords

[*=zero or more characters]

Appendix 2. Search strategy for PubMed

1. For **Breast cancer** the following MeSH headings and text words will be used:

breast cancer OR breast cancers OR breast neoplasm OR breast neoplasms OR breast neoplasm* OR mamma carcinoma OR mamma carcinomas OR mammary gland carcinoma or mammary gland carcinomas OR Neoplasm, Breast OR Neoplasms, Breast OR Tumors, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Mammary Carcinoma, Human OR Carcinoma, Human Mammary OR Carcinomas, Human Mammary OR Human Mammary Carcinomas OR Mammary Carcinomas, Human OR Human Mammary Carcinoma OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Cancer, Breast OR Cancer of the Breast OR Cancer of Breast

2. For **Second tumor** the following MeSH headings and text words will be used:

Neoplasms, Radiation-Induced OR Neoplasms, Radiation Induced OR Radiation-Induced Neoplasms OR Neoplasm, Radiation-Induced OR Radiation Induced Neoplasms OR Radiation-Induced Neoplasm OR Radiation-Induced Cancer OR Cancers, Radiation-Induced OR Radiation Induced Cancer OR Radiation-Induced Cancers OR Cancer, Radiation-Induced OR Cancer, Radiation Induced OR Neoplasms, Second Primary OR Neoplasm, Second Primary OR Second Primary Neoplasm OR Metachronous Second Primary Neoplasms OR Neoplasms, Metachronous OR Second Primary Neoplasms, Metachronous OR Second Malignancy OR Malignancies, Second OR Malignancy, Second OR Second Malignancies OR Second Neoplasm OR Neoplasm, Second OR Neoplasms, Second OR Second Neoplasms OR Second Primary Neoplasms OR Metachronous Neoplasms OR Metachronous Neoplasm OR Neoplasm, Metachronous OR Neoplasms, Metachronous Second Primary OR Neoplasms, Therapy-Associated OR Neoplasm, Therapy-Associated OR Neoplasms, Therapy Associated OR Therapy-Associated Neoplasm OR Neoplasms, Treatment-Associated OR Neoplasm, Treatment-Associated OR Neoplasms, Treatment Associated OR Treatment-Associated Neoplasm OR Neoplasms, Treatment-Related OR Neoplasm, Treatment-Related OR Neoplasms, Treatment Related OR Treatment-Related Neoplasm OR Therapy-Related Neoplasms OR Therapy Related Neoplasms OR Treatment-Associated Neoplasms OR Treatment Associated Neoplasms OR Treatment-Related Neoplasms OR Treatment Related Neoplasms OR Neoplasms, Therapy-Related OR Neoplasm, Therapy-Related OR Neoplasms, Therapy Related OR Therapy-Related Neoplasm OR Therapy-Associated Neoplasms OR Therapy Associated Neoplasms OR Therapy-Associated Cancer OR Cancer, Therapy-Associated OR Cancers, Therapy-Associated OR Therapy Associated Cancer OR Therapy-Associated Cancers OR Therapy-Related Cancer OR Cancer, Therapy-Related OR Cancers, Therapy-Related OR Therapy Related Cancer OR Therapy-Related Cancers OR Treatment-Related Cancer OR Cancer, Treatment-Related OR Cancers, Treatment-Related OR Treatment Related Cancer OR Treatment-Related Cancers OR Treatment-Associated Cancer OR Cancer, Treatment-Associated OR Cancers, Treatment-Associated OR Treatment Associated Cancer OR Treatment-Associated Cancers OR Cancer, Second Primary OR Cancers, Second Primary OR Second Primary Cancer OR Second Primary Cancers OR Second Cancer OR Cancer, Second OR Cancers, Second OR Second Cancers OR Neoplasms, Radiation-Induced/etiology OR Neoplasms, Radiation-Induced/epidemiology OR Neoplasms, Radiation effects OR Neoplasms, Second Primary/epidemiology[Mesh] OR Neoplasms, Second Primary/etiology[Mesh] OR Radiotherapy/adverse effects[Mesh] OR Radiotherapy/complications[Mesh] OR second primary malignancy OR second primary malignancies OR second malignant neoplasm OR second malignant neoplasms OR SMN OR second neoplasm OR second neoplasms OR secondary breast cancer OR subsequent malignant neoplasm OR subsequent malignant neoplasms OR subsequent neoplasm OR subsequent neoplasms OR second malignancy OR new malignancy OR new malignancies

3. For **Survivors** the following MeSH headings and text words will be used:

Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR Survivor, Long-Term OR Survivors, Long-Term OR survivo* OR surviving

Final search: 1 and 2 and 3
[*=zero or more characters; mh=MeSH term]

Appendix 3. Search strategy for EMBASE (OVID)

1. For **Breast Cancer** the following Emtree terms and text words will be used:

1. exp breast cancer/
2. (breast cancer or breast cancers).mp.
3. exp breast tumor/
4. (breast neoplasm or breast neoplasms or breast neoplasm\$).mp.
5. exp breast carcinoma/
6. (mamma carcinoma or mamma carcinomas).mp.
7. (mammary gland carcinoma or mammary gland carcinomas).mp.
8. (breast tumor or breast tumour).mp.
9. (human mammary carcinoma or human mammary carcinomas).mp.
10. (human mammary neoplasm or human mammary neoplasms).mp.
11. cancer of the breast.mp.
12. cancer of breast.mp.
13. or/1-12

2. For **Second tumor** the following Emtree terms and text words will be used:

1. exp radiation injury/ or exp radiation induced neoplasm/ or exp radiation carcinogenesis/
2. (radiation induced neoplasm or radiation induced neoplasms or radiation reduced cancer or radiation reduced cancers).mp.
3. second cancer/
4. (second primary neoplasm or second primary neoplasms or metachronous second primary neoplasm or metachronous second primary neoplasms).mp.
5. (second malignancy or second malignancies or second neoplasm or second neoplasms).mp.
6. (metachronous neoplasm or metachronous neoplasms).mp.
7. (treatment related neoplasm or treatment related neoplasms).mp.
8. (treatment associated neoplasm or treatment associated neoplasms).mp.
9. (therapy related neoplasm or therapy related neoplasms).mp.
10. (therapy associated cancer or therapy associated cancers).mp.
11. (therapy related cancer or therapy related cancers).mp.
12. (treatment related cancer or treatment related cancers).mp.
13. (second primary cancer or second primary cancers).mp.
14. (second cancer or second cancers).mp.
15. exp neoplasm/co, ep, et, rt, si [Complication, Epidemiology, Etiology, Radiotherapy, Side Effect]
16. exp RADIOTHERAPY/ae, co [Adverse Drug Reaction, Complication]
17. (second primary malignancy or second primary malignancies).mp.
18. (second malignant neoplasm or second malignant neoplasms or SMN).mp.
19. (second neoplasm or second neoplasms).mp.
20. secondary breast cancer.mp.
21. (subsequent malignant neoplasm or subsequent malignant neoplasms).mp.
22. (subsequent neoplasm or subsequent neoplasms).mp.
23. (second malignancy or second malignancies or new malignancy or new malignancies).mp.
24. or/1-23

3. For **Survivors** the following Emtree terms and text words will be used:

1. (survivor or survivors or (long adj term survivor) or (long adj term survivors) or survivo\$).mp.
2. survivor/ or cancer survivor/
3. surviving.mp.
4. 1 or 2 or 3

Final search 1 and 2 and 3

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title or abstract; / = Emtree term; \$= zero to many characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

HISTORY

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DECLARATIONS OF INTEREST

None known.

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