Risks of Second Non-Breast Primaries Following Breast Cancer in Women: A Systematic Review and Meta-Analysis

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Abstract

**Background:**

Second primary cancer incidence is rising among breast cancer survivors. We examined the risks of non-breast second primaries, in combination and at specific cancer sites, through a systematic review and meta-analysis.

**Methods:**

We conducted a systematic search of PubMed, Embase, and Web of Science, seeking studies published by March 2022. We included studies that reported standardized incidence ratios (SIRs), with associated standard errors, assessing the combined risk of second non-breast primaries following breast cancer. We performed meta-analyses of combined second primary risks, stratifying by age, follow-up duration, and geographic region. We also assessed second primary risks at several specific sites, stratifying by age. The inverse-variance method with DerSimonian-Laird estimators was used in all meta-analyses, assuming a random-effects model. Associated biases and study quality were evaluated using the Newcastle-Ottawa scale.

**Results:**

One prospective and twenty-seven retrospective cohort studies were identified. SIRs for second non-breast primaries combined ranged from 0.84 to 1.84. The summary SIR estimate was 1.24 (95%CI: 1.14-1.36, I2: 99%). This varied by age: the estimate was 1.59 (95%CI: 1.36-1.85) when breast cancer was diagnosed before age 50, which was significantly higher than in women first diagnosed at 50 or over (SIR: 1.13, 95%CI: 1.01-1.36, p for difference: < 0.001). SPC risks were also significantly higher when based on Asian, rather than European, registries (Asia - SIR: 1.47, 95%CI: 1.29-1.67. Europe - SIR: 1.16, 95%CI: 1.04-1.28). There were significantly increased risks of second thyroid (SIR: 1.89, 95%CI: 1.49-2.38), corpus uteri (SIR: 1.84, 95%CI: 1.53-2.23), ovary (SIR: 1.53, 95%CI: 1.35-1.73), kidney (SIR: 1.43, 95%CI: 1.17-1.73), oesophagus (SIR: 1.39, 95%CI: 1.26-1.55), skin (melanoma) (SIR: 1.34, 95%CI: 1.18-1.52), blood (leukaemia) (SIR: 1.30, 95%CI: 1.17-1.45), lung (SIR: 1.25, 95%CI: 1.03-1.51), stomach (SIR: 1.23, 95%CI: 1.12-1.36) and bladder (SIR: 1.15, 95%CI: 1.05-1.26) primaries.

**Conclusions:**

Breast cancer survivors are at significantly increased risk of second primaries at many sites. Risks are higher for those diagnosed with breast cancer before age 50 and in Asian breast cancer survivors compared to European breast cancer survivors. This study is limited by a lack of data on potentially confounding variables. The conclusions could inform clinical management decisions following breast cancer.

# Keywords

1. Breast Neoplasms
2. Second Primary
3. Second Cancer
4. Multiple Primary
5. Multiple Cancer
6. Risk
7. Incidence
8. Epidemiology
9. Systematic Review
10. Meta-analysis

# Background

Multiple studies have compared the risk of second primary cancers (SPCs) following a first breast cancer (BC) to the corresponding first-cancer risks in the general population (1–33). Although most of these studies report an elevated risk (1,2,4–6,8–33), the magnitudes of the reported associations vary widely. Since a 2015 review reported a 17% increase in SPC risks following BC (34), many new studies have been published (1,5,6,9,12,16,17,19,20,23,24,27,32). In addition, BC is both increasing in incidence and improving in survival outcomes (35–37), exacerbating the public health problem posed by SPCs in BC survivors. Updated pooled estimates of SPC risks following BC are hence due.

Most published studies to date drew their data from European or North American population-based cancer registries (1–17,28–31,33), although several also drew their data from Asian registries (18–27,32). Many studies have found BC survivors to be at increased risk of melanoma (1,7,13,14,29–31,33), thyroid cancer (1,15,19,20,23–25,27,29–31,33,38), and several cancers of the urogenital and gastrointestinal systems (1,2,4,6–33), although the estimated magnitude of these risks varies.

A systematic review of the latest published evidence on SPC risks is helpful in guiding clinical management following BC. This could lead to improvements in SPC prevention and early detection.

In this review, we examine the latest evidence regarding the combined risks of developing SPCs following a first primary BC. We also evaluate the variability in SPC risks caused by confounding variables such as patient characteristics and demographic information. Finally, we identify which cancer sites may drive the combined risk of SPCs and quantify the magnitude of these site-specific risks.

# Methods

## Exposure, outcome and measures of association:

The exposure was the diagnosis of a primary BC. The outcome was the later diagnosis of a non-breast SPC. The measure of association was the standardized incidence ratio (SIR) comparing the incidence of second non-breast primaries among BC survivors to the incidence of first non-breast primaries in the general population.

To ensure the review accurately assessed second primary risks, a key condition of inclusion was that a study should have made a clear effort to differentiate SPCs from recurrences or metastatic developments of the first primary BC. To make use of more data, we did not restrict on the types of such efforts a study made.

Guidance on the topic is provided by the Surveillance, Epidemiology and End Results (SEER) program(39). Separate guidelines are also provided by the International Association of Cancer Registries (IACR)/International Agency for Research on Cancer (IARC) (40,41). A study by Coyte et al. found counts of second breast primaries following a first BC to differ between the SEER and IARC/IACR guidelines and counts of all other primaries to agree very closely (42). Since the SEER guidelines entail standard practice in North America and the IARC/IACR guidelines entail standard practice in all other areas, it was anticipated that most studies would use these guidelines, and therefore that we would have been unable to draw meaningful conclusions about second primary BC risk. As a result, only second non-breast cancers were considered as an outcome in this review.

## Data sources and search strategy:

Embase, PubMed, and Web of Science were searched on 11th March 2022 using the below queries:

**Embase:**

*(Breast Neoplasms/ or "breast cancer") and (Neoplasms, Second Primary/ or "second cancer" or "second primary") and risk*

**PubMed:**

*("Breast Neoplasms"[MeSH] OR "breast cancer") AND ("Neoplasms, Second Primary"[MeSH] OR "second cancer" OR "second primary") AND risk*

**Web of Science:**

*(TS = (("breast cancer" OR "breast neoplasm") AND ("second cancer" or "second primary") AND risk)) OR (AB = (("breast cancer" OR "breast neoplasm") AND ("second cancer" or "second primary") AND risk))*

## Inclusion and exclusion criteria:

To be included in the review, a study had to provide all information needed to extract a SIR and associated standard error evaluating the combined risk of non-breast SPCs in female BC survivors. It also had to take clearly described steps to discern SPCs from recurrences or metastases of the first BC, use data predominantly on those aged 15 and above at BC diagnosis and be written in English.

A study would be excluded if it evaluated SPC risks only in survivors of a non-invasive BC or only following a specific treatment of the first BC. Studies would also be excluded if data on third or subsequent primaries could not be excluded from their SPC risk estimates or if their data overlapped entirely with another accepted study.

Studies with data that partly but not fully overlapped were included in the review. In this case, the study with a greater sample size was the only one included in any meta-analyses. If this could not be established, the study including the most recent data was the one included.

There is a particularly close data link between the Swedish Family Cancer Database and the Swedish national cancer registry (43). The same is true of the Taiwanese Registry of Catastrophic Illness and the national cancer registry of Taiwan (44). We therefore considered data from these centres to overlap. Similarly, data from the Osaka Medical Centre for Cancer and Cardiovascular Diseases (OMCC) is primarily a subset of Osaka Cancer Registry (OCR) data (45). Accordingly, if a study based on OMCC data overlapped with a study based on OCR data, the latter was considered the larger study if there was missing information on sample size.

## Data extraction:

Title and abstract screening were performed by two authors as part of an independent double-screening process. Conflicts regarding twelve studies were resolved by another author. We closely read the full text, swept the bibliographies, and whenever applicable searched the PubMed “cited by” sections of each the studies that passed the title and abstract screening in search of additional studies.

## Statistical analysis:

We assumed there would be some between-study variance in SIRs not attributable to sampling error, and therefore assumed a random-effects model in all meta-analyses (46), using the generic inverse variance method with DerSimonian-Laird estimators (47,48). Standard errors were extracted routinely (49) and were used to weight the studies in meta-analyses (46).We used Byar’s approximation to calculate confidence intervals (CIs), unless CIs could be taken directly from a study (49).

We firstly performed an unstratified meta-analysis. We quantified the heterogeneity in these results by inspecting Cochran’s Q (48)and the I2 statistic (50,51). We also performed leave-one-out analyses to identify which studies were the main drivers of heterogeneity (46), which we defined as the studies causing Cochran’s Q to decrease by over 10% once they were removed from the unstratified meta-analysis. We also defined outlier studies to be studies whose 95% confidence interval lay wholly outside the confidence interval around the summary SIR generated by the unstratified meta-analysis (46). We then performed two further meta-analyses after respectively eliminating all the main drivers of heterogeneity and all outlier studies, to assess the remaining heterogeneity and the effect on the summary SIR. We examined publication bias by visually assessing funnel plots and performing Egger’s test (52).

We also performed further meta-analyses stratifying on 1) Age at BC diagnosis - Under 50 years and 50 years or above. Data on those diagnosed before age 56 and at age 56 or over were respectively included in the younger and older strata if no stratification at 50 was provided, 2) Follow-up time duration following BC diagnosis - Under 5 years or 5 years and over. We also performed a second meta-analysis stratifying at 10 years, 3) Geographic region **–** the continent of the data centre (i.e: hospital, registry) used in a particular study.

We evaluated for differences in risks by age, follow-up duration, and geographic region using the Cochran’s Q statistic, by considering each stratum as a subgroup, and by comparing the resulting statistic to a chi-squared distribution (46).

We also examined the Cochran’s Q and I2 statistics in each stratum for each stratified meta-analysis, to assess if a particular risk factor explained some of the heterogeneity in the unstratified analysis of non-breast SPC risks.

We extracted SIRs that quantified SPC risks at specific sites, together with associated standard errors, from the studies included in the unstratified meta-analysis. We then estimated summary SIRs for SPC risks at these sites by conducting meta-analyses of the relevant site-specific SIRs. This was done to elucidate which cancer sites were driving the combined risks of all non-breast SPCs. We first examined site-specific risks for all ages. We then stratified by age at BC diagnosis, using the same stratification points as in the analyses of combined non-breast primary risks. These analyses were performed for each of the 20 non-breast cancer sites with the highest incidences among women worldwide in 2020, excluding non-melanoma skin cancer due to known underreporting and excluding oral cavity and lip cancer due to SPC risks at this site often being combined with other sites at the head and neck (6,23,33). These sites are the bladder, the blood (leukaemia, myeloma and non-Hodgkins lymphoma), the brain and central nervous system (CNS), the cervix uteri, the corpus uteri, the colorectum, the gallbladder, the kidney, the liver, the lung, the oesophagus, the ovary, the pancreas, the skin (melanoma), the stomach, the thyroid and the vulva (53).

Forest plots were generated as a visual aid to accompany each meta-analysis. We evaluated the methodological quality of each study using the Newcastle-Ottawa scale (NOS) (54), as recommended by the Cochrane Collaboration (47) (details in Additional File). RStudio version 4.1.2 was used for all analyses (55). We defined statistical significance to be present when a p-value of under 0.05 was observed.

The reader seeking a more detailed explanation of the statistical techniques described in this section is encouraged to consult Breslow and Day (49) and, for a specific focus on meta-analysis methodology, Harrer et al. (46).

# Results

## Results of literature search:

112 studies were accepted for review at the full-text level after passing the title and abstract screening stage. 65 of these were selected from the 2011 studies returned after the database searches. 38 of the 112 studies were found following sweeps of the bibliographies of 69 studies: the 65 studies previously mentioned, and four additional studies which only failed the title and abstract sweeping due to exclusively examining male BC survivors. We identified the final 9 of the 112 studies after sweeping the “cited by” section of PubMed for 66 of these 69 studies, as the remaining three studies (56–58) were unavailable in PubMed. In this way, we hoped to capture additional relevant literature published both before and after the studies identified through the database searches. Following close reading, we included 28 of the 112 studies in this review. Reasons for exclusions of the remaining 84 studies, as well as a full explanation of the search process, are shown in Figure 1.

**Figure 1: Search process**

PubMed, Embase, and Web Of Science database searches: **n = 2011**

Screening titles and abstracts:

**n = 1946 eliminated**

**n = 112**

**n = 65**

**Studies included: n = 28**

Screening (at full-text level):

**n = 84 eliminated**

Unable to eliminate second BC as an endpoint – **18**

Overlaps fully with larger study/studies - **17**

SIRs/standard errors unreported – **16**

Only evaluates risks of SPCs at specific sites – **11**

Unable to exclude new primaries after the second – **8**

Poster, summary, or review – **7**

Cohort composed of non-breast cancer survivors– **5**

Only examines SPCs following non-invasive first BC - **1**

Only examines BC survivors after specific treatment - **1**

Sweeping bibliographies of 69 studies:

* 65 that passed title/abstract screening
* 4 that failed title/abstract screening solely due to including only male BC survivors

**n = 38 added**

Sweeping PubMed “cited by” sections for of 66 of the above 69 studies:

**n = 9 added**

All studies included were cohort studies, only one of which was prospective (12). Three studies were hospital-based (13,15,20) and the remainder were wholly or predominantly registry-based. The centre/centres (hospital or registry/registries) were European in fourteen studies (1–5,7,9–14,16,17) Asian in ten studies (18–27) and North American in three studies (6,8,15). One study (33) drew their cohort from registries based across four continents. Since the bulk of the cohort was taken from European registries, this study was treated as European for the purposes of any stratifications based on geographic region. Three (4,5,12) studies used data from multiple countries in Europe, although all the data drawn from non-German centres in Chen et al. (5) fully overlapped with larger studies (17,33). Therefore, we only included the German data from Chen et. al. in this review.

The longest follow-up period was 57 years(17). The shortest was 11 years (12,26).

Six studies set minimum ages at first cancer diagnosis, at age 15yr (5,11,16,23) and age 20yr (18,20). Six studies set maximum ages: at age 39yr (16), age 79yr (23,25,26), age 84yr (7) and age 89yr (2). The cohort in one study (12) was taken from a pre-existing larger observational cohort study: there was a minimum age of 35yr and a maximum age of 70yr for recruitment into the larger study, whose cohort was recruited without regard to cancer status. The subset of this larger cohort which subsequently developed a first primary BC was the cohort included in this review. All remaining nineteen studies imposed no age-related restrictions when selecting their cohorts.

Fifteen studies excluded data on second primaries occurring within some given follow-up duration following the first BC diagnosis (2–4,8–11,13,18,20–23,25,26). All other studies included data on second primaries diagnosed immediately following the first BC, although the study by the AIRTUM Working Group (1) also gave a separate analysis excluding SPCs diagnosed in the first 2 months of follow-up. The data excluding the earlier SPCs were explicitly stated as less prone to bias by the authors, so these were the data used in any statistical analyses.

All but one study (5) gave site-specific risks of second primaries.

The reported SIRs ranged from 0.84(3) to 1.84 (23). All but five (3,7,18,20,23) estimated SIRs ranging between 1.00 and 1.50.

The characteristics of all 28 studies are detailed in Table 1 and Table 2. The NOS scores assigned to each study may be seen in the Additional File, together with an explanation of the methods used.

## Results of meta-analyses:

### Unstratified results:

The unstratified meta-analysis consisted of nineteen studies (1,3,5–7,9–11,13–15,18–20,23,24,26,27,33). All but two (3,7) reported an increase in SPC risks following a first primary BC.

The summary SIR was estimated as 1.24 (95%CI: 1.14-1.36, Figure 2). Significant evidence for heterogeneity was found (Q: 1839.32, I2: 99%, p < 0.001).

**Figure 2: Second non-breast primary risks following first primary breast cancers.**

Chart

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*Pooled overall random-effects point estimate represented by dashed line.*

Following leave-one-out analyses, we found the studies by Diab et al. (6), Odani et al. (23), Mellemkjær et al. (33), Evans et al. (7), and Hung et al. (19) to contribute the most to heterogeneity, with Cochran’s Q falling by 40%, 23%, 20%, 15% and 13% in the meta-analyses consisting of all studies in the unstratified meta-analysis other than the respective study under investigation. Eliminating all these studies did not appreciably affect the summary SIR estimate (SIR: 1.24, 95%CI: 1.13-1.35), and there remained significant evidence for heterogeneity (Q: 154.89, I2: 92%, p < 0.001).

We identified 7 outlier studies (3,6,7,15,18,19,23). Eliminating all outlier studies also had little effect on the SIR estimate (SIR: 1.25, 95%CI: 1.19-1.31), and significant evidence for heterogeneity was still present (Q: 166.23, I2: 93%, p < 0.001).

Examining a funnel plot and performing Egger’s test revealed no significant evidence of publication bias (Additional File).

### Effects of geographic region:

We found significant evidence that summary SIRs varied by geographic region (SIR: 1.47, 95%CI: 1.29-1.67 for Asian studies vs 1.16 (1.04-1.28) for European studies vs 1.03 (1.02-1.04) for North American studies, p for difference: < 0.001, Figure 3).

**Figure 3: Second non-breast primary risks following first primary breast cancers. Stratification: geographic region.**

Chart

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Significant heterogeneity was found for the Asian subgroup analysis (Q: 222.36, I2: 97%, p < 0.001) and for the European subgroup analysis (Q: 561.95, I2: 98%, p < 0.001). No significant evidence for heterogeneity was found in the North American subgroup analysis (Q: 0.09, I2: 0%, p: 0.77).

There was significant evidence that Asian BC survivors had higher SPC risks in comparison to European BC survivors, for whom the largest amount of data was available (p for difference: 0.005). There was also significant evidence that American BC survivors were at lower risks of SPCs compared to European BC survivors (p for difference: 0.027).

## Effects of age at BC onset:

Eight studies were included in the age-stratified meta-analyses (1,6,7,11,13,14,19,33). One small study also stratified by age at breast cancer diagnosis but was not included in this analysis due to a discrepancy between the number of SPCs reported in total and within each age stratum (20). SPC risks were significantly elevated in both age groups compared to the risks of first primaries and there was significant evidence for a difference in summary SIRs between these groups (SIR: 1.59, 95%CI: 1.36-1.85 for those aged under 50 at first BC diagnosis vs. 1.13 (95%CI: 1.01-1.26) for those aged over 50 at first BC diagnosis, p for difference: < 0.001, Figure 4). Heterogeneity was present in both strata (Aged under 50 at first BC diagnosis: Q: 318.11, I2: 98%, p < 0.001. Aged 50 or over at first BC diagnosis: Q: 717.72, I2: 99%, p < 0.001).

**Figure 4: Second non-breast primary risks following first primary breast cancers. Stratification: age at breast cancer diagnosis.**

Chart

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### Effects of follow-up time duration:

Stratification of BC survivors by follow-up duration revealed no significant evidence for a difference in SPC risks. Full results may be seen in the Additional File.

### Second primary risks at specific sites:

Point estimates of summary SIRs estimating SPC risks unstratified by age at the nineteen examined sites ranged from 0.80 (for the brain and CNS) to 1.89 (for the thyroid). BC survivors were found to be at significantly lower risk of brain and CNS cancers (SIR: 0.80, 95%CI: 0.71-0.91) and cervix uteri cancers (SIR: 0.88, 95%CI: 0.77-1.00). In contrast, there was significant evidence for elevated second primary bladder (SIR: 1.15, 95%CI: 1.05-1.26), corpus uteri (SIR: 1.84, 95%CI: 1.53 – 2.23), kidney (SIR: 1.43, 95%CI: 1.17-1.73), blood (leukaemia) (SIR: 1.30, 95%CI: 1.17-1.45), lung (SIR: 1.25, 95%CI: 1.03-1.51), skin (melanoma) (SIR: 1.34, 95%CI: 1.18-1.52), oesophagus (SIR: 1.39, 95%CI: 1.26-1.55), ovary (SIR: 1.53, 95%CI: 1.35-1.73), stomach (SIR: 1.23, 95%CI: 1.12-1.36) and thyroid (SIR: 1.89, 95%CI: 1.49-2.38) cancer risks following BC.

We found BC survivors first diagnosed with BC at under age 50 to be at elevated risk of second primaries at the bladder (SIR: 1.32, 95%CI: 1.17-1.48), blood (leukaemia) (SIR: 1.91, 95%CI: 1.77-2.05), corpus uteri (SIR: 1.40, 95%CI: 1.12-1.76), kidney (SIR: 1.29, 95%CI: 1.15-1.43), lung (SIR: 1.65, 95%CI: 1.49-1.82), oesophagus (SIR: 2.21, 95%CI: 1.89-2.60), ovary (SIR: 2.24, 95%CI: 1.59-3.13), pancreas (SIR: 1.35, 95%CI: 1.16-1.57), skin (melanoma) (SIR: 1.34, 95%CI: 1.23-1.45), stomach (SIR: 1.90, 95%CI: 1.75-2.06) and thyroid (SIR: 2.06, 95%CI: 1.83-2.31).

We found there to be significantly increased risks of second primaries at three sites in BC survivors diagnosed with BC at age 50 or over: the corpus uteri (SIR: 1.75, 95%CI: 1.29-2.37), the oesophagus (SIR: 1.20, 95%CI: 1.06-1.37) and the skin (melanoma) (SIR: 1.25, 95%CI: 1.17-1.35).

BC survivors diagnosed with breast cancer before age 50 were at significantly increased risk of second primary lung cancer compared to BC survivors diagnosed with breast cancer at age 50 or over (SIR: 1.65, 95%CI: 1.49-1.82 for those aged under 50 at first BC diagnosis vs. 0.81 (95%CI: 0.55-1.20) for those aged over 50 at first BC diagnosis, p for difference: < 0.001). They were also at significantly increased risks of second primaries at the pancreas (SIR: 1.35, 95%CI: 1.16-1.57 vs. 0.92 (95%CI: 0.81-1.04), p for difference: < 0.001), blood (leukaemia) (SIR: 1.91, 95%CI: 1.77-2.05 vs. 1.34 (95%CI: 0.99-1.81), p for difference: 0.026), oesophagus (SIR: 2.21, 95%CI: 1.89-2.60 vs. 1.20 (95%CI: 1.06-1.37), p for difference: < 0.001), ovary (SIR: 2.24, 95%CI: 1.59-3.13 vs. 1.04 (95%CI: 0.93-1.16), p for difference < 0.001), stomach (SIR: 1.90, 95%CI: 1.75-2.06 vs. 1.10 (95%CI: 0.91-1.34), p for difference < 0.001), and thyroid (SIR: 2.06, 95%CI: 1.83-2.31 vs. 1.17 (95%CI: 0.90-1.52), p for difference < 0.001).

Full results may be seen in Table 3.



# Discussion

In this review we found significant evidence for elevated SPC risks among BC survivors, particularly when first diagnosed with BC at under age 50 or in Asian hospitals/registries. Risks of second primary bladder, kidney, blood, lung, skin (melanoma), oesophagus, ovary, stomach, thyroid and corpus uteri cancers were significantly increased, whereas risks of brain and CNS and cervix uteri SPCs were significantly decreased.

This review has several strengths. The studies were of high quality (Additional File), and we found no significant evidence for publication bias (Additional File). It includes an array of studies with large sample sizes (1,4–7,14,17,19,21,33), long follow-up periods (1,2,4,6–8,10,13,16,17,20,21,25,27,33) and recently updated data (1,5,6,16,17,19,20,23). Another strength is the inclusion of several studies from outside Europe and North America (18–27), allowing comparisons between regions with different demographics and BC incidence rates (59).

There are two main weaknesses of this review. The first is the high level of heterogeneity observed, and the second is the underreporting of potentially confounding risk factors.

Regarding the first point, much of the heterogeneity was contributed by Diab et al. (6), a very large study from North America, and the only study that was explicitly stated to use the SEER multiple tumour coding rules. It is therefore possible that the differences between such rules could account for some of the between-study differences in SPC risks such as the significantly decreased SPC risks among North American studies compared to European studies. This would be at odds with the small study by Coyte et al. (42), which found non-breast SPC counts to be close to identical under both the SEER and the IARC/IACR rules. Larger studies comparing SPC counts observed under these two common sets of guidelines would help clarify this issue. However, even if SPC coding discrepancies do account for the majority of the heterogeneity contributed by Diab et al., this would not explain the rest of the heterogeneity, which remained significant even following the elimination of four further studies identified as major drivers of heterogeneity (7,19,23,33).

It is likely that including studies from three different continents contributed to heterogeneity, since SPC risks in these continents were found to vary significantly. Similarly, if ages at BC diagnoses varied widely between studies, then this would account for some of the heterogeneity, as younger age groups were found to be at significantly increased risk in comparison to those older. However, although heterogeneity was attenuated, it remained significant among Asian and European studies as well as in both age younger and older age groups, so these points cannot fully explain the observed heterogeneity.

It is also possible that differences in the treatments administered between studies could affect SPC risks (60–62) and thus contribute to heterogeneity. Unfortunately, this could not be assessed in this review since treatment effects were generally unreported. Information on other important variables also tended to be unavailable. For example, there was a paucity of information reported on obesity, tobacco intake, alcohol intake, the pathology of the initial BC, or family history of BC, which are known to influence cancer risks. We cannot therefore rule out confounding in the results due to these unreported confounding variables, nor can we rule out that unreported risk factors contributed to the significant heterogeneity observed.

It is known that cancer survivors may be more prone to being diagnosed with second cancers simply due to increased surveillance for cancer development, rather than a genuine increase in risk compared to the general population. This is known as “detection bias”, and we cannot rule out that it may have affected some results in this review (1). However, many studies were included that excluded SPCs diagnosed within some time period following the first BC (2–4,8–11,13,18,20–23,25,26) when detection bias is likely to be most pronounced (1). Therefore, detection bias is unlikely to be a major weakness of this review.

It is also possible that reported SIRs could vary between studies due to usage of different methodologies or data sources of varying quality when calculating expected cancer counts, distorting our results. For example, Diab et al. calculated their expected SPC counts using the SEER database, a population-based dataset of very high quality (6,63) and with a very limited amount of data integral to SIR calculations missing (64). If other studies estimate their expected counts relying on hospital-based data or data of lower quality, this could account for some of the observed heterogeneity and partly explain the significant differences in SPC risks by geographic region. All studies in the meta-analyses which reported the specific data source used to calculate expected cancer counts used population-based registry data (1,10,11,14,15,19,20,24,27,33), although most did not report on the quality of this data. Therefore, it cannot be ruled out that differences in data quality affected study estimates of expected cancer counts, and therefore affected our results. Furthermore, a large study included in the meta-analyses included second and subsequent primaries in their calculations of expected cancer counts (1) whereas others included only first cancers (1,5,9), although this information was generally not reported. However, excluding rather than including these data should not sizeably alter SIR estimates (1), and hence is unlikely to have notably affected our results.

Finally, although every effort was made to capture all relevant studies, it cannot be ruled out that some studies were not found or were excluded erroneously.

This review adds to the previously published review (34) in several ways. Firstly, the previous review included no studies published since June 2013, whereas this updated review included twelve studies published since (1,5,6,9,12,16,17,19,20,23,24,27). This review also includes studies with cohorts consisting of survivors of any given set of initial cancers provided SPC risks could be extracted for the subset of BC survivors, yielding three new studies published before June 2013 (15,25,26). In total, eighteen of the twenty-eight studies in this review were not included in the previous review (1,4–6,8,9,12,15–20,23–27), including several large multicentre studies and two sizeable monographs (1,4–6,8,9,12,16). Several of the new studies are drawn from Asian registries (18–20,23,24,27) and North American registries (6,8,15), whereas the previous review did not include any North American studies. This enabled us to assess differences in SPC risks between these geographic regions. Finally, the previous review found follow-up duration to significantly affect SPC risks, whereas this updated review found no significant evidence of this (Additional File). The overall summary female SIR of 1.24 (95% CI: 1.14-1.36) is slightly higher than the summary SIR reported in the previous review (1.17 (95% CI: 1.10-1.25)).

The increased SPC risks could be partly due to treatment effects of the initial BC, such as the administration of hormonal therapy such as tamoxifen, or the administration of chemotherapy or radiotherapy (60–62). The latter may explain the increased risks of second oesophagus and lung primaries in BC survivors diagnosed at under age 50, as radiotherapy confers increasing risks of lung and oesophagus primaries with time since administration (63). Similarly, chemotherapy is associated with leukaemia (66,67) and is more commonly administered to younger BC survivors (68), possibly explaining the significantly higher risks of second primary leukaemias we found for this group. Shared risk factors between breast and other cancers such as obesity will also contribute to the elevated SPC risks among BC survivors (69,70). For example, thyroid cancer risks may be elevated by obesity or hormonal risk factors shared with BC (38). The increased risk of SPCs at the lung (71), in the urogenital system (71) in the gastrointestinal system (71), and at other sites (12,71,72) could be partly attributable to increased tobacco intake among BC survivors in comparison to the general population (73), with smoking recently confirmed to be the leading cancer risk factor globally (72).

Germline susceptibility to BC may also raise specific SPC risks (74). For example, pathogenic variants in known BC susceptibility genes are associated with risks for other cancers. Pathogenic variants in *BRCA1/2* have been found to be associated with risks of multiple primary cancers, including pancreatic and stomach cancers (75). Pathogenic variants in *BRCA1/2* are also associated with ovarian cancer risk (76,77)*,* as are pathogenic variants in *PALB2* (78), *RAD51C* (79,80),and *RAD51D* (80,81). Such observations may explain the elevated ovarian SPC risks found in this review, particularly among younger BC survivors (82,83). There also exist common genetic variants with pleiotropic effects, associated with elevated breast and ovarian cancer risks (84). Elevated polygenic risk scores are often associated with risks for more than one cancer (84); for example, a BC polygenic risk score has been associated with colorectal cancer risk (85) and a recent large study found the prevalence of pathogenic protein-truncating variants in established BC susceptibility genes among female BC survivors to be 5.6% (86). Genetic susceptibility could therefore account for a notable proportion of second primaries following BC in women.

If germline susceptibility does increase SPC risk in female BC survivors, this may partly explain our finding of elevated SPC risks in women diagnosed with BC at under age 50 compared to those diagnosed when older, since genetic susceptibility to BC is associated with earlier BC diagnosis (82,87). This finding will also partly account for the increased SPC risks among those diagnosed with BC in Asian registries, as BC is diagnosed at younger ages in Asia (88,89).

The decreased risks of blood (myeloma), brain and CNS, and liver SPCs among BC survivors aged 50 or over at first BC diagnosis may be explained by under-ascertainment of SPCs in older age groups (7). We also found brain and CNS SPC risks to be significantly decreased when unstratified by age, which is likely attributable to misclassifications of second primaries as metastases (90).

The decreased risk of second cervix uteri cancer is intriguing since oral contraceptive usage is a shared BC (91) and cervical cancer (92) risk factor, and thus might be expected to raise the risks of cervix uteri SPCs. Parity may provide a partial explanation as higher parity is a protective factor for BC (93) and a risk factor for cervix uteri cancer (94), but additional large studies would be helpful in clarifying this.

# Conclusions

In conclusion, this review found that the combined risks of second non-breast cancer following a first primary BC were significantly elevated. Female BC survivors aged under 50 at BC onset or who were from Asian registries/hospitals were found to be at higher risks than other groups. Finally, we found second cancers at the bladder, corpus uteri, kidney, blood, lung, skin (melanoma), oesophagus, ovary, stomach and thyroid to notably contribute to the observed elevated SPC risks.

The results may lead to increased awareness of the magnitudes and distribution by site of SPC risks following BC. They could also better inform cancer risk management such as screening recommendations for BC survivors, particularly among women diagnosed with BC at a young age.

# Declarations

# **Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

All data generated or analysed during this study are included in the previously referenced published articles (1–27,33)(and their supplementary information files).

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

IA conducted the database searches, screened the studies at the title and abstract and at the full-text level, performed all data extraction and statistical analyses, and wrote the manuscript. HH also screened the studies at the title and abstract stage, with ES being responsible for resolving conflicts. MT, PP and AA all edited the manuscript and supervised the research. All authors provided input and suggestions for improvement in the draft phase of the manuscript.

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# Abbreviations

All abbreviations used are listed below in order of appearance:

1. SPC – Second Primary Cancer

2. BC – Breast Cancer

3. SIR – Standardized Incidence Ratio

4. SEER – Surveillance, Epidemiology and End Results

5. IACR – International Association of Cancer Registries

6. IARC – International Agency for Research on Cancer

7. OMCC - Osaka Medical Centre for Cancer and Cardiovascular Diseases

8. OCR – Osaka Cancer Registry

9. CI – Confidence Interval

10. CNS – Central Nervous System

11. NOS – Newcastle-Ottawa Scale

12. BRCA1/2 – BReast CAncer gene 1/2

13. PALB2 – Partner and Localizer of BRCA2

14. RAD51C – RAD51 paralog C

15. RAD51C – RAD51 paralog

**Table 1: Study characteristics**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author and publication year** | **Period of first BC1 dx2 for cohort** | **Follow-up period** | **Study design** | **Country and centre of data derivation** | **Definition of cohort** | **Definition of second primary cancers** |
| AIRTUM Working Group 2013 (1) | Dx: 1976-2010 (varied by registry). | Start: At BC dx.  End: At SPC dx, death, date of last known vital status, or end of last year of registration (dates varied by registry). | Retrospective cohort. | Italy (Multiple cancer registries covering 48% of the population). | All patients dx with a first cancer, although melanoma skin cancer cases, cases based on death certificate only, cases based on autopsy only, and cases with follow-up time equal to zero were excluded. Cohort was stratified by first cancer site, allowing analysis for first BC. | IARC/IACR4 rules. |
| Andersson 2008 (2) | Dx 1977-2001. | Start: 1y after BC dx.  End: SPC dx, death, emigration, or study end (2002). | Retrospective cohort. | Denmark (Danish Breast Cancer Cooperative Group). | Female BC patients with record of BC dx at under age 90 in both the Danish Breast Cancer Cooperative Group and the Danish Cancer Register, who survived at least 1y5 post-BC dx, with no prior cancer history other than non-melanoma skin cancer, treated and followed accorded to a Danish Breast Cancer Cooperative Group protocol. | SPC6 coding rules unstated, but the Danish Breast Cancer Cooperative Group is linked to the Danish Cancer Register, which uses IARC/AICR rules. |
| Brenner 1993 (3) | Dx 1968-1987. | Start: 1y after BC dx.  End: study end given as 1987. No details of other censoring events provided. | Retrospective cohort. | Germany (Saarland Cancer Registry). | Women dx with a first BC (first 1y post dx excluded from analysis). | SPC coding rules unstated, but German registries use IARC/IACR rules. Secondary malignancies and tumours of unspecified location, the skin, the bone, the brain and nervous system, the lung and the liver were excluded. |
| Brown 2007 (4) | Dx 1943-1999 (Denmark), 1953-2002 (Finland), 1953-2000 (Norway), 1958-2002 (Sweden). | Start: 1y after BC dx.  End: SPC dx, death, or study end (1999-2002, depending on registry). | Retrospective cohort. | Denmark, Finland, Norway, Sweden (all national registries). | Women dx with a first BC, who survived for at least 1y (first 1y post dx excluded from analysis). | SPC coding rules unstated, but all participating registries use IARC/AICR rules. Non-haematological malignancies excluded. |
| Chen 2015 (5) | Dx 1997-2010. | Start: At BC dx.  End: SPC dx, death, emigration, or study end (2010). | Retrospective cohort. | Germany (12 German cancer registries covering 33% of population). Data was also reported for Sweden, but is not included here due to fully overlapping with several larger studies. | Patients aged 15y or over at dx of a first primary malignant tumour. Patients with only death certificate/autopsy information were excluded. Cohort was stratified by first cancer site, allowing analysis for first BC. | According to IARC/IACR rules, not including non-melanoma skin cancer. All cancers must be discordant. 95%+ of were cancers microscopically verified. |
| Diab 2016 (6) | Dx 1973-2012. | Start: At BC dx.  End: SPC dx, death, or study end (2015). | Retrospective cohort. | United States of America - 9 SEER7 registries (Connecticut, Detroit, Atlanta, San Francisco (Oakland), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah). | Women dx with breast cancer. In situ malignancies, dx made without microscopic confirmation, and dx from death certificates and autopsy reports were not included. | SEER rules. |
| Evans 2001 (7) | Two cohorts pooled: Dx 1961-1970 and dx 1971-1995. | Start: At BC dx.  End: SPC dx, death, loss to follow-up, 85th birthday, or study end (1982 for those dx 1961-70, 1996 for those dx 1971-1995). | Retrospective cohort. | England (Thames Cancer Registry). | Women dx with first BC at under age 85. | Second tumours at a separate anatomical site and of a distinct histological type to the first tumour, or stated as a new tumour by the treating clinician. Non-melanoma skin cancers, non-malignant cancers, second cancers occurring within 1y of the initial cancer at the same site with the same laterality and histology, or cancers in patients without residency information available at date of dx or a without given date of dx, were all excluded. |
| Gulhan 2009 (18) | 1992-2006. | Start: 1y after BC dx.  End: study end given as 2006. No details of other censoring events provided. | Retrospective cohort. | Turkey (Izmir Cancer Registry). | Women aged at least 20 with histologically confirmed invasive BC, with at least 1m8 of follow-up. | IARC/IACR rules. |
| Harvey 1985 (8) | 1935-1982. | Start: 2m after BC dx.  End: At SPC dx, death, date of last known vital status, or study end (1982). | Retrospective cohort. | United States of America (Connecticut Tumour Registry). | Individuals diagnosed with a first primary invasive BC when they were resident in Connecticut, that survived without a second cancer developing for at least 2m after the diagnosis, who were observed for at least 2m after the diagnosis, and whose cancer was not diagnosed only from an autopsy report or death certificate. | Most of the data used in this study predates the publication of the SEER SPC coding rules, the most common rules applied in North America. However, SPC coding rules used in this study were very similar. Briefly, study defined SPCs as invasive cancers that developed at least 2m after the first cancer, excluding in situ cancers or non-melanoma skin cancers. SPCs diagnosed only from autopsy reports or death certificates were included. |
| Hung 2016 (19) | 1997-2010. | Start: At BC dx.  End: SPC dx, death, dropout from program providing study data, or study end (2011). | Retrospective cohort. | Taiwan (Registry of Catastrophic Illness). | Patients dx with a first BC. | SPC coding rules unstated, but the registry histologically confirms cancer cases. Oncologists are required to give evidence of the diagnosis, including cytology reports, pathology reports, laboratory studies, and imaging studies, for review by commissioned expert panels. |
| Jégu 2014 (9) | Dx 1989-2004. | Start: 2m (62 days) after BC dx.  End: At SPC dx, death, date of last known vital status, or study end (2007). | Retrospective cohort. | France (10 registries covering the Bas-Rhin, Calvados, Doubs, Hérault, Isère, Manche, Somme and Tarn administrative regions). | Patients dx with a first cancer, who did not develop a SPC within 2m (62 days) after their first cancer. Cohort was stratified by first cancer site, allowing analysis for first BC. | IARC/IACR rules. |
| Jung 2017 (20) | Dx 1989-2014. | Start: At BC dx.  End: At SPC dx, death, date of last known hospital visit, or study end (2014). | Retrospective cohort. | Korea (3 medical centres in Soeul, Bucheon, and Choenan). | Women aged at least 20y dx with BC and with at least 1 visit to the Soeul, Bucheon, or Choenan centres within 2m from dx and with treatment records, who contributed at least 2m of follow-up time. | SPC coding rules unspecified, but second cancers must be at discordant sites, dx at least 2m after BC diagnosis, with each case "thoroughly reviewed, and misleading information from breast cancer metastasis excluded”. |
| Lee 2008 (21) | Dx 1979-2003. | Start: At BC dx.  End: At SPC dx, death, or study end (2003). | Retrospective cohort. | Taiwan (National Cancer Registry). | Women dx with first BC, without missing dates of birth, follow-up dates or death statuses, and who survived without a second cancer for at least 1m post BC dx. | According to IARC/IACR rules. Second cancers reported within 1m of BC dx excluded. |
| Levi 2003 (10) | Dx 1974-1998. | Start: At BC dx.  End: At SPC dx, death, emigration, or study end (1998). | Retrospective cohort. | Switzerland (Swiss Cancer Registries of Vaud and Neuchâtel). | Women dx with a first BC with at least 1m of follow-up. | SPC rules unstated, but the Vaud and Neuchâtel registries use IARC/IACR rules. Second cancers diagnosed at autopsy, death, by death certification alone, or within 1m of first BC were excluded. Second cancers must be morphologically different or at different anatomical sites. |
| Mellemkjaer 2006 (33) | Australia, New South Wales: 1972-1997, Canada, British Colombia: 1970-1998, Canada, Manitoba: 1970-1998, Canada, Saskatchewan: 1967-1998, Denmark: 1943-1997, Finland: 1953-1998, Iceland: 1955-2000, Norway: 1953-1999, Singapore: 1968-1992, Slovenia: 1961-1998, Spain, Zaragoza: 1978-1998, Sweden: 1961-1998, UK, Scotland: 1960-1996. | Start: At BC dx.  End: At SPC dx, death, emigration, or study end (between 1992 and 2000, depending on registry). | Retrospective cohort. | 13 large cancer registries. Canada (British Columbia, Manitoba and Saskatchewan), Singapore, Slovenia, Norway, Denmark, Scotland, Australia (New South Wales), Sweden, Finland, Iceland, Spain (Zaragoza). | Women dx with a first BC. | IARC/IACR rules. Tumours identified by following the recording practices of the included registries. |
| Molina-Montes 2013 (11) | Dx 1985-2007. | Start: At BC dx.  End: At SPC dx, death, or study end (2007). | Retrospective cohort. | Spain (Granada Cancer Registry). | Women dx with a first BC, aged 15y or over at BC dx. | According to IARC/IACR rules. Second cancers only included if they occurred at least 3m after the BC dx. |
| Murakami 1987 (22) | Dx 1965-1982. | Start: Unstated, but less than 1y after BC dx.  End: At SPC dx, death, or study end (1983). | Retrospective cohort. | Japan (Osaka Cancer Registry). | Women dx with a first BC who survived at least 3m after the BC dx. | SPC rules unspecified but Osaka Cancer Registry follows IARC/IACR rules. Second cancers only included if they occurred at least 3m after the BC dx. |
| Odani 2022 (23) | 2000-2014. | Start: 3m after BC dx.  End: At SPC dx, death, 10y after BC dx, or study end (2015). | Retrospective cohort. | Japan (Osaka Cancer Registry). | Dx with first primary invasive cancer, aged 15–79 years and resident in Osaka at dx. Dx with death certificate only were excluded. Cohort was stratified by first cancer site, allowing analysis for first BC. | IARC/AICR rules. |
| Ricceri 2015 (12) | Individuals recruited to cohort of generally healthy individuals between 1992 and 1998. The subset of these that developed a first primary BC during 11y of follow-up was taken as the cohort of BC survivors in this study. | Start: At BC dx.  End: at SPC dx, death, or end of study (year of study end unstated). | Prospective cohort. | EPIC9 cohort is drawn from generally healthy individuals aged 35-70 from 23 centres from Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. Follow-up for cancer was based on population cancer registries except in France, Germany and Greece, where a combination of methods including health insurance records, cancer and pathology registries and active follow-up were used. | Female subset of EPIC cohort that developed a first BC after recruitment into study, or that developed a BC as their second cancer after a first non-melanoma skin cancer. Cases identified using death certificate only were excluded. | IARC/IACR rules. Second cancers dx on same date as initial BC or identified using death certificate only were excluded. |
| Rubino 2000 (13) | 1954-1984. | Start: 1973, for those dx with BC 1954-1971. 1y after BC dx, for those dx with BC 1972-1984.  End: At SPC dx, death, loss to follow-up, or study end (1992). | Retrospective cohort. | France (Institut Gustave Roussy). | Women dx with first BC, born and living in France, with at least 1y of follow-up since BC dx. | SPC rules unspecified. All second malignancies were histologically confirmed. Second bilateral BCs and non-melanoma skin cancers were excluded. |
| Schaapveld 2008 (14) | Groningen and Amsterdam: 1989-2003.  Eindhoven: 1989-2002. | Start: At BC dx.  End: at SPC dx, death, or end of study (Groningen and Amsterdam: 2005. Eindhoven: 2004). | Retrospective cohort. | The Netherlands (Comprehensive cancer centres of Groningen, Amsterdam, and Eindhoven). | Women dx with first BC with no prior cancer history, or a first BC following non-melanoma skin cancer. | According to IARC/IACR coding rules. All unknown primary adenocarcinomas, meningiomas, myelodysplastic syndromes, polycythemia veras, and nonmelanoma skin cancers were excluded as second cancers. A cancer occurring after a nonmelanoma skin cancer that followed the BC was classed as the second cancer rather than the nonmelanoma skin cancer. |
| Schottenfeld 1971 (15) | Treatment (rather than dx) of breast, endometrial, ovarian, vagina, vulva, or cervix uteri cancers at Memorial Sloan Kettering Cancer Centre between 1949-1962. | Start: Unstated.  End: Unstated. Study ended in 1962. | Retrospective cohort. | United States of America (Memorial Sloan Kettering Cancer Centre). | Patients with cancer of the breast, endometrium, ovary, vagina, vulva, or cervix uteri treated at the Memorial Sloan Kettering Cancer Centre between 1949-1962. Cohort was stratified by first cancer site, allowing analysis for first BC. | The study predates the publication of the SEER SPC coding rules, the most common rules applied in North America. However, medical records were reviewed to validate the pathologic findings (where presumably recurrences and metastases were ruled out) whenever SPC incidence "increased significantly". |
| Silverman 2016 (24) | 1990-2006. | Start: At BC dx. Also provided results for a start of follow-up at 6m after BC dx.  End: at SPC dx, death, or end of study (2011). | Retrospective cohort. | Israel - Israel National Cancer Registry. | Women with first BC, excluding breast lymphomas. | SPC coding rules unstated, but Israel National Cancer Registry uses IARC/IACR rules with the following optional rules:  1: Two tumours of different laterality, but of the same morphology, diagnosed in paired organs (e.g. breast) are registered separately unless stated to have originated from a single primary.  2: Cancers that occur in any 4th character subcategory of colon (C18) and skin (C44) are registered as multiple primary cancers. |
| Tabuchi 2012 (25) | Dx 1985-2004. | Start: 3m after BC dx.  End: At SPC dx, death, 10y after BC dx, 80th birthday, or study end (2005). | Retrospective cohort. | Japan (Osaka Cancer Registry). | All individuals aged 0-79 dx with a first primary cancer who survived at least 3m. Cohort was stratified by first cancer site, allowing analysis for first BC. | According to IARC/IACR rules. Only discordant second cancers included. |
| Trama 2022 (16) | Dx at and followed up until various periods starting from 1976, respectively according to the establishment dates of and the most recent incidence data entry dates of the registries in study. | Start: At BC dx.  End: At SPC dx, death, emigration, or end of last year of data entry into registry records (dates varied by registry). | Retrospective cohort. | Italy - 34 cancer registries covering 43% of Italian population as of 2019. | Individuals diagnosed with a first primary cancer (invasive or of uncertain behaviour), aged 15-39 at the first cancer diagnosis, who survived at least 5y after the first diagnosis. Cohort was stratified by first cancer site, allowing analysis for first BC. | IARC/AICR rules. |
| Tsukuma 1994 (26) | 1966-86, but information on standardized incidence ratios for SPCs following BC only available for those dx 1978-86. | Start: At BC dx.  End: At SPC dx, death, 80th birthday, or study end (1989). | Retrospective cohort. | Japan (Osaka Cancer Registry). | All individuals aged 0-79 dx with a first primary cancer, who survived at least 3m after the first cancer dx. Cohort was stratified by first cancer site, allowing analysis for first BC. | IARC/IACR rules. Second cancers only included if they occurred at least 3m after the BC dx. |
| Utada 2014 (27) | 1985-2007. | Start: At BC dx.  End: At SPC dx, death, or study end (2008). | Retrospective cohort. | Japan (Nagasaki Cancer Registry). | All individuals dx with a first primary cancer. Cohort was stratified by first cancer site, allowing analysis for first BC. | IARC/IACR rules. Only discordant second cancers included. |
| Zheng 2018 (17) | 1958-2015. | Start: At BC dx.  End: At SPC dx, death, emigration, or study end (2015). | Retrospective cohort. | Sweden (FCD10). | The Swedish FCD is composed of two separate cohorts. 1: Swedish people born after 1931 (“offspring generation”), and 2: their parents (“parental generation”). This study examined the subset of the offspring generation dx with BC between 1958-2015. | Swedish FCD data is linked to national registry, which uses IARC/IACR rules. All second cancers undergo "rigorous histological diagnostics". A request for separate and consistent tumour notifications from clinicians and pathologists is required. |

1: Breast Cancer

2: Diagnosis/Diagnoses/Diagnosed

3: Follow Up

4: International Association of Cancer Registries/International Agency for Research on Cancer

5: Year/Years

6: Second Primary Cancer

7: Surveillance, Epidemiology, and End Results

8: Month/Months

9: European Prospective Investigation into Cancer and Nutrition

10: Family Cancer Database

**Table 2: Further study characteristics**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author and publication year** | **Total person years** | **FU1 time since BC2 dx3 strata** | **Age strata at BC dx** | **Specific SPC4s for which SIR5s reported** | **N6 first BC/N SPCs** | **SIR (95% CI7) for combined risk of non-breast SPCs** |
| AIRTUM Working Group 2013 (1) | 1274882 | 0-1m8, 2-11m, 12-59m, 60-119m, >=120m | 0-19, 20-29, 30-39, 40-49, 50-69, >=70 | Oral cavity, Pharynx, Larynx, Oesophagus, Stomach, Colon, Rectum, Liver, Gallbladder, Pancreas, Lung, Skin melanoma, Mesothelioma, Kaposi sarcoma, Soft tissue, Bone, Corpus Uteri, Cervix Uteri, Ovary, Kidney and renal pelvis, Bladder and urinary tract, Brain and central nervous system, Thyroid, Hodgkin’s lymphoma, Non-Hodgkin’s lymphomas, Multiple myeloma, Leukaemias (Lymphoid leukaemia, Myeloid leukaemia, Other leukaemias), Other sites. | 215809/10597 | 1.12 (1.10-1.14) |
| Andersson 2008 (2) | 256563 | 1-9y9, 10-19y, >=20y | <50, 50-59, 60-69, 70-89 | Lip, Tongue, Salivary glands, Mouth, Pharynx, Oesophagus, Stomach, Small intestine, Colon, Rectum, Liver, Gallbladder, Pancreas, Nose (sinuses), Larynx, Lung, Pleura, Cervix Uteri, Corpus Uteri, Uterus (other), Ovary (uterine adnexa), Other female genital organs, Kidney, Bladder (and other unspecified related sites), Melanoma of skin, Eye, Brain and nervous system, Thyroid, Bone, Soft tissues, Non-Hodgkin’s Lymphoma, Hodgkin’s disease, Multiple myeloma, Acute leukaemia, Other leukaemia. | 31818/1993 | 1.04 (0.99-1.08) |
| Brenner 1993 (3) | 43642.25 | Unreported | <50, >=50 | Stomach, Colon, Rectum, Gallbladder and bile ducts, Pancreas, Corpus Uteri, Cervix Uteri, Ovaries, Urinary bladder, Kidneys, Lymphomas and leukaemias. | 9678/206 | 0.84 (0.73-0.96) |
| Brown 2007 (4) | 2990587 | 1-9y, 10-19y, 20-29y, >=30y | <40, 40-49, 50-64, >64 | Salivary gland, Oesophagus, Lung, Pleura, Thyroid, Bone, Connective tissue, Uterine corpus, Lip, Tongue, Mouth, Pharynx, Stomach, Small intestine, Colon, Rectum/anus, Liver, Pancreas, Gallbladder, Nose/nasal cavity, Larynx, Cervix, Ovary, Kidney, Bladder, Malignant Melanoma, Eye, Brain and central nervous system. | 376825/23158 | 1.15 (1.14-1.17) |
| Chen 2015 (Germany) (5) | Unreported | Unreported | Unreported | Unreported | 234863 (male and female combined)/3676 | 1.15 (1.13-1.17). 1.15 is the midpoint of the reported 95% CI – it was taken as an approximation for the SIR due to early rounding in the study. |
| Diab 2016 (6) | Unreported | Unreported | <50, >=50 | Oral cavity and pharynx, Digestive system, Colon, rectum, and anus, Pancreas, Peritoneum, omentum and mesentery, Respiratory system, Bones and joints, Soft tissue including heart, Skin excluding basal and squamous, Breast, Female genital system, Corpus and uterus (not otherwise specified), Ovary, Urinary system, Brain and other nervous system, Endocrine system, Lymphoma, Leukaemia. | 514479/45509 | 1.03 (1.02-1.04) |
| Evans 2001 (7) | 832958.1 | Unreported | <50, >=50 | Tongue, Mouth, Oesophagus, Stomach, Colon, Rectum, Liver, Gallbladder, Pancreas, Larynx, Lung and bronchus, Bone, Connective tissue, Skin melanoma, Cervix Uteri, Corpus Uteri, Ovary, Bladder, Kidney, Brain and nervous system, Thyroid, Non-Hodgkin’s Lymphoma, Multiple myeloma, Lymphoid Leukaemia, Myeloid Leukaemia. | 145677/4470 | 0.89 (0.86-0.92) |
| Gulhan 2009 (18) | 16377 | Unreported | Unreported | Endometrial, Ovary, Cervical. | 6356/88 | 1.76 (1.43-2.17) |
| Harvey 1985 (8) | 271524 | <1y, 1-4y, 5-9y, >=10y | <45, 45-54, >=55 | Lip, Tongue, Salivary gland, Gum and other mouth, Pharynx, Oesophagus, Stomach, Colon, Rectum, Liver (biliary), Pancreas, Nasal cavities and sinuses, Larynx, Trachea, bronchus, and lung, Cervix uteri, Corpus uteri, Uterus (not otherwise specified), Ovary and fallopian tubes, Kidney and renal pelvis and ureter, Bladder and other urinary, Skin (melanoma), Eye, Brain and central nervous system, Thyroid gland, Bone, Connective tissue, Non-Hodgkin’s lymphoma, Hodgkin’s disease, Multiple myeloma, Leukaemias, Chronic lymphocytic leukaemia, Acute nonlymphocytic leukaemia. | 41109/2057 | 1.15 (1.10-1.20) |
| Hung 2016 (19) | 527009 | <1y, 1-4y, >=5y | 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, >=80 | Head and neck, Oesophagus, Stomach, Colon and rectum and anus, Liver and biliary tract, Liver, Lung and mediastinum, Bone and soft tissue, Skin, Cervix, Uterus, Ovary, Bladder, Kidney, Thyroid, Hematologic malignancies, All others. | 100915/3,080 | 1.50 (1.44-1.55) |
| Jégu 2014 (9) | 351434 | Unreported | Unreported | Corpus Uteri. | Unreported/2476 | 1.31 (1.26-1.36) |
| Jung 2017 (20) | 13433.5 | Unreported | 30-39, 40-49, 50-59, 60-69, >=70 | Oesophagus, Stomach, Colon and rectum, Anus, Liver, Gallbladder and common bile duct, Lung, Cervix, Endometrium, Ovary, Kidney, Bladder, Thyroid, Hodgkin’s lymphoma, Non-Hodgkin’s lymphoma, Acute myeloid leukaemia, Skin, Muscle. | 3344/93 | 1.56 (1.27-1.91) |
| Lee 2008 (21) | 290966 | <=5y, 6-10y, >10y | <50, >=50 | Bone, Corpus uteri, Ovary, Non-melanoma skin, Thyroid, Head and neck, Nasopharynx and nasal cavity, Oesophagus, Stomach, Small intestine, Colon and rectum, Liver, Biliary system, Pancreas, Lung, Thymus, Sarcoma, Cervix uteri, Urinary bladder, Kidney and other urinary organs, Brain, Leukaemia or lymphoma, Others. | 53783/1085 | 1.09 (1.03-1.16) |
| Levi 2003 (10) | 61834 | <5y, >=5y | Unreported | Mouth and pharynx, Oesophagus, Stomach, Colorectum, Gallbladder, Pancreas, Lung, Soft tissue, Skin melanoma, Cervix Uteri, Corpus Uteri, Ovary, Other female genital organs, Bladder, Kidney, Thyroid, Non-Hodgkin’s lymphomas, Multiple myelomas, Leukaemias, Other and unknown sites. | 9729/443 | 1.14 (1.04-1.25) |
| Mellemkjaer 2006 (33) | 3784660 | <1y, 1-9y, >=10y | <=45, 46-55y, >=56 | Oral cavity and pharynx, Oesophagus, Stomach, Small intestine, Colorectal, Liver, Pancreas, Larynx, Lung, Bone, Soft tissue sarcoma (of thorax and upper lim inc. shoulder), Melanoma, Non-melanoma skin cancer, Corpus Uteri, Ovary, Bladder, Kidney, Brain and nervous system, Thyroid gland, Non-Hodgkin’s lymphoma, Leukaemia, Myeloid leukaemia. | 525527/31399 | 1.25 (1.24-1.26) |
| Molina-Montes 2013 (11) | 37605 | <5y, >=5y | <50, >=50 | Endometrium, Colon and rectum, Stomach, Ovary, Thyroid gland, Non-melanoma skin, Kidney, Bladder, Hematologic malignancies (lymphoid leukaemia, myeloid leukaemia, and multiple myeloma). | 5897/314 | 1.39 (1.24-1.55) |
| Murakami 1987 (22) | 53738 | <1y, 1-4y, 5-9y, >=10y | <45y, 45-54, >=55 | Buccal cavity, Stomach, Oesophagus, Colon, Rectum, Liver, Pancreas, Lung, Cervix Uteri, Corpus Uteri, Ovary, Urinary bladder, Thyroid gland, Leukaemia. | 9503/254 | 1.34 (1.18 - 1.52) |
| Odani 2022 (23) | 266685 | 3m-1y, 1-5y, 5-10y | Unreported | Oral cavity/pharynx, Stomach, Colorectum, Liver, Gallbladder, Pancreas, Lung, Uterus, Ovary, Kidney/urinary tract/bladder, Thyroid, Blood. | 47622/1843 | 1.84 (1.76–1.92) |
| Ricceri 2015 (12) | 56496 | Unreported | Unreported | Colorectum, Lung, Pancreas, Melanoma, Endometrium, Ovary, Kidney, Thyroid gland, Lymphomas. | 10045/352 | 1.30 (1.18-1.42) |
| Rubino 2000 (13) | 33044 | 1-10y, >=10y | <50, >=50 | Oral cavity, Oesophagus, Stomach, Colon and rectum, Liver and gallbladder, Pancreas, Larynx, Lung and bronchus, Uterus, Ovaries, Bladder, Kidney, Melanoma, Nervous system, Thyroid, Other endocrine, Bone, Soft tissue, Undefined sites, Myeloma, Lymphoma, Leukaemia. | 4416/193 | 1.40 (1.21-1.62) |
| Schaapveld 2008 (14) | 362470 | Not reported in a fashion that allows accurate extraction of age-stratified SIRs and corresponding 95% standard errors. | <50, >=50 | Head and neck, Thyroid, Oesophagus, Stomach, Pancreas, Gallbladder/extrahepatic bile ducts, Colon, Rectum and Anus, Lung, Soft tissue sarcomas, Melanoma of skin, Ovary, Cervix, Uterus, Vulva, Kidney, Bladder, Brain, Acute myeloid leukaemia, Other Leukaemia, Non-Hodgkin’s lymphoma, Multiple myeloma. | 58068/2578 | 1.22 (1.17-1.27) |
| Schottenfeld 1971 (15) | Unreported | Unreported | Unreported | Ovary, Corpus Uteri, Cervix Uteri, Vulva and vagina, Buccal cavity and Pharynx, Oesophagus, Stomach, Colon, Rectum, Pancreas, Liver and bile ducts, Larynx, Lung, Kidney, Bladder, Lymphoma and leukaemia, Salivary glands, Thyroid, Soft-part sarcomas, Bone sarcomas. | 9792/231 | 1.01 (0.9-1.1) |
| Silverman 2016 (24) | 363333 | Unreported | <50, >=50 | Colorectum, Uterus, Lung, Ovary, Non-Hodgkin's Lymphoma, Brain, Melanoma (invasive), Thyroid, Leukaemia, Uterine Cervix. | 43794/3866 | 1.26 (1.23-1.30) |
| Tabuchi 2012 (25) | 197571 | <1y, 1-5y, 5-10y | Unreported | Mouth/pharynx, Stomach, Oesophagus, Colorectal, Liver, Gallbladder, Pancreas, Lung, Uterus, Ovary, Thyroid, Kidney/urinary tract/bladder, Blood. | Unreported/1007 | 1.48 (1.39-1.57) |
| Trama 2022 (16) | 102629 | <5y, 5-10y, 10-15y, 15-20y, 20-25y, >25y | Unreported | Soft tissue sarcomas, Colorectal, Stomach, Pancreatic, Liver, Bladder, Kidney, Cervical, Ovarian, Corpus Uteri, Central nervous system, Germ cell. | 11328/299 | 1.13 (1.0-1.3) |
| Tsukuma 1994 (26) | Unreported | <1y, 1-4y, 5-9y | Unreported | Stomach, Colon, Lung, Thyroid. | Unreported/226 | 1.42 (1.25-1.62) |
| Utada 2014 (27) | Unreported | Not reported in a fashion that allows accurate extraction of age-stratified SIRs and corresponding 95% standard errors. | Unreported | Lung, Uterus, Ovary, Thyroid. | Unreported/727 | 1.16 (1.08-1.25) |
| Zheng 2018 (17) | Unreported | Unreported | Unreported | Upper aerodigestive tract, Oesophagus, Stomach, Small intestine, Colorectum, Anus, Liver, Nose, Pancreas, Lung, Cervix, Endometrium, Uterus, Ovary, Other female genitals, Kidney, Bladder, Melanoma, Skin (squamous cell carcinoma), Eye, Nervous system, Thyroid gland, Endocrine gland, Bone, Connective Tissue, Non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, Myeloma, Leukaemia, Cancer of unknown primary, Colon, Rectum. | 87752/6299 | 1.43 (1.40-1.47) |

1: Follow Up

3: Breast Cancer

2: Diagnosis/Diagnoses/Diagnosed

4: Second Primary Cancer

5: Standardized Incidence Ratio

6: Number (of)

7: Confidence Interval

8: Month/Months

9: Year/Years

**Table 3: Risks of second primaries at specific sites.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cancer site** | **SIR (95% CI) – breast cancer diagnosed at any age** | **SIR (95% CI) – breast cancer diagnosed at under age 50** | **SIR (95% CI) – breast cancer diagnosed at age 50 or over** | **Number of studies in meta-analysis** | | |
| *Unstratified by age at BC dx* | *Aged under 50 at BC dx* | *Aged 50 or over at BC dx* |
| Bladder1 | 1.15 (1.05 - 1.26) | 1.32 (1.17-1.48) | 1.08 (0.89-1.30) | 8 | 4 | 4 |
| Blood (leukaemia)2 | 1.30 (1.17 - 1.45) | 1.91 (1.77-2.05) | 1.34 (0.99-1.81) | 8 | 4 | 4 |
| Blood (myeloma)3 | 0.83 (0.68 - 1.02) | 1.01 (0.53-1.94) | 0.63 (0.48-0.82) | 4 | 1 | 1 |
| Blood (non-Hodgkin’s lymphoma) | 1.04 (0.91 - 1.19) | 1.17 (0.96-1.42) | 0.93 (0.65-1.33) | 7 | 2 | 2 |
| Brain and central nervous system4 | 0.80 (0.71 - 0.91) | 0.95 (0.81-1.11) | 0.75 (0.69-0.81) | 7 | 4 | 3 |
| Cervix uteri5 | 0.88 (0.77 - 1.00) | 0.65 (0.46-0.93) | 0.57 (0.23-1.39) | 10 | 2 | 2 |
| Colorectum6 | 1.12 (0.99 - 1.27) | 1.30 (0.91-1.86) | 1.02 (0.87-1.19) | 11 | 5 | 5 |
| Corpus uteri7 | 1.84 (1.53 - 2.23) | 1.40 (1.12-1.76) | 1.75 (1.29-2.37) | 16 | 5 | 5 |
| Gallbladder8 | 1.13 (0.68-1.87) | 0.49 (0.12-1.96) | 0.86 (0.63-1.17) | 7 | 1 | 1 |
| Kidney9 | 1.43 (1.17 - 1.73) | 1.29 (1.15-1.43) | 1.35 (0.95-1.92) | 11 | 4 | 4 |
| Liver10 | 0.86 (0.60 - 1.24) | 0.93 (0.71-1.21) | 0.56 (0.33-0.96) | 7 | 1 | 2 |
| Lung11 | 1.25 (1.03 - 1.51) | 1.65 (1.49-1.82) | 0.81 (0.55-1.20) | 12 | 3 | 3 |
| Oesophagus | 1.39 (1.26 - 1.55) | 2.21 (1.89-2.60) | 1.20 (1.06-1.37) | 9 | 3 | 3 |
| Ovary | 1.53 (1.35 - 1.73) | 2.24 (1.59-3.13) | 1.04 (0.93-1.16) | 16 | 6 | 6 |
| Pancreas | 1.09 (0.93 - 1.27) | 1.35 (1.16-1.57) | 0.92 (0.81-1.04) | 11 | 3 | 4 |
| Skin (melanoma) | 1.34 (1.18 - 1.52) | 1.34 (1.23-1.45) | 1.25 (1.17-1.35) | 7 | 3 | 3 |
| Stomach | 1.23 (1.12 - 1.36) | 1.90 (1.75-2.06) | 1.10 (0.91-1.34) | 13 | 4 | 4 |
| Thyroid | 1.89 (1.49 - 2.38) | 2.06 (1.83-2.31) | 1.17 (0.90-1.52) | 14 | 4 | 3 |
| Vulva12 | 0.92 (0.63-1.35) | - | - | 2 | 0 | 0 |

1Meta-analysis also includes data on cancer risks at the “urinary bladder”.

2Meta-analysis includes data on combined lymphoid leukaemia and myeloid leukaemia risks.

3Meta-analysis only includes data on “multiple myeloma(s)” risks.

4Meta-analysis also includes data on cancer risks at the “brain and nervous system”, brain only, and nervous system only.

5Meta-analysis also includes data on “cervical”, “cervix”, and “uterine cervix” cancer risks.

6Meta-analysis includes data on combined colon and rectum cancer risks.

7Meta-analysis also includes data on cancer risks at the “uterus” and “endometrium”.

8Meta-analysis also includes data on cancer risks at the “gallbladder and bile ducts”, “gallbladder and common bile duct”, and “gallbladder/extrahepatic bile ducts”.

9Meta-analysis also includes data on cancer risks at the “kidney and renal pelvis”.

10Meta-analysis also includes data at the “liver and biliary tract” and “liver and bile ducts”.

11Meta-analysis also includes data at the “lung and bronchus”.

12Meta-analysis also includes data at the “vulva and vagina”.

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