



Review

Risk of second cancers cancer after a first primary breast cancer: A systematic review and meta-analysis



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HIGHLIGHTS

- The scientific evidence and the risk of second primary cancers in women diagnosed with a first breast cancer was examined.
- This is the first review and meta-analysis in regards to risk of second cancer after breast cancer.
- Women diagnosed with breast cancer have a 17% higher second cancer risk, with this risk being higher in premenopausal women.

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ABSTRACT

Objective. To examine the scientific evidence and the risk of second primary cancers in women diagnosed with a first primary breast cancer.

Methods. The literature was searched in Pubmed and Embase and included studies published up to June 2013, using population-based data and IARC/AICR codification rules for multiple primary cancers. A qualitative synthesis was carried out and the methodological quality of the studies evaluated. Standardised incidence ratios (SIRs) on second cancer risk, weighted by the standard error of each study, were pooled using fixed and random effects models. SIRs were also pooled by age at diagnosis (<50 and ≥50 years), and time since diagnosis of the first breast cancer (<10 and ≥10 years).

Results. 15 out of 710 articles fulfilled the inclusion criteria. All of them were retrospective cohort studies either population-based (13 studies) or hospital-based studies (2 studies). The studies varied with respect to number of cases, selection criteria, definition of multiple primary cancers, and the second cancer sites included. SIRs reported in these studies for all cancers combined varied from 1.0 to 1.4. The pooled SIR estimate for second cancer risk was 1.17 (95% CI: 1.10–1.25). By age groups, SIR estimates were 1.51 (95% CI: 1.35–1.70) for women younger than 50 years and 1.11 (95% CI: 1.02–1.21) for those who were older. Women with breast cancer are at risk of second cancers within the first 10 years after the first breast cancer diagnosis (SIR: 1.19; 95% CI: 1.06–1.33), and thereafter (SIR: 1.26; 95% CI: 1.05–1.52).

Conclusion. This higher risk of second cancers in women diagnosed with a first primary breast cancer with respect to the general population emphasises the importance of prevention and control policies aimed at reducing incidence of second cancers.

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Introduction

Breast cancer represents a major public health issue worldwide. It is the most commonly diagnosed cancer among women, with 1.38 million new cases estimated in 2012 [1]. In Europe, estimates of cancer incidence and mortality in 2012 show that it remains being the most common cancer and cause of cancer-related death in women [2]. Early detection through systematic screening, better access to care, and advances in treatments have been leading to a decline in mortality rates [3,4]. Thus, as the number of women who overcome a breast cancer is considerably increasing, the likelihood of developing subsequent cancers, i.e. Multiple Primary Tumours (MPT), becomes higher. Subsequent cancers after an initial breast cancer could be attributed either to common risk factors predisposing to both the first and second cancer, such as genetic predisposition or other identified risk factors, or to treatment-related side effects [5].

Several population-based cancer registry studies [6–11] as well as studies involving several cancer registries [12,13], have evaluated the risk of developing second primary cancers among women diagnosed with a first primary breast cancer with respect to the general population. Most of these studies were derived from European data [6–13] and from the National Cancer Institute's Surveillance, Epidemiology (SEER) cancer registries in the United States [14–16]. However, risk estimates provided by these studies are largely different, with an overall excess risk ranging between 15 and 45% for all cancer sites combined. Risk differences by age groups have also been examined in some of these studies [7, 10–13], showing that women diagnosed with breast cancer at premenopausal ages were at higher risk of developing a second cancer. In general, second primary cancers of the endometrium, ovary, melanoma, stomach and colon cancer have been reported to occur more frequently [6–10], although there is no consensus between studies.

Some studies have also provided risk estimates of second cancers according to treatment of the breast cancer, such as radiotherapy [14, 17–20], chemotherapy and surgery [17–20] or hormonal therapy [18–20], to assess how treatment-related factors may influence this risk. However, as information on treatment is not systematically collected in population-based cancer registries, most of these studies reported risk estimates on a limited number of observed cases with information available on primary treatment for breast cancer. For this reason, calendar year and time since diagnosis of the first breast cancer have been used as a proxy for treatment in some studies [6,9,12,17]. However, results reported by these studies are rather inconsistent as some support an increased risk during the first years after the breast cancer diagnosis [6,12] whilst others report that risk increases or remains high over time [9,17].

The aim of the current study is to examine the scientific evidence related to the risk of developing a second primary cancer after a breast cancer diagnosis for all sites combined, by age at breast cancer diagnosis and by time since breast cancer diagnosis, and to further combine the results of these studies by using meta-analysis.

Methods

Search strategy

A search was carried out to find relevant studies and reviews published up to 30 June 2013 (no starting date was fixed). The databases used were Pubmed and Embase.

Table 1

Search strategy for Medline and Embase (30 June 2013).

Search strategy using MeSH terms in Medline	
No.	Search
1	"Neoplasms, Multiple Primary/Epidemiology" [MESH] OR "Neoplasms, Multiple Primary/Prevention and control" [MESH] OR "Neoplasms, Second Primary/Epidemiology" [MESH] OR "Neoplasms, Second Primary/Prevention and control" [MESH] AND "Breast Neoplasms/epidemiology" [MESH] N = 632
2	Limits: female, adults N = 488
Search strategy using keywords in Medline	
1	"Breast cancer"[subheading] N = 265,587
2	"Second cancer" [subheading] N = 70,611
3	"Second malignancies" [subheading] N = 26,324
4	"Multiple primary cancer" [subheading] N = 41,254
5	"Multiple primary malignancies" [subheading] N = 39,289
6	#2 OR #3 OR #4 OR #5 N = 108,982
7	#1 AND #6 N = 15,109
8	Population-based N = 58,126
9	Risk N = 1,509,093
10	#7 AND #8 AND #9 N = 235
11	Limits: female, adults N = 192
Search strategy using keywords in Embase	
1	Second AND ('cancer'/exp OR cancer) OR second AND malignancies OR multiple AND primary AND ('cancer'/exp OR cancer) OR multiple AND primary AND malignancies N = 4390
2	'breast'/exp OR breast AND ('cancer'/exp OR cancer) N = 338,811
3	#1 AND #2 N = 854
4	#3 AND 'human'/exp AND ('breast cancer'/exp OR 'multiple cancer'/exp OR 'second cancer'/exp) AND 'population based' AND [embase]/lim N = 30

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