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Review Article

Second Cancers in breast Cancer survivors: a systematic review

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ABSTRACT

Introduction: Breast cancer is one of the most important problems in general health of women in the world. Advances in the treatment have led to longevity of patients, resulting in the risk of other diseases, including second cancers. The aim of this study was to determine the types and risks of second primary cancers after breast cancer. Methods: A protocol was developed and a sensitive search in databases including PubMed, PubMed central, and Google scholar and also in the list of referenced articles was conducted without time limitation. All letters, comments, editorial studies and studies about breast cancer metastases and inhumane studies were excluded. The quality of papers was verified with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Results: 15 papers were selected and reviewed, including colorectal, bone marrow malignancies, esophageal cancer, soft tissue sarcoma, lung cancer, thyroid malignancies and ovarian cancer as second cancers in breast cancer patient. These articles declared their review and findings regarding these cancers as second cancer after breast cancer. All of these second cancers were associated with chemotherapy and/or auxiliary radiotherapy, especially intensive doses of radiation. Conclusion: The studies have been shown the treatment approach of BC may be the main cause of second cancer development after BC which consisted of bone marrow neoplasm, sarcoma, thyroid, esophageal, lung and uterine cancer. Intensive radiotherapy and chemotherapy had the potential risk of second cancer development, as well as they had syngism effect with each other.

Keywords: breast cancer, second primary cancer, Survivors, radiotherapy, chemotherapy.

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women, BC alone is expected to account for 29% of all new cancer cases among women and In women between the ages of 20 and 59, BC is the leading cause of death from cancer [1].

The overall survival rate of patients with advanced BC has increased over the years, mainly due to the development of therapeutic approaches, such as using chemotherapy, radiation therapy, or hormone therapy [2]. Although most women with BC do not receive second cancer, the survivors of this disease are at risk of other cancers.

According to previous studies, the 5 years risk of second cancer in BC survivors was 3.6%, over 10 years it was 8.2%, and 13.9% over the past 15 years, and also patients with less than 50 years old are at a higher risk of developing second cancer than patients over 50 years old [3].

second malignancies that occur in cancer-survived patients at long-term may be due to environmental or genetic factors, or because of the complications of first cancer treatment methods, especially after radiotherapy. Studies have shown that the risk of lung, esophageal and sarcoma cancers increase in BC patients [4, 5].

Increasing the risk for leukemia, ovarian cancer and female sexual organs cancer also increases the risk of GI cancers [6] in survived BC patients. Increasing leukemia has been associated with chemotherapy (with alkaline factors) and radiation alone has a significant effect on the development of cancer. But it has

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not been significant in comparison with the whole population [7].

Studies confirm the increased detection of thyroid cancer after BC [8]. Although the diagnosis timing of second malignancies cannot be determined due to heterogeneity in the studies, there is a significant increase in the incidence of second cancers, which can be verified and studied as a pathophysiologic effect. Considering the high prevalence of BC and the increased survival of patients with this cancer, this study was conducted to evaluate the types of second cancers in BC patients and to compare prevalence and risk of it in current studies.

Materials and Methods

A protocol was developed and the English papers from 1966 to 2018 were searched to extract complete articles about the incidence of second cancers in BC patients. A sensitive search was done in databases including PubMed, PubMed central, and Google scholar. To search based on MeSH terms, the keywords of "cancer", "tumor", "malignancy", "neoplasm", "breast", "esophagus", "AML", "sarcoma", "thyroid", "colon", "uterine", "ovarian", "lung", "second" and "after" were used in which the word "OR" between the words of cancer, tumor, malignancy and neoplasm and also between the words of esophagus, AML, sarcoma, thyroid, colon, uterine, ovarian and lung and the words of second and after which could be used as an equal to each other, were applied.

To complete the studies, the reference list of papers was searched for all related articles. Abstracts and topics related conferences were also searched. English language articles were selected and the human cases that investigated second cancer in primary BC patients with any grade and stage were included. All non-research studies such as letters, comments, editorials and studies on BC metastases, and studies with other problems (effects on fertility, depression, etc.) were excluded. The studies that looked at the reverse side (the incidence of BC as second cancer in patients with other cancers) were excluded. Studies that had two or more purpose were separately examined in the desired purpose. If there were three or more studies in a completely similar topic, then studies that were more recent and more comprehensive and with a larger sample size were selected.

Investigating and screening the studies was done by studying the title and abstract of paper.

The quality of papers was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and unqualified studies were removed. Each paper was reviewed by two researchers using a standardized information extraction card. The Disagreement between researchers about some of the papers was solved in consultation with the team.

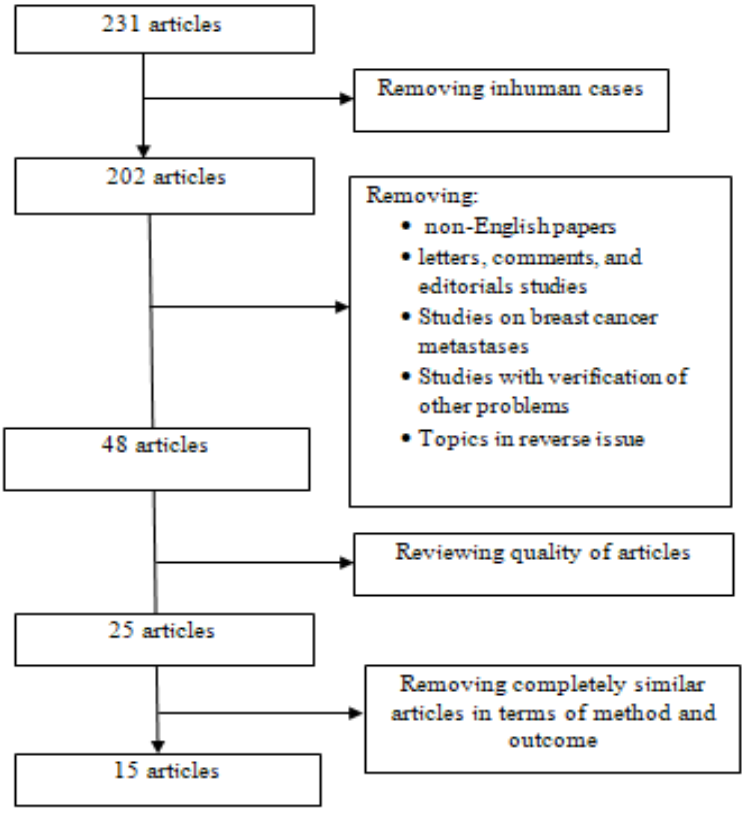

Figure 1: Flow chart for literature selection process of second cancer after breast cancer

There were 15 articles containing relevant statistical data and enough and suitable descriptions to entering the study.

Results

Table 1: Studies investigating second primary cancers after breast cancer

Author and year	Second cancer	Data source source & time	Design & fallow up time	Cases	Controls	Measurement result
Lu et al. (2016)	Colorectal cancer	Swedish Cancer Register, January 1961 to December 2010	a cohort study, mean follow-up was 9.7 years	179,733 breast cancer patients ages of 15 and 75 years	General population	Adenocarcinoma in the proximal colon showed a non-significantly higher SIR[5] (1.72, 95%CI: 1.61, 1.82) compared with the distal colon (1.46, 95%CI: 1.34, 1.58).
Shukla et al. (2012)	Colorectal cancer and adenomas	cancer registry of MD Anderson Cancer Center (MDACC),	Comparison of patients with matched controls Fallowed 2000 -2006	302 Eligible survivors of breast cancer <85 years of age	302 age-, sex-, and race-matched controls	Adenomas OR = 1.42, tubular adenoma OR = 1.42 and villous adenoma OR = 1.34
Wolff et al. (2015)	bone marrow neoplasms	National Comprehensive Cancer Network institution 1997- 2007	Prospective study, median follow-up: 5.1 years	20,063 patients with stage I to III breast cancer	Breast cancer patients with no treatment of chemotherapy	Risk of bone marrow neoplasm was significantly increased after surgery plus chemotherapy (HR, 6.8; 95% CI, 1.3 to 36.1) or after all modalities (surgery, chemotherapy, and radiation; HR, 7.6; 95% CI, 1.6 to 35.8), compared with no treatment with chemotherapy.
Smith et al. (2003)	AML	Six completed NSABP[1] 1996 - 2001	Prospective study. Median Follow-Up: 7.4 years	8,563 patients with follow-up were randomized to AC regimens	-	In patients receiving two or four cycles of C[7], cumulative incidence of AML/MDS was 1.01%, compared with 0.21% for patients treated with standard AC. Patients who received breast radiotherapy experienced more secondary AML/MDS than those who did not (RR 2.38, P .006)
Curtis et al. (1992)	leukemia	five population-based cancer registries[2] 1975 - 1985	A case-control study in a cohort of women with breast cancer follow-up: time between BC diagnosis and onset of leukemia	82,700 women with invasive breast cancer	For each case patient, three control patients were selected by means of random sampling	The risk of acute nonlymphocytic leukemia was increased after regional radiotherapy alone (RR= 2.4), alkylating agents alone (RR=10.0), and combined radiation and drug therapy (RR=17.4).
Levi et al. (2005)	esophageal cancer	the Swiss cantons of Vaud and Neucha^tel , 1974 -2002	A prospective study, follow up: to the end of 2002	11 130 breast cancer patients	Normal population	SIR was 1.6 in the first 10 years and 3.3 for >10 years after diagnosis,

Zablotska et al. (2005)	Esophageal Cancer	The SEER Program of the US National Cancer Institute. 1973 -2000	A Population based cohort study, he average follow-up times were 9.1 years	244,624 women with non metastatic invasive breast cancer.	BC patients who did not receive radiation therapy	relative risks of 2.83 for squamous cell esophageal cancer at 5–9 years and 2.17 for ≥10 years
Scholl et al (2001)	Esophageal cancer	University Hospital, Lausanne, Switzerland, 1985 -1993	A hospital-based case-control study, a minimum follow-up of 3 years	118 patients treated for esophageal cancer.	Patients with Other primary cancers	5 women with esophageal squamous cell carcinomas had been treated BC
Rubino et al. (2005)	soft tissue and bone sarcoma	Institut Gustave Roussy (IGR) 1954- 1983	A cohort-study, patients followed for 8.3 years on average.	6597 breast-cancer patients followed for 8.3 years on average.	general French population	12 women who had initially received radiotherapy treatment developed a bone or soft tissue sarcoma during the follow-up period.
Grantzau et al.	Lung cancer	DBCG[3],Denmark, 1982 to 2007	a population-based cohort, The followup the initial of BC diagnosis & second cancer diagnosis	151 cases diagnosed with first primary lung cancer	For each case, we attempted to select three controls	The rate of lung cancer increased with 8.5% per Gray ($p < 0.001$). This rate was enhanced for ever smokers with an excess rate of 17.3% per Gray ($p < 0.005$).
Zablotska et al. (2003)	Lung Carcinoma	The SEER Program. 1973-1998	A cohort study, follow-up: 8.3 years with radiation & 8.7 years without radiation.	271,120 women with non metastatic breast carcinoma	BC patients who did not receive radiation after surgery	RR[6] of 2.06 and 2.09 for ipsilateral lung carcinoma at 10–14 years and 15 years after postmastectomy radiation therapy.
Park et al. (2007)	Thyroid Cancer	In Yongdong Severance Hospital , 2001-2004	A prospective study, Follow up: the first 2 or 3 years after BC	518 breast cancers	-	Among 518 breast cancers, total 13 cases (2.5%) were diagnosed with papillary thyroid carcinoma
Huang et al. (2001)	Thyroid carcinoma	SEER program. 1973 -1993	Retrospective cohort study, follow-up: 7.2 years for non-RTcohort & 5.9 years for RT cohort.	48,495 women received radiation therapy after initial courseof BC treatment	146,303 women did not receive radiation therapy for BC.	SIR of thyroid carcinoma was 1.1
Bergman et al. (2000)	endometrial cancer	Netherlands Cancer Registry, 1987 -1997	a nationwide case-control study, median follow-up: 30 months	309 endometrial cancer cases diagnosis after BC.	Three controls were individually matched per case.	Risk of endometrial cancer increased with longer duration of tamoxifen use ($p<0{\cdot}001$), with RR of 2·0 for 2–5 years and 6·9 for > 5 years.
Jones et al. (2012)	Endometrial cancer	combined study[4], from 1972 to 1996	A pooled study from the three case-control studies, follow up: average for 5.8 years	Patients with endometrial cancer after breast cancer who received tamoxifen treatment	Patients with endometrial cancer who did not received tamoxifen treatment	Patients with endometrioid tumors, with tamoxifen use, had a greater mortality risk from endometrial cancer than endometrioid patients with no tamoxifen exposure (HR = 2.11).

1: National Surgical Adjuvant Breast and Bowel Project

2: Connecticut, Iowa, and the metropolitan areas of Detroit, Atlanta

3: Danish Breast Cancer Cooperative Group

4: combined study of nine regional cancer registries (Netherlands, England, Scotland and Wales and the US SEER registries.

5: Standardised Incidence Ratio

6: Relative Risk

7: Cyclophosphamide

Two studies [9, 10] highlighted the risk of colorectal cancer after BC. In one study the risk of colorectal adenocarcinoma - especially in the proximal colon - was increased in BC group, but the risk of second cancer did not alter significantly compared with that in the general population. In another study, BC was not significantly associated with an increased risk of advanced adenoma of colorectal. Three studies [11-13] examined the risk of bone marrow neoplasm (BMN) in patients with BC. The BMN risk after chemotherapy and/or auxiliary chemotherapy was low but significant in one study, and in two other studies, chemotherapy and radiotherapy of BC patients were associated with increased risk of BMN. Three studies [14-16] were conducted on esophageal cancer after BC. In all three studies, the risk of SCC (Squamous Cell Carcinoma) in esophagus increased after BC radiotherapy. One study [17] examined the risk of soft tissue and bone marrow sarcoma after BC according to radiation dose and methods of radiotherapy and it showed that high doses of radiation significantly increased the risk of soft tissue and bone marrow sarcoma. Two studies [18, 19] examined the risk of lung cancer after BC, and in one study radiotherapy after mastectomy increased risk of lung cancer, significantly, but after lumpectomy radiotherapy did not increase the risk. In the second study [19], the risk of lung cancer has increased and the increased risk was significant in smokers. Two studies [20, 21] examined the risk of thyroid cancer after BC. The risk of thyroid cancer after BC had a significant increase in one study, but did not increase significantly in another study. Two studies [22, 23] focused on the risk of endometrial cancer after BC with tamoxifen consumption that in which, in studies, the increased risk and significant mortality rates for endometrial cancer reported.

Discussion

In the verification of accomplished research, the risk of second cancers after BC has been associated with the treatment approach. So that 10 of the articles have been studied separately the methods of chemotherapy and radiotherapy, and 3 have been treated as alternative therapies (chemotherapy-radiotherapy and 2 post-operative radiotherapy treatments), which indicate the probable significance of the therapeutic approach to second cancers.

Colorectal Cancer After BC: Lu et al. showed an increased risk of colorectal adenocarcinoma in BC patients, but did not prove the relationship between BC treatment and increased risk of adenocarcinoma [9] and Shukla et al. showed that anti-estrogen treatment of BC was not significantly associated with an increased risk of advanced adenoma and colorectal adenocarcinoma [10].

Bone marrow cancers: Wolf et al. Evaluated the risk of breast cancer-related bone marrow neoplasms. The risk of developing bone marrow cancers after BC was significantly higher with chemotherapy and the bone marrow cancer cumulative incidence doubled between 5 and 10 years [11]. Smith et al. were also predicting the probability of having acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) after doxorubicin-cyclophosphamide adjuvant therapy of BC patienrs. The incidence of AML and MDS increased strongly due to intensified doses of cyclophosphamide requiring G-CSF support and BC radiation therapy [12].

In Curtis et al. study, the risk of acute non lymphocytic leukemia significantly increased after regional radiotherapy alone (relative risk, 2.4), alkylating agents alone (relative risk, 10.0), and combined radiation and drug therapy (relative risk, 17.4). Melphalan leukemogenic effect was 10 times higher than cyclophosphamide (relative risk, 31.4 vs. 3.1) [13].

Rubino et al. observed the risk of soft tissue and bone marrow sarcomas after BC according to doses and method of radiation, that high doses of radiation significantly increased the risk of soft tissue and bone marrow sarcoma and the risk of sarcoma was 30.6 higher for doses of more than 44 Gray than for doses of less than 15 Gray [17].

Esophageal Cancer: Levi et al. investigated effect of radiation therapy on BC in the development of second cancers of the esophagus.

The SIR (standardised incidence ratio) was 1.6 in the first 10 years after diagnosis and 3.3 for more than 10 years after diagnosis [14].

In Zablotska et al. study, the relative risks of esophageal squamous cell carcinoma were 2.83 in the first five to nine years and 2.17 after ten years from radiation therapy of BC [15]. And in Scholl et al. study, an increased incidence of second cancers in the esophagus was observed after BC adjuvant radiotherapy [16]. Therefore, the increased risk of esophageal cancer after BC was confirmed in these three studies.

Lung cancer: Grantzau et al. showed in a large cohort that the rate of second pulmonary cancer in BC patients increased compared to the general population (risk of 8.5% per Gray) and this increase was higher in smokers (17.3% per Gray) [19].

Zablotska et al. examined the effects of post-mastectomy radiotherapy on the incidence of second lung carcinoma. Radiotherapy after mastectomy increased the risk of lung carcinoma 10 years after exposure, in a moderate way. The increased risk continues for up to 20 years. However, post-

lumpectomy radiotherapy did not significantly affect the risk of second lung cancer [18].

Thyroid cancer: In the study of Park et al., patients with BC had a high incidence of thyroid cancer (2.5%) [20], but in the cohort study of Huang et al., thyroid carcinoma incidence rate in women with breast carcinoma was similar to that of the general population of women after 20 years [21].

Endometrial cancer: In the study of Jones et al., The mortality rate of endometrial cancer in people who took tamoxifen for 5 years after BC was higher than those who did not take tamoxifen [23]. Bergman et al. investigated the effect of tamoxifen on the increased risk of endometrial cancer in BC. Risk of endometrial cancer increased with longer duration of tamoxifen use, with relative risks of 2·0 for 2–5 years and 6·9 for at least 5 years compared with non-users. In spite of this, the benefit of tamoxifen to BC survival was far greater than the mortality rate of endometrial cancer after BC [22].

With regard to the prevalence of most of second cancers after BC associated with the type of primary BC treatment, the results of this study indicate the probable significance of the therapeutic approach to the development of second cancers.

In this regard, the department of oncology at the University of Aarhus has conducted a systematic review study, which showed that radiotherapy significantly increased the risk of second cancers after the breast, especially in adjacent organs. The relative risks of second cancers were 1.39 in lung cancer, 1.53 in esophageal cancer and 2.53in second sarcoma, so, although the relative risks were low, they were not forbidden [24].

In a study in 2017, Burt et al. showed that second cancers after BC were increased in patients who received radiotherapy (SIR =1.33) and in non-radiotherapy patients (SIR= 1.2) [25].

Chemotherapy, especially with alkylating factors, can increase the risk of second cancers after BC. Other studies have shown an increased risk of second cancer following the treatment of other cancers with alkylating factors such as hereditary retinoblastoma cancer [26], Hodgkin's lymphoma [27], and chronic lymphocytic lymphoma [28].

In terms of genetic effects on development of second cancers in studies, only ovarian cancer has been taken into account. Studies have shown that patients with BRCA-dependent epithelial ovarian cancer with BC history had a worse progression-free survival and progression-free interval than those without BC [29]. Regarding the fact that specific genes may have particular effects in the onset of second cancers, it is necessary to review previous studies in this field and to carry out further research.

Conclusion

The studies have been shown the treatment approach of BC may be the main cause of second cancer development after BC which consisted of bone marrow neoplasm, sarcoma, thyroid, esophageal, lung and uterine cancer. Intensive radiotherapy and chemotherapy had the potential risk of second cancer development, as well as they had syngism effect with each other. The effect of the spatial genes on the development of second cancer after BC was also reported.

Further studies are suggested in the effect of any risk factors on development of second cancers, especially the effects of therapeutic and lifestyle factors.

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