Risk of primary lung cancer after breast cancer radiotherapy: A systematic review and meta-analysis

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Abstract

Background: Epidemiological studies have shown that the risk of secondary malignancies may increase by radiotherapy. Lung cancer is the most important long-term complication of breast cancer radiotherapy.

Methods: Major electronic databases including Scopus, Web of Science, and MEDLINE were searched. All cohort studies that investigated the association between radiotherapy for breast cancer and risk of primary lung, bronchus and trachea cancers conducted until March 2021 were included. The study participants were evaluated regardless of their age and ethnicity. The Newcastle-Ottawa Scale was used to assess the quality of the studies. The designated effects were risk ratio (RR). The random-effects model was used to estimate the average effects.

Results: Fifteen studies including 1,640,247 women with primary breast cancer were identified of which 937,151 had not received radiotherapy and 703,096 subjects had received radiotherapy. In general, there was no significant association between breast cancer radiotherapy and lung cancer based on 10 studies (RR=0.95, 95%CI: 0.87-1.02, P=0.15), There was no association between breast cancer radiotherapy and lung, bronchus, and trachea cancers either based on 5 studies (RR=0.98, 95%CI: 0.93-1.02, P=0.32).

Conclusion: Radiotherapy for breast cancer is not associated with an excess risk of lung cancer. Due to the limited number of studies, further research about lung doses from breast cancer radiotherapy varied substantially worldwide, is suggested to the risk of lung cancer after breast cancer radiotherapy.

Introduction

Randomized clinical trial studies have shown that radiotherapy significantly reduces breast cancer recurrence. On average, it can reduce breast cancer mortality by a few percent depending on the characteristics of cancer. The benefits of radiotherapy are greater than the long-term complications for patients with breast cancer (1–4).

During radiotherapy for the breast and chest wall, the lungs are exposed to radiation, which is unavoidable. This accidental exposure may increase the risk of primary lung cancer, pneumonitis, and pulmonary fibrosis(5). Because most women with breast cancer are treated in the early stages, survival is important(1, 2). Epidemiological studies have shown that the risks of secondary malignancies may be increased by radiotherapy or systemic therapy(6, 7). Primary lung cancer and heart disease are the most important long-term complications of breast cancer radiotherapy(8, 9).

Exposure to radiation in women undergoing radiotherapy may increase the risk of primary lung cancer. A meta-analysis of 75 randomized clinical trials of breast cancer radiotherapy showed that the risk of lung cancer due to radiotherapy increased by 11% (95% confidence interval (CI): 9%, 19%) (10, 11).

In this study, the absolute potential risks of primary lung cancer following radiotherapy in women with primary breast cancer were evaluated based on the irradiated site, method, and treatment location. Therefore, the study aimed to assess the benefits and harms of breast cancer radiotherapy.

Materials And Methods

Criteria for including studies

Each of the PICOS elements was defined as follows: the patients were women with primary breast cancer (P), the intervention was radiotherapy after breast cancer (I), the comparison group was patients who did not receive radiotherapy (C), and the outcome was primary lung, bronchus and trachea cancers (O), the studies included cohort studies without language restrictions (S). Risk ratio with 95% confidence interval (95% CI) extracted from the studies. The exclusion criteria included the following: (a) studies that did not have a non-exposed group, (b) studies that did not mention the size of the exposed and non-exposed groups, (c) studies with sample size less than 50, (d) review articles, letters, and case reports.

Search methods

The following terms were searched: (lung malignancy or lung tumor or lung cancer or lung neoplasms) and (breast neoplasms or breast cancer) and (radiation therapy or radiation or radiotherapy) and (second primary). The main databases including MEDLINE, Web of Science, and Scopus were searched until March 2021.

Data extraction

Two authors (BZ & MAR) extracted the data independently. The data file contains the following variables: first author, year of publication, country, outcome (lung, bronchus, and trachea cancers), effect size with its 95% CI, sample size, language, study design, age, and follow-up time.

The methodological quality

The methodological quality assessment of the studies was based on the Newcastle–Ottawa Scale (NOS)(12). The quality of included studies was considered based on the following classification: low quality: 0 to 6 scores, high quality: 7 to 9 scores (13).

Statistical analyses

Association between breast cancer radiotherapy and risk of lung, bronchus, and trachea cancers was estimated by risk ratio (RR) and 95% confidence interval. The significant level was less than 0.05. The heterogeneity of included studies was measured by using the chi-square test and the I^2 statistic. We performed analyses using review manager (version 5.4.1) and Stata software (version 16.0). A random random-effects model was used to estimate the average effects. Publication bias analysis was evaluated with Begg's and Egger's tests and the Trim and Fill method.

Results

Literature search

The PRISMA study selection process is described in Fig. 1. We collected a total of 992 references through searching the three databases PubMed, Web of Science, and Scopus. After removing the number of duplicate references and irrelevant articles, the number of remaining articles reached 15 (14-28).

Studies characteristics

This meta-analysis consisted of 15 articles; six of them were done in America, five in Europe, and four in Asia. Articles are from 1987 to 2018. In this study, two comparisons were made; in the first comparison, the risk of lung

cancer after breast cancer radiotherapy compared with those who did not receive radiotherapy and in the second comparison, the risk of lung, bronchus, and trachea cancers after breast cancer radiotherapy compared with those who did not receive radiotherapy. The comparisons were reported in 10 and 5 studies, respectively. Generally, 1,640,247 women with primary breast cancer were enrolled in the studies, of which 937,151 had not received radiotherapy and the remaining 703,096 had received radiotherapy (Table 1).

The methodological quality

NOS checklist was used for evaluation of the quality of included studies. All articles were prospective or retrospective cohorts whose data was linked to the surveillance, epidemiology, and results (SEER) cohort. The NOS score for each article was 7-9. Therefore, in general, the quality of articles in this meta-analysis was high.

Synthesis of results

Based on Fig. 2, there was no significant relationship between lung cancer and breast cancer radiotherapy (9 studies; RR=0.95, 95%CI: 0.87-1.02, P=0.15, heterogeneity: I^2=46%). Similarly, according to Fig. 3, there was no significant relationship between lung, bronchus, and trachea cancers and breast cancer radiotherapy (4 studies; RR=0.98, 95%CI: 0.93-1.02, P=0.32, heterogeneity: I2=48%).

Sensitivity analysis

There was high heterogeneity across studies investigating the relationship between lung, bronchus, and trachea cancers and breast cancer radiotherapy (I^2=87%). Grantzau's study (17) was the source of the heterogeneity. After excluding this study, the heterogeneity reached 48% (Table 2). In lung cancer meta-analysis results, heterogeneity reached 46% after the removal of Huang’s article(18).

Publication bias

There was no evidence of publication bias based on the results of the Begg test (P=0.767). However, there was some evidence of publication bias based on the Egger test (P=0.038). Based on the Trim and Fill method, the incorrect risk ratio was 0.99 (95%CI: 0.83-1.18) and after adding two miss studies, the risk rate was equal to 0.93 (95% CI: 0.63-1.37) (Figure 4).

Discussion

The results of this study showed that there is no significant relationship between the risk of lung cancer as well as lung, bronchus, and trachea cancers and breast cancer radiotherapy.

The answer to the question of whether radiotherapy after breast cancer may increase the risk of lung cancer can be examined in two ways. In the first step, the fundamental question is to what extent is breast cancer alone can increase the risk of primary lung cancer? So, we referred to the common risk factors for lung cancer and breast cancer. Regardless of radiotherapy, it is necessary to mention to what extent lung and breast cancers shared common risk factors. Patients with prior colorectal, pancreatic, renal, and breast cancer are at significantly higher rates of non-small cell lung cancer specifically adenocarcinoma (29). Although the reasons are unclear, several factors seem to be effective such as biology and patient risk factors including smoking history and hormone

replacement therapy during postmenopausal period (30). The overall standardized incidence rate of lung cancer after breast cancer is reported to be 4.88 (95% CI: 4.70–5.07) (29).

Furthermore, we examined the known risk factors for lung cancer that interact with radiotherapy. Even this interaction can occur with systemic therapy for breast cancer. One of these risk factors is smoking. Smoking increases the risk of lung cancer by up to 11 times in the general population. The risks of lung cancer after breast cancer radiotherapy are significant for smokers(11). Smoking cessation has had a significant effect even during radiation therapy(31, 32). According to Taylor et al., in a systematic literature review of lung and heart doses in breast cancer regimens, women who received overvoltage in previous years were at greater risk than other women (RR = 1.57; 95% CI:1.24–1.99). In this article, the risk of modern radiotherapy for incidence lung cancer after radiotherapy in patients with breast cancer for long-term continuing in smokers and non-smokers is estimated at 4% and 0.3%, respectively(11). A meta-analysis conducted by Grantzau et al. included 11 studies involving 113,516 women exposed to radiotherapy and 203,957 women without exposure. They showed no significant increased risk of lung cancer among women who did not receive radiotherapy. Conversely, the risk was higher in women who received radiotherapy(33). The standardized incidence rate of lung cancer after 5 years exposure was 1.25 (95% CI: 1.05–1.40), after 10 years was 1.58 (95% CI: 1.21, 2.05) and after 15 years was 1.91 (95% CI: 1.11–3.29) (33). The results of this study were different from our results in many aspects including effect size, study duration, inclusion criteria.

One of the studies that were omitted in the sensitivity analysis is the study by Huang et al(18). Cox regression results show that the adjusted hazard ratio was 10.078 times higher in the radiation therapy group than the non-radiation therapy group. The frequency distribution of patients' stages in this study is not known. One specific characteristic of this study was using relatively aggressive computed tomography of the thorax, which is not routinely performed during follow-up of patients with early-stage. The high rate of lung cancer reported in this study may be attributed to the treatment approach of the study.

The results of a meta-analysis conducted by Aznar and et al. showed that lung exposure to breast cancer radiotherapy is very different in different countries and among various regimens. The extent of the irradiated region, using breathing adaptation, and using prone or lateral decubitus patient positioning or proton therapy can be the main determinants of the amount of exposure(34).

The main limitation of the study was the lack of access to predisposing factors such as smoking status, a dose of radiotherapy, and classification of patients based on their follow-up years.

Conclusion

Radiotherapy for breast cancer is not associated with an excess risk of lung cancer. Due to the limited number of studies, further research is required.

Declarations

Authors' contributions

JP and BZ conceived of and coordinated the study. BZ, and MAR searched the literature, extracted and analyzed the data, and drafted the manuscript. JP, BZ, and MAR interpreted the results, and drafted and revised the

manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable (The current study was performed based on published literature and no datasets were generated).

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not Applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table1: Summary of articles in the meta-analysis

First author, year	Country	Outcome	Effect size	Sample size	Risk Ratio (95%CI)	Quality	Follow-up time
Murakami [22], 1987	Japan	lung cancer	Risk Ratio	8671	0.46 [0.13-1.63]	high	17
Lavey [20],1990	USA	lung cancer	Risk Ratio	366	2.26 [0.21-24.76]	high	11
Anderson [14],1991	Denmark	Respiratory system	Risk Ratio	2674	0.65 [0.18-2.36]	high	5
Travis [26],1995	USA	lung cancer	Risk Ratio	27387	0.87 [0.76-1.00]	high	18
Rubino [25],2000	French	Lung, bronchus and trachea	Risk Ratio	3629	4.89 [0.27-88.50]	high	30
Roychoudhuri [24],2004	UK	lung cancer	Risk Ratio	64782	1.10 [0.92-1.31]	high	39
Levi [21],2006	Switzerland	lung cancer	Risk Ratio	6119	1.91 [0.90-4.07]	high	24
Grantzau [17],2013	Denmark	Lung, bronchus and trachea	Risk Ratio	46176	0.60 [0.50-0.73]	high	25
Withrow [28],2017	USA	Lung, bronchus and trachea	Risk Ratio	52556	1.18 [0.98-1.41]	high	20
Burt [15],2017	USA	Respiratory system	Risk Ratio	374993	0.96 [0.91-1.01]	high	35
Rong Wang [27],2018	China	lung cancer	Risk Ratio	620429	0.98 [0.93-1.03]	high	16
De Gonzalez [16], 2009	USA	lung cancer	Risk Ratio	182057	0.95 [0.88-1.04]	high	32
Kamigaki [19], 2011	Japan	lung cancer	Risk Ratio	33043	0.88 [0.64-1.22]	high	28
Neugut [23], 1993	USA	lung cancer	Risk Ratio	54946	0.77 [0.63-0.94]	high	13
Huang [18], 2017	Taiwan	lung cancer	Risk	7277	9.82	high	10

			Ratio		[3.64-26.53]		

Table2: Results before and after sensitivity analysis in terms of each outcome

Outcome	Studies	I^2	Number of RT	Number of NRT	Effect size 95%CI
Lung, bronchus, and trachea cancers					
Before sensitivity analysis	5	87%	206037	273991	0.94 (0.90-0.99)
After sensitivity analysis	4	48%	182410	251442	0.98 (0.93-1.02)
Lung cancer					
Before sensitivity analysis	10	75%	497059	663160	0.97 (0.86-1.10)
After sensitivity analysis	9	46%	491491	661451	0.95 (0.87-1.02)

Figures

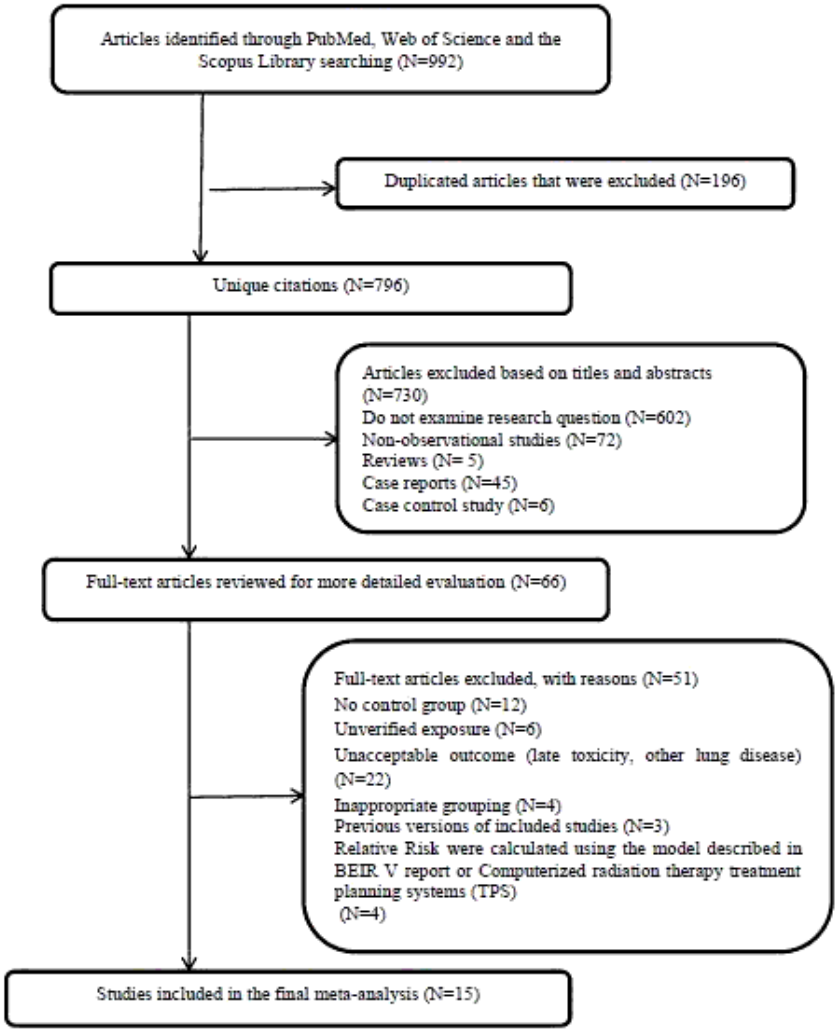

Figure 1

PRISMA flow chart showing the study selection process

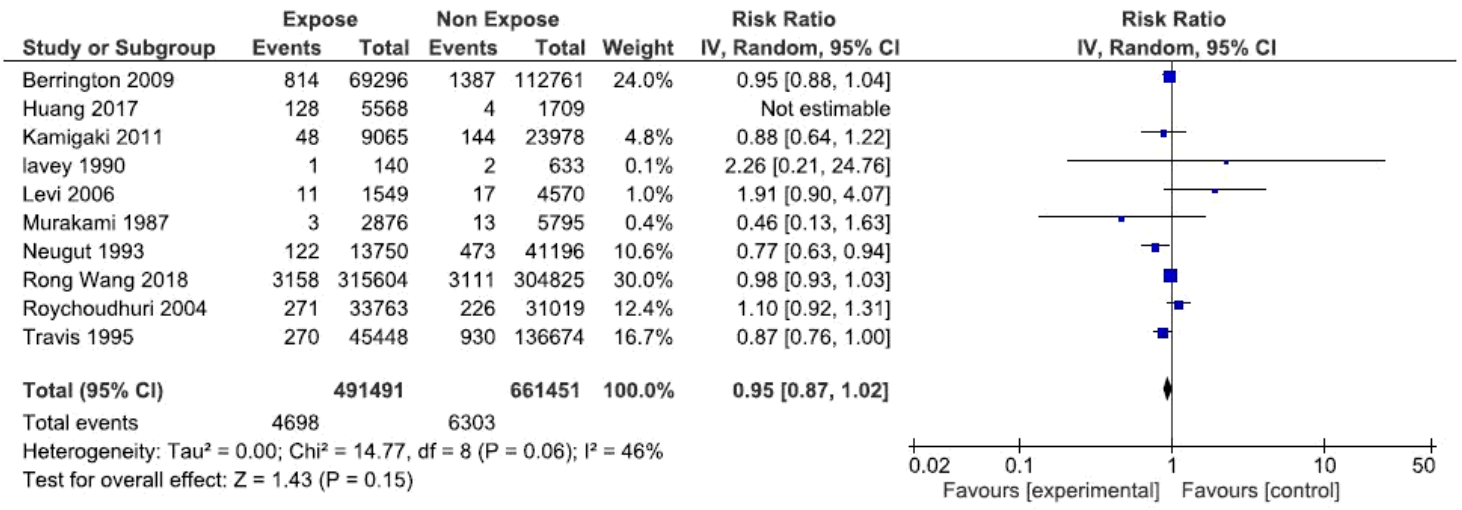

Figure 2

Forest plots of meta-analysis of the included studies on the association between radiotherapy for breast cancer and primary lung cancer.

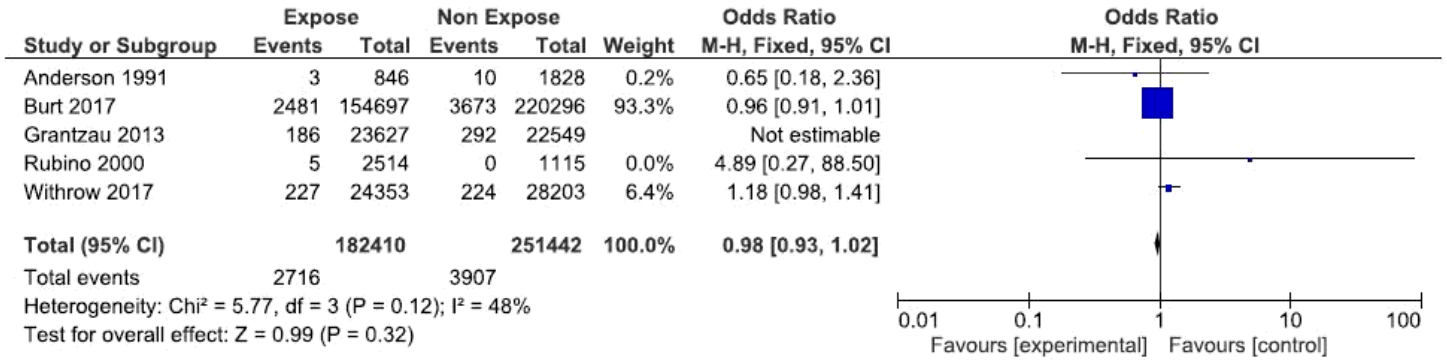

Figure 3

Forest plots of meta-analysis of the included studies on the association between radiotherapy for breast cancer and primary, lung, bronchus, and trachea cancers

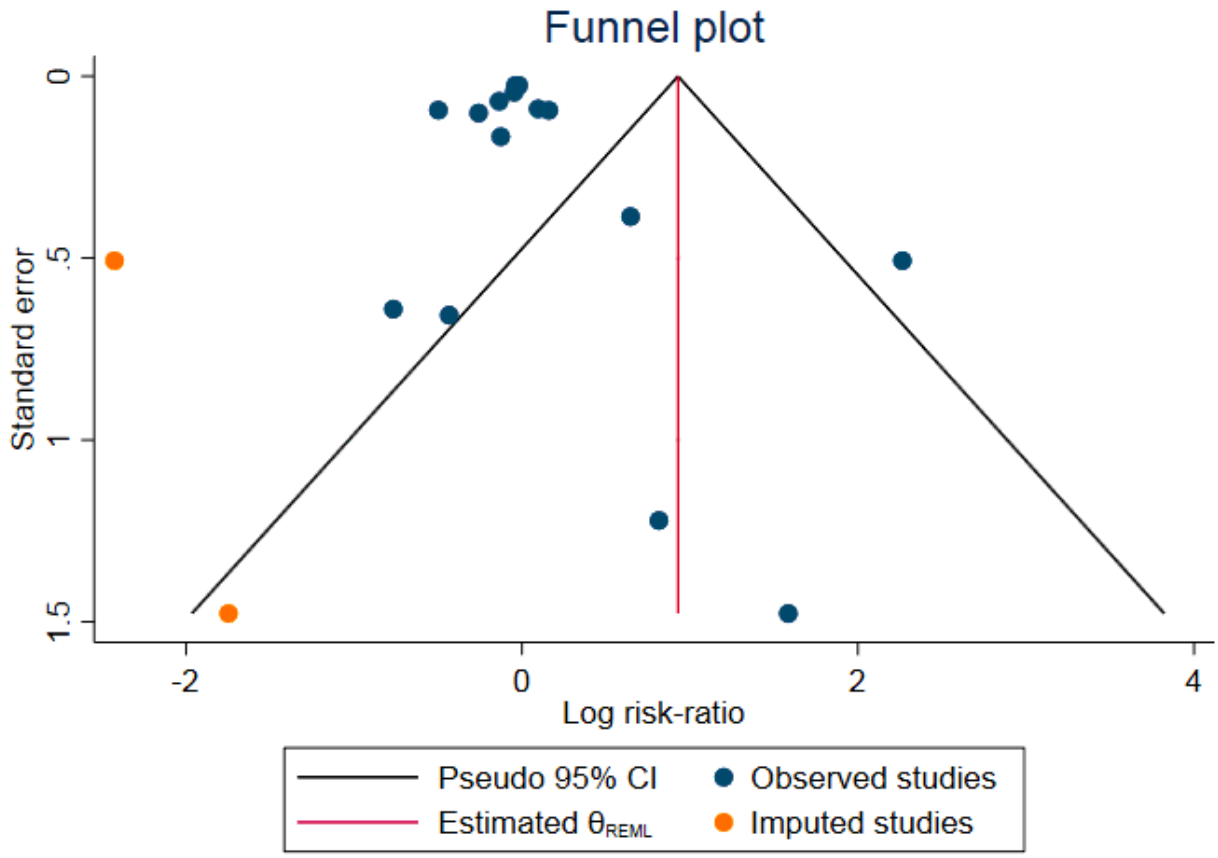

Figure 4

Trim & Fill analysis estimating the number of possible missing studies for the association between radiotherapy for breast cancer and primary, lung, bronchus, and trachea cancers