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SYSTEMATIC REVIEW

Assessment of radiation-induced thyroid gland damage in breast cancer patients: A systematic review

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ABSTRACT

Introduction: The thyroid gland is known as particularly sensitive to radiation therapy. Numerous research studies have indicated that radiation treatment for breast cancer can expose this organ to significant levels of radiation. Hence, the primary objective of this study is to investigate the thyroid gland as a potential organ at risk following radiation therapy for breast cancer, utilizing a systematic review methodology.

Methods: In this systematic review, two independent reviewers conducted a comprehensive search identify relevant studies. The search included various electronic databases such as PubMed, WOS, Scopus, Embase, Science Direct, and Google Scholar. The search criteria encompassed articles published in English up until January 1, 2024.

Results: In the initial search of the relevant databases, 3288 articles were identified and transferred to the information management software (EndNote). A thorough analysis was conducted on a total of 39 studies with varying sample sizes. Among these studies, hypothyroidism was found to be the most common thyroid disorder following radiation therapy for breast cancer, accounting for 40% of the cases. The findings indicate that radiation doses ranging from 20 to 40 Gray- particularly those exceeding 36 Gray-can contribute to the development of hypothyroidism.

Conclusion: The research lightened the significant effect of radiation therapy on the thyroid gland. It is recommended to adopt improved techniques and protective measures to protect the thyroid during radiation treatment. Additionally, regular monitoring of breast cancer patients after radiation therapy is essential to better assess any potential dysfunction of the thyroid gland.

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer-related deaths among women [1]. Therefore, its impact on both individual health and the overall population cannot be ignored [2]. The incidence of this particular cancer is notably higher among older women, resulting in an increase in the average age of breast cancer diagnosis to 69 years between 2015 and 2019 [3, 4]. In 2020, breast cancer surpassed lung cancer to become the most prevalent malignant tumor in humans. The number of new breast cancer cases diagnosed is approximately 2.3 million, accounting for 11.7% of all cancer cases [5]. Radiation therapy plays a crucial role in the treatment of breast cancer following surgery, as it can decrease the likelihood of distant metastasis [6, 7]. Recent studies have demonstrated that external beam radiation therapy, which involves the breast and regional lymph nodes such as the axillary and supraclavicular lymph nodes, can reduce the risk of local recurrence and improve long-term survival in breast cancer patients [8, 9]. However, radiation therapy-induced toxicities can damage adjacent normal tissues and result in severe complications in breast cancer patients [10, 11]. The thyroid gland, an important endocrine organ located near the supraclavicular nodal region, is susceptible to disturbances as a side effect of breast cancer radiation therapy [12, 13]. The thyroid gland regulates the body's metabolism by producing hormones such as thyroxine (T4) and triiodothyronine (T3) [12]. Symptoms of a thyroid disorder manifest when hormone levels are either too low or too high [14]. Numerous studies have indicated that radiation can cause disorders like hypothyroidism and even thyroid cancer [15].

Darvish et al. conducted a similar systematic review in this topic [16], which encompasses articles published from 1985 to 2017. Following their recommendations many articles have been published in the past five years focusing on this subject. Acknowledging its significance, the thyroid gland has been selected for examination as a vulnerable organ after radiation therapy for breast cancer.

METHODS

Ethical approval

This study is exempt from ethical approval since this is a systematic review of anonymized data, and it will not use confidential patient data and interventions (Approval ID: IR.KUMS.MED.REC.1403.006).

Search strategy

The process of selecting the systematic review in our study is documented in Figure 1 of the Guidelines for the Flowchart of Systematic Reviews and Meta-Analyses (PRISMA) [17]. In this systematic review, 6 databases of PubMed, Web of Science, Scopus, Embase, Science Direct and Google Scholar (Top 10%, sorted by relevance) were searched using the keywords such as: "Thyroid", "Breast cancer", "Radiotherapy" and "Radiation therapy". Boolean operators such as "and" and "or" were employed to combine these key terms. The search query for each database was as follows: ((Radiation therapy OR Radiotherapy [Title/Abstract]) AND (thyroid [Title/Abstract])) AND (breast [Title/Abstract]). In addition to excluding reviews, conference abstracts, case reports, animal studies, and non-English articles, only studies that were published until January 1, 2024 were extracted.

Inclusion and exclusion criteria

All articles published until the beginning of 2024 were encompassed in this comprehensive review. This study evaluated and incorporated all observational studies conducted within the specified years. Inclusion criteria included original articles written in English, the full text of which was available. Articles were included if they were pertinent to our research topic and furnished satisfactory and desired data. Conversely, studies meeting the exclusion criteria were those written in languages other than English, lacking sufficient data, or falling under the categories of review, repetition, meta-analyses, case reports, conference abstracts, editorials, letters, RCT, thyroid-breast interaction at the gene or hormone level and other non-original articles. It should also be mentioned that in this study, keywords were chosen more generally so that no relevant study was lost. In this study, it has been tried to remove all irrelevant studies from the study process with great care.

Data collection

The two researchers independently conducted the search. If there was any disagreement between them regarding the studies examined, a third person reviewed the study in question. The checklist consisted of the first author's name, year of publication, study location, sample size (women with breast cancer) and age group, type of study, method, and results. Our study included studies published up to the beginning of 2024 without any time limit. A data extraction form was utilized for the study's purpose.

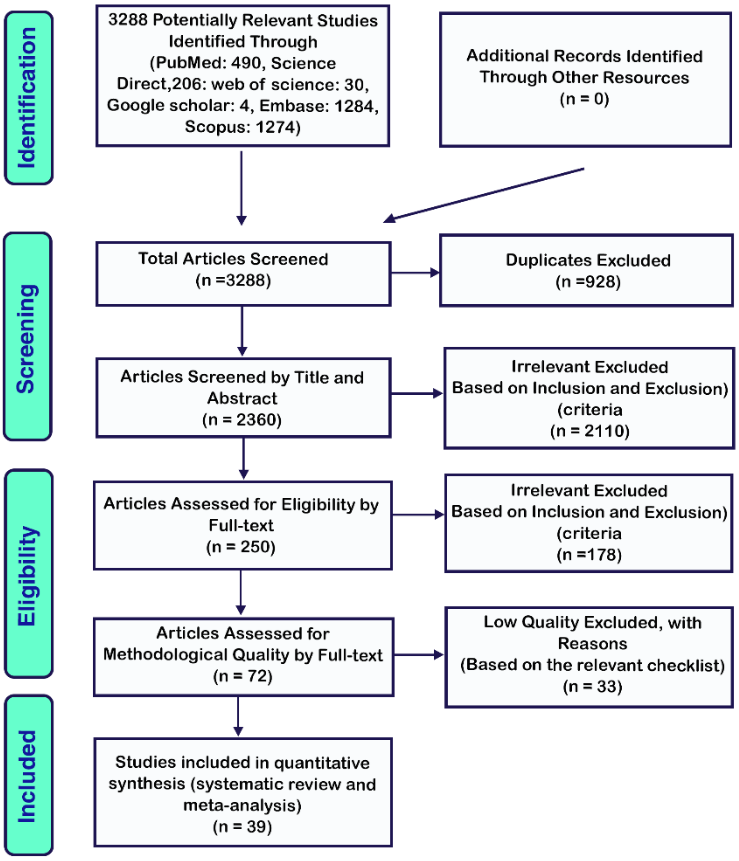

Figure 1. PRISMA flowchart to describe the process of the selected study

The STROBE checklist, which contains 22 items and assesses the standard report in this article, was used to evaluate general reporting for articles and descriptive observational studies exploring the relationship between exposure and health outcomes [18].

Assessment of study quality

In order to validate and evaluate the quality of the studies being reviewed, a checklist suitable for observational studies (STROBE) was used. This checklist contains six scales including: title, abstract, introduction, methods, results, and discussion. In total, this checklist consists of 32 items. For this particular study, articles that achieved a score of 16 or higher were categorized as a good to moderate methodological quality and were consequently included in the study. Conversely, studies with poor methodological quality, scoring below 16, were excluded from the study process. The risk of bias was independently determined by two external investigators using the Newcastle-Ottawa scale. This checklist is applicable to case-control, cohort, and cross-sectional studies. The maximum score attainable in the Newcastle-Ottawa scale is 9, and in our evaluation, a study was considered highly eligible if it achieved a score of 7 points or higher [19].

RESULTS

A systematic review was conducted in this study to assess the thyroid gland as a vulnerable organ after radiation therapy for breast cancer, following the PRISMA guidelines. Initially, a search in various databases yielded a total of 3288 potentially relevant articles, which were then imported into information management software (Endnote). After eliminating 928 duplicate articles, the remaining studies underwent a screening process based on the evaluation of their titles and abstracts. Subsequently, 2,110 articles were excluded based on predefined inclusion and exclusion criteria. In the next phase, a thorough examination of the full texts led to the exclusion of 178 articles that did not meet the inclusion and exclusion criteria. During the qualitative evaluation stage, articles with low methodological quality were further excluded by assessing their full texts and using the STROBE checklist. Ultimately, a total of 39 studies were included in the final evaluation (Figure 1). The findings and relevant information from these 39 studies are summarized in Table 1.

Table 1. Details of the studies included in this systematic review

Results	Evaluating the quality of studies	Methods	Age (year)	Type of study	Breast cancer sample size	Location	Year	Ref
As a result of this study, 6% had hypothyroidism with low S-T_4 level and high S-TSH level. Also, 15% of patients had high S-TSH and normal S-T_4 levels.	18	The patients were exposed to 45 Gy of radiation for 3-4 weeks and their S-TSH[1] and S-T_4[2] levels were evaluated.	54.9±8.2	Descriptive, retrospective	80	Finland	1986	[35]
As a result of this study, it was found that the prevalence of hypothyroidism reported by breast cancer patients is higher compared to the control group without radiation therapy (18% vs. 6%, P < 0.001).	16	Women with breast cancer completed a questionnaire about thyroid diseases and a blood sample was taken from each of them to check thyroid function.	32 to 78	Case control, prospective	403	Norway	2009	[24]
The 5-year incidence of hypothyroidism in irradiated patients compared to non-irradiated patients was 14% (P=0.52).	13	Women with breast cancer without a history of hypothyroidism were identified. These patients were compared in two groups, one with and one without radiation therapy.	>65	Cohort, retrospective	38255	Texas	2008	[34]
After 52 months of follow-up, 90% of patients had normal thyroid function, while 10% of them had hypothyroidism (P<0.001).	15	In this study, tests related to the normal function of the thyroid gland were taken from women with breast cancer. These patients underwent radiation therapy after contouring the thyroid gland.	23 to 76	Prospective, pilot	40	Saudi Arabia	2015	[13]
As a result of this study, no significant difference was observed in the thyroid hormone levels before and after radiation therapy in the target patients (P < 0.05).	17	In this study, women diagnosed with breast cancer underwent radiation therapy, with dose volume histograms of 30, 40, and 50 Gy. The levels of T3, T4, and TSH in each patient were measured both before and after the radiation therapy.	25 to 38	Descriptive, prospective	30	Iran	2016	[36]
As a result of this study, hypothyroidism was diagnosed in 21% of patients within the first 9 months. The thyroid dose varied from 19 to 48 Gy, and doses exceeding 36 Gy significantly contributed to an increase in hypothyroidism.	16	In this study, tests related to thyroid gland function were conducted before radiation therapy, then every 3 months during the first year, and subsequently at 18 and 24 months.	25 to 75	Descriptive, prospective	28	Turkey	2014	[26]

[1] Serum thyroid stimulating hormone
[2] Serum thyroxine

As a result, no statistically significant difference was observed between the V20 and V50 Gy values or the median of the total Gy. Additionally, the mean volume of Gy matter in the control group was 2.3 times higher than that in the other group (r=0.003).	17	In this study, breast cancer patients were divided into two groups: one group underwent radiation therapy using the 4-field technique, and the other did not. Both groups were subjected to radiation therapy with a dose of 46-50 Gy over a period of 3-4 weeks. Following this, the individual dose distribution in their thyroid gland was compared.	≤ 75	Retrospective	403	Norway	2011	[37]
No significant results were obtained regarding the development of hypothyroidism or the relationship of clinical factors, such as age, thyroid volume, and treatment methods, with the development of this complication.	15	Patients with breast cancer were divided into two groups: one group received supraclavicular radiation therapy, and the control group received only chest wall radiation therapy. Thyroid function was then assessed after a period of 24 months.	58	Randomized, prospective	70	Zielona Gora	2016	[38]
As a result of this study, the average thyroid dose was 6.6 Gy in the case group and 9.4 Gy in the control group. The overall relative risk of developing thyroid cancer after radiation therapy for breast cancer was 1.2 (95% confidence interval, 0.2-6.2). Finally, no correlation was found between the radiation dose and the risk of thyroid cancer (P = 0.8).	18	In this study, the risk of developing thyroid cancer following breast cancer treatment was investigated in a group of 8 patients (cases) and a matched control group of 192 patients (controls).	37 to 68	Cohort, Case–control	8	France	2003	[39]
The average radiation dose to the thyroid gland in this study was 22.5 Gy. The dose level was higher than 26 Gy in 44% of patients who are at risk of developing thyroid function abnormalities	17	Patients in this study were treated with 3D conformal radiation therapy (3D CRT). A total dose of 46 Gy was delivered in 25 days to the area of supraclavicular lymph nodes and a total dose of 50 Gy was delivered to the entire chest wall. The thyroid gland was contoured to a thickness of 2-5 mm.	23 to 79	Retrospective	122	Turkey	2014	[40]
hIMRT technique was able to show improvement in maximum dose of brachial plexus and thyroid.	16	Breast cancer patients were treated using hIMRT[3] technique.	45 to 88	Cohort, Retrospective	17	Australia	2022	[33]
As a result of this study, the average thyroid dose was 26 ± 9.45 cGy, but no significant difference was observed in thyroid hormone levels before and after radiation therapy (P < 0.05). A significant relationship was found between the increasing thyroid absorption dose and changes in TSH and T4 levels (P < 0.05), but this relationship was not significant for T3 levels (P = 0.1).	18	Patients with breast cancer underwent treatment with external beam radiation therapy using 6 and 18 MV x-rays. The absorbed thyroid dose was measured using Gafchromic EBT2 film. Levels of thyroid hormones, specifically TSH, T3, and T4, were measured both before and after the radiation therapy.	25 to 35	Cohort	46	Iran	2020	[22]

[3] Hybrid intensity-modulated radiation therapy

The Distal thyroid lobe and the isthmus received doses of 2.9 ± 0.7 Gy and 3.69 ± 0.77 Gy, respectively, which indicates that the thyroid receives a dose equal to the prescribed dose for breast cancer patients.	15	In this study, all patients were treated with cobalt 60 gamma rays, and the absorbed dose of a thyroid lobe was measured using semiconductor dosimeters.	...	Descriptive, prospective	12	France	2003	[41]
As a result of this study, 53 people out of 10,832 primary patients were diagnosed with second primary thyroid cancer.	18	In this study, breast cancer patients were followed for 14 years in order to investigate the risk of thyroid cancer.	35 to 70	Cohort	10832	Poland	2022	[30]
During a mean follow-up period of 7.9 years, 1212 patients developed hypothyroidism. An increased risk of hypothyroidism was observed in the group that underwent treatment with regional lymph node radiation therapy.	17	Women diagnosed with breast cancer, who had not been prescribed thyroid hormones previously and had not been diagnosed with malignancy in the ten years prior to their breast cancer diagnosis, were included in the study to investigate thyroid diseases.	All age groups	Population-based cohort	21268	Sweden	2024	[31]
Breast cancer survivors had a slightly higher incidence of hypothyroidism than the control group.	16	Women diagnosed with non-metastatic breast between the years 1996 and 2009 were included in the study in order to investigate thyroid diseases.	35≤	Cohort	44574	Denmark	2020	[42]
The average thyroid dose of the patients was 140±45 mg per single fraction unit. There was a significant relationship between the thyroid dose and the shape of the shield as well as the patient's adjustment time.	14	The thyroid dose of women with breast cancer was measured using three TLD-100 chips placed on the surface of their thyroid gland. Study variables, such as shield shape, patient placement time, the experience and qualification of technicians were considered.	46±10	Descriptive, prospective	31	Iran	2016	[28]
Serum levels of TSH increased at 3- and 6-months post-RT, but this increase was not statistically significant ($p > 0.05$). Nevertheless, serum levels of fT4 were significantly elevated at 3- and 6-months post-RT ($p < 0.01$).	15	Thyroid function and the prevalence of radiation-induced hypothyroidism were evaluated and compared by measuring the levels of TSH and fT4[4] in the serum before radiation therapy, and then again at 3 and 6 months after radiation therapy.	49.24 ± 10.31	Cross-sectional	21	Iran	2022	[18]
Differences between treatment plans with or without thyroid dose with respect to D (mean) and V (30) values were statistically significant ($P < 0.05$).	18	In this study, the received thyroid dose was compared using different radiation therapy techniques, with or without thyroid dose limitation, for breast cancer patients. Initially, patients were treated in the contralateral tangential field for the chest wall and anteroposterior fields for the ipsilateral supraclavicular field.	...	Retrospective	10	Turkey	2019	[43]

[4] Free thyroxine hormone

37 patients developed Hypothyroidism following radiation therapy at a median 25 months. For smaller thyroids, mean dose and thyroid volume were found to be predictive of the risk of developing hypothyroidism.	17	The individual dose-volume histogram was analyzed to determine the thyroid volume both inside and outside the specified isodose lines, as well as the dose rate. Additionally, multivariate logistic regression was also performed to evaluate the influence of clinical and therapeutic factors on the onset of hypothyroidism.	≥ 18	Retrospective	192	USA	2020	[44]
1year after treatment, a significant decrease in thyroid volume (P < 0.0001) was observed. By 4 years after treatment, the average thyroid volume decreased by 29.7%. Hypothyroidism was diagnosed in 17 patients. Patients with hypothyroidism had a greater reduction in thyroid volume when they received between 20 and 40 Gy at the 12-month mark (p = 0.033).	17	In this study, the thyroid gland was tracked on CT simulation images and analyzed in separate dose-volume histograms in order to determine the thyroid volume inside and outside certain isodose lines.	≥ 18	Retrospectively	61	USA	2023	[11]
Finally, 28 women in the radiation therapy group and 112 women in the non-radiation therapy group were subsequently diagnosed with thyroid carcinoma. No significant increase in the risk of thyroid cancer was observed in the radiation therapy group or the non-radiation therapy group compared to the general population.	16	The incidence of thyroid cancer among women diagnosed with breast cancer between 1973 and 1993 was evaluated using data from the Epidemiology Surveillance Program.	…	Population-based, retrospective cohort	194798	Canada	2001	[25]
21 patients developed hypothyroidism at a follow-up of 1 year after the end of radiation treatment.	15	In this study, women with breast cancer treated with radiation therapy were evaluated for hypothyroidism.	25 to 79	Prospective	52	Iran	2022	[45]
LAR values of thyroid were higher for IMRT than Three-dimensional conformal radiation therapy in left breast cancer patients requiring regional node treatment without including internal mammary node.	17	Patients with left breast cancer treated with radiation therapy after breast conserving surgery were included in the study. Three-dimensional conformal radiation therapy consisting of two opposed half tangential breast fields and IMRT plans were performed and excess absolute risks, excess relative risks, and LAR[5] were calculated.	35 to 64	Cohort	8	Korea	2021	[44]
Thyroid dose limitations were observed in one case.	17	This study was designed to confirm the technical feasibility of partial breast radiation in breast cancer patients with small breasts. A total of 40 Gy was administered in 10 fractions on consecutive days using three-dimensional conformal radiation therapy.	62	Prospective	42	Korea	2015	[46]

[5] lifetime attributable risks

Hypothyroidism was diagnosed in 51 patients, which represents 21% of the total.	15	In this study, the incidence of hypothyroidism was estimated by evaluating the factors predicting its development after radiation therapy for breast cancer patients, focusing on the volume parameters of the radiation dose.	≥ 18	Retrospective	243	Turkey	2017	[47]
A total of 37 patients were diagnosed with hypothyroidism, of which 8.8% were clinical and 7.5% were subclinical.	16	In this study, the incidence of hypothyroidism was investigated by examining the files of patients with breast cancer who visited the radiation therapy center from 2016 to 2018.	35 to 68	Cohort	304	Iran	2023	[32]
One patient was diagnosed with hypothyroidism and six patients with subclinical hypothyroidism with an average TSH level of 8.27 µU/mL.	17	SH and fT4 levels were measured in patients with invasive breast cancer who were irradiated. The prevalence of hypothyroidism is determined by high levels of TSH and low levels of fT4 in serum, and the prevalence of subclinical hypothyroidism is determined by high serum TSH and normal fT4.	All age groups	Prospective, cohort	42	Japan	2017	[23]
In other studies, breast cancer patients with thyroid nodules smaller than 8 cc were more prone to hypothyroidism. In this study, the average thyroid volume was 7.4 cc.	17	In this study, breast cancer patients were treated with three-dimensional conformal radiation therapy and the dose-volume parameters for their thyroid gland were measured.	20 to 80	Prospective	131	India	2020	[48]
The mean organ dose value of these patients was 6.8 Gy in the thyroid. In addition, excess absolute risks for cancer incidence were calculated as 105 Gy-1 for these organs.	15	Patients with left-sided breast cancer who were treated with a total breast dose of 50 Gy in a fraction of 2 Gy were included in the study. Differential dose volume histograms and values of mean organs dose were calculated.	33 to 55	Cross-sectional	60	Iran	2021	[20]
As a result of this study, the mean thyroid doses measured in patients who were treated with tangential fields were significantly lower than patients treated with tangential fields with supraclavicular field ($P < 0.001$).	18	In this study, the risk of developing secondary cancer in the thyroid using the biological effects of ionizing radiation in breast cancer patients was carried out.	50	…	64	Iran	2018	[49]
From the findings of this study, it was observed that 4% of the women with breast cancer developed hypothyroidism, with an average monitoring period of 77.7 months.	17	All breast cancer patients who underwent total breast irradiation from 2009 to 2016 were included in the study. Individual dose-volume histograms were used to generate LKB[6] model.	≥ 40	Retrospective, cohort	1063	Korea	2024	[50]
In patients with a tilted neck, the values for Dmean, V15, V20, V25, V30, and V35 were significantly lower compared to the patients who participated in the study with a straight neck.	17	Patients with breast cancer who received chest wall/breast and supraclavicular radiation were included in the study based on the neck position in two ways: one with the neck positioned straight and the other with the neck tilted to contralateral side.	59	Retrospective	72	Kerala	2022	[51]

[6] Lyman–Kutcher–Burman

When IORT was applied to the right lobe, it absorbed a significantly larger dose compared to the left lobe. A similar pattern was noticed in the left lobe and left breast when they were subjected to IORT treatment (P-values of 0.0001 and 0.018, respectively).	19	This study was conducted on women with breast cancer undergoing IORT[7]. Immediately after removing their tumor resection, a single dose of 20 Gy was delivered to them at the applicator surface using 50 kV X-rays.	…	Cross-sectional	49	Iran	2021	[21]
There was a statistically significant increase in mean TSH levels over baseline when measured at 3-, 6-, and 9-months post-treatment, with p values of 0.0047, 0.0002, and <0.0001, respectively. 4 patients had thyroid function tests outside the normal ranges.	15	In this study, which was conducted on patients with breast cancer, the pre- and post-treatment values of TSH, fT4, and fT3 were compared using the Wilcoxon signed-rank test.	32 to 71	Prospective descriptive	42	Tanzania	2023	[52]
The 5-year incidence of hypothyroidism was identical (14%) in irradiated patients with 41 LN, 0 LN, and non-irradiated patients (P= 0.52). Hypothyroidism risk did not increase in irradiated patients with 41 LN versus 0 LN.	17	A comparison of hypothyroidism incidence was conducted among several groups. These included irradiated patients with 41 positive lymph nodes, irradiated patients with no positive nodes, non-irradiated patients, and a control group.	>65	Cohort	38255	Texas	2008	[34]
It was observed that women diagnosed with breast cancer showed a significantly increased risk of developing thyroid cancer later. However, within the cohort of women with breast cancer, the risk of thyroid cancer was not significantly different between those who underwent radiation therapy and those who did not.	16	This study was conducted on women with breast cancer, both with and without exposure to radiation therapy, to investigate the risk of thyroid cancer.	20 to 54	Population-based cohort	55318	Taiwan	2015	[53]
20 patients out of 96 developed hypothyroidisms.	17	Patients diagnosed with nonmetastatic breast cancer underwent supraclavicular lymph node irradiation as part of their adjuvant radiation therapy. They were followed up for a period of 18 months. All these patients received three-dimensional conformal radiation therapy.	>60	Prospective	96	Egypt	2022	[27]
As a result of this study, 131 patients were diagnosed with hypothyroidism.	16	An evaluation was conducted on breast cancer patients who underwent hypofractionated radiation therapy. The assessment was based on various factors related to the patient, tumor, and treatment, to investigate any potential correlation with the risk of hypothyroidism.	…	Prospective Cohort	500	China	2023	[54]

[7] Intraoperative radiation therapy

The research involved breast cancer patients with different sample sizes and age range. The highest sample size was 194,798, while the lowest consisted of only eight cases of women with breast cancer. The studies were conducted over different time periods from 1986 to 2024. Iran has had the largest number of studies in this field with a total of 11 studies.

The data indicated that many articles were a combination of retrospective and prospective observations in the form of case-control studies, while others were cohorts. Three cross-sectional studies [18, 20, 21] and one pilot study [13] focused on hypothyroidism post radiation therapy for breast cancer. In four studies, a reduction in thyroid volume was observed following radiation therapy [21-23]. This reduction was remarkable one year after treatment, with one study showing a 29.7% decrease in thyroid volume four years post-treatment. In one of the studies, it was shown that applying a dose between 20 and 40 Gray after one year can reduce the thyroid volume [22]. However, in another study, the reduction of thyroid volume was evident when applying doses higher than 40 Gray [22]. The importance of thyroid volume reduction may have a direct relationship with hypothyroidism [21-23]. The findings revealed that hypothyroidism was reported in over 40% of the studies. Five studies utilized the 3D conformal radiation therapy method, while three others employed a different method: hIMRT, IMRT, or IORT. The highest radiation dose administered in the studies was 50 Gray, and in one study with a total dose of 50 Gray to the breast; the average thyroid dose was 6.8 Gray [24]. Some studies looked for an association between thyroid cancer in women with breast cancer who underwent radiation therapy and found no significant association between the risk of thyroid cancer after breast cancer radiation therapy [25, 26]. However, a more recent study from 2022 presented different results. After 14 years of follow-up, 53 out of 10,832 breast cancer patients who underwent radiation therapy were diagnosed with thyroid cancer [27].

Given the well-established relationship between radiation dose and the risk of hypothyroidism in numerous studies, the present investigation specifically analyzes the percentage of patients with hypothyroidism at different radiation doses, alongside the assessment of cancer risk (Table 2).

The data in the Table indicate varying percentages of hypothyroidism across different radiation doses.

Table 2. Relationship between radiation dose and the risk of hypothyroidism in some studies

Radiation dose (Gy)	Hypothyroidism (%)	Ref
45	6	[35]
19-47 (Significant increase in dose of 36)	21	[26]
20-40	29.7	[11]
10-50	21	[47]
53	8.8% were clinical and 7.5% were subclinical	[32]
≥10	4	[50]
21	26	[54]

DISCUSSION

A systematic analysis of various research studies has revealed a clear association between breast radiation and thyroid disorders. Numerous studies have indicated that these disorders often manifest as hypothyroidism [28-32]. Previous investigations on hypothyroidism have involved tests to measure TSH, T4, and T3 levels [22]. The prevalence of hypothyroidism is typically characterized by elevated serum TSH levels and decreased fT4 levels. Conversely, subclinical hypothyroidism is often identified by high serum TSH levels while maintaining normal fT4 levels [23].

During the treatment of breast cancer with radiation therapy, the thyroid gland is exposed to secondary radiation. Creating multiple disturbances in thyroid function observed in breast cancer patients before and after radiation therapy underscores the critical importance of the radiation dosage received by the thyroid gland. Several related studies have been conducted in this regard. For example, one study reported that the incidence of hypothyroidism in breast cancer patients increased from 6% before radiation therapy to 18% after the treatment [24]. Another study showed that thyroid received a dose equal to the prescribed dose in breast cancer patients so that in breast carcinoma irradiation, the distal thyroid lobe and the isthmus received 2.9 ± 0.7 Gray (6.55 ± 1.56%) and 3.69 ± 0.77 Gray (8.39 ± 1.76%), respectively [33]. However, there have been studies with no significant difference in the incidence of thyroid gland disorders between the group that underwent radiation therapy and the group that did not [25].

Although the exact timeline for the development of hypothyroidism is not yet established, ongoing prospective trials are actively seeking to clarify this aspect. In one study, it was discovered that 21% of breast cancer patients developed hypothyroidism after 9 months through thyroid function examinations [26]. Another study revealed that after 18 months of follow-up, nearly 21% of patients experienced this complication [27].

Furthermore, there have been several investigations into specific factors that contribute to thyroid dysfunction, in addition to the cases mentioned earlier. For instance, a study conducted by Farhood et al. in 2016 examined the thyroid dose in women with breast cancer. They utilized three TLD-100 chips placed on the surface of the patients' thyroid gland to measure the dose. The study took into account various variables such as shield shape, patient placement time, and the experience and qualifications of the technicians involved. The findings revealed that the average thyroid dose for the patients was 140±45 mGy per single fraction unit. The study also established a significant correlation between the thyroid dose and both the shape of the shield and the patient's adjustment time [28].

In 2022 Jang et al. focused on patients with left-sided breast cancer who underwent radiation therapy after breast-conserving surgery. The study employed three-dimensional conformal radiation therapy, which consisted of two opposed half tangential breast fields and IMRT plans. The researchers calculated excess absolute risks, excess relative risks, and LAR (lifetime attributable risk). The results indicated that the LAR values for the thyroid were higher in patients who received IMRT compared to those who underwent three-dimensional conformal radiation therapy, specifically in cases where regional node treatment was required, excluding the internal mammary node [29].

Ambrose et al. studied breast cancer patients were treated using the hIMRT technique in 2022 [33]. The study demonstrated that this technique led to an improvement in the maximum dose received by the brachial plexus and the thyroid.

In 2021, Ramezani Farkhani et al. conducted a study examining women with breast cancer who were undergoing IORT [21]. After tumor resection, a single dose of 20 Gy was administered to the applicator surface using 50 kV X-rays. The dose at the right and left lobes of the thyroid gland as well as the mid-thyroid line was found to be 40.18±35.44 mGy, 35.50±27.32 mGy, and 40.61±32.47 mGy, respectively. The study revealed that the right lobe of the thyroid gland received a significantly higher absorbed dose than the left lobe of the thyroid gland when treated with IORT. The same trend was observed in the left lobe and left breast under IORT treatment (P=0.0001 and P=0.018, respectively).

In 2022, Pulickal et al. conducted another study involving patients with breast cancer who had received chest wall/breast and supraclavicular radiation. The study categorized patients based on two different neck positions: a straight neck position and a neck tilted to the contralateral side. The results showed that D_{mean}, V15, V20, V25, V30, and V35 were significantly lower in patients with a tilted neck compared to those with a straight neck [34]. A study conducted by Akyureki et al. in 2014 demonstrated that thyroid dose ranged from 19 to 48 Gy, and doses exceeding 36 Gy increased the risk of hypothyroidism, significantly [35]. Therefore, it is recommended to consider the thyroid gland as an organ at risk during treatment planning for breast cancer, and the dose received by the thyroid should be calculated. Additionally, the use of a Multi Leaf Collimator, blocks, and maintaining a midline position during treatment may help reduce complications [36].

The purpose of this investigation is to explore the impact of radiation therapy for breast cancer on the thyroid gland by conducting a systematic review. This will enable us to pinpoint the factors influencing this issue and propose recommendations to mitigate complications to this particular organ. Given the lack of research in this area, there is a necessity for additional cohort studies to enhance the level of certainty. Furthermore, a drawback of this study is its exclusive focus on English-language publications, potentially overlooking studies in other languages. Moreover, several studies were excluded from the analysis due to inadequate quality, such as those failing to disclose sample sizes.

As mentioned above, examining thyroid disorders across all levels and dimensions was a very difficult task. This study primarily focused on the relationship between radiation dose and the development of thyroid dysfunction, particularly hypothyroidism, and other studies were excluded during the evaluation stages. Furthermore, due to differences in the study population, patient follow-up time, and radiation dose, as well as a lack of information on pre-existing conditions in breast cancer patients, a definitive and clear link between radiation dose and the risk of thyroid cancer could not be established. This necessitates conducting a study with a large population and relatively uniform sample conditions.

CONCLUSION

This systematic review examined the thyroid gland as a vulnerable organ in patients receiving radiation therapy for breast cancer. The findings of this study can provide valuable insights to oncologists and physicists, helping them recognize the thyroid gland as a susceptible organ and take appropriate measures to protect it during breast cancer radiation therapy. Given the genetic and hormonal connections between the thyroid and the breast tissue, it is inaccurate to attribute thyroid damage and dysfunction solely to the radiation dose. However, it can be concluded that breast cancer patients are at a higher risk for thyroid disorders and may experience more complications. The study found that high radiation doses to the thyroid gland can lead to thyroid dysfunction such as hypothyroidism and increase the risk of thyroid cancer. Therefore, it is essential to minimize the radiation dose to the thyroid gland by implementing more optimal techniques or protective devices during treatment planning. It is advisable to conduct thyroid function tests for patients who undergo supraclavicular field radiation therapy after breast cancer radiation therapy. Considering the different outcomes observed in various studies, the sample size is identified as a factor that can impact the accuracy of the results. Thus, future research should focus on investigating each factor that affects the thyroid gland following radiation therapy for breast cancer.

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