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Association between thyroid cancer and the risk of osteoporosis and fracture: a systematic review and meta-analysis

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 November 2024 and was last updated on 7 November 2024.

INTRODUCTION

Review question / Objective There are numerous studies on the impact of thyroid cancer on osteoporosis and fracture, but the conclusions drawn are inconsistent. And there has been no systematic review and meta-analysis on the relationship between thyroid cancer and osteoporosis or fracture. Therefore, we conduct a systematic review and meta-analysis on this topic, aiming to comprehensively sort out and assess the impact of thyroid cancer on the risk of osteoporosis and fracture, in order to fill the research gap in this field.

The findings of this study will provide high-quality evidence-based medical evidence for the association between thyroid cancer and the risk of osteoporosis and fracture, deepen the public and medical community's understanding and attention to thyroid cancer, and offer more effective support and intervention recommendations for patients to prevent the occurrence of osteoporosis and fracture.

Rationale Thyroid cancer has been found to be associated with various health issues, while osteoporosis and fracture also constitute significant public health problems globally now. Recently, numerous studies explored the impact of thyroid cancer on the risk of osteoporosis and fracture, yet their findings are inconsistent. For instance, Chang (2017), utilizing the Korea National Health and Nutrition Examination Survey (KNHANES) database, found no significant difference in bone density between thyroid cancer patients and individuals without thyroid cancer. Conversely, Papaleontiou et al. (2019), through a study of veterans' data, discovered that thyroid cancer patients were more prone to osteoporosis compared with individuals without thyroid cancer, although no difference in the risk of fracture was observed between the two groups. However, Lin et al. (2018), leveraging data from the National Health Insurance Research Database(NHIRD), found that thyroid cancer increases the risk of both osteoporosis and fracture.

However, there has been no systematic review and meta-analysis on the relationship between thyroid cancer and osteoporosis or fracture. Therefore, it is necessary to conduct a omprehensive and integrated study on this topic.

Condition being studied Thyroid cancer ranks as one of the prevalent malignancies within the endocrine system. It has multiple pathological types and approximately 84% of thyroid cancers are attributed to papillary thyroid cancer. Imaging examinations and pathological examinations can be used for the diagnosis of thyroid cancer. Surgery is a prevalent treatment approach for thyroid cancer, with the majority of thyroid cancer cases being curable through surgical intervention. Furthermore, radioactive iodine administration and levothyroxine therapy can serve as adjuvant modalities in the management of thyroid cancer. Thyroid cancer accounts for 3% of all cancer incidence rates worldwide, and its incidence rate has increased in many countries and regions as time goes on. As of 2010, the estimated number of new thyroid cancer cases globally was approximately 449,000 in women and 137,000 in men, which translated to 10.1 new cases per 100,000 women and 3.1 new cases per 100,000 men. The adverse effects of thyroid cancer manifest primarily in multiple aspects, including physiological, psychological, and social life impacts. Currently, an increasing number of studies are focusing on the health impacts of thyroid cancer on patients, such as the risk of developing osteoporosis and fracture.

Both osteoporosis and fracture are significant global public health issues. Osteoporosis is a bone disease characterized by decreased bone mass and reduced bone strength, leading to fragile bones and increasing an individual's susceptibility to fracture in skeletal areas such as the hip, wrist, and spine. The International Classification of Diseases 9th Revision (ICD-9) codes are codes that can be used to identify osteoporosis and fracture. Currently, ICD-9 and bone mineral density(BMD) T score ≤-2.5SD are commonly used to identify osteoporosis. And ICD-9, Current Procedural Terminology 4th Revision (CPT-4) codes, diagnostic codes of claims data, and Genant's method are used to identify fracture. Fracture has a profound impact, not only by impairing patients' ability to work and reducing productivity, but also by potentially leading to disabilities and severely disrupting patients' daily routines. Furthermore, these injuries not only undermine individual health and quality of life but also entail substantial healthcare costs, placing significant economic burdens on individuals, families, and society at large. Statistically, approximately 178 million people globally experienced fracture for the first time in 2019[10]. Hence, it is of utmost importance to delve deeply into the factors influencing osteoporosis and fracture occurrences.

METHODS

Search strategy (1) PubMed: ("thyroid neoplasms"[MeSH Terms] OR ("thyroid"[Title/Abstract] AND ("cancer"[Title/Abstract] OR "carcinoma"[Title/Abstract] OR "tumor"[Title/Abstract] OR "neoplasm"[Title/Abstract] OR "malignancy"[Title/Abstract]))) AND ("osteoporosis, postmenopausal"[MeSH Terms] OR "osteoporosis"[MeSH Terms] OR "fracture, bone"[MeSH Terms] OR ("osteoporosis"[Title/Abstract] OR "osteoporoses"[Title/Abstract] OR "fracture*"[Title/Abstract] OR "broken bone*"[Title/Abstract] OR "bone loss*"[Title/Abstract] OR "low bone mass"[Title/Abstract]));
(2) Web of Science: #1: TS=(thyroid) AND #2: ((((TS=(cancer)) OR TS=(carcinoma)) OR TS=(tumor)) OR TS=(neoplasm)) OR TS=(malignancy) AND #3: (((((TS=(osteoporosis)) OR TS=(osteoporoses)) OR TS=(fracture*)) OR TS=(broken bone*)) OR TS=(bone loss*)) OR TS=(low bone mass) and Preprint Citation Index (Exclude – Database);
(3) Scopus: (TITLE-ABS-KEY (thyroid)) AND ((TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (carcinoma) OR TITLE-ABS-KEY (tumor) OR TITLE-ABS-KEY (neoplasm) OR TITLE-ABS-KEY (malignancy))) AND ((TITLE-ABS-KEY (osteoporosis) OR TITLE-ABS-KEY (osteoporoses) OR TITLE-ABS-KEY (fracture*) OR TITLE-ABS-KEY (broken AND bone*) OR TITLE-ABS-KEY (bone AND loss*) OR TITLE-ABS-KEY (low AND bone AND mass)))
(4) Embase: #1: thyroid:ab,ti AND #2: cancer:ab,ti OR carcinoma:ab,ti OR tumor:ab,ti OR neoplasm:ab,ti OR malignancy:ab,ti AND #3: osteoporosis:ab,ti OR osteoporoses:ab,ti OR fracture*:ab,ti OR 'broken bone*':ab,ti OR 'bone loss*':ab,ti OR 'low bone mass':ab,ti.

Participant or population Population (P): sample size ≥ 60; Exposure (E): thyroid cancer with or without treatment; Comparison: (C): people without thyroid cancer.

Intervention None.

Comparator None.

Study designs to be included Outcome (O): studies providing or enabling the calculation of effect value regarding the association between

thyroid cancer and the risk of osteoporosis and fracture, including odds ratio (OR), hazard ratio (HR), and 95% confidence interval (95%CI); Study design (S): cross-sectional or cohort studies.

Eligibility criteria
Exclusion criteria: (1) studies that were unable to get full text or important data;
(2) articles from the review, conference, letter, editorial material, book, book chapter, or case;
(3) animal studies;
(4) studies published in non-English language publications;
(5) experimental and retrospective studies.

Information sources A search for pertinent literature was conducted in PubMed, Embase, Web of Science, and Scopus, spanning from their inception until August 28, 2024.
Additionally, to ensure a more comprehensive inclusion in the article, we conducted a further review of the references cited within the retrieved literature and incorporated those that were closely related to the research topic into our study scope.

Main outcome(s) A total of 7,722 articles were retrieved, and ultimately, 11 studies (12 reports), encompassing 614,840 samples, were included in the study. Compared with individuals without thyroid cancer, patients with thyroid cancer were more prone to developing osteoporosis [OR (95% CI): 1.48 (1.14-1.94); I^2 = 87%]. But there was no statistically significant association between thyroid cancer and the risk of fracture [OR (95% CI): 1.10 (0.91-1.33); I^2 = 71%]. In subgroup analysis, it was found that age might influence the relationship between thyroid cancer and fracture (P<0.05).

Additional outcome(s) Thyroid cancer patients are more susceptible to osteoporosis compared with individuals without thyroid cancer. Effective monitoring and preventive measures should be formulated and implemented.

Data management EndNote was used for data management.

Quality assessment / Risk of bias analysis An eight-item assessment instrument for cross-sectional studies was employed to determine the quality of cross-sectional studies, categorizing them into low (0-3), medium (4-6), and high (7-8) quality brackets. All included cohort studies were evaluated according to the Newcastle-Ottawa scale (NOS). The scores for each study ranged from 0 to 9 points, with a maximum of 9 points. The study with a NOS score of 0-3 was considered as low-quality, 4-6 as medium-quality, and 7-9 as high-quality.
The execution of publication bias analysis necessitated ten or more reports, without which, the analysis was unfeasible. If necessary, Begg's funnel plot was used to assess the effect of publication bias. A value of P less than 0.05 was considered statistically significant across all tests, utilizing a two-tailed approach.

Strategy of data synthesis ORs, HRs, and 95% CIs were used to evaluate the relationship between thyroid cancer and fracture or osteoporosis. HRs were considered as ORs according to a previous study. Cochrane's Q test and I2 statistics were used to evaluate the heterogeneity between the studies in the articles. If I2≤50%, the homogeneity between the included studies was good and the fixed-effect model could be used. If I2>50%, the heterogeneity between the included studies was significant and the random-effect model should be used. With osteoporosis and fracture as outcome variables, if two or more studies had reported on the relationship between thyroid cancer and the same outcome variable, a meta-analysis would have been conducted. If two or more studies investigated the relationship between thyroid cancer and osteoporosis or between thyroid cancer and fracture in the same population, only the study with the most comprehensive and extensive data would be included. If the study provided both overall population data and subgroup population data, we prioritized the inclusion of the most comprehensive overall population data with the largest amount of data for meta-analysis. For instance, Jin et al.'s study simultaneously provided subgroup data stratified by sex as well as for the overall population, this meta-analysis only incorporated data from the overall population. If the study only contained subgroup population data, all subgroup data were included for comprehensive consideration. For example, in the analysis, two subgroups divided by age in Blackburn et al.'s study were treated as two separate reports for inclusion in our analysis.

Subgroup analysis If the heterogeneity was significant between studies, subgroup analysis was used to find the source of heterogeneity. The following categorical variables were utilized to conduct subgroup analyses by using the median split method[25]: study design (i.e., Cross-sectional, Cohort study), countries region by (i.e., Asia, Other), female, % (i.e., ≤76, >76), mean age (years) (i.e., ≤55, >55 or ≤53, >53), sample size (i.e., ≤15,587, >15,587), and quality (i.e., Medium, High). Since 3 studies did not clarify the treatment methods for thyroid cancer, and in the two

categories of studies that separately investigated the relationship between thyroid cancer and osteoporosis, as well as between thyroid cancer and fracture, studies in each category that only included patients who did not undergo thyroidectomy or receive levothyroxine therapy was less than two. Therefore, it was unable to conduct subgroup analyses of the included studies based on thyroid cancer treatment methods, which included thyroidectomy and levothyroxine therapy.

Sensitivity analysis The execution of sensitivity analysis necessitated ten or more reports, without which, the analysis was unfeasible. And the stability of the results was judged by sensitivity analysis. Its principle is excluding one study at a time and then combining the data of the other remaining studies to assess the impact of a single study. A value of P less than 0.05 was considered statistically significant across all tests, utilizing a two-tailed approach.

Language restriction The search limited the language to English.

Country(ies) involved China.

Keywords Thyroid cancer; Osteoporosis; Fracture; Meta-analysis.

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