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Familial Risk Factors in Thyroid Cancer Across Generations and Geographics: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 June 2025 and was last updated on 6 June 2025.

INTRODUCTION

Review question / Objective To systematically evaluate and synthesize the evidence on how familial risk factors, including family history, degree of relatedness, and demographic/lifestyle characteristics, affect the risk of developing thyroid cancer across different generations and geographic regions.

Rationale Thyroid cancer is a rapidly increasing malignancy worldwide, with significant geographic and demographic variability in incidence and outcomes. While hereditary syndromes and certain environmental exposures are established risk factors, the broader impact of family history and degree of familial relationship on thyroid cancer risk remains incompletely understood, particularly across diverse populations. Recent evidence suggests that familial factors may play a more substantial role in both disease risk and progression than previously recognized; however, findings are heterogeneous and have not been systematically synthesized. A comprehensive systematic review and meta-analysis are needed to clarify the magnitude and patterns of familial risk, including the influence of demographic and lifestyle factors, and to inform risk stratification and surveillance strategies for high-risk groups.

Condition being studied Thyroid cancer (including all histologic subtypes) and its association with familial risk factors such as family history, genetic predisposition, and degree of relatedness (e.g., first-degree relatives, maternal vs. paternal lineage). The review also examines geographic variability in these associations.

METHODS

Search strategy A comprehensive literature search will be conducted in PubMed, Web of Science, and Embase databases. The search will cover all publications up to August 17, 2024. The

search strategy will use the following terms and Boolean operators: ((Lifestyle) OR (Genetics) OR (Epigenetics) OR (Benign Thyroid Conditions)) AND (Family History) AND (Thyroid Cancer)
No language restrictions will be applied during the initial search, but only studies published in English will be included in the review. Reference lists of included articles will be manually screened to identify additional relevant studies. The search strategy will be adapted as necessary for each database to ensure comprehensive coverage. All identified records will be imported into a reference management tool, and duplicates will be removed prior to screening.

Participant or population Individuals of any age, sex, or ethnicity from any geographic region who have been studied in relation to thyroid cancer risk and have documented family history or familial risk factors. Included studies must report on cohorts with and without thyroid cancer, providing data on family history, degree of relatedness, or other heritable risk factors. Both general population cohorts and high-risk groups (e.g., those with a family history of thyroid cancer, first-degree relatives, or known hereditary syndromes) will be considered.

Intervention The primary exposures of interest are familial risk factors for thyroid cancer, including:
- Family history of thyroid cancer (presence/absence)
- Degree of relatedness (e.g., first-degree relatives, maternal vs. paternal lineage)
- Hereditary syndromes associated with thyroid cancer (such as multiple endocrine neoplasia type 2, familial medullary thyroid cancer, familial non-medullary thyroid carcinoma)
- Family history of benign thyroid conditions (e.g., goiter, benign nodules) where studied
No active therapeutic or preventive intervention is being evaluated; the review focuses on the association between these familial/genetic factors and the risk of developing thyroid cancer.

Comparator The primary comparator group consists of individuals without a family history of thyroid cancer or those without identified familial risk factors. Where available, studies comparing different degrees of relatedness (e.g., first-degree vs. second-degree relatives), maternal vs. paternal lineage, or populations with and without benign thyroid conditions will be included. The review will also consider comparisons between individuals with and without other established thyroid cancer risk factors (such as radiation exposure or iodine deficiency), as reported in the literature.

Study designs to be included This review will include observational studies that evaluate the association between familial risk factors and thyroid cancer. Eligible study designs are: Cohort studies (prospective or retrospective), Case-control studies, Cross-sectional studies. Randomized controlled trials (RCTs), case reports, case series, editorials, letters, reviews, meta-analyses, and studies not published in peer-reviewed journals will be excluded.

Eligibility criteria
Inclusion Criteria:
- Observational studies (cohort, case-control, or cross-sectional) reporting on the association between familial risk factors (e.g., family history, degree of relatedness, hereditary syndromes) and thyroid cancer.
- Studies including human participants of any age, sex, or ethnicity.
- Studies that report on both individuals with and without thyroid cancer, or that compare groups with and without family history of thyroid cancer.
- Studies providing data on demographic or lifestyle factors in relation to familial risk.
- Studies published in peer-reviewed journals.
- Studies published in English.

Information sources The following electronic databases will be systematically searched to identify relevant studies:
PubMed
Web of Science
Embase
In addition, the reference lists of all included articles will be manually screened to identify any further eligible studies. Only studies published in peer-reviewed journals and English will be included. No restrictions will be placed on publication date during the initial search. All identified records will be managed using a reference management tool, and duplicates will be removed prior to screening.

Main outcome(s) The following electronic databases will be systematically searched:
PubMed
Web of Science
Embase
Additionally, the reference lists of all included articles will be manually screened to identify any further eligible studies. No restrictions will be placed on publication date during the initial search. Only studies published in English in peer-reviewed journals will be included. All identified records will be managed using a reference management tool, and duplicates will be removed prior to screening.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of included studies will be independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS), which is widely recommended for observational studies (cohort, case-control, and cross-sectional designs). The NOS evaluates studies across three domains: the selection of study groups, the comparability of groups, and the ascertainment of exposure or outcome. Each study will be awarded a maximum of nine stars, with higher scores indicating higher methodological quality. Discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer.
Sensitivity analyses will be conducted to assess the impact of study quality on pooled results. Additionally, publication bias will be assessed using funnel plots and Egger's test, as applicable.

Strategy of data synthesis Data from the included studies will first be summarized in evidence tables, detailing study characteristics, participant demographics, exposures (including familial risk factors), and outcomes. Where studies are sufficiently homogeneous in terms of design, population, exposures, and outcomes, a quantitative synthesis (meta-analysis) will be conducted using RStudio. Pooled effect estimates (e.g., odds ratios or relative risks with 95% confidence intervals) will be calculated using a fixed-effects model; if substantial heterogeneity is detected ($I^2 > 50\%$), a random-effects model will be applied. Heterogeneity will be assessed using the I^2 statistic and the Chi-square test. Subgroup analyses will explore the impact of degree of relatedness, maternal vs. paternal lineage, and geographic region on thyroid cancer risk. Sensitivity analyses will be performed to assess the influence of study quality and risk of bias.
Where meta-analysis is not feasible due to heterogeneity or insufficient data, a narrative synthesis will be provided, summarizing study findings in a structured textual format and highlighting patterns, trends, and gaps in the evidence. Publication bias will be assessed using funnel plots and Egger's test. All synthesis methods will adhere to PRISMA guidelines and established best practices for systematic reviews and meta-analyses.

Subgroup analysis Subgroup analyses will be conducted to investigate potential sources of heterogeneity and to determine whether the association between familial risk factors and thyroid cancer differs across specific groups. Planned subgroup analyses include:

- Degree of relatedness: Comparing risk estimates for first-degree relatives (parents, siblings, children) versus more distant relatives.
- Maternal vs. paternal lineage: Assessing whether the risk differs based on whether the affected family member is on the maternal or paternal side.
- Geographic region: Comparing results across different countries or regions to evaluate geographic variability in familial risk.
- Demographic factors: Where data permit, subgroup analyses by age group, sex, and ethnicity will be conducted.
- Lifestyle and environmental factors: If sufficient data are available, analyses will be stratified by the presence of additional risk factors (e.g., radiation exposure, benign thyroid conditions).

Interaction tests (where possible) will be used to assess the statistical significance of subgroup differences. All subgroup analyses will be pre-specified and interpreted cautiously, considering the potential for confounding, multiple testing, and chance findings, as recommended by the Cochrane Handbook and relevant methodological literature.

Sensitivity analysis To assess the robustness of our findings, the following sensitivity analyses will be conducted:
1- Influence of Study Quality:
Repeat the meta-analysis excluding studies with a high risk of bias (as determined by Newcastle-Ottawa Scale scores <6).
Compare results from high-quality studies with those from lower-quality studies.
2- Statistical Model Selection:
Re-run analyses using both fixed-effects and random-effects models to evaluate consistency of pooled effect estimates.
3- Publication Bias Impact:
Perform a sensitivity analysis using the "trim-and-fill" method if funnel plot asymmetry or Egger's test ($p < 0.1$) indicates potential publication bias.
4- Leave-One-Out Analysis:
Sequentially exclude individual studies to assess their influence on overall effect size and heterogeneity (I^2).
5- Cumulative Meta-Analysis:
Add studies chronologically to evaluate how evidence evolves over time and identify shifts in effect size trends.
6- Definitional Variability:
Stratify analyses based on how "family history" is defined (e.g., first-degree relatives only vs. broader definitions).
7- Geographic Subgroups:
Exclude studies from regions with outlier incidence rates (e.g., high-income vs. low-income countries) to assess geographic consistency.

These analyses adhere to the PRISMA guidelines and recommendations outlined in the Cochrane Handbook, ensuring methodological rigor and transparency. Results will be interpreted cautiously, with emphasis on consistency across models and subgroup findings.

Country(ies) involved USA and Saudi Arabia.

Keywords Thyroid cancer; Family history; Genetics; Geographic trends; Relative risk.

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