# Childhood and adolescent factors and thyroid cancer incidence in adult women in the Sister Study cohort

**Running title: Early-life factors and thyroid cancer incidence**

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# Abstract (316 words)

**Background:** The etiology of thyroid cancer, primarily differentiated thyroid cancer (DTC), remains largely unclear. As DTC is often diagnosed at relatively young ages and predominantly in women, we aimed to investigate the association between childhood and adolescent factors and subsequent DTC incidence in women.

**Methods**: We examined data from 47913 women who were cancer-free at baseline (2003–2009) in the U.S. nationwide cohort Sister Study. We used Cox regression models to assess associations between baseline self-reported perceived body size, reproductive, lifestyle, and socioeconomic factors during childhood and adolescence and DTC incidence during follow-up. The models were adjusted for attained age (timescale), and race/ethnicity.

**Results**: The median age at baseline was 55.4 (interquartile range: 48.9‑62.1). Over the follow-up (median: 13.1 years), 239 DTC cases were identified. Factors associated with a higher DTC incidence included being taller than peers at age 10 (hazard ratio [HR] = 1.41, 95% confidence interval [CI] 1.06-1.89), being lighter (HR=1.37, 95%CI 0.97-1.91) or heavier (HR=1.28, 95%CI 0.96-1.71) than peers during teen years, and ever not having enough to eat during childhood (HR=1.67, 95%CI 1.15–2.43). Conversely, we observed lower incidence in women who ever used hormonal birth control, regardless of start age (before 20: HR=0.72, 95%CI 0.50-1.05) and after 20: HR=0.69, 95%CI 0.48-1.00), and in those who had higher household education level at age 13 (bachelor’s degree or higher vs high school, or less: HR=0.75, 95%CI 0.55-1.03). These associations remained consistent when adjusted simultaneously and when stratifying by baseline BMI and adult socioeconomic factors, except for the association of being lighter than peers during teen years, which attenuated in women with a baseline BMI of 30 or more. We found no significant associations for other childhood and adolescent factors.

**Conclusions**: Our findings suggest that early-life growth-related factors, but not reproductive factors, may influence the development of thyroid cancer in women. Further research with objective measurements of anthropometric factors and growth-related hormones is warranted.

# Introduction

Thyroid cancer ranks as the fifth most common cancer in women globally.1 Few modifiable risk factors have been identified, apart from obesity and childhood exposure to ionizing radiation.2 Given the slow growth of most thyroid nodules,3,4 the relatively young age at diagnosis compared to other cancers,2 and the higher incidence in women compared to men starting from early adolescence,5 biological factors contributing to thyroid cancer development may originate at a very young age.

Thyroid cancer is well known to be hormone sensitive. During childhood and adolescence, particularly during puberty, women experience significant changes in levels of sex steroid hormones,6 growth hormone,7 insulin-like growth factor-1 (IGF-1),8,9 which contribute to sexual development, and changes in growth and body composition. These hormones have been shown to promote the growth of both benign and malignant thyroid cells,10-12 with thyroid tumors also commonly overexpressing estrogen,13 and insulin-like growth factor receptors.14 Body size and reproductive factors during these developmental periods may serve as proxies for these early-life hormonal exposures and have been associated with several female-predominant cancers.15-17

However, the scarcity of longitudinal studies with data on both early-life factors and thyroid cancer incidence makes it challenging to investigate these associations. To date, the few longitudinal studies examining early-life body size and thyroid cancer incidence18-21 have suggested positive associations for childhood and adolescent height and body mass index (BMI), but most of them did not account for adult obesity.18-20 Evidence on early-life reproductive factors is mostly limited to age at menarche, with inconsistent results,22-25 while data on other factors, such as age at breast development, start age for hormonal birth control, are scarce. Additionally, lifestyle (e.g., smoking) and socioeconomic factors, which are known to influence hormone levels either directly or by increasing exposure to endocrine disruptors,26,27 could also contribute to drive thyroid cancer incidence.

Therefore, we aimed to investigate the associations of childhood and adolescent – anthropometric, reproductive, lifestyle, and socioeconomic factors through age 20 and thyroid cancer incidence, using data from the large U.S. nationwide cohort Sister Study. We hypothesized that factors that reflect early-life exposure to high levels of sex steroid hormones, growth hormone, and IGF-1, would be associated with an increased risk of thyroid cancer, specifically differentiated thyroid carcinoma (DTC), which accounts for >90% of all cases.

# Methods

**Study population**

The study design, data collection, and outcome measurements of the Sister Study cohort have been previously described.28 Briefly, the Sister Study is a U.S. nationwide prospective cohort of 50,884 women aged 35–74 at the time of enrollment (2003–2009). All participants had a sister with breast cancer but were breast cancer-free themselves at baseline. Baseline data were collected from self-administered questionnaires and computer-assisted telephone interviews. Anthropometric measurements and biospecimens were obtained via in-person home visits. Participants were recontacted every 2-3 years for health and lifestyle updates, with response rates consistently exceeding 85%.29 All participants provided written informed consent, and the National Institutes of Health's institutional review board approved the study. Data are complete through mid-September 2021 (data release 11.1).

We excluded individuals who had a history of invasive cancer (n=2911) or chemotherapy or radiotherapy for cancer (n=55) before baseline, and those who withdrew from the study (n=5). After exclusions, the study population comprised 47,913 individuals (**Figure 1**).

**Outcome definition:**

By the end of follow-up in mid-September 2021, 252 first primary thyroid cancer diagnoses were reported. Of these, 188 (74.6%) were confirmed through medical records/pathology reports (n=187) or National Death Index/death certification/next of kin (n=1). To restrict the case group to DTCs, we further excluded poorly differentiated thyroid carcinoma (confirmed with pathology reports; n=5), anaplastic thyroid carcinoma (histology code: 8021; n=1), medullary thyroid carcinoma (histology codes: 8346, 8347, 8510, n=5), and indeterminate histology (histology code: 8265, 9084, n=2). DTC cases with confirmed histology codes (n=174) were further classified as papillary thyroid carcinomas (histology codes: 8050, 8260, 8340-8344, 8350, 8450-8460, n=164), follicular thyroid carcinomas (histology codes: 8290, 8330-8335, n=7), or unspecified carcinomas and neoplasms (histology code: 8000, 8010, n=3).

**Exposure definition:**

Self-reported childhood and adolescent factors were ascertained with baseline questionnaires. Anthropometry and reproductive factors included relative weight (lighter/same weight/heavier) and height (shorter/same height/taller) compared to peers at age 10, relative weight (lighter/same weight/heavier) compared to peers during teen years, age reached full adult height (continuous), age at breast development (continuous, categorized as less than 11 years of age/11-13 years of age/14 years of age or more/unknown), age at menarche (continuous, categorized as less than 12 years of age/12-14 years of age/14 years of age or more/unknown), start age for hormonal birth control (categorized as never used birth control/started before 20 years of age/started at 20 years of age or older/unknown birth control status). For age at breast development and age at menarche, we considered responses indicating age 21 or older as implausible and assigned missing values to those individuals. Lifestyle factors included physical activity between age 5 and 20 measured in average MET-hours per week (continuous, categorized as less than 21 MET-hours, 21-<42 MET-hours, 42 MET-hours or more, unknown; calculated based on the reported average weekly hours of sports/exercise activities done at least once a week for two or more months), age started drinking regularly (never drinker/before 20 years of age/20 years of age or older/unknown), number of drinks per year in the years drank between age 5 and 20 (0 drinks/less than 60 drinks, 60-229 drinks, 230 drinks or more, unknown), age started smoking (never smoker/started between age 1 and 20/started after age 20/unknown smoking status), number of pack-years between age 1 and 20 (5 pack-years or less/more than 5 pack-years), and total years of secondhand smoking under age 18 from caregiver or other household member (no secondhand smoking during childhood/10 years or less/more than 10 years/unknown). Socioeconomic status during childhood and adolescence was determined by family income while growing up (well off/middle income/low income/poor/unknown), ever not having enough to eat during childhood (yes/no/unknown), highest household education level at age 13 (high school or GED or less/some college or associate or technical degree/bachelor's degree or higher/unknown), household composition at age 13 (two parents/single parent/unknown), and childhood residence (urban, suburban, small town (combined for analysis)/rural areas/unknown).

**Baseline covariates**

In-person measurements of weight and height at baseline were used to calculate BMI (weight in kilograms divided by the square of height in meters). Information on other characteristics, including age, self-identified race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Non-Hispanic all other races, Unknown), personal education level (high school or GED or less/some college or associate or technical degree/bachelor's degree or higher/unknown), and household annual income (<$50,000/$50,000-$99,999/$100,000+) were assessed during the computer-assisted telephone interview.

**Statistical analysis**

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with attained age as the time scale and self-reported race/ethnicity as covariates. Follow-up time was calculated from age at baseline to age at first diagnosis of invasive cancer (excluding non-melanoma cancer), death, loss of follow-up, or mid-September 2021, whichever occurred first, unless otherwise specified. Missing data were excluded from analyses of continuous variables. We assessed proportional hazards assumptions with plots of scaled Schoenfeld residuals against attained age, and formal testing included introducing an interaction term between exposures and attained age. No evidence of violation was found. We found no evidence of departure from linearity for the association between continuous variables and DTC incidence using with Martingale residuals.

We considered health- and medical surveillance-related factors during adulthood as potential modifying factors for the associations between childhood and adolescent factors and DTC incidence. Therefore, we conducted stratified analyses by baseline examiner-measured BMI, personal education level, and household annual income.

The impact of early-life carcinogenic exposures on early- and late-onset DTCs, defined as diagnoses before and after 50 years of age, may vary. Therefore, we conducted a sensitivity analysis assessing early- and late-onset DTCs separately. For the late-onset DTC analysis, we restricted the study population to individuals aged 50 years or more at baseline. For the early-onset DTC analysis, we included only individuals under 50 at baseline, with the 50th birthday added as an additional endpoint for follow-up. We also performed sensitivity analyses restricted to medically confirmed DTC cases, and papillary thyroid carcinomas, separately. We accounted for competing risks (i.e., death and diagnosis of invasive cancer other than thyroid and non-melanoma cancers) using Fine-Gray models. Lastly, we calculated E-values for both the observed association estimates and the limit of the confidence interval closest to the null. The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome, conditional on the measured covariates, to fully explain the observed associations.

Data analyses were conducted using SAS 9.4 and R version 4.3.1.

# Results

The median age at baseline was 55.4 years (interquartile range [IQR]: 48.9-62.1). **Table 1** presents the baseline descriptive statistics. Most women were non-Hispanic White (n=39,863, 83.4%), and 61.7% (n=29487) were categorized as having a BMI over 25. Over half of the participants held a bachelor's degree or higher (n=24,408, 51.1%), while 33.7% reported a household annual income of $100,000 or more (n=16,108).

**Table 2** shows multivariable-adjusted HRs for childhood and adolescent factors and DTC incidence. During the follow-up (median 13.1 years, interquartile range, IQR 11.5-15), there were 239 reported cases of incident DTC. Being taller than peers at age 10 was associated with DTC incidence (HR=1.41; 95%CI 1.06–1.89). Women who were either lighter (HR=1.37, 95%CI 0.97-1.91) or heavier (HR=1.28, 95%CI 0.96-1.71) than peers during teen years had higher DTC incidence, although the associations were not statistically significant. Women who ever used hormonal birth control had a lower incidence of DTC, with no variation in risk estimates for those starting before (HR=0.72, 95%CI 0.50-1.05) or after 20 years of age (HR=0.69, 95%CI 0.48-1.00). Ever not having enough to eat during childhood was associated with a higher DTC incidence (HR=1.67, 95%CI 1.15–2.43). Conversely, women from households where the highest education level at age 13 was a bachelor’s degree or higher had a lower DTC incidence (HR=0.75, 95%CI 0.55-1.03) compared to those with high school education or GED or less as the highest household education level. Other anthropometry, reproductive, lifestyle, and socioeconomic factors were not associated with DTC incidence.

Risk estimates remained consistent when simultaneously adjusting for relative height compared to peers at age 10, relative weight compared to peers during teen years, ever not having enough to eat during childhood, and highest household education level at age 13. Further adjustment for other childhood socioeconomic factors showed a more pronounced association for ever not having enough to eat during childhood (HR=1.92, 95%CI 1.26-2.90) (**Table 3**). All associations remained consistent across baseline socioeconomic status and BMI strata (p-interactions>0.05, **Supplementary Figure 1**), except the association for relative weight compared to peers during teen years which varied according to baseline BMI (p-interaction=0.03).

We further examined the joint association between relative weight compared to peers during teen years and baseline BMI on DTC incidence (**Figure 2, Supplementary table 1**). The reference group was women with a baseline BMI under 25 who reported having same teenage weight as peers. Among women with a baseline BMI under 25, both being lighter (HR=2.70, 95%CI 1.61-4.50) or heavier (HR=2.34, 95%CI 1.06-5.13) compared to peers during teen years were associated with higher DTC incidence. For those with a baseline BMI over 25, we observed increased DTC incidence regardless of relative weight compared to peers during teen years, except those with a lighter weight compared to peers during teen years and a baseline BMI over 30 (9 cases, HR=1.55, 95%CI 0.70-3.41). We repeated these analyses with relative weight compared to peers at age 10 instead of during adolescence and observed similar results (**Supplementary table 2**).

The E-values for the associations between thyroid cancer incidence and being taller than peers at age 10, ever not having enough to eat during childhood, and having a bachelor’s degree or higher as the highest household education level at age 13 were 2.18, 2.73, and 1.99, respectively. The association for relative height compared to peers at age 10, ever not having enough to eat during childhood, and highest household education level at age 13 appeared to be stronger for early- versus later-onset DTC. The interpretation of the findings did not change when considering competing risk, medically confirmed cases, or papillary histology only (**Supplementary table 3**).

# Discussion

To our knowledge, this is one of the few longitudinal studies on the association between early-life factors and DTC incidence beyond ionizing radiation exposure. The current study found higher DTC incidence associated with perceived early-life body size (i.e., being taller compared to peers at age 10, being lighter or heavier than peers during teen years) and ever not having enough to eat during childhood. In contrast, our study did not show significant associations for most early-life reproductive and hormonal factors, except a lower DTC incidence for those who used hormonal birth control, regardless of start age. Additionally, we observed a lower DTC incidence among individuals with higher household education levels at age 13. These associations generally did not vary according to baseline BMI and socioeconomic status.

Few longitudinal studies have examined early-life body size and DTC incidence. In a population-based cohort of children and adolescents in Denmark with a median follow-up of 38.6 years, taller height and greater BMI measured at every age between 7 and 13 were associated with higher adult thyroid cancer incidence. The associations for BMI were generally stronger for those diagnosed at younger ages.18 Similarly, data from an Israeli nationwide cohort showed positive associations between increased height19 and BMI20 measured at ages 16-18 and thyroid cancer incidence after mean follow-up periods of 10 and 19 years, respectively. However, these studies did not account for adult anthropometric factors, which limits the interpretation of body size effects at different life stages.18-20

In our study, we observed consistently positive associations for being taller and heavier compared to peers during childhood and adolescence across adult BMI categories, with particularly strong associations in women with a baseline BMI of 30 or more. These findings suggest that large body size at any time, starting from early life, may influence DTC incidence, with potential cumulative effects throughout the life course.

On the other hand, our study also found a higher DTC incidence among women who reported being lighter than peers during childhood and adolescence and those who reported ever not having enough to eat during childhood. These observations suggest the involvement of mechanisms beyond excessive adiposity. Before the U.S. obesity epidemic began in the late 1970s,30 being lighter than peers and ever not having enough to eat in early life could have indicated lower socioeconomic status,31 which is often associated with increased exposure to environmental and lifestyle risk factors for cancer.27 However, in our study, these associations either persisted or were more pronounced after adjusting for both childhood and adult socioeconomic factors, suggesting that socioeconomic status may not be the primary driver. Another plausible explanation is that being lighter than to peers during childhood and adolescence and ever not having enough to eat during childhood could be associated with hormonal imbalances and growth disruptions,32 specifically variations in growth hormone and IGF-1 levels, which may contribute to thyroid cancer development.

IGF-I has been suggested to involve in carcinogenesis given its role in cell proliferation, differentiation, metabolism, and apoptosis, and in angiogenesis.33 Experimental studies have found that IGF-1 is more highly expressed in thyroid cancer than in normal tissues and benign lesions.34 Moreover, there has been extensive evidence of increased risk of thyroid cancer in individuals with elevated growth hormone/IGF‑1 signaling, such as patients with acromegaly.35,36 Recent large European population-based studies have further showed a positive association between adult IGF-1 levels and subsequent thyroid cancer risk.37,38 However, there is limited epidemiological evidence on IGF-1 and growth hormone levels in early life. Future studies with objective longitudinal measurements of early-life anthropometric factors, IGF-1, and growth hormone levels are warranted to confirm our findings and elucidate the underlying mechanisms.

Experimental studies have demonstrated that estrogen not only directly stimulates growth in both benign and malignant thyroid cells, but also potentially simulates the tyrosine kinase signaling pathways MAPK and PI3K and plays a role in angiogenesis regulation for thyroid cancer.12 In the current study, we did not find any significant association for factors reflecting early-life early or delayed exposure to endogenous sex steroid hormones, including age at menarche and age at breast development. This finding aligns with some,24,25 but not all,22,23 previous studies. However, we observed lower risks associated with the use of hormonal birth control regardless of start age (before or after 20). Previous studies have shown inconsistent results on the associations for hormonal birth controls,22-25 which could be due to the evolving formulations of birth controls over the years, and the duration of use. In the Sister Study, most individuals (99.4%) who started hormonal birth control before age 20 used combined oral contraceptive, and given the cohort periods, possibly the first generation of birth controls.

Strengths of this study include the large sample size, long follow-up, and wide range of childhood and adolescent exposures. We were able to control for potential mediating factors could influence the likelihood of incidental detection of thyroid cancer, such as baseline BMI, household annual income, and education levels; except for interaction between early life body size and baseline BMI, accounting for these factors had little impact on our results.

The current study has several limitations. As the Sister Study enrolled exclusively women with a sister diagnosed with a breast cancer, the results may not be generalizable to men or to women without a family history of breast cancer. The data, collected between 1930s and 1970s, may not reflect modern context, considering that the lifestyles and environmental exposures during early life and young adulthood changed substantially over time. For example, the earlier timing of the study data is likely to be less exposed to obesogenic diet, lifestyle, and environmental factors that have become more commonplace since the late 1970s.39 Owing to the reliance on personal recollection on childhood and adolescent exposures as the main source of data, assessment of early-life exposures may be prone to recall and misclassification bias. Although we found high E-values of the analyses concerning early life body size, ever not having enough to eat during childhood, and highest household education level at age 13, which indicate that additional unmeasured confounding associated with early-life factors and thyroid cancer incidence by a HR of at least 2 to 3-fold each would be necessary to explain the observed associations, the absence of information on diet during childhood and adolescence is an important limitation. Lastly, we did not have information on exposure to ionizing radiation in childhood of thyroid cancer, but it is unlikely to be a strong confounder as it is not associated with childhood and adolescent exposures.

# Conclusion

In conclusion, the current study supports the influence of early-life exposures, including perceived body size, ever not having enough to eat, and higher household education levels, on subsequent DTC incidence. These findings offer further insights into understanding the DTC early age at diagnosis, which may involve altered growth-related hormone levels.

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# Author Contribution statement

T.V.T.T. contributed to the analysis, interpretation, drafting of the article, and approval of the final version; C.M.K. contributed to the concept, interpretation, critical review of the manuscript, and approval of the final version; K.O., R.T., and D.S. contributed to the interpretation, critical review of the manuscript, and approval of the final version.

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