# 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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**Keywords**: Thyroid neoplasms, incidence, childhood exposures, adolescent exposures, risk factors, observational study

**Word count**: 3427

# Abstract (short version, 189 words)

The etiology of differentiated thyroid cancer (DTC), which is diagnosed predominantly in women, remains largely unclear. This study investigated the association between childhood and adolescent factors and subsequent DTC incidence in women using data from 47,913 cancer-free women at baseline (2003–2009) in the U.S. nationwide Sister Study cohort. We used Cox regression models to assess associations for DTC and baseline self-reported information, including perceived body size, hormonal, lifestyle, and socioeconomic factors through age 20, adjusting for attained age (timescale), and race/ethnicity. Over 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). Moreover, we observed lower incidence in women who had higher household education levels at age 13 (HRBachelor’s degree or higher vs high school, GED or less=0.75, 95%CI=0.55-1.03). We found no significant associations for other factors. Our findings suggest that early-life growth-related factors may influence the development of DTC in women.

# 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 suggest that biological factors contributing to thyroid cancer development may originate at a very young age.

During childhood and adolescence, particularly during puberty, women experience significant changes in levels of sex steroid hormones,6 growth hormone,7 and 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 either represent or 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 incidence have suggested positive associations for childhood and adolescent height and body mass index (BMI),18-21 but most of them did not account for adult obesity at diagnosis.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 and start age for hormonal birth control, are scarce. Additionally, lifestyle (e.g., smoking) and socioeconomic factors known to influence hormone levels either directly or by increasing exposure to endocrine disruptors,26,27 could also contribute to promoting thyroid cancer incidence.

We aimed to investigate the associations of anthropometric, reproductive, lifestyle, and socioeconomic factors experienced during childhood and adolescence 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 higher rates of thyroid cancer, specifically differentiated thyroid carcinoma (DTC), which accounts for 95% of all cases.28

# Methods

**Study population**

The Sister Study is a U.S. nationwide prospective cohort of 50,884 women aged 35–74 at the time of enrollment (2003–2009).29 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%.30 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=2,911) 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.

**Outcome definition**

By the end of follow-up, 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 (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 thyroid cancer of indeterminate histology (histology code: 8265, 9084, n=2). We further classified DTC cases with confirmed histology codes (n=174) 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) to peers at age 10, relative weight (lighter/same weight/heavier) to peers during teen years, 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/12-13 years of age/14 years of age or more/unknown), age started using hormonal birth control (categorized as never used birth control before 20 years of age/started before 20 years of age /unknown birth control status). Responses for age at breast development and age at menarche 21 or older were assigned missing values.

Lifestyle factors included physical activity between age 5 and 20 measured in average metabolic equivalent of task (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),31 age started drinking regularly (never drank before 20 years of age/started before 20 years of age/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; calculated based on the reported average drinks per week),32 age started smoking (never smoked before 20 years of age/started between age 1 and 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), family type at age 13 (two parents/single parent/unknown), and childhood residence (urban, suburban, small town (combined for analysis)/rural areas/unknown).

Missing data were less than 5% for all variables except for number of drinks per year between age 5 and 20 (9.3%). For continuous variables, we imputed the missing data using mean values.

**Baseline covariates**

Baseline examiner-measured BMI was calculated using in-person measurements of weight and height, i.e., weight in kilograms divided by the square of height in meters. Demographic and socioeconomic characteristics, including age, self-identified race/ethnicity (non-Hispanic White/non-Hispanic Black/Hispanic/non-Hispanic all other races/unknown), personal attained 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 collected through 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 a covariate. Follow-up time was calculated from age at baseline until age at DTC diagnosis, with censoring at age at first diagnosis of any other invasive cancer (excluding non-melanoma cancer), death, loss of follow-up, or mid-September 2021, whichever occurred first, unless otherwise specified. 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 assessed non-linearity in the association between continuous variables and DTC incidence by visually inspecting plots of Martingale residuals against each variable and found no evidence of departure from linearity.

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 BMI, personal attained education level, and household annual income. Tests for multiplicative interactions were conducted by including a cross‐product term in the model and evaluating the F‐test‐based P‐value. P‐values were two‐sided with an alpha of 0.05.

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. Hence, we performed a sensitivity analysis assessing early- and late-onset DTCs separately. For the early-onset DTC analysis, we included only individuals under 50 at baseline, and censored them at 50 years. For the late-onset DTC analysis, we accounted for follow-up time both after individuals turned 50 during the study and for those who aged 50 years or more at baseline. We also performed sensitivity analyses restricted to medically confirmed DTC cases, and papillary thyroid carcinomas, separately. 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.33,34

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

# Results

**Table 1** presents the baseline descriptive statistics. The median age at baseline was 55.4 years (interquartile range [IQR]: 48.9-62.1). Most women were non-Hispanic White (n=39,947, 83.4%), and 61.7% (n=29,566) had a BMI of 25 or more. Over half of the participants held a bachelor's degree or higher (n=24,450, 51.0%), while 33.7% reported a household annual income of $100,000 or more (n=16,161).

**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. Ever not having enough to eat during childhood was associated with a higher DTC incidence (HR=1.67, 95%CI 1.15–2.43). Moreover, 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.

Early-life socioeconomic characteristics may be interrelated and could influence childhood and adolescent body size. Therefore, we performed two models: (1) one adjusted simultaneously for height relative to peers at age 10, weight relative to peers during teen years, ever not having enough to eat during childhood, and highest household education level at age 13, and (2) another model adjusted for family income while growing up, household composition at age 13, and childhood residence in addition to all previously mentioned variables. The risk estimates remained consistent, except for a more pronounced association for ever not having enough to eat during childhood (HR=1.92, 95%CI 1.26-2.90) when further adjusted for other childhood socioeconomic factors (**Table 3**).

All associations remained consistent across baseline socioeconomic status and BMI strata (p-interactions>0.05, **Supplementary Figure 1**), except the association for weight relative to peers during teen years which varied according to baseline BMI (p-interaction=0.03). The higher DTC incidence for being lighter or heavier than peers during teen years were more pronounced in women with a baseline BMI under 25.

Therefore, we further examined the joint association between weight relative to peers during teen years and baseline BMI on DTC incidence (**Figure 1, 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, being either 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 women with a baseline BMI of 30 or more, compared to the reference group, we did not observe a higher incidence of DTC for those who were lighter than their peers (HR=1.55, 95%CI 0.70-3.41). However, women who had the same weight as their peers (HR=3.00, 95%CI 1.75-5.12) or were heavier (HR=3.13, 95%CI 1.79-5.48) had notable higher incidences. We repeated these analyses with relative weight to peers at age 10 instead of during teen years 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, indicating that an HR of at least 2 to 3-fold for any unmeasured confounders associated with early-life factors and thyroid cancer would be necessary to explain the observed associations. The association for weight relative to peers during teen years, ever not having enough to eat during childhood, and highest household education level at age 13 remained consistent regardless of early- or late-onset DTC. Meanwhile, the association for relative height compared to peers at age 10 appeared to be stronger for early- versus later-onset DTC. The interpretation of the findings did not change when considering medically confirmed cases, or papillary histology only (**Supplementary table 3**).

# Discussion

To our knowledge, this is one of the few longitudinal studies of the association between early-life factors and DTC incidence beyond childhood exposure to ionizing radiation. The current study found higher DTC incidence associated with perceived early-life body size - specifically being taller compared to peers at age 10, being lighter or heavier than peers during teen years - as well as ever not having enough to eat during childhood. We also observed a potentially lower DTC incidence among individuals with a higher level of household education at age 13. Our study did not show any associations for early-life reproductive factors. We were able to account for potential mediating factors in adulthood such as baseline BMI, household annual income, and education levels. We noted possible interactions between weight relative to peers during teen years and baseline BMI while there was no variation by socioeconomic factors.

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 39 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 greater 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. The associations for being heavier than peers during these periods were stronger in women with a baseline BMI of 30 or more (e.g., HRduring teen years=3.13, 95%CI 1.79-5.48) than in those with a baseline BMI between 25-29.9 (HRduring teen years=1.89, 95%CI 0.91-3.95) or under 25 (HRduring teen years=2.34, 95%CI 1.06-5.13) (**Supplementary tables 1-2**). 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,35 being lighter than peers and ever not having enough to eat in early life could have indicated lower socioeconomic status,36 which is often associated with greater 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 involves suboptimal nutritional exposures in early life, including nutritional deficiencies, and physiological adaptive responses. Currently, there is limited epidemiological data on thyroid cancer incidence and early-life nutritional deficiencies, as most studies have focused on adult dietary intake, yielding mixed findings regarding the intake of certain macro- (e.g., polyunsaturated fat, sugar) and micronutrients (e.g., iodine, and selenium).37 Suboptimal nutrition in early life may also trigger adaptive epigenetic changes,38 and hormonal imbalances and growth disruptions,39 specifically variations in growth hormone and IGF-1 levels. Notably, while high IGF-1 levels during childhood, which reflect nutritional status, are typically associated with taller stature and heavier weight,40 some evidence suggests that early-life acute exposure to caloric restriction may result in higher IGF-1 levels in adulthood,41 which could contribute to the development of thyroid cancer.

IGF-I has been suggested to influence carcinogenesis given its role in cell proliferation, differentiation, metabolism, and apoptosis, and in angiogenesis.42 Experimental studies have found that IGF-1 is more highly expressed in thyroid cancer than in normal tissues and benign lesions.43 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.44,45 Recent large European population-based studies have further showed a positive association between adult IGF-1 levels and subsequent thyroid cancer risk,.46,47 however, there is limited epidemiological evidence of how IGF-1 and growth hormone levels in early life may affect cancer later in 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.

In the current study, we did not find any significant association for factors reflecting early or delayed exposure to endogenous sex steroid hormones early in life, including age at menarche and age at breast development in agreement with some,24,25 but not all,22,23 previous studies. We also did not observe any association with age started hormonal birth control. Previous studies have shown inconsistent results on the associations for hormonal birth control,22-25 which could be due to the variability in the duration of use and the evolving formulations of birth controls over the years. In the Sister Study, most individuals (99.4%) who started hormonal birth control before age 20 used combined oral contraceptive. These individuals were likely exposed to early formulations in the 1960s with high dose of estrogen up to 150 μg of mestranol,48 compared to current formulations, which contain as low as 20 μg of ethinyl estradiol.49 Experimental studies have demonstrated that estrogen not only directly stimulates growth in both benign and malignant thyroid cells, but potentially simulates the tyrosine kinase signaling pathways MAPK and PI3K and plays a role in angiogenesis regulation for thyroid cancer.12

Strengths of this study include the large sample size, long follow-up, and wide range of childhood and adolescent exposures. The current study also has several limitations. First, 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. However, there is limited evidence to suggest that family history of breast cancer influences thyroid cancer incidence. Second, we started the follow-up at baseline, excluding women who had previously diagnosed with DTC, which could potentially lead to missing associations for early-onset DTC. However, most associations in our study remained consistent for early- or late-onset cancers. Additionally, the age at baseline of the study population (median [interquartile range]: 55.4 [48.9, 62.1]) captured the most relevant period when DTC incidence peaks.5 Third, the data, referring to the period between 1930s and 1970s, may not be generalizable to modern-day populations in or outside the United States, considering that some childhood and adolescent lifestyle and environmental exposures have changed substantially over time and place. For example, obesogenic diet, lifestyle, and environmental factors have become more commonplace since the late 1970s.50,51 Owing to the reliance on personal recollection of childhood and adolescent exposures as the main source of data, assessment of early-life exposures may be prone to recall and misclassification, although any bias would be unlikely to differ by early-life exposures or cancer diagnosis that occurred after participant reporting. Although we were missing information on some potential confounders (e.g., diet during childhood and adolescence), our assessment of E-values showed that their effects would have to be large to strongly influence results. Lastly, we did not account for exposure to ionizing radiation in childhood, but it is unlikely to be a strong confounder as we would not expect it to be associated with the childhood and adolescent exposures examined in the current study.

# 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 during the childhood and adolescent years.

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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.

All authors have no disclosure to report.

# Funding statement

This research was funded by the Intramural Research Program of the National Cancer Institute, and the Intramural Research Program of the National Institute of Environmental Health Sciences, National Institutes of Health (Z1AES044005 to D.P.S.).

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