# 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 (short version, 199 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 cohort Sister Study. We used Cox regression models to assess associations for baseline self-reported perceived body size, hormonal, lifestyle, and socioeconomic factors through age 20, adjusting for attained age (timescale), and race/ethnicity. 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 started hormonal birth control before 20 (HRvs never-users=0.72, 95%CI=0.50-1.05), and in those 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 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 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 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.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 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 (**Figure 1**).

**Outcome definition:**

By the end of follow-up (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). 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 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/12-13 years of age/14 years of age or more/unknown), age started using 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).

For age started using hormonal birth control, age started drinking regularly, and age started smoking, we considered exposures only through age 20 and excluded individuals who reported starting at 20 years of age or older in our analyses.

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**

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 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 covariate. Follow-up time was calculated from age at baseline to age at first diagnosis of any 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 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. Hence, we performed 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. 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.31,32

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. Women who started hormonal birth control before age 20 had a lower incidence of DTC (HR=0.73, 95%CI 0.49-1.07). 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 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. Further adjustment for other childhood socioeconomic factors (i.e., family income while growing up, household composition at age 13, and childhood residence) 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 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 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, 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. 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 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 childhood exposure to ionizing radiation. 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 factors, except a lower DTC incidence for those who started hormonal birth control before 20. Additionally, we observed a lower DTC incidence among individuals with a higher level of household education at age 13. These associations did not vary according to baseline BMI and socioeconomic status, except the stronger association for weight relative to peers during teen years in women with a baseline BMI under 25.

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,33 being lighter than peers and ever not having enough to eat in early life could have indicated lower socioeconomic status,34 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).35 Suboptimal nutrition in early life may also trigger adaptive epigenetic changes,36 and hormonal imbalances and growth disruptions,37 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,38 some evidence suggests that early-life acute exposure to caloric restriction may result in higher IGF-1 levels in adulthood,39 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.40 Experimental studies have found that IGF-1 is more highly expressed in thyroid cancer than in normal tissues and benign lesions.41 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.42,43 Recent large European population-based studies have further showed a positive association between adult IGF-1 levels and subsequent thyroid cancer risk.44,45 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. 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,46 compared to current formulations, which contain as low as 20 μg of ethinyl estradiol.47

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 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.48,49 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 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.

# References

1 Ferlay J, E. M., Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. *Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer*, <https://gco.iarc.fr/today> Accessed December 29, 2023, (2020).

2 Kitahara, C. M. & Schneider, A. B. Epidemiology of Thyroid Cancer. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **31**, 1284-1297 (2022).

3 Durante, C. *et al.* The natural history of benign thyroid nodules. *Jama* **313**, 926-935 (2015).

4 Angell, T. E. *et al.* Differential Growth Rates of Benign vs. Malignant Thyroid Nodules. *The Journal of clinical endocrinology and metabolism* **102**, 4642-4647 (2017).

5 Surveillance Research Program, N. C. I. *SEER\*Explorer: An interactive website for SEER cancer statistics [Internet]*, <https://seer.cancer.gov/statistics-network/explorer/> Accessed April 17, 2024.

6 Frederiksen, H. *et al.* Sex-specific Estrogen Levels and Reference Intervals from Infancy to Late Adulthood Determined by LC-MS/MS. *The Journal of clinical endocrinology and metabolism* **105**, 754-768 (2020).

7 Toublanc, J. E. Modifications of growth hormone secretion during female puberty. *Ann N Y Acad Sci* **816**, 60-75 (1997).

8 Savage, M. O., Smith, C. P., Dunger, D. B., Gale, E. A., Holly, J. M. & Preece, M. A. Insulin and growth factors adaptation to normal puberty. *Horm Res* **37 Suppl 3**, 70-73 (1992).

9 Löfqvist, C., Andersson, E., Gelander, L., Rosberg, S., Blum, W. F. & Wikland, K. A. Reference Values for IGF-I throughout Childhood and Adolescence: A Model that Accounts Simultaneously for the Effect of Gender, Age, and Puberty. *The Journal of Clinical Endocrinology & Metabolism* **86**, 5870-5876 (2001).

10 Manole, D., Schildknecht, B., Gosnell, B., Adams, E. & Derwahl, M. Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. *The Journal of clinical endocrinology and metabolism* **86**, 1072-1077 (2001).

11 Dumont, J. E., Maenhaut, C., Pirson, I., Baptist, M. & Roger, P. P. Growth factors controlling the thyroid gland. *Bailliere's clinical endocrinology and metabolism* **5**, 727-754 (1991).

12 Derwahl, M. & Nicula, D. Estrogen and its role in thyroid cancer. *Endocrine-related cancer* **21**, T273-283 (2014).

13 Yane, K. *et al.* Expression of the estrogen receptor in human thyroid neoplasms. *Cancer letters* **84**, 59-66 (1994).

14 Manzella, L. *et al.* Activation of the IGF Axis in Thyroid Cancer: Implications for Tumorigenesis and Treatment. *Int J Mol Sci* **20** (2019).

15 Hurson, A. N. *et al.* Risk factors for breast cancer subtypes by race and ethnicity: A scoping review. *Journal of the National Cancer Institute* 10.1093/jnci/djae172 (2024).

16 Raglan, O. *et al.* Risk factors for endometrial cancer: An umbrella review of the literature. *International journal of cancer* **145**, 1719-1730 (2019).

17 La Vecchia, C. Ovarian cancer: epidemiology and risk factors. *Eur J Cancer Prev* **26**, 55-62 (2017).

18 Kitahara, C. M., Gamborg, M., Berrington de González, A., Sørensen, T. I. & Baker, J. L. Childhood height and body mass index were associated with risk of adult thyroid cancer in a large cohort study. *Cancer research* **74**, 235-242 (2014).

19 Farfel, A. *et al.* Predictors for thyroid carcinoma in Israel: a national cohort of 1,624,310 adolescents followed for up to 40 years. *Thyroid : official journal of the American Thyroid Association* **24**, 987-993 (2014).

20 Furer, A. *et al.* Adolescent obesity and midlife cancer risk: a population-based cohort study of 2·3 million adolescents in Israel. *The lancet. Diabetes & endocrinology* **8**, 216-225 (2020).

21 Kim, K. N. *et al.* Adolescent overweight and obesity and the risk of papillary thyroid cancer in adulthood: a large-scale case-control study. *Sci Rep* **10**, 5000 (2020).

22 Mannathazhathu, A. S. *et al.* Reproductive factors and thyroid cancer risk: Meta-analysis. *Head Neck* **41**, 4199-4208 (2019).

23 O'Grady, T. J. *et al.* Association of hormonal and reproductive factors with differentiated thyroid cancer risk in women: a pooled prospective cohort analysis. *International journal of epidemiology* **53** (2024).

24 Schubart, J. R., Eliassen, A. H., Schilling, A. & Goldenberg, D. Reproductive Factors and Risk of Thyroid Cancer in Women: An Analysis in the Nurses' Health Study II. *Womens Health Issues* **31**, 494-502 (2021).

25 Abe, J. V. *et al.* Reproductive Factors and Thyroid Cancer Risk: The Multiethnic Cohort Study. *J Womens Health (Larchmt)* 10.1089/jwh.2023.0947 (2024).

26 Gu, F. *et al.* Urinary concentrations of estrogens and estrogen metabolites and smoking in caucasian women. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **22**, 58-68 (2013).

27 Denny, L. *et al.* Social inequalities in cancer risk factors and health-care access. (2021).

28 Lim, H., Devesa, S. S., Sosa, J. A., Check, D. & Kitahara, C. M. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *Jama* **317**, 1338-1348 (2017).

29 Sandler, D. P. *et al.* The Sister Study Cohort: Baseline Methods and Participant Characteristics. *Environ Health Perspect* **125**, 127003 (2017).

30 *Cohort participation status & response rates*, <https://sisterstudy.niehs.nih.gov/English/response-rates.htm> Accessed January 2, 2023.

31 VanderWeele, T. J. & Ding, P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* **167**, 268-274 (2017).

32 Mathur, M. B., Ding, P., Riddell, C. A. & VanderWeele, T. J. Web Site and R Package for Computing E-values. *Epidemiology* **29**, e45-e47 (2018).

33 Fryar, C. D., Carroll, M. D. & Ogden, C. L. Prevalence of overweight, obesity, and extreme obesity among adults: United States, trends 1960–1962 through 2009–2010. *Hyattsville, MD: National Center for Health Statistics* (2012).

34 Bann, D., Johnson, W., Li, L., Kuh, D. & Hardy, R. Socioeconomic inequalities in childhood and adolescent body-mass index, weight, and height from 1953 to 2015: an analysis of four longitudinal, observational, British birth cohort studies. *Lancet Public Health* **3**, e194-e203 (2018).

35 Kitahara, C. M., Schneider, A. B. & Brenner, A. V. 839Thyroid Cancer. In: Michael Thun, Martha S. Linet, James R. Cerhan, Christopher A. Haiman, & David Schottenfeld (eds). *Cancer Epidemiology and Prevention* 10.1093/oso/9780190238667.003.0044 0 (Oxford University Press, 2017).

36 González-Rodríguez, P., Füllgrabe, J. & Joseph, B. The hunger strikes back: an epigenetic memory for autophagy. *Cell Death Differ* **30**, 1404-1415 (2023).

37 Thissen, J. P., Ketelslegers, J. M. & Underwood, L. E. Nutritional regulation of the insulin-like growth factors. *Endocr Rev* **15**, 80-101 (1994).

38 Ong, K., Kratzsch, J., Kiess, W. & Dunger, D. Circulating IGF-I levels in childhood are related to both current body composition and early postnatal growth rate. *The Journal of clinical endocrinology and metabolism* **87**, 1041-1044 (2002).

39 Elias, S. G. *et al.* Long term consequences of the 1944-1945 Dutch famine on the insulin-like growth factor axis. *International journal of cancer* **108**, 628-630 (2004).

40 Pollak, M. N., Schernhammer, E. S. & Hankinson, S. E. Insulin-like growth factors and neoplasia. *Nat Rev Cancer* **4**, 505-518 (2004).

41 Karagiannis, A., Kassi, E., Chatzigeorgiou, A. & Koutsilieris, M. IGF Bioregulation System in Benign and Malignant Thyroid Nodular Disease: A Systematic Review. *In Vivo* **34**, 3069-3091 (2020).

42 Siegel, G. & Tomer, Y. Is there an association between acromegaly and thyroid carcinoma? A critical review of the literature. *Endocr Res* **31**, 51-58 (2005).

43 Dal, J. *et al.* Cancer Incidence in Patients With Acromegaly: A Cohort Study and Meta-Analysis of the Literature. *The Journal of clinical endocrinology and metabolism* **103**, 2182-2188 (2018).

44 Schmidt, J. A. *et al.* Insulin-like growth factor-i and risk of differentiated thyroid carcinoma in the European prospective investigation into cancer and nutrition. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **23**, 976-985 (2014).

45 Knuppel, A. *et al.* Circulating Insulin-like Growth Factor-I Concentrations and Risk of 30 Cancers: Prospective Analyses in UK Biobank. *Cancer research* **80**, 4014-4021 (2020).

46 Piper, J. M. & Kennedy, D. L. Oral contraceptives in the United States: trends in content and potency. *International journal of epidemiology* **16**, 215-221 (1987).

47 Gallo, M. F., Nanda, K., Grimes, D. A., Lopez, L. M. & Schulz, K. F. 20 µg versus >20 µg estrogen combined oral contraceptives for contraception. *Cochrane Database Syst Rev* **2013**, Cd003989 (2013).

48 National Institute of Diabetes and Digestive and Kidney Diseases. *Overweight & Obesity Statistics*, <https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity> Accessed August 08, 2024.

49 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet (London, England)* **403**, 1027-1050 (2024).

# 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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