Prevention and Epidemiology

Childhood Height and Body Mass Index Were Associated with Risk of Adult Thyroid Cancer in a Large Cohort Study

Cari M. Kitahara, Michael Gamborg, Amy Berri

got de González, Thorkild I.A. Sørensen, and Jennifer L. Baker

Abstract

Taller stature and obesity in adulthood have been consistently associated with an increased risk of thyroid cancer, but few studies have investigated the role of childhood body size. Using data from a large prospective cohort, we examined associations for height and body mass index (BMI) at ages 7 to 13 years with risk of thyroid cancer in later life. The study population included 321,085 children from the Copenhagen School Health Records Register, born between 1930 and 1989 in Copenhagen, Denmark, with measurements of height and weight from 7 to 13 years of age. These data were linked with the Danish Cancer Registry to identify incident thyroid cancer cases (1968–2010). Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for age- and sex-specific height and BMI SD scores (SDS) using proportional hazards models stratified by birth cohort and sex. During follow-up (median = 38.6 years), 171 women and 64 men were diagnosed with thyroid cancer. Both height and BMI were positively associated with thyroid cancer risk, and these associations were similar by age at measurement. Using age 10 as an example, HRs per 1 unit increase in SDS for height (–6–7 cm) and BMI (~1.5–2 kg/m²) were 1.22 (95% CI, 1.07–1.40) and 1.15 (95% CI, 1.00–1.34), respectively. These results, together with the relatively young ages at which thyroid cancers are diagnosed compared with other malignancies, suggest a potential link between early-life factors related to growth and body weight and thyroid carcinogenesis. Cancer Res; 74(1); 235–42. ©2013 AACR.

Introduction

Thyroid cancer is the most common endocrine malignancy and accounts for 1.3% of cancer diagnoses and 0.5% of cancer-related deaths worldwide each year (1). Several countries, including Denmark (2), have reported increases in thyroid cancer incidence over the past three decades (3–10), with particularly marked increases observed in more recent years. Enhanced detection of the disease, due in part to more widespread use of imaging technologies and sensitive diagnostic tools, at least partially accounts for the increasing number of thyroid cancers diagnosed each year (11). However, considering the increase in incidence of large, advanced tumors during this time period, thyroid cancer incidence trends may also be attributable to secular changes in certain lifestyle characteristics or environmental exposures (6).

The rising incidence of thyroid cancer in many countries may be partially explained by secular trends in height and weight, which have been observed in Denmark and elsewhere around the world (12–14). Height and body mass index (BMI; weight in kg/height in m²), typically assessed at one point in time during middle-to-older adulthood, have been positively associated with thyroid cancer risk in several observational studies (15–27), with relative risks typically ranging from >1.0 to 1.2 per 5 cm difference in height and 1.1 to 1.3 per 5 kg/m² difference in BMI. The few studies examining body size during childhood and thyroid cancer risk in later life were limited, in part, by the reliance on height and weight recalled much later in life (17, 18, 24, 28), and the results from these studies have been inconsistent. Nonetheless, the relatively young age at diagnosis of thyroid cancer compared with other malignancies (29) suggests that exposures in early life, including those related to growth and body weight, may be involved in thyroid cancer development.

In the Copenhagen School Health Records Register (CSHRR), measurements of weight and height from 7 to 13 years of age were recorded for schoolchildren born in Copenhagen between 1930 and 1989 and linked with thyroid cancer incidence data later in life from the Danish Cancer Registry. Using these data, we prospectively investigated the relationship between height and BMI during childhood and subsequent risk of thyroid cancer.
Materials and Methods

Study population

The CSHRR is a database of school health records on 372,636 children who were born between 1930 and 1989 and attended public or private school in the Copenhagen Municipality (30). The CSHRR includes annual height and weight measures at each age between 7 years and 13 years for nearly all children until the 1983 school year, and, thereafter, children were measured at school entry and exit or more frequently if the child had special health needs. Measurements were conducted by physicians and nurses using standardized procedures. Since 1943, information on birth weight was provided through parental reports at the first school examination and recorded in the health records. In addition, unique government-issued identification numbers are included in the CSHRR database for 329,968 children, enabling linkages to national registers. Because this analysis was register based, consent from individual participants was not required. Approval for the use of these data was obtained through the Danish Data Protection Agency.

From an eligible population of 327,240 participants (165,978 men and 161,262 women) who were alive and living in Denmark at the age of 15 years, we excluded two subjects with a missing date at thyroid cancer diagnosis and three subjects diagnosed with thyroid cancer before the age of 15 years or April 2, 1968 (Fig. 1). We also excluded 6,141 subjects with missing data on height and/or BMI at every age and nine subjects with outlying values of height or BMI [z-score or SD

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Figure 1. Flowchart describing the criteria for eligibility in the analytic study population.
Follow-up

Unique personal identification numbers for each participant were used to link the anthropometric data to the Danish national Cancer Registry for data on thyroid cancer incidence and death (30, 31). Coverage for these registers was virtually complete between April 2, 1968 and December 31, 2010. Thyroid cancer was defined as malignant carcinoma of the thyroid gland (International Classification of Diseases 10 site code C73.9, morphology codes 8010–8021, 8031–8040, 8050–8056, and behavioral code 3). Eight subjects with morphology codes outside the defined range were reclassified as noncases and censored at the time of diagnosis. The following morphology codes were used to define histologic subtypes: papillary (8050, 8260, 8340–8350), follicular (8290, 8330–8335), medullary (8345, 8510–8513), and anaplastic (8020–8021, 8031).

Follow-up began at the age of 15 years or in 1968 when the Danish Civil Registration System was established, whichever occurred last. Subjects were censored at the age of thyroid cancer diagnosis, emigration, death, or the date of the latest cancer registry update on December 31, 2010, whichever occurred first.

Statistical analysis

The associations between anthropometric measures and the risk of total thyroid cancer and histologic subtypes of papillary and follicular thyroid cancer were assessed using Cox proportional hazards regression, using attained age as the time-varying effect of height and BMI by attained age, and no deviations from linearity, examined by modeling quartiles of height and BMI SDSs and by restricted cubic splines with three knot points (not shown). We also analyzed changes in height and BMI SDS between ages 7 and 10 years, 10 and 13 years, and 7 and 13 years adjusting for baseline height or BMI SDS, respectively. Multiplicative interactions by sex were tested by comparing the fit of a model including a cross-product term between height or BMI SDS and sex to a model that did not include this cross-product term using the likelihood ratio test. Results are presented separately by sex to account for differences in growth trajectories during this age period as well as combined. All tests of statistical significance were two sided. Analyses were conducted using Stata statistical software, version 12.1.

Results

During follow-up (median: 38.6 years), 235 subjects (64 men and 171 women) were diagnosed with thyroid cancer. The median age at thyroid cancer diagnosis was 47.1 for women (5th–95th percentiles: 25.2–68.7) and 47.1 for men (5th–95th percentiles: 27.6–70.3). The oldest age at the end of follow-up was 81 years. The main histologic subtypes of thyroid cancer, in order of predominance, were papillary (n = 145 cases; 36 men and 107 women), follicular (n = 60 cases; 13 men and 47 women), anaplastic (n = 16; 9 men and 7 women), and medullary (n = 10 cases; 5 men and 5 women). Six thyroid cancers were of unspecified histology (1 man and 5 women).

The median values of height and BMI for girls and boys at each age between 7 and 13 years are shown in Table 1.

Table 1. Medians (5th and 95th percentiles) of height and BMI at each age between 7 and 13 years

<table>
<thead>
<tr>
<th>Age at measurement</th>
<th>Height (in cm)</th>
<th>BMI (in kg/m²)</th>
<th>Height (in cm)</th>
<th>BMI (in kg/m²)</th>
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<td>Men</td>
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<tr>
<td>7</td>
<td>121.7 (113.0–130.0)</td>
<td>15.3 (13.5–18.0)</td>
<td>122.6 (114.0–131.2)</td>
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<tr>
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<td>15.8 (13.7–18.7)</td>
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<td>132.1 (122.7–142.9)</td>
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<td>133.1 (123.8–142.9)</td>
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<tr>
<td>13</td>
<td>155.5 (143.0–167.0)</td>
<td>18.3 (15.3–23.2)</td>
<td>153.5 (141.5–167.6)</td>
<td>17.8 (15.3–22.3)</td>
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</table>
Height and thyroid cancer risk

Height (per 1 SDS) was positively associated with thyroid cancer risk at each age at measurement (Fig. 2). Using height at the age of 10 years as an example, the hazard ratio (HR) per 1 SDS difference in height at the age of 10 years (7–7 cm) was 1.22 [95% confidence interval (CI), 1.07–1.40]. Although, for all of these results, the magnitudes of the HRs were generally stronger for men than for women, no statistically significant differences were observed by sex (Table 2). In addition, in women but not in men, the association between height and

Table 2. HRs\textsuperscript{a} and 95% CIs for total thyroid cancer per 1 SDS difference in height at each age from 7 to 13 years

<table>
<thead>
<tr>
<th>Age at measurement</th>
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<th>Cases</th>
<th>HR</th>
<th>95% CI</th>
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<th>Cases</th>
<th>HR</th>
<th>95% CI</th>
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<td>1.07–1.76</td>
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<td>0.97–1.64</td>
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<td>0.96–1.34</td>
<td>138,610</td>
<td>58</td>
<td>1.25</td>
<td>0.93–1.66</td>
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</tbody>
</table>

\textsuperscript{a}Models used attained age as the time metric and were stratified by birth cohort in 5-year intervals.
thyroid cancer risk seemed to weaken with increasing age at height measurement (HR per 1 SDS, at the age of 7 years = 1.27, 95% CI, 1.09–1.48; HR at the age of 13 years = 1.17, 95% CI, 1.00–1.37; Table 1). The magnitudes of these associations were similar for papillary and follicular thyroid cancer subtypes overall (Table 3), although nonsignificantly stronger for papillary thyroid cancer in women and follicular thyroid cancer in men (Supplementary Table S1).

The results showed indications of stronger associations between height and thyroid cancer risk for individuals diagnosed with thyroid cancer at younger compared with older ages (Supplementary Table S2). The differences by age at diagnosis were not statistically significant, although the numbers of cases in each group were relatively small.

BMI and thyroid cancer risk

BMI (per 1 SDS) at each age of measurement was positively associated with total thyroid cancer risk (Fig. 2). As an example, the HR per 1 SDS difference in BMI at the age of 10 years (∼1.5–2 kg/m²) was 1.15 (95% CI, 1.00–1.34). We observed no evidence of a multiplicative interaction by sex, although the magnitudes of the HRs were slightly stronger for men (Table 2). All of the HRs increased in magnitude and became statistically significant after restricting the outcome to papillary thyroid cancer (per 1 SDS in BMI at the age of 10 years, HR = 1.27; 95% CI, 1.06–1.53; Table 3), with the strongest associations observed for papillary thyroid cancer in men (per 1 SDS in BMI at the age of 10 years, HR = 1.51; 95% CI, 1.05–2.16; Supplementary Table S1). No associations were observed between BMI and follicular thyroid cancer risk.

The results suggested a pattern in which associations between BMI and thyroid cancer risk were generally stronger for individuals diagnosed at younger versus older ages (Supplementary Table S3).

All HRs were attenuated in models mutually adjusted for height SDS and BMI SDS and in height and BMI models after additional adjustment for birth weight SDS, but the patterns remained (Supplementary Tables S4 and S5). No clear associations were observed for change in height or BMI SDS between ages 7 and 13 years, 10 and 13 years, or 7 and 13 years and thyroid cancer risk in either females or males (Supplementary Tables S6 and S7).

Discussion

Secular trends of increasing childhood and adolescent height and BMI have been observed in several countries (12, 13), including Denmark (14), but the long-term health implications remain largely unknown, and few high-quality resources are available to study these questions. The incidence of thyroid cancer, particularly papillary carcinoma, has also increased in Denmark since the 1940s, at a similar rate in men (1.7%; 0.41–4.17 per 100,000 per year) and women (1.8%; 0.9–4.11 per 100,000 per year; ref. 2). In this unique study population, we found that taller height relative to one’s peers and greater BMI at each age between 7 and 13 years were associated with an increased risk of total and, to a greater extent, papillary thyroid cancer risk in adulthood. All of these associations were nonsignificantly stronger in magnitude for men compared with women. We also observed some evidence, though based on small numbers of

Table 3. HRs and 95% CIs for papillary and follicular thyroid cancer per 1 SDS difference in height and BMI at each age from 7 to 13 years

<table>
<thead>
<tr>
<th>Age at measurement</th>
<th>Study population</th>
<th>Cases</th>
<th>HR</th>
<th>95% CI</th>
<th>Cases</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
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<td><strong>Height (per 1 SDS)</strong></td>
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<td></td>
</tr>
<tr>
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<td>137</td>
<td>1.35</td>
<td>1.14–1.60</td>
<td>56</td>
<td>1.31</td>
<td>1.01–1.71</td>
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</table>

*Models used attained age as the time metric and were stratified by birth cohort in 5-year intervals and sex.
of an association between taller height during childhood and follicular thyroid cancer risk.

Height and BMI in adulthood have been consistently positively associated with thyroid cancer risk in observational studies (15–27). The few previous studies on the relationship between childhood and young adulthood height and weight have relied on self-reported measures, recalled by participants typically during middle-to-older adulthood. Some of these studies found positive associations between BMI in young adulthood (ages 17–21) and thyroid cancer risk (17, 18, 24). However, no associations were observed for recalled body shape (lean, medium-large, large) at the age 8 years or age at menarche and thyroid cancer risk in a cohort of French women (28). These studies were limited because of the potential for bias arising from inaccurate recall of self-reported height and weight at younger ages. Our cohort study is unique in having measured values of childhood height and weight, as well as long-term follow-up allowing for a comparison of the associations by age at thyroid cancer diagnosis. As most thyroid cancers are diagnosed at relatively young ages (median age at diagnosis = 49 for women and 54 for men; ref. 29), it is plausible that early-life exposures have a greater influence on early-onset thyroid cancer compared with thyroid cancer diagnosed later. We found some support for this hypothesis in the current study, in which we observed slightly, albeit nonsignificantly, stronger associations of BMI with thyroid cancer diagnosed at younger versus older ages.

Considering the relatively young age at thyroid cancer diagnosis compared with other malignancies, childhood height and BMI could conceivably represent exposures that are more relevant to thyroid cancer development compared with adult measures. In the current study, we lacked information on adulthood height and weight to directly compare the magnitude of the associations between childhood and adulthood height and BMI with thyroid cancer risk. Because height and BMI track over the life course, it is possible that associations observed in the current study may reflect a true biologic effect occurring in late, as opposed to early, life, as our relative risk estimates were similar to those from previous studies among adults using equivalent units of differences in height and BMI (15–27). However, there is some evidence to the contrary. For instance, a case–control study in French Polynesia found that BMI in young adulthood was more strongly associated with larger (≥10 mm) versus smaller (<10 mm) thyroid tumors, suggesting a promotional effect of excess body weight from an early age, whereas a stronger association for smaller versus larger thyroid tumors, which is more indicative of surveillance bias, was observed for BMI at the time of thyroid cancer diagnosis (18).

The associations observed for taller height and greater BMI and thyroid cancer risk in this study may indicate shared underlying biologic processes. Obese children tend to be taller than their peers, with accelerated growth due to, in part, alterations in growth hormone, growth hormone-binding protein, insulin-like growth factor-1 (IGF-1), and IGF-binding protein levels, and responsiveness to these levels (33). Although there is little direct evidence to support an association between growth-related hormone levels during childhood and thyroid cancer risk, IGF-I levels have been associated with cancers of the colon, prostate, and breast (34–36). Alternatively, elevated levels of insulin and leptin commonly associated with obesity may promote thyroid tumor growth by enhancing the production of thyroid-stimulating hormone in the pituitary gland (37). Interestingly, among women but not men in this study, the magnitude of the association between height and thyroid cancer risk seemed to weaken with increasing age at measurement. Furthermore, despite having observed consistent positive associations for discrete height measurements and BMI at each age and thyroid cancer risk, we observed no associations between within-individual changes in height and BMI SDS between ages 7 to 10 years, 10 to 13 years, and 7 to 13 years. These results suggest that taller prepubertal, as opposed to postpubertal height or puberty-related growth, may be the more relevant proxy for exposures involved in thyroid carcinogenesis, such as early-life nutritional status or genetic components influencing both height and thyroid cancer development. Lending support to this hypothesis, we observed nonsignificantly stronger associations for height measured during this age period in men, most of whom would have reached peak height velocity after the age of 13 years (38). Unfortunately, we did not have complete information on height and BMI measured at older ages to examine the association between change in height around the time of puberty and thyroid cancer risk for men. Another potential explanation for our findings is that greater height and weight in childhood may reflect larger thyroid volume, and thus greater likelihood for malignant transformation of thyroid cells (39).

The major strengths of this study include the prospective study design and availability of measured, as opposed to recalled, height and weight during childhood. However, there were some limitations as well. For the majority of our study participants, the prevalence of childhood overweight and obesity was relatively low during the years in which height and weight were measured compared with the prevalence among children born more recently (12). These low levels may have limited our ability to detect associations between excess body weight in childhood and thyroid cancer risk. Nonetheless, this limitation would have still applied had the study occurred in any other setting, including the United States, which has one of the highest proportions of childhood overweight and obesity worldwide (40, 41), and without historical data, such a prospective evaluation of measured childhood height and weight and thyroid cancer risk would not have been feasible. As previously mentioned, we were unable to directly compare the magnitude of the associations for childhood height and BMI with corresponding measurements in adulthood in this population, or to attempt to disentangle the independent effects of childhood versus adulthood measures on thyroid cancer risk. However, an indirect comparison with the published data revealed that, for approximately the same per unit increase, the associations we observed for height and, in particular, BMI were generally stronger in magnitude than that in
studies of adulthood measures [HRs between 1.0–1.2 per 5 cm increase in height and 1.1–1.3 per 5 kg/m² increase in BMI (15–27)]. The observation that height and BMI seemed to be more strongly associated with thyroid cancer diagnoses in younger versus older ages is also consistent with a true effect of body size at younger ages. Nonetheless, we did not have the full range of follow-up time for individuals born in the earliest birth cohorts because personal identifying numbers were not introduced until 1968, thus limiting our ability to disentangle associations by age at diagnosis and birth cohort. Finally, although height may also be a proxy for socioeconomic status, and thus a greater access to care and increased likelihood of detection and diagnosis of the disease (42), this explanation is less plausible in a setting, such as Denmark, in which participants have universal and free access to medical care.

In this prospective study, taller height and greater BMI during childhood were associated with an increased risk of thyroid cancer. Our results support a potential role of early-life exposures, such as hormones and nutritional status, associated with childhood growth and body weight in thyroid carcinogenesis. These data also suggest that secular trends in height and weight during childhood may be one explanation for the rapid increase in thyroid cancer observed in several countries worldwide, including Denmark.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: C.M. Kitahara, T.I.A. Sørensen, J.L. Baker
Development of methodology: J.L. Baker
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T.I.A. Sørensen, J.L. Baker
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.M. Kitahara, M. Gamborg, A. Berrington de Gonzalez, T.I.A. Sørensen, J.L. Baker
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