Title page

Adult height and head and neck cancer: a pooled analysis within the INHANCE Consortium

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89 Medical Subject Headings (MeSH)
Head and Neck Neoplasms, Meta-Analysis [Publication Type], Height

92 Conflict of interest statement
The authors declare no conflict of interest.
Abstract

Background

Several epidemiological studies have shown a positive association between adult height and cancer incidence. The only study conducted among women on mouth and pharynx cancer risk, however, reported an inverse association. This study aims to investigate the association between height and the risk of head and neck cancer (HNC) within a large international consortium of HNC.

Methods

We analyzed pooled individual-level data from 24 case-control studies participating in the International Head and Neck Cancer Epidemiology Consortium. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were estimated separately for men and women for associations between height and HNC risk. Educational level, tobacco smoking, and alcohol consumption were included in all regression models. Stratified analyses by HNC subsites were performed.

Results

This project included 17,666 cases and 28,198 controls. We found an inverse association between height and HNC (adjusted OR per 10 cm height =0.91, 95% CI 0.86-0.95 for men; adjusted OR=0.86, 95% CI 0.79-0.93 for women). In men, the estimated OR did vary by educational level, smoking status, geographic area, and control source. No differences by subsites were detected.

Conclusions

Adult height is inversely associated with HNC risk. As height can be considered a marker of childhood illness and low energy intake, the inverse association is consistent with prior studies showing that HNC occur more frequently among deprived individuals. Further studies designed to elucidate the mechanism of such association would be warranted.
BACKGROUND

Head and neck cancer (HNC) is the sixth most common cancer worldwide, with more than half a million cases and 300,000 deaths in 2008 [1]. These malignancies, the majority of which are squamous cell carcinomas, include cancers of the oral cavity, oropharynx, hypopharynx and larynx. Tobacco smoking and alcohol consumption are predominant risk factors for HNC, although other factors, including passive smoking [2, 3], human papillomavirus (HPV) infection [4], low body-mass index [5], low levels of recreational physical activity [6], poor dietary pattern [7], low socioeconomic status [8] and family history of cancer [9], affect the risk. Increasing cancer risk with increasing adult height has been reported for all cancers combined [10-12], and for several specific cancer sites, such as breast, ovary, prostate, colon, rectum, testis, malignant melanoma, endometrium, kidney, non-Hodgkin lymphoma and leukaemia [13-20]. The World Cancer Research Fund reported in 2007 that evidence of an increasing risk associated with attained adult height was convincing for colorectal and postmenopausal breast cancer only, while it is probable for pancreatic, ovarian, and premenopausal breast cancer. Evidence was limited, however, for endometrial cancer [21]. A positive association has also been reported between adult height and cancer mortality [15, 22, 23]. On the other hand, an inverse relation was reported for stomach and oesophagus cancer in some studies [24, 10, 25-27], and recently also for mouth and pharynx cancer [11]. Based on 1,095 incident cases of mouth and pharynx cancers within the Million Women cohort Study [11], a risk reduction of 6% per 10 cm increasing adult height was reported. Additionally, the Emerging Risk Factors Collaboration reported a reduction of 13% per 6.5 cm increasing adult height for oral cancer mortality (95% CI: 5%-21%), based on a pooled analysis of 632 cancer deaths from a large number of cohort studies [23]. In general, a person’s maximum height is determined by a combination of genetic factors and environmental exposures both in utero and during childhood and adolescence, so that height can
be considered as a biomarker of the interplay of genetic endowment and early-life experiences [28, 29]. The extent to which a person can reach his/her genetically determined height is therefore strongly influenced by living conditions and the family’s and previous generations’ socioeconomic status (SES) [30]. Besides SES, insulin-like growth factor I (IGFI) circulating levels are also strongly related with childhood and adolescence skeletal growth [31], with IGFI being positively associated with cancer risk [32].

The purposes of this study are to examine the association between height and the risk of HNC in a pooled analysis of case-control studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, and to test this association in HNC subsites.
MATERIALS AND METHODS

Studies and Participants

We conducted the pooled analysis by using data from independent case-control studies participating in the INHANCE Consortium. The INHANCE Consortium was established in 2004 and includes 35 head and neck cancer case-control studies (several of which are multicenter) on 25,478 cases and 37,111 controls (data version 1.5) [33]. Cases included patients with invasive tumors of the oral cavity, oropharynx, hypopharynx, larynx, oral cavity or pharynx not otherwise specified or overlapping, as defined previously [34].

Details of the case-control studies and data pooling methods for the INHANCE consortium have been previously described [34]. Face-to-face interviews are conducted in all studies by trained personnel, except for the following studies: Boston, Germany-Saarland, MSKCC New York, and Japan (2001-2005), in which subjects completed self-administered questionnaires. All the studies were performed according to the Declaration of Helsinki and were approved by the local ethics committees. Written informed consents were obtained from all study subjects.

Inclusion criteria

All case-control studies in the INHANCE Consortium were eligible for inclusion in the current analysis only if information on height was available for at least 80% of the subjects. Additionally, among the eligible studies, subjects were excluded if they were: aged <18; <120 cm in height; had missing information on age, gender or height; or had missing information on the site of origin of cancer.

Study variables

Variables were formatted to be consistently classified across studies into standard categories, including age (<50, 50–59, 60–69, ≥70 years), body-mass index (<18.5 [underweight], 18.5–24.9 [normal weight], 25–29.9 [overweight], ≥30 [obese] kg/m²), education level (no formal
education, less than junior high school, some high school, high-school graduate, vocational/some college, or college graduate/postgraduate), cigarette smoking status (never, former, current), years of smoking (<10, 10-19, 20-29, 30-39, ≥40), number of cigarettes smoked per day (<10, 10-19, 20-29, 30-39, ≥40), alcohol drinking status (never, former, current), alcohol consumption as number of drinks consumed per day (<1, 1-2, 3-4, ≥5), geographic area (Europe, North America, Central and South America, and Asia), source of control subjects (hospital-based versus population-based), cancer subsite (oral cavity, oropharynx, hypopharynx, and larynx) [34]. Body mass index was calculated as the weight divided by the height squared (weight (kg)/height (m)²) and categorized into four groups according to World Health Organization criteria as previously reported [35]. Subjects, who have not attained a high school graduation, were classified as having low education in the data analysis. A detailed description on the method used for data pooling on smoking and alcohol across different studies is provided in a previous paper [34].

Height and weight were self-reported at the time of interview in all studies. All pooled data were cleaned and checked for internal consistency, and clarifications were requested from the original investigators when needed.

Statistical analysis

Descriptive analyses were conducted to describe the study population by demographic and known HNC risk factors. Height was expressed as quartiles of the distribution for the combined control group of all studies and for each gender respectively (<168, 168–172, 173–178, >178 cm for men; <157, 157–160, 161–165, >165 cm for women).

The associations between HNC risk and height (per 10 cm increase) were assessed by estimating odds ratios (ORs) and 95% confidence intervals (CIs), using unconditional logistic regression for each case-control study, adjusted by education level, cigarette smoking status, years of smoking,
number of cigarettes smoked per day, and alcohol consumption as number of drinks consumed per day. The pooled effect estimates from all studies, were estimated with random effect models and presented in a Forest plot. We quantified inconsistencies across studies and their impact on the analysis by using Cochrane’s $Q$ and the $I^2$ statistic [36, 37]. An estimate of the between-study variance was also computed using $\tau^2$ statistic [38]. To assess the impact of other potentially confounding factors, we examined the percent change in the age-adjusted pooled OR with the addition of each factor. Subgroup analyses were also conducted by geographic area, source of control subjects, cancer subsite, and selected characteristics at recruitment: age, body-mass index, education level, smoking status, and alcohol drinking status. Statistical analyses were performed separately for men and women and were done with Stata software, version 12 (StataCorp. 2011. College Station, TX: StataCorp LP). All statistical tests were two-sided, and p-values < alpha (0.05) were considered statistically significant.

RESULTS

Overall, of the 35 studies participating in the INHANCE Consortium (version 1.5 with 25,478 cases and 37,111 controls), 11 were immediately excluded, as 6 did not have data on height (Baltimore, Beijing, France multicenter [1989-1991], Germany-Heidelberg, HOTSPOT, and Houston), and 5 did not provide data on height at the time of the analysis (Buffalo, Iowa, France [1987-1992], Rome, and Sao Paulo). Furthermore, two centers (Goiania, Sao Paulo) from the Latin America multicenter study, and six centers (Australia, Aviano, Cuba, Milan, Sudan, Udine) from the International multicenter study were excluded. Figure 1 shows our selection process and lists excluded case control studies with reasons for their exclusion.
Of the 24 case-control studies, we also excluded participants with missing data on height, age, and gender (1,148 cases and 581 controls). The final analysis included 17,666 cases and 28,198 controls. Among the cases, 4,714 were oral cancer, 6,254 were pharyngeal cancer, 1,970 were cancers of the oral cavity or pharynx not otherwise specified, 4,407 were laryngeal cancer and 321 overlapping. Details of the case-control studies are provided in Table 1. Nine studies were conducted in Europe, ten in North America, two in Central and South America, two in Asia, one study was conducted on four continents and coordinated by the International Agency for Research on Cancer (IARC).

Table 2 reports the characteristics of the study population, which included 34,072 men (74.3% of the entire population; 13,792 cases and 20,280 controls), and 11,792 women (25.7%; 3,874 cases and 7,918 controls). Among these participants, both men and women, cases were more likely than controls to be underweight or normal weight, cigarette smokers, and alcohol drinkers.

Controls had higher education levels than cases.

Table 3 shows the distribution of age and selected risk factors in control subjects according to gender-specific height quartiles. Both in men and women, the taller group tended to be younger, to have a higher level of education, and more likely to be current drinkers. Among men, taller individuals were less likely to be current smokers, while the reverse was true among women.

The adjusted ORs for HNC risk per 10 cm increase in height for the 24 studies are shown in Figure 2. Among men, the pooled OR for height was 0.91 (95% CI: 0.86-0.95). There was little heterogeneity between the effect sizes, accounting for 18% of the variation in point estimates by using the statistic $I^2$. The estimate of the heterogeneity variance was 0.002. The point estimate of the pooled ORs was less than 1.0 for 18 of the 24 studies (sign test, $p<0.05$).
Among women, the pooled OR was 0.86 (95% CI: 0.79-0.93), and there was no evidence of heterogeneity across studies. The point estimate of the pooled ORs was less than 1.0 for 19 of the 24 studies (sign test, p<0.05).

Figure 3 shows the ORs for HNC per 10 cm increase in height, in subgroups defined by geographic area, control source (hospital-based or population-based), cancer subsite, and selected characteristics at recruitment. In men, the adjusted ORs varied by education level ($\hat{I}^2 = 62.7\%$; $\tau^2 = 0.004$), smoking status ($\hat{I}^2 = 68.2\%$; $\tau^2 = 0.003$), geographic area ($\hat{I}^2 = 63.3\%$; $\tau^2 = 0.003$), and control source ($\hat{I}^2 = 87.7\%$; $\tau^2 = 0.006$). The OR was 0.87 (95% CI: 0.82-0.91) for hospital-based case-control studies and 0.97 (95% CI: 0.91-1.03) for population-based case-control studies.

There was little association between height and HNC risk among men with at least high-school education, and in American populations. There was no substantial heterogeneity in the estimated association with height across strata of the variables among women.

We also examined whether estimates varied by gender. We found that pooled ORs and ORs in every group considered were consistent and do not differ by gender for the association between increasing height and HNC risk (data not shown).
DISCUSSION

In this pooled analysis of 24 case-control studies including 13,792 men and 3,874 women with HNC, we found an inverse association between height and HNC risk. The estimated association was stronger in women than in men (14% vs. 9% risk reduction for per 10 cm increase in adult height). Furthermore, the estimated associations were reasonably homogeneous across studies.

Our results are consistent with those from the only previous investigation on mouth and pharynx cancers from a large prospective female cohort study in UK, which reported a relative risk of 0.94 (95% CI: 0.82-1.08) per 10 cm increase in height [11]. Additionally, the Emerging Risk Factors Collaboration recently reported an inverse association between adult height and oral cancer mortality, based on a large set of pooled cohort studies [23]. In our study, the inverse association between height and HNC risk was minimal among American men, and it was weaker in population-based studies than in hospital-based studies among men (adjusted OR = 0.97 vs. 0.87).

Within ethnic groups within countries, studies have shown that short stature is associated with poor health status [27]. It is known that people with high SES tend to be taller than those in lower socioeconomic classes [39, 40]. The key role of environmental factors in determining adult height is also evident when considering that mean adult height in industrialized countries markedly increased during the 20th century [41]. Therefore, since height can be considered as a marker of early life illness, nutrition and psychosocial stress [42], it is not surprising that several studies reported an inverse association between adult height and cardiovascular and respiratory disease risk [26, 43, 44]. The relationship between height and cancer, however, is conflicting. Some cohort studies conducted in different ethnic groups [10, 12, 11, 14], reported a positive association between height and overall cancer incidence. However, for the mouth and pharynx [11] as well as stomach and esophagus, inverse associations were found [24, 10, 25-27].
The results of our pooled analysis suggest that taller people might be at a lower risk for HNC and corroborates the knowledge that HNC is more common among socio-economically deprived people [45, 8]. We cannot exclude the possibility that the observed inverse association between height and HNC risk is attributable to the unmeasured confounders of childhood or adolescent nutrition status, which are expected to influence both adult height and cancer risk. Childhood growth is indeed associated with parental SES [46, 47], and our pooled estimates are adjusted by adult education status, which is again a good proxy of parental education/SES [48]. However, we cannot rule out confounding by childhood nutrition.

In this study the association between height and HNC risk differed by educational level, especially among men. Those with at least a high school degree are no longer at an increased risk, which suggests a possible residual confounding due to other unknown variables related to SES being the underlying factors of the height-HNC association in the overall analysis.

In a Scottish study [26], authors postulated that the inverse association between stature and stomach cancer was due to *Helicobacter pylori*, which is associated with suboptimal childhood growth and is a causal component for gastric cancer [49, 50]. Additionally, the contribution of the infective component causes of HPV [4] in HNC etiology is not supposed to influence directly childhood and/or adolescent growth, so that we exclude *a priori* the potential for confounding or effect modification by HPV.

In our analysis, the population-based studies among men did not show an inverse association of height with HNC risk, indicating the possible presence of selection bias with hospital controls. On the other hand, this modifying effect of control source was not evident among women. When stratifying on geographic region among men, an effect modification was found. American studies did not show an inverse association between stature and HNC risk. Both scenarios might be due to selection bias by education level, as hospital based studies have lower educational level among
men in our pooled analysis (data not shown), while in North America we observed a higher
education level of participants compared with the other regions (data not shown). Even though
the stratified analyses are adjusted by educational level, some residual confounding might persist.
While the present study has its strengths, including its very large size, its capacity to explore
effect modification by several characteristics and the stratified analyses according to cancer
subsites, it is not without limitations. Firstly, we did not have information on SES or education of
the parents, and used the adult education of the subjects as a proxy, which might result in residual
confounding. Secondly, we did not have information on diet during childhood and/or
adolescence, which affects the growth thus might be key factors underlying the observed
associations. Thirdly, we did not have information on trunk and leg length, which represent a
more direct height component that some studies related with cancer outcomes [51]. Fourthly, we
could not quantify the amount of information bias of self-reported height in our study, though we
believe that its effect would be modest [52]. Fifthly, residual confounding by tobacco and alcohol
cannot be excluded as these key risk factors for HNC might have been measured with error.
Lastly, we could not assess the influence of birth cohort effect on the association between height
and HNC, although we accounted for that by adjusting for age at diagnosis and showing the
effect estimates in each study.
In conclusion, in the present project of a large pool of case-control studies, taller men and women
experienced a lower risk of HNC, controlling for potential confounding due to smoking, alcohol,
and educational level. As it is thought that associations between height, birth weight, and cancer
risk reflect some causal association with a combination of genetics, hormonal, nutritional, and
other factors [21], we believe that the biological mechanisms underlying the association between
height and HNC warrants further investigation.
A Mendelian Randomization approach has been recently suggested to address the aforementioned research question [53]. By using the genes that regulate the height as a proxy of the effect of measured adult height in the association between height and cancer, we would expect to dissect the true effect of height on HNC, without confounding by environmental variables.
Acknowledgments

The authors would like to thank all of the participants who took part in this research for providing us very insightful and constructive comments, which helped improve this manuscript.

Funding

Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center. MSKCC study:

NIH (R01CA051845). New York Multicenter study: National Institutes of Health (NIH) US
(NIH) US (R01CA061188), and in part by a grant from the National Institute of Environmental
Health Sciences (P30ES010126). Seattle-LEO study: NIH (R01CA030022). Seattle study:
National Institutes of Health (NIH) US (R01CA048996, R01DE012609). Tampa study: National
Institutes of Health (NIH) US (P01CA068384, K07CA104231, R01DE013158). US Multicenter
study: The Intramural Program of the NCI, NIH, United States. Puerto Rico study: jointly funded
by National Institutes of Health (NCI) US and NIDCR intramural programs. Latin America
study: Fondo para la Investigacion Cientifica y Tecnologica (FONCYT) Argentina, IMIM
(Barcelona), Fundaco de Amparo a Pesquisa no Estado de Sao Paulo (FAPESP) (No 01/01768-2), and European Commission (IC18-CT97-0222). Japan (1988-2000 and 2001-2005): Scientific
Research grant from the Ministry of Education, Science, Sports, Culture and Technology of
Japan (17015052) and grant for the Third-Term Comprehensive 10-Year Strategy for Cancer
Control from the Ministry of Health, Labor and Welfare of Japan (H20-002). IARC Multicenter
study: Fondo de Investigaciones Sanitarias (FIS) of the Spanish Government (FIS 97/0024, FIS
97/0662, BAE 01/5013), International Union Against Cancer (UICC), and Yamagiwa-Yoshida
Memorial International Cancer Study Grant. The work of EL was supported by Fondazione
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Higgins JPT GS, editor.


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This table does not include subjects that do not meet the inclusion criteria.


Population-based for UK centers.

NOS = not otherwise specified.

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<td>80+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n=13,972)</td>
</tr>
<tr>
<td>Cases (n=3,874)</td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>Men (n=17,468)</td>
</tr>
<tr>
<td>Cases (n=7,920)</td>
</tr>
<tr>
<td>Controls</td>
</tr>
</tbody>
</table>

Table 2 - Characteristics of the 17,666 Head and Neck Cancer (HN) cases and 28,198 controls from the 24 studies reporting on current smoking status with risk estimates adjusted for other covariates.
<table>
<thead>
<tr>
<th>Years of smoking</th>
<th>Current</th>
<th>Former</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62.9</td>
<td>66.0</td>
<td>63.8</td>
</tr>
<tr>
<td>1</td>
<td>64.7</td>
<td>68.4</td>
<td>66.2</td>
</tr>
<tr>
<td>2</td>
<td>66.5</td>
<td>70.1</td>
<td>67.8</td>
</tr>
<tr>
<td>3</td>
<td>68.3</td>
<td>71.8</td>
<td>69.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drinks per day</th>
<th>Current</th>
<th>Former</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.2</td>
<td>5.6</td>
<td>5.8</td>
</tr>
<tr>
<td>1</td>
<td>5.6</td>
<td>6.0</td>
<td>6.2</td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>6.4</td>
<td>6.6</td>
</tr>
<tr>
<td>3</td>
<td>6.4</td>
<td>6.8</td>
<td>7.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of cigarettes per day</th>
<th>Current</th>
<th>Former</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.4</td>
<td>3.9</td>
<td>3.3</td>
</tr>
<tr>
<td>1</td>
<td>3.8</td>
<td>4.4</td>
<td>3.8</td>
</tr>
<tr>
<td>2</td>
<td>4.2</td>
<td>4.8</td>
<td>4.3</td>
</tr>
<tr>
<td>3</td>
<td>4.6</td>
<td>5.2</td>
<td>4.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol drinking status</th>
<th>Current</th>
<th>Former</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 40</td>
<td>1.07</td>
<td>1.11</td>
<td>1.13</td>
</tr>
<tr>
<td>41-60</td>
<td>1.16</td>
<td>1.24</td>
<td>1.27</td>
</tr>
<tr>
<td>61-80</td>
<td>1.27</td>
<td>1.35</td>
<td>1.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years of smoking</th>
<th>Current</th>
<th>Former</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.2</td>
<td>4.9</td>
<td>4.6</td>
</tr>
<tr>
<td>1</td>
<td>4.6</td>
<td>5.3</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>5.7</td>
<td>5.4</td>
</tr>
<tr>
<td>3</td>
<td>5.4</td>
<td>6.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Low Educational Level = No education or ≤ Junior High School</td>
<td>Mean ± SD or Percentage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Alcohol Drinkers</td>
<td>78.9% ± 4.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Cigarette Smokers</td>
<td>43.4% ± 5.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Educational Level</td>
<td>82.3% ± 4.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.0 (±12.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>61.48 ± 11.89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Mean Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1.86 ± 0.79</td>
</tr>
<tr>
<td>Men</td>
<td>1.88 ± 0.79</td>
</tr>
</tbody>
</table>

Table 8: Distribution of age and selected factors by quartiles of height (cm) by sex, INHANCE controls.
Figure 1 - Adjusted odds ratios (OR) and 95% confidence intervals (CI) per 10 cm increase in height in relation to head and neck cancer risk by sex in 14 INHANCE studies

Figure 2 - Adjusted odds ratios (OR) and 95% confidence intervals (CI) per 10 cm increase in height in relation to geographic area, study design, cancer site, and selected characteristics, by sex, in 14 INHANCE studies

Table 1. WA / USA (1)=1983-87 and (2)=2000 and (3)=2001-06
Ia) / A: Michigan (1)=1966-99 and (2)=2000-09: North Carolina. USA (1)=1969-77 and (2)=2002-06:

OR adjusted by age; education level; smoking status; cigarette duration; cigarette intensity; alcohol intensity; and study center.

Study center