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

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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/m^2), 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 τ^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 (I^2= 62.7%; τ^2=0.004), smoking status (I^2= 68.2%; τ^2=0.003), geographic area (I^2= 63.3%; τ^2=0.003), and control source (I^2= 87.7%; τ^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 suggests 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.

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REFERENCES

1. Ferlay J SH, Bay F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 cancer incidence and mortality worldwide: IARC CancerBase No.10. Lyon, France: International Agency for Research on Cancer, 2010.

2. Lee YC, Boffetta P, Sturgis EM, Wei Q, Zhang ZF, Muscat J et al. Involuntary smoking and head and neck cancer risk: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2008;17(8):1974-81. doi:17/8/1974 [pii] 10.1158/1055-9965.EPI-08-0047.

3. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10(11):1033-4.

4. IARC. IARC monographs on the evaluation of carcinogenic risks to humans, volume 90, human papillomaviruses. Lyon, 2007.

5. Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lissowska J et al. Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Int J Epidemiol. 2010;39(4):1091-102. doi:dyp380 [pii] 10.1093/ije/dyp380.

6. Nicolotti N, Chuang SC, Cadoni G, Arzani D, Petrelli L, Bosetti C et al. Recreational physical activity and risk of head and neck cancer: a pooled analysis within the international head and neck cancer epidemiology (INHANCE) Consortium. Eur J Epidemiol. 2011;26(8):619-28. doi:10.1007/s10654-011-9612-3.

7. Chuang SC, Jenab M, Heck JE, Bosetti C, Talamini R, Matsuo K et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control. 2012;23(1):69-88. doi:10.1007/s10552-011-9857-x.

8. Conway DI, McKinney PA, McMahon AD, Ahrens W, Schmeisser N, Benhamou S et al. Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe. Eur J Cancer. 2010;46(3):588-98. doi:S0959-8049(09)00725-4 [pii] 10.1016/j.ejca.2009.09.028.

9. Negri E, Boffetta P, Berthiller J, Castellsague X, Curado MP, Dal Maso L et al. Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Int J Cancer. 2009;124(2):394-401. doi:10.1002/ijc.23848.

10. Sung J, Song YM, Lawlor DA, Smith GD, Ebrahim S. Height and site-specific cancer risk: A cohort study of a korean adult population. Am J Epidemiol. 2009;170(1):53-64. doi:kwp088 [pii] 10.1093/aje/kwp088.

11. Green J, Cairns BJ, Casabonne D, Wright FL, Reeves G, Beral V. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. Lancet Oncol. 2011;12(8):785-94. doi:S1470-2045(11)70154-1 [pii] 10.1016/S1470-2045(11)70154-1.

12. Kabat GC, Heo M, Kamensky V, Miller AB, Rohan TE. Adult height in relation to risk of cancer in a cohort of Canadian women. Int J Cancer. 2012. doi:10.1002/ijc.27704.

13. Albanes D, Winick M. Are cell number and cell proliferation risk factors for cancer? J Natl Cancer Inst. 1988;80(10):772-4.

14. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. Epidemiol Rev. 2001;23(2):313-42.

15. Batty GD, Shipley MJ, Langenberg C, Marmot MG, Davey Smith G. Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall study. Ann Oncol. 2006;17(1):157-66. doi:mdj018 [pii] 10.1093/annonc/mdj018.

16. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst. 2006;98(13):920-31. doi:98/13/920 [pii] 10.1093/jnci/djj246.

17. Olsen CM, Green AC, Zens MS, Stukel TA, Bataille V, Berwick M et al. Anthropometric factors and risk of melanoma in women: a pooled analysis. Int J Cancer. 2008;122(5):1100-8. doi:10.1002/ijc.23214.

18. Schouten LJ, Rivera C, Hunter DJ, Spiegelman D, Adami HO, Arslan A et al. Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev. 2008;17(4):902-12. doi:1055-9965.EPI-07-2524 [pii] 10.1158/1055-9965.EPI-07-2524.

19. Zuccolo L, Harris R, Gunnell D, Oliver S, Lane JA, Davis M et al. Height and prostate cancer risk: a large nested case-control study (ProtecT) and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2008;17(9):2325-36. doi:17/9/2325 [pii] 10.1158/1055-9965.EPI-08-0342.

20. Lerro CC, McGlynn KA, Cook MB. A systematic review and meta-analysis of the relationship between body size and testicular cancer. Br J Cancer. 2010;103(9):1467-74. doi:6605934 [pii] 10.1038/sj.bjc.6605934.

21. World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007.

22. Batty GD, Barzi F, Woodward M, Jamrozik K, Woo J, Kim HC et al. Adult height and cancer mortality in Asia: the Asia Pacific Cohort Studies Collaboration. Ann Oncol. 2010;21(3):646-54. doi:mdp363 [pii]
10.1093/annonc/mdp363.

23. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int J Epidemiol. 2012;41(5):1419-33. doi:dys086 [pii]
10.1093/ije/dys086.

24. La Vecchia C, Negri E, Parazzini F, Boyle P, D'Avanzo B, Levi F et al. Height and cancer risk in a network of case-control studies from northern Italy. Int J Cancer. 1990;45(2):275-9.

25. D'Avanzo B, La Vecchia C, Talamini R, Franceschi S. Anthropometric measures and risk of cancers of the upper digestive and respiratory tract. Nutr Cancer. 1996;26(2):219-27. doi:10.1080/01635589609514478.

26. Davey Smith G, Hart C, Upton M, Hole D, Gillis C, Watt G et al. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. J Epidemiol Community Health. 2000;54(2):97-103.

27. Jousilahti P, Tuomilehto J, Vartiainen E, Eriksson J, Puska P. Relation of adult height to cause-specific and total mortality: a prospective follow-up study of 31,199 middle-aged men and women in Finland. Am J Epidemiol. 2000;151(11):1112-20.

28. Eveleth PB. Population differences in growth: environmental and genetic factors. In: Falkner F, Tanner JM, eds. Human growth 3. Neurobiology and nutrition. New York, NY: Plenum Publishing Corporation, 1979:373-94.

29. Proos LA. Anthropometry in adolescence--secular trends, adoption, ethnic and environmental differences. Horm Res. 1993;39 Suppl 3:18-24.

30. Peck MN, Lundberg O. Short stature as an effect of economic and social conditions in childhood. Soc Sci Med. 1995;41(5):733-8. doi:0277953694003798 [pii].

31. Clayton PE, Banerjee I, Murray PG, Renehan AG. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Nat Rev Endocrinol. 2011;7(1):11-24. doi:nrendo.2010.171 [pii]
10.1038/nrendo.2010.171.

32. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004;363(9418):1346-53. doi:10.1016/S0140-6736(04)16044-3
S0140-6736(04)16044-3 [pii].

33. Conway DI, Hashibe M, Boffetta P, Wunsch-Filho V, Muscat J, La Vecchia C et al. Enhancing epidemiologic research on head and neck cancer: INHANCE - The international head and neck cancer epidemiology consortium. Oral Oncol. 2009;45(9):743-6. doi:S1368-8375(09)00046-3 [pii]
10.1016/j.oraloncology.2009.02.007.

34. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 2007;99(10):777-89. doi:99/10/777 [pii]
10.1093/jnci/djk179.

35. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1-452.

36. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. doi:10.1136/bmj.327.7414.557
327/7414/557 [pii].

37. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc. 2009;172(1):137-59. doi:10.1111/j.1467-985X.2008.00552.x.

38. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. In: Higgins JPT GS, editor.

39. Kuh DL, Power C, Rodgers B. Secular trends in social class and sex differences in adult height. Int J Epidemiol. 1991;20(4):1001-9.

40. Magnusson PK, Rasmussen F, Gyllensten UB. Height at age 18 years is a strong predictor of attained education later in life: cohort study of over 950,000 Swedish men. Int J Epidemiol. 2006;35(3):658-63. doi:dyl011 [pii]
10.1093/ije/dyl011.

41. Hauspie RC, Vercauteren M, Susanne C. Secular changes in growth. Horm Res. 1996;45 Suppl 2:8-17.

42. Gunnell D. Can adult anthropometry be used as a 'biomarker' for prenatal and childhood exposures? Int J Epidemiol. 2002;31(2):390-4.

43. McCarron P, Okasha M, McEwen J, Smith GD. Height in young adulthood and risk of death from cardiorespiratory disease: a prospective study of male former students of Glasgow University, Scotland. Am J Epidemiol. 2002;155(8):683-7.

44. Lee CM, Barzi F, Woodward M, Batty GD, Giles GG, Wong JW et al. Adult height and the risks of cardiovascular disease and major causes of death in the Asia-Pacific region: 21,000 deaths in 510,000 men and women. Int J Epidemiol. 2009;38(4):1060-71. doi:dyp150 [pii] 10.1093/ije/dyp150.

45. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LM. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008;122(12):2811-9. doi:10.1002/ijc.23430.

46. Silventoinen K. Determinants of variation in adult body height. J Biosoc Sci. 2003;35(2):263-85.

47. Meyer HE, Selmer R. Income, educational level and body height. Ann Hum Biol. 1999;26(3):219-27.

48. (OECD) TOfEC-oaD. Economic Policy Reforms: Going for Growth 2010. Chapter 5, Part II, 2010.

49. Patel P, Mendall MA, Khulusi S, Northfield TC, Strachan DP. Helicobacter pylori infection in childhood: risk factors and effect on growth. BMJ. 1994;309(6962):1119-23.

50. La Vecchia C. Hypothesis: is the fall in Helicobacter pylori related to the global rise in body mass index? Eur J Cancer Prev. 2011;20(6):556. doi:10.1097/CEJ.0b013e32834a8018.

51. Gunnell D, May M, Ben-Shlomo Y, Yarnell J, Smith GD. Height, leg length, and cancer: the Caerphilly Study. Nutr Cancer. 2003;47(1):34-9. doi:10.1207/s15327914nc4701_4.

52. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr. 2002;5(4):561-5. doi:10.1079/PHN2001322 S1368980002000782 [pii].

53. Cook MB, Chia VM, Berndt SI, Graubard BI, Chanock SJ, Rubertone MV et al. Genetic contributions to the association between adult height and testicular germ cell tumors. Int J Epidemiol. 2011;40(3):731-9. doi:dyq260 [pii]
10.1093/ije/dyq260.

Table 1 - Description of the 24 INHANCE studies included in the analysis of height and the risk of head and neck cancer

Study location	Age eligibility	Control source	Recruitment period	Cases/ Controls	Site of tumour (#)			
					oral cavity	pharynx	oral/pharynx NOS	larynx
Europe								
Central Europe	≥15	Hospital based	1998-2003	762/907	196	150	32	384
France, Paris	18-<75	Population based	2002-2005	2,237/3,555	468	1105	155	509
Germany, Saarland	50-75	Population based	2001-2003	94/94	15	43	9	27
Italy, Aviano	>18	Hospital based	1987-1992	482/855	85	218	33	146
Italy, Milan (1)	<80	Hospital based	1984-1989	416/1,531	48	61	65	242
Italy, Milan (2)	18-80	Hospital based	2006-2009	368/755	85	38	18	227
Italy Multicenter	18-80	Hospital based	1990-1996	1,260/2,715	209	502	90	459
Switzerland	<80	Hospital based	1991-1997	516/883	138	247	7	124
Western Europe	na	Hospital based (§)	2000-2005	1,728/1,989	482	593	106	539
North America								
Boston, MA	18-90	Population based	2003	584/659	139	291	43	111
Los Angeles, CA	<65	Population based	1999-2004	428/1,038	53	173	112	90
New York, NY	na	Hospital based	1992-1994	139/169	72	23	2	42
New York Multicenter	21-80	Hospital based	1981-1990	1,118/904	536	518	64	0
North Carolina (1)	>17	Hospital based	1994-1997	180/202	42	61	25	52
North Carolina (2)	20-80	Population based	2002-2006	1,368/1,396	194	442	251	481
Seattle, WA (1)	20-74	Population based	1983-1987	656/547	183	211	47	209
Seattle, WA (2)	18-65	Population based	1992-1995	284/477	157	116	11	0
Tampa, FL	≥18	Hospital based	1994-2000	208/898	22	58	65	63
US Multicenter	18-79	Population based	1983-1984	1,114/1,268	386	510	218	0
Central and South America								
South America	15-79	Hospital based	2000-2003	1,295/1,029	279	267	81	612
Puerto Rico	21-79	Population based	1992-1995	351/520	94	200	57	0
Asia								
Japan (1)	18-79	Hospital based	1988-2000	402/1,532	119	85	198	0
Japan (2)	20-79	Hospital based	2001-2005	526/3,102	116	154	166	90
Multi-Regional								
IARC Multicenter	na	Hospital based	1992-1997	1,150/1,173	596	188	115	0

Total	17,666/28,198	4,714	6,254	1,970	4,407

na = not available, NOS = not otherwise specified

(§) Population-based for UK centers

Italy, Milan (1)=1984-89 and (2)=2006-09; North Carolina (1)=1994-97 and (2)=2002-06; Seattle, WA (1)=1983-87 and (2)=1992-95; Japan (1)=1988-2000 and

(#) 321 overlapping head and neck cases were included: Western Europe, n=8; Seattle WA (1), n=6; South America, n=56; IARC Multicenter, n=251

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

Table 2 - Characteristics of the 17,666 head and cancer (HNC) cases and 28,198 controls from the 24 studies reporting on height within INHANCE

Characteristics	Men				Women			
	Cases (n=13,792)		Controls (n=20,280)		Cases (n=3,874)		Controls (n=7,918)	
	n	%	n	%	n	%	n	%
Age (years)								
<50	2,501	18.1	4,092	20.2	719	18.6	1,827	23.1
50-59	4,896	35.5	6,481	32.0	1,150	29.7	2,236	28.2
60-69	4,431	32.1	6,556	32.3	1,224	31.6	2,314	29.2
≥70	1,964	14.2	3,151	15.5	781	20.2	1,541	19.5
Body-mass index (kg/m^2)								
<18.5	859	6.7	430	2.2	507	14.2	347	4.6
18.5-24.9	7,019	54.4	8,544	43.5	1,937	54.4	3,830	50.4
25.0-25.9	3,821	29.6	8,107	41.3	717	20.1	2,202	29.0
≥30.0	1,194	9.3	2,541	12.9	400	11.2	1,223	16.1
Height (cm)								
<160	630	4.8	922	4.6	1,582	43.0	3,137	40.5
160-169	3,865	29.2	5,971	30.0	1,662	45.2	3,676	47.4
170-179	6,330	47.8	9,567	48.1	419	11.4	897	11.6
180-189	2,229	16.8	3,132	15.7	11	0.3	37	0.5
≥190	175	1.3	295	1.5	3	0.1	1	0.0
Educational level								
No education	338	2.5	545	2.7	329	8.6	389	4.9
< Junior high school	4,919	36.4	6,280	31.2	972	25.4	2,542	32.2
Some high school	3,071	22.7	3,924	19.5	808	21.1	1,292	16.4
High school graduate	1,761	13.0	2,223	11.0	577	15.0	936	11.9
Technical school, some college	1,997	14.8	3,668	18.2	773	20.2	1,558	19.8
> College graduate	1,421	10.5	3,513	17.4	375	9.8	1,169	14.8
Cigarette smoking status								
Never	1,142	8.3	5,841	28.9	1,294	33.5	5,100	64.6
Former	4,396	32.0	8,409	41.6	646	16.7	1,510	19.1
Current	8,213	59.7	5,980	29.6	1,926	49.8	1,290	16.3

Years of smoking									
	≤10	405	3.2	1,572	11.0	108	4.2	496	17.8
	11-20	778	6.2	2,487	17.4	186	7.3	572	20.6
	21-30	2,299	18.3	3,407	23.8	489	19.1	702	25.2
	31-40	4,347	34.7	3,664	25.6	898	35.1	597	21.5
	>40	4,703	37.5	3,159	22.1	875	34.2	416	14.9
		12,532							
Number of cigarettes per day									
	≤10	1,383	11.3	3,389	25.3	541	21.4	1,209	44.4
	11-20	5,142	41.9	5,811	43.3	1,025	40.5	1,019	37.4
	21-30	2,549	20.8	1,987	14.8	488	19.3	256	9.4
	31-40	2,116	17.3	1,394	10.4	347	13.7	163	6.0
	>40	1,073	8.7	834	6.2	132	5.2	76	2.8
Alcohol drinking status									
	Never	663	6.7	2,041	15.8	976	35.3	2,545	45.0
	Former	2,384	24.0	2,006	15.6	524	19.0	590	10.4
	Current	6,889	69.3	8,852	68.6	1,265	45.8	2,521	44.6
Drinks per day									
	Never	851	6.6	3,059	16.1	1,214	33.2	3,433	45.2
	<1	2,010	15.6	5,694	30.0	1,237	33.8	2,828	37.2
	1-2	2,992	23.1	5,157	27.2	655	17.9	1,081	14.2
	3-4	2,079	16.1	2,427	12.8	250	6.8	173	2.3
	≥5	4,993	38.6	2,623	13.8	306	8.4	77	1.0

Table 3 - Distribution of age and selected risk factors by quartiles of height (cm), by sex, INHANCE controls

	Men				Women			
	<169	169-173	174-178	>178	<157	157-160	161-165	>165
Number of subjects	6,148	5,141	4,188	4,408	2,079	1,986	1,862	1,821
Age (years)	60.5 (±10.2)	58.3 (±10.7)	57.1 (±10.7)	56.3 (±11.0)	60.0 (±12.0)	58.1 (±12.1)	57.8 (±12.1)	56.0 (±12.6)
Low educational level	48.7%	36.9%	27.3%	16.6%	48.2%	39.5%	33.4%	26.2%
Current cigarette smokers	33.4%	29.3%	28.5%	25.3%	12.3%	15.8%	17.7%	20.0%
Current alcohol drinkers	58.9%	72.4%	73.9%	70.4%	30.6%	44.3%	50.6%	53.6%

Mean ± SD or percentage

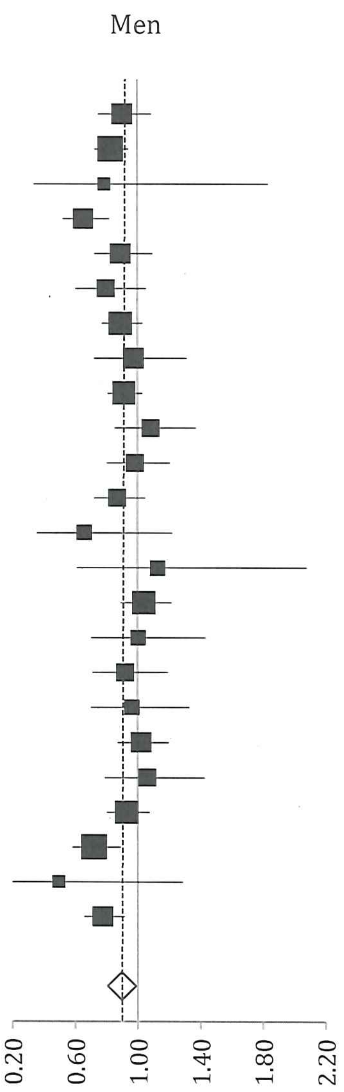
Low educational level = No education or ≤ junior high school

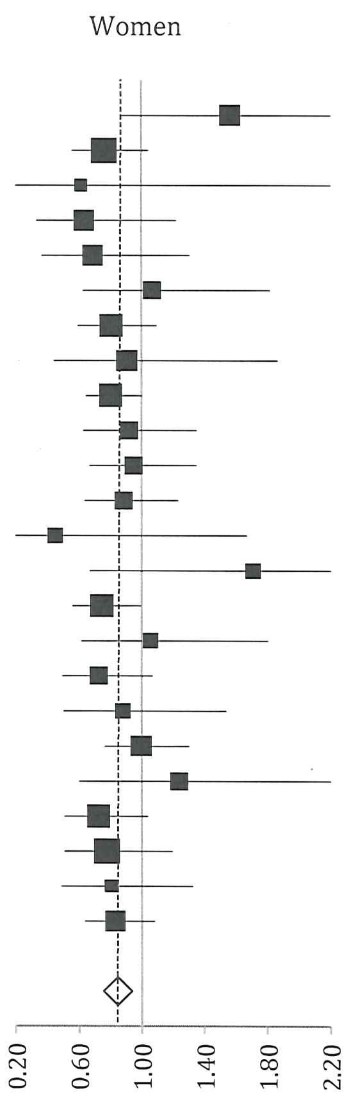
Figure 1 - Adjusted odds ratios (ORs) and 95% confidence intervals (CI) per 10 cm increase in height in relation to head and neck cancer risk, by sex, in 24 INHANCE studies

OR adjusted by age, education level, smoking status, cigarette duration, cigarette intensity, alcohol intensity.
Italy, Milan (1)=1996-99 and (2)=2006-09; North Carolina, USA (1)=1994-97 and (2)=2002-06;
Seattle, WA, USA (1)=1983-87 and (2)=1992-95; Japan (1)=1988-2000 and (2)=2001-05

Figure 2 - Adjusted odds ratios (ORs) and 95% confidence intervals (CI) per 10 cm increase in height according to geographic area, study design, cancer site, and selected characteristics, by sex, in 24 INHANCE studies

OR adjusted as appropriate for age, education level, smoking status, cigarette duration, cigarette intensity, alcohol intensity, and study center





Study	Men OR	Men 95% CI	Women OR	Women 95% CI
Central Europe	0.91	(0.75-1.09)	1.57	(0.87-2.81)
France	0.83	(0.73-0.94)	0.77	(0.56-1.05)
Germany, Saarland	0.79	(0.34-1.83)	0.62	(0.05-7.26)
Italy, Aviano	0.66	(0.53-0.82)	0.64	(0.33-1.22)
Italy, Milan (1)	0.89	(0.73-1.10)	0.69	(0.37-1.31)
Italy, Milan (2)	0.80	(0.61-1.06)	1.07	(0.63-1.82)
Italy Multicenter	0.89	(0.77-1.03)	0.81	(0.60-1.10)
Switzerland	0.97	(0.72-1.31)	0.91	(0.44-1.87)
Western Europe	0.91	(0.81-1.03)	0.81	(0.65-1.00)
Boston, MA, USA	1.08	(0.86-1.37)	0.92	(0.63-1.35)
Los Angeles, CA, USA	0.99	(0.81-1.21)	0.95	(0.67-1.35)
New York Multicenter	0.87	(0.72-1.05)	0.89	(0.64-1.23)
New York, NY, USA	0.66	(0.36-1.22)	0.45	(0.12-1.67)
North Carolina, USA (1)	1.13	(0.61-2.08)	1.71	(0.67-4.37)
North Carolina, USA (2)	1.04	(0.89-1.22)	0.75	(0.56-1.00)
Seattle, WA, USA (1)	1.01	(0.71-1.43)	1.06	(0.62-1.81)
Seattle, WA, USA (2)	0.92	(0.71-1.19)	0.73	(0.50-1.07)
Tampa, FL, USA	0.97	(0.70-1.33)	0.88	(0.51-1.54)
US Multicenter	1.02	(0.87-1.20)	1.00	(0.77-1.30)
Puertorico	1.06	(0.79-1.43)	1.24	(0.60-2.55)
South America	0.93	(0.80-1.07)	0.73	(0.51-1.04)
Japan (1)	0.72	(0.58-0.89)	0.78	(0.51-1.20)
Japan (2)	0.49	(0.19-1.29)	0.80	(0.49-1.33)
IARC Multicenter	0.78	(0.66-0.91)	0.83	(0.64-1.08)
Overall	0.90	(0.86-0.94)	0.85	(0.79-0.92)

	Men OR	Men 95% CI	Women OR	Women 95% CI
Age				
<50	0.87	(0.79-0.95)	1.01	(0.87-1.18)
50-59	0.93	(0.87-0.99)	0.86	(0.74-0.99)
60-69	0.88	(0.82-0.94)	0.85	(0.73-0.97)
70 or more	0.92	(0.83-1.01)	0.75	(0.63-0.89)
Body-mass index				
<18.5	0.80	(0.62-1.02)	1.11	(0.81-1.52)
18.5-24.9	0.92	(0.86-0.97)	0.81	(0.72-0.90)
25.0-29.9	0.91	(0.85-0.97)	0.80	(0.69-0.93)
30.0 or more	0.94	(0.84-1.05)	0.93	(0.76-1.12)
Education level				
No education	0.63	(0.48-0.83)	0.71	(0.51-0.98)
< Junior high school	0.85	(0.79-0.91)	0.81	(0.70-0.93)
Some high school	0.89	(0.82-0.97)	0.86	(0.72-1.04)
High school graduate	0.96	(0.85-1.07)	0.93	(0.76-1.15)
Technical school, some college	0.96	(0.87-1.06)	0.96	(0.82-1.12)
> College graduate	0.94	(0.84-1.05)	0.82	(0.66-1.01)
Smoking				
Never	0.97	(0.85-1.10)	0.91	(0.80-1.03)
Former	0.90	(0.84-0.96)	0.75	(0.63-0.90)
Current	0.85	(0.81-0.90)	0.83	(0.73-0.95)
Alcohol				
Never	0.88	(0.78-1.00)	0.92	(0.82-1.04)
Ever	0.90	(0.86-0.93)	0.85	(0.77-0.93)
Geographic area				
Europe	0.87	(0.82-0.92)	0.82	(0.73-0.93)
North America	0.98	(0.92-1.05)	0.92	(0.82-1.03)
Central and South America	0.94	(0.82-1.06)	0.80	(0.59-1.09)
Asia	0.82	(0.70-0.96)	0.83	(0.66-1.05)
Study design				
Hospital based controls	0.86	(0.82-0.91)	0.87	(0.79-0.95)
Population based controls	0.96	(0.90-1.02)	0.88	(0.78-0.99)
Cancer site				
Oral cavity	0.86	(0.81-0.92)	0.89	(0.80-0.98)
Oropharynx	0.90	(0.85-0.95)	0.79	(0.69-0.89)
Hypopharynx	0.80	(0.73-0.88)	0.74	(0.58-0.95)
Larynx	0.93	(0.88-0.99)	0.94	(0.80-1.11)