Original Article

Adult height is not associated with the risk of stomach cancer in a meta-analysis

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Background: Adult height has been suggested as a biomarker for a wide range of diseases. However, there are epidemiologic inconsistencies regarding the association between adult height and stomach cancer risk.

Methods: We retrieved PubMed, EMBASE and Cochrane library databases to identify relevant studies assessing the relationship between height and risk of stomach cancer, published from inception to June 4, 2019. We pooled effect sizes for 5-cm height increments using a random-effect model and obtained the cumulative relative risk (RR) and 95% confidence interval (CI). Additionally, we performed subgroup investigation with sensitivity analysis and tested for publication bias using the Begg rank correlation test.

Results: We analyzed 11 studies involving 137,451 cases. The summary of effect size (95% CI) of stomach cancer for a 5-cm-increase in adult height was 0.99 (0.95–1.02). A "leave-one-out" sensitivity analysis indicated that the heterogeneity decreased by a half and the result showed significance (RR, 0.972; 95% CI, 0.948–0.997). Subgroup analyses found no significant associations, with one exception. The exception also depended entirely on one study. We found no significant publication bias (P=0.276).

Conclusions: Height is not associated with increased stomach cancer risk. Epidemiologic studies of potential confounders are needed to clarify the association.

Keywords: Height; stomach cancer; meta-analysis

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Introduction

Stomach cancer is one of common cancers and leading causes of cancer-related death worldwide, responsible for more than one million incident cases and an estimated 783,000 deaths in 2018 (1). Multiple factors have a role in the etiology of stomach cancer. Some of them (e.g., age, sex, ethnicity, and genetic factors) are not modifiable, whereas nutritional and behavioral factors potentially are (2). Non-modifiable factors are not preventable but identifying them would be helpful to design effective screening programs.

Adult height is an indicator of the interplay between genetics and various environmental exposures during childhood, such as fetal, nutritional, socioeconomic, and psychological circumstances (3). Height is related to the risk of mortality and major diseases such as cancers and cardiovascular diseases (4,5). Taller adults are reported to have increased risk for overall cancer and several common cancers. However, findings regarding height and stomach cancer are inconsistent.

Because height range is usually narrow and large numbers of events are needed to reliably estimate risk, a pooled analysis is warranted. Notably, many studies relevant to this question were obscured by titles that emphasized other cancers or total cancers. Thus, to clarify the association between height and risk of stomach cancer comprehensively, we performed a meta-analysis with rigorous search strategies. We present the following article in accordance with the PRISMA 2009 reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-199.

Methods

Search strategy

This meta-analysis followed the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines (6). We used PubMed, EMBASE and Cochrane library databases to identify relevant studies published from inception to June 4, 2019 that investigated the association between adult height and incident stomach cancer. The following keywords were used to extract the articles: ("anthropometry" OR "body size" OR "height") AND ("cancer" OR "neoplasm" OR "carcinoma") AND "risk". No restrictions were applied for language. We also manually searched the reference lists of all related articles and reviews to identify undetected relevant studies.

Selection and processing

Two authors (MS Seo and DK Park) performed all processes independently and resolved disagreements through discussion. Studies were included if they met the following criteria: (I) reported an association of adult height with stomach cancer; (II) reported risk estimates for incident stomach cancer, including relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs) with 95% confidence intervals (CIs). When duplicate records were present for the same population, we selected studies with the most informative reporting or the larger sample size.

The following variables were extracted from each study: the first author's name; publication year; country where the study was performed; study design; participants; number of stomach cancer cases; follow-up years; assessment of height; the fully adjusted estimate with the corresponding 95% CI; and covariates adjusted for the analysis.

We used the Newcastle-Ottawa Scale (NOS) to assess the study quality and allowed a total of 9 points to summarize eight aspects (with 9 points representing the highest quality) (7). An NOS score ≥8 was defined as "high quality".

Statistical methods

Pooled measure was calculated as the inverse-variance weighted mean of the logarithm of RR (95% CI) for stomach cancer for a 5-cm-increase in height. We considered HRs or ORs equivalent to RRs (8). We unified the forms of estimate as an RR for a 5-cm-increase in height, to minimize variability in categorization across the studies. For studies that did not provide estimates per unit of height, we used the Greenland and Longnecker method, which requires the case numbers and person-years or non-cases and RRs with variance estimates for at least three height groups (9). We computed subgroup estimates (e.g., sex-specific or site-specific estimates) before inclusion in the meta-analysis.

We performed statistical analyses using Stata v9.2 (Stata Corp, College Station, TX, USA). Heterogeneity was tested using I^2 statistics: I^2 >50% is considered a high heterogeneity (10). A random effects model was used if substantial heterogeneity was observed; otherwise, a fixed effects model was applied. We performed subgroup analyses according to sex, study design, ethnicity, height assessments, body mass index (BMI) adjustment, and study quality. We also performed a leave-one-out sensitivity analysis by excluding one study at a time to assess results stability and potential sources of heterogeneity (11). Visual inspection of funnel plots and the Begg rank correlation test were used to assess publication bias.

Results

Search and characteristics

A flowchart of the study selection procedure is shown in *Figure 1*. After a first screening of duplicate and non-relevant articles by title and/or abstract, we selected 36 articles for further assessment and reading of the full text. After detailed evaluations, we identified 11 observational studies that met all criteria for this meta-analysis (12-22). Detailed information about the studies included is summarized in *Table 1*.

Quantitative analysis

The pooled RR was 0.99 (95% CI, 0.95–1.02) with each

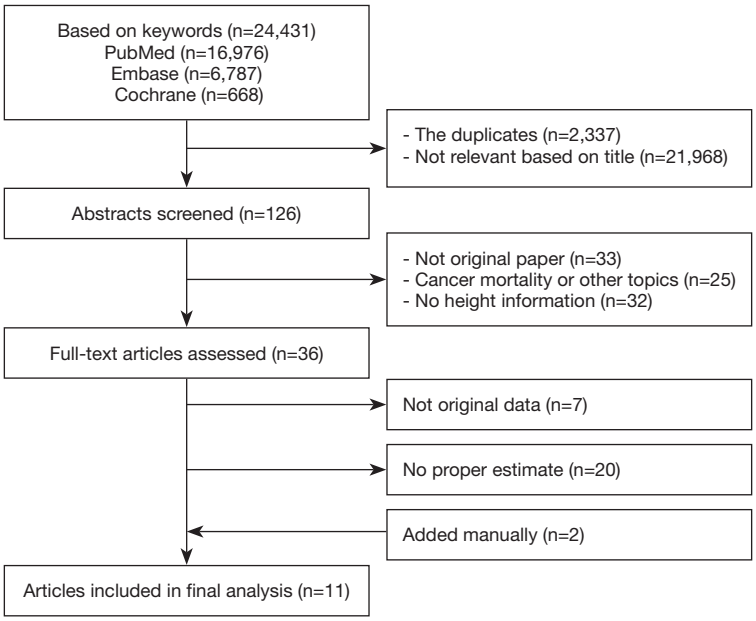

Figure 1 Flow diagram of the study selection process.

Table 1 Characteristics of studies on the effect of height on stomach cancer risk

Study	Country	Design	Participants	Cases	Follow-up years	Height assessment	Adjusted core variates other than age and sex	Quality*
Choi, 2019	Korea	Nested case-control	22,809,722 adults	131,682	5	Measured	BMI, smoking, alcohol, exercise, diabetes	9
Wiren, 2014	Austria, Norway, Sweden	Prospective (Me-Can cohort)	5,885,928 adults	1,202	12.7	Measured	None	7
Kabat, 2014	USA	Prospective (NIH-AARP)	481,197 adults	909	10.5	Self-reported	BMI, smoking, SES, menarche age	7
Kabat, 2013	USA	Prospective (WHI)	144,701 women	152	12	Measured	BMI, smoking, alcohol, SES	9
Green, 2011	UK	Prospective	1,297,124 women	1,177	9.4	Self-reported	BMI, smoking, alcohol, exercise, SES, menarche age	8
Minami, 2008	Japan	Case-control	1,730 controls	584	NR	Self-reported	Smoking, alcohol, occupation, family cancer history	4
Merry, 2007	The Netherlands	Prospective	120,852 adults	163	13.3	Self-reported	BMI, smoking, SES	8
MacInnis, 2006	Australia	Prospective	41,295 adults	98	11.3	Measured	Exercise, SES	7
Gunnell, 2003	UK	Prospective	2,393 men	22	21	Measured	BMI, smoking, SES	8
Ji, 1997	China	Case-control	1,451 controls	1,124	NR	Self-reported	Smoking, alcohol, SES, chronic gastric diseases	4
Hansson, 1994	Sweden	Case-control	679 controls	338	NR	Self-reported	BMI	4

*, based on the Newcastle-Ottawa Scale (0–9). Me-Can, Metabolic syndrome and Cancer project; NIH-AARP, National Institutes of Health-American Association of Retired Persons; WHI, Women's Health Initiative; BMI, body mass index; SES, socioeconomic status.

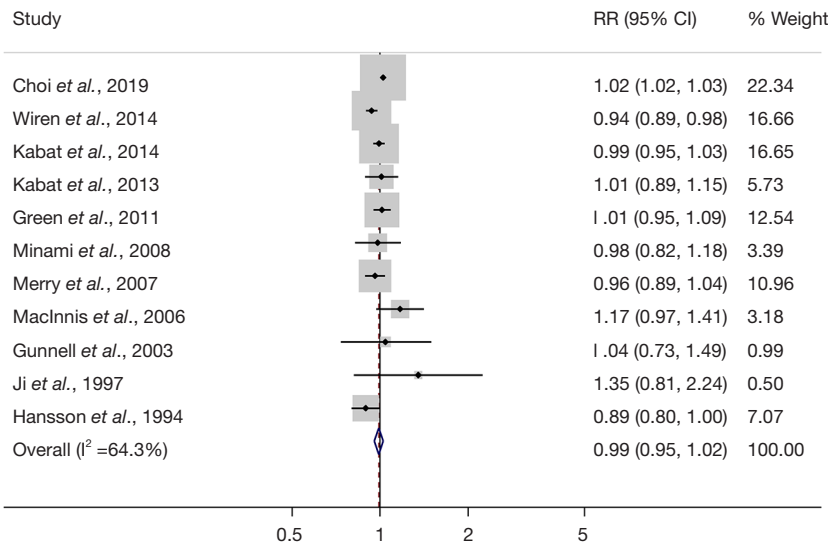

Figure 2 Forest plot of the association between height and stomach cancer risk. RR refers to the risk for developing stomach cancer per a 5-cm increase in height. RR, relative risk; CI, confidence interval.

5-cm increase of adult height (*Figure 2*). Subgroup analysis and sensitivity analysis results are shown in *Table 2*. A "leave-one-out" sensitivity analysis—excluding Choi *et al.*'s study—revealed that the heterogeneity decreased by a half and the result showed significance (RR, 0.972; 95% CI, 0.948–0.997). Overall, subgroup analysis findings depended on the study by Choi *et al.* In the analysis that found a significant positive result, the proportional weight of Choi *et al.*' study was more than 95%. The funnel plot of the analysis of height and the risk of stomach cancer is shown in *Figure 3* and a significant publication bias was not observed (P=0.276).

Discussion

In this pooled meta-analysis, we found no significant trend indicating an increased stomach cancer risk with increasing height. Rather, shorter Caucasians seemed to have higher risk for stomach cancer, and other subgroup analyses yielded no informative conclusions.

Stomach cancer has distinct epidemiological and clinical characteristics by the site (i.e., cardia *vs.* non-cardia) (23). Western countries have a higher proportion of and absolute increase in the incidence of cardia stomach cancer relative to non-cardia stomach cancer (24,25). Obesity is a major risk factor for gastric cardia cancer, possibly through the association with gastroesophageal reflux disease (26). Short people have a higher BMI and higher obesity risk than taller people of the same weight. This is also true for non-cardia gastric cancer, mainly caused by the infection with *Helicobacter Pylori* (*H. pylori*) (27). Chronic *H. pylori* infection is associated with poor growth in children (28), and thus this might explain the inverse association between height and stomach cancer (29). Notably, the NIH-AARP Diet and Health cohort reported that patients with non-cardia gastric cancer tend to be short in stature (30).

Adult height is determined both by genetics and early life exposures, and the outcomes of genetic potentials depend on environmental circumstances (3). Mechanisms have been proposed to explain the association between adult height and cancer (5). One explanation is that an insulin-like growth factor related to skeletal growth would also promote cell proliferation, inhibit apoptosis, and eventually lead to cancer (31,32). Cellularity provides another potential explanation: taller people have larger organs composed of more individual cells, which translates to more opportunities for mutations that could lead to malignant transformation (33,34). However, it is unclear if the above mechanisms contribute to stomach cancer risk.

Our meta-analysis has several limitations. First, the current findings are severely depended on only one study. In addition, lack of some information did not allow us to further address the association (e.g., the tallest group *vs.* the shortest group). Second, although some risk factors

Table 2 Stomach cancer risk of a 5-cm increment in height

Variables	No. of studies	Summary RR (95% CI)	Heterogeneity, I^2	Model
Overall	11	0.99 (0.95–1.02)	64.3%	Random
Excluding Choi *et al.*	10	**0.972 (0.948–0.997)**$^{\#}$	32.2%	Fixed
Sex				
Male	7	0.98 (0.94–1.02)	56.3%	Random
Female	7	**1.04 (1.03–1.05)**$^{\#}_{choi}$	45.7%	Fixed
Study design				
Case-control	4	0.98 (0.90–1.08)	57.0%	Random
Prospective	7	0.976 (0.950–1.001)	35.8%	Fixed
Ethnicity				
Caucasian	8	**0.971 (0.947–0.996)**$^{\#}$	39.9%	Fixed
Asian	3	**1.02 (1.02–1.03)**$^{\#}_{choi}$	0%	Fixed
Height assessment				
Self-reported	6	0.98 (0.95–1.01)	11.8%	Fixed
Measured	5	1.00 (0.94–1.07)	76.4%	Random
BMI adjustment				
No	4	1.02 (0.90–1.16)	58.3%	Random
Yes	7	**1.02 (1.02–1.03)**$^{\#}_{choi}$	39.8%	Fixed
Study quality*				
Low	6	0.97 (0.92–1.03)	53.7%	Random
High	5	**1.02 (1.02–1.03)**$^{\#}_{choi}$	0%	Fixed

"Choi" in the subscripts refers to inclusion of the Choi *et al.* study; however, when it was excluded, the result was null. *, assessed using the Newcastle-Ottawa Scale score (<8 *vs.* ≥8). $^{\#}$, statistical significance shown in bold. RR, relative risk; CI, confidence interval.

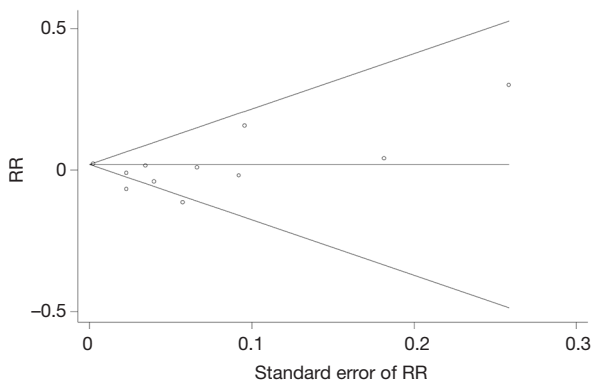

Figure 3 Funnel plot with 95% confidence limits for the incidence of stomach cancer among the included studies. RR, relative risk.

were controlled, the possibility of unknown or residual confounding cannot be ruled out. The current evidence is flawed by a lack of data for certain factors, particularly the site of stomach cancer (i.e., cardia *vs.* non-cardia) and presence of *H. pylori* infection. Third, height assessments varied across the studies. Self-reporting to assess height may have led to overestimation of the actual heights, although high correlation has been reported between measured and self-reported one (35). Finally, the potential publication bias remains, despite no evidence of small study effects with the statistical tests in our study. It is still possible that many studies with null findings have been left unpublished.

In conclusion, this meta-analysis found no association between height and stomach cancer risk. Large-scale

multicenter hospital-based studies with detailed clinical information are warranted to elucidate subsite- and infection-specific associations.

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Footnote

Reporting Checklist: The authors have completed the PRISMA 2009 reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-199

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-199). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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