



Original article

Body mass index and height in relation to brain tumor risk in a Japanese population



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ARTICLE INFO

Article history:

Received 31 May 2019

Accepted 2 June 2020

Available online 18 August 2020

Keywords:

JPHC study

Japanese

Brain tumor

Body mass index

Height

Prospective study

ABSTRACT

Purpose: Although height and body mass index (BMI) are reported to be positively associated with several common cancers, evidence regarding their association with brain tumor risk remains sparse, particularly in Asian populations. In this study, we analyzed the association between height and BMI and brain tumor risk in a Japanese population using a large population-based prospective cohort study.

Methods: A total of 102,925 participants (48,213 men and 54,712 women) enrolled in the Japan Public Health Center-based Prospective Study were followed from baseline, namely 1990 for cohort I and 1993 for cohort II, until 2012. Information on participants' dietary and lifestyle habits, including height and body weight, was collected through survey questionnaires administered at baseline. We used the Cox proportional hazards regression model to estimate hazard ratios and 95% confidence intervals (CIs) for brain tumor incidence, with adjustment for potential confounding variables.

Results: During an average follow-up of 18.1 years, 157 (70 men and 87 women) cases of brain tumor were newly diagnosed. BMI showed a statistically insignificant positive association with the risk of brain tumor. In addition, statistically significant positive trends were seen for men and meningioma, with multivariable-adjusted hazard ratios for a BMI of 27.5 to less than 40 versus 18.5 to less than 23 kg per m² of 2.14 (95% CI = 0.99–4.59) (P = 0.03) and 1.98 (95% CI = 0.84–4.67) (P = 0.046), respectively. In contrast, height showed no clear association with brain tumor risk, overall or in subgroup analysis.

Conclusions: Compared with a BMI of 18 to less than 23.5 kg per m², a higher BMI was associated with higher risk of brain tumor, particularly in men and with meningioma.

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Grant support: This study was supported by a National Cancer Center Research and Development Fund (since 2011) and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (from 1989 to 2010).

Novelty and impact statements: In this study, we found a significant positive association between BMI and brain tumor risk, especially in men. Furthermore, meningioma risk increases with increasing BMI. The novelty of our study is its focus on the association of BMI with brain tumor risk among an Asian population, whose distribution of anthropometric data differs from Westerners.

Authors' contribution: T. O. and N. S. conceived and performed conceptualization, analysis, and data calculation. T. O. and N. S. wrote the manuscript. M. I., S. B., T. Y., T. S., Y. N. and S.T. provided expertise and feedback.

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<https://doi.org/10.1016/j.annepidem.2020.06.001>

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Introduction

Although obesity is an established risk factor for several types of cancer, evidence linking obesity to the risk of brain tumor is not consistent. Two recent meta-analyses which summarized evidence regarding the association between meningioma and glioma risk associated with body mass index [1,2]; both reported an increased risk associated with high body mass index (BMI) for meningioma in both men and women. However, the observation for glioma risk was inconsistent: although one study found no clear association between high BMI and glioma risk among total participants [2], the second meta-analysis of two cohorts reported an increased risk of glioma associated with high BMI, but only among women [1]. Moreover, all the previous prospective studies included in these two meta-analyses were conducted in Western countries [1,2]. Among reports from Asia, a prospective study in Korea reported a positive association between BMI and total brain tumor [3], whereas a pooled analysis of the Asia–Pacific Cohort Studies showed no association between BMI and mortality of the brain and nervous system [4]. However, these studies in Asian populations did not analyze meningioma and glioma separately [3].

Although epidemiologic evidence suggests a higher risk of several types of cancer associated with taller height [5–9], only a few reports have presented the association between height and brain tumors. A pooled analysis from 13 prospective and two case-control studies reported a greater than two-fold higher risk of glioma among tall persons (≥ 190 cm) compared with that in short persons (< 160 cm) (hazard ratio (HR) = 2.12, 95% confidence interval (CI) = 1.25–3.58), but this pooled analysis included only one prospective study from Asia [10], namely the Shanghai Men's and Women's Health Study, which showed no association. In addition, a large prospective study in 1.8 million Norwegian residents showed no association between height and meningioma and glioma [11].

Based on GLOBOCAN 2012 estimates, the incidence rate of brain, central nervous system group in Asia (age standardized rate of 3.3 in men and 2.7 in women (per 100,000)) is lower than that in Europe (age standardized rate of 6.3 in men and 4.6 in women (per 100,000)) [12]. Evidence from Japanese populations, whose distribution of anthropometric data differs from that among Westerners, may help clarify the cause of these differences in the brain tumor incidence rate.

In this analysis, we investigated the association of BMI, height, and brain tumor in a middle-aged Japanese population using data obtained from a prospective cohort study.

Methods

The Japan Public Health Center–based Prospective Study consists of two cohorts with a total of 140,420 participants from 11 public health center areas across Japan. The first cohort was started in 1990 and included 61,595 residents aged 40–59 years, whereas the second cohort was started in 1993 and included 78,825 residents aged 40–69 years. Details of the study design are presented elsewhere [13]. For this analysis, we excluded one public health center area (Tokyo) because of a lack of incidence data ($n = 7097$). In addition, we also excluded participants with non-Japanese nationality ($n = 51$), late report of emigration occurring before the start of follow-up ($n = 188$), incorrect birth date ($n = 7$), and duplicate registration ($n = 10$), leaving a total of 133,067 participants in the eligible cohort. The protocol of the Japan Public Health Center–based Prospective Study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

Questionnaire

At baseline, all enrolled participants were encouraged to complete self-administered survey questionnaires. These questionnaires inquired about various lifestyle and demographic factors, including current height and weight in 1990 for cohort I and in 1993–1994 for cohort II. A total of 106,324 participants completed and returned the baseline questionnaires, giving a response rate of 80%. Of these, 102,925 participants provided information on BMI, and were used for analysis. BMI was calculated as weight in kilograms divided by the squared height in meters. For the present analysis, we divided participants into five categories based on the distribution of BMI as 14 to less than 18.5, 18.5 to less than 23, 23 to less than 25, 25 to less than < 27.5 , and 27.5 to less than 40 kg per m^2 . Participants with an implausible response for BMI (≤ 14 or ≥ 40 ; $n = 27$) were excluded. We divided height into sex-specific tertile categories because of the narrow range, particularly in women. Our validation study showed a high correlation between self-reported and measured values for BMI.

Follow-up

We followed study participants from baseline to the end of 2012. During the follow-up period, changes in residency and the vital status of participants were determined annually through the residential registry in each municipality of the study areas, whereas information on cause of death was confirmed using death certificates, with the permission of the Ministry of Health, Labor and Welfare. Among study participants, 18.0% died, 10.7% moved out of the study area, and 0.2% was lost to follow-up.

We identified incident cancer cases through the records of major local hospitals in the study area and population-based cancer registries. Brain tumor cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), codes C70 (meninges), C71 (brain), C72 (spinal cord, cranial nerves and other parts of the central nervous system (CNS)), and C75 (other endocrine glands and related structures). Metastatic tumors are excluded. Subgroups of brain tumors were defined using the ICD-O-3 histology codes 9380–9480 for gliomas, 9530–9539 for meningiomas, 9560 for schwannomas, 9590–9591/9680 for lymphomas, and 8270–8290 for pituitary adenomas and others. Histological type was determined by histology (78%) and imaging (10%) in glioma and by histology (68%) and imaging (5%) in meningioma. The others were mainly reported by death certificates only, and we recognized them as “8000”. Death certificate information was used as a supplementary information source for cancer incidence, and the proportion of brain tumor cases for which information was available from the death certificate only was 8.6%. A total of 157 brain tumor incident cases (70 men and 87 women) were newly diagnosed during this analysis.

Statistical analysis

We calculated person years of follow-up for each participant from the date of response to the baseline questionnaire to the date of brain tumor diagnosis, date of death, date of emigration from the study area, or December 31, 2012, whichever came first. HRs and 95% CIs of brain tumor incidence in accordance with categories of height and BMI were estimated using Cox proportional hazards model, with adjustment for potential confounding variables. We adjusted for potential confounding variables in two multivariate models; the first included age and sex, whereas the second further adjusted for pack-years of cigarette smoking (never/past smoker, 0–20, > 20 pack-years), alcohol intake (never, past and 1–3 times/month, regular drinker with ≤ 150 g of ethanol/week, or > 150 g of

ethanol/week), coffee (non and 1–4 times/week, 1–2 cups/day, ≥ 3 cups/day), green tea (non and 1–4 times/week, 1–2 cups/day, ≥ 3 cups/day), past history of allergy, and past history of diabetes mellitus (DM). We tested trends across 18.5 to less than 23, 23 to less than 25, 25 to less than 27.5, and 27.5 to less than 40 kg per m² using ordinal numbers 0–3 assigned to each category among participants with BMI greater than or equal to 18.5. All *p*-values were evaluated using the two-sided test with 0.05 as the statistical significance level. All analyses were conducted with SAS statistical software, version 9.3 (SAS Institute INC., Cary, NC).

Results

During an average follow-up of 18.1 years, 157 incident cases of brain tumor were newly identified, included glioma (*n* = 60) and meningioma (*n* = 51). By sex, 70 cases were in men and 87 were in women. For glioma cases, distribution by sex was specified, with 30 each in men and women. Distribution by sex was also specified for meningioma cases, with 17 in men and 34 in women.

The baseline characteristics of the cohort participants in accordance with BMI and height are presented in Tables 1 and 2. With regard to the number of participants, the moderate BMI category of 18.5–23 accounted for approximately half of total participants. Participants with higher BMI were less likely to be smokers. Alcohol drinkers had the highest proportion in the middle categories. Participants with higher BMI had a lower proportion of coffee and green tea consumption and, conversely, a higher proportion of DM. Participants with higher height had a higher proportion of smoking, alcohol consumption, allergy, coffee consumption, and green tea consumption. In contrast, those with a higher proportion of DM showed the opposite trend.

Table 3 shows the association between BMI and risk of brain tumors in total, men, women, and by subtype analysis (glioma and meningioma) with multivariate models. We observed a positive but insignificant association between BMI and brain tumor risk in the overall population, with HRs for BMI categories of 14 to less than 18.5, 23 to less than 25, 25 to less than 27.5, and 27.5 to less than 40 kg per m² compared with the reference category of 18.5 to less than 23 kg per m² of 0.54 (95% CI 0.17–1.71), 0.90 (0.59–1.39), 1.45 (0.96–2.18), and 1.27 (0.74–2.18), respectively (*P* trend = .12). When we repeated this analysis by gender, BMI showed a significant positive trend with brain tumor risk in men [HRs for BMI categories of 23–<25, 25–<27.5, and 27.5–<40 kg per m² compared with the reference category of 18.5–<23 kg per m² of 1.01 (0.53–1.93), 1.62 (0.87–3.05), and 2.14 (0.99–4.59), respectively, (*P* trend .03)] but not in women (*P* trend .75). In another analysis by tumor subtype, we observed HRs for a significant positive association between BMI and meningioma risk [HRs for BMI categories of 23–<25, 25–<27.5, and 27.5–<40 kg per m² compared with the reference category of 18.5–<23 kg per m² of

0.98 (95% CI = 0.45–2.16), 1.88 (0.91–3.85), and 1.98 (0.84–4.67), respectively, (*P* trend .046)]. After analyzing meningioma by sex, both groups showed a tendency for people with a BMI greater than 25 to be at higher risk of meningioma compared with those with 18.5 to less than 23, albeit that this was not statistically significant because of the small number of cases in this subgroup. Although the lower HR in the lowest BMI category might have been biased by representative malnutrition from competing health issues that interfered with the development or diagnosis of CNS tumor, these results were not changed by competing risk analysis for death. In addition, results did not substantially change after exclusion of participants with a history of severe disease like cancer, cardiovascular disease, and DM at baseline (data not shown), or after exclusion of those with a history of brain tumor (*n* = 19) (data not shown). On the other hand, we observed an insignificant but inverse association with height (*P* trend .08) among the total population (Table 4). In subgroup analysis, association between body height and glioma or meningioma risk was not substantially changed.

Discussion

In this large prospective study of Japanese adults, we found that higher BMI showed a tendency to be associated with increased overall brain tumor risk compared with a BMI of 18.5 to less than 23 kg per m². In contrast, height showed only a suggestive inverse association with brain tumor risk in the overall population although this association was largely null in subgroup analysis.

Previous studies have reported positive associations between BMI and the risk of several cancers, including colorectal and breast among others [7,14,15]. With regard to brain tumor, two meta-analyses reported a clearer association between BMI and meningioma, which is consistent with our results [1,2]. One meta-analysis reported that overweight and obesity were associated with increased risk of meningioma (pooled relative risk (RR) (95% CI) = 1.21 (1.01–1.43) and 1.54 (1.32–1.79), respectively)[2], and another meta-analysis reported that overweight or obesity correlated with increased meningioma risk in men (pooled RR = 1.58, 95% CI: 1.22–1.04) and in women (pooled RR = 1.27, 95% CI: 1.13–1.43)[1]. However, the association between BMI and glioma was not clear [1, 2]. Our study showed a similar result to this meta-analysis.

The reason that the positive association of high BMI with meningioma is clearer than that with glioma may be at least in part explained by obesity-related chronic inflammation. Adipose tissue induces proinflammatory cytokines, for example, tumor necrosis factor-alpha and interleukin-6. High-BMI participants may have developed the capacity to initiate and develop neoplastic processes within a metabolic environment which is exposed to a chronic inflammatory state [16,17]. A second possible mechanism involves sex hormones. Excess estrogen is produced in adipose tissue [18],

Table 1
Characteristics of the study participants by body mass index

	Body mass index (kg/m ²)					P-value
	14–<18.5	18.5–<23	23–<25	25–<27.5	27.5–<40	
Number of participants, (<i>n</i>)	4458	44,450	26,055	18,646	9316	
Age at baseline (Y), mean (SD)	53.3 (9.0)	51.5 (8.2)	51.7 (7.8)	52.1 (7.7)	52.1 (7.6)	<.001
Body mass index at baseline (kg/m ²), mean (SD)	17.6 (0.8)	21.1 (1.2)	24.0 (0.6)	26.1 (0.7)	29.5 (1.9)	<.001
Smoking status (past or current smoker), %	31.2	30.7	27.4	25.4	22.4	<.001
Alcohol drinking status (regular drinkers), %	17.5	22.5	24.6	23.6	20.00	<.001
Past history of diabetes mellitus (yes), %	4.6	4.2	4.8	5.6	6.6	<.001
Past history of allergy (yes), %	6.2	5.9	5.3	5.5	5.3	.004
Coffee drinking status (regular drinkers), %	38.5	41.8	39.2	38.2	35.6	<.001
Green tea drinking status (regular drinkers), %	74.4	76.3	75.2	73.3	70.0	<.001

Table 2
Characteristics of the study participants by height

	Height (cm)			P-value
	<150	150–<154	≥154	
Women				
Men	<162	162–<167	≥167	
Number of participants (n)	32,929	32,776	37,220	
Age at baseline (y), mean (SD)	54.6 (7.8)	51.8 (7.7)	49.3 (7.5)	<0.001
Body mass index at baseline (kg/m ²), mean (SD)	23.7 (3.1)	23.5 (3.0)	23.1 (3.0)	<0.001
Smoking status (past or current smoker), %	26.2	27.9	30.2	<0.001
Alcohol drinking status (regular drinker), %	22.0	22.6	23.6	<0.001
Past history of diabetes mellitus (yes), %	5.6	4.9	4.1	<0.001
Past history of allergy (yes), %	4.8	5.6	6.4	<0.001
Coffee drinking status (regular drinker), %	33	39.1	45.4	<0.001
Green tea drinking status (regular drinker), %	72.8	74.4	75.1	<0.001

and sex steroid hormone receptors are indeed present in most meningiomas, of which around 40% express the estrogen receptor [19]. Findings that meningioma progresses during pregnancy may suggest that sex steroid hormones are involved in the progression of meningioma [20]. Moreover, our present finding of a stronger association between BMI and brain tumor in men but not in women may suggest that chronic inflammation factors are related with meningioma and brain tumor in Japanese populations.

Previous studies showed positive associations with adult height and brain tumors in large cohorts [21,22] and glioma in a pooled analysis [10], albeit that the results for glioma in Asian populations were inconsistent in some previous studies [10,22,23]. It is hypothesized that the link between adolescent height and cancer risk is predicated on levels of insulin-like growth factor during childhood [6]. Here, however, we observed an insignificant inverse association between high height and brain tumor in all participants.

Japanese people are generally shorter than Western populations and additionally have a narrower height range. Considering that the highest category in one of these studies, which showed a statistically significant positive association, was more than 190 cm [10], it might be hard to reflect influence of insulin-like growth factor due to high height.

The strengths of our study include its prospective cohort design and long follow-up. The response rate to participation was high (approximately 80%), and the proportion of participants lost to follow-up was relatively low (0.2%). Information on other lifestyle covariates was also prospectively collected, thus minimizing concerns of recall bias.

This cohort study also has several limitations. First, the anthropometric information used in the analysis was based on self-report, and some misclassification might have necessarily occurred in the exposure assessment. Nonetheless, our validation study

Table 3
Hazard ratios and 95% confidence intervals of brain tumor by body mass index

	Body mass index (kg/m ²)					P trend (among participants with BMI ≥18.5)
	14–<18.5	18.5–<23	23–<25	25–<27.5	27.5–<40	
Total cases (n = 157)						
Case (n)	3	60	34	41	19	
Person year	73,669	795,869	477,786	342,666	170,505	
HR (95% CI)*	0.50 (0.16–1.60)	1.00 (ref)	0.92 (0.60–1.40)	1.50 (1.01–2.24)	1.34 (0.79–2.26)	.07
HR (95% CI)†	0.54 (0.17–1.71)	1.00 (ref)	0.90 (0.59–1.39)	1.45 (0.96–2.18)	1.27 (0.74–2.18)	.12
Men (n = 70)						
Case (n)	1	24	16	19	10	
Person year	28,316	348,436	233,078	162,851	68,799	
HR (95% CI)*	0.48 (0.07–3.54)	1.00 (ref)	1.00 (0.53–1.89)	1.70 (0.92–3.12)	2.11 (0.99–4.48)	.03
HR (95% CI)†	0.53 (0.07–3.90)	1.00 (ref)	1.01 (0.53–1.93)	1.62 (0.87–3.05)	2.14 (0.99–4.59)	.03
Women (n = 87)						
Case (n)	2	36	18	22	9	
Person year	45,353	447,432	244,708	179,815	101,706	
HR (95% CI)*	0.52 (0.12–2.15)	1.00 (ref)	0.88 (0.50–1.55)	1.42 (0.83–2.42)	0.98 (0.47–2.05)	.52
HR (95% CI)†	0.54 (0.13–2.25)	1.00 (ref)	0.84 (0.47–1.50)	1.36 (0.79–2.36)	0.86 (0.40–1.87)	.75
Glioma (n = 60)						
Case (n)	1	24	13	16	6	
Person year	73,665	795,508	477,552	342,376	170,368	
HR (95% CI)*	0.45 (0.06–3.36)	1.00 (ref)	0.85 (0.43–1.68)	1.43 (0.76–2.70)	1.07 (0.43–2.63)	.48
HR (95% CI)†	0.50 (0.07–3.72)	1.00 (ref)	0.86 (0.44–1.71)	1.43 (0.75–2.73)	1.06 (0.43–2.63)	.48
Meningioma (n = 51)						
Case (n)	0	17	11	15	8	
Person year	73,646	795,430	477,531	342,366	170,368	
HR (95% CI)*	—	1.00 (ref)	1.11 (0.52–2.37)	2.06 (1.02–4.16)	2.02 (0.86–4.75)	.03
HR (95% CI)†	—	1.00 (ref)	0.98 (0.45–2.16)	1.88 (0.91–3.85)	1.98 (0.84–4.67)	.046

* Adjusted for age and sex.

† Further adjusted for pack-years of cigarette smoking (never and past, 0–20, >20), alcohol intake (none and past and 1–3 times/month, drinking of ≤150, 150g of ethanol/week), coffee (none and 1–4 times/week, ≥3 cups/day), green tea (none and 1–4 times/week, 1–2 cups/day, 3–4 cups/day, ≥5 cups/day), past history of diabetes mellitus and allergy.

Table 4
Hazard ratios and 95% confidence intervals by height

	Height (cm)			P-value
	<150 cm	150–<154 cm	≥154 cm	
Women				
Men	<162 cm	162–<167 cm	≥167 cm	
Total (n = 157)				
Case (n)	67	47	43	
Person years	598461	597201	664833	
HR (95% CI)*	1.00 (ref)	0.78 (0.53–1.14)	0.68 (0.45–1.03)	0.06
HR (95% CI)†	1.00 (ref)	0.80 (0.54–1.18)	0.70 (0.46–1.06)	0.08
Men (n = 70)				
Case (n)	29	24	17	
Person years	278889	269729	292863	
HR (95% CI)*	1.00 (ref)	0.95 (0.55–1.65)	0.69 (0.37–1.31)	0.28
HR (95% CI)†	1.00 (ref)	0.98 (0.56–1.71)	0.68 (0.36–1.31)	0.28
Women (n = 87)				
Case (n)	38	23	26	
Person years	319571	327473	371970	
HR (95% CI)*	1.00 (ref)	0.65 (0.38–1.10)	0.67 (0.40–1.14)	0.13
HR (95% CI)†	1.00 (ref)	0.66 (0.39–1.14)	0.70 (0.41–1.21)	0.18
Glioma (n = 60)				
Case (n)	27	18	15	
Person years	598067	596878	664523	
HR (95% CI)*	1.00 (ref)	0.73 (0.40–1.34)	0.60 (0.31–1.18)	0.13
HR (95% CI)†	1.00 (ref)	0.77 (0.42–1.41)	0.64 (0.33–1.25)	0.18
Meningioma (n = 51)				
Case (n)	21	14	16	
Person years	597967	596833	664541	
HR (95% CI)*	1.00 (ref)	0.71 (0.36–1.42)	0.72 (0.36–1.46)	0.35
HR (95% CI)†	1.00 (ref)	0.74 (0.37–1.48)	0.70 (0.34–1.44)	0.33

* Adjusted for age and sex.

† Further adjusted for pack-years of cigarette smoking (never and past, 0–20, >20), alcohol intake (none and past and 1–3 times/month, drinking ≤150, >150g of ethanol/week), coffee (none and 1–4 times/week, ≥3 cups/day), green tea (none and 1–4 times/week, 1–2 cups/day, ≥3 cups/day), past history of diabetes mellitus, and past allergy.

showed a high correlation between self-reported and measured values for BMI and height, and any such misclassification is likely to be small. Second, the low incidence of CNS tumor meant that the sample size we had to investigate the association between BMI and CNS tumor risk was relatively small, the very large total population notwithstanding. Third, the association between BMI and brain tumor risk was evaluated using information obtained at a single point (i.e. baseline). Thus, the possibility of misclassification by change in BMI during follow-up cannot be ruled out. To reduce this possibility, we excluded participants with a history of severe disease like cancer, cardiovascular disease, and DM at baseline in sensitivity analysis, but the results were not substantially changed. Furthermore, we also repeated the analysis after excluding brain tumor cases diagnosed in the first three years of follow-up, but again the results did not substantially change.

Conclusion

To our knowledge, this is the first prospective cohort study to evaluate the association between BMI and meningioma and glioma risk in an Asian population. Compared with people with a BMI of 18.5 to less than 23 kg per m², those with higher BMI had higher risk of brain tumor, particularly in men and with meningioma but not glioma. Further studies are needed to confirm our results.

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