

Association of Daily Alcohol Consumption and Drinking Patterns with Risk of Primary Malignant Brain Tumor in Korean Adults: A Retrospective Cohort Study

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Evidence on whether alcohol consumption and drinking patterns contribute to the risk of primary malignant brain tumors remains limited. We examined associations of daily alcohol consumption, drinking frequency, and heavy episodic drinking with tumor incidence in a nationwide cohort. We analyzed data from the National Health Insurance Service–National Sample Cohort (version 2.2), including 240,948 adults aged ≥ 20 years who completed a general health screening between 2006 and 2008. Alcohol-related behaviors were assessed using standardized questionnaires. Incident primary malignant brain tumors were identified using code C71 and the special registration code V193. Hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models adjusting for sociodemographic and lifestyle factors. Over a mean follow-up of 12 years, 209 incident malignant brain tumors occurred (7.2 per 100,000 person-years). Daily alcohol consumption and heavy episodic drinking were not associated with tumor risk. In contrast, drinking frequency showed a positive association: participants who drank almost daily had a higher risk (vs. non-drinkers) (HR, 2.61; 95% CI, 1.21–5.61; P -trend = 0.0347). Sensitivity analyses restricted to adults aged ≥ 40 years and excluding early cases (3- or 5-year latency) yielded similar results. No effect modification was observed. In this nationwide Korean cohort, near-daily drinking, rather than daily alcohol consumption or amount consumed per occasion, was associated with an elevated risk of primary malignant brain tumors. These findings suggest that drinking frequency may represent an independent dimension of alcohol exposure relevant to brain tumor risk.

Key Words Alcohol drinking, Drinking patterns, Primary malignant brain tumor, Risk factors, Cohort studies

INTRODUCTION

Primary malignant brain tumors are rare but devastating cancers with persistently poor survival [1]. Aside from ionizing radiation and a few hereditary syndromes, their etiology remains largely unknown [2], underscoring the need to identify modifiable lifestyle factors relevant to prevention. Evidence from other cancers suggests that modifiable lifestyle factors contribute meaningfully to the overall cancer burden at the population level [3–5], often quantified using population attributable fractions (PAFs). However, such population-level estimates for primary malignant brain tumors remain largely unavailable, reflecting the limited evidence on modifiable risk factors.

Alcohol consumption is classified as a Group 1 carcinogen by the International Agency for Research on Cancer, with strong evidence linking it to cancers of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast [6]. Globally, alcohol-attributable cancers accounted for 741,300 cases, corresponding to 4.1% of all incident cancer cases in 2020, representing the population attributable fraction of alcohol consumption [7,8]. While this indicates a measurable population-level impact of alcohol on cancer burden, its potential role in the etiology of primary malignant brain tumors remains uncertain, and corresponding PAF estimates are not available.

Epidemiologic evidence to date on alcohol consumption and primary malignant brain tumors has been inconsistent.

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Gliomas represent the majority of malignant brain tumors [9]. Prior pooled or meta-analyses reported no association between overall alcohol consumption and glioma risk (drinkers vs. non-drinkers) [2,10], although more recent prospective analyses suggested a modest inverse association for low-to-moderate consumption [11]. However, these studies primarily relied on total or average alcohol consumption, offering limited evaluation of drinking patterns that may capture distinct exposure dimensions.

Given that drinking patterns vary substantially—particularly in drinking frequency and the amount consumed per occasion—assessing these dimensions may yield additional insight into alcohol-related cancer risk. Evidence from two large US cohorts has shown that drinking frequency and per occasion consumption contribute to the risk of alcohol-related cancers (colorectal, breast, oral, cavity, larynx, liver, and esophageal) [12]. In South Korea, frequent high-risk drinking is common, particularly among males, with approximately 37.3% reporting high-risk drinking at least weekly, compared with 14.7% of females [13]. Yet no cohort study, either in South Korea or elsewhere, has evaluated whether such drinking patterns are associated with primary malignant brain tumors.

Therefore, this study aimed to evaluate whether distinct drinking patterns—including average daily alcohol consumption, drinking frequency, and heavy episodic drinking—are independently associated with the incidence of primary malignant brain tumors in a nationwide Korean cohort (the National Health Insurance Service–National Sample Cohort, NHIS-NSC; $n = 240,948$ adults aged ≥ 20 years).

MATERIALS AND METHODS

Source database and study population

In South Korea, approximately 97% of the population is insured under the NHIS, which covers employee and regional subscribers and their dependents, while the remaining population receives the Medical Aid program. This structure ensures universal health coverage. The present study utilized the NHIS-NSC (version 2.2), a representative one-million-person sample (2.2% of the total population) established in 2006 through stratified random sampling by sex, age, type of insurance eligibility, income-based insurance premium level, and residential region [14]. However, sampling weights were not applied in the analyses, as the primary objective was to evaluate associations between alcohol consumption patterns and incident brain tumors rather than to produce nationally representative estimates.

The cohort provides longitudinal data from 2002–2019, including retrospective records (2002–2005), baseline (2006), and annual follow-up updates. The dataset includes information on insurance eligibility, medical diagnoses and healthcare utilization, health examination results, and death records. Insurance eligibility information was obtained from adminis-

trative records maintained by the National Health Insurance Service for insurance management purposes. Medical diagnoses and healthcare utilization data were derived from insurance claims submitted by healthcare providers for reimbursement. Health examination results were collected through the National Health Screening Program. Death records were ascertained through linkage to the national mortality registry. All data were de-identified, and access was limited to secure remote servers to ensure confidentiality.

The source population was restricted to 353,324 adults aged ≥ 20 years who completed at least one general health screening between 2006 and 2008, because the questionnaire was revised in 2009 [15]. To minimize potential reverse causation bias due to behavioral changes following a tumor diagnosis, individuals with any tumor history were excluded at baseline ($n = 87,584$). Participants without drinking frequency data ($n = 15,142$), those with missing covariates ($n = 9,646$), and individuals listed with brain tumor (C71) as a cause of death but without corresponding medical records ($n = 4$) (as these likely represented pre-existing cases) were further excluded. The final analytic sample comprised 240,948 adults (Fig. S1).

Alcohol consumption assessment

In this study, three alcohol-related variables were considered: daily alcohol consumption, drinking frequency, and heavy episodic drinking. These variables were obtained from two questions of a self-administered questionnaire completed at baseline (2006–2008). First, habitual drinking frequency was assessed at the time of the health examination by asking “How often do you drink alcohol?” with five response categories: “(Almost) never,” “2–3 times a month,” “1–2 times a week,” “3–4 times a week,” and “Almost every day.” Then, for participants who reported drinking at least 2–3 times per month, drinking quantity was assessed by the question, “If you drink, how much do you usually consume per occasion?” using one bottle of soju as the standard reference unit, with four options: “Half a bottle of soju or less,” “One bottle of soju,” “One and a half bottles of soju,” and “Two or more bottles of soju” [15].

From 2006 to 2008, the most popular *soju* products (e.g., Chum-Churum) contained approximately 19.5%–20% alcohol by volume (ABV) and were sold in 360 mL bottles [16]; consistent with previous Korean studies [17,18], we assumed 20% ABV, corresponding to approximately 60 g of alcohol per bottle (volume [360 mL] $\times$ ABV [0.2] $\times$ specific gravity [0.8]). Three alcohol variables were defined as follows: (1) Drinking frequency was categorized as non-drinkers, 2–3 times/month, 1–4 times/week, and almost daily.

For descriptive purposes (e.g., calculation of median and range), drinking frequency categories were converted into approximate weekly numerical values using category midpoints; for the estimation of daily alcohol consumption, these values were further converted into times per day. (2) Daily alcohol consumption (g/day) was estimated by multiplying the usual

amount consumed per occasion (in grams) by the drinking frequency (times/day); categories were non-drinkers, < 15 g/day, ≥ 15 and < 30 g/day, and ≥ 30 g/day; (3) Heavy episodic drinking was defined as ≥ 60 g of alcohol per occasion, consistent with World Health Organization definition [19]. Participants who answered “(Almost) never”—interpreted as drinking approximately once or less per month—were defined as non-drinkers, and this definition was consistently applied across all alcohol-related exposure variables, including daily alcohol consumption, drinking frequency, and heavy episodic drinking.

Ascertainment of primary malignant brain tumor

In the NHIS-NSC (version 2.2), diagnostic and death codes follow the Korean Standard Classification of Disease (KCD) [15]. Incident primary malignant brain tumors were defined as cases with both (1) ≥ 1 inpatient or outpatient claim under KCD code C71 and (2) registration under the special case code V193, which requires physician certification for rare and intractable diseases. Histological confirmation and detailed tumor subtype information were not available in the NHIS-NSC database; therefore, primary malignant brain tumors were identified based on administrative claims data.

Assessment of covariates

Covariates were selected based on established or potential risk factors identified in previous systematic reviews and cohort studies [20-25] and availability in the NHIS-NSC (version 2.2). Variables included sex, age, income level, smoking status, physical activity, and body mass index (BMI), all assessed at the first general health screening (2006-2008) and modeled as baseline covariates. Other potential factors, such as family history of brain tumor, allergic and atopic conditions, or occupational and environmental exposures, were unavailable in this database [20-22].

Age was treated as a continuous variable; sex was categorized as male or female. Income level was categorized into four groups: 1st (lowest 20%), 2nd (20-50%), 3rd (50-80%), and 4th group (highest 20%). Smoking status was categorized as never, former, and current based on self-reported questionnaire data from health examinations. Information required to construct pack-years (e.g., duration and intensity) was available but incomplete and therefore not used to avoid substantial reduction in sample size. Physical activity was assessed using a single questionnaire item on the weekly frequency of exercise causing sweating and was categorized as none, 1-4 times/week, and ≥ 5 times/week. Information on exercise type, duration, or intensity was not available. Sex, age, income level, smoking status, physical activity, and BMI were all assessed at the first general health screening (2006-2008) and modeled as baseline covariates. BMI was calculated as weight (kg)/height squared (m^2) and analyzed continuously. Self-reported data (sex, age, income, smoking

status, and physical activity) were collected via self-administered questionnaires, while BMI was measured by nurses at health screening centers.

Statistical analysis

All statistical analyses were performed using SAS Enterprise Guide version 8.3 (SAS Institute). Baseline characteristics were summarized as means $\pm$ SD for continuous variables and numbers (percentages) for categorical variables. The non-drinker group served as the reference category for alcohol variables. General linear models were used to assess differences, adjusting for age and sex; multivariable models were further adjusted for income, smoking status, physical activity, and BMI. In models of drinking frequency and heavy episodic drinking, the amount of alcohol consumed on a single occasion and drinking frequency were both included as continuous covariates for mutual adjustment. Linear trends were evaluated by assigning the median value of each drinking category as a continuous variable.

Time-to-event was defined in days from baseline to diagnosis, death, or the end of follow-up (December 31, 2019). Participants without diagnosis were censored at death or end of follow-up. Hazard ratios (HRs) and 95% CIs for primary malignant brain tumor incidence were estimated using Cox proportional hazards models [26]. Proportional hazards assumptions were verified using log-log survival plots and Schoenfeld residuals [26,27]. All variables had VIF values below 2, under the conventional threshold of 10, indicating no multicollinearity [28].

To distinguish the independent associations of drinking frequency and the amount consumed per occasion, these variables were evaluated in separate models with mutual adjustment. Daily alcohol consumption was derived as a composite measure of these two components and was therefore not additionally adjusted for them in the same model. To examine potential effect modification and the consistency of associations across subgroups, stratified analyses were performed by sex (males or females), income (1st-2nd quartiles, 3rd-4th quartiles), smoking status (never, ever), physical exercise (none, ≥ 1 times/week), BMI (< 23 , ≥ 23 kg/m^2) according to baseline covariate levels. Interaction terms were tested by including cross-product terms in the Cox models. In addition, sensitivity analyses were conducted to evaluate robustness (1) after restricting analyses to participants aged ≥ 40 years to minimize potential selection bias, as adults aged 20-39 years in the NHIS health screening cohort included only employee subscribers and household heads, while dependents were not eligible for inclusion and (2) after excluding cases diagnosed within 3 and 5 years of baseline to account for potential latency following exposure [29,30].

A two-sided P -value < 0.05 was considered statistically significant. To account for multiple testing in subgroup analyses, Bonferroni correction was applied by dividing the conventional alpha level (0.05) by the number of comparisons

Table 1. Age- and sex-adjusted characteristics of the study population according to alcohol consumption patterns

Characteristic	Frequency of alcohol drinking (times)			P for trend ^a	Daily alcohol consumption (g/d)			P for trend ^a	Heavy episodic drinking (≥ 60 g/occasion)			P for trend ^a
	Non-drinkers	1-4/wk	Almost daily		Non-drinkers	≥15 and < 30	≥ 30		Non-drinkers	No (< 60)	Yes (≥ 60)	
n	119,531	66,623	6,854		119,531	16,928	20,628		119,531	36,753	83,509	
Median (g)	0	1.5	7		0	19.3	45		0	30	60	
Total follow-up years	1,429,315	807,681	78,759		1,429,315	205,422	244,343		1,429,315	442,764	1,015,209	
Incident cases (n)	122	37	14		122	5	21		122	38	48	
Incidence rate per 100,000 person years	8.56	4.6	17.8		8.5	2.4	8.6		8.5	8.6	4.7	
Age at baseline (yr)	48.9 ± 0.04	41.5 ± 0.06	53.5 ± 0.17	0.002	48.9 ± 0.04	39.3 ± 0.11	46.6 ± 0.10	< 0.0001	49.1 ± 0.04	44.3 ± 0.07	39.4 ± 0.05	< 0.0001
Females (%)	62.3	17.1	7.7	< 0.0001	62.4	9.9	7.8	< 0.0001	62.9	47.9	13.2	< 0.0001
Income level (%) ^b												
1st	17.7	17.6	20.4	< 0.0001	17.7	17	19	< 0.0001	17.7	18.1	17.1	0.0038
2nd	29	28.4	34.6	< 0.0001	28.9	27.9	31.6	< 0.0001	28.9	28.4	28.8	0.3868
3rd	32	31.8	30.2	0.003	32	32.3	30.8	0.003	32	31.9	31.8	0.3947
4th	21.4	22.2	14.8	< 0.0001	21.4	23	18.6	< 0.0001	21.4	21.6	22.4	< 0.0001
Smoking status (%)												
Never	78.9	50.7	47.2	< 0.0001	78.9	45.7	44.1	< 0.0001	79.5	68	48.5	< 0.0001
Former	4.9	10.7	9.8	< 0.0001	4.9	10.9	10.2	< 0.0001	4.8	9.7	11.5	< 0.0001
Current	16.3	38.7	43	< 0.0001	16.2	43.4	45.7	< 0.0001	15.8	22.3	40	< 0.0001
Physical activity (%)												
None	60.7	48.8	66	0.0002	60.6	48.6	56.5	< 0.0001	60.7	51.6	49.1	< 0.0001
1-4 times/wk	32.2	43.5	23.3	0.03	32.3	43.6	34.5	< 0.0001	32.2	40.5	43.4	< 0.0001
≥ 5 times/wk	7.1	7.6	10.8	< 0.0001	7.1	7.8	9	< 0.0001	7.1	7.9	7.5	0.0007
BMI (kg/m ²)	23.5 ± 0.01	23.7 ± 0.01	22.9 ± 0.04	< 0.0001	23.5 ± 0.01	24.1 ± 0.02	23.6 ± 0.02	< 0.0001	23.5 ± 0.01	23.0 ± 0.02	23.8 ± 0.01	< 0.0001

All values were adjusted for age and sex, except age, and expressed as the mean ± SE for continuous variables or percentage for categorical variables. BMI, body mass index. ^aP for trend from linear regression using median daily alcohol consumption of each category as a continuous variable. ^b1st: lowest 20%; 2nd: 20%-50%; 3rd: 50%-80%; 4th: 80%-100% of income distribution.

($n = 10$), and statistical significance was determined based on an adjusted threshold of $P < 0.005$. As this study used anonymized secondary NHIS data, written informed consent was waived, and the study protocol was approved by the Institutional Review Board of Hanyang University (IRB no. HYUIRB-202405-021-3) and conducted in accordance with the Declaration of Helsinki.

RESULTS

Characteristics of the study population

General characteristics of the study population are summarized in Table S1. The analytic cohort included 240,948 participants (mean age = 45.0 ± 14.4 years, and 43.3% females) who were free of any tumor at baseline. During a mean follow-up of approximately 12 years, a total of 209 incident cases of primary malignant brain tumors were identified (7.20 per 100,000 person-years).

Table 2. HRs and 95% CIs for primary malignant brain tumors (C71) according to alcohol consumption patterns

Measure	Alcohol drinking frequency (times)				P-trend ^a
	Non-drinkers	2-3/mo	1-4/wk	Almost daily	
Median (range)	0 (0-0)	0.5 (0.5-0.5)	1.5 (1.5-3.0)	7.0 (7.0-7.0)	
n	119,531	47,940	66,623	6,854	
Incident cases/follow-up years	122/1,429,315	36/585,590	37/807,681	14/78,759	
Incidence rate per 100,000 person years	8.5	6.1	4.6	17.8	
Sex, age-adjusted	1.00 (reference)	1.17 (0.79-1.74)	0.75 (0.50-1.12)	1.56 (0.88-2.79)	0.271
Multivariable-adjusted ^b	1.00 (reference)	1.71 (0.98-3.00)	1.24 (0.65-2.34)	2.61 (1.21-5.61)	0.0347
Sensitivity analysis					
Only among ≥ 40 yr old	1.00 (reference)	1.84 (0.99-3.42)	1.27 (0.63-2.58)	2.88 (1.27-6.50)	0.0227
After excluding cases within 3 yr	1.00 (reference)	1.50 (0.83-2.70)	1.07 (0.55-2.10)	2.59 (1.18-5.69)	0.0182
After excluding cases within 5 yr	1.00 (reference)	1.51 (0.81-2.83)	1.08 (0.53-2.21)	2.38 (1.003-5.64)	0.0651

Measure	Daily alcohol consumption (g/day)				P-trend ^a
	Non-drinkers	< 15	≥ 15 and < 30	≥ 30	
Median (range)	0 (0-0)	6.43 (2.47-12.9)	19.29 (15-25.7)	45 (30-120)	
n	119,531	82,706	16,928	20,628	
Incident cases/follow-up years	122/1,429,315	60/1,008,208	5/205,422	21/244,343	
Incidence rate per 100,000 person years	8.5	6	2.4	8.6	
Sex, age-adjusted	1.00 (reference)	1.05 (0.75-1.48)	0.44 (0.18-1.10)	1.05 (0.64-1.73)	0.9104
Multivariable-adjusted ^c	1.00 (reference)	1.04 (0.73-1.47)	0.43 (0.17-1.08)	1.03 (0.62-1.71)	0.8595
Sensitivity analysis					
Only among ≥ 40 yr old	1.00 (reference)	1.11 (0.76-1.63)	0.38 (0.12-1.22)	1.02 (0.59-1.77)	0.8351
After excluding cases within 3 yr	1.00 (reference)	0.99 (0.68-1.43)	0.48 (0.19-1.21)	1.15 (0.69-1.93)	0.7281
After excluding cases within 5 yr	1.00 (reference)	1.01 (0.68-1.50)	0.42 (0.15-1.17)	1.05 (0.59-1.85)	0.9309

Measure	Heavy episodic drinking (≥ 60 g/occasion)			P-trend ^a
	Non-drinkers	No	Yes	
Median (range)	0 (0-0)	30 (30-30)	60 (60-120)	
n	119,531	36,753	83,509	
Incident cases/follow-up years	122/1,429,315	38/442,764	48/1,015,209	
Incidence rate per 100,000 person years	8.5	8.6	4.7	
Sex, age-adjusted	1.00 (reference)	1.19 (0.82-1.73)	0.83 (0.56-1.22)	0.4916
Multivariable-adjusted ^b	1.00 (reference)	1.05 (0.68-1.61)	0.69 (0.43-1.12)	0.1478
Sensitivity analysis				
Only among ≥ 40 yr old	1.00 (reference)	1.09 (0.69-1.73)	0.67 (0.39-1.16)	0.1749
After excluding cases within 3 yr	1.00 (reference)	0.93 (0.59-1.47)	0.69 (0.42-1.14)	0.1551
After excluding cases within 5 yr	1.00 (reference)	0.96 (0.59-1.57)	0.71 (0.42-1.20)	0.2065

Values are expressed as HRs (95% CI). HR, hazard ratio. Missing values in daily alcohol consumption corresponded to missing responses for alcohol amount per drinking occasion. Drinking frequency categories were converted into approximate weekly numerical values to calculate summary statistics. ^a P for trend from linear regression using median of each category as a continuous variable (daily alcohol consumption, alcohol drinking frequency, and heavy episodic drinking). ^bModels for drinking frequency and amount consumed per occasion were mutually adjusted. ^cMultivariable model for daily alcohol consumption included age (continuous), sex (males, females), income level (1st, 2nd, 3rd, 4th), smoking status (never, former, current), physical activity (none, 1-4 times/wk, ≥ 5 times/wk), and body mass index (kg/m^2 , continuous).

Table 1 presents baseline characteristics according to alcohol consumption variables (drinking frequency, daily consumption, and heavy episodic drinking). Across all three alcohol-related variables, participants in higher or more frequent alcohol consumption groups were more likely to be males and current smokers (Table 1, Table S2-4). However, other characteristics differed across the alcohol variables: participants were younger, more likely to exercise regularly, and had higher BMI in the higher daily consumption and heavy episodic drinking groups, whereas those with more frequent drinking were less likely to exercise regularly and had lower BMI. Regarding income, the proportion of participants in the highest income group was lower in the higher daily consumption and frequent drinking groups, but higher in the heavy episodic drinking group.

Association between alcohol consumption and patterns with malignant brain tumor risk

In the multivariable-adjusted models, while daily alcohol consumption and heavy episodic drinking were not associated with the risk of primary malignant brain tumors (Table 2), higher drinking frequency showed a modest positive association with tumor incidence. Participants who drank more frequently (almost-daily) had higher hazard ratios compared with non-drinkers, and a significant positive trend was observed (HR, 2.61; 95% CI, 1.21-5.61; P -trend = 0.0347).

Sensitivity analyses supported the robustness of these associations. Restricting analyses to adults aged ≥ 40 years, to address potential selection bias from younger dependents, did not materially change the results. Likewise, excluding cases diagnosed within the first 3 and 5 years of follow-up to account for possible latency yielded consistent estimates,

Table 3. Multivariable-adjusted HRs and 95% CIs according to drinking frequency after stratification of covariates at baseline

Subgroup	Alcohol drinking frequency (times)				P -trend ^a	P -interaction ^b
	Non-drinkers	2-3/mo	1-4 times/wk	Almost daily		
Median (range)	0 (0-0)	0.5 (0.5-0.5)	1.5 (1.5-3.0)	7.0 (7.0-7.0)		
Sex						
Male (Cases/PY)	50/534,228	25/369,508	30/671,957	13/72,229		
	1.00 (reference)	1.75 (0.88-3.48)	1.12 (0.53-2.37)	2.55 (1.09-6.01)	0.0457	0.6739
Female (Cases/PY)	72/895,087	11/216,082	7/135,724	1/6,530		
	1.00 (reference)	1.64 (0.48-5.64)	1.83 (0.44-7.68)	3.05 (0.31-30.17)	0.4018	
Income level						
1st-2nd quartiles (Cases/PY)	51/651,401	9/275,808	10/355,720	5/34,855		
	1.00 (reference)	1.31 (0.45-3.79)	1.06 (0.32-3.51)	2.88 (0.75-11.14)	0.0829	0.2124
3rd-4th quartiles (Cases/PY)	71/777,914	27/309,782	27/451,961	9/43,904		
	1.00 (reference)	2.04 (1.05-3.97)	1.41 (0.66-3.03)	2.66 (1.04-6.78)	0.1457	
Smoking status						
Never smokers (Cases/PY)	106/1,216,523	18/330,729	13/287,172	4/23,712		
	1.00 (reference)	1.25 (0.55-2.84)	0.89 (0.33-2.39)	1.68 (0.46-6.18)	0.4967	0.6315
Former and current smokers (Cases/PY)	16/212,792	18/254,861	24/520,509	10/55,047		
	1.00 (reference)	2.87 (1.18-6.94)	1.96 (0.78-4.97)	4.18 (1.46-11.94)	0.0461	
Physical activity						
None (Cases/PY)	76/880,900	14/282,409	16/361,103	6/46,262		
	1.00 (reference)	1.78 (0.76-4.16)	1.40 (0.54-3.62)	2.11 (0.67-6.67)	0.375	0.5695
Yes (Cases/PY)	46/548,415	22/303,181	21/446,578	8/32,497		
	1.00 (reference)	1.77 (0.83-3.78)	1.21 (0.51-2.90)	3.60 (1.27-10.17)	0.0234	
Obesity status						
< 23 kg/m ² (Cases/PY)	51/649,152	13/277,668	17/311,676	6/31,996		
	1.00 (reference)	1.50 (0.62-3.65)	1.61 (0.61-4.20)	2.62 (0.81-8.50)	0.1627	0.7308
≥ 23 kg/m ² (Cases/PY)	71/780,163	23/307,922	20/496,005	8/46,763		
	1.00 (reference)	1.79 (0.86-3.70)	1.00 (0.42-2.31)	2.57 (0.94-7.06)	0.1123	

HR, hazard ratio; PY, person-years. ^a P for trend was obtained from Cox proportional hazard models by assigning the median value of each drinking frequency category as a continuous variable, stratified by covariates such as sex (male or female), income level (1st-2nd quartiles, 3rd-4th quartiles), smoking status (never smokers, former and current smokers), physical activity (none, 1-6 times/wk or almost every day), and body mass index (BMI) (< 23 or ≥ 23 kg/m²). The model included all covariates such as age (continuous), sex (male, female), income level (1st, 2nd, 3rd, 4th), smoking status (never, former, current), physical activity (none, 1-4 times/wk, 5-6 times/wk or almost every day), and BMI (kg/m², continuous), except the stratifying variable, as well as amount of alcohol consumption on a single occasion (continuous). ^b P for interaction was evaluated using cross-product terms in Cox proportional hazard models.

with the positive association for almost-daily drinking remaining evident.

Association between alcohol consumption and patterns with malignant brain tumor risk by covariates

Stratified analyses showed that the positive association for drinking frequency was generally consistent across most subgroups (Table 3). Although significantly elevated risks were observed among males (HR, 2.55; 95% CI, 1.09-6.01; P -trend = 0.0457), ever-smokers (HR, 4.18; 95% CI, 1.46-11.94; P -trend = 0.0461), and physical activity (HR, 3.60; 95% CI, 1.27-10.17; P -trend = 0.0234), these linear trends did not remain statistically significant after Bonferroni correction ($P < 0.005$; 0.05/10) and there was no significant interaction (all P for interaction > 0.10). Stratified analyses for daily alcohol consumption and heavy episodic drinking (Table S5, 6) revealed no notable associations across any subgroups, except for a marginal inverse association for heavy episodic drinking among lower-income participants (HR, 0.37; 95% CI, 0.16-0.86; P -trend = 0.022), which was an unexpected finding.

DISCUSSION

In this large NHIS-NSC-based cohort study of Korean adults aged ≥ 20 years, participants who reported drinking alcohol almost daily had a significantly higher risk of developing primary malignant brain tumors compared with non-drinkers. Total daily alcohol consumption and heavy episodic drinking showed no association with tumor risk.

Globally, the age-standardized incidence of primary malignant brain tumors has shown a gradual but significant increase over the past three decades. According to recent Global Burden of Disease estimates, the incidence rose from approximately 3.8 per 100,000 population in 1990 to 4.8 per 100,000 in 2019 in males, and from 3.1 to 3.6 per 100,000 in females, with consistently higher rates in high-income regions [31]. According to the Korean Central Cancer Registry, the age-standardized incidence of brain and CNS tumors (C70-C72) ranged from 3.6 to 4.4 per 100,000 persons between 1999 and 2022 [32]. Approximately 90% of these cases were classified as malignant brain tumors (C71) based on registry reports [33]. Furthermore, estimates from the Global Cancer Observatory 2020 database reported an age-standardized incidence rate of 3.2 per 100,000 in Asia overall and 3.0 per 100,000 in South Korea [34]. However, in this study, a relatively higher incidence rate (7.2 per 100,000 person-years) was observed. Several factors may partly explain this elevation. First, health-screening participants may have greater healthcare utilization and are more likely to undergo diagnostic evaluation [35]. Second, NHIS claims capture virtually all clinical encounters, and the special registration code (V193) enhances ascertainment of malignant brain tumors,

potentially leading to more complete or earlier case detection compared with registry-based estimates. Third, increasing access to neuroimaging (brain MRI) may also have contributed to higher case detection [36]. Finally, differences in age structure, as well as the accumulation of cases during follow-up, may have further contributed to the higher incidence observed in this cohort [37].

Evidence on alcohol consumption linked to brain tumor risk has largely focused on daily alcohol consumption. In this study, no significant association was observed between daily alcohol consumption and malignant brain tumors, consistent with most previous investigations reporting null results [2,10,38-40]. However, some cohort studies have reported positive associations at higher consumption levels, including a threefold higher risk among individuals consuming 40-59 g/day (vs. non-drinkers) in an Australian cohort [41] and increased brain cancer mortality among Korean males consuming ≥ 90 g/day (vs. non-drinkers) in a prior NHIS-based cohort [42]. Compared with these results, the highest daily alcohol consumption in this study was considerably lower (≥ 30 g/day). The earlier Korean NHIS-based cohort reported substantially higher consumption levels (mean 28.5 g/day in males, 11.0 g/day in females, maximum 180 g/day) [42], whereas our participants reported markedly lower daily consumption (mean 8.0 g/day; maximum 120 g/day). This lower and narrower exposure range may have limited our ability to detect a positive association in the highest category. In addition to positive evidence, modest inverse associations at low-to-moderate intake levels have been noted in a meta-analysis as well [11] and in U.S. cohorts [43,44].

Unlike daily alcohol consumption, very few studies have evaluated drinking patterns, such as heavy episodic or frequent drinking, in relation to brain tumor risk. In this study, heavy episodic drinking was not associated with tumor incidence, whereas near-daily drinking showed a clear positive association, suggesting that drinking frequency may capture risk dimensions not reflected by per-occasion quantity alone. An unexpected inverse association observed for heavy episodic drinking among lower-income participants should be interpreted with caution (Table S6). This subgroup included a higher proportion of younger individuals, who may have had shorter cumulative exposure, and drinking trajectories may have changed during follow-up, which could limit the ability to detect meaningful associations, particularly given the sharp increase in malignant brain tumor incidence after age 40 [37]. In addition, a small proportion of participants (approximately 0.5%) had missing data on alcohol amount, and drinking frequency analyses restricted to participants with complete alcohol amount data showed similar overall patterns of association, suggesting that the impact of missing data on the observed findings was minimal.

Alcohol metabolism produces acetaldehyde, a reactive metabolite capable of crossing the blood-brain barrier and inducing DNA damage, oxidative stress, and inflammatory

responses [45–48]. These events contribute to genomic instability and have been implicated in carcinogenesis across multiple cancer types [47,48]. Acetaldehyde can also be present within the brain [46,47], where it may induce oxidative stress, DNA damage, and neuroinflammatory responses in neural tissue [47,48], processes that have been suggested to be involved in glioma development and progression, although direct evidence remains limited. Notably, such mechanisms may be triggered not only by repeated low-to-moderate exposure but also by high daily intake or episodes of heavy consumption. These effects are less likely to occur following occasional heavy drinking, where recovery intervals allow partial tissue repair [49,50].

In this study, an association emerged only for near-daily drinking, which may reflect a pattern of exposure with insufficient recovery time, allowing alcohol-related cellular injury and inflammatory signaling to accumulate over time. By contrast, heavy episodic drinking, which was not associated with risk, may involve longer recovery intervals in some individuals, attenuating cumulative biological stress despite high per-occasion doses. Therefore, while the underlying carcinogenic mechanisms are not specific to drinking frequency, the exposure pattern most reflective of cumulative biological burden in this cohort may have been near-daily consumption.

Several limitations should be considered in interpreting the findings of this study. First, although average lifetime alcohol exposure, which incorporates drinking duration and age-specific consumption, is associated with overall cancer [51], the NHIS-NSC (version 2.2) did not include information on lifetime drinking history, limiting our ability to account for cumulative exposure. In addition, alcohol consumption was assessed at baseline to reflect habitual drinking patterns at study entry; however, changes in drinking behavior over time were not captured, which may have led to some exposure misclassification. Furthermore, alcohol intake was estimated using a soju-based standard reference unit, which may not fully capture variation in beverage types and drinking amounts per occasion, potentially leading to misclassification and resulting in either overestimation or underestimation. Second, former drinkers could not be distinguished from lifetime abstainers and were grouped with never-drinkers, which may have introduced misclassification and potential reverse-causation bias. Third, because primary malignant brain tumors are rare, daily alcohol consumption could not be stratified into heavier categories (e.g., ≥ 60 g/day or ≥ 90 g/day), restricting our ability to evaluate higher-level exposures. Fourth, Medical Aid beneficiaries became eligible for national health screenings only after 2012, and dependents aged 20–39 years only after 2019. As these groups were not included in this analytic cohort, generalizability to younger adults and lower socioeconomic groups may be limited. Fifth, although both claims-based diagnostic codes (C71) and the special registration code (V193) were used to enhance case ascertainment, histological confirmation and tumor subtypes were

unavailable, and therefore some degree of outcome misclassification cannot be ruled out. Finally, although we adjusted for key covariates, some established or suspected risk factors, such as genetic mutations, ionizing radiation, or occupational and environmental exposures, were not captured in the NHIS-NSC and could not be controlled for.

In addition, although we conducted stratified analyses to assess potential effect modification, the relatively small number of incident cases within several subgroups may have resulted in reduced statistical power and imprecise estimates. Therefore, these findings should be interpreted cautiously. Despite these limitations, the study benefits from a large, nationally representative cohort and the availability of detailed alcohol-related variables that allowed assessment of drinking patterns beyond daily intake.

In conclusion, in this large South Korean cohort, drinking frequency, rather than the amount of alcohol consumed per occasion or daily alcohol consumption, was associated with the risk of primary malignant brain tumors. These findings suggest that a frequent drinking pattern may represent an important dimension of alcohol exposure in relation to brain tumor risk. Given their poor prognosis and the steadily increasing incidence of malignant brain tumors, recognizing frequent drinking as a potential risk factor may help develop future prevention approaches. Further studies incorporating lifetime drinking histories, repeated exposure assessments, and relevant genetic or environmental factors are needed to clarify the nature and consistency of these associations.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via <https://doi.org/10.15430/JCP.26.006>.

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