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Current smoking status as a predictor of cerebral infarction in men: a retrospective cohort study in South Korea

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ABSTRACT

Objectives We examined the relationship between duration (pack-year) of smoking and the risk of developing cerebral infarction in Korean men.

Design Retrospective cohort study.

Setting National Health Insurance Service-National Sample Cohort in Korea.

Participants Of 125 743 male participants from the National Health Insurance System undergoing medical health check-up in 2009, 114 377 were included in the final analysis.

Primary and secondary outcome measures Development of cerebral infarction according to smoking duration after adjusting for age, body mass index, systolic blood pressure, fasting blood glucose, total cholesterol, γ-glutamyltransferase, estimated glomerular filtration rate, alcohol intake and physical activity.

Results During 495 827.3 person-years of follow-up, 1450 incident cases of cerebral infarction developed between 2009 and 2013. The multivariate adjusted HRs (95% CI) for cerebral infarction between groups 2, 3 and 4 by duration of smoking were 1.02 (0.88 to 1.19), 1.36 (1.19 to 1.56) and 1.49 (1.28 to 1.74), respectively. In our secondary analysis by smoking status, the HR (95% CI) of former smokers showed a significant relationship in the unadjusted model but did not show statistically significant associations in the multivariate adjusted model. The HR (95% CI) of current smokers showed significant relationship in both the unadjusted and multivariate adjusted models (p for trend <0.001).

Conclusions The study indicates that the prolonged duration of smoking (pack-year) increases the risk of cerebral infarction. Current smoking poses a higher risk for the development of cerebral infraction than former smoking among Korean men, indicating that current smoking cessation would be more protective.

Strengths and limitations of this study

- ► Although smoking is a well-known risk factor for cerebral infarction, it still has a high prevalence rate.
- ► Since the smoking status and duration were classified based on the self-report questionnaire, the group classification may not be accurate.
- ► Careful consideration should be made while generalising the results of this study as it is confined to a single geographical area and to Korean men.
- ► The association between current smoking and the development of cerebral infarction was found using a retrospective cohort design.
- ► A major strength of our study is its national representativeness (we used administrative data from the National Health Insurance System for our analysis); however, administrative data are susceptible to coding errors.

INTRODUCTION

Every one in five adults in the world smokes tobacco; however, the prevalence of smoking may vary by sex or country.[1] Smoking is well known to have deleterious effects on various organs including cardiovascular and cerebrovascular system.[2 3] The prevalence of current smoking in Korea is substantially higher than that in the USA, particularly among men (39.7% vs 21.17%).[4 5] Despite the high prevalence, smoking is a well-established risk factor for cerebral infraction.[6 7] According to the WHO reports, one person dies every 3.70 min of a stroke, entailing a substantial economic burden.[8] Because of the high proportion of current smokers among men, the investigation of smoking and stroke should be of value for the formulation of public health recommendations for the stroke prevention. Although there are studies on the relationship between smoking status and cerebral infarction, there is a paucity of evidence on the risk of smoking duration in pack-years and cerebral infarction.

In this study, we examined the relationship between the quantity of cigarettes smoked (pack-year) and the risk of developing cerebral infarction in men and whether their smoking status can affect their risk of cerebral infarction.

MATERIALS AND METHODS

Data sources

The National Health Insurance System (NHIS) covers 97% of the entire population of South Korea. This suggests that the database of NHIS can be representative of the medical service usage of the entire Korean population.[9] In addition, almost all Koreans aged over 40 years are required to undergo a medical health check-up at least once every 2 years. Information on medical health check-ups is collected and stored by the National Health Insurance Corporation (NHIC) in South Korea. The diagnoses were coded in the International Classification Disease, 10th revision (ICD-10).[10] In the recent years, NHIS in South Korea provides the sampled database for research purposes after deleting personal identification information. National Health Insurance Service–National Sample Cohort (NHIS-NSC) is a population-based cohort based on the NHIS database. The NHIS-NSC was first established in 2002, where 1 025 340 individuals (2.2% of 46 605 433 Korean population) were randomly sampled and registered in NHIS database.[9] The NHIS-NSC database contains their medical information from January 2002 to December 2013. From NHIS-NSC, we were provided with data of 114 377 Koreans men who underwent health check-up linked with the development of cerebral infarction in Statistics Korea in 2009. The requirement for informed consent was waived by the institutional review board because researchers only accessed a retrospectively deidentified database for analysis.

Study participants

In total, 125 743 male participants who received health check-ups in 2009 according to the National Health Information Database were included. We excluded 1419 individuals who had previously received treatment for cerebral infarction (ICD-I63) between 2002 and the date of their health examination in 2009. Among the 124 324 participants, 9947 were excluded based on the following exclusion criteria as these might influence cerebral infarction or smoking amount: 4230 did not have information with regard to baseline smoking amount in 2009, and 5757 were diagnosed with cancer (ICD C00-C97) from 2002 to the date before their medical health examination in 2009. Because some participants fit multiple exclusion criteria, a total of 114 377 participants were included in the final analysis and observed for the development of cerebral infarction. The total follow-up period was 495 827.3 person-years, and the average follow-up period was 4.33 (SD 0.51) person-years.

Health survey examinations and laboratory measurements

The general health check-up of the NHIC was conducted in two stages. The first-stage examination consists of a large-scale screening test to determine the presence or absence of disease among a general, asymptomatic population. The second-stage examination consists of a consultation for a screening test and a more detailed examination to confirm the presence of disease. These health examinations also included a lifestyle medical history questionnaire. The study data included physical activity information provided by a questionnaire, anthropometric measurements and laboratory measurements. Smoking status included non-smoker, former smoker and current smoker. Smoking status was defined according to a self-reported questionnaire at baseline in 2009. Smoking amount was defined as pack-year. The pack-year was calculated from a smoking-related section of the questionnaire, which included the average smoking amount and both the past and present smoking duration. Participants were divided into four groups based on smoking amount: group 1 (non-smoker), group 2 (0–15 pack-years), group 3 (15–30 pack-years) and group 4 (>30 pack-years). The percentage of individuals consuming alcohol at least more than three times per week was quantified. We quantified the percentage of individuals who performed at least 30 min per day of physical activity for more than 4 days per week or vigorous-intensity physical activity at least 20 min per day for more than 4 days per week.[11] Body mass index (BMI) was calculated as weight (kg) divided by the square of height (metres). Systolic blood pressure (BP) and diastolic BP were measured by trained examiners. The following laboratory indices were measured simultaneously when the participants underwent health examinations: fasting blood glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum creatinine (SCr), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT). Kidney function was measured using the estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation: $eGFR=141\times \min(SCr/K, 1)^{a}\times \max(SCr/K, 1)^{-1.209}\times 0.993^{age}\times 1.018$ [if female]$\times 1.159$ [if Black], where SCr is serum creatinine, K is 0.7 for females and 0.9 for males, a is −0.329 for females and −0.411 for males, min indicates the minimum SCr/K or 1 and max indicates the maximum SCr/K or 1.[12]

Outcome definitions

The National Health Insurance database was linked to the disease diagnosis data from Statistics Korea. In this study, the entry date was the first health check-up time in 2009 and the last follow-up date for diagnosis of cerebral infarction was 31 December 2013. The diagnosis of cerebral infarction was defined as ICD-I63. The primary clinical endpoint of interest of our study was the development of cerebral infarction as a composite endpoint.

Statistical analysis

Data were expressed as means (±SD) or medians (IQR) for continuous variables and percentages of the number for categorical variables.

One-way analysis of variance and χ^2 test were used to analyse the statistical differences among the characteristics of the four groups classified by the smoking duration (pack-year) at the time of enrolment.

Table 1 Baseline characteristics of participants according to four groups of smoking duration in male (N=114 377)

Characteristic	Overall	Smoking duration (pack-year) Group 1 (non-smoker, n=40 415)	Group 2 (>0, ≤15, n=32 149)	Group 3 (>15,≤30, n=29 037)	Group 4 (>30, n=12 776)	P for trend*
Person-year (total)	495 827.3	175 686.1	139 439.8	125 655.2	55 046.2	
Person-year (average)	4.33 ± (0.51)	4.35 ± (0.52)	4.34 ± (0.45)	4.32 ± (0.50)	4.30 ± (0.61)	<0.001
Age (years)	57.1 ± (8.4)	58.6 ± (9.0)	55.3 ± (7.5)	55.7 ± (7.7)	59.9 ± (8.3)	<0.001
BMI (kg/m^2)	24.0 ± (2.8)	24.1 ± (2.8)	24.0 ± (2.7)	24.0 ± (2.8)	23.9 ± (2.9)	<0.001
Systolic BP (mm Hg)	126.4 ± (14.7)	127.0 ± (15.0)	125.8 ± (14.3)	125.9 ± (14.5)	126.7 ± (15.0)	0.037
Diastolic BP (mm Hg)	78.9 ± (9.8)	79.0 ± (9.9)	78.9 ± (9.7)	78.8 ± (9.7)	78.6 ± (9.8)	<0.001
Total cholesterol (mg/dL)	196.2 ± (36.5)	194.1 ± (35.9)	197.0 ± (35.8)	198.0 ± (37.2)	196.7 ± (38.1)	<0.001
Triglyceride (mg/dL)	127 (88–185)	117 (82–170)	126 (87–185)	135 (94–198)	138 (97–202)	<0.001
HDL cholesterol (mg/dL)	53.2 ± (29.7)	54.0 ± (33.8)	52.9 ± (24.7)	52.6 ± (26.7)	52.8 ± (33.6)	<0.001
LDL cholesterol (mg/dL)	114.2 ± (38.5)	114.3 ± (38.8)	114.9 ± (37.9)	114.0 ± (38.6)	112.4 ± (39.7)	<0.001
Fasting blood glucose (mg/dL)	103.0 ± (27.2)	102.5 ± (26.5)	102.4 ± (26.3)	103.4 ± (27.6)	105.5 ± (30.8)	<0.001
SCr (mg/dL)	1.33 ± (1.76)	1.28 ± (1.67)	1.42 ± (1.93)	1.34 ± (1.77)	1.20 ± (1.52)	<0.001
eGFR (mL/min per 1.73 m^2)	80.2 ± (20.9)	79.2 ± (20.2)	80.1 ± (22.0)	81.0 ± (21.3)	80.3 ± (19.1)	<0.001
AST (U/L)	25 (21–30)	25 (21–30)	25 (21–30)	25 (20–30)	25 (20–31)	<0.001
ALT (U/L)	23 (18–32)	23 (18–31)	23 (18–32)	23 (18–33)	23 (17–33)	0.001
GGT (U/L)	33 (21–55)	29 (20–48)	33 (21–54)	36 (24–61)	38 (25–64)	<0.001
Smoking amount (pack-year)	13.8 ± (16.0)	0	8.7 ±(4.7)	24.3 ±(4.6)	46.5 ±(14.4)	<0.001
Smoking status						<0.001
Non-smoker	40 415 (35.3)	40 415 (100.0)	0	0	0	
Former smoker	36 885 (32.3)	0	20 051 (54.4)	12 146 (32.9)	4688 (12.7)	
Current smoker	37 077 (32.4)	0	12 098 (32.6)	16 891 (45.6)	8088 (21.8)	
Alcohol intake	23.9	15.6	22.8	30.7	37.5	<0.001
Physical activity	18.1	18.5	19.5	16.7	16.5	<0.001
Development of cerebral infarction (%)	1450 (1.27)	534 (1.32)	290 (0.90)	364 (1.25)	262 (2.05)	<0.001

Data are means (SD), medians (IQR) or percentages.
*P value by analysis of variance test for continuous variables and χ^2 test for categorical variables.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine.

Table 2 HRs and 95% CIs for the incidence of cerebral infarction according to four groups of smoking duration

	Person-year	Incident cases	Incidence density (per 10000 person-year)	HR (95% CI)* Unadjusted	Multivariate adjusted model
Smoking amount					
Group 1	175686.1	534	30.4	1.00 (reference)	1.00 (reference)
Group 2	139439.8	290	20.8	0.69 (0.60 to 0.79)	1.02 (0.88 to 1.19)
Group 3	125655.2	364	28.9	0.96 (0.84 to 1.09)	1.36 (1.19 to 1.56)
Group 4	55046.2	262	47.6	1.57 (1.35 to 1.82)	1.49 (1.28 to 1.74)

Multivariate adjusted model was adjusted for age, BMI, systolic BP, fasting blood glucose, total cholesterol, GGT, eGFR, alcohol intake and physical activity.
HR: hazard ratio, 95% CI: 95% confidence interval.
*p-value <0.05 was chosen as significance level.
BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase.

The person-years were calculated as the sum of follow-up duration from the start until the time of diagnosis of cerebral infarction development or until 31 December 2013.

To evaluate the associations of the four groups, classified based on the smoking amount, with incident cerebral infarction, we used Cox proportional hazards models to estimate the adjusted HRs and 95% CIs for incident cerebral infarction by comparing groups 2, 3 and 4 versus group 1 (non-smoker). The Cox proportional hazard models were adjusted for the multiple confounding factors. In the multivariate models, we included variables that might confound the relationship between smoking amount and incident cerebral infarction, such as age, BMI, systolic BP, fasting blood glucose, total cholesterol, GGT, eGFR, alcohol consumption and physical activity. To test the validity of the Cox proportional hazard models, we checked the proportional hazard assumption, which was assessed by a log-minus-log survival function and found to be graphically unviolated. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were performed using SAS (V.9.4, SAS Institute, Cary, North Carolina, USA).

Patient and public involvement

There were no patients or members of the public involved in the design, implementation, analyses or reporting of our research.

RESULTS

During 495827.3 person-years of follow-up, we observed 1450 (1.27 %) incident cases of cerebral infarction developed between 2009 and 2013. The characteristics of the participants in relation to the four groups classified by smoking amount are presented in table 1. At baseline, the mean (±SD) age and BMI of participants were 57.1 (±8.4) years and 24.0 (±2.8) kg/m^2, respectively. There were significant differences between all the listed variables and cerebral infarction.

Table 3 HRs and 95% CIs for the incidence of cerebral infarction according to four groups of smoking duration in smoking status subgroups

	Hr (95% CI) Former smoker+non-smoker group (n=77300)		Current smoker+non smoker group (n=77492)	
	Unadjusted	Multivariate adjusted model	Unadjusted	Multivariate adjusted model
Smoking amount				
Group 1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Group 2	0.58 (0.48 to 0.69)	0.82 (0.69 to 0.99)	0.88 (0.73 to 1.06)	1.45 (1.19 to 1.76)
Group 3	0.81 (0.67 to 0.99)	0.98 (0.81 to 1.19)	1.06 (0.91 to 1.24)	1.78 (1.52 to 2.09)
Group 4	1.53 (1.22 to 1.90)	1.16 (0.93 to 1.46)	1.59 (1.34 to 1.89)	1.78 (1.49 to 2.13)
P for trend	<0.001	0.158	<0.001	<0.001

Multivariate adjusted model was adjusted for age, BMI, systolic BP, fasting blood glucose, total cholesterol, GGT, eGFR, alcohol intake and physical activity.
BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase.

In contrast to participants without incident cerebral infarction, those with incident cerebral infarction were older (65.1 vs 57.0) and more likely to have less favourable metabolic profiles at baseline. As expected, all clinical variables showed significant differences between the groups except for BMI, total cholesterol, HDL-cholesterol, LDL-cholesterol, AST, alcohol consumption and physical activity (online supplemental table 1).

Table 2 shows the HRs and 95% CIs for cerebral infarction according to the four groups classified by smoking amount. In the unadjusted model, the HRs and 95% CIs for cerebral infarction on comparing groups 2, 3 and 4 with group 1 (non-smoker) were 0.69 (0.60 to 0.79), 0.96 (0.84 to 1.09) and 1.57 (1.35 to 1.82), respectively. The adjusted HRs and 95% CIs for cerebral infarction of group 2, 3 and 4 were 1.02 (0.88 to 1.19), 1.36 (1.19 to 1.56) and 1.49 (1.28 to 1.74), respectively, even after further adjustments for covariates in the multivariate adjusted model.

The smoking status of the subgroup analysis indicated that the current smoker group was significantly associated with an increased risk of incident cerebral infarction even after adjusting covariates (p for trend <0.001). The former smoker group also showed a significant association in the unadjusted model, which subsequently did not show a significant association after adjustment for covariates (p for trend=0.158) (table 3).

DISCUSSION

There is published evidence of a dose–response relationship between the duration (pack-year) of smoking and the risk of stroke.[13] Our study demonstrated this finding using a retrospective cohort design with national representative data and extended the finding to the population of Korean men. Compared with the former smoker group, the current smoker group showed a strong positive relationship between smoking duration (pack-year) and development of cerebral infraction even after adjusting for various covariates such as age, BMI, systolic BP, Fasting Blood Sugar (FBS), Total Cholesterol (T-chol), GGT, eGFR, alcohol consumption and level of physical activity. The result of this study is in line with that of previous case–control studies with populations of young women and men[7 14] and is consistent with that of a Japanese prospective cohort study.[15] A recent birth cohort study conducted in Finland also found that the accumulation of smoking history is associated with an increased risk of stroke.[16] Regarding the smoking status, the published study results showed that current smoking was a significant risk factor for stroke.[17] The result of the increased risk in both former and current smokers were found, which is consistent with a recent meta-analysis.[13] That is, cessation of smoking reduces the risk of stroke.

The result of our study should be interpreted in light of several limitations. First, smoking status (former or current) and duration (pack-year) were self-reported as a part of a health survey examination and not defined by confirmative laboratory examinations. Second, there might have been coding errors or redundant entries from the administrative data source. Third, residual confounding that could influence the results presented in this study cannot be ruled out. Additionally, the sample population was confined to males only and was in a single geographical area; therefore, the study's generalisability to women, the entire population or to other racial groups is uncertain.

Despite these limitations, our study is one of the largest with 114377 subjects. The large sample size allowed relatively precise estimates of relationship. The results of our study are representative of the population of Korea because they were derived from a national representative data source. Finally, we controlled for covariates such as alcohol consumption and physical activity in our model, which may have resulted in more precise estimates in our study.

The clinical implications of our findings highlight the importance and beneficial effect of stopping smoking now rather than past quitting.

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Contributors SML, M-HK and JHR analysed and interpreted the results and were the major contributors to writing the manuscript. C-MO, M-HK and EH contributed to organising data collection. MH and JHR were the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved of the final manuscript.

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Competing interests None declared.

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