Life Cycle | The best science From birth To senescence

eISSN: 2799-8894
Life Cycle 2024;4:e2
https://doi.org/10.54724/lc.2024.e2

Letters

Association of transitioning from combustible cigarettes to noncombustible nicotine or tobacco products with subsequent cancer risk: a nationwide cohort study in South Korea

Ho Geol Woo[1#], Yejun Son[2#], Sunyeup Kim[3#], Jongnam Kim[4], Jiseung Kang[5,6], Seung Won Lee[7*]

[1]Department of Neurology, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea
[2]Department of Precision Medicine, Kyung Hee University College of Medicine, Seoul, South Korea
[3]Department of Medical AI, Sungkyunkwan University School of Medicine, Suwon, South Korea
[4]Department of Metabiohealth, Sungkyunkwan University, Suwon, South Korea[5]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
[6]Division of Sleep Medicine, Harvard Medical School, Boston, MA, USA
[7]Department of Precision Medicine, Sungkyunkwan University School of Medicine, Suwon, South Korea

Received: date: Nov 2, 2023.
Revised date: Jan 12, 2024.
Accepted date: Jan 12, 2024.
Published date: Jan 28, 2024.

# These authors contributed equally to this work

***Correspondence**:
Seung Won Lee
E-mail: lsw2920@gmail.com

ORCID
Seung Won Lee
https://orcid.org/0000-0001-5632-5208

1. Introduction

While the prevalence of Combustible cigarette (CC) smoking has declined in many high-income countries over recent decades, the use of noncombustible nicotine or tobacco products (NNTP) has risen due to its promotion as a helpful aid for adults looking to quit CC smoking.[1, 2] Although evaluations of the components of various NNTPs have revealed the presence of various well-known carcinogenic agents, there has been limited research examining their carcinogenic effects, such as cancer development.[3] Thus, this study aimed to assess the association of changes in NNTP and CC use habits and subsequent overall cancer risk.

2. Methods

This study utilized data from the National Health Insurance Service of South Korea (NHIS), which includes demographics, socioeconomic status, and medical data for the diagnosis and treatment modalities of participants who underwent complimentary national health checkups biannually.[4] The study population consisted of 5,312,023 adults aged 20 years and older who underwent health checkups during both the first period (2014) and second period (2018). Starting from the second health screening date, participants were followed up until the date of the overall cancer event or death, whichever came earliest.

Smoking status was assessed through a self-reported survey during the first and second health check-up periods.[2] NNTP use was evaluated through a survey during the second health check-up period. CC quitters were classified into long-term (≥5 years) and recent (<5 years) quitters, as it is considered to take 5 years for CC quitters to gradually decrease overall cancer risk.[2] Similar to a previous study[2], the participants were classified into six groups: continual

CC-only smokers, CC and NNTP users, recent (<5 years) CC quitters, long-term (≥5 years) CC quitters without NNTP use, long-term (≥5 years) CC quitters with NNTP use, and never smokers. In this study, all cancer cases were identified using the International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes, specifically C00-C99.[5]

Multivariate Cox proportional hazards regression was used to calculate the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for overall cancer based on changes in CC and NNTP use status. Stratified analysis of the association between smoking status and overall cancer risk was performed across age and sex subgroups, adjusting for all covariates except for the variable used to stratify the subgroups. Statistical significance was determined at a 2-sided P-value of less than 0.05. All data collection and statistical analyses were performed using the SAS software (version 9.4; SAS Inc., Cary, NC, USA).

3. Result

Among 4,187,557 participants (Table 1), The risk of overall cancer according to changes in CC and NNTP usage habits according to age and sex is presented in Table 2. Compared with continual CC-only smokers, CC and NNTP users (aHR, 0.86 [95% CI, 0.79–0.93]), recent CC quitters (0.92 [0.87–0.97]), long-term CC quitters without NNTP use (0.74 [0.71–0.77]), and never smokers (0.61 [0.59–0.63]) had lower risk for overall cancer in male participants aged 40 years or older. Additionally, compared with continual CC-only smokers, CC and NNTP users, recent CC quitters, long-term CC quitters without NNTP use, long-term CC quitters with NNTP use, and never smokers exhibited lower trends of overall cancer risk in female participants aged 40 years or older. However, there were significant differences in the association between changes in CC and NNTP use habits and overall cancer risk across the different age subgroups (Table 2).

Table 1. Baseline character of the study population

Characteristics	Continual CC–only smokers	CC and NNTP users	Recent (<5 y) CC quitters	Long–term (≥5 y) CC quitters without NNTP use	Long–term (≥5 y) CC quitters with NNTP use	Never smokers
Overall, n	692,479	101,751	147,093	506,358	3,901	2,735,975
Age, years old, mean (SD)	48.12 (12.03)	40.93 (8.63)	49.47 (12.73)	54.42 (12.27)	41.33 (9.06)	52.57 (14.66)
Age group, n (%)						
20–39 years old	172,336 (24.89%)	46,672 (45.87%)	35,729 (24.29%)	60,500 (11.95%)	1,761 (45.14%)	570,033 (20.83%)
40–59 years old	390,874 (56.45%)	52,166 (51.27%)	76,405 (51.94%)	264,662 (52.27%)	1,961 (50.27%)	1,238,875 (45.28%)
≥60 years old	129,269 (18.67%)	2,913 (2.86%)	34,959 (23.77%)	181,196 (35.78%)	179 (4.59%)	927,067 (33.88%)

Table 1. Continued

Characteristics	Continual CC–only smokers	CC and NNTP users	Recent (<5 y) CC quitters	Long–term (≥5 y) CC quitters without NNTP use	Long–term (≥5 y) CC quitters with NNTP use	Never smokers
Sex, n (%)						
Male	643,919 (92.99%)	96,749 (95.08%)	134,786 (91.63%)	484,720 (95.73%)	3,467 (88.87%)	603,415 (22.05%)
Female	48,560 (7.01%)	5,002 (4.92%)	12,307 (8.37%)	21,638 (4.27%)	434 (11.13%)	2,132,560 (77.95%)
Region of residence, n (%)						
Rural	386,341 (55.79%)	50,873 (50.00%)	78,441 (53.33%)	262,901 (51.92%)	1,814 (46.50%)	1,473,766 (53.87%)
Urban	306,138 (44.21%)	50,878 (50.00%)	68,652 (46.67%)	243,457 (48.08%)	2,087 (53.50%)	1,262,209 (46.13%)
Household income, n (%)						
Low income	252,210 (36.42%)	28,900 (28.40%)	47,121 (32.03%)	132,937 (26.25%)	1,085 (27.81%)	990,715 (36.21%)
Middle income	307,767 (44.44%)	46,579 (45.78%)	63,593 (43.23%)	208,302 (41.14%)	1,766 (45.27%)	1,058,208 (38.68%)
High income	132,502 (19.13%)	26,272 (25.82%)	36,379 (24.73%)	165,119 (32.61%)	1,050 (26.92%)	687,052 (25.11%)
BMI, mean (SD)	24.71 (4.24)	25.54 (3.64)	25.2 (3.36)	25.02 (4.69)	25.19 (3.61)	23.88 (3.77)
BMI, n (%)						
<25 kg/m^2	389,189 (56.20%)	47,396 (46.58%)	73,115 (49.71%)	262,777 (51.90%)	1,940 (49.73%)	1,806,624 (66.03%)
25–30 kg/m^2	251,834 (36.37%)	43,286 (42.54%)	62,495 (42.49%)	214,310 (42.32%)	1,617 (41.45%)	781,720 (28.57%)
≥30 kg/m^2	51,455 (7.43%)	11,069 (10.88%)	11,483 (7.81%)	29,271 (5.78%)	344 (8.82%)	147,590 (5.39%)
SBP, mean (SD)	124.41 (14.03)	123.56 (13.24)	125.16 (13.93)	126.05 (13.78)	122.22 (13.24)	121.88 (15.24)
DBP, mean (SD)	77.97 (10.08)	78.17 (10.06)	78.17 (10.02)	78.22 (9.74)	77.1 (10.26)	74.86 (9.96)
Fasting blood glucose, mean (SD)	105.1 (29.51)	102.38 (25.78)	105.08 (27.56)	105.25 (24.87)	100.62 (21.68)	99.33 (21.91)
Serum total cholesterol, mean (SD)	198.03 (43.13)	202.64 (40.2)	197.31 (42.46)	194.1 (41.31)	199.57 (38.25)	196.76 (40.29)
Alcohol consumption; drinks per week, n (%)						
<1	263,400 (38.04%)	37,673 (37.02%)	62,706 (42.63%)	228,988 (45.22%)	1,604 (41.12%)	2,116,530 (77.36%)
1–3	342,126 (49.41%)	53,785 (52.86%)	69,855 (47.49%)	231,326 (45.68%)	1,922 (49.27%)	574,419 (21.00%)

Table 1. Continued

Characteristics	Continual CC–only smokers	CC and NNTP users	Recent (<5 y) CC quitters	Long–term (≥5 y) CC quitters without NNTP use	Long–term (≥5 y) CC quitters with NNTP use	Never smokers
≥4	86,952 (12.56%)	10,293 (10.12%)	14,532 (9.88%)	46,044 (9.09%)	375 (9.61%)	45,015 (1.65%)
Exercise, n (%)						
Sufficient	200,376 (28.94%)	28,029 (27.55%)	49,578 (33.71%)	191,468 (37.81%)	1,215 (31.15%)	887,460 (32.44%)
Non-sufficient	492,101 (71.06%)	73,722 (72.45%)	97,514 (66.29%)	314,885 (62.19%)	2,686 (68.85%)	1,848,501 (67.56%)
Pack–years of smoking, median (IQR)	15.0 (7.5-24)	10.5 (6.5-18.75)	12.5 (5.0-23.0)	10.0 (5.0-20.0)	7.5 (4.2-15.0)	0.0 (0.0-0.0)
CCI, n (%)						
0	448,678 (64.79%)	75,761 (74.46%)	87,330 (59.37%)	283,130 (55.91%)	2,849 (73.03%)	1,594,672 (58.29%)
1	162,023 (23.40%)	20,085 (19.74%)	37,103 (25.22%)	138,530 (27.36%)	785 (20.12%)	720,220 (26.32%)
≥2	81,778 (11.81%)	5,905 (5.80%)	22,660 (15.41%)	84,698 (16.73%)	267 (6.84%)	421,083 (15.39%)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CC, combustible cigarette; DBP, diastolic blood pressure; IQR, interquartile range; NNTP, noncombustible nicotine or tobacco product; SBP, systolic blood pressure

Table 2. The HR with 95% CI for the association of changes in CC and NNTP use habits with overall cancer risk according to subgroups of age and sex

Parameter	N (%)	Events	Person–years	IR*	HR (95% CI)			
					Model 1	Model 2	Model 3	
Male, aged ≥40								
Continual CC–only smokers	482,771	12,759	1,393,617	9.2	1.62 (1.57–1.66)	1.69 (1.64–1.73)	1.64 (1.59–1.68)	1.0 (ref)
CC and NNTP users	52,666	676	151,828	4.5	1.38 (1.27–1.49)	1.45 (1.34–1.57)	1.41 (1.30–1.52)	0.86 (0.79–0.93)
Recent (<5 y) CC quitters	103,007	3,042	300,423	10.1	1.53 (1.47–1.59)	1.56 (1.50–1.63)	1.51 (1.45–1.58)	0.92 (0.87–0.97)
Long–term (≥5 y) CC quitters without NNTP use	430,641	12,290	1,275,574	9.6	1.20 (1.17–1.24)	1.24 (1.20–1.27)	1.21 (1.18–1.24)	0.74 (0.71–0.77)
Long–term (≥5 y) CC quitters with NNTP use	1,956	21	5,041	4.2	1.15 (0.75–1.76)	1.17 (0.76–1.80)	1.14 (0.74–1.75)	0.70 (0.45–1.07)

Table 2. Continued

Parameter	N (%)	Events	Person–years	IR*	HR (95% CI)			
					Model 1	Model 2	Model 3	
Never smokers	399,332	10,579	1,171,591	9.0	1.0 (ref)	1.0 (ref)	1.0 (ref)	0.61 (0.59–0.63)
Male, aged <40								
Continual CC–only smokers	161,148	595	491,802	1.2	0.84 (0.76–0.94)	0.91 (0.81–1.01)	0.92 (0.80–1.06)	1.0 (ref)
CC and NNTP users	44,083	216	133,120	1.6	1.09 (0.94–1.27)	1.13 (0.97–1.32)	1.16 (0.97–1.38)	1.26 (1.00–1.58)
Recent (<5 y) CC quitters	31,779	158	96,888	1.6	1.09 (0.92–1.29)	1.14 (0.96–1.36)	1.16 (0.96–1.40)	1.26 (1.00–1.60)
Long–term (≥5 y) CC quitters without NNTP use	54,079	301	169,955	1.8	1.10 (0.96–1.25)	1.15 (1.00–1.32)	1.17 (1.00–1.35)	1.27 (1.04–1.56)
Long–term (≥5 y) CC quitters with NNTP use	1,511	4	4,044	1.0	0.67 (0.25–1.79)	0.70 (0.26–1.87)	0.71 (0.27–1.91)	0.77 (0.29–2.07)
Never smokers	204,083	850	624,272	1.4	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.09 (0.94–1.25)
Female, aged ≥40								
Continual CC–only smokers	37,372	954	103,617	9.2	1.22 (1.14–1.30)	1.33 (1.25–1.42)	1.26 (1.17–1.35)	1.0 (ref)
CC and NNTP users	2,413	48	6,358	7.5	1.13 (0.85–1.50)	1.25 (0.94–1.66)	1.20 (0.90–1.59)	0.95 (0.71–1.28)
Recent (<5 y) CC quitters	8,357	211	23,438	9.0	1.20 (1.05–1.37)	1.27 (1.11–1.46)	1.22 (1.06–1.39)	0.97 (0.83–1.13)
Long–term (≥5 y) CC quitters without NNTP use	15,217	359	42,493	8.4	1.17 (1.05–1.30)	1.24 (1.12–1.38)	1.20 (1.08–1.34)	0.95 (0.84–1.08)
Long–term (≥5 y) CC quitters with NNTP use	184	1	419	2.4	0.37 (0.05–2.62)	0.40 (0.06–2.81)	0.38 (0.05–2.72)	0.30 (0.04–2.23)
Never smokers	1,766,610	41,973	508,2480	8.3	1.0 (ref)	1.0 (ref)	1.0 (ref)	0.79 (0.74–0.85)
Female, aged <40								
Continual CC–only smokers	11,188	78	31,561	2.5	0.87 (0.70–1.09)	0.91 (0.73–1.14)	0.88 (0.68–1.14)	1.0 (ref)
CC and NNTP users	2,589	18	6,882	2.6	0.91 (0.58–1.45)	0.95 (0.60–1.52)	0.92 (0.57–1.49)	1.05 (0.61–1.80)
Recent (<5 y) CC quitters	3,950	27	10,721	2.5	0.85 (0.58–1.24)	0.89 (0.61–1.29)	0.86 (0.58–1.27)	0.98 (0.61–1.56)
Long–term (≥5 y) CC quitters without NNTP use	6,421	74	17,786	4.2	1.29 (1.02–1.62)	1.35 (1.07–1.70)	1.32 (1.04–1.68)	1.50 (1.05–2.13)

Table 2. Continued

Parameter	N (%)	Events	Person–years	IR*	HR (95% CI)			
					Model 1	Model 2	Model 3	
Long–term (≥5 y) CC quitters with NNTP use	250	2	565	3.5	1.19 (0.30–4.76)	1.27 (0.32–5.08)	1.24 (0.31–4.96)	1.41 (0.34–5.77)
Never smokers	365,950	3,187	1,031,750	3.1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.14 (0.88–1.47)

Abbreviation: CC, combustible cigarette; CI, confidence interval; HR, hazard ratio; IR, indicate rate; NNTP, noncombustible nicotine or tobacco product.

* Incidence rate expressed as per 1000 person-years.

Model 1: adjusted for age (20–39, 40–59, and ≥60 years) and sex.

Model 2: adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); Charlson comorbidity index (0, 1, and ≥2); body mass index (<25 kg/m^2, 25–30 kg/m^2, and ≥30 kg/m^2); systolic blood pressure; diastolic blood pressure; fasting blood glucose; serum total cholesterol; alcohol consumption (<1 times per week, 1–3 times per week, and ≥4 times per week); exercise (sufficient and non-sufficient).

Model 3: adjusted for age (20–39, 40–59, and ≥60 years); sex; household income (low income, middle income, and high income); region of residence (urban and rural); Charlson comorbidity index (0, 1, and ≥2); body mass index (<25 kg/m^2, 25–30 kg/m^2, and ≥30 kg/m^2); systolic blood pressure; diastolic blood pressure; fasting blood glucose; serum total cholesterol; alcohol consumption (<1 times per week, 1–3 times per week, and ≥4 times per week); exercise (sufficient and non-sufficient); pack–years of smoking.

Numbers in bold indicate a significant difference ($P < 0.05$).

4. Discussion

In summary, switching to NNTP among initially CC-only smokers was associated with a lower overall cancer risk than continual CC-only use in participants aged 40 years or older. There is a trend of decreasing cancer incidence in women aged 40 years or older, but this was difficult to determine owing to the insufficient sample size. To the best of our knowledge, this is the first study to demonstrate the overall cancer risk associated with changes in NNTP and CC habits.

Several limitations must be considered when interpreting the results. First, because 97% of all women in South Korea are nonsmokers, there may be a discrepancy between smoking status, as reported in surveys, and the actual smoking status. Additional follow-up will enhance the reliability of the results obtained in this cohort.

Ethics Statements

The research protocol received approval from both the Institutional Review Board of Kyung Hee University. Under the terms of the approval, the requirement for informed consent was waived as this study utilized deidentified administrative data.

Patient and public involvement

No patients were directly involved in designing the research question or conducting the

research. No patients were asked to interpret or write up the results. However, we plan on disseminating the results of this study to any of the study participants or wider relevant communities on request.

Data Availability Statement

Data are available on reasonable request.

Transparency Statement

The leading author (HGW) are an honest, accurate, and transparent account of the study being reported.

Author Contribution

Dr HGW had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. Study concept and design: all authors; Acquisition, analysis, or interpretation of data: all authors; Drafting of the manuscript: all authors; Critical revision of the manuscript for important intellectual content: all authors; Statistical analysis: SK; Study supervision: all authors. HGW supervised the study and is guarantor for this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. HGW, YS, and SK were equally contributed.

Funding

There is no funding source.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Provenance and peer review

Not commissioned; externally peer reviewed.

Reference

1. Elias J, Dutra LM, St Helen G, Ling PM. Revolution or redux? Assessing IQOS through a precursor product. Tobacco control. 2018;27(Suppl 1):s102-s10.
2. Choi S, Lee K, Park SM. Combined associations of changes in noncombustible nicotine or tobacco product and combustible cigarette use habits with subsequent short-term cardiovascular disease risk among south Korean men: A nationwide cohort study. Circulation. 2021;144(19):1528-38.
3. Tang M-s, Wu X-R, Lee H-W, Xia Y, Deng F-M, Moreira AL, et al. Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. Proceedings of the National Academy of Sciences. 2019;116(43):21727-31.
4. Lee SW, Yang JM, Moon SY, Kim N, Ahn YM, Kim JM, et al. Association between mental

illness and COVID-19 in South Korea: a post-hoc analysis. Lancet Psychiatry. 2021;8(4):271-2.

5. Woo A, Lee SW, Koh HY, Kim MA, Han MY, Yon DK. Incidence of cancer after asthma development: 2 independent population-based cohort studies. J Allergy Clin Immunol. 2021;147(1):135-43.