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Original Research

The relationship between heated cigarette smoking and blood white blood cell count: a population-based cross-sectional study

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ABSTRACT

Objectives: Conventional cigarette smoking increases inflammation and white blood cell (WBC) counts. However, there have been limited studies on the relationship between heated cigarette smoking and WBC counts. This study aimed to examine this relationship using nationally representative population-based health data.

Study design: This was a population-based cross-sectional study.

Methods: The Korea National Health and Nutrition Examination Survey database was used to analyze this relationship. Data related to sex, age, body mass index (BMI), WBC count, and smoking history were obtained from the database. The smoking-related questionnaires included smoking status, smoking type (heated or conventional cigarettes), and smoking amount. The summary statistics of the WBC counts were calculated according to sex, smoking status, and smoking type. In addition, the exposure–response relationship between the smoking amount and WBC count was examined by smoking type, controlling for sex, age, and BMI.

Results: In total, 9747 WBC measurements were used in the analyses. WBC count increased in conventional cigarette smokers, while there was no significant difference in WBC count between heated cigarette smokers and non-smokers. The WBC count showed a positive dose–response relationship with the smoking amount in both conventional and heated cigarette smokers.

Conclusions: The results confirm that conventional cigarette smoking increases WBC counts. Furthermore, the results suggest that heated cigarette smoking does not lead to a significant increase in WBC counts, although it indicates a potential dose–response relationship with WBC count. Further research with larger sample sizes is needed to confirm whether these results reflect true associations.

Introduction

Tobacco smoking is a well-known health hazard that causes various diseases, such as lung cancer and chronic obstructive pulmonary disease.[1] The smoking prevalence among individuals aged 15 years and older was 32.7% among men and 6.6% among women worldwide.[2] Tobacco smoking accounted for 20% of all-cause deaths among men.[2]

Cigarette smoke contains thousands of hazardous materials, including particulates and gases.[3] A large number of particulates composed of complex combustion by-products of organic materials are inhaled while smoking.[4] Gas-phase chemicals may include carbon monoxide, nitrogen oxides, and benzene;[3] however, there is no clear cut-point between particulate matter and gas-phase materials. Moreover, gas-phase materials such as hydrocarbons can bind to the agglomerates of particulate matter.[3]

Heated tobacco products (HTPs) produce aerosols containing nicotine and have been developed as an alternative to conventional cigarette smoking. Cigarettes are heated to a high temperature of up to 350 °C without combustion (heat-not-burn).[5] Heated cigarette smoking is considered less harmful than conventional cigarette smoking because it emits lesser amounts of particulate matter and chemicals than conventional cigarette smoking;[6–9] however, debates over adverse health effects continue.[10–12]

Conventional cigarette smoking increases white blood cell (WBC) counts in peripheral blood.[13–15] It has been postulated that particulates and gases in smoke enhance the innate immune response, including macrophages and neutrophils, while also

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increasing the adaptive immune response, including T and B lymphocytes.[16,17]

Regarding the association between heated cigarette (or HTPs) smoking and WBC counts, there have been several studies; most studies[18–21] reported a significant decrease in WBC count after switching to heated cigarettes, except for one study.[22] Importantly, heated cigarette smoking has only started to increase in popularity recently; therefore, there is currently insufficient evidence to establish a clear relationship.

Korea was one of the first countries to increase the use of heated cigarettes rapidly. In Korea, the HEET (refills inserted into the IQOS holder) market share was up to 8% in the second quarter of 2018, an increase of 7.8 points from the prior year.[23] Here, the present study aimed to investigate the relationship between heated cigarette smoking and WBC count using a national database representing the Korean population. This is the first study to investigate this relationship using a nationwide population-based cross-sectional survey.

Methods

Data sources

Data from the Korea National Health and Nutrition Examination Survey (KNHANES), representing the Korean population, were used.[24] The KNHANES has been conducted every three years since 1998. As the use of e-cigarettes (vaping) and heated cigarettes has increased, KNHANES has incorporated relevant questionnaires on liquid-type e-cigarettes (2013) and heated cigarette smoking (2018). E-cigarettes heat liquid to generate aerosols that the user inhales. The liquid contains nicotine (but not tobacco) and typically contains several chemical additives. HTPs heat tobacco to generate nicotine-containing aerosols.

Heated cigarettes (IQOS) entered the market in June 2017 in Korea.[25] For heated cigarette smoking (i.e., IQOS, glo, and lil), detailed questionnaires, including smoking frequency and amount, have been integrated into the KNHANES since 2019. Data from the 8th (VIII-1 and 2; 2019–2020) KNHANES were used for the analyses.

In the 8th KNHANES, the WBC count was analyzed in a central laboratory (Seegene Inc.) using laser flow cytometry with an automated cell counter XN-9000 (Sysmex, Japan).

Definition of smoking-related exposures

Smoking history was assessed using self-report questionnaires. Smoking-related questionnaires were divided into three groups. The first group was related to smoking status, which included the question, 'Do you smoke conventional cigarettes now?' (conventional smoking status: current/ex/non-smokers). The second group dealt with non-conventional cigarette smoking, which included questions about e-cigarette and heated cigarette use. The third group was about the current smoking amount, which included the question, 'Average number of cigarettes smoked in the past 30 days' (smoking amount: conventional and heated cigarettes, separately). As a result, the subjects were divided into four categories of smoking status: non-smokers, ex-smokers, heated cigarette smokers, and conventional cigarette smokers.

Statistical analysis

Subjects were limited to 20–79 years of age, and those with no body mass index (BMI), WBC levels, or response to smoking-related questionnaires were excluded from subsequent analyses. In addition, subjects with vaping experience or a history of lymphohematopoietic cancers such as leukemia and lymphoma were excluded. Participants who smoked both conventional and heated cigarettes were also excluded. The detailed selection process for the study participants is presented in Supplemental Figure 1.

For all study subjects, summary statistics, including mean and standard deviation (SD), were calculated for age, BMI, smoking amount, and WBC count by sex and four smoking statuses (non-/ex-/heated cigarette/conventional cigarette smoker).

WBC counts showed a right-skewed distribution; thus, WBC counts were log-transformed and approximated to a normal distribution. To examine differences in WBC count across four smoking statuses (non-/ex-/heated cigarette/conventional cigarette smoker), analysis of variance (ANOVA) tests and multiple comparison tests were conducted. For multiple comparison tests, 'multcomp' package[26] of R[27] was used. Multiple regression analyses were also performed by sex, incorporating log-transformed WBC counts as a dependent variable and age, BMI, and four smoking statuses (non-/ex-/heated cigarette/conventional cigarette smoker) as independent variables, to evaluate the relationship between smoking status and WBC counts, controlling for the effects of age and BMI.

For smokers, summary statistics, including mean and SD, were calculated for the categories of smoking amount ($\leq$5/6–10/11–15/>15 cigarettes/day) by smoking type (heated cigarette/conventional cigarette smoking). Multiple regression analyses were performed by smoking type (heated cigarette/conventional cigarette smoking), incorporating log-transformed WBC count as a dependent variable, and sex, age, BMI, and smoking amount category ($\leq$5/6–10/11–15/>15 cigarettes/day) as independent variables to evaluate the relationship between the smoking amount and WBC counts, controlling for the effects of sex, age, and BMI.

For statistical analyses, 'survey' package[28] of R was used to account for a complex sampling scheme, including strata, clusters, and sampling weights. Each year was equally weighted by multiplying by 0.5 by each weight of the year.

Results

A total of 9747 WBC measurements sampled from 3952 men and 5795 women were included in the analysis, consisting of 6490 non-smokers, 1999 ex-smokers, 76 heated cigarette smokers, and 1182 conventional cigarette smokers (Table 1).

Summary statistics of age, BMI, smoking amount, and WBC count, including mean and SD, by sex and four smoking statuses (non-/ex-/heated cigarette/conventional cigarette smokers) are presented in Table 1. Conventional cigarette smokers showed the highest WBC count, whereas heated cigarette smokers showed a WBC count similar to that of non-smokers and ex-smokers (Table 1).

There was a significant difference in WBC count among the four categories of smoking status (ANOVA, $P < 0.001$). Heated cigarette smokers showed no difference in WBC count compared to non-smokers in multiple comparison tests, but they showed significantly lower WBC counts than conventional cigarette smokers (Table 2).

The results of multiple regression analyses of the relationship between WBC counts and four smoking statuses (non-/ex-/heated cigarette/conventional cigarette smokers), controlling for age and BMI, are presented in Table 3. Conventional cigarette smokers showed a significantly higher WBC count than non-smokers, whereas heated cigarette smokers showed no significant difference compared to non-smokers (Table 3).

Summary statistics of WBC count, including mean and SD, by smoking type (heated cigarette/conventional cigarette smoking) and the categories of smoking amount ($\leq$5/6–10/11–15/>15

Table 1
WBC counts and general characteristics by sex and smoking status.

Sex	Smoking status	N	Age		BMI		Smoking amount (cigarettes/day)		WBC counts (×1000/μℓ)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male	Non-smoker	1191	41.05	15.98	25.12	3.91	0	0	6.27	1.60
	Ex-smoker	1715	54.70	12.97	24.91	3.07	0	0	6.21	1.50
	Heated cigarette smoker	61	44.08	6.97	25.55	3.59	11.88	5.67	6.16	1.05
	Conventional cigarette smoker	973	49.93	13.42	24.40	3.51	13.05	7.61	7.25	1.84
Female	Non-smoker	5289	48.92	15.67	23.38	3.75	0	0	5.81	1.56
	Ex-smoker	277	45.76	14.28	23.65	4.27	0	0	6.03	1.63
	Heated cigarette smoker	15	36.67	11.05	22.63	3.61	6.85	3.92	6.01	1.93
	Conventional cigarette smoker	206	47.74	15.28	23.25	3.98	7.69	6.19	7.19	2.17
Both	Non-smoker	6480	47.10	16.09	23.78	3.86	0	0	5.92	1.58
	Ex-smoker	1992	53.60	13.45	24.76	3.27	0	0	6.19	1.52
	Heated cigarette smoker	76	42.90	8.15	25.08	3.73	11.08	5.72	6.14	1.22
	Conventional cigarette smoker	1179	49.61	13.72	24.23	3.60	12.26	7.65	7.24	1.89

WBC, white blood cell; N, number of subjects; SD, standard deviation; BMI, body mass index.

cigarettes/day) are presented in Table 4. In general, the WBC count showed a positive dose-related tendency with the smoking amount in both types (heated cigarette/conventional cigarette smoking) (Table 4).

The results of multiple regression analyses of the relationship between WBC counts and the smoking amount by smoking type (heated cigarette/conventional cigarette smoking), controlling for sex, age, and BMI, are presented in Table 5. In heated smokers, the category of 11–15 cigarettes/day showed a significantly higher WBC count than the reference category (≤5 cigarettes/day), whereas other categories (6–10 and >15 cigarettes/day) showed a non-significant increase. In conventional smokers, all three categories (6–10, 11–15, >15 cigarettes/day) showed significantly higher WBC counts than the reference category (≤5 cigarettes/day). The test for trend demonstrated a dose–response association between smoking amount and WBC count in both types (headed cigarette smoking: $P = 0.004$; conventional cigarette smoking: $P < 0.001$).

Discussion

Conventional cigarette smoking is known to increase blood WBC counts.[13–15] However, there are still limited studies on the relationship between heated cigarette smoking and WBC count. Previous studies were randomized trials,[18–22] which examined the effect of switching from conventional cigarette to heated cigarette smoking on WBC count. In this study, we examined this relationship using data from a population-based cross-sectional study at the national level.

In the current study, conventional cigarette smokers showed a higher WBC count than non-smokers, which is consistent with current knowledge.[15] Conventional cigarette smoke contains complex mixtures of thousands of particulates, heavy metals, gases, and radioisotopes.[3] The generated particulates are combustion by-products that range from nanoparticles to larger particles with abundant respirable particles.[29] Nano-sized particles coagulate or agglomerate into larger particles over time.[30] Respirable particles less than 10 μm in diameter are easily deposited in alveoli and terminal bronchioles.[30] High levels of particulates and gas phase chemicals, including acrolein, cause excessive inflammation through activated immune cells and cytokines, which eventually damage normal lung tissues.[4] This increase in the immune activity aimed at eliminating smoke may disrupt the equilibrium or balance of the immune system.[16] An overly activated immune system may increase the risk of autoimmune diseases such as rheumatoid arthritis.[31] Conversely, the dysfunction of immune activity due to prolonged smoking may lead to a reduced ability to remove bacteria, viruses, and cancer cells.[32,33]

Heated cigarette smokers showed no significant increase in WBC count compared to non-smokers, whereas conventional cigarette smokers showed a significant increase. The results align

Table 2
Results of multiple comparison tests on WBC count by sex and smoking status.

Sex	Smoking status		Estimate	SE	z value	*P*-value
Male	Ex-smoker	Non-smoker	−0.009	0.010	−0.894	0.794
	Heated cigarette smoker	Non-smoker	−0.002	0.025	−0.071	1.000
	Conventional cigarette smoker	Non-smoker	0.144	0.012	11.876	<0.001
	Heated cigarette smoker	Ex-smoker	0.007	0.024	0.318	0.988
	Conventional cigarette smoker	Ex-smoker	0.153	0.012	13.144	<0.001
	Conventional cigarette smoker	Heated cigarette smoker	0.146	0.025	5.747	<0.001
Female	Ex-smoker	Non-smoker	0.035	0.019	1.845	0.225
	Heated cigarette smoker	Non-smoker	0.036	0.058	0.626	0.914
	Conventional cigarette smoker	Non-smoker	0.203	0.023	8.786	<0.001
	Heated cigarette smoker	Ex-smoker	0.001	0.061	0.021	1.000
	Conventional cigarette smoker	Ex-smoker	0.169	0.029	5.855	<0.001
	Conventional cigarette smoker	Heated cigarette smoker	0.167	0.062	2.689	0.030
Both	Ex-smoker	Non-smoker	0.048	0.007	7.056	<0.001
	Heated cigarette smoker	Non-smoker	0.053	0.023	2.348	0.0752
	Conventional cigarette smoker	Non-smoker	0.203	0.009	21.803	<0.001
	Heated cigarette smoker	Ex-smoker	0.005	0.023	0.227	0.9953
	Conventional cigarette smoker	Ex-smoker	0.155	0.010	14.809	<0.001
	Conventional cigarette smoker	Heated cigarette smoker	0.149	0.025	6.081	<0.001

WBC, white blood cell; SE, standard error.

Table 3
Results of regression analyses on log-transformed WBC counts by sex and smoking status.

		Estimate	SE	t value	*P*-value
Male	(Intercept)	1.526	0.042	36.560	<0.001
	Age	−0.001	0.000	−2.981	0.003
	BMI	0.013	0.001	9.147	<0.001
	Smoking status				
	Non-smoker	ref			
	Ex-smoker	0.006	0.010	0.625	0.533
	Heated cigarette smoker	−0.004	0.026	−0.166	0.869
	Conventional cigarette smoker	0.162	0.012	13.020	<0.001
Female	(Intercept)	1.427	0.025	56.39	<0.001
	Age	−0.003	0.000	−9.42	<0.001
	BMI	0.018	0.001	17.59	<0.001
	Smoking status				
	Non-smoker	ref			
	Ex-smoker	0.022	0.017	1.33	0.18
	Heated cigarette smoker	0.019	0.053	0.35	0.73
	Conventional cigarette smoker	0.203	0.022	9.15	<0.001
Both	(Intercept)	1.490	0.024	62.325	<0.001
	Sex				
	Male	ref			
	Female	−0.035	0.007	−4.714	<0.001
	Age	−0.002	0.000	−8.694	<0.001
	BMI	0.015	0.001	18.551	<0.001
	Smoking status				
	Non-smoker	ref			
	Ex-smoker	0.022	0.008	2.708	0.007
	Heated cigarette smoker	0.004	0.024	0.179	0.858
	Conventional cigarette smoker	0.179	0.011	16.742	<0.001

WBC, white blood cell; SE, standard error; BMI, body mass index.

Table 4
Summary statistics of WBC counts by smoking type and amount.

Smoking type	Smoking amount	N	Mean	SD
Heated cigarette smokers	≤5 (cigarettes/day)	16	5.74	0.83
	6–10 (cigarettes/day)	30	5.88	1.33
	11–15 (cigarettes/day)	15	6.61	1.17
	>15 (cigarettes/day)	15	6.63	1.14
Conventional cigarette smokers	≤5 (cigarettes/day)	247	6.64	1.65
	6–10 (cigarettes/day)	371	7.24	1.99
	11–15 (cigarettes/day)	195	7.57	1.75
	>15 (cigarettes/day)	366	7.50	1.93

WBC, white blood cell; N, number of participants; SD, standard deviation.

with previous randomized trial studies,[18–21] though an exception also exists.[22] It has been reported that heated cigarette smoking produces less emission of toxic chemicals than conventional cigarette smoking;[6,9] nicotine was comparable[34,35] or reduced to 70–80% of conventional cigarette smoking,[36] and water accounted for 75–85% of gaseous and particulate matter compared to 17–27% of conventional cigarette smoke.[6,37] On the contrary, heated cigarette smoking produces more exposure to some chemicals, including propylene glycol, glycerol, and acetol, than conventional cigarette smoking.[6] Conventional cigarette smoking produces combustion-related particles containing elements such as carbon, calcium, and silicon, while heated cigarette smoke is composed of semi-volatile organic constituents.[38] Particulate matter emission from heated cigarette smoking was reported much less than that for conventional cigarette smoking.[39,40] It can be suspected that emitting less particulate matter and gases in heated cigarette smoking is associated with lower WBC counts than conventional cigarette smoking.[36]

Although there was no significant difference in WBC counts between heated cigarette smokers and non-smokers, a potential dose–response relationship between smoking amount and WBC count was also observed, similar to conventional cigarette smoking.[15] The results may imply that although heated cigarette smoking induces less inflammation than conventional cigarette smoking, it may affect WBC count in a dose–response manner. However, to establish if these associations reflect a genuine effect, further research with larger sample sizes is warranted.

In the statistical analyses, the potentially relevant factors associated with WBC counts, such as physical activity and alcohol intake, were not controlled. The influence of physical activity and alcohol intake on WBC counts was much lower than that of cigarette smoking and BMI.[41–43] Including these two factors might decrease the statistical power. Therefore, this study sought to simplify the association between cigarette smoking and WBC count by excluding physical activity and alcohol intake variables. Secondhand smoke (SHS) is reported to increase WBC counts in non-smokers; however, SHS was excluded from the analysis because the effect of SHS was not statistically significant in either heated cigarette smokers or conventional cigarette smokers (data not shown).

Table 5
Results of regression analyses on log-transformed WBC counts by smoking type and amount.

Smoking type	Variable	Estimate	SE	t value	*P*-value
Heated cigarette smokers (N = 76)	(Intercept)	1.444	0.230	6.288	<0.001
	Sex				
	Male	ref			
	Female	0.035	0.062	0.558	0.580
	Age	0.000	0.002	0.036	0.972
	BMI	0.010	0.006	1.627	0.112
	Smoking amount				
	"≤5 (cigarettes/day)	ref			
	6 - 10 (cigarettes/day)	0.005	0.045	0.112	0.911
	11–15 (cigarettes/day)	0.145	0.063	2.288	0.028
	>15 (cigarettes/day)	0.128	0.065	1.958	0.057
Conventional cigarette smokers (N = 1179)	(Intercept)	1.626	0.081	19.958	<0.001
	Sex				
	Male	ref			
	Female	0.028	0.025	1.103	0.271
	Age	0.000	0.001	0.195	0.845
	BMI	0.008	0.002	3.497	0.001
	Smoking amount				
	≤5 (cigarettes/day)	ref			
	6 - 10 (cigarettes/day)	0.075	0.024	3.172	0.002
	11–15 (cigarettes/day)	0.137	0.023	5.852	<0.001
	>15 (cigarettes/day)	0.120	0.023	5.131	<0.001

N, number of participants; WBC, white blood cell; SE, standard error; BMI, body mass index.

Previous studies have shown that it may take up to 2 years for WBC counts to return to non-smoker levels after smoking cessation.[44] Initially, there is a steep decline in WBC levels after quitting smoking, followed by a gradual decline over time.[13,45] Therefore, individuals who recently switched from smoking to heated cigarettes may be more susceptible to residual effects. When the duration of smoking cessation was analyzed as an independent variable in regression models, no significant effect on WBC count was observed (data not shown). Among heated cigarette smokers, 87% had quit smoking for more than 12 months, which may explain the non-significant effect of quitting duration on WBC count.

In dual smokers who smoked both conventional and heated cigarettes simultaneously, conventional cigarette smoking was positively associated with WBC counts, whereas heated cigarette smoking showed negative associations (Supplemental Table 1). The results are largely consistent with our primary outcomes; however, the topic is beyond our study's aim, and thus, we did not analyze it further.

This study used a database representing the Korean population over two years. However, this study has several limitations. First, despite the large data set, the number of heated cigarette smokers was small; therefore, the study power was limited in examining the effects of heated cigarette smoking on WBC count. Second, the study design was neither longitudinal nor contained repeated measurements; therefore, it could not examine temporal changes in health effects relevant to smoking status. Third, underlying conditions affecting WBC counts, such as infection, were not considered. Fourth, self-administered questionnaires were used to estimate exposure levels, which poses a potential bias.[46]

Conclusions

Using nationally representative survey data, this study examined the association between heated cigarette smoking and WBC count. There was no significant difference in WBC count between heated cigarette smokers and non-smokers. In addition, a positive dose–response relationship between smoking amount and WBC count was observed, which implies that excessive heated cigarette smoking may lead to an increase in inflammation. Further investigation with larger sample sizes is necessary to confirm these associations in future studies. The nicotine contained in heated cigarette smoke was comparable to or less than conventional cigarette smoke,[34,36] which indicates that heated cigarette smoking also induces addiction to nicotine, similar to conventional cigarette smoking. While heated cigarette smoking may reduce inflammation compared with conventional cigarette smoking, quitting smoking cannot be overemphasized to protect health.

Author statements

Ethical approval

The review of the study protocol was exempted by the Institutional Review Board of the Catholic Kwandong University, International St. Mary's Hospital, Incheon, Korea (IS22EISI0004).

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Competing interests

The author declares that he has no conflict of interest.

Data availability

The data in this study were obtained from the Korea National Health and Nutrition Examination Survey (KNHANES), Korea Disease Control and Prevention Agency, Ministry of Health and Welfare, Republic of Korea. The KNHANES data are available to the public free of charge at https://knhanes.kdca.go.kr/knhanes/eng/index.do.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.07.006.

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