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Current cigarette smoking is a reversible cause of elevated white blood cell count: Cross-sectional and longitudinal studies

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ABSTRACT

While cigarette smoking is a well-recognized cause of elevated white blood cell (WBC) count, studies on longitudinal effect of smoking cessation on WBC count are limited. We attempted to determine causal relationships between smoking and elevated WBC count by retrospective cross-sectional study consisting of 37,972 healthy Japanese adults who had a health check-up between April 1, 2008 and March 31, 2009 and longitudinal study involving 1730 current smokers who had more than four consecutive annual health check-ups between April 1, 2007 and March 31, 2012.

In the cross-sectional study, younger age, male gender, increased body mass index, no alcohol habit, current smoking, and elevated C-reactive protein level were associated with elevated WBC count. Among these factors, current smoking had the most significant association with elevated WBC count. In subgroup analyses by WBC differentials, smoking was significantly associated with elevated counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Ex-smoking was not associated with elevated WBC count. In the longitudinal study, both WBC and neutrophil counts decreased significantly in one year after smoking cessation and remained down-regulated for longer than next two years. There was no significant change in either WBC or neutrophil count in those who continued smoking.

These findings clearly demonstrated that current smoking is strongly associated with elevated WBC count and smoking cessation leads to recovery of WBC count in one year, which is maintained for longer than subsequent two years. Thus, current smoking is a significant and reversible cause of elevated WBC count in healthy adults.

1. Introduction

It is not uncommon to find leukocytosis in otherwise healthy individuals. Epidemiological data indicate that cigarette smoking is associated with elevated white blood cell (WBC) count (Petitti and Kipp, 1986; Yarnell et al., 1987; Schwartz and Weiss, 1991; Schwarz and Weiss, 1994; Freedman et al., 1996; Sunyer et al., 1996; Van Tiel et al., 2002; Fröhlich et al., 2003; Smith et al., 2003; Lao et al., 2009). In addition, a variety of factors such as younger age (Schwartz and Weiss, 1991; Nagasawa et al., 2004), male gender (Schwartz and Weiss, 1991; Brown et al., 2001), increased body mass index (BMI) (Schwartz and Weiss, 1991; Nagasawa et al., 2004; Herishanu et al., 2006; Jee et al., 2005; Imano et al., 2007), high blood pressure (HBP) (Nagasawa et al., 2004; Brown et al., 2001; Jee et al., 2005; Imano et al., 2007; Lee et al., 2009), hyperlipidemia (Nagasawa et al., 2004; Jee et al., 2005), diabetes (Nagasawa et al., 2004; Jee et al., 2005), and decreased alcohol consumption (Schwartz and Weiss, 1991; Nakanishi et al., 2003) have been reported to be associated with elevated WBC count. On the other hand, elevated WBC count has been reported to be an independent predictor of coronary heart disease (CHD) and cardiovascular disease (CVD) (Brown et al., 2001; Madjid et al., 2004) and reduction in the WBC counts may be related to the reduction in the CHD and CVD risks.

A number of studies have reported that smoking cessation leads to a decrease in WBC count which appears to be associated with the duration of the smoking abstinent (Petitti and Kipp, 1986; Yarnell et al., 1987; Schwartz and Weiss, 1991; Schwarz and Weiss, 1994; Van Tiel et al., 2002; Fröhlich et al., 2003; Smith et al., 2003; Lao et al., 2009; Kawada, 2004; Ishizaka et al., 2007; Parry et al., 1997). However, most of these studies are based on cross-sectional studies. Although some prospective studies have shown that smoking cessation with nicotine replacement therapy (Jensen et al., 1998; Eliasson et al., 2001) or bupropion (Abel et al., 2005) or without pharmaceutical support

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(Sunyer et al., 1996; Green and Harari, 1995) led to a time-dependent decrease in WBC count which was apparent as early as eight weeks after cessation, there have been few reports on longitudinal effects of smoking cessation on WBC count. Especially, there is only one cross-sectional study which investigated the association of smoking cessation and WBC count in Japanese cohort but longitudinal effect of smoking cessation on WBC count in Asian population has not been studied (Kawada, 2004).

The aim of this study was to determine causal relationship between smoking and elevated WBC count in a large cohort of healthy Japanese adults. Our results adds to the literature further evidence of the causal relationship between smoking and WBC count and demonstrate that the effect of smoking on WBC count is reversible within one year after smoking cessation.

2. Patients and methods

This study is a retrospective observational study approved by The Ethics Committee of St. Luke's International Hospital and all the individuals had approved the use of their data.

2.1. Cross-sectional study

A total of 40,279 healthy adults (≥20 years old) had a general health check-up from April 1, 2008 to March 31, 2009 in the department of preventive medicine affiliated with a tertiary referral hospital in Tokyo Japan. Subjects who had known hematological and/or solid tumors and 50 subjects with incomplete questionnaire were excluded, leaving 37,972 individuals who comprised the subjects of the retrospective cross-sectional study (Fig. 1A). Age, gender, height, body weight, complete blood cell count with differentials of WBC, and C-reactive protein (CRP) level were collected from medical records. BMI was categorized into three categories; <22 kg/m^2, ≤22 kg/m^2 and <25 kg/m^2, and 25 kg/m^2 ≤. BMI < 22 kg/m^2 was used as reference in logistic regression analysis. Smoking history including number of cigarettes per day, years of smoking, and alcoholic consumption history were collected from self-administered questionnaire for the general health check-up. Smoking factors were categorized into current, past, and non-smoker. WBC and its differentials of individuals who had quitted smoking (ex-smokers) and current smokers were compared with those who had never smoked (never smokers). WBC counts equal to or >9.0 × 10^9/L were defined to be increased. For each differential of WBC, neutrophil counts > 7.5 × 10^9/L, monocyte counts > 1.0 × 10^9/L, eosinophil counts > 0.7 × 10^9/L, and basophil counts > 0.15 × 10^9/L were defined to be increased.

2.2. Longitudinal study

Healthy adult smokers who had more than four consecutive annual health check-ups from April 1, 2007 to March 31, 2012 in the same institution were studied. Among 83,752 individuals who had health check-ups during this period, 25,003 had more than four consecutive annual health check-ups. CRP data on one or more occasions were missing in 2822 individuals and they were excluded. Four thousand five hundred fifty-seven patients with hematological and/or solid tumors, who were taking steroids and/or whose CRP value was equal to or above 0.3 mg/dL as well as two individuals with incomplete date were excluded, thus leaving 17,622 individuals. Fifteen thousand eight hundred ninety-two individuals who had never smoked, who had a smoking history but quitted smoking before the study period, and who quitted smoking after the first visit but resumed afterward before the fourth visit were also excluded. The remaining 1730 individuals were current smokers at their first visit, of whom 1499 continued smoking for longer than three years while 231 quitted smoking within one year after the first visit and remained abstinent from smoking until the fourth visit (Fig. 1B). Longitudinal changes of the WBC and differential counts were evaluated retrospectively.

2.3. Hematological analyses

Fasting venous blood samples were drawn from all subjects into vacuum tube containing EDTA. WBC count and differentials were determined by applying the samples within 15 min to Beckman Coulter

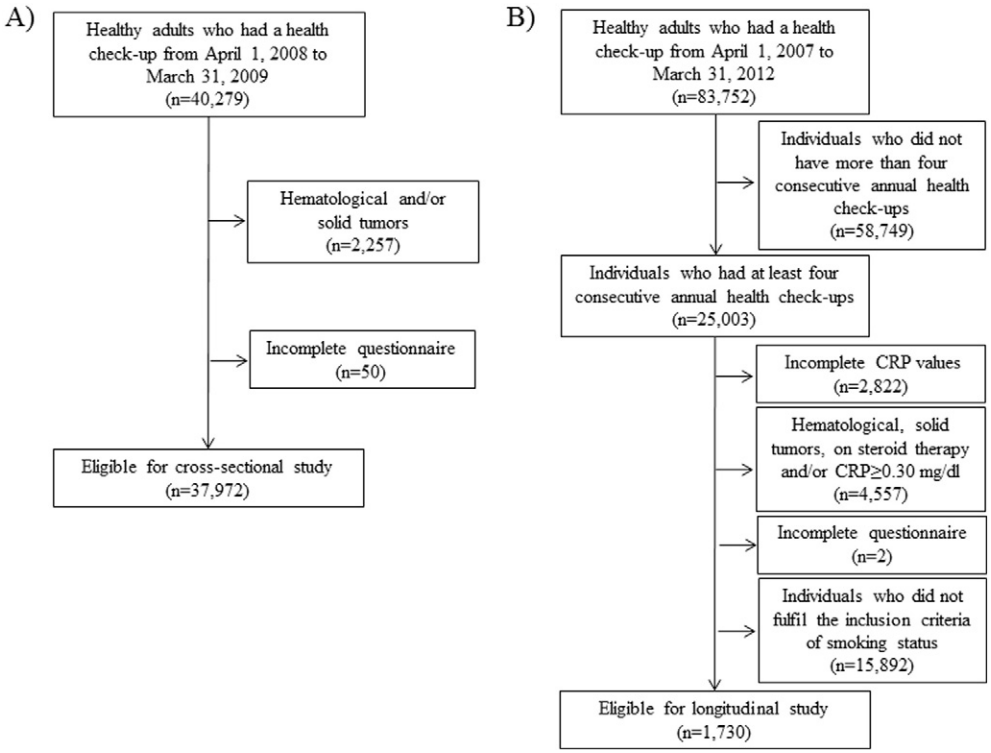

Fig. 1. Study flow diagrams of cross-sectional (A) and longitudinal (B) studies.

Table 1
Factors associated with increased white blood cell count.

	Odds ratio	95% CI	*P* value
Age	0.98	0.98–0.99	<0.0001
Male gender	1.60	1.30–1.96	<0.0001
BMI < 22	1		
22 ≤ BMI < 25	1.49	1.21–1.83	0.0002
25 ≤ BMI	2.15	1.74–2.65	<0.0001
Alcohol habit	0.68	0.57–0.80	<0.0001
Ex-smoker	1.10	0.86–1.42	0.44
Current smoker	6.60	5.43–8.02	<0.0001
CRP (mg/dL)	2.22	2.00–2.47	<0.0001

Hosmer-Lemeshow test, $P = 0.002$.
BMI, body mass index; CRP, C-reactive protein; CI, confidence interval.

GEN-S (until February 2009) or Sysmex XE-2100 (after March 2009) automated hematology analyzer.

2.4. Statistical analyses

Comparisons of continuous variable and proportions were performed using unpaired Student's *t*-test and Fisher's exact test, respectively. In the cross-sectional study, the associations of each independent variable with elevated WBC count and differential counts were analyzed by simple and multivariate logistic regression analyses. In the longitudinal analysis, paired Student's *t*-test was applied. Simple and multivariate logistic regressions were conducted using the outcome of decreased WBC count on the second and fourth visits compared with the baseline WBC count. Model fit of multivariate logistic regression was checked by Hosmer-Lemeshow test.

All analyses were two tailed and *P* values < 0.05 were considered to be statistically significant. All variables with *P* value < 0.2 in simple regression were included in multivariate mode. All analyses were performed using JMP® version 10 (SAS Institute, Inc. Cary, NC, USA) and STATA® version 14.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Cross-sectional study

In the cross-sectional study, multivariate analysis revealed that elevated WBC count was significantly associated with younger age, male gender, increased BMI, no habit of drinking alcohol, current smoking, and elevated CRP (Table 1). The factor most strongly associated with elevated WBC count was current smoking (odds ratio [OR], 6.60; 95% confidence interval [CI], 5.43–8.02). Ex-smoking was not associated with elevated WBC count.

The associations of these factors with each WBC differential were also studied (Table 2). Current smoking was significantly associated with increase of all differentials including neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Elevated CRP was associated with increase of neutrophils and monocytes but not with that of lymphocytes, eosinophils, and basophils. Male gender was associated with elevated neutrophil, lymphocyte, monocyte, and eosinophil counts. BMI was not associated with increase of any differentials in spite of the positive association with total WBC count (Tables 1 and 2).

Table 3
Characteristics of the participants.

	Quitters (n = 231)	Continuing smokers (n = 1499)	*P* value
Age, mean (SD)	51 (10)	48 (10)	0.0003
Male gender, n (%)	172 (74)	1092 (73)	0.63
BMI (kg/m^2), mean (SD)	23 (2.9)	23 (3.2)	0.43
Cigarettes/day, mean (SD)	13 (8)	18 (10)	<0.0001
WBC count (10^9/L), mean (SD)	5.64 (1.59)	6.03 (1.67)	0.0009

BMI, body mass index; WBC, white blood cell; SD, standard deviation.

3.2. Longitudinal study

In the longitudinal study, baseline characteristics of 1730 individuals who were current smokers at their first visits are presented in Table 3. 231 individuals of 1730 smokers quitted smoking within one year after the first visit, and continued to be abstinent from smoking until the fourth visit (quitters). The remaining 1499 smokers continued smoking for longer than four years after the first visit (continuing smokers). The baseline WBC counts of the quitter were significantly lower than those of continuing smokers (Table 3). The quitters were significantly older and smoked less cigarettes per day than the continuing smokers.

In one year after the first visit, a significant decrease in WBC count (mean, 5.374×10^9/L) from baseline (mean, 5.642×10^9/L) was observed in the quitters' group ($P = 0.001$) (Fig. 2A). The decrease in WBC count remained significant compared to the baseline level for the next two years ($P < 0.0001$). The mean WBC counts of the continuing smokers did not change either one year after the first visit (mean, 6.087×10^9/L) or two years afterward (mean, 6.059×10^9/L) from baseline (6.031×10^9/L) (Fig. 2A).

As there were differences in age, baseline WBC count, number of cigarettes per day between quitters and continuing smokers at baseline, logistic regression analyses were performed including these factors. As expected, smoking cessation was significantly associated with decrease of WBC count in one year with an adjusted OR of 1.85 (95% CI, 1.39–2.48) (Table 4) and after the following two years (adjusted OR, 2.54; 95% CI, 1.88–3.46) (Table 5). The higher WBC count at baseline was also significantly associated with decrease in WBC count within one year after cessation (adjusted OR, 1.37; 95% CI, 1.28–1.46) (Table 4) and the association was maintained after two years (adjusted OR, 1.55; 95% CI, 1.44–1.67) (Table 5).

Table 2
Factors associated with increase of white blood cell differentials.

	Neutrophils		Lymphocytes		Monocytes		Eosinophils		Basophils	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age	0.98	0.96–0.99	1.0	0.96–1.04	1.0	0.99–1.1	0.99	0.97–0.99	1.0	0.95–1.01
Male gender	1.6	1.1–2.4	6.5	1.5–45	4.0	1.2–17	2.2	1.6–2.9	0.5	0.2–1.2
BMI < 22	1		1		1		1		1	
22 ≤ BMI < 25	1.2	0.8–1.7	1.0	0.3–3.1	1.1	0.4–3.4	0.8	0.6–1.1	1.3	0.5–3.1
25 ≤ BMI	1.3	0.9–1.8	1.0	0.3–3.3	1.1	0.3–3.5	0.9	0.7–1.3	1.0	0.3–3.0
Alcohol habit	1.0	0.7–1.4	0.5	0.2–1.4	0.4	0.2–1.2	0.7	0.5–0.9	1.6	0.7–4.0
Ex-smoker	0.9	0.6–1.5	1.8	0.4–7.8	1.7	0.5–6.1	1.0	0.7–1.4	2.0	0.7–5.2
Current smoker	3.9	2.8–5.6	6.1	1.9–24	4.6	1.4–16	1.9	1.4–2.6	3.8	1.5–9.6
CRP (mg/dL)	1.9	1.7–2.1	1.4	0.5–1.8	2.0	1.7–2.3	0.9	0.5–1.3	1.4	0.9–1.8
P value of HL test	0.15		0.51		0.26		0.51		0.20	

BMI, body mass index; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval; HL, Hosmer-Lemeshow.

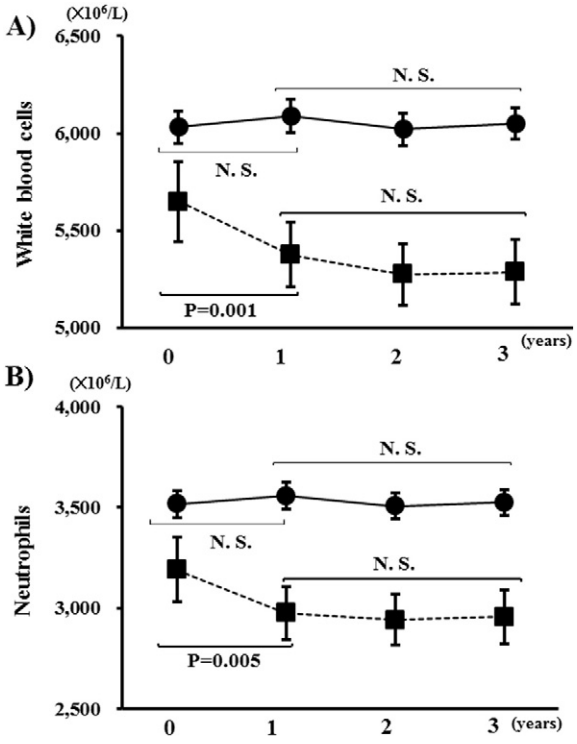

Fig. 2. Longitudinal change of white blood cell (A) and neutrophil (B) counts in healthy adults divided by quitting or continuing cigarette smoking. In individuals who were current smokers at the first visit (year 0) and quitted smoking before the second visit (year 1) and remained abstinent for at least next two years, both white blood cell (WBC) and neutrophil counts significantly decreased within one year ($P = 0.001$ for WBC and 0.005 for neutrophil counts, respectively, Paired *t*-test) and remained decreased for the abstinent period (squares and dotted lines). On the other hands, both WBC and neutrophil counts did not change in individuals who continued smoking during the same period (circles and straight lines). N. S., not significant.

Effects of smoking cessation on neutrophil and lymphocyte counts were studied in longitudinal study. Neutrophil count decreased significantly after smoking cessation in one year ($P = 0.005$) and remained down-regulated after the following two years, however, it did not change among continuing smokers (Fig. 2B). The lymphocyte count also decreased in one year after smoking cessation, however, the difference from baseline was not significant ($P = 0.082$) with no further changes after the following two years. These results indicated that smoking cessation lead to decreases in total WBC and neutrophil counts in one year and these effects remained for longer than next two years.

BMI of the quitters was significantly increased from baseline (mean, 22.65 kg/m^2) in one year (mean, 23.0 kg/m^2; $P < 0.0001$) and, as the period of abstinence became longer, BMI further increased during next two years (mean, 23.26 kg/m^2; $P < 0.0001$). BMI of continuing smokers did not change from baseline (mean, 22.86 kg/m^2) in one year (mean, 22.85 kg/m^2; $P = 0.59$), however, BMI increased significantly in the following two years (22.94 kg/m^2; $P < 0.0001$). Increase of BMI in quitters was not associated with decrease of WBC at the second visit (adjusted OR, 0.85; 95% CI, 0.70–1.03) (Table 4), however, was inversely associated with decrease in WBC count two years later at the fourth visit (adjusted OR, 0.73; 95% CI, 0.60–0.89) (Table 5), indicating that decrease in WBC count after smoking cessation was associated with decrease of BMI.

4. Discussion

Our study demonstrated that younger age, male gender, increased BMI, no habit of alcohol drinking, and current smoking were significantly associated with increased WBC count. This increase was reversed by quitting smoking in one year and continued to be down-regulated at least for the following two years. The questionnaire did not include the question when the quitters stopped smoking and we could not obtain the exact date of smoking cessation and, thus, the duration of the abstinence of the quitters before the second visit differed in each individual. Accordingly, the precise time-dependent changes of WBC count within one year after the smoking cessation could not be studied in detail. Nonetheless, these findings clearly demonstrated that the effect of smoking cessation on WBC count became apparent in one year and lasted at least for the following two years.

Elevated WBC count has been reported to be associated with CHD (Imano et al., 2007; Madjid et al., 2004) and cardiovascular mortality (Brown et al., 2001; Jee et al., 2005; Tamakoshi et al., 2007) and has been identified as an independent risk factor of CHD (Brown et al., 2001; Madjid et al., 2004). Elevated WBC count is also associated with components of metabolic syndrome, which is a well-known risk factor for CHD/CVD (Nagasawa et al., 2004; Kim et al., 2008; Yanbaeva et al., 2007). Therefore, detection of the cause of elevated WBC count and its reduction may be expected to contribute to the prevention of CHD/CVD.

While there have been several reports which did not support the association between male gender and elevated WBC count (Schwarz and Weiss, 1994), the rest of our findings were compatible with previous reports (Schwartz and Weiss, 1991; Nagasawa et al., 2004; Brown et al., 2001; Herishanu et al., 2006; Jee et al., 2005; Imano et al., 2007; Lee et al., 2009; Nakanishi et al., 2003). Of note is that the result of the cross-sectional study demonstrated positive association between increased BMI and elevated WBC count as previously reported (Schwartz and Weiss, 1991; Nagasawa et al., 2004; Herishanu et al., 2006; Jee et al., 2005; Imano et al., 2007) and, in addition, the association was confirmed by multivariate logistic regression analysis in the longitudinal study.

The association between elevated WBC count and cigarette smoking, a well-established cardiovascular risk factor, has been reported in many epidemiological studies and also it has been reported that smoking cessation leads to a reduction in WBC counts (Petitti and Kipp, 1986; Yarnell et al., 1987; Schwartz and Weiss, 1991; Schwarz and Weiss, 1994; Freedman et al., 1996; Sunyer et al., 1996; Van Tiel et al., 2002; Fröhlich et al., 2003; Smith et al., 2003; Lao et al., 2009). Elevated WBC count may reflect the existence of low-grade inflammatory response in smokers (Lee et al., 2009; Yanbaeva et al., 2007) and it is assumed that reduction in WBC count reflects the improvement of the systemic inflammation and, possibly, of vascular endothelial inflammation. The association between elevated CRP level and elevated WBC count

Table 4
Factors associated with decrease in WBC count in one year since the first visit.

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age at the first visit	1.00 (0.99–1.01)	0.43		
Male gender	0.97 (0.79–1.2)	0.81		
Increase of BMI (kg/m^2)	0.87 (0.72–1.05)	0.14	0.85 (0.70–1.03)	0.095
Smoking abstinence	1.56 (1.18–2.07)	0.002	1.85 (1.39–2.48)	<0.0001
Baseline WBC count (10^9/L)	1.35 (1.27–1.44)	<0.0001	1.37 (1.28–1.46)	<0.0001
Cigarettes/day	1.00 (0.99–1.01)	0.52		

Hosmer-Lemeshow test, $P = 0.81$.
BMI, body mass index; WBC, white blood cell; OR, odds ratio.

Table 5
Factors associated with decrease in WBC count at the fourth visit.

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age at the first visit	1.01 (0.999–1.02)	0.097	1.01 (0.995–1.02)	0.29
Male gender	1.00 (0.81–1.24)	0.97		
Increase of BMI (kg/m^2)	0.78 (0.65–0.95)	0.012	0.73 (0.60–0.89)	0.002
Smoking abstinence	1.91 (1.44–2.55)	<0.0001	2.54 (1.88–3.46)	<0.0001
Baseline WBC count (10^9/L)	1.51 (1.41–1.62)	<0.0001	1.55 (1.44–1.67)	<0.0001
Cigarettes/day	1.01 (0.996–1.02)	0.25		

Hosmer-Lemeshow test, $P = 0.51$.
BMI, body mass index; WBC, white blood cell; OR, odds ratio.

observed in the cross-sectional study and the decrease in neutrophils in one year after smoking cessation support these assumptions. Moreover, WBCs are, by themselves, considered to be involved in vascular injury through pressure dependent plugging of microvessels by WBCs, rheological abnormalities, increased adhesiveness, and release of substances resulting in cytotoxic injury to the vessel wall (Brown et al., 2001). Thus, the reduction in WBC count may reflect the alleviation of the vascular damage caused by WBCs. In addition to these possible direct damage to the vascular system, increased WBCs may contribute to the development of CHD and CVD indirectly through modification of various risk factors such as HBP (Nagasawa et al., 2004; Brown et al., 2001; Jee et al., 2005; Imano et al., 2007; Lee et al., 2009), hyperlipidemia (Nagasawa et al., 2004; Jee et al., 2005), and diabetes (Nagasawa et al., 2004; Jee et al., 2005).

In these contexts, it should be emphasized that not only neutrophils and monocytes, which were associated with elevated CRP, but also the other differentials were elevated in current smokers. These observations indicate that smoking habit leads to increase of all components of WBC by mechanisms not elucidated yet. These observations have not been reported before.

Though it has been reported that changes in smoking habit influence WBC count and smoking cessation leads to a decrease in WBC count, which depends on the duration of the smoking abstinent (Petitti and Kipp, 1986; Yarnell et al., 1987; Schwarz and Weiss, 1994; Van Tiel et al., 2002; Smith et al., 2003), there have been only a few longitudinal studies which investigated the effect of smoking cessation on WBC count (Sunyer et al., 1996; Jensen et al., 1998; Green and Harari, 1995). Especially regarding the Asian population, only one cross-sectional study reported the effects of smoking on WBC count among Japanese adults (Kawada, 2004) and the effect of smoking cessation on WBC count has not been studied longitudinally. This report is the first study which evaluated the longitudinal effects of smoking cessation in a large Asian population and clearly demonstrated the association between smoking cessation and decrease in WBC count.

There are some limitations in our study. First, this is a retrospective study and there may be an information bias as the data on smoking status were collected and evaluated based on the self-reported questionnaire. Second, study participants of this longitudinal study were those who had health check-ups for at least consecutive four years. These participants are estimated to be more conscious about their health status than general populations. Third, there was no information about medication used for smoking cessation. As it has been reported that WBC count decreased after cessation of smoking with use of nicotine replacement (Jensen et al., 1998; Eliasson et al., 2001), we cannot exclude the possibility that WBC count decreased by taking such medication. However, as the WBC count remained down-regulated for more than two years after smoking cessation, we think that the effects of such medication were minimal if some of the quitters actually used it. Fourth, as this is a retrospective observational study of participants of general health check-ups, important factors which might influence WBC counts were not evaluated, thus, our results did not allow us to attempt to investigate scientific explanation of the association between cigarette smoking and WBC count, for which studies beyond the frame of general health check-up should be performed. Fifth, one of Hosmer-Lemeshow tests was significant (Table 1) but this would be due to large sample number.

There are some criteria proposed to show causal association. One of these criteria is strong association and temporal relationship where cause precedes the outcome (Grobbee, 2009). Our study supported temporal relationship between smoking cessation and decrease in WBC count by adding longitudinal study to cross-sectional study. This shall be the strength of our study.

In conclusion, current smoking is strongly associated with elevated WBC count in healthy adults with increase of all WBC differentials. Smoking cessation is associated with recovery of WBC count in one year and this effect lasts for at least next two years. It is important to keep in mind that cigarette smoking is one of differential diagnoses and a reversible cause of elevated WBC count.

Conflicts of interest

None.

Transparency document

The Transparency document associated with this article can be found in the online version.

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