Editorial Comment

The Relationship between White Blood Cell Count and Risk of Hypertension in Populations with High Prevalence of Smoking

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Recently, markers of chronic inflammation have been recognized as risk factors of cardiovascular disease. Although various inflammatory factors, such as C-reactive protein (CRP), albumin, and fibrinogen, have been examined in many epidemiologic studies, WBC count is a widely used examination to detect inflammation in a routine blood test. Previous population-based cohort studies indicated that WBC count was associated with the risk of coronary heart disease (*1–3*) and stroke (*2–4*). Furthermore, several studies have also demonstrated a positive relationship between WBC count and hypertension (*5–7*). For example, in a 10-year NHANES I epidemiologic follow-up study, Gillum *et al*. showed a statistically significant 50% increase in risk of hypertension in white men aged 25–74 years with WBC count >8,600 compared to men with WBC count <6,200 cells/mm^3 (*6*).

However, these findings could not be globally generalized since most of previous studies were reported from Western populations. Smoking is a major risk factor for cardiovascular disease and also raises WBC count (*8*). Accordingly, the relationship between WBC count and cardiovascular disease or hypertension should be examined in Asian populations, where male smoking prevalence is much higher than Westerner males. To our knowledge, three cohort studies in Japanese general populations reported the relationship between WBC count and cardiovascular disease or hypertension. Imano *et al*. showed that increased WBC count was associated with incidence of myocardial infarction in middle-aged Japanese workers, both in smokers and non-smokers (*9*). In NIPPON DATA90 (the National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1990), Tamakoshi *et al*. also demonstrated that subjects who never smoked with WBC counts of 9,000–10,000 had a 3.2-fold risk for cardiovascular mortality compared with those having WBC counts of 4,000–4,900 (*10*). Furthermore, Nakanishi *et al*. reported that WBC count was a risk factor for hypertension, and the increased risk for hypertension associated with WBC count was more pronounced in non-smokers (*11*). In a study of Koreans whose smoking status is similar to that of the Japanese, the association of increased WBC count with cardiovascular mortality was more evident among those who never smoked compared to smokers (*12*). These results suggest that the elevated WBC count is a risk factor for cardiovascular disease or hypertension independent of smoking even in East Asian populations.

Tatsukawa *et al*. have now added further evidence concerning the relationship between WBC count and hypertension incidence from a 40-year cohort of 9,383 Japanese men and women published in this issue of *Hypertension Research* (*13*). They showed that elevated WBC count predicted an increased incidence of hypertension in both men and women after adjusting for smoking status, although WBC count for men was a significant risk for hypertension only in the time-varying model. In many cohort studies, a single medical examination and questionnaire was performed as a baseline survey. However, because biological data and lifestyle status of the participants have changed during the follow-up periods, the predictive power of data from a single baseline survey was attenuated, especially with a long-term follow-up

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period. Furthermore, all data include random errors, which are also evident when data are based on a single measurement. Thus, the above-mentioned study design produces "a kind of misclassification," which underestimates the relationship between candidate risk factors and outcomes. Usually, underestimation is not a problem because overestimation should be avoided in scientific research. There are some methods to remove these "misclassifications." Adjustment for regression dilution bias is used for decreasing random errors (*14*). However, time-varying Cox regression or pooled logistic regression (*15*) is used for accounting for the long-term change of risk factors. The relationship between WBC count and hypertension for men was only detected by a time-varying Cox model in this study. A single measurement of WBC count for men may not reflect lifetime WBC count due to dramatic changes in the prevalence of smoking over 40 years. We should pay attention to this underestimate when dealing with a long-term cohort study with a single baseline survey.

Tatsukawa *et al*. also suggested that the neutrophils for women were contributing to the increased risk of hypertension in differential WBC counts (*13*). Although there are pathological findings that monocytes, the precursor of macrophages, are present during the progression of atherosclerosis, neutrophils may be a marker of systemic inflammation and a risk factor for cardiovascular disease and hypertension among those who had advanced atherosclerosis. Horne *et al*. showed that the neutrophil count was more strongly associated with the risk for myocardial infarction compared with monocyte count among patients undergoing coronary angiography (*16*). Activated neutrophils tend to adhere on vascular endothelium, which are increasing vascular resistance (*17*). Furthermore, neutrophils release reactive oxygen species, which may impair endothelium-dependent vasorelaxation (*18*).

What are the underlying mechanisms for an association between WBC count and cardiovascular disease? First, as already discussed, WBC count is a marker for inflammation in the process of atherosclerosis. Second, WBCs may stimulate platelets and promote thrombosis (*19*). Finally, WBCs migrate into the vessel wall and cause the release of chemical products from proliferating endothelial cells and from WBCs, such as neutrophils, which may cause hypertension. However, to clarify the effect of *in vivo* inflammatory status on hypertension and cardiovascular disease, further cohort studies are warranted in large populations using measurements of other inflammatory markers, such as CRP, albumin (*20*) and pro-inflammatory cytokines.

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