Original Article

White Blood Cell Count, Especially Neutrophil Count, as a Predictor of Hypertension in a Japanese Population

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Although several studies have shown that high WBC count is a risk factor for hypertension, the relationship between WBC count and the incidence of hypertension in Japanese is poorly understood, as are the effects of WBC components on that relationship. Our objective was to verify in a Japanese population whether WBC or differential WBC count predicts hypertension incidence. A total of 9,383 initially hypertension-free subjects (3,356 men and 6,027 women), whose WBC counts were within the normal range (3,000 to <10,000 cells/mm^3), were followed from 1965 to 2004. During this 40-year follow-up, 4,606 subjects developed hypertension. After adjusting for conventional risk factors, including smoking status, we found that elevated WBC count was associated with hypertension incidence in a Cox regression model with both fixed and time-varying covariates for women. For men, elevated WBC count was a significant risk factor for hypertension only in the time-varying Cox-regression covariate. We also observed a significant association between increased neutrophil count and hypertension incidence among women. In a fully adjusted model, the relative risks of hypertension incidence, from the lowest to the highest quartiles of neutrophil count, were 1.00, 1.18, 1.28, and 1.22 in women (*p* for trend <0.001). In conclusion, elevated WBC count predicted an increased incidence of hypertension in Japanese, especially among females. Moreover, neutrophils were the major WBC component contributing to the increased risk. (*Hypertens Res* 2008; 31: 1391–1397)

***Key Words*: hypertension, leukocyte, neutrophil, epidemiology, follow-up study**

Introduction

Numerous epidemiological studies have demonstrated an association between cardiovascular disease (CVD) and inflammatory markers, such as elevated levels of WBCs (*1–6*) or of C-reactive protein (CRP) (*6–8*). Several studies have also shown a positive association between hypertension and elevated WBC (*9–12*), CRP (*13*, *14*), or interleukin (IL)-6 (*14*) levels. The subjects of those studies, however, were middle-aged or elderly, and the follow-up periods ranged from 4 to 20 years.

The activation of neutrophils, a major inflammatory WBC, leads to the release of reactive oxygen species (ROS), which

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contribute to oxidative stress (*15–17*). Oxidative stress has recently emerged as a factor in the pathogenesis of hypertension (*18–20*). In experimental models of hypertension, neutrophil counts rise prior to the development of hypertension (*21*, *22*), but no epidemiological study has focused on the association between neutrophil count and hypertension incidence.

In the present study, we investigated the relationship between WBC count, including differential WBC count, and the incidence of hypertension over a 40-year period in 9,383 subjects (3,356 men and 6,027 women) who did not have hypertension at baseline.

Methods

Study Population

Approximately 20,000 subjects were invited to participate in biennial health examinations conducted by clinical physicians of the Atomic Bomb Casualty Commission (and later succeeded by the Radiation Effects Research Foundation) beginning in July 1958 in Hiroshima and Nagasaki. A detailed description of the examinations is available elsewhere (*23*). We obtained informed consent from all participants, and the study was approved by the Radiation Effects Research Foundation institutional ethics committee and the Human Investigation Committee.

A total of 12,870 subjects underwent a health examination in Hiroshima and Nagasaki at baseline (1965–1967). This study excluded 2,718 subjects who had a history of hypertension, 295 subjects whose smoking habits were unknown, and 409 subjects who did not return for the next follow-up examination. We also excluded an additional 65 subjects whose WBC count at baseline was outside the normal range (3,000 to $<$10,000 cells/mm^3) on the assumption that they might have had an infection or acute illness. The remaining 9,383 subjects, with ages ranging from 19 to 85 years old at baseline, were analyzed in the present study. Although follow-up was stopped in 1974 for the quartile of all subjects who were not in the cities at the time of the bombing, a high participation rate (75–90%) was maintained for the rest of the subjects (*24*).

Measurements

Blood pressure (BP) was measured at least twice by an experienced nurse with a mercury column sphygmomanometer and a cuff of appropriate size applied to the sitting subject's left arm at heart level after a sufficient sedentary period. Systolic and diastolic BP was determined by Korotkoff phases I and V, respectively. Standing height and body weight were measured without shoes or outer clothing. Body mass index (BMI) was calculated as body weight divided by the square of the standing height (kg/m^2). Until 1967 in Hiroshima and 1976 in Nagasaki, WBC count was measured by the Melangeur method after venous blood was diluted with 3% acetic acid, and Wright staining was used for differential WBC counts. After that, hematological autoanalyzers were used. WBC counts by each autoanalyzer were compared by the Melangeur method, and a good correlation was confirmed. WBC values were coded at the 100-unit level. Total serum cholesterol level was also measured by an automated method. The examinations were performed separately in Hiroshima and Nagasaki Laboratories, depending on where the subject lived. The machines in both laboratories were calibrated every month with control blood samples to maintain reproducibility and consistency. Values were standardized based on the machine used in 1986. Diabetes was diagnosed according to 1985 WHO criteria (*25*).

We obtained information about cigarette smoking, alcohol consumption, physical activity, and menopause status from a mail survey and a self-administered lifestyle questionnaire. The subject was categorized as a "never smoker," "former smoker," or "current smoker" and as a "drinker" or "nondrinker." Physical activity level was converted into an oxygen consumption index as defined in the Framingham cohort study (*26*). The most sedentary physical activity was represented by a physical activity index score $\leq$28.

Table 1. Baseline Clinical Characteristics of Study Subjects

Characteristics	Men	Women
Number of subjects	3,356	6,027
Age at baseline (years)	45.0±14.1	44.4±12.5
White blood cell (10^3/mm^3)	6.7±1.7	6.0±1.6
Neutrophil (10^3/mm^3)	3.8±1.3	3.5±1.3
Lymphocyte (10^3/mm^3)	2.1±0.7	1.9±0.6
Monocyte (10^3/mm^3)	0.5±0.2	0.4±0.2
Body mass index (kg/m^2)	20.7±2.9	21.5±3.7
Systolic blood pressure (mmHg)	120±15	116±16
Diastolic blood pressure (mmHg)	76±10	73±10
Total cholesterol (mmol/L)	4.3±1.6	4.3±1.9
Diabetes (%)	5.3	2.3
Most sedentary physically active* (%)	72.3	82.3
Current smoker (%)	76.0	13.6
Former smoker (%)	9.9	1.6
Alcohol drinking (%)	70.0	14.3
Menopause (%)		29.8

Each continuous variable is expressed as mean±SD. *Physical activity index score $\leq$28.

Assessment of Hypertension Incidence

Incident cases of hypertension were defined when subjects were newly diagnosed or newly started on antihypertensive medication between follow-up exams and the diagnosis was confirmed by an AHS examining physician. Subjects with secondary hypertension were excluded from incident cases. In our data, most hypertension cases had a diagnosis of hyper-

Table 2. Relative Risk of Hypertension by WBC Count Quartile for Men and Women

Men	Quartile of WBC count ($\times 10^3$/mm^3)				*p* for trend
	≤5.4	>5.4–6.4	>6.4–7.7	>7.7	
Number of observation	904	786	830	836	
Number of cases	429	377	411	437	
Rate per 1,000 person-years	33.5	31.6	32.8	35.4	
Age-adjusted RR (95% CI)	1.00	1.02 (0.88–1.17)	1.08 (0.94–1.24)	1.22 (1.07–1.40)	0.003
Multivariate-adjusted RR* (95% CI)	1.00	0.92 (0.80–1.17)	0.90 (0.78–1.03)	1.02 (0.89–1.17)	0.88
Women	Quartile of WBC count ($\times 10^3$/mm^3)				*p* for trend
	≤4.9	>4.9–5.8	>5.8–6.9	>6.9	
Number of observation	1,586	1,599	1,354	1,488	
Number of cases	740	753	693	766	
Rate per 1,000 person-years	26.9	28.3	31.5	31.1	
Age-adjusted RR (95% CI)	1.00	1.15 (1.04–1.27)	1.30 (1.17–1.44)	1.40 (1.27–1.55)	<0.001
Multivariate-adjusted RR* (95% CI)	1.00	1.08 (0.97–1.19)	1.14 (1.03–1.27)	1.21 (1.09–1.35)	<0.001

RR, relative risk; CI, confidence interval. *Adjusted for age at baseline, city, radiation exposure, body mass index, smoking status, total cholesterol, diabetes mellitus, physical activity, alcohol drinking, and systolic blood pressure. For females, menopause status was additionally adjusted.

Table 3. Risk of Hypertension by Continuous WBC Count in Time-Varying and Fixed Covariate Cox Regression Models

Cox regression model	RR* (95% CI) of hypertension with increasing WBC count (per 10^3/mm^3)	*p*
Men		
Fixed covariate	1.02 (0.99–1.05)	0.22
Time-varying covariate†	1.10 (1.07–1.13)	<0.001
Women		
Fixed covariate	1.04 (1.01–1.06)	0.002
Time-varying covariate†	1.05 (1.03–1.07)	<0.001

RR, relative risk; CI, confidence interval. *Adjusted for age at baseline, city, radiation exposure, body mass index (BMI), smoking status, total cholesterol, diabetes mellitus, physical activity, alcohol drinking, and systolic blood pressure. For females, menopause status was additionally adjusted. †In the time-varying Cox regression model, WBC, BMI, and total cholesterol were the time-varying covariates.

tension at least twice in different examination cycles. We assumed the date of onset of hypertension to be the midpoint between the exam date when hypertension was first noted and the previous exam date. All participants were followed from the baseline examination to the date of incident hypertension or, for those with no hypertension, the last examination date through 2004.

Statistical Analysis

For each sex, we categorized the baseline WBC count into quartiles. The Cox proportional hazards model was used to evaluate the independent effect of WBC count on the risk of hypertension incidence. We assessed the proportionality assumption of the Cox model by plotting the Kaplan-Meier curves for all categorical predictors and by performing the proportionality test for continuous predictors. Based on the plots and test results, we estimated the final Cox models for each sex in order to examine the independent effect of WBC count on hypertension incidence.

We used two models in our analysis: an age-adjusted model and a multivariate-adjusted model. The latter adjusted for age at baseline, city (Hiroshima or Nagasaki), smoking status (never smoker, former smoker, or current smoker), BMI, radiation exposure, total cholesterol level, alcohol consumption status (drinker or nondrinker), systolic BP, menopausal status for women (yes or no), diabetes (present or absent), and physical activity level (≤28 or >28). Quartiles and continuous WBC count were both analyzed. Furthermore, since WBC and covariates such as BMI and total cholesterol level change over time, we also conducted a time-varying Cox regression model. We used Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, USA) for all statistical procedures.

Results

The average age at baseline was 45.0 years in men and 44.4 years in women (Table 1). The average WBC count was slightly higher for men than for women. More than 70% of men were current smokers and drinkers, respectively. Most women were never smokers and did not drink.

During the 40-year follow-up, 1,654 men and 2,952 women developed hypertension. The median follow-up period of the incident cases was 9.0 years. Table 2 shows the relative risk

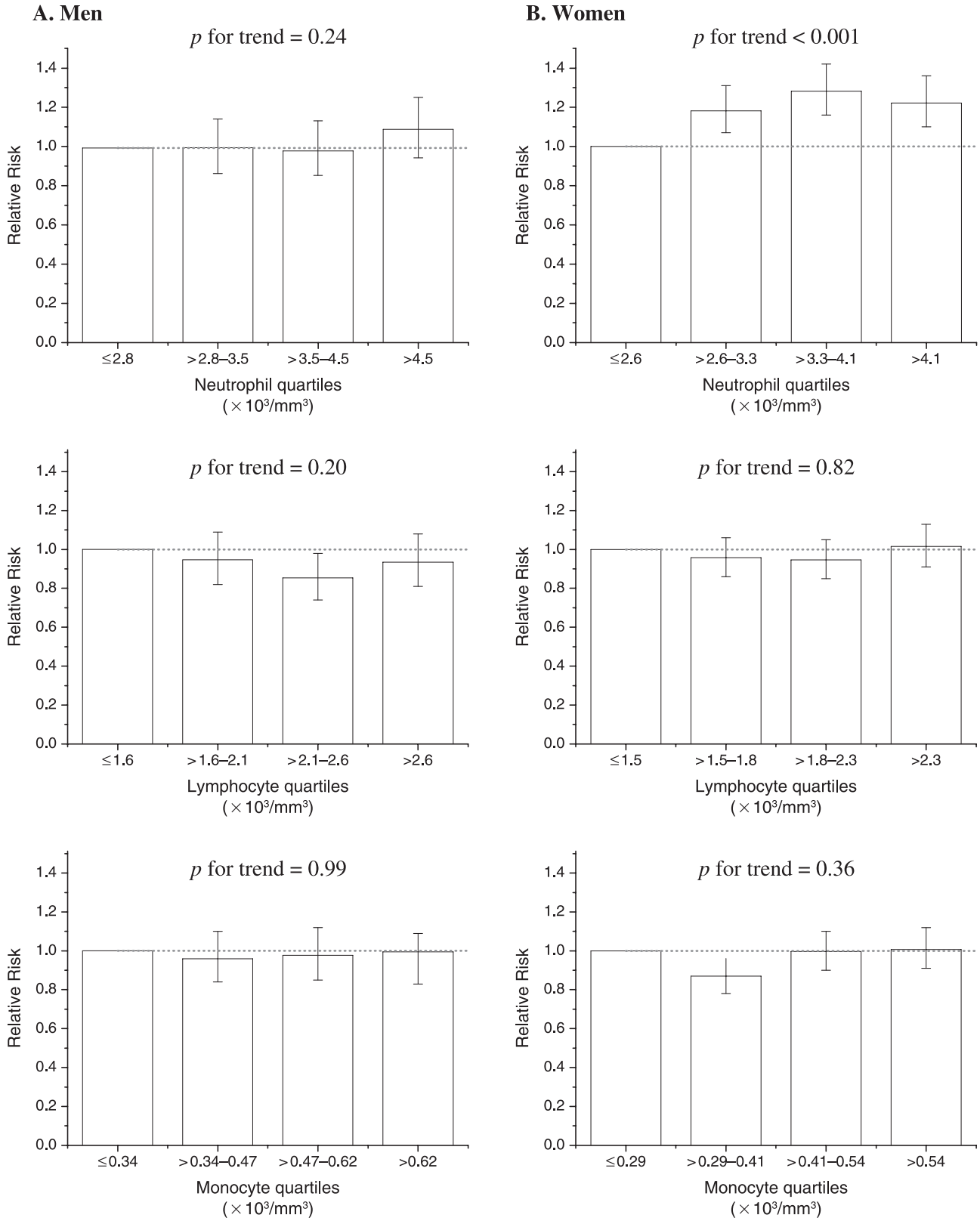

Fig. 1. *Multivariate-adjusted relative risk of hypertension by quartile of differential WBC count in men (A) and women (B). The relative risks were adjusted for age at baseline, city, radiation exposure, body mass index, smoking status, total cholesterol, diabetes mellitus, physical activity, alcohol drinking, and systolic blood pressure. For females, the risk was adjusted also for menopause status. The error bars represent 95% confidence intervals.*

(RR) of hypertension incidence by WBC quartiles for each sex. In the age-adjusted model, the highest WBC count quartile for men and the top three quartiles for women were significantly associated with the incidence of hypertension, and the RR of hypertension incidence increased from the lowest (referent) to the highest WBC count in both men (p for trend 0.003) and women (p for trend <0.001). In the multivariate-adjusted model, the significance of WBC's effect on hypertension incidence in men was diminished (p for trend 0.88). On the other hand, for women, the RR was attenuated but still positively associated with hypertension incidence, with elevated risk from the lowest to the highest quartiles of WBC count. Current smoker, higher BMI, and higher systolic BP were associated with an increased risk of hypertension for both men and women, while drinking was a statistically significant risk factor only for men (data not shown).

The relationship between continuous WBC count and the incidence of hypertension in the fixed and time-varying multivariate Cox regression models is shown in Table 3. Although the RRs for the fixed multivariate Cox regression models were almost the same as those for women in the time-varying multivariate Cox regression model, WBC count was also significantly associated with the incidence of hypertension in men.

The RRs of hypertension incidence in the multivariate-adjusted model by quartiles of differential WBC count are shown by sex in Fig. 1. Similar to the result for WBC count, no significant association was observed in any differential WBC counts for men. For women, only the neutrophil count quartiles, and not the monocyte or lymphocyte count quartiles, were significantly associated with hypertension incidence (p for trend <0.001).

Discussion

This cohort study covered a large number of subjects with a wide range of ages (19 to 85 years) for a long follow-up period (about 40 years). To our knowledge, this is the first demonstration that neutrophil count is, like total WBC count, significantly associated with the incidence of hypertension. The analysis was adjusted for conventional cardiovascular risk factors, and all subjects had normal WBC counts at baseline.

Many studies have suggested that elevated levels of inflammatory markers (WBC count, CRP, or IL-6) are associated with increased risks of hypertension (*9–14*) and CVD (*1–8*), and recent epidemiologic studies have shown a positive association between neutrophil count and CVD (*4*, *5*, *27*). Although we have not seen any epidemiologic study indicating an association between neutrophil count and hypertension, elevated WBC and neutrophil counts have been shown to precede the development of hypertension in animal models (*21*, *22*). Our results support those studies and further suggest that neutrophils may be the major component of WBCs responsible for an increased risk of hypertension.

When we analyzed the relationship between differential WBC counts and hypertension incidence, we found that an elevated neutrophil count was a significant risk factor, though only for women. Lee *et al*. (*4*) showed that CVD incidence and mortality were independently associated with elevated granulocyte counts and to a lesser degree with elevated monocyte counts. However, there has been no report of a significant relationship between monocyte count and the incidence of CVD (*5*, *27*). The effect of monocytes on CVD seems to be still unclear.

In women, we detected a significant association between WBC count and the incidence of hypertension. In men, a significant relation between WBC count and the incidence of hypertension was observed only in the time-varying Cox regression model. This sex difference may be attributable to several factors. In this cohort, most of the women were nonsmokers, but the majority of men were current smokers at baseline. For men, the prevalence of smoking has changed dramatically during the study period, whereas the change in the prevalence of smoking among women was small, as it was in the rest of the Japanese population (*28*). Since WBC count tends to increase with the number of cigarettes smoked (*2*, *29*), the true association between WBC count and the incidence of hypertension might be detected only when the WBC count is treated as a time-varying covariate. BMI might have had a similar effect, since the average BMI change from 1976 to 1995 has been greater in men than in women in Japan (*30*). WBC count increased with increased BMI (*31*). Since the cohort in the present study has had a very long follow up, using the baseline measurement in the time-invariant Cox model may not fully capture the association between WBC and hypertension incidence. Thus, the time-varying Cox model seems to be the most suitable method for detecting any such relationship.

Although we did not measure pro-inflammatory cytokines or CRP, the effect of neutrophils on the development of hypertension may follow from their role in inflammation. Accumulating evidence suggests that the inflammatory process, in part, mediates the development and progression of atherosclerosis (*32*, *33*). Pro-inflammatory cytokines, especially IL-6 and IL-8, are associated with obesity (*34*, *35*), diabetes mellitus (*36*), and cardiovascular disease (*37*). IL-8 is also the major cytokine responsible for neutrophil recruitment and activation (*38*, *39*). Activated neutrophils have an increased tendency to adhere to vascular endothelium, which may result in capillary leukocytosis and increased vascular resistance (*40*). In addition, activated neutrophils release ROS, which contribute to oxidative stress (*15–17*), which in turn is involved in the pathogenesis of hypertension through impairment of endothelium-dependent vasorelaxation (*18–20*). In animal hypertension models, elevated neutrophil and ROS levels preceded the development of hypertension (*21*, *22*).

Our study had some limitations. First, the criteria for hypertension have changed during the long follow-up (from BP

≥160/95 mmHg to ≥140/90 mmHg) (*41*, *42*), but the bias resulting from the change in criteria would be small because most of the incident cases were diagnosed before the criteria were changed, and subjects with grade 2 or 3 hypertension by the WHO criteria had already been assessed. Also, the frequency of hypertension did not change in the general Japanese population (*43*). Furthermore, we confirmed that the result did not include a major change when we analyzed the models using 1992 as the last follow-up year, which is the year before the criteria changed. Second, some bias may have resulted from the end of follow-up in 1974 for the quartile of all subjects who were not in the cities at the time of the bombing. However, our study results (not shown here) also confirmed that no major change resulted from that exclusion. Another limitation is the lack of smoking information over time. As is well known, smoking is a significant risk factor for elevated WBC count (*2*, *29*). In the time-varying Cox regression model, however, we updated only WBC count, BMI, and total cholesterol during the follow-up. Finally, dietary intake of sodium and potassium is also a major determinant of BP (*44*, *45*). However, we had no dietary information, and we thus did not use such data as adjustment factors in the present study.

In conclusion, elevated WBC count, especially neutrophil count, was significantly associated with an increased risk of developing hypertension among Japanese men and women, although the relative risks were modest. This study provides evidence that inflammation may play a role in the development of hypertension, and that neutrophils may be involved in that role. This finding may be useful for clarifying the mechanism underlying the development of hypertension.

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