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1980年、1990年、2000年の循環器基礎調査に基づいた、日本人心房細動患者数の推計

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背景： 心房細動は死亡リスクを高めるばかりではなく、心不全や脳卒中発症リスクを高めることにより、医療費や介護などの社会経済的な負担を増大させていることが欧米では示されている。高齢化が進む社会では心房細動患者が今後さらに増加することが予想される。しかし、世界で最も急速に高齢化が進行している日本では心房細動の疫学研究は殆どみられず、日本人心房細動有病率も十分に明らかにされていない。

目的： 日本人一般住民を対象として、過去20年間の心房細動の有病率を明らかにして心房細動患者数の推移を検討するとともに今後の心房細動患者数を予測すること。

対象と方法： 対象は、全国300地区の30歳以上の者を対象として行われた、過去3回の循環器疾患基礎調査(1980年、1990年、2000年)参加者で、基礎調査で心電図記録が行われた23,713人。循環器基礎調査では、全国から300地点を無作為抽出し、性別・年代構成を日本人の人口構成に一致させて対象者を選択している。安静時心電図記録は調査時に1回行われ、心電図判読はミネソタコードに従ってコーディングされ、ミネソタコードの８－３にコードされた場合を心房細動あり、と定義した。10歳階級ごとに心房細動有所見率を男女別に明らかにし、1980年、1990年、2000年の各調査で年齢階級別に心房細動有所見率を男女別にχ二乗検定で比較した。人口動態統計を用いて過去20年間の日本人成人心房細動患者数を推計し、人口問題研究所の提供する2010年から2030年までの人口推計（中位推計）を参考として、将来の心房細動患者数を推計した。

結果: 過去20年間の性・年齢階級別心房細動有病率に差はみられなかった。30歳以上の男性の心房細動有所見率は1.0%で女性の有所見率は0.6%であり、男性の有所見率が高かった。10歳階級別の心房細動有所見率を男女で比較すると、30代から60代で性差はみられず、70代以降で男性の心房細動有所見率が高かった。過去3回の調査全体の性年齢階級別心房細動有病率を人口動態統計に当てはめて心房細動患者数を推計すると、1980年は日本全体で39.1万人、1990年53.4万人、2000年72.9万人存在していたことになる。尚、将来の日本人人口推計に当てはめて心房細動患者数を推計すると、2010年は日本全体で99.5万人、2020年は105.5万人、2030年は108.1万人の心房細動患者が存在することが示唆された。

結語: 日本人一般住民を対象とした1980年から2000年までの過去20年間の調査結果によると、性年齢階級別の心房細動の有病率には変化は見られなかった。しかし、人口の高齢化により20年間で心房細動患者数はおよそ2倍となり、今後更に人口の高齢化が進むことで、心房細動患者が急激に増加することが予測された。

Short Communication

Rapid Increase in Estimated Number of Persons with Atrial Fibrillation in Japan: An Analysis from National Surveys on Cardiovascular Diseases in 1980, 1990 and 2000

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Atrial fibrillation (AF) is one of the common arrhythmia and a potent risk factor associated with increased cardiovascular morbidity and mortality. Not only mortality but also burden of disability and medical cost associated with AF are critical issues. Prevalence of atrial fibrillation increases with advance of age. The number of adults with AF has been increasing with the aging population in western countries.[1]

AF is also an important disease in Japan. Ischemic strokes associated with cardiogenic embolism accounted for 20% in Japanese general population, and an approximately three fold excess risk of cerebral infarction was observed in subjects with AF.[2] The prevalence and incidence of stroke in Japan are higher than those in western countries. Japan has the most rapidly aging population in the world. It is important to determine the trends in the prevalence of AF and to estimate the numbers of Japanese persons with AF currently and in the future. However, there is no report in which trends in the prevalence of AF in Japan are described, and there are only a few reports in which the prevalence of AF among Japanese is mentioned.

In this study we compared the sex- and age-specific prevalences of AF (proportions of persons with AF in each age- and sex-specific group) in the Japanese general population over the past two decades. We also estimated the number of Japanese with AF in the past and predicted the number of Japanese adults with AF in the future.

SUBJECTS, METHODS, AND RESULTS

A national survey on cardiovascular diseases in Japan has been carried out every 10 years. About 300 districts were selected using a stratified random sampling method based on the latest national census. All residents aged 30 years or older were invited to take part in this survey. A total of 27,121 persons (10,897 in 1980, 8,926 in 1990 and 7,298 in 2000; response rate: 78.9%) participated in three national surveys.[3-5] Resting 12-lead electrocardiograms were recorded in 23,713 participants (10,376 subjects (75.0%) in 1980, 8,139 subjects (74.3%) in 1990, and 5,198 subjects (62.2%) in 2000). We used data from 23,713 participants (10,042 men and 13,671 women). This study is based on published reports from three national surveys.[3-5]

The electrocardiographic findings were independently evaluated by two trained physicians according to the Minnesota Code. In cases of inconsistent judgments, the final judgments were undertaken after deliberations of the approval committee. Atrial fibrillation was defined as 8-3 (including paroxysmal atrial fibrillation and atrial flutter) according to the Minnesota Code.[3-5]

We determined sex- and age-specific prevalences of AF in 1980, 1990, and 2000 (expressed as percentages). The averaged sex- and age-specific prevalences of AF were calculated using pooled data of three surveys. The averaged sex- and age-specific prevalences were applied to the Japanese census data (1980, 1990, and 2000) to calculate the number of adults with AF. Furthermore, the averaged sex- and age-specific prevalences were

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applied to the projected Japanese census data (using medium variant estimates in 2010, 2020, and 2030) provided by National Institute of Population and Social Research[6] to calculate the number of Japanese adults with AF in the future. The prevalences of AF in groups were compared using the chi squared test. A p value less than 0.05 was considered to be statistically significant.

Table 1 shows sex- and age-specific prevalences of AF for each 10-year age group in 1980, 1990, and 2000. The prevalence of AF in men aged 30 years or older was higher than that in women (1.0% vs. 0.6%; p<0.001). Age-specific prevalence of AF in men aged 70 years or older was higher than that in women (p=0.006), but other age-specific prevalences in each age group (30-, 40-, 50-, and 60-year age group) in men were not statistically different from those in women (p: 0.06-0.17). Prevalence of AF increased with advance of age in both men and women (from 0.1% in adults younger than 50 years to 2.9% in persons aged 70 years or older). The sex- and age specific prevalences of AF in the three surveys were similar.

Table 2 shows estimated numbers of Japanese adults with AF in 1980, 1990 ,and 2000. It also shows the projected numbers of Japanese adults with AF in 2010, 2020, and 2030. The estimated numbers of Japanese adults with AF were 391 thousand in 1980 and 729 thousand in 2000. The number of Japanese adults with AF in 2030 is predicted to be 1,081 thousand.

Table 1. Sex- and age-specific prevalence (%) of atrial fibrillation in three national surveys in Japan.

Age (year)	Mean prevalence in 3 surveys	1980	1990	2000	p value
		Men			
30-39	0.1	0.2	0.0	0.0	0.46
40-49	0.3	0.3	0.2	0.0	0.55
50-59	0.7	0.8	0.8	0.4	0.70
60-69	1.3	1.0	1.6	1.4	0.64
70+	3.8	3.7	4.3	3.5	0.82
		Women			
30-39	0.0	0.0	0.0	0.0	-
40-49	0.1	0.1	0.0	0.2	0.40
50-59	0.4	0.5	0.1	0.7	0.13
60-69	0.9	1.4	0.7	0.5	0.09
70+	2.2	2.6	1.9	2.1	0.67
		Both sexes			
30-39	0.0	0.1	0.0	0.0	0.42
40-49	0.1	0.2	0.1	0.1	0.71
50-59	0.5	0.6	0.4	0.6	0.53
60-69	1.1	1.3	1.1	0.9	0.66
70+	2.9	3.1	2.9	2.7	0.84
30+	-	0.7	0.7	0.9	

These data are based on published reports from three national surveys.[3-5]
Comparisons in the prevalence of atrial fibrillation among three surveys were performed using the chi squared test.

Table 2. Estimated numbers of Japanese adults with atrial fibrillation in the past and predicted numbers of Japanese adults with atrial fibrillation in the future (in thousand).

	Calendar year					
	1980	1990	2000	2010	2020	2030
Men	228	306	416	522	598	603
Women	163	229	313	473	457	477
Both sexes	391	534	729	995	1,055	1,081

DISCUSSION

We found that sex- and age-specific prevalences of AF have not changed in Japan during the past two decades. The prevalence of AF in adults aged 30 years or older has increased from 0.7% to 0.9% with the aging population during this period. The prevalence of AF in men aged 30 years or older was higher than that in women. The prevalence of AF has increased with advance of age in both men and women.

There have been a few reports on the prevalence of AF in Japan. In a hospital-based study, the prevalence of AF among outpatients was 14%.[7] In a population-based study, it was found that the prevalence of AF in a mixed group of men and women increased from 0.2% in persons aged 40 to 59 years to 2.5% in persons 80 years or older.[8] The results of our study are similar to those of that study.

The prevalences of AF in adults in western countries have been higher than those in Japan.[1,9,10] The number of adults with AF has been increasing with aging of the population1 and the age-specific prevalence of AF has also been increasing in western countries.[9,10] It is not clear why the age-specific prevalence of AF has been increasing in western countries. The prevalences of predisposing factors for AF such as past history of myocardial infarction, past history of congestive heart failure, presence of valvular heart disease, obesity, hypertension, and diabetes mellitus have been changing, and these changes might have contributed to the changes in the prevalence of AF in western countries.

In Japan, mean total cholesterol levels and mean body mass index have been increasing in men[5] and the prevalence of diabetes mellitus has been increasing.[11] These changes might have elevated the prevalence of AF in Japan. On the other hand, mean systolic blood pressures have been dramatically decreasing in both men and women during the past two decades,[5] and this decline might have decreased the prevalence of AF in Japan. The different trends in prevalences of predisposing factors to AF in Japan and western countries may explain the different trends in age-specific prevalence of AF in Japan and western countries.

The total number of Japanese adults with AF has almost doubled during the past two decades, and the number will certainly continue to increase with aging of the population. The number of Japanese with AF is expected to exceed one million in 2020. AF is not only a potent risk factor for cardiovascular morbidity and mortality but also a factor that increases both medical costs and burden of nursing care.[12] We should be aware that an excessive burden associated with AF will certainly impose responsibilities on Japanese people in the future.

There are several limitations of this study. Persons who did not participate in the survey were probably poor health condition and might have had heart disease. Some participants might think that they did not have to undergo electrocardiography because they already had treatment histories of heart disease. These factors might have reduced the number of cases with AF in this study; thus, the prevalences of AF might be underestimated. We applied mean prevalence of pooled data from three surveys to the projected national census because sex- and age-specific prevalences of AF have not changed in Japan during the past two decades. However, the age-specific prevalence of AF will increase in the future if the prevalences of predisposing factors for AF increase as well as western countries, and the number of Japanese adults with AF in the future should exceed the number that we estimated in this study.

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Erratum

Some errors have been revealed, and should be corrected on Volume 15 Supplement 2.

Page S-113. This paper was received on December 25, 2004, not on December 24, 2005.
Page S-120. This paper was received on December 25, 2004, not on December 24, 2005.
Page S-126. This paper was received on December 25, 2004, not on December 24, 2005.
The first headline should be "BACKGROUND", not "BACKGROUD".
Page S-180. This paper was received on December 25, 2004, not on December 24, 2005.

研究成果の要約

白血球数と総死亡、心血管疾患死亡との関連

Tamakoshi K, Toyoshima H, Yatsuya H et al. White Blood Cell Count and Risk of All-cause and Cardiovascular Mortality in Nationwide Sample of Japanese: Results from the NIPPON DATA 90. Circulation Journal. in press.

【研究の目的】日本を代表する集団において、白血球数と総死亡、心血管疾患死亡との関連を明らかにする。

【研究の方法】1990 年、全国から無作為抽出された 300 地域に居住する 30 歳以上の住民 10,956 名を対象に、循環器疾患基礎調査が行われた。そのうち健診成績と生活習慣や既往歴を含むアンケート結果を有し、2000 年 11 月 15 日まで追跡できた者は 8,384 名であった。本研究では、さらに心血管疾患の既往歴を有する者、研究に必要な情報が欠損している者、追跡開始時の白血球数が 4,000 個/mm^3 未満と 10,000 個/mm^3 を超える者を除いた 6,756 名(平均年齢 52.3 歳、男性 2,773 名、女性 3,983 名)を解析対象とした。1990 年の白血球数を 4,000 個/mm^3 から 1,000 個/mm^3 毎に 10,000 個/mm^3 まで 6 群に分け、総死亡、心血管疾患死亡(脳卒中を含む)に対する年齢、(性)、Body mass index、喫煙状況、飲酒状況、運動習慣、拡張期血圧、総コレステロール値、HDL コレステロール値、ヘモグロビン A1c 値で調整した相対危険度(4,000-4,900 個/mm^3 の群を基準)を算出した。

【結果】解析対象者の平均観察年数は 9.6 年(男性 9.5 年、女性 9.7 年)、追跡期間中に 576 名(男性 307、女性 269)の死亡が観察され、そのうち 161 名が心血管疾患による死亡であった。全解析対象者では、白血球数が増加するほど総死亡のリスクが統計学的に有意に上昇する傾向がみられた。また、心血管疾患死亡に対しても白血球数の増加は高いリスクを示した。これらの関連は特に女性において顕著に認められた。

白血球数と総死亡、心血管疾患死亡との関連

	総死亡		心血管疾患死亡	
全体	相対危険度	(95%信頼区間)	相対危険度	(95%信頼区間)
4,000-4,900	1.00	(基準)	1.00	(基準)
5,000-5,900	1.06	(0.81-1.37)	1.05	(0.65-1.69)
6,000-6,900	1.08	(0.82-1.41)	1.00	(0.61-1.66)
7,000-7,900	1.12	(0.84-1.50)	0.82	(0.46-1.45)
8,000-8,900	1.32	(0.95-1.84)	1.46	(0.80-2.65)
9,000-10,000	1.61	(1.07-2.40)	1.79	(0.97-3.71)
傾向性p値		0.02		0.2
男性				
4,000-4,900	1.00	(基準)	1.00	(基準)
5,000-5,900	1.08	(0.75-1.57)	1.09	(0.53-2.23)
6,000-6,900	0.98	(0.67-1.43)	0.93	(0.45-1.93)
7,000-7,900	0.99	(0.66-1.48)	0.72	(0.31-1.64)
8,000-8,900	1.30	(0.84-2.02)	1.04	(0.44-2.49)
9,000-10,000	1.48	(0.89-2.48)	1.23	(0.44-3.40)
傾向性p値		0.2		0.9
女性				
4,000-4,900	1.00	(基準)	1.00	(基準)
5,000-5,900	1.03	(0.72-1.49)	1.02	(0.53-1.96)
6,000-6,900	1.23	(0.84-1.80)	1.12	(0.56-2.24)
7,000-7,900	1.32	(0.87-1.98)	0.88	(0.39-1.97)
8,000-8,900	1.38	(0.82-2.32)	2.04	(0.90-4.64)
9,000-10,000	1.78	(0.92-3.47)	2.66	(0.95-7.45)
傾向性p値		0.03		0.08

白血球数単位:個/mm^3

【メッセージ】日本人においても白血球数の増加は、既知の危険因子とは独立した死亡の予測因子であり、その関連は女性において顕著であった。我々は白血球の持つ生理学的意義に着目し、予防や臨床分野での白血球数の死亡予測因子としての可能性を探るべきである。

White Blood Cell Count and Risk of All-cause and Cardiovascular Mortality in Nationwide Sample of Japanese: Results from the NIPPON DATA 90

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Short title: White Blood Cell Count and Mortality

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Background The association of white blood cell (WBC) count with all-cause and cardiovascular disease (CVD) mortality were examined in the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA) 90.

Methods and Results A total of 6,756 Japanese community residents (2,773 men and 3,983 women) throughout Japan without a history of CVD were followed for 9.6 years. Cox proportional hazards regression model was used to estimate the relative risk (RR) and 95% confidence interval (CI). We documented 576 deaths with 161 deaths from CVD. Overall, after adjusting for several confounders including age, sex, body mass index at baseline, smoking status, alcohol consumption, regular exercise, diastlic blood pressure, total cholesterol, high density lipoprotein cholesterol, and hemoglobin A1c, a graded association between WBC count and higher risk of all-cause mortality was observed (WBC of 9,000-10,000 cells/mm^3 vs. WBC of 4,000-4,900: RR = 1.61, 95% CI: 1.07-2.40, p for trend=0.02). Elevated WBC count was borderline significantly associated with high risk of CVD mortality (WBC of 9,000-10,000 vs. WBC of 4,000-4,900: RR = 1.79, 95% CI: 0.97-3.71). These associations strengthened among women. Stratified by smoking status, never-smokers with WBC counts of 9,000-10,000 had a 3.2 fold elevated risk for CVD death compared with those with WBC counts of 4,000-4,900.

Conclusions: The WBC count may have potential as a predictor for all-cause mortality, particularly CVD mortality.

Key Words: White Blood Cell Count; Mortality; Cardiovascular Disease

Recently, evidence has been put forward indicating that chronic inflammation is associated with cardiovascular disease (CVD).[1-4] The White blood cell (WBC) count is recognized as an important cellular marker of systemic inflammation. An elevated WBC count has been associated with cardiovascular risk factors such as cigarette smoking, obesity, and metabolic disorders including hypertension, diabetes mellitus, and dyslipidemia.[5,6] Several studies have also shown an increased risk of coronary heart disease (CHD),[7-11] stroke,[11-14] and all-cause mortality[15,16] among persons with a high WBC count. However, these findings could not be generalized since most of them come from studies on occidental populations. They may not be true of Asian people, particularly among Japanese men who have a higher rate of smoking and Japanese women who have a lower rate than people in other developed countries (smoking rate of men and women: 52.8% and 13.4% in Japan, 25.7% and 21.5% in United State of America, 27.0% and 26.0% in United Kingdom, and 38.6% and 30.3% in France, respectively).[17] Moreover, the WBC count is known to be positively associated with body mass index,[6] and Japanese people are much leaner than occidental people.[18]

One purpose of our study is to examine the relationship of the WBC count with all-cause and CVD mortality in a cohort study of representative Japanese men and women randomly selected throughout Japan.

Methods

Study Population

NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged) 80 and 90 are Japanese nationwide studies to prospectively evaluate the various risks and/or protective factors regarding circulatory disease mortality among the adult population for use in the development of future preventive measures. Study methods and ethical issues have been described in detail elsewhere.[19-21] In the present study, data from NIPPON DATA 90 were analyzed because WBC count was not measured in NIPPON DATA 80. Briefly, the baseline survey in NIPPON DATA 90 was performed in 1990 for all household members age 30 years or older in 300 districts randomly selected throughout Japan. Of 10,956 enrolled in this survey, a total of 8,384 community residents (3,504 men and 4,880 women) provided the data on medical examinations, blood tests, and self-administered questionnaires about lifestyle and were followed until November 15, 2000. The survey response rate was 76.5%. Of the 8,384 participants, we excluded subjects with any of the following criteria: past history of stroke (n = 159), past history of coronary heart disease (n = 230), missing information on lifestyle factors or body size (n = 113), no available data to evaluate a vital status during follow-up period (n = 182),

missing information on WBC count at baseline, or metabolic parameters (n = 550), subjects with WBC counts of less than 4000 cells/mm^3 indicating clinically leucopenia (n=217), and subjects with WBC counts of more than 10,000 cells/mm^3 indicating clinically relevant inflammatory conditions (n = 306). We limited WBC count from 4,000 to 10,000 cells/mm^3 to minimize the potential influences of acute bacterial infection and reduced level of immune surveillance. In all, 1,628 subjects were excluded, and the remaining 6,756 (2,773 men and 3,983 women) were included in the present study.

Follow-up Survey

Vital statistics for determining causes of death were obtained from the Management and Coordination Agency, Government of Japan. The underlying causes of death for the National Vital Statistics were coded according to the 9^{th} International Classification of Disease (ICD-9) until 1994 and the 10^{th} International Classification of Disease (ICD-10) from 1995.

The present study protocol was approved by the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Baseline Examination

Non-fasting blood samples were collected in the tubes containing anticoagulant. These tubes were stored at room temperature and collected during the morning of the day after blood collection by a commercial hematological laboratory (SRL, Tokyo). The WBC counts were measured with an automatic hematology analyzer (E-3000, Toa Medical Electronics, Kobe) and expressed by 100 cells/mm^3. Hemoglobin A1c (HbA1c) was measured by the latex agglutination method. The serum was separated and centrifuged soon after coagulation. Serum total cholesterol (TC) was measured enzymatically and high density lipoprotein cholesterol (HDL-C) was measured by the precipitation method using heparin-calcium. Systolic and diastolic blood pressures (SBP and DBP) were measured by trained observers using a standard mercury sphygmomanometer. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Information on smoking status, drinking habits, and medical histories was obtained by public health nurses.

Statistical Analysis

Subjects were divided into 6 categories of WBC count (cells/mm^3) as follows: 4,000-4,900, 5,000-5,900, 6,000-6,900, 7,000-7,900, 8,000-8,900, and 9,000-10,000. We speculated a threshold effect of elevated WBC count on mortality. So we divided

WBC counts into 6 categories by 1,000.

First, to elucidate the differences in potential confounding variables among WBC categories, we calculated proportions, means, and standard deviations by sex. Chi-square test or analysis of variance was performed to explore the potential association between WBC count and potential confounding variables.

Secondly, the Cox proportional hazards regression model was used to estimate, by means of the hazard ratio, the relative risk (RR) and 95% confidence interval (CI) of each WBC category for all-cause or cause-specific mortality in the age and multivariate-model. Persons who died of other causes in cause-specific analysis were censored at the date of death. Survivors were censored at the date of the last follow-up. RRs of mortality in individual WBC categories were computed with the WBC category of 4,000-4,900 cells/mm^3 considered as the reference. Multivariate models were adjusted for age (continuous), BMI (continuous), smoking status (never, former, current: dummy code), alcohol consumption (current, former, never: dummy code), regular exercise (yes, no), DBP, TC, HDL-C, HbA1c (continuous) since DBP was significantly associated with WBC counts. The model including SBP instead of DBP showed the same results. A linear trend of association was assessed by the regression model assigning score (0, 1, 2,...) to the levels of the WBC category. We checked the assumption of proportional hazards by the log-minus-log (LML) plot. Each categorical covariate remained intact and each continuous covariate was categorized into the quartiles, and the LML plots were examined. For each covariate, the plots were parallel, indicating that the proportional hazard assumption was not violated.

To elucidate the modification of the effects of WBC count by smoking status, subjects were stratified into three subgroups (never, former, current). In addition, we estimated multivariate RR of each WBC category. We also stratified the subjects into two subgroups by BMI of 25 kg/m^2 according to criteria recommended by the Japan Society for the Study of Obesity[22] and thereafter performed the same analysis.

All analyses were performed using the SPSS 11.0 statistical package. $P < 0.05$ was considered statistically significant.

Results

The mean (standard deviation [SD]) of age at baseline was 52.3 (13.6) years [53.0 (13.4) for men and 51.9 (13.7) for women]. Mean (SD) and median values of WBC (cells/mm^3) were significantly higher among men [mean (SD), 6,821 (1,427); median, 6,700] than women [6,330 (1,326); 6,200] ($p < 0.001$).

The baseline characteristics of the subjects according to WBC category are shown in Table 1. Compared with those in lower WBC categories, subjects in higher

WBC categories were likely to be young, obese, and current smokers among both men and women. DBP, TC, HDL-C, and HbA1c were significantly different among the WBC categories. The WBC counts were positively associated with DBP, TC, and HbA1c and negatively with HDL-C.

Total person-years were 64,788 (26,245 for men and 38,543 for women), the mean follow-up period was 9.6 years (9.5 for men and 9.7 for women), and the range of follow-up period was 1.6-10.0 years (1.6-10.0 for men and 1.8-10.0 for women). During follow-up, there were 576 deaths (307 among men and 269 among women). Of them, 161 deaths (28%) were due to cardiovascular disease.

Table 2 shows the association between WBC and all-cause mortality. Overall, after multivariate-adjustment, a graded association between WBC count and higher risk of all-cause mortality was observed (p for trend=0.02; WBC of 9,000-10,000 cells/mm^3 vs. WBC of 4,000-4,900 cells/mm^3: RR = 1.61, 95% CI: 1.07-2.40). Stratified by sex, this graded association was observed only among women (p for trend=0.03).

Table 3 presents the association between WBC and CVD mortality. For the entire sample, subjects in the highest category were likely to have a higher risk of death from CVD (RR = 1.79, 0.97-3.71), but the estimates showed no significant trend. Sex-specific multivariate-adjusted analyses showed borderline significantly increased RR for cardiovascular disease mortality only among women, with RR and 95% CIs for the lowest, 2nd, 3rd, 4th, 5th, highest categories of 1.00 (referent), 1.02 (0.53-1.96), 1.12 (0.56-2.24), 0.88 (0.39-1.97), 2.04 (0.90-4.64), and 2.66 (0.95-7.45), respectively (p for trend = 0.08). Since similar RRs for lowest to 4th and 5th to highest were observed, these categories were analyzed in combination. Women with WBC counts of 8,000-10,000 cells/mm^3 had over a 2-fold elevated risk of CVD (RR = 2.18, 1.23-3.88) compared with those with WBC counts of 4,000-7,900 cells/mm^3. No significant association was observed in men.

The effect modification of smoking status on the associations between WBC count and all-cause and CVD mortality was assessed (Table 4). The associations of WBC count with all-cause and CVD mortality were pronounced in never-smokers. Elevated WBC count was borderline significantly associated with increased risk of all-cause mortality in a graded manner (p for trend=0.07). Never-smokers with WBC counts of 9,000-10,000 cells/mm^3 had over a 3-fold elevated risk for CVD death compared with those with WBC counts of 4,000-4,900 cells/mm^3 (RR = 3.20, 1.25-8.24). When 6 categories were combined into 2 categories, never-smokers with WBC counts of 8,000-10,000 cells/mm^3 had a 2-fold high risk of CVD (RR = 2.05, 1.12-3.76) compared with those with WBC counts of 4,000-7,900 cells/mm^3.

Table 5 shows the effect modification of BMI on the associations between

WBC count and all-cause and CVD mortality. Among the subjects with BMI of <25 kg/m^2 and over, WBC count was borderline significantly and positively associated with all-cause mortality risk and CVD mortality risk in a dose-dependent manner (p for trend=0.08, 0.09, respectively). On the other hand, among the subjects with BMI of >=25 kg/m^2, those with WBC count of >=8,000 cells/mm^3 seemed have high RRs for all-cause and CVD mortality although statistically not significant.

Discussion

In this study of a nationally representative cohort of Japanese men and women, WBC count was significantly and positively associated with increased risk of all-cause mortality among overall subjects even after adjustment for well-known confounding factors including age, BMI, smoking status, alcohol consumption, regular exercise, DBP, TC, HDL-C, HbA1c (p value for trend=0.02). After stratification by sex, this association was obvious among women (p value for trend=0.03). Moreover, as for CVD mortality, the subjects, especially women, with WBC count of >=8,000 cells/mm^3 were likely to have increased risk. In addition, stratified by smoking status, we found the associations of elevated WBC count with all-cause and CVD mortality in never-smokers.

First, the gender difference observed in the present study requires consideration. Our study showed a significant association of WBC count with all-cause mortality and CVD mortality among women but not among men. These findings may in part be explained by the difference in smoking status between men and women since the WBC count increases with the amount smoked. In our study, the proportions of current smokers were 54.2% and 8.7% among men and women, respectively, and the smoking rate of men was higher than those of other studies conducted in occidental countries,[12,15] which demonstrated the usefulness of the WBC count as a strong predictor of mortality. In a study of Koreans whose smoking status was similar to that of Japanese, the strong association of elevated WBC with mortality was observed among never smokers rather than smokers.[10] In our study, overall, the associations of WBC count with all-cause and CVD mortality were observed in never-smokers though analyses by sex could not be performed because of insufficient sample size. Smoking may conceal the true association. To confirm sex difference of the effect of WBC count on mortality in Japan, it is necessary to examine this issue among non-smoker men and women in much larger prospective studies.

The present study showed that an elevated WBC count predicted all-cause mortality among overall subjects and especially among women. A few earlier studies have presented data stratified by sex or included only women. Only three studies found a positive association between the WBC count and all-cause mortality in women.[10,11,21]

The WBC count broadly indicates the level of host response to stressors and provides an index of acute and chronic inflammatory processes. Although this association remained after adjustment for clinical diagnosis of major chronic diseases, subclinical diseases may have affected the observed association. The association may be in part a consequence of the association between WBC count and CVD mortality, as mentioned below.

We found that an elevated WBC count was an independent predictor of CVD mortality among Japanese women. Several studies have assessed the WBC count as a predictor of CVD in women[7,9-11,13,14] though the researches for women are far fewer than those for men. Of them, the Women's Health Initiative Observational Study (WHI-OS) provided some interesting findings.[11] The WHI-OS reported that the RRs of CHD, stroke, and CVD were 2.36 (95% CI: 1.51-3.68), 1.46 (95% CI: 1.17-1.81), and 1.47 (95% CI: 1.26-1.72) among women in the upper quartile of WBC counts (6,710-15,000 cells/mm3) compared with those in the lowest quartile (2,500-4,700 cells/mm3) although elevated WBC counts caused by acute bacterial infection and decreased WBC counts caused by reduced immune function need to be considered in the interpretation of the result. WHI-OS also showed that the upper quartile was a threshold for elevated risk and was approximated by a WBC count of greater than 6,700 cells/mm3 [RR of CVD mortality: 1.00 (lowest quartile: referent), 1.01 (second quartile), 1.12 (third quartile), 1.47 (upper quartile)]. Such a threshold effect was also observed in our study [RR of CVD mortality: 1.00 (WBC of 4,000-4,900 cells/mm3: referent), 1.02 (WBC of 5,000-5,900 cells/mm3), 1.12 (WBC of 6,000-6,900 cells/mm3: referent), 0.88 (WBC of 7,000-7,900 cells/mm3), 2.04 (WBC of 8,000-8,900 cells/mm3), 2.66 (WBC of 9,000-10,000 cells/mm3); WBC of 8,000-10,000 vs. WBC of 4,000-7,900: RR = 2.18, 1.23-3.88)]. This finding may be relevant to the underlying mechanisms between elevated WBC and CVD mortality risk. In addition, the WHI-OS conducted the nested case-control study to evaluate the association between WBC and CHD mortality under consideration of high sensitive C-reactive protein (hsCRP) which is widely recognized not only as inflammatory indicator but also as cardiovascular risk factor. The WBC count was still an independent predictor of CHD risk, comparable in magnitude to hsCRP although adjustment for hsCRP attenuated the association between WBC count and CHD death. Unfortunately, the information on hsCRP was not available in our study.

We also examined whether BMI modified the association between WBC count and mortality risk. There were the borderline significant and positive associations between WBC count and all-cause and CVD mortality risk among the subjects with BMI of <25 kg/m^2. Among the subjects with BMI of >=25 kg/m^2, the RRs for those

with WBC count of >=8,000 cells/mm^3 were also likely to be high although statistically not significant. The number of obese subjects was too small to judge the modification by BMI in our study. Speculatively, together with the results in previous studies[7-9,11-15] on occidentals with high BMI, BMI may not modify the association between WBC count and mortality risk.

It is not known whether WBC is involved directly in the pathogenesis of CVD events or is merely a risk marker for other factors causing CVD. The association of elevated WBC count with CVD risk remained after adjusting for other CVD risk factors, suggesting a causal relationship. A number of pathogenetic mechanisms have been postulated to help explain the association. WBCs influence blood rheology and adhesive properties, and have a role in endothelial injury by adhering to endothelium and damaging it with toxic oxygen compounds and proteolytic enzymes.[23] It is possible that the WBC count in healthy persons is a sign of active atherogenesis and helps to identify high-risk candidates for CVD.

This study has several important strengths. First, these data are from a large nationally-representative cohort and, thus, our findings can be generalized to the Japanese population. Second, we excluded participants with WBC counts below and above the clinically-defined normal range to remove potential contributions from reduced immune function and infections, particularly chronic infections, respectively. This study has several potential limitations. First, only one measurement of WBC count was performed. Multiple WBC measurements over time and their change may provide more accurate and detailed information to predict future mortality. If this proves true, the present study may underestimate the true association between WBC and mortality. We would like to examine individual variation of WBC count in future. Second, a few previous studies[8,16] provided the positive associations of neutrophils with all-cause and CVD mortality. Unfortunately, we had no data on differential WBC counts. Third, the sample was too small to study the associations between WBC counts and specific sites of CVD. Finally, unfortunately, hsCRP was not measured in our study. Therefore, we may overestimate the association between WBC count and mortality because we could not used hsCRP as a covariate.

In conclusion, our results suggest the associations of elevated WBC count with all-cause and CVD mortality among Japanese people, especially among women and among never-smokers. In the context of public health practice, women with WBC counts of 8,000-10,000 cells/mm^3 had a 1.5-fold borderline significantly high risk for all-cause mortality (RR=1.50, 0.95-2.37) and a 2.2-fold significantly high risk for CVD mortality (RR=2.22, 1.06-4.62) compared to those with WBC counts of 4,000-4,900 cells/mm^3, which may indicate a role for inflammation in the pathogenesis. Additionally,

the method of WBC measurement is well-standardized, widely available, and inexpensive. It is necessary to pay further attention to the potentiality of WBC count as a predictor of mortality.

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Appendix

List of the NIPPON DATA90 Research group:

NIPPON DATA90: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged 1990"

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Table 1 Baseline characteristics by sex according to white blood cell count, NIPPON DATA90, 1990-2000

	White blood cell conut (cells/mm^3)						P for
	4,000-4,900	5,000-5,900	6,000-6,900	7,000-7,900	8,000-8,900	9,000-10,000	difference
Men							
Number of subjects	281	555	691	579	427	240	
*Age**	59.0±14.4	54.1±13.8	53.2±13.4	52.3±12.6	50.4±12.7	48.7±12.2	<0.001
*Body mass index (kg/m^2)**	22.0±2.97	22.7±2.85	23.0±2.88	23.2±3.08	23.3±3.19	23.3±3.03	<0.001
*Systolic blood pressure (mmHg)**	136.4±21.0	136.1±19.9	138.4±20.6	137.8±19.8	138.6±20.3	138.8±19.5	0.2
*Diastlic blood pressure (mmHg)**	81.9±11.2	82.6±11.8	84.4±11.8	84.2±11.4	84.3±11.6	84.8±11.7	<0.01
*Total cholesterol (mg/dl)**	188.6±34.9	192.9±35.5	199.2±34.6	199.4±36.1	203.4±38.0	202.1±36.3	<0.001
*HDL cholesterol (mg/dl)**	53.4±15.3	51.6±14.7	51.6±15.6	49.9±14.3	49.4±15.6	48.0±14.4	<0.001
*Hemoglobin A1c (%) **	4.97±0.77	4.95±0.67	5.00±0.86	4.99±0.61	5.00±0.61	5.15±0.87	<0.05
Smoking status							
Never-smoker (%)	35.2	27.7	22.6	18.8	12.6	8.8	<0.001
Former-smoker (%)	33.5	28.5	27.4	21.8	17.8	11.3	
Current smoker (%)	31.3	43.8	50.1	59.4	69.6	80.0	
Alcohol consumption							
Never-drinker (%)	32.0	37.1	34.4	34.5	36.1	30.0	0.10
Former-drinker (%)	7.5	8.1	4.9	5.2	4.9	4.6	
Current drinker (%)	60.5	54.8	60.6	60.3	59.0	65.4	
Regular exercise (%)	29.5	24.1	23.0	22.5	16.6	22.9	<0.01
Medical history							
Hypertension (%)	20.6	19.6	23.2	19.9	20.1	23.3	0.5
Diabetes (%)	5.7	6.5	7.5	5.7	5.2	5.4	0.3
Dyslipidemia (%)	4.3	4.0	8.0	7.3	5.4	6.3	<0.05
Women							
Number of subjects	625	1099	1013	745	350	151	
*Age**	55.1±13.9	53.0±13.6	51.3±13.7	50.4±13.3	49.4±13.3	48.0±13.0	<0.001
*Body mass index (kg/m^2)**	22.3±3.16	22.7±3.18	22.8±3.14	23.2±3.42	23.2±3.43	23.3±3.58	<0.001
*Systolic blood pressure (mmHg)**	132.8±20.2	132.9±20.5	133.2±21.1	133.5±21.1	133.9±19.7	135.6±21.7	0.7
*Diastlic blood pressure (mmHg)**	78.5±11.4	79.4±11.3	79.4±12.1	79.5±11.7	80.8±12.0	80.9±12.2	<0.05
*Total cholesterol (mg/dl)**	200.2±37.2	206.7±37.7	208.9±38.3	208.3±36.4	210.7±39.7	206.3±40.5	<0.001
*HDL cholesterol (mg/dl)**	57.9±15.2	58.1±15.4	57.4±14.8	55.5±14.5	55.0±14.3	53.7±12.6	<0.001
*Hemoglobin A1c (%) **	4.82±0.57	4.89±0.69	4.88±0.65	4.93±0.80	4.93±0.78	5.09±0.92	<0.001
Smoking status							
Never-smoker (%)	93.4	90.9	89.4	86.0	80.3	79.5	<0.001
Former-smoker (%)	1.9	3.0	2.3	3.1	2.3	1.3	
Current smoker (%)	4.6	6.1	8.3	10.9	17.4	19.2	
Alcohol consumption							
Never-drinker (%)	92.6	92.7	92.8	92.3	90.9	93.4	0.5
Former-drinker (%)	1.6	0.8	0.5	1.2	1.4	0.0	
Current drinker (%)	5.8	6.5	6.7	6.4	7.7	6.6	
Regular exercise (%)	19.4	18.5	18.3	18.7	17.7	21.9	0.9
Medical history							
Hypertension (%)	22.2	19.6	19.4	22.6	18.3	19.2	0.4
Diabetes (%)	3.4	4.5	3.1	3.4	1.7	6.0	0.09
Dyslipidemia (%)	8.2	6.9	7.7	8.2	3.7	6.0	0.1

*mean±standard deviation