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Total and differential white blood cell counts predict eight-year incident coronary heart disease in elderly Japanese-American men: The Honolulu Heart Program

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ABSTRACT

Background: Previous studies have reported an association between total and differential white blood cell (WBC) counts and incident coronary heart disease (CHD), but data from elderly populations are scarce. The purpose of this study was to examine the association between total and differential WBC counts and incident CHD in an elderly Japanese-American population. **Methods**: Total and differential WBC counts were examined at a baseline examination from 1991 to 1993 in the Honolulu Heart Program. Subjects were Japanese-American men aged 71–93 years free of CHD at baseline ($N = 2879$), who were divided into quartiles of total and differential WBC counts for analysis, and were followed for incident CHD for 8 years. **Results**: During the follow up period, 279 men developed CHD. Hazard ratio for incident CHD for each quartile of total and differential WBC counts were obtained by Cox regression using the lowest quartile as the reference group. After full adjustment including age, cardiovascular risk factors, chronic diseases and medication use, the hazard ratios in the highest quartiles of total WBC, granulocyte and neutrophil counts were 1.75 (95% confidence interval [CI], 1.18–2.62; $P = 0.006$), 1.66 (95%CI, 1.11–2.48; $P = 0.01$), and 1.57 (95%CI, 1.06–2.34; $P = 0.03$), respectively. No significant associations were found between lymphocyte or monocyte counts and incident CHD. **Conclusions**: Higher total WBC, granulocyte and neutrophil counts were associated with higher risk of incident CHD in a population of elderly Japanese-American men. Further studies are needed to establish cut-points and treatment options with anti-inflammatory medications.

1. Introduction

Coronary heart disease (CHD) is the leading cause of death in the U.S., accounting for more than 1 in 6 deaths in 2009 [1]. The incidence of CHD progressively increases with age [2]. Previous studies have suggested that inflammation plays an important role in atherosclerosis, the underlying pathogenesis of CHD [3–5]. White blood cell (WBC) count and leukocyte count on WBC differential have been recognized as possible markers of inflammation. These tests are widely used and inexpensive.

Previous studies have shown mixed results regarding the association between WBC count and incident CHD. Some studies have found significant associations [6–12], while others have not found significant associations between WBC and incident CHD [13–16]. A meta-analysis of seven large prospective studies found a combined CHD risk ratio of 1.4 (95%CI 1.3–1.5) in the highest tertile of WBC count, using the lowest tertile as reference [17]. Previous studies on this subject have been primarily in young and middle-aged populations, and only two studies have been in Asian populations [18,19]. To our knowledge, there have been only two longitudinal

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population-based studies of total WBC count and incident CHD in elderly populations, neither of which studied the relationship with differential WBC counts. There have been no studies of either WBC or differential counts and incident CHD in elderly Asian populations, one of the fastest-growing U.S. minority populations.

We hypothesized that higher levels of WBC and each differential count would predict incident CHD in an elderly Asian population. To evaluate this hypothesis, we analyzed the association between WBC count and differential counts (granulocytes, neutrophils, lymphocytes, monocytes) and incident CHD over 8 years of follow-up in a population-based cohort of elderly Japanese-American men in Hawaii.

2. Methods

2.1. Study design and population

The Honolulu Heart Program (HHP) is a long-term prospective cohort study to investigate cardiovascular diseases among American men of Japanese ancestry who were living on the island of Oahu in 1965 [20,21]. A total of 8006 men, born between 1900 and 1919, were identified from the World War II Selective Service Registry. Details of the cohort selection process have been previously published [22]. The first examination was performed between 1965 and 1968, and subjects underwent repeat examinations as part of a comprehensive follow up of surviving cohort members. The entire cohort has undergone twelve full examinations. The study was approved by the Institutional Review Board of Kuakini Medical Center, and written informed consent was obtained from all participants at each examination.

The baseline for this analysis is the fourth examination of the cohort which was performed between 1991 and 1993, with follow-up for incident CHD through December 31, 1999. At the fourth examination, a total of 3741 men were assessed, representing 80% of survivors of the original HHP cohort. Subjects with prevalent CHD at baseline ($n = 724$) and those with missing WBC count ($n = 138$) were excluded from this analysis (total 862 subjects excluded). The final analytic sample for the present study included 2879 subjects aged 71–93 years and free of CHD at baseline.

2.2. Measurement of total and differential white blood cell count

Blood for WBC count measurements was sent to a local laboratory, Diagnostic Laboratory Services, Inc. Whole blood specimens were obtained in EDTA vacutainer tubes. Complete blood cell counts were measured within 6 h after collection if stored at room temperature, or within 24 h after collection when stored at 4 °C. Any specimens which were clotted or filled less than half of the tube were rejected. Repeat blood collections were attempted if the participant gave consent, and response rates for blood collection were excellent as noted in the paragraph above. The total and differential WBC counts were assessed using the Technicon H-1 automated hematology analyzer (Technicon Instruments Corp, Terrytown, NY, USA) [23,24]. Using this methodology compared to the gold standard, studies have found that the coefficient of correlation for total WBC count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils were 0.999, 0.994, 0.999, 0.946, 0.994, and 0.976, respectively [25]. The ratio of neutrophils, lymphocytes, monocytes, eosinophils, and basophils were provided as a result of differential WBC count. Granulocyte count was calculated as the sum of neutrophils, eosinophils and basophils. Absolute count for each differential count was calculated from the total WBC count and the ratio of each differential WBC count.

2.3. Outcome

Since the beginning of the HHP, there has been continuous, comprehensive surveillance for all mortality and selected morbidity, including incident cardiovascular diseases. All data obtained at follow-up exams, hospital records on the island of Oahu, death certificates, and autopsy records were reviewed. Surveillance for this cohort is believed to be virtually complete, with minimal attrition [2].

Incident CHD was defined and classified by the following criteria: death attributable to CHD which included death within one month after the onset of myocardial infarction (MI) with documented ECG or enzyme evidence, and sudden death within 1 h after the onset of acute episode without other evidence of CHD; nonfatal myocardial infarction confirmed with diagnostic ECG, enzyme elevation, or with temporal changes of ECG considered diagnostic of MI in intervals between examinations with or without supportive history; acute coronary insufficiency which was diagnosed by severe chest pain lasting more than 30 min, with documented transient ST-T wave changes on ECG and without elevation of enzyme levels; and angina pectoris which was ascertained by episodic substernal pain brought on by exertion and relieved by rest or taking nitroglycerin; or having surgical treatment for CHD. All final CHD diagnoses were adjudicated and confirmed after review by the HHP Morbidity and Mortality Committee [2]. A more detailed description of the definition of CHD has been published previously [20,21].

2.4. Covariates

Covariates included body mass index (BMI), hypertension, diabetes mellitus, smoking history, physical activity index (PAI), total cholesterol, high-density lipoprotein (HDL) cholesterol, alcohol consumption, fibrinogen level, prevalent cerebrovascular accident (CVA), cancer, or emphysema, and medication use including aspirin or nonsteroidal anti-inflammatory drug (NSAID). BMI was defined as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure of 140 mmHg or greater, or diastolic blood pressure of 90 mmHg or greater, or use of antihypertensive drugs. Diabetes mellitus was defined as fasting glucose of 126 mg/dL or greater, or 2-h post-load glucose of 200 mg/dL or greater, or taking medications for diabetes (insulin or oral hypoglycemics). Smoking status was defined as current smokers, past smokers and never smokers, by self-report. PAI was calculated by summing up the products of the hours a day at each level of activity multiplied by a weighting factor based on the oxygen consumption required for that activity (basal activity = 1.0, sedentary = 1.1, slight = 1.5, moderate = 2.4, and heavy = 5.0). High scores indicate an active life style and low scores indicate inactive life styles [26]. Serum total cholesterol and HDL cholesterol were measured by standard procedures after an overnight fast of at least 12 h. Plasma fibrinogen level was measured at the Laboratory for Clinical Biochemistry Research, University of Vermont, Colchester, as the rate of clot formation by a semiautomated modification of the Clauss method, using a BBL fibrometer (Becton Dickinson) [27]. History of alcohol consumption was self-reported as ounces consumed per month. Prevalent stroke and cancer were identified by surveillance of hospital records using standardized criteria. Prevalent emphysema was identified by self-reported history. Subjects were asked to bring in all prescription and non-prescription medications, which were documented including use of aspirin or NSAID.