Leukocyte Count as a Predictor of Cardiovascular Events and Mortality in Postmenopausal Women

The Women’s Health Initiative Observational Study

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Background: Increasing evidence supports a role for inflammation in the atherosclerotic process. The role of the leukocyte count as an independent predictor of risk of a first cardiovascular disease (CVD) event remains uncertain. Our objective was to describe the relation between the baseline white blood cell (WBC) count and future CVD events and mortality in postmenopausal women.

Methods: In this prospective cohort study set in 40 US clinical centers, the study population comprised 72242 postmenopausal women aged 50 to 79 years, free of CVD and cancer at baseline, enrolled in the Women’s Health Initiative Observational Study. Main outcome measures included incident fatal coronary heart disease (CHD), nonfatal myocardial infarction, stroke, and total mortality.

Results: At baseline, the mean±SD age of the women was 63±7.3 years, 84% were white, 4% had diabetes, 35% had hypertension, and 6% were current smokers. The mean WBC count was 5.8±1.6 × 10^9 cells/L. During a mean of 6.1 years of follow-up, there were 187 CHD deaths, 701 nonfatal myocardial infarctions, 738 strokes, and 1919 deaths from all causes. Compared with women in the first quartile (2.5-4.7 × 10^9 cells/L), women in the fourth quartile (6.7-15.0 × 10^9 cells/L) had over a 2-fold elevated risk for CHD death (hazard ratio, 2.36; 95% confidence interval, 1.51-3.68), after multivariable adjustment for age, race, diabetes, hypertension, smoking, hypercholesterolemia, body mass index, alcohol intake, diet, physical activity, aspirin use, and hormone use. Women in the upper quartile of the WBC count also had a 40% higher risk for nonfatal myocardial infarction, a 46% higher risk for stroke, and a 50% higher risk for total mortality. In multivariable models adjusting for C-reactive protein, the WBC count was an independent predictor of CHD risk, comparable in magnitude to C-reactive protein.

Conclusions: The WBC count, a stable, well-standardized, widely available and inexpensive measure of systemic inflammation, is an independent predictor of CVD events and all-cause mortality in postmenopausal women. A WBC count greater than 6.7 × 10^9 cells/L may identify high-risk individuals who are not currently identified by traditional CVD risk factors.

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Increasing evidence supports a role for inflammation in the atherosclerotic process.\(^1,2\) Initiation, growth, and complications of atherosclerotic plaques are each judged to be an inflammatory response to vascular injury,\(^3,4\) and inflammatory markers and cytokines originating in the heart, vessel walls, macrophages, adipose tissue, and liver have been associated with the risk of coronary events.\(^5\) In light of the multitude of pathobiological factors involved in inflammation, a large number of targets for measurement have been proposed to identify and monitor the inflammatory process in patients with, or at risk for, coronary heart disease (CHD). These include proinflammatory factors such as oxidized low-density lipoproteins, proinflammatory cytokines (eg, interleukin 1 and tumor necrosis factor-α), adhesion molecules (eg, intercellular adhesion molecule 1 and selectins), inflammatory stimuli with hepatic effects (eg, interleukin 6), or the products of the hepatic stimulation, such as serum amyloid A, C-reactive protein (CRP), and other acute-phase reactants.\(^6\) In addition, indicators of cellular responses to inflammation, such as elevated white blood cell (WBC) count, have also been considered.\(^6\)
As early as 1954, Cole et al. made the observation that patients with myocardial infarction (MI) with elevated WBC counts had a 4-fold higher risk of death compared with patients with WBC counts in the normal range. Since then, prospective studies have suggested a relation between higher total leukocyte count and cardiovascular disease (CVD) events and mortality. Furthermore, in the Multiple Risk Factor Intervention Trial (MRFIT), a decline in the WBC count over time was associated with reduced CHD mortality. Although the WBC count is associated with other established CVD risk factors, most notably cigarette smoking, many studies have found an independent association of WBC counts and CVD risk. A number of the studies cited above have included women, although only a few presented data stratified by sex. Only 2 studies found a positive relationship between the leukocyte count and future cardiovascular events in women after adjusting for other CVD risk factors.

The Women’s Health Initiative (WHI) Observational Study (WHI-OS) is a multicenter longitudinal cohort study of 93,676 postmenopausal women, composed of diverse racial/ethnic and socioeconomic groups. At baseline, participants in the WHI had leukocyte counts measured, in addition to giving an extensive history and undergoing a physical examination. Because of its large size and broad representation of women from across the United States, this cohort provides an opportunity to determine whether the association of WBC count with future cardiovascular events is present in postmenopausal women and to examine the independence of this association from other known CVD risk factors and biomarkers. In this article, we describe the relation between the baseline leukocyte count and future cardiovascular events in women enrolled in the WHI Observational Study who were initially free of clinical CVD and cancer.

STUDY POPULATION

As described elsewhere, the WHI has clinical trial and observational study components. The latter component is an ongoing prospective cohort study of postmenopausal women, and is designed to examine the association between clinical, socioec- onomic, behavioral, and dietary risk factors and the subsequent incidence of health outcomes. Between September 1, 1994, and December 31, 1998, the WHI-OS enrolled 93,676 women aged 50 to 79 years at 40 clinical centers throughout the United States. Participants were recruited from areas surrounding the 40 clinical centers in 24 states and the District of Columbia. Women were eligible to participate in the WHI-OS if they were postmenopausal; unlike to change residence or die within 3 years; did not have complicating conditions such as alcoholism, drug dependency, or dementia; and were not enrolled in the WHI or any other clinical trial. The baseline characteristics of the WHI-OS cohort have been described in detail. All participants provided informed consent using materials approved by institutional review boards at each center.

Participants entered the WHI-OS by expressing initial interest in either the diet modification or hormone therapy arms of the WHI Clinical Trial but proved ineligible or unwilling to participate or responded to a direct invitation to be screened for the WHI-OS. More than 80% of WHI-OS participants preferred to participate in an observational rather than interventional component of WHI or did not meet the requirements for the diet modification part of the clinical trial (fat intake >32% of calories and ≤10 meals per week away from home). Home common reasons for participation in the WHI-OS were closure of the appropriate age clinical trial stratum (about 10%) or a history of breast cancer (about 5%). The following participants were excluded from the original cohort of 93,676 for these analyses: 1635 with a missing WBC count, 141 with a WBC count less than 2.5×10^9 cells/L, 213 with a WBC count greater than 15.0×10^9 cells/L, 12075 with any cancer diagnosis at baseline except nonmelanoma skin cancer, 7992 women with a history of CVD at baseline, and 1423 women with missing data on CVD at baseline. Some women had more than 1 exclusion criterion, yielding a final sample of 72,242.

DATA COLLECTION

Participants underwent initial screening visits, during which personal information, medical history, health-related habits, and medication and vitamin use were assessed. Anthropometric measurements, blood pressure, and fasting blood specimens were obtained. The blood collection took place in the morning after a 12-hour tobacco-free fast. The hemogram sample was collected in a tube containing the anticoagulant edetic acid. These samples were analyzed at local laboratories at each of the 40 WHI Clinical Centers. Certified staff performed physical measurements and obtained blood samples at the baseline clinic visit. Women were asked to specify their race/ethnicity from 6 categories: American Indian or Alaskan Native, Asian or Pacific Islander, black or African American (not of Hispanic origin), Hispanic/Latino, non-Hispanic white, and other. Women were considered to have previous cancer or CVD if they self-reported a history of any type of cancer except nonmelanoma skin cancer, myocardial infarction (MI), stroke, angina, congestive heart failure, coronary revascularization, or peripheral arterial disease. Participants were asked whether they had ever been told by a physician that they had hypertension or high blood pressure, diabetes, or high blood glucose when they were not pregnant, or high cholesterol that required taking pills. Family history of MI at a young age in first-degree relatives (men <55 years and women <65 years), past or current smoking status, aspirin use, and frequency of alcohol consumption were queried. Fiber intake, fruit and vegetable intake, and polyunsaturated-saturated fatty acid ratio were obtained using a validated food frequency questionnaire based on instruments previously used in large-scale dietary intervention trials. A participant was considered a current or former hormone therapy user if she used an estrogen or progestin containing pill or patch for at least 3 months following menopause. Recreational physical activity was assessed by questions on the frequency and duration of several types of recreational activity, and metabolic equivalent task scores were computed as the product of days per week, minutes per day, and the metabolic equivalent task value for each activity.

FOLLOW-UP AND ASCERTAINMENT OF CASES

The WHI-OS follow-up was conducted by annual mailed self-administered medical update questionnaires (except for year 3, when participants attended a clinical follow-up visit). Participants mailed their completed questionnaires to their local clinical center for data entry and outcomes processing. As of August 31, 2003, the response rates for medical history updates from years 1 through 6 were 96%, 94%, 96%, 94%, 94%, and 93%, respec-
tively; 1.8% of the WHI-OS participants had been lost to follow-up, an additional 1.8% had stopped follow-up, and 4.2% had died.

At each annual contact, initial reports of treatment or hospitalization for “problems with the heart or circulation, stroke, or transient ischemic attack” were obtained using a self-administered questionnaire. Medical records and death certificates were obtained and reviewed by a trained local physician adjudicator to verify all events. Coronary heart disease death was defined as death consistent with CHD as the underlying cause plus 1 or more of the following: hospitalization for MI within 28 days of death, previous angina or MI and no potentially lethal noncoronary cause of death, death related to a procedure for coronary artery disease, or death certificate consistent with CHD as the underlying cause. The diagnosis of acute MI was established according to an algorithm adapted from standard criteria that included clinical symptoms, cardiac enzymes and troponin levels, and electrocardiogram readings. Stroke diagnosis was based on the rapid onset of a persistent neurological deficit attributable to an obstruction or rupture of the arterial system supported by imaging studies when available. The neurological deficit must have lasted more than 24 hours, unless death supervened or there was a demonstrable radiographic lesion compatible with acute stroke. A sample of the locally verified events was reviewed by central cardiovascular adjudicators. For the WHI-OS, the agreement of central review with local adjudication was 79% for CHD death and 82% for MI. Although strokes were not centrally adjudicated for the WHI-OS, the agreement of central review with local adjudication in the WHI clinical trials was 91% for stroke.

A previously published ancillary study from the WHI-OS, using a prospective, nested case-control design, measured total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and CRP on stored baseline serum samples with a high-sensitivity assay. Among 73 343 women with no history of CVD...
or cancer, 304 women with incident first MI or death from CHD during 2.9 years of follow-up were defined as cases and matched by age, smoking status, ethnicity, and follow-up time with 304 study participants who remained event free. In this study, a CRP level in the upper quartile was independently associated with about a 2-fold increase in the risk of developing CHD, after matching for the above variables, and after adjusting for TC/HDL-C ratio, body mass index, hypertension, diabetes, family history of premature coronary artery disease, exercise frequency, alcohol consumption, and use of hormone therapy. We performed additional logistic regression analyses using this data set with WBC count as the main predictor variable.

STATISTICAL ANALYSIS

To describe participant characteristics across levels of WBC count, WBC was categorized using quartile divisions and cross-tabulations were examined. Hazard ratios (HRs) and nominal 95% confidence intervals (CIs) from Cox proportional hazards regression analyses are reported for the outcomes CHD death, nonfatal MI, stroke, total CVD events (CHD death, MI, or stroke) and total mortality. An additional 430 participants with no follow-up and 5551 participants without complete case data for all covariates included in the multivariate modeling were excluded from all Cox regression models (n=66261). The initial model adjusted only for age, race, and ethnicity. The fully adjusted model also included baseline hypertension, diabetes, hypercholesterolemia, smoking, body mass index, alcohol intake, polyunsaturated-saturated fatty acid ratio, dietary fiber, fruit and vegetable intake, physical activity, and current use of aspirin or hormone therapy. Follow-up time for each woman was accrued from enrollment to the date of CVD event, loss to follow-up, or administrative censoring date (August 31, 2003). Mean length of follow-up for the cohort was 6.1 years (range, 0.002-8.9 years).

The assumption of proportionality was tested by including indicators for the upper 3 WBC count quartiles, product terms between these indicators and follow-up time, and using a likelihood ratio procedure to test for zero coefficients for the 3 product terms. The assumption was met for all of the outcomes included in the analysis. Trends across WBC count quartiles were assessed by including a variable that equaled the median of the WBC quartiles. Starting in the ninth decile of the WBC values within the pertinent quartile. Corresponding P values are reported. Stratified Cox models were also examined separately by age, race/ethnicity, smoking, history of diabetes, hypertension, body mass index, and history of hypercholesterolemia, adjusting for all other variables previously listed for the fully adjusted models. Interactions of age, race/ethnicity, smoking, and diabetes with WBC count quartile were tested separately for each covariate, using likelihood ratio tests, comparing fully adjusted Cox models with and without the interaction terms.

Logistic regression modeling was performed using the WHI-OS case-control data to examine the effect of WBC count, as well as the joint effect of WBC count × CRP, on CHD. A progression of 3 models (crude, adjusted for TC/HDL-C ratio and CRP, and fully adjusted) was used to examine the main effect of WBC count by quartile on CHD. The joint effect of WBC count × CRP level quartiles was examined after adjusting for TC/HDL-C ratio. Models were based on case-control pairs for whom data were available on all variables of interest. All statistical analyses were performed using the SAS System for Windows (version 9.00; SAS Inc, Cary, NC).

RESULTS

Table 1 shows the baseline characteristics of the WHI-OS participants in this analysis by quartile of WBC count. Age increased across the WBC count quartiles, with women in the fourth quartile about 1.5 years older, on average, than women in the first quartile. Blacks and Asian/Pacific Islanders were more likely to be in the first WBC count quartile compared with members of other racial/ethnic groups. Women in lower income categories were more likely to be in the upper WBC count quartiles. There was a striking increase in the prevalence of cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia, family history of MI, and current smoking) across the WBC quartiles. Alcohol intake of at least 1 drink per week, fiber intake, fruit and vegetable intake, polyunsaturated-saturated fatty acid ratio and physical activity were inversely related to WBC count quartile; whereas body size and both systolic and diastolic blood pressure were positively related to WBC count; use of aspirin and both unopposed estrogen and combined estrogen and progesterin increased across the WBC count quartiles. All of these differences were significant at P<.001.

The association between WBC count quartile and incident cardiovascular events is shown in Table 2. Included in this analysis were 187 CHD deaths, 701 nonfatal MIs, 738 strokes, 1510 total CVD events, and 1919 deaths from all causes. Each of these events had a strong and graded association with WBC count quartile in the age and race/ethnicity adjusted models. The strength of the association was attenuated by further adjustment for other CVD risk factors but still remained statistically significant for all outcomes. After multivariable adjustment, compared with women with WBC counts in the first quartile, women in the fourth quartile had a more than 2-fold elevated risk for CHD death and 40% to 50% higher risks for nonfatal MI, stroke, total CVD, and total mortality. A secondary analysis was performed for the outcome of total CVD events using deciles of the WBC count. Starting in the ninth decile (WBC, 6.8-7.6×10^9 cells/L) and 10th decile (WBC, 7.7-15.0×10^9 cells/L) the HRs were significantly elevated compared with the first decile: 1.30 (95% CI, 1.02-1.65; P=.03) and 1.56 (95% CI, 1.23-1.98; P<.001), respectively. When WBC count was modeled as a continuous variable, the HR for total CVD events per 1.0×10^9-cells/L increase in WBC count was 1.11 (95% CI, 1.08-1.15; P<.001).

In the 608 women included in the WHI-OS case-control study of CHD events, the median CRP level in cases was 0.33 mg/dL and in controls was 0.25 mg/dL (P<.001). The TC/HDL-C ratio was 4.2 in cases and 3.7 in controls (P=.001). A WBC count in the upper quartile was associated with more than 2-fold increase in events even after adjusting for multiple other risk factors including CRP level and TC/HDL-C ratio (Table 3 and Table 4). In the fully adjusted model, the odds ratio for CHD events for the fourth vs first WBC count quartile was 2.36 (95% CI, 1.33-4.19; P for trend =.01). In contrast, the odds ratio for CHD events for the fourth vs first CRP level quartile was 1.95 (95% CI, 0.95-4.01; P for trend =.02). Table 5 presents logistic regression analyses of the risk of CHD based on the joint relationship between CRP and WBC count, adjusted for TC/HDL-C ratio. The referent group is the first quartile of both the WBC count and CRP. The risk of CHD was generally close to unity in the categories defined by the lower 3 quartiles of WBC count × CRP, and was more than doubled in
The upper quartile of most joint categories, with an additive nearly 7-fold elevation of risk for women with WBC count and CRP in the upper quartile of both biomarkers (odds ratio, 6.8; 95% CI, 2.7–16.9; P < .001).

We examined risk of total CVD events for the highest compared with the lowest WBC count quartiles in subgroups defined by age, race, and other CVD risk factors (Figure). For age, race, and CVD risk factor subgroups, the HRs and 95% CIs were consistent with the 50% excess risk seen in the whole cohort, and tests for interaction did not reveal any evidence for effect modification. For women without current smoking, diabetes, hypertension, obesity, or history of hypercholesterolemia, the adjusted HR for the fourth vs first quartile was 1.70 (95% CI, 1.28–2.27; P for trend, <.001).

These data indicate that the WBC count is an independent predictor of CHD events, stroke, and all-cause mortality in postmenopausal women. The upper quartile appears to be a reasonable threshold for elevated risk and is approximated by a WBC count of greater than 6.7 × 10^9 cells/L. Furthermore, a WBC count in the upper quartile is associated with an increased risk of cardiovascular events in subgroups of postmenopausal women without other risk factors, including older age, smoking, diabetes, hypertension, and obesity. The WBC count remains a significant predictor of CHD events even after further adjustment for lipids and CRP.

Few previous studies have assessed the WBC count as a predictor of CVD events in generally healthy women, and none has also controlled for CRP. A meta-analysis including nearly 6000 subjects from 14 population-based studies concluded that the risk ratio for CHD events in the upper vs lower tertile of WBC count was 1.5 (95% CI, 1.4–1.6). Of the 3 studies that included women and presented results stratified by sex, only the first National Health and Nutrition Examination Survey (NHANES I) epidemiologic and follow-up study found a positive association between the WBC count and CHD events in women after adjustment for other risk factors. Several subsequent studies have found a significant relationship between the WBC count and cardiovascular events in women. In the NHANES II mortality study, women in the upper tertile of WBC count had an adjusted CHD mortality HR of 1.7. In the Atherosclerosis Risk in Communities (ARIC) prospective study, the risk of incident stroke was doubled in women with WBC counts in the upper quartile. In contrast, in NHANES I no significant associations of the WBC count with stroke were observed in men or women after adjustment for smoking, despite a similar number of events (625 strokes in NHANES I vs 708 in ARIC).

In a recent American Heart Association/Centers for Disease Control and Prevention scientific statement, many measures of the inflammatory process were considered for their potential utility in the clinical setting for CHD risk assessment. Factors regarded as important for selection of new markers included the following: ability to standardize the assay and to control measurement variability; independence of the new measure from established risk factors; association with cardiovascular end points in observational studies and clinical trials; presence of population norms to guide interpretation of results; ability to improve the overall prediction beyond that of traditional risk factors; generalization of results to various population groups; and acceptable cost of the assays. Based on these parameters, CRP was judged potentially capable of having utility in the clinical assessment of inflammation and CHD risk evaluation. Considering the factors outlined for assessment of the utility of inflammatory markers for CHD risk assessment, the WBC count appears comparable to CRP.

Prospective studies and nested case-control studies have shown a graded dose-response relationship between levels of CRP and higher long-term risk for fu-
ture cardiovascular events among apparently healthy individuals, and CRP has been suggested as an adjunct to traditional risk factor measurement in those with intermediate levels of cardiovascular risk. To our knowledge, there are no previously published studies in which WBC count and CRP have been compared head-to-head in individuals without known CVD or dyslipidemia. However, in patients with acute coronary syndromes, WBC...

Table 3. Crude and Adjusted Odds Ratios* for Coronary Heart Disease According to Baseline WBC Count Quartiles

<table>
<thead>
<tr>
<th>Model</th>
<th>Quartile of WBC Count, ×10^4 cells/L</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1, 2.6-4.9</td>
<td>Q2, 5.0-5.9</td>
</tr>
<tr>
<td>Crude analysis (n = 288)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.0</td>
<td>0.84 (0.53-1.36)</td>
</tr>
<tr>
<td>P value</td>
<td>.49</td>
<td>.77</td>
</tr>
<tr>
<td>Adjusted for TC/HDL-C ratio and CRP level (n = 286)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.0</td>
<td>0.82 (0.50-1.35)</td>
</tr>
<tr>
<td>P value</td>
<td>.44</td>
<td>.56</td>
</tr>
<tr>
<td>Adjusted for all risk factors† (n = 265)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.0</td>
<td>0.83 (0.45-1.52)</td>
</tr>
<tr>
<td>P value</td>
<td>.54</td>
<td>.97</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; n, number of case-control pairs included in the analysis; CRP, C-reactive protein; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol; WBC, white blood cell.
*Analyses matched on age, ethnicity, smoking, and length of follow-up.
†Adjusted for CRP level, as well as TC/HDL-C ratio, body mass index, hypertension, family history of premature coronary artery disease, diabetes, physical activity, alcohol intake, and prior use of hormone therapy.

Table 4. Crude and Adjusted Odds Ratios* for Coronary Heart Disease According to Baseline CRP Level Quartiles

<table>
<thead>
<tr>
<th>Model</th>
<th>Quartile of CRP Level, mg/dL</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1, 0.02-0.12</td>
<td>Q2, 0.13-0.27</td>
</tr>
<tr>
<td>Crude analysis (n = 288)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.0</td>
<td>1.13 (0.70-1.85)</td>
</tr>
<tr>
<td>P value</td>
<td>.61</td>
<td>.24</td>
</tr>
<tr>
<td>Adjusted for TC/HDL-C ratio and WBC count (n = 286)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.0</td>
<td>1.07 (0.63-1.80)</td>
</tr>
<tr>
<td>P value</td>
<td>.81</td>
<td>.78</td>
</tr>
<tr>
<td>Adjusted for all risk factors† (n = 265)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.0</td>
<td>0.94 (0.48-1.87)</td>
</tr>
<tr>
<td>P value</td>
<td>.87</td>
<td>.67</td>
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</table>

Abbreviations: CI, confidence interval; CRP, C-reactive protein; n, number of case-control pairs included in the analysis; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol; WBC, white blood cell.
*Analyses matched on age, ethnicity, smoking, and length of follow-up.
†Adjusted for WBC count, as well as TC/HDL-C ratio, body mass index, hypertension, family history of premature coronary artery disease, diabetes, physical activity, alcohol intake, and prior use of hormone therapy.

Table 5. Odds Ratios (95% CIs) From a Bivariate Logistic Regression Model* Predicting Coronary Heart Disease Based on the Joint WBC Count×CRP Level Relationship

<table>
<thead>
<tr>
<th>Quartile of CRP Level, mg/dL</th>
<th>Quartile of WBC Count, ×10^4 cells/L</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1, 0.02-0.12</td>
<td>No. of Cases/Total No.</td>
<td>27/60</td>
<td>16/40</td>
<td>14/37</td>
<td>9/18</td>
</tr>
<tr>
<td>Q2, 0.13-0.27</td>
<td>1.22 (0.51-2.93)</td>
<td>1.22 (0.51-2.93)</td>
<td>1.38 (0.63-3.06)</td>
<td>1.43 (0.76-2.70)</td>
<td>2.83 (0.84-9.59)</td>
</tr>
<tr>
<td>Q3, 0.28-0.59</td>
<td>0.94 (0.37-2.39)</td>
<td>0.94 (0.37-2.39)</td>
<td>1.08 (0.43-2.70)</td>
<td>1.21 (0.63-2.34)</td>
<td>2.70 (1.01-7.23)</td>
</tr>
<tr>
<td>Q4, 0.60-4.26</td>
<td>2.83 (0.84-9.59)</td>
<td>2.83 (0.84-9.59)</td>
<td>1.91 (0.95-4.01)</td>
<td>2.70 (1.01-7.23)</td>
<td>3.10 (1.20-7.99)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; WBC, white blood cell.
*Model matched on age, ethnicity, smoking and length of follow-up and adjusted for total cholesterol to high-density lipoprotein cholesterol ratio.
count and CRP were found to be independent, additive predictors of 6-month mortality. In a prospective study of patients with angiographically proven coronary artery disease and no recent MI, adjusting for CRP eliminated the association of the WBC count with long-term mortality. In a nested case-control study of dyslipidemic men enrolled in the Helsinki Heart Study, the joint effect of a high CRP level and high WBC count on incident CHD events was additive.

It is not known whether leukocytes are involved directly in the pathogenesis of cardiovascular events or are only a risk marker for other factors causing the disease. The independence of the risk associated with higher WBC counts from other risk factors suggests that the relationship may in fact be causal. Plausible biological mechanisms also exist to support a causal link. Monocytes contribute to atherosclerosis by giving rise to foamy macrophages and reactive oxygen species and have been implicated as one of the leukocyte types associated with CHD events. Both macrophages and lymphocytes secrete proinflammatory cytokines, and mast cells secrete serine proteases that activate matrix metalloproteases. Monocytes also participate in vascular thrombosis via interactions with platelets and are a rich source of highly thrombogenic tissue factor.

A number of limitations of this analysis must be considered. Only 1 measurement of WBC was performed, and the analyses were done in 40 local laboratories on automated counters. Multiple measurements in a central laboratory would have reduced measurement error and increased the precision of our results; thus, our current results are likely to be underestimates of the true associations because of nondifferential misclassification. The participants in WHI were generally healthy, well-educated volunteers; therefore, our results may not apply to the general population, despite the broad geographic representation of the 40 clinical centers. Another important issue is that other laboratory measurements were performed only in the nested case-control study and in a 1% subsample of the WHI-OS cohort; therefore, we are unable to adjust for blood markers of cardiovascular risk, such as lipoproteins, clotting factors, and other inflammatory markers in the entire cohort. However, we included the self-report of elevated cholesterol level requiring medication in our multivariable models. The similar relative risk estimate that we obtained for the upper quartile of the WBC count in the WHI-OS case-control sample suggests that the results would have changed little with the addition of the above blood measurements.

In summary, we have demonstrated that a WBC count in the upper quartile is independently associated with cardiovascular events and death in older women after adjustment for traditional risk factors. This offers a stable, well-standardized, widely available and inexpensive measure of systemic inflammation. These data add to available evidence in men suggesting a similar link and suggest that the predictive role of the WBC count is independent of

*Figure. Hazard ratios (95% confidence intervals) for cardiovascular event in the highest compared with the lowest white blood cell count quartiles in subgroups of age, race, and cardiovascular risk factors. All models were adjusted for age, race/ethnicity, diabetes, hypertension, high cholesterol, smoking status, body mass index, alcohol intake, physical activity, aspirin use, dietary fiber, fruit and vegetable intake, polyunsaturated/saturated fatty acid ratio, and prior use of hormone therapy. BMI indicates body mass index (calculated as weight in kilograms divided by the square of height in meters); CVD, cardiovascular disease.*
CRP. Cardiovascular risk categorization by inflammatory markers, including the WBC count, may identify high-risk individuals who are not currently identified by traditional risk factors; further studies are needed to assess the effectiveness of risk reduction in these patients.

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