Original Contribution

White Blood Cell Count and Total and Cause-Specific Mortality in the Women's Health Initiative

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White blood cell (WBC) count appears to predict total mortality and coronary heart disease (CHD) mortality, but it is unclear to what extent the association reflects confounding by smoking, underlying illness, or comorbid conditions. We used data from the Women's Health Initiative to examine the associations of WBC count with total mortality, CHD mortality, and cancer mortality. WBC count was measured at baseline in 160,117 postmenopausal women and again in year 3 in 74,375 participants. Participants were followed for a mean of 16 years. Cox proportional hazards models were used to estimate the relative mortality hazards associated with deciles of baseline WBC count and of the mean of baseline + year 3 WBC count. High deciles of both baseline and mean WBC count were positively associated with total mortality and CHD mortality, whereas the association with cancer mortality was weaker. The association of WBC count with mortality was independent of smoking and did not appear to be influenced by previous disease history. The potential clinical utility of this common laboratory test in predicting mortality risk warrants further study.

cause-specific mortality; comorbidity; C-reactive protein; reverse causality; smoking; total mortality; white blood cell count

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task; NSAIDs, nonsteroidal antiinflammatory drugs; SD, standard deviation; WBC, white blood cell; WHI, Women's Health Initiative.

Elevated white blood cell (WBC) count is a nonspecific marker of inflammation associated with immune system response to both acute and chronic infection and exposure to irritating and toxic exposures, such as tobacco smoke (1–4). Elevated WBC has been associated with an approximate doubling of total mortality and with increased cardiovascular disease (CVD) incidence and mortality in population-based studies, including populations without a history of CVD (5, 6). In a number of studies, after adjustment for established CVD risk factors, WBC count appeared to be an independent risk factor for mortality, and the magnitude of its association was comparable to, or stronger than, those for serum cholesterol, low-density lipoprotein cholesterol, and hypertension (7–14).

While previous studies have suggested that WBC count may be a valuable predictor of total mortality and coronary

heart disease (CHD) incidence and mortality, questions remain about the nature of the association. First, to what extent is the association due to disease history or the presence of preclinical disease? Second, at what level of WBC count within the normal range is an increase in risk detectable? Third, is a single WBC measurement, as has been used in most studies (8, 10, 14, 15), adequate to classify individuals with respect to mortality risk? Finally, there are inconsistencies among studies regarding the association of WBC count with CVD incidence and total mortality by smoking status and by sex. In some studies an association is observed only in smokers (16) or nonsmokers or never smokers (17, 18) or is stronger in nonsmokers (12), whereas in other studies the association is independent of smoking status (8–11, 14). Therefore, it is unclear whether the association of WBC

count with mortality is independent of smoking and whether the association varies by smoking status.

In order to address these questions, we examined the association of WBC count with total and cause-specific mortality in the Women's Health Initiative (WHI), a large and well-characterized cohort study of postmenopausal women with information on prevalent illness and detailed information on risk factors for chronic disease.

METHODS

The WHI is a large, multicenter prospective study designed to identify the causes of major chronic diseases in postmenopausal women (19). Between 1993 and 1998, women aged 50–79 years and representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the United States. In total, 68,132 and 93,676 women were enrolled in the clinical trial and the observational study of the WHI, respectively. Details on the study design and the reliability of the baseline measures of demographic and health characteristics have been published elsewhere (19, 20).

Data collection and variable definition

At study entry, self-administered questionnaires were used to collect information on demographic characteristics, medical, reproductive, and family history, and dietary and lifestyle factors, including smoking history, alcohol consumption, and physical activity. Questions about physical activity at baseline referred to a woman's usual pattern of activity, including walking and recreational physical activity. From these data, current total leisure-time physical activity (metabolic equivalent of task (MET)-hours/week) was computed by multiplying the number of hours per week of specific leisure-time physical activities by the MET values of the activities and summing over all types of activities (21). Women were also asked whether they had ever had a chronic disease, including diabetes, CHD, cerebrovascular disease, pulmonary disease, connective tissue disorders, hematological cancer, a solid tumor, or other conditions. We employed a modified version of the Charlson comorbidity index, adapted for use in the WHI, to summarize the presence of comorbidity at enrollment (22). The modified index was created by assigning 1 point for each of the following conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcerative colitis, and liver disease; 2 points were assigned for diabetes, leukemia, lymphoma/myeloma, or a solid tumor. Owing to the relatively small number of women with multiple comorbidity ($n = 25,082$), we created a dichotomous variable: no comorbidity vs. 1 or more comorbid conditions.

Blood measurements

Fasting blood samples were obtained from all participants at baseline and were analyzed for WBC count, as well as hemoglobin, hematocrit, and platelet count, by certified laboratories at each of the 40 clinical centers as part of a complete blood count (23). Results were entered into the WHI

database at each clinical center and were reviewed by clinical center staff for accuracy and patient safety (23). In year 3, a second blood sample was obtained from women in the observational study; data on blood parameters (including WBC count) measured at this visit were available for 81% of observational study participants (74,375/93,676). In addition, measurements of C-reactive protein (CRP), triglycerides, and total cholesterol were available for a subgroup of 24,044 WHI participants (25% in the observational study; 75% in the clinical trial). These latter assays were performed in a single laboratory using the same methods. High-sensitivity CRP was measured in serum or plasma using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, Indiana) and read on the Roche Modular P Chemistry analyzer (Roche Diagnostics). Total cholesterol was measured in serum using a cholesterol oxidase method (Roche Diagnostics) on the Roche Modular P Chemistry analyzer. Triglyceride was measured in serum using Triglyceride GB reagent (Roche Diagnostics).

Ascertainment of outcome

Cause of death was determined by centralized review of medical records and death certificates at each WHI clinical center; regular linkages to the National Death Index were conducted to ensure complete mortality ascertainment (24). In the total cohort, after a median of 16 years of follow-up, 25,165 total deaths had been ascertained, including 3,351 CHD deaths, 7,233 CVD deaths, and 8,233 cancer deaths. Fifty-eight percent of deaths were in the observational study.

Statistical analysis

In the total WHI cohort (observational study + clinical trial), 1,691 women were missing baseline data on WBC count. For the present analysis, we included all women with baseline WBC count ($n = 160,117$), among whom there were 24,880 total deaths, 3,316 CHD deaths, and 8,133 cancer deaths. We used Cox proportional hazards models to assess the associations of deciles of baseline WBC count with total mortality, CHD mortality, and cancer mortality. In addition, for women in the observational study who had had WBC count measured at baseline and at year 3, we examined the mean value of the 2 measurements as a predictor. For the analysis of CHD and cancer mortality, deaths due to causes other than the event of interest were considered competing risks. Follow-up time was calculated as days from enrollment to death, the end of follow-up, or loss to follow-up, whichever occurred first, and days to event was used as the time scale. Covariates included in the main model were: age (years; continuous), smoking status (never, former, or current smoker), pack-years of smoking (continuous), alcohol intake (servings/week; continuous), body mass index (weight (kg)/height (m)²; continuous), physical activity (MET-hours/week; continuous), use of hormone therapy (ever, never), educational level (less than high school, high school graduation/some college, college graduation, postcollege study), race/ethnicity (white, black, or other), self-reported health status ("excellent," "very good," or "good" vs. "fair" or "poor"), comorbidity at baseline (at least 1 condition vs. no conditions;

defined above), and WHI study assignment (observational study vs. allocation to the intervention or control or placebo arm of each of the clinical trials). We repeated this analysis after first excluding women with comorbidity at baseline and, second, excluding the first 3 years of follow-up to address the possibility of reverse causation. Further analyses focused on the subgroup in the observational study who had both baseline and year 3 measurements and in which we assessed the associations of the mean of baseline + year 3 WBC count with the 3 outcomes. In analyses of mean WBC count, follow-up started at year 3. We repeated this analysis after excluding women with 1 or more comorbid conditions reported at baseline, excluding the first 6 years of follow-up (i.e., excluding the 3 years following the year 3 WBC count measurement) to address the possibility of reverse causation, and then excluding both groups simultaneously.

We repeated the main analyses including hemoglobin and platelet count as covariates to determine whether the association of WBC count with mortality was independent of these blood parameters, which are themselves associated with mortality (25). In alternative models, we included baseline use of aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), antibiotics, and other medications that may decrease WBC count (antibiotics, antihistamines, antithyroid drugs, anticonvulsants, or diuretics). We also repeated the main analysis after excluding women with extreme values for WBC count (<2,500 cells/ μ L ($n = 191$) or >41,000 cells/ μ L ($n = 126$)) and with values beyond what is considered the normal range (WBC count <4,000 cells/ μ mL ($n = 12,237$) or >11,000 cells/ μ L ($n = 1,630$)). Because the association of

WBC count with mortality might be confounded by CRP, another marker of inflammation, triglycerides, or total cholesterol levels (11, 13), we adjusted for each of these variables separately in the subgroup of approximately 24,000 participants in whom these analytes were measured (25% in the observational study; 75% in the clinical trial). Finally, we repeated the analyses for baseline and mean WBC count after excluding participants who reported using aspirin, NSAIDs, antibiotics, or any medications capable of decreasing WBC count.

Because smoking is associated with elevated WBC count (26), we compared models containing WBC count deciles and all covariates except smoking status and pack-years with the same models including smoking status and pack-years.

We tested the proportional hazards assumption by using PROC LIFETEST (SAS Institute, Inc., Cary, North Carolina). Results of the formal tests for nonproportional hazards, performed for the analysis of both baseline and mean WBC count, were significant due to the large sample size, but the log-log survival plots did not indicate any marked deviation from normality. All analyses were performed in SAS 9.4.

RESULTS

Baseline characteristics of the cohort according to decile of WBC are presented in Table 1. Body mass index increased slightly across deciles of WBC count, whereas the proportion of current smokers and mean pack-years of smoking increased

Table 1. Baseline Characteristics of Participants According to Extreme and Middle Deciles of Baseline White Blood Cell Count ($n = 160,117$), Women's Health Initiative, 1993–1998

	Decile of White Blood Cell Count					
	First Decile (<4,100 cells/ μ L) ($n = 17,173$)		5th Decile (5,300–5,699 cells/ μ L) ($n = 13,735$)		10th Decile ($\geq 8,000$ cells/ μ L) ($n = 15,571$)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years	62.1 (7.3)		63.4 (7.2)		63.7 (7.2)	
Body mass index ^a	26.0 (5.2)		27.8 (5.7)		29.9 (6.7)	
Educational level (% with postcollege study)		33.2		28.3		24.1
Race/ethnicity (% white)		74.7		84.2		83.8
Current smoker		2.2		4.2		20.8
Pack-years of smoking (among ever smokers)	14.5 (17.4)		18.5 (20.3)		28.1 (24.7)	
Alcohol intake, drinks/day	2.7 (5.0)		2.5 (5.0)		1.9 (4.6)	
Physical activity, MET-hours/week	14.3 (15.0)		12.0 (13.5)		9.2 (12.1)	
Ever use of hormone therapy		54.1		55.2		58.0
Study arm (% in observational study)		61.2		57.3		54.1
Health status (% excellent–good)		93.1		92.5		83.3
History of cardiovascular disease		15.1		17.0		23.6
History of diabetes		2.7		4.7		12.7
History of cancer		10.1		9.0		10.4

Abbreviations: MET, metabolic equivalent of task; SD, standard deviation.

^a Weight (kg)/height (m)².

markedly across deciles. Educational level, alcohol intake, and physical activity (MET-hours/week) decreased across deciles of WBC count. The proportion of women in the observational study decreased over increasing deciles of WBC count, as did the proportion of women who reported their health status as “excellent.” The proportions of women who reported a history of CVD and diabetes at baseline increased across deciles, but the proportions of women with a history of cancer did not.

In age-adjusted analyses, deciles of baseline WBC count were positively associated with total mortality, CHD mortality, and cancer mortality in the total WHI cohort (Table 2, Figure 1). In multivariable-adjusted analyses, the associations were somewhat attenuated but still robust and statistically significant.

Relative to the fifth decile, the hazard ratio for all 3 outcomes increased in a graded fashion with increasing WBC count. There was also some suggestion of a slight increase in CHD and cancer mortality for women with WBC counts less than 4,100 cells/ μ L (the lowest decile). The pattern of results was similar when women with comorbidity and the first 3 years of follow-up were excluded (data not shown). The results were also unchanged after the exclusion of extreme values. Findings for CVD were similar to those for CHD (data not shown).

Mean WBC count showed results generally similar to those based on the baseline measure only (Table 3). When women with comorbidity reported at baseline were excluded, relatively high mean WBC counts were associated

Table 2. Association of Baseline White Blood Cell Count With Total Mortality, Coronary Heart Disease Mortality, and Cancer Mortality ($n = 160,117$), Women’s Health Initiative, 1993–2013

Decile of WBC Count, cells/ μ L	Total Mortality ($n_{\text{deaths}} = 24,880$)		CHD Mortality ($n_{\text{deaths}} = 3,316$)		Cancer Mortality ($n_{\text{deaths}} = 8,133$)	
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI
Age-adjusted results						
<4,100	0.97	0.91, 1.03	1.01	0.84, 1.21	1.06	0.95, 1.18
4,100–4,599	0.89	0.83, 0.95	0.75	0.61, 0.92	1.04	0.93, 1.17
4,600–4,999	0.92	0.86, 0.98	0.90	0.75, 1.08	0.99	0.89, 1.11
5,000–5,299	0.92	0.86, 0.98	0.82	0.69, 0.98	1.01	0.91, 1.13
5,300–5,699	1.00	Referent	1.00	Referent	1.00	Referent
5,700–6,099	1.03	0.97, 1.10	1.14	0.96, 1.35	1.07	0.96, 1.19
6,100–6,499	1.14	1.07, 1.20	1.20	1.02, 1.42	1.17	1.06, 1.30
6,500–7,099	1.26	1.19, 1.34	1.51	1.28, 1.78	1.27	1.14, 1.41
7,100–7,999	1.48	1.40, 1.56	1.95	1.67, 2.27	1.41	1.27, 1.55
$\geq 8,000$	2.07	1.96, 2.19	2.68	2.30, 3.11	1.91	1.73, 2.10
<i>P</i> for linear trend	<0.0001		<0.0001		<0.0001	
Multivariable-adjusted results						
<4,100	1.07	1.00, 1.14	1.21	1.00, 1.47	1.19	1.06, 1.34
4,100–4,599	0.97	0.91, 1.05	0.83	0.66, 1.04	1.13	1.00, 1.27
4,600–4,999	0.98	0.92, 1.05	0.98	0.81, 1.20	1.07	0.96, 1.21
5,000–5,299	0.95	0.89, 1.01	0.86	0.71, 1.05	1.06	0.95, 1.19
5,300–5,699	1.00	Referent	1.00	Referent	1.00	Referent
5,700–6,099	1.03	0.96, 1.10	1.17	0.97, 1.40	1.05	0.94, 1.18
6,100–6,499	1.10	1.04, 1.17	1.19	0.99, 1.42	1.13	1.01, 1.26
6,500–7,099	1.17	1.10, 1.25	1.39	1.16, 1.67	1.18	1.06, 1.32
7,100–7,999	1.29	1.22, 1.37	1.63	1.38, 1.93	1.24	1.12, 1.39
$\geq 8,000$	1.58	1.48, 1.67	1.86	1.57, 2.20	1.45	1.30, 1.61
<i>P</i> for linear trend	<0.0001		<0.0001		<0.0001	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; WBC, white blood cell.

^a Adjusted for age, smoking status (never, past, or current smoker), pack-years of smoking (continuous), alcohol intake (drinks/week), hormone therapy (yes, no), body mass index (weight (kg)/height (m)²; continuous), physical activity (MET-hours/week; continuous), educational level (less than high school graduation, high school graduation/some college, college graduation, postcollege study), race/ethnicity (white, black, or other), history of diabetes (yes, no), history of cardiovascular disease (yes, no), history of cancer (yes, no), self-reported health status (“excellent,” “very good,” or “good” vs. “poor” or “fair”), comorbidity (none, any), and allocation to the observational study or the intervention or control arm of the clinical trial.

Figure 1. Associations between selected deciles of baseline white blood cell (WBC) count and total mortality (A), coronary heart disease (CHD) mortality (B), and cancer mortality (C) in the Women's Health Initiative ($n = 160,117$), 1993–2013. Hazard ratios were adjusted for age, smoking status (never, former, or current smoker), pack-years of smoking (continuous), alcohol intake (drinks/week), hormone therapy (yes, no), body mass index (weight (kg)/height (m)²; continuous), physical activity (metabolic equivalent of task-hours/week; continuous), educational level (less than high school graduation, high school graduation/some college, college graduation, postcollege study), race/ethnicity (white, black, or other), history of diabetes (yes, no), history of cardiovascular disease (yes, no), history of cancer (yes, no), self-reported health status ("excellent," "very good," or "good" vs. "poor" or "fair"), comorbidity (none, any), and allocation to the observational study or the intervention or control arm of the clinical trial. Bars, 95% confidence intervals.

with all 3 outcomes; however, the association with cancer mortality was somewhat attenuated (data not shown). When the first 6 years of follow-up were excluded to minimize the possibility of reverse causation, the association of high WBC count with all 3 outcomes was unchanged (data not shown). When women with comorbidity and the first 6 years of follow-up were excluded, high WBC count remained associated with total and CHD mortality but not with cancer mortality (Table 4).

The association of baseline and mean WBC count with all 3 outcomes was unchanged after adjustment for hemoglobin and platelet levels or for use of aspirin, NSAIDs, antibiotics, or medications capable of decreasing WBC count reported at baseline or during follow-up (data not shown). When users of these medications either at baseline or during follow-up were excluded from analyses of baseline and mean WBC count, respectively, the positive association of WBC with all 3 outcomes remained robust.

In analyses restricted to the subcohort with baseline CRP, triglycerides, and total cholesterol measurements ($n = 24,044$), after adjustment for CRP, WBC count was positively associated with all 3 outcomes, although the hazard ratios were somewhat attenuated compared with those observed without adjustment for CRP (hazard ratios for highest decile vs. the referent group, before and after adjustment for CRP: total mortality—hazard ratio (HR) = 1.68 (95% confidence interval (CI): 1.47, 1.92) vs. HR = 1.58 (95% CI: 1.38, 1.81); CHD mortality—HR = 1.64 (95% CI: 1.18, 2.28) vs. HR = 1.47 (95% CI: 1.05, 2.04); cancer mortality—HR = 2.02 (95% CI: 1.56, 2.62) vs. HR = 1.89 (95% CI: 1.45, 2.47)). Adjustment for triglycerides and total cholesterol level did not affect the results.

Mean WBC count at baseline was 6,000 cells/ μ L (standard deviation (SD), 10,800) in never smokers, 6,200 cells/ μ L (SD, 13,300) in former smokers, and 7,300 cells/ μ L (SD, 9,000) in current smokers ($P < 0.0001$) and increased with increasing pack-years of smoking (>0–<20 pack-years: 6,120 cells/ μ L

Table 3. Association of the Mean of Baseline and Year 3 White Blood Cell Counts With Total Mortality, Coronary Heart Disease Mortality, and Cancer Mortality ($n = 74,375$), Women's Health Initiative Observational Study, 1993–2013

Decile of WBC Count, cells/ μ L	Total Mortality ($n_{\text{deaths}} = 10,510$)		CHD Mortality ($n_{\text{deaths}} = 1,265$)		Cancer Mortality ($n_{\text{deaths}} = 3,283$)	
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI
<4,100	1.05	0.94, 1.16	0.94	0.69, 1.29	1.12	0.94, 1.32
4,100–4,599	0.97	0.88, 1.08	0.81	0.59, 1.12	1.05	0.89, 1.25
4,600–4,999	0.95	0.87, 1.05	0.82	0.60, 1.10	0.97	0.82, 1.15
5,000–5,299	1.02	0.94, 1.13	0.97	0.73, 1.30	0.98	0.83, 1.15
5,300–5,699	1.00	Referent	1.00	Referent	1.00	Referent
5,700–6,099	1.03	0.94, 1.13	0.97	0.73, 1.29	1.06	0.90, 1.24
6,100–6,499	1.05	0.96, 1.16	1.27	0.98, 1.66	0.98	0.83, 1.15
6,500–7,099	1.15	1.05, 1.26	1.23	0.94, 1.61	1.03	0.87, 1.21
7,100–7,999	1.28	1.17, 1.40	1.64	1.27, 2.12	1.21	1.03, 1.42
$\geq 8,000$	1.73	1.59, 1.89	2.06	1.60, 2.65	1.35	1.15, 1.59
<i>P</i> for linear trend	<0.0001		<0.0001		0.0002	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; WBC, white blood cell.

^a Adjusted for age, smoking status (never, past, or current smoker), pack-years of smoking (continuous), alcohol intake (drinks/week), hormone therapy (yes, no), body mass index (weight (kg)/height (m)²; continuous), physical activity (MET-hours/week; continuous), educational level (less than high school graduation, high school graduation/some college, college graduation, postcollege study), race/ethnicity (white, black, or other), history of diabetes (yes, no), history of cardiovascular disease (yes, no), history of cancer (yes, no), self-reported health status ("excellent," "very good," or "good" vs. "poor" or "fair"), and comorbidity (none, any).

Table 4. Association of the Mean of Baseline and Year 3 White Blood Cell Counts With Total Mortality, Coronary Heart Disease Mortality, and Cancer Mortality After Exclusion of Women With Comorbidity and With Follow-up Starting at Year 6 ($n = 46,080$), Women's Health Initiative Observational Study, 1993–2013

Decile of WBC Count, cells/ μ L	Total Mortality ($n_{\text{deaths}} = 4,449$)		CHD Mortality ($n_{\text{deaths}} = 431$)		Cancer Mortality ($n_{\text{deaths}} = 1,445$)	
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI
<4,100	1.08	0.93, 1.24	1.31	0.80, 2.14	0.98	0.77, 1.26
4,100–4,599	0.95	0.83, 1.10	0.81	0.47, 1.39	0.99	0.78, 1.26
4,600–4,999	0.95	0.83, 1.09	1.03	0.63, 1.68	0.89	0.70, 1.13
5,000–5,299	1.03	0.90, 1.19	1.21	0.75, 1.94	1.02	0.81, 1.29
5,300–5,699	1.00	Referent	1.00	Referent	1.00	Referent
5,700–6,099	1.00	0.87, 1.15	1.17	0.72, 1.88	0.96	0.76, 1.22
6,100–6,499	1.05	0.92, 1.20	1.62	1.04, 2.53	0.96	0.76, 1.21
6,500–7,099	1.10	0.96, 1.27	1.25	0.78, 2.01	1.01	0.80, 1.29
7,100–7,999	1.21	1.05, 1.38	1.76	1.12, 2.76	1.04	0.82, 1.32
$\geq 8,000$	1.52	1.33, 1.75	2.48	1.59, 3.86	1.18	0.92, 1.50
<i>P</i> for linear trend	<0.0001		<0.0001		0.10	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; WBC, white blood cell.

^a Adjusted for age, smoking status (never, past, or current smoker), pack-years of smoking (continuous), alcohol intake (drinks/week), hormone therapy (yes, no), body mass index (weight (kg)/height (m)²; continuous), physical activity (MET-hours/week; continuous), educational level (less than high school graduation, high school graduation/some college, college graduation, postcollege study), race/ethnicity (white, black, or other), and self-reported health status ("excellent," "very good," or "good" vs. "poor" or "fair").

Table 5. Association of Baseline White Blood Cell Count With Total Mortality, Coronary Heart Disease Mortality, and Cancer Mortality, With and Without Smoking Included in the Model ($n = 160,117$), Women's Health Initiative, 1993–2013

Decile of WBC Count, cells/ μ L	Total Mortality ($n_{\text{deaths}} = 22,672$)		CHD Mortality ($n_{\text{deaths}} = 2,975$)		Cancer Mortality ($n_{\text{deaths}} = 7,459$)	
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI
Without smoking in model						
<4,100	1.01	0.94, 1.08	1.12	0.93, 1.35	1.11	0.99, 1.24
4,100–4,599	0.93	0.87, 1.00	0.78	0.63, 0.97	1.10	0.98, 1.24
4,600–4,999	0.95	0.89, 1.01	0.95	0.79, 1.15	1.04	0.93, 1.16
5,000–5,299	0.93	0.87, 0.99	0.83	0.68, 1.00	1.04	0.93, 1.16
5,300–5,699	1.00	Referent	1.00	Referent	1.00	Referent
5,700–6,099	1.04	0.98, 1.11	1.13	0.95, 1.36	1.08	0.97, 1.21
6,100–6,499	1.13	1.07, 1.20	1.16	0.97, 1.38	1.20	1.08, 1.34
6,500–7,099	1.24	1.17, 1.32	1.44	1.21, 1.71	1.30	1.16, 1.45
7,100–7,999	1.42	1.34, 1.50	1.75	1.48, 2.05	1.44	1.30, 1.60
$\geq 8,000$	1.88	1.78, 1.99	2.12	1.80, 2.49	1.90	1.71, 2.11
<i>P</i> for linear trend	<0.0001		<0.0001		<0.0001	
With smoking status and pack-years of smoking in model						
<4,100	1.07	1.01, 1.14	1.21	1.00, 1.47	1.19	1.06, 1.34
4,100–4,599	0.97	0.91, 1.05	0.83	0.67, 1.04	1.13	1.00, 1.27
4,600–4,999	0.98	0.92, 1.05	0.99	0.81, 1.20	1.08	0.96, 1.21
5,000–5,299	0.95	0.89, 1.02	0.86	0.71, 1.05	1.06	0.95, 1.19
5,300–5,699	1.00	Referent	1.00	Referent	1.00	Referent
5,700–6,099	1.03	0.96, 1.10	1.17	0.97, 1.40	1.05	0.94, 1.17
6,100–6,499	1.10	1.03, 1.17	1.18	0.99, 1.42	1.13	1.01, 1.26
6,500–7,099	1.17	1.10, 1.25	1.39	1.16, 1.67	1.18	1.05, 1.32
7,100–7,999	1.29	1.22, 1.37	1.63	1.38, 1.93	1.25	1.12, 1.39
$\geq 8,000$	1.58	1.49, 1.68	1.87	1.58, 2.22	1.45	1.30, 1.61
<i>P</i> for linear trend	<0.0001		<0.0001		<0.0001	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; WBC, white blood cell.

^a Adjusted for age, alcohol intake (drinks/week), hormone therapy (yes, no), body mass index (weight (kg)/height (m)²; continuous), physical activity (MET-hours/week; continuous), educational level (less than high school graduation, high school graduation/some college, college graduation, postcollege study), race/ethnicity (white, black, or other), self-reported health status ("excellent," "very good," or "good" vs. "poor" or "fair"), comorbidity (none, any), and allocation to the observational study or the intervention or control arm of the clinical trial.

(SD, 12,500); 20–<40 pack-years: 6,600 cells/ μ L (SD, 10,500); ≥ 40 pack-years: 7,100 cells/ μ L (SD, 15,300)). In models excluding smoking status and pack-years, the hazard ratios for the association of the highest decile of WBC count with total mortality, CHD mortality, and cancer mortality were 1.88 (95% CI: 1.78, 1.99), 2.12 (95% CI: 1.80, 2.49), and 1.90 (95% CI: 1.71, 2.11), respectively (Table 5). When smoking status and pack-years were included in the models, the corresponding hazard ratios for the highest decile of WBC count were 1.58 (95% CI: 1.49, 1.68), 1.87 (95% CI: 1.58, 2.22), and 1.45 (95% CI: 1.30, 1.61), respectively. For all 3 outcomes, the coefficient for pack-years was highly significant, and the hazard ratio for being a current smoker was 1.9–2.1 and highly significant, while that for being an ex-smoker was weaker (Table 6).

DISCUSSION

In this large cohort study of postmenopausal women, high WBC count showed robust associations with total mortality and CHD mortality and a weaker association with cancer mortality. Both baseline WBC count and the mean of baseline + year 3 WBC count showed similar results for total mortality and CHD mortality, which were not affected by exclusion of women with comorbidity reported at baseline or by exclusion of the early years of follow-up. Associations with cancer mortality were less consistent and weaker. Both WBC count and smoking habits showed strong, independent associations with mortality.

Our results showing that elevated WBC count within the normal range is associated with increased risks of total and

Table 6. Associations of Smoking Status and Pack-Years of Smoking With Total Mortality, Coronary Heart Disease Mortality, and Cancer Mortality, Adjusted for White Blood Cell Count ($n = 160,117$), Women's Health Initiative, 1993–2013

	Total Mortality ($n_{\text{deaths}} = 22,672$)		CHD Mortality ($n_{\text{deaths}} = 2,975$)		Cancer Mortality ($n_{\text{deaths}} = 7,459$)	
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI
Smoking status						
Never smoker	1.00	Referent	1.00	Referent	1.00	Referent
Current smoker	1.88	1.78, 1.98	2.06	1.78, 2.38	2.02	1.85, 2.20
Former smoker	1.04	1.01, 1.08	1.07	0.98, 1.18	1.08	1.02, 1.15
Pack-years of smoking (continuous)	1.01	1.01, 1.01	1.01	1.01, 1.01	1.01	1.01, 1.02
<i>P</i> for trend	<0.0001		<0.0001		<0.0001	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task.

^a Adjusted for age, decile of white blood cell count, alcohol intake (drinks/week), hormone therapy (yes, no), body mass index (weight (kg)/height (m)²; continuous), physical activity (MET-hours/week; continuous), educational level (less than high school graduation, high school graduation/some college, college graduation, postcollege study), race/ethnicity (white, black, or other), self-reported health status ("excellent," "very good," or "good" vs. "poor" or "fair"), comorbidity (none, any), and allocation to the observational study or the intervention or control arm of the clinical trial.

CHD mortality are in agreement with those of most previous studies (5, 6). The sensitivity analyses in which women with chronic disease at baseline and the early years of follow-up were excluded suggested that the observed association was not due to preexisting disease. Based on the analysis of mean WBC count excluding women with comorbidity as well as the first 6 years of follow-up, there was a clear indication of increased risk of total and CHD mortality at WBC counts greater than 6,500 cells/ μL , which is in agreement with the results of a number of prior studies (9, 11, 13–17, 27).

Studies examining the association of WBC count with cancer mortality have yielded inconsistent results. In the high-risk population in the Multiple Risk Factor Intervention Trial (MRFIT), Grimm et al. (8) found that WBC count was positively associated with risk of cancer death. Similarly, Erlinger et al. (28) reported that WBC count was associated with total cancer mortality among participants in the Second National Health and Nutrition Examination Survey (NHANES II). However, in a large cohort of South Koreans, Jee et al. (12) found no suggestion of an association of leukocyte count with cancer mortality in men or women. Compared with the association with total mortality and CHD mortality, we found a generally weaker association of WBC count with cancer death.

WBC count is elevated in current smokers (8, 16, 26) and is positively associated with intensity of smoking (7, 26). In our analysis, when the association of WBC count with all 3 outcomes was adjusted for smoking status and pack-years of smoking, the hazard ratio was reduced by 20%–30% but continued to show a robust association. Current smoking and pack-years remained highly significant in the presence of WBC count, suggesting that, although they were correlated, both factors make independent contributions to mortality risk.

The fact that WBC count is a nonspecific marker of systemic inflammation in response to infection and toxic irritants

may account for its association with multiple outcomes in which inflammation is hypothesized to play a central role, including CHD and cancer (12). One mechanism proposed to explain the association of WBC count with CHD and atherosclerosis is that high triglyceride levels may activate leukocytes to produce free radicals (29, 30). In addition, leukocytes influence blood rheology and adhesive properties, and they may promote endothelial injury by adhering to the endothelium and damaging it with reactive oxygen compounds and proteolytic enzymes (31). Other possible mechanisms underlying the association of WBC count and WBC differentials with total mortality and cause-specific mortality require elucidation (16).

Strengths of the present study include the large size of the WHI cohort and the availability of information on comorbidity and on a wide range of lifestyle factors. A particular strength was the availability of measurements of WBC count taken at 2 points in time, 3 years apart, on women in the observational study (58% of participants). Only a few studies have had more than 1 measurement of WBC count (8, 10, 14, 15), and other investigators have recognized this as a limitation (12, 14). In general, similar results were observed in analyses using the single baseline measurement and using the mean of the baseline and year 3 measurements, adding to the credibility of the results. However, when women with comorbidity were excluded from the analysis of mean WBC count, the association with cancer mortality was attenuated and no longer significant (Table 4). This suggests that in some cases, a second measurement may improve the reliability of the WBC count measurement. Finally, we conducted a number of secondary analyses, adjusting for hemoglobin and platelet count and excluding women taking aspirin, NSAIDs, antibiotics, or medications that can affect WBC count from the total cohort and adjusting for baseline CRP, triglycerides, and total cholesterol in a subgroup.

Our study had several limitations. First, the number of CHD deaths was limited, and the numbers of blacks and Hispanics were too small to permit more detailed analyses in these groups. Second, information on WBC differentials (neutrophils, monocytes, and eosinophils) was not available. Third, most covariates used in the analysis of mean WBC count were measured at baseline, and this may have introduced some degree of misclassification and residual confounding. Finally, our results were limited to postmenopausal women, and therefore may not apply to younger women or to men.

In conclusion, in this large cohort of postmenopausal women, increased WBC count showed a graded positive association with total mortality and CHD mortality and a weaker association with cancer mortality. Our data provide convincing evidence that high WBC counts are associated with increased all-cause and CHD mortality in otherwise healthy postmenopausal women, and that the association is independent of the effects of smoking. The clinical utility of WBC count for risk prediction warrants further study.

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G.C.K. had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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