

# WBC Count and the Risk of Cancer Mortality in a National Sample of U.S. Adults: Results from the Second National Health and Nutrition Examination Survey Mortality Study

Thomas P. Erlinger,<sup>1,2</sup> Paul Muntner,<sup>3</sup> and Kathy J. Helzlsouer<sup>1,2</sup>

<sup>1</sup>Department of Medicine, the Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>2</sup>Department of Epidemiology, the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and <sup>3</sup>Tulane University School of Public Health, New Orleans, Louisiana

## Abstract

Inflammation has been shown to be a risk factor for several chronic diseases. Few epidemiologic studies have examined the relationship between markers of inflammation and cancer. The current study included 7,674 Second National Health and Nutrition Examination Survey (NHANES II) participants, 30 to 74 years of age, between 1976 and 1980. Mortality follow-up through December 31, 1992 was assessed using the National Death Index and Social Security Administration Death Master File. A graded association between higher WBC and higher risk of total cancer mortality was observed [highest versus lowest quartile (relative risk [RR] 2.23; 95% confidence interval [CI], 1.53-3.23)] after adjusting for age, sex, and race. After further adjustment for smoking, physical activity, body mass index, alcohol intake, education, hematocrit, and

diabetes, WBC remained significantly associated ( $P$  trend = 0.03) with total cancer mortality [highest versus lowest quartile (RR 1.66; 95% CI, 1.08-2.56)]. In stratified analyses, increased WBC was associated with higher risk of non-lung cancer ( $P$  trend = 0.04), but not lung cancer ( $P$  trend = 0.18). Among never smokers, a 1 SD increase in WBC ( $2.2 \times 10^9$  cells/L) was associated with greater risk of total (RR 1.32; 95% CI, 1.05-1.67) and non-lung (RR 1.30; 95% CI, 1.03-1.63) cancer mortality. These findings support the hypothesis that inflammation is an independent risk factor for cancer mortality. Additional studies are needed to determine whether circulating levels of inflammatory markers are associated with increased risk of incident cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(6):1052-6)

## Introduction

Chronic inflammation has been hypothesized to play a role in the pathogenesis of several cancers (1). Numerous examples exist that suggest an association between chronic inflammation and the development of cancer. For example, cigarette smoking, which is associated with elevated levels of inflammatory markers (2), is a well-known risk factor for several cancers, most notably, lung cancer (3). In addition, numerous infectious agents (e.g., hepatitis viruses B and C, herpes virus, Epstein-Barr virus, human papilloma virus, and HIV) have been associated with an increased risk of a variety of malignancies (4). Finally, patients with chronic inflammatory bowel disease, particularly ulcerative colitis, are known to have a significantly higher risk of developing colorectal cancers (5).

Few epidemiologic studies have examined the association between markers of inflammation and the risk of cancer. In one large prospective study, persons with WBC counts in the highest quartile had a 30% increased risk of developing cancer and 40% increased risk of dying from cancer compared with persons in the lowest

quartile (6). However, the association was strongest for smoking-related cancers and was not significant in persons who never smoked, suggesting that WBC count was primarily reflecting the risk associated with smoking (7, 8).

WBC count is a nonspecific marker of inflammation that is often increased during acute or chronic infections and is known to be chronically elevated in smokers compared with nonsmokers (9). Several prospective studies have shown that elevations in WBC count within the clinically normal range are associated with increased risk of several chronic diseases, including cardiovascular disease (10) and diabetes (11). These findings suggest that elevations in WBC within the clinically normal range reasonably reflect nonspecific chronic inflammation.

In this study, we hypothesized that inflammation, as reflected by elevated WBC, would be associated with increased risk of cancer mortality in a national sample of U.S. adults. We additionally hypothesized that this association would be independent of smoking.

## Subjects and Methods

**Study Population.** The Second National Health and Nutrition Examination Survey (NHANES II) was conducted from 1976 to 1980. Participants were selected using a stratified multistage probability sampling design with certain subpopulations purposely oversampled. As

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**Requests for reprints:** Thomas P. Erlinger, Johns Hopkins Medical Institutions, The Welch Center for Prevention, Epidemiology and Clinical Research, 2024 E. Monument Avenue, Suite 2-602, Baltimore, MD 21201. Phone: (410) 614-6466; Fax: (410) 955-0476. E-mail: terlinge@jhmi.edu

described elsewhere, interview and examination data were collected from 14,407 NHANES II participants 17 to 74 years of age (response rate: 73%; ref. 12). The current analyses were limited to the 9,250 participants ages 30 to 74 years whose vital status as of December 31, 1992 was determined in the NHANES II Mortality Study. Additionally, persons who had a self-reported history of cancer were excluded ( $n = 465$ ). Because WBC has been shown to be elevated in persons with cardiovascular disease (13) and predicts cardiovascular events, persons with cardiovascular disease ( $n = 760$ ) at baseline were also excluded to eliminate a major source of competing mortality. Additionally, persons missing any covariate information were excluded from this study ( $n = 246$ ). Because of concerns that subclinical cancer may affect WBC count, we excluded persons with less than 2 years of follow-up ( $n = 163$ ) and/or who developed cancer within 2 years of follow-up ( $n = 55$ ). After these exclusions, 7,674 participants were included in the analyses.

**Measurements.** Venipuncture blood collection occurred during each participant's visit to the mobile examination center and blood was processed and shipped to the CDC for measurement following a standardized protocol. WBC count was done on a Coulter Counter (model FN). Hematocrit measurements were done by the spun microhematocrit method.

In addition to demographic information, aspirin usage (frequency and amount), alcohol consumption, highest grade of education completed, current and former smoking status, and physical inactivity were assessed from self-reported information. Physical inactivity was defined as little or no recreational exercise. Heavy alcohol consumption was defined as consuming 14 or more alcoholic beverages per week. Two blood pressure measurements were obtained by a specially trained physician using a mercury sphygmomanometer. Body mass index (BMI) was calculated as the ratio of weight (kilograms) divided by height (meters) squared ( $\text{kg}/\text{m}^2$ ). Diabetes was defined as a self-reported history of the disorder or a fasting plasma glucose level  $\geq 126$  mg/dL.

**Mortality Assessment.** Vital status as of December 31, 1992 was assessed for all NHANES II participants, 30 to 74 years of age at the baseline examination, using the National Death Index and the Social Security Administration Death Master File as described elsewhere (14). The sensitivity of and specificity of cause-specific outcome assessment using the National Death Index with the same variables but different matching criteria has been estimated to be 87% to 97% and 99% (15-18), respectively. The sensitivity of matching to the Social Security Administration has been estimated to be 70% (14). The following cause-specific mortality definitions (International Classification of Diseases Code 9) were used in our analyses: all cancer (140 to 208), lung cancer (162 to 162.9), and non-lung cancer (140 to 208 excluding 162 to 162.9).

**Statistical Methods.** Categorization of WBC into quartiles was based on the distribution of WBC count among the total population of adults ages 30 to 74 at baseline. Mortality rates and relative hazards were calculated by attained participant age (19). Because cancer mortality was disproportionately high after age

85 years and few participants contributed person-time experience in this age category, all analyses were truncated at this age. Crude cumulative mortality rates were calculated and cumulative mortality curves were plotted, according to quartile of WBC. Because the calculation of cumulative mortality is sensitive to small sample sizes, assessment of cumulative mortality was limited to participants 45 to 85 years of age during follow-up. Cox proportional hazards regression was used to determine the adjusted relative risks (RR) and 95% confidence intervals (95% CI) of mortality from cancer, lung cancer, and non-lung cancer associated with quartile of WBC after adjustment for age, race, and sex and additional adjustment for baseline systolic blood pressure, cholesterol level, diabetes mellitus, BMI, education, and physical inactivity. Cox models with quartile of WBC as a continuous variable were used to assess the trends in risk.

Consistency of the associations were assessed by subgroup analysis using categories of smoking status: current, former, and never smokers. To achieve added statistical power, WBC was modeled as a continuous variable for the subgroup analyses. Relative hazards for the continuous models represent a 1 SD higher WBC ( $2.2 \times 10^9$  cells/L).

In secondary analyses, we included interaction terms for WBC and gender, as well as WBC and race. In addition, we did site-specific analyses for colon (International Classification of Diseases codes : 153 to 153.9), breast (International Classification of Diseases codes : 174 to 174.9), and prostate (International Classification of Diseases codes : 185 to 185.9) cancers. All analyses were conducted using Stata 6.0 (STATA Corp., College Station, Texas) and Coxreg, a program developed by the National Cancer Institute for analysis of weighted time-to-event data from multi-stage complex sample surveys.

## Results

Table 1 shows characteristics of the study population according to quartiles of WBC count. WBC tended to be higher in males and lower in African-Americans. In addition, current smoking, increased BMI, physical inactivity, diabetes, and lower education were associated with higher WBC. Heavy alcohol consumption was not associated with WBC count, whereas aspirin use was weakly positively associated with WBC count. Finally, hematocrit levels were positively associated with WBC count.

There were 410 deaths from all cancer causes, including 119 from lung cancer and 291 from non-lung cancers. Cumulative mortality from all cancer, lung cancer, and non-lung cancer by quartile of WBC count is shown in Fig. 1. Persons in the highest quartile of WBC count had significantly higher risk of mortality from all cancer ( $P < 0.001$ ), lung cancer ( $P < 0.001$ ), and non-lung cancer ( $P = 0.02$ ). Table 2 shows adjusted RR of cancer mortality. After adjusting for age, race, and sex, the risk of all cancer mortality remained significantly higher among persons with higher WBC count (RR Q4 versus Q1: 2.23; 95% CI, 1.53-3.23;  $P < 0.001$ ). The higher risk associated with increased WBC was also seen for both lung (RR Q4 versus Q1: 4.14; 95% CI, 2.08-8.22;  $P < 0.001$ )

**Table 1. Characteristics of population by quartile of WBC count**

Characteristic	Q1 ( $\leq 5.7$ ) <i>N</i> = 2,061	Q2 (5.8-6.8) <i>N</i> = 1,829	Q3 (6.9-8.2) <i>N</i> = 1,922	Q4 ( $\geq 8.3$ ) <i>N</i> = 1,862	<i>P</i> trend
WBC quartile (range, $1 \times 10^9$ cells/L)					
Age, years	48.5	48.9	48.5	47.2	0.007
Black race, %	16.0	10.3	7.5	5.2	<0.001
Male sex, %	42.2	46.0	47.5	53.8	<0.001
Smoking					
Never, %	53.5	44.3	34.1	22.9	<0.001
Current, %	17.4	26.8	41.1	60.1	<0.001
Former, %	29.1	28.8	24.8	17.0	<0.001
Diabetes, %	3.0	4.9	4.9	5.1	0.005
Finished HS, %	67.5	65.5	62.3	62.8	0.005
BMI, kg/m <sup>2</sup>	25.2	26.0	26.0	26.4	<0.001
Aspirin use, %*	27.2	26.3	27.2	30.1	0.04
Heavy drinker, %†	3.6	3.3	2.8	3.7	0.93
Hematocrit, %	40.9	41.5	42.1	43.4	<0.001
Physical inactivity, %	35.6	39.6	39.7	40.6	0.03

\*Use aspirin weekly.

† $\geq 3$  alcoholic beverages per day.

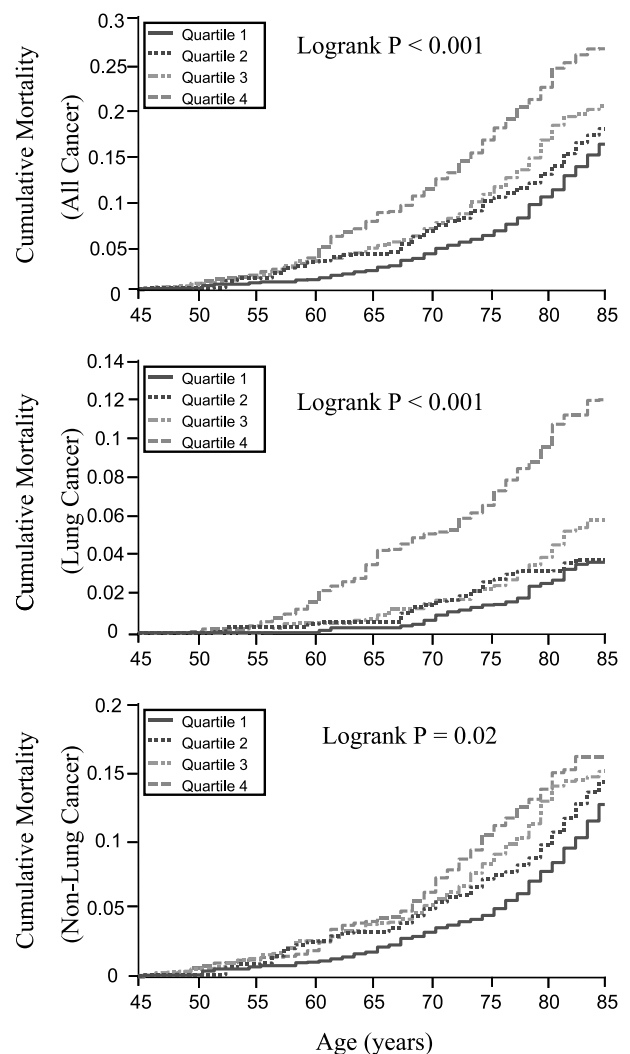
and non-lung (RR Q4 versus Q1: 1.67; 95% CI, 1.08-2.56;  $P = 0.02$ ) cancers. Tests for linear trend across quartiles of WBC were significant for total ( $P < 0.001$ ), lung ( $P < 0.001$ ), and non-lung cancers ( $P = 0.02$ ). After adjusting for smoking and additional potential confounders, the association between WBC count and cancer mortality remained significant for total and non-lung cancers ( $P$  trend = 0.03 and 0.04, respectively). For lung cancer, the risk of mortality with higher WBC did not reach significance ( $P$  trend = 0.18).

To more fully examine the relationship between WBC count, smoking, and cancer mortality, we performed stratified analyses according to smoking status. As shown in Table 3, among persons who reported never smoking, there was an increased risk of total and non-lung cancer mortality associated with increasing WBC. For each SD increase in WBC, never smokers had a 32% higher risk of total cancer mortality (RR 1.32; 95% CI, 1.05-1.67) and a 30% higher risk of mortality from non-lung cancers (RR 1.30; 95% CI, 1.03-1.63). Among current smokers, each 1 SD higher baseline WBC was associated with a 36% higher risk of non-lung cancer (RR 1.36; 95% CI, 1.02-1.82). Among former smokers, higher WBC was associated with an increased risk of mortality from all cancers and lung cancer (RR 1.36; 95% CI, 1.15-1.62 and RR 1.83; 95% CI, 1.04-3.24, respectively).

No significant interactions were present between WBC count and gender or race, and risk of total, lung, or non-lung cancer mortality. In site-specific analyses (Table 4), no significant association was found between WBC and subsequent risk of mortality from colon ( $n = 45$ ), prostate ( $n = 28$ ), or breast cancer ( $n = 33$ ). However, the number of cases included in site-specific analyses were small and, hence, there was limited power to detect modest associations.

## Discussion

In this study, a positive independent association was present between WBC count and cancer mortality in a nationally representative cohort of adults. In the current study, we observed a positive and graded association



**Figure 1.** Cumulative all, lung, and non-lung cancer mortality for 7,674 NHANES II study participants during 16 years of follow-up by quartile of WBC.

**Table 2. Risk of cancer mortality by quartile of WBC count**

Outcome	WBC quartile (range, $1 \times 10^9$ cells/L)				P trend
	Q1 ( $\leq 5.7$ )	Q2 (5.8-6.8)	Q3 (6.9-8.2)	Q4 ( $\geq 8.3$ )	
Number at risk, N	2061	1829	1922	1862	
All cancer, n	84	89	113	124	
Mortality rate per 100,000	23.4	31.0	39.5	45.9	
Age, race, sex adjusted	1.00	1.28 (0.94-1.76)	1.70 (1.17-2.47)	2.23 (1.53-3.23)	<0.001
Full adjustment*	1.00	1.20 (0.87-1.64)	1.43 (0.99-2.08)	1.66 (1.08-2.56)	0.03
Lung cancer, n	20	21	28	50	
Mortality rate per 100,000	4.9	9.1	10.5	20.0	
Age, race, sex adjusted	1.00	1.65 (1.27-2.14)	1.97 (0.85-4.59)	4.14 (2.08-8.22)	<0.001
Full adjustment*	1.00	1.34 (0.73-2.45)	1.16 (0.50-2.70)	1.79 (0.88-3.62)	0.18
Non-lung cancer, n	64	68	85	74	291
Mortality rate per 100,000	18.5	22.0	29.0	26.0	<0.001
Age, race, sex adjusted	1.00	1.19 (0.77-1.83)	1.63 (1.12-2.37)	1.67 (1.08-2.56)	0.02
Full adjustment*	1.00	1.15 (0.72-1.84)	1.55 (1.07-2.25)	1.54 (0.94-2.50)	0.04

\*Further adjusted for blood pressure, heavy alcohol consumption, diabetes, education, BMI, hematocrit, current and former smoking, any and weekly aspirin use, and physical activity.

between WBC count and total and non-lung cancer mortality. No statistically significant associations were found between WBC count and mortality from any site-specific cancer. However, we had limited power to detect associations between WBC count and site-specific cancer mortality. Because smoking is a known risk factor for cancer and is associated with higher levels of inflammatory markers (20), our finding that WBC is associated with cancer mortality among never, current, and former smokers suggests that inflammation may be a risk factor for cancer mortality independent of smoking status.

Inflammation has been hypothesized to be a risk factor for several cancers (1). However, few prospective studies have examined the link between markers of inflammation and cancer risk. Consistent with our findings, two previous prospective studies have found an association between WBC count and cancer mortality (21, 22). Whether or not WBC count reflects the risk associated with smoking is not clear. In one study, the association between WBC and cancer was observed in smokers (21). By contrast, in a study by Grimm et al. (22), WBC was associated with cancer mortality after adjusting for smoking and serum thiocyanate levels. Among three large cohorts in Britain and the U.S., Phillips et al. (23) found a positive association between leukocyte count and lung cancer in men after adjusting for the number of cigarettes smoked per day. In the current study, WBC was associated with cancer mortality after adjusting for smoking and in never smokers, suggesting that the risk of cancer mortality associated with leukocyte count is not fully explained by smoking. In Table 2, we demonstrate a very strong association between WBC and lung cancer

mortality after adjusting for age, race, and sex. However, when we adjust for smoking and other potential confounders, the association for lung cancer is attenuated. Rather than suggesting that inflammation is not important in the pathophysiology of lung cancer, it might suggest that inflammation is in the causal pathway of smoking and lung cancer mortality. However, this does not discount possible direct effects of smoking on risk of mortality from lung cancer.

In addition to WBC count, several studies have examined the association between cancer risk and markers of inflammation using acute phase proteins with mixed results. A recent nested case-control study found no association between C-reactive protein levels and subsequent risk of cancer, predominantly breast cancer, in women (24). However, this study had a brief duration of follow-up (mean of 58 months) and did not account for menopausal status or hormone use. Still other studies have found a positive association between fibrinogen and cancer mortality (25), and an inverse association between serum albumin (a negative acute phase protein) and risk of colon cancer (26).

Several lines of evidence support a link between inflammation and cancer risk. Indirect evidence that chronic inflammation may play a role in carcinogenesis comes from data implicating infectious agents in the etiology of site-specific cancers (e.g., hepatitis, human papilloma virus, Epstein-Barr virus). In addition, several non-infectious chronic inflammatory conditions also increase the risk of cancer (e.g., inflammatory bowel disease, prostatitis; ref. 23). Smoking, a well-known carcinogen, increases several markers of inflammation,

**Table 3. Adjusted standardized relative risk of cancer mortality for WBC by smoking status**

	All cancer N = 410	Lung cancer N = 119	Non-lung cancer N = 291
Total population	1.27 (1.09-1.48)	1.18 (0.90-1.55)	1.29 (1.10-1.51)
Current smokers	1.20 (0.95-1.52)	1.04 (0.77-1.40)	1.36 (1.02-1.82)
Former smokers	1.36 (1.15-1.62)	1.83 (1.04-3.24)	1.22 (0.91-1.64)
Never smokers	1.32 (1.05-1.67)	NA	1.30 (1.03-1.63)

NOTE: Adjusted for age, race, sex, blood pressure, heavy alcohol consumption, diabetes, education, BMI, hematocrit, any and weekly aspirin use, and physical activity.

Abbreviation: N/A, not enough data for model to converge.

**Table 4. Adjusted standardized relative risk of site-specific cancer mortality for WBC**

Cancer type	Standardized relative risk (95% CI) (per 1 SD increase in WBC)
Colon (N = 45)	0.87 (0.61-1.25)
Breast (N = 33)	0.87 (0.61-1.25)
Prostate (N = 28)	1.65 (0.86-3.15)

NOTE: Adjusted for age, race, sex, blood pressure, heavy alcohol consumption, diabetes, education, BMI, hematocrit, any and weekly aspirin use, and physical activity.

including WBC (20). While smoking may have direct carcinogenic effects, it is also conceivable that the general inflammatory response induced by smoking could increase risk of cancers. More directly, *in vitro* studies have implicated several inflammatory constituents in carcinogenesis (1). Finally, anti-inflammatory medications seem to reduce the risk of developing some types of cancer, notably colon cancer (27, 28). Whether anti-inflammatory medications could reduce the risk of other cancers is not known, but evidence from several observational studies suggest a protective association (29, 30).

This study has several important strengths. These data are from a large nationally representative cohort and, thus, our findings can be generalized to the U.S. population. In addition, there was a relatively long length of follow-up and we were able to exclude cases developing in the first 2 years of follow-up, thereby reducing the likelihood that subclinical cancer at baseline explains our findings. Several potential limitations to the current study also deserve consideration. Only one measurement of the exposure (WBC) was available. Hence, we cannot determine whether an acute episode of inflammation or prolonged low-grade inflammation was responsible for the associations observed. It was not possible to determine the cause of increased WBC from data collected in the current study. However, the effect of this nonspecificity, if anything, would be that our RR is an underestimate of the true association between WBC and cancer mortality. Due to the small numbers of site-specific cases, we were likely underpowered to examine the association between WBC and colon, breast, or prostate cancers. The lack of an association between WBC and these cancers should, therefore, not be taken as evidence that a modest association does not exist. Finally, in the current study, we were unable to examine associations with incident cancer, an outcome that could be more relevant to the pathophysiology of cancer.

In summary, our findings suggest that inflammation may be an independent risk factor for cancer mortality. Additional studies are needed to confirm these results and determine the risk of incident site-specific cancers associated with inflammation. Such findings could help to identify novel risk factors for cancer risk and potential targets for prevention and treatment.

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