Association Between Circulating White Blood Cell Count and Cancer Mortality

A Population-Based Cohort Study

Anoop Shankar, MD, PhD; Jie Jin Wang, PhD; Elena Rochtchina, MSc; Mimi C. Yu, PhD; Richard Kefford, MD; Paul Mitchell, MD, PhD

Background: Inflammatory processes are implicated in the development and progression of cancer. However, it is not clear whether systemic markers of inflammation predict cancer. We examined the prospective relationship between circulating white blood cell (WBC) count and cancer mortality.

Methods: Population-based cohort study of 3189 individuals, aged 49 to 84 years and free of cancer at the baseline examination (January 1, 1992, to December 31, 1994), in the Blue Mountains region, west of Sydney, Australia. The main outcome of interest was all cancer mortality ascertained from vital status as of December 31, 2001.

Results: Higher WBC count was found to be associated with all cancer mortality. In proportional hazards models adjusting for age, sex, education, body mass index, hematocrit level, alcohol consumption, physical inactivity, smoking, weekly aspirin use, diabetes mellitus or fasting hyperglycemia status, and fasting glucose levels, the multivariable relative risk of all cancer mortality comparing quartile 4 of WBC count (≥7400 cells/µL) with quartile 1 (≤5300 cells/µL) was 1.73 (95% confidence interval [CI], 1.18-2.55). In subgroup analyses, the relative risk of cancer mortality comparing quartile 4 of WBC count with quartile 1 was higher among those with diabetes or fasting hyperglycemia (3.03 [95% CI, 1.01-9.15]) than among those with normoglycemia (1.68 [95% CI, 1.12-2.52]). Also, the relative risk of cancer mortality associated with joint exposure to quartile 4 of WBC count and aspirin nonuse was 2.42 (95% CI, 1.46-4.01) compared with their absence.

Conclusion: These data provide new epidemiological evidence of an association between circulating WBC count, a widely available marker of inflammation, and subsequent cancer mortality.

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Inflammation has been hypothesized to be related to several cancers. However, few prospective studies have examined the putative association between systemic markers of inflammation and incident cancer. Two recent nested case-control studies examined the relationship between C-reactive protein level and colon cancer, but yielded inconsistent results. In contrast, Erlinger et al recently examined the association between an elevated white blood cell (WBC) count and total cancer mortality in the second US National Health and Nutritional Examination Survey mortality study and reported a statistically significant, dose-dependent association, even after adjusting for smoking. However, these studies failed to address the possible confounding effect of diabetes mellitus and hyperglycemia, because an elevated WBC count and other inflammatory markers have been found to be related to diabetes, and diabetes and hyperglycemia have been found to be related to several cancers. Previous studies also reported a protective association between aspirin and other anti-inflammatory medications and several cancers. It is not clear whether aspirin intake modifies the relationship between WBC count and cancer.

In this report, we examined the association between WBC count and all cancer mortality in an older Australian population, after adjusting for diabetes or fasting hyperglycemia status, aspirin intake, smoking, and other confounding variables.

Methods

Study Population

The Blue Mountains Eye Study is a population-based cohort study of age-related eye diseases and other health outcomes in an urban Australian population. Study details were described previously. After a door-to-door cen-
sus of residents living in 2 postal codes in the Blue Mountains region, west of Sydney, Australia, persons born before January 1, 1943, were invited to attend a detailed examination at a local hospital. Baseline examination was performed on 3654 (82.4%) of 4433 eligible persons between January 1, 1992, and December 31, 1994. Of this cohort, 98% was white, reflecting the community studied. This study followed the recommendations of the Declaration of Helsinki and was approved by the Western Sydney Area Human Ethics Committee. Written, informed consent was obtained from all participants.

The present study included 3189 cancer-free individuals at baseline, after excluding those with self-reported cancer (n = 223), with missing WBC count and covariate information (n = 438), and with a WBC count less than 200 cells/µL or greater than 1200 cells/µL (n = 38) (not mutually exclusive categories).

EXPOSURE MEASUREMENT

The baseline examination included measurement of weight, height, pulse rate, and systolic and diastolic blood pressures by a trained observer who administered a standardized questionnaire that collected information regarding participants’ demographic characteristics, cigarette smoking, alcohol intake, physical activity, medical history, and medications taken, including aspirin. Fasting blood specimens were drawn from 3222 participants (88.2%), centrifuged on-site, and then sent by courier within the same day to the Westmead Hospital, Sydney, for hematological analysis and clinical biochemistry assessment. The WBC count was determined using a Coulter counter method. Reliability coefficients, based on blind replicate control data, ranged from 0.96 to 1.00. Hematocrit and fasting plasma glucose levels were measured by spin microhematocrit and hexokinase methods, respectively.

Age was defined as the age at the baseline examination. Education was categorized into beyond high school, high school, and less than high school. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Diabetes status was categorized using the following criteria of the American Diabetes Association: diabetes (diagnosis of diabetes by a physician and use of diabetic medications or fasting glucose levels of at least 126 mg/dL [7.0 mmol/L]), fasting hyperglycemia (fasting glucose levels of ≥110 mg/dL [≥6.1 mmol/L] but <126 mg/dL [≤7.0 mmol/L]), and normoglycemia (fasting glucose levels <110 mg/dL [<6.1 mmol/L]). Cigarette smoking was categorized into current (current smoker or had given up smoking <12 months before the study examination), former (answered positively to “Have you ever smoked regularly before?” and had given up smoking ≥12 months before the study examination), and never. Alcohol intake was categorized into heavy (≥3 drinks/d), moderate (<3 drinks/d), and never. Physical inactivity (yes or no) was categorized as answering negatively to “Have you participated in any recreational exercise/walk in the last 2 weeks?” Weekly aspirin intake was categorized into 3 times/wk or more and less than 3 times/wk (including none) by combining information on aspirin intake frequency in the questionnaire to get an adequate sample size in each category.

MORTALITY ASSESSMENT

Vital status as of December 31, 2001, was assessed for all baseline participants by matching demographic data to the Australian National Death Index data set. We used a probabilistic linkage package, adopting a multiple-pass procedure in which both data sets were grouped on the basis of different characteristics (eg, date of birth, surname and first name, and sex) each time. Matches were divided into exact and nonexact. All nonexact matched records were examined manually and accepted if there was only 1 nonexact matched characteristic that was noncritical. Information provided by family members during follow-up was also included if the participant was reported to have died on or before December 31, 2001. The sensitivity and specificity of the Australian National Death Index data have been estimated to be 93.7% and 100.0%, respectively, for all deaths, and 95.2% and 99.2%, respectively, for deaths due to cancer. Use of multiple unique identifiers as in our study can improve the sensitivity. The following cause-specific mortality codes from the International Classification of Diseases, Ninth Revision (ICD-9), were used in our analyses: all cancer (codes 140-208), lung cancer (codes 162-162.9), and nonlung cancer (codes 140-208, excluding 162-162.9).

STATISTICAL ANALYSIS

We categorized baseline WBC count into quartiles. We also analyzed WBC count as a continuous variable (per 1-SD increase). The main study outcome was all cancer deaths. Because smoking is related to lung cancer and higher WBC count, we performed subgroup analyses stratified by lung and nonlung cancer. We used proportional hazards models to estimate the relative risk (RR) of cancer mortality, controlling simultaneously for potential confounders. We constructed 3 models. Model 1 adjusted for age (in years) and sex. Model 2 additionally adjusted for education, body mass index, hematocrit level, alcohol consumption, physical inactivity, smoking status, weekly aspirin use, and diabetes or fasting hyperglycemia status (present or absent). Model 3 additionally adjusted for fasting glucose levels because increasing fasting glucose levels among those without diabetes have been shown to be related to cancer. We used proportional hazards models with WBC count quartiles as ordered categories scaled to the median for each quartile to assess trend in risk. To examine the consistency of the association between WBC count and cancer mortality, we performed analyses within subgroups of selected variables, including smoking status, alcohol intake, diabetes status, and aspirin intake. We examined the joint exposure effects of (1) WBC count (quartile 4 or quartiles 1-3) and diabetes status and (2) WBC count (quartile 4 or quartiles 1-3) and the aspirin intake categories by stratifying the cohort into 4 corresponding groups in each case. We used cross-product interaction terms to examine effect modification. All analyses used SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

Table 1 shows the characteristics of the study population by WBC count quartiles. Individuals with higher WBC counts were more likely to be male; to be current smokers; to have diabetes, higher fasting glucose levels, or higher hematocrit levels; to use aspirin; and to be physically inactive.

There were 212 deaths due to all cancers, including 22 due to lung cancer and 190 due to nonlung cancer. Table 2 presents the RR of cancer mortality by quartile of WBC count for all deaths due to cancer and separately for those due to lung and nonlung cancers. In general, increasing quartiles of WBC count were associated with increasing RRs of cancer mortality. Compared with the age- and sex-adjusted model, RRs in the multivariable-adjusted model 2 were attenuated. Additional adjustment for fasting glucose levels in the multivariable-
Adjusted model 3 further attenuated the RR. Models of trend were statistically significant (P < .05 for trend) for all cancer and nonlung cancer mortality as the outcomes; the P value for trend for the models analyzing the 22 deaths due to lung cancer failed to reach statistical significance (P = .06 to P = .09). The association between WBC count and cancer mortality appeared stronger for deaths due to lung cancer than for those due to nonlung cancer.

In Table 3, we examined the association between the highest vs the lowest quartile of WBC count and cancer mortality within subgroups of several related variables,
including smoking status, alcohol intake, diabetes status, and aspirin intake. Because of the limited number of cancer outcomes, RR estimates failed to reach statistical significance (α=.05) in certain subgroups. Overall, WBC count was positively associated with cancer mortality within these subgroups; the multivariable RRs ranged from 1.22 to 3.05 for all deaths due to cancer, lung cancer, and nonlung cancer. The association between WBC count and all cancer mortality was stronger among those with diabetes or fasting hyperglycemia and slightly weaker among those using aspirin at least 3 times/wk at baseline.

We were further interested in the role of diabetes or fasting hyperglycemia and aspirin intake in the relationship between WBC count and cancer mortality. Diabetes and fasting hyperglycemia was associated with cancer mortality in our cohort (Table 4). Joint exposure to diabetes and the highest WBC count quartile was associated with a higher RR of cancer mortality than the effect of either alone. Individuals with diabetes and WBC count in the highest quartile had a multivariable RR of 2.26 for all deaths due to cancer compared with normoglycemic individuals in the lower WBC count quartiles (P=.08 for interaction).

Aspirin nonuse was associated with cancer mortality in our cohort (Table 5). Compared with individuals in the lowest quartile of WBC count who used aspirin, individuals in the highest quartile of WBC count and not using aspirin had an RR of 2.42 (P=.06 for interaction) for all cancer mortality.

We performed several sets of supplementary analyses. To address the concern that subclinical cancer may lead to an elevated WBC count, we repeated the main analysis after excluding the first 2 years of follow-up. The results were not materially different. For example, compared with quartile 1 of the WBC count, the multivariable-adjusted RR of all cancer mortality (n=199) was 1.19 (95% confidence interval [CI], 0.78-1.82) for quartile 2, 1.23 (95% CI, 0.81-1.88) for quartile 3, and 1.96 (95% CI, 1.34-2.86) for quartile 4. Because cardiovascular disease is a major competing cause of mortality, we repeated the analyses after excluding those with self-reported cardiovascular disease at the baseline examination (n=322). The results were essentially similar. Compared with quartile 1 of the WBC count, the RR of all cancer mortality was 1.39 (95% CI, 0.88-2.19) for quartile 2, 1.40 (95% CI, 0.89-2.20) for quartile 3, and 2.05 (95% CI, 1.36-3.11) for quartile 4. We also examined the association between WBC count and some site-specific cancers, including cancers of the gastrointestinal tract liver, and intrahepatic bile ducts (ICD-9 codes 140-151.9, 153-154.9, 155-155.9, and 157-157.9 [n=54]); breast cancer (ICD-9 codes 174-174.9 [n=18]); and prostate cancer (ICD-9 codes 185-185.9 [n=11]). A 1-SD increase in WBC count was associated with a multivariable RR of 1.09 (95% CI, 0.98-1.21) for gastrointestinal tract cancer, 0.94 (95% CI, 0.53-1.67) for breast cancer, and 1.69 (95% CI, 0.86-3.32) for prostate cancer.

**COMMENT**

In the Blue Mountains Eye Study cohort of older Australians, we found that an elevated WBC count was associated with cancer mortality, independent of smoking, diabetes mellitus, fasting glucose levels, and other related factors. The RR of cancer mortality increased in a dose-dependent manner with increasing WBC count.
Table 4. Effect of High WBC Count and Diabetes Mellitus on Cancer Mortality

<table>
<thead>
<tr>
<th>WBC Count Quartiles, Cells/µL</th>
<th>RR (95% CI)†</th>
<th>Comparing Diabetes Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartiles 1-3 (≤7400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk (No. of cases)</td>
<td>2128 (120)</td>
<td>679 (61)</td>
</tr>
<tr>
<td>Joint exposure to WBC count and diabetes</td>
<td>1.00 (Referent)</td>
<td>1.74 (1.29-2.35)</td>
</tr>
<tr>
<td>Diabetes or fasting hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk (No. of cases)</td>
<td>245 (15)</td>
<td>137 (16)</td>
</tr>
<tr>
<td>Joint exposure to WBC count and diabetes</td>
<td>1.11 (0.64-1.90)</td>
<td>2.26 (1.38-3.71)</td>
</tr>
<tr>
<td>WBC count quartiles‡</td>
<td>1.00 (Referent)</td>
<td>1.51 (1.14-1.99)</td>
</tr>
</tbody>
</table>

Table 5. Effect of High WBC Count and Aspirin Intake on Cancer Mortality

<table>
<thead>
<tr>
<th>Aspirin Intake Categories</th>
<th>WBC Count Quartiles, Cells/µL</th>
<th>Comparison of Diabetes Mellitus Categories, RR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 Times/wk</td>
<td>Quartiles 1-3 (≤7400)</td>
<td>Quartile 4 (≥7400)</td>
</tr>
<tr>
<td>No. at risk (No. of cases)</td>
<td>496 (19)</td>
<td>190 (15)</td>
</tr>
<tr>
<td>Joint exposure with WBC count and diabetes</td>
<td>1.00 (Referent)</td>
<td>1.24 (0.57-2.68)</td>
</tr>
<tr>
<td>&lt;3 Times/wk (including none)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk (No. of cases)</td>
<td>1877 (116)</td>
<td>626 (62)</td>
</tr>
<tr>
<td>Joint exposure with WBC count and diabetes</td>
<td>1.40 (0.87-2.27)</td>
<td>2.42 (1.46-4.01)</td>
</tr>
<tr>
<td>WBC count quartiles‡</td>
<td>1.00 (Referent)</td>
<td>1.51 (1.14-1.99)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; WBC, white blood cell.
*Data are given as RR (95% CI) unless otherwise indicated. All RRs are adjusted for age, sex, education, body mass index, hematocrit level, alcohol intake, physical inactivity, smoking, and diabetes or fasting hyperglycemia status (P = .08 for interaction). Characteristics and diabetes categories are described in the “Exposure Measurement” subsection of the “Methods” section.
†Additionally adjusted for weekly aspirin use.
‡Additionally adjusted for diabetes mellitus status.

quartiles. The WBC count is a stable, well-standardized, and inexpensive marker that reflects systemic inflammation. Results from our study further extend recent evidence from Erlinger et al linking levels of C-reactive protein, a highly specific marker of inflammation, and cancer to the more widely available measure of WBC count.

The activation of WBCs and their increased production and cytokine secretion are intimately involved in several steps of the inflammatory pathway.1,2,24,25 The WBC count is often increased during acute or chronic infections and is known to be chronically elevated in smokers compared with nonsmokers.26 Several prospective studies have shown a higher WBC count within the clinical reference range to be associated with cardiovascular disease,27 hypertension,28 and diabetes.29 These findings suggest that a higher WBC count within the clinical reference range is a reasonable but nonspecific biomarker of inflammation.

Evidence linking inflammation and cancer development and progression is considerable.1 Stromal tissues of tumors contain large numbers of WBCs, and the inflammatory cell number and their cytokine production correlate with tumor severity and prognosis.30 Cytokines produced by inflammatory cells promote cellular growth and block apoptosis in tumor cells through central signaling molecules, including nuclear factor κB, contributing to tumor progression.2-25 Indirect evidence linking inflammation and cancer comes from data implicating infectious agents in the etiology of specific cancers (eg, hepatitis B and C viruses and liver cancer),30 noninfectious chronic inflammatory conditions associated with the development of malignant disease (eg, chronic inflammatory bowel disease and bowel cancer),31 and the chemopreventive effect of aspirin and other nonsteroidal anti-inflammatory agents against cancer.16-18

However, few prospective studies3-9 have examined the association between markers of inflammation and subsequent development of cancer, and the results are not conclusive. Three previous prospective studies5-9 reported a positive association between WBC count and cancer mortality; the association was observed only among smokers in one study,9 whereas it was found to be independent of smoking in the other two.3,9 In our study, WBC count was associated with cancer mortality, even after adjusting for smoking status (Table 2), and in subgroup analyses, the association was also present among those who never smoked (Table 3), suggesting that the observed association between WBC count and cancer mortality is not fully explained by smoking.

Diabetes and hyperglycemia status is another important confounder in the relationship between WBC count and cancer. An elevated WBC count and other inflammatory markers have been found to be related to diabetes,10-12 and diabetes and hyperglycemia have been shown to be related to several cancers.13-15 Erlinger et al9 reported that the association between WBC count and cancer mortality persisted even after adjusting for diabetes status in multivariable models. Our finding is in keeping with this previous observation; the association remained even after adjusting for fasting glucose levels in addition to diabetes status (Table 2). Joint exposure to diabetes and high WBC count was associated with a higher RR of cancer mortality than was the effect of either alone. This finding is consistent with the hypothesis that individuals with diabetes and high levels of inflammatory bio-
markers constitute a more insulin-resistant group.32,33 which in turn may further contribute to their cancer risk.34

In the present study, the association between WBC count and cancer mortality was higher among those not using aspirin at baseline, consistent with the findings of several previous studies.16-18 In joint-exposure categories, the RR of cancer mortality was higher among individuals with high WBC counts who were not using aspirin (Table 5). As a corollary, this finding suggests a greater potential beneficial effect for aspirin intake among those with high WBC count. Our findings are analogous to those of studies in cardiovascular disease, where the use of aspirin appears to modify the association between C-reactive protein level and cardiovascular outcomes; the association was found to be weaker among those using aspirin at baseline.35 We did not have enough site-specific cancer outcomes to examine whether the effect of aspirin intake on the association between WBC count and cancer mortality was present for all cancer sites or was predominantly driven by specific cancers.

The strengths of this study include its population-based sample, high participation rate, use of a standardized protocol for exposure measurement, simultaneous availability of fasting glucose level and WBC count measurements from prediagnostic samples, and use of validated Australian National Death Index data with multiple unique identifiers for outcome ascertainment. The main limitation is the lack of adequate cancer outcomes to look at site-specific cancer deaths. Furthermore, our exposure assessment for important covariates related to cancer such as smoking, alcohol intake, and physical activity was not performed exhaustively, although it used standardized questions administered by trained interviewers. Although we excluded those with cardiovascular disease at the baseline examination, it is possible that the observed association between WBC count and cancer mortality is explained by time-dependent confounding by comorbidities such as incident cardiovascular disease that are known to be related to WBC count and have an impact on cancer survival. The mean age of the population studied in this report was 65.9 years. Our results may not be generalizable to other age groups. Finally, the observed findings may be explained by undiagnosed cancer or subclinical disease at the baseline examination. In conclusion, results from this study support the hypothesis of an association between high WBC count and cancer mortality. These data provide important new epidemiologic evidence of an essential link between inflammation and cancer mortality. Our findings suggest that local inflammatory processes that have long been known to be associated with tumor progression may be reflected in the systemic inflammatory marker of higher WBC count.

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Correspondence: Anoop Shankar, MD, PhD, Department of Community, Occupational, and Family Medicine, National University of Singapore, Singapore 117597 (ashankar@nus.edu.sg).
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Author Contributions: Dr Shankar accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Role of the Sponsor: The funding agencies had no role in the research presented herein, and the researchers were fully independent in pursuing this research.

REFERENCES

Sleep Theme Issue

A special issue of the Archives of Internal Medicine will be devoted to further our understanding of the relationship of sleep and metabolic, cardiovascular, or immunological disorders and the effects of chronic medical disease on sleep disorders.

The importance of sleep quality for health has been reported yet remains underappreciated by both health care professionals and the general public. Several lines of evidence indicate that sleep quality may be a marker of overall health. Epidemiologic surveys show an association between shortened sleep duration and obesity, cardiovascular disease, and diabetes. Physiological studies indicate that short-term sleep loss results in alterations in metabolic and immune function. Survey data show that medical disorders are often associated with self-reported poor sleep. Patients with chronic pain (arthritis, fibromyalgia) and gastrointestinal (gastroesophageal reflux disease), cardiovascular (coronary heart disease, congestive heart failure, hypertension), pulmonary (chronic obstructive pulmonary disease, asthma), and metabolic disorders (obesity, diabetes) are at increased risk for disturbed sleep. Increasing evidence points to a bidirectional relationship between sleep and health, so that sleep disturbances contribute to the development of or increase in the severity of various medical disorders; these same disorders result in poor sleep quality. Still, little is known about the mechanisms for these relationships and whether improving sleep can modify the course of comorbid medical disorders.

Papers on medical topics, whether descriptive or mechanistic, will be considered. The deadline for submission is March 15, 2006. Peer-reviewed and accepted sleep theme manuscripts will appear in the September 11, 2006, issue.


**Correction**

Errors in Table. In the Original Investigation by Shankar et al titled “Association Between Circulating White Blood Cell Count and Cancer Mortality: A Population-Based Cohort Study,” published in the January 23 issue of the *ARCHIVES* (2006;166:188-194), errors occurred in Table 5 on page 192. In that table, the last column heading should have read as follows: “Comparison of Aspirin Intake Categories†.” In addition, the third and fifth sideheadings should have read as follows: “Joint exposure to WBC count and aspirin intake.” The corrected Table 5 is reproduced here.

**Table 5. Effect of High WBC Count and Aspirin Intake on Cancer Mortality***

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†Additionally adjusted for weekly aspirin use.

‡Additionally adjusted for WBC count.

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