



Association of absolute lymphocyte count and cancer incidence and mortality: the Atherosclerosis Risk in Communities (ARIC) study

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Introduction

• Several prospective studies have reported a positive association between total white blood cell (WBC) count, a non-specific marker of systemic inflammation, and cancer incidence and mortality.

• However, subtypes of total WBC count may have distinct roles in inflammation-mediated tumorigenesis

–This study focused on lymphocytes, a subtype of total white blood cells (WBC), which include B cells and T cells (part of the adaptive immune response), and natural killer (NK) cells (part of the innate immune response).

–In addition, we also examined the association of granulocytes, another broad subtype of total WBC, which are involved in the acute inflammatory response.

• Elevated lymphocyte and granulocyte levels may be subclinical inflammatory markers of the carcinogenic effects of common exposures, including obesity and cigarette smoke.

Goal of the study

• We hypothesized that higher circulating levels of pre-diagnostic lymphocyte count would be associated with higher cancer incidence and mortality in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

• The ARIC study is a prospective cohort study conducted in four centers: Forsyth County, NC; Jackson, Mississippi; Minneapolis, MN; Washington County, MD.

• Participants received five exams in 1987-89, 1990-92, 1993-95, 1996-98, and 2011-2013, which included medical examination and questionnaires.

–Cancer incidence and mortality was ascertained by linkage to cancer registries and supplemented by hospital records.

–In our analytic cohort, 2,914 incident primary cancers and 1,164 cancer deaths occurred during follow up through 2012.

• Total WBC counts and differentials were assessed at baseline. On average, lymphocyte counts constituted 33% (range: 7% - 86%) of WBC count

–Among Whites: 31% (range: 7% - 82%)

–Among African-Americans: 40% (range: 7% - 86%)

• The normal range for lymphocyte and granulocyte counts was defined as the mean +/- 2 standard deviations

–Race-specific lymphocyte and granulocyte counts were categorized as below the normal range, tertiles within the normal range (first tertile was a reference), and above the normal range.

Statistical Analysis

• Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for overall and site-specific cancer incidence and mortality

- Model 1: Adjusted for age, sex, race, and study center
- Model 2: Model 1 additionally adjusted for education level, alcohol consumption, smoking history, pack years of smoking, BMI and Physical activity
- Model 3: Model 2 additionally adjusted for hypertension, diabetes status, history of CVD, aspirin use and hormone therapy + menopausal status for breast cancer

Figure 1. Association between lymphocyte levels, overall cancer incidence and overall cancer mortality

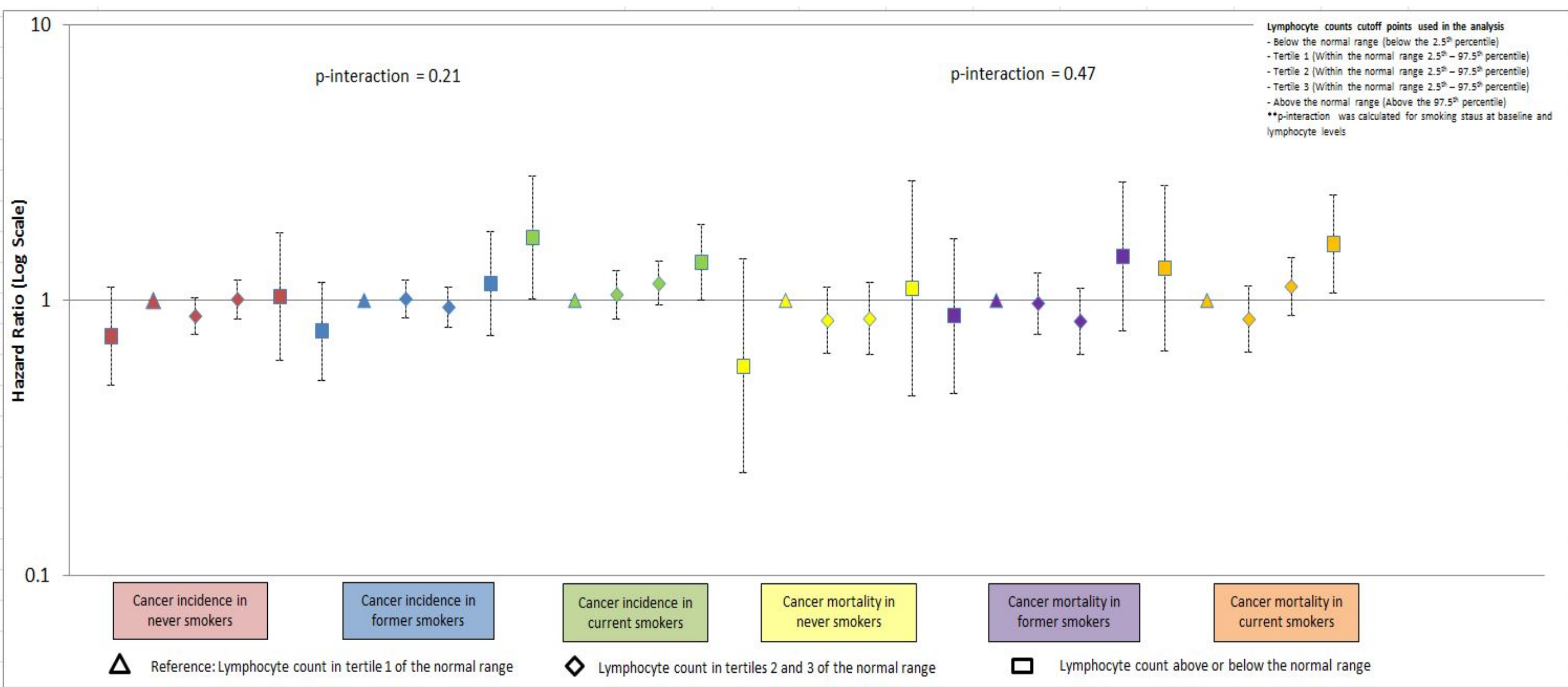


Figure 2. Association between lymphocyte levels, non-lung cancer incidence and non-lung cancer mortality

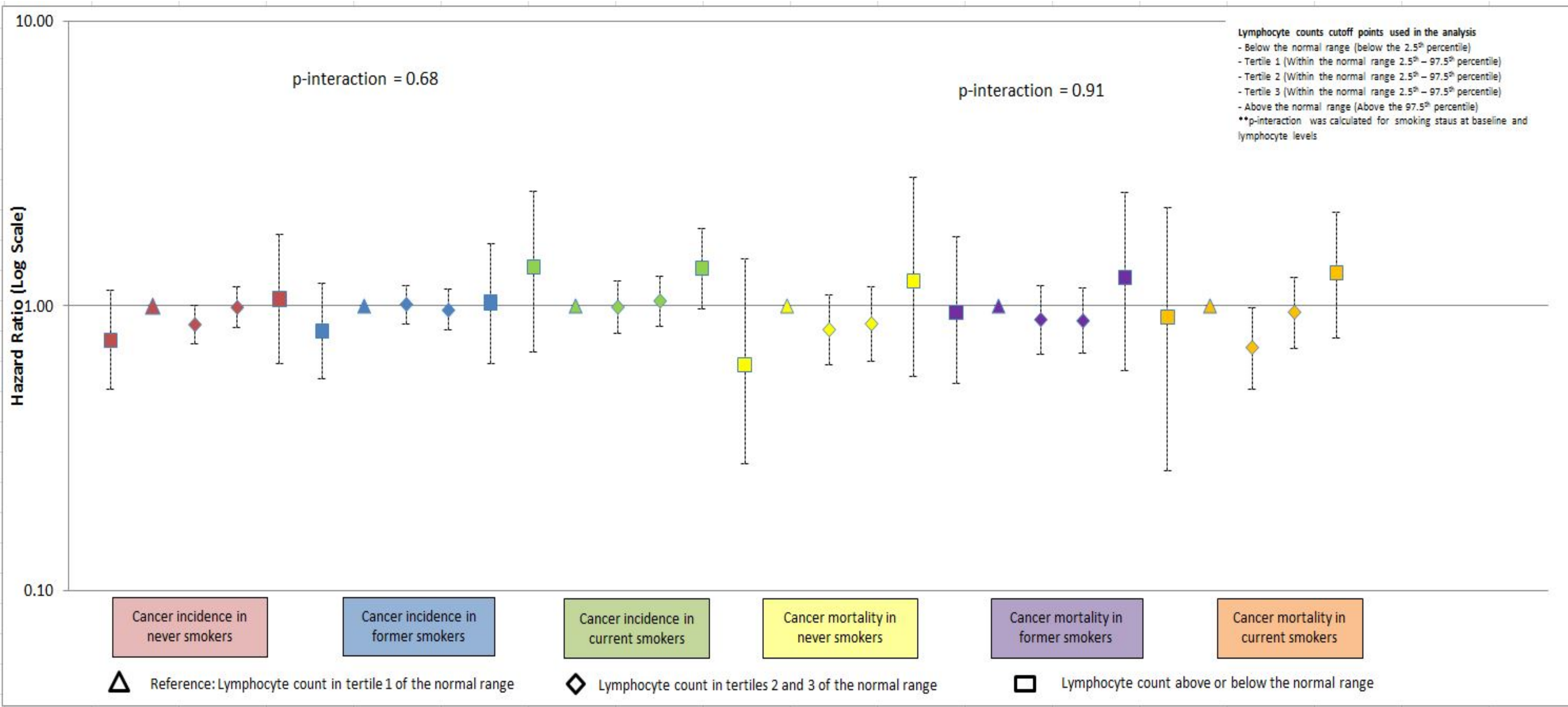


Table 1. Association between granulocyte levels, overall cancer incidence and overall cancer mortality.

Overall Cancer Incidence							
Granulocyte Category							
Category	Number of Cases	Q1 (Below normal range)	Q2 (T1 of normal range)	Q3 (T2 of normal range)	Q4 (T3 of normal range)	Q5 (Above Normal Range)	p-trend
		0.86 - 2.05 x 10 ⁹ /L	1.14 - 3.30 X10 ⁹ /L	2.34 - 4.34 x10 ⁹ /L	3.35 - 7.34 x 10 ⁹ /L	6.40 - 8.85 x10 ⁹ / L	
Total Cohort	2914	HR (95%CI)		HR (95%CI)	HR (95%CI)	HR (95%CI)	
Model 1		0.99 (0.77 - 1.28)	1.00 (Reference)	1.10 (1.00 - 1.20)	1.16 (1.06 - 1.28)	1.25 (0.99 - 1.58)	0.02
Model 2		1.02 (0.78 - 1.32)	1.00 (Reference)	1.04 (0.94 - 1.14)	1.04 (0.94 - 1.15)	0.99 (0.77 - 1.26)	0.93
Model 3		1.02 (0.79 - 1.33)	1.00 (Reference)	1.04 (0.94 - 1.15)	1.05 (0.95 - 1.16)	1.00 (0.78 - 1.28)	0.90
Never Smokers	982						
Model 2		1.04 (0.73 - 1.47)	1.00 (Reference)	1.03 (0.89 - 1.20)	0.95 (0.80 - 1.13)	0.92 (0.43 - 1.95)	0.91
Former Smokers	975						
Model 2		0.99 (0.64 - 1.53)	1.00 (Reference)	0.96 (0.82 - 1.13)	0.99 (0.84 - 1.17)	0.72 (0.39 - 1.32)	0.85
Current Smokers	954						
Model 2		1.01 (0.41 - 2.49)	1.00 (Reference)	1.19 (0.95 - 1.49)	1.23 (0.99 - 1.51)	1.19 (0.86 - 1.65)	0.44
Overall Cancer Mortality							
Total Cohort	1164						
Model 1		0.79 (0.49 - 1.29)	1.00 (Reference)	1.30 (1.11 - 1.53)	1.83 (1.57 - 2.13)	2.59 (1.87 - 3.59)	0.001
Model 2		0.88 (0.54 - 1.44)	1.00 (Reference)	1.11 (0.94 - 1.30)	1.34 (1.14 - 1.57)	1.49 (1.07 - 2.09)	0.002
Model 3		0.93 (0.57 - 1.52)	1.00 (Reference)	1.11 (0.94 - 1.31)	1.31 (1.11 - 1.54)	1.39 (0.99 - 1.96)	0.01
Never Smokers	289						
Model 2		0.77 (0.36 - 1.65)	1.00 (Reference)	1.15 (0.87 - 1.52)	1.27 (0.94 - 1.74)	1.85 (0.58 - 5.85)	0.39
Former Smokers	363						
Model 2		0.74 (0.33 - 1.69)	1.00 (Reference)	0.90 (0.68 - 1.17)	1.24 (0.95 - 1.62)	1.18 (0.48 - 2.92)	0.15
Current Smokers	510						
Model 2		2.15 (0.78 - 5.97)	1.00 (Reference)	1.33 (0.97 - 1.82)	1.51 (1.12 - 2.02)	1.71 (1.11 - 2.64)	0.04

Results

• Lymphocyte counts above the normal range were associated with increased overall cancer mortality (HR: 1.44 (95% CI:1.05 - 1.97)), but did not reach statistical significance for overall cancer incidence (HR: 1.26 (95% CI:0.99 - 1.60)).

• When stratified by smoking status, an association was observed among current smokers for both incidence and mortality. Lymphocyte counts above the normal range were associated with increased overall cancer incidence (HR: 1.38 (95% CI:1.00 - 1.89)), and mortality (HR: 1.60 (95% CI:1.06 - 2.42)) (Figure 1).

• The association between increased lymphocyte counts and cancer risk in smokers was not statistically significant when lung cancer cases were excluded (HR: 1.35 (95% CI:0.94 - 1.95) and HR: 1.31 (95% CI:0.75 – 2.30) for non-lung cancer incidence and mortality, respectively) (Figure 2).

• In site specific analyses, lymphocyte counts above the normal range were associated with higher lung cancer mortality (HR: 1.91 (95% CI: 1.14 - 3.19)), but not lung cancer incidence (HR: 1.59 (95% CI: 0.95 - 2.62)). No other site-specific cancer associations were found with increased lymphocyte levels.

• Increased granulocyte counts were associated with increased overall cancer mortality (p-trend = 0.01), but not overall cancer incidence (p-trend=0.90) (Table 1).

• When stratified by smoking status, granulocyte counts above the normal range were associated with increased overall cancer mortality (HR: 1.71 (95% CI:1.11 – 2.64)), but did not reach statistical significance for overall cancer incidence (HR: 1.00 (95% CI:0.78 - 1.28))(Table 1).

Conclusions

• Our findings support existing evidence of a positive association between increased pre-diagnostic lymphocyte counts and increased cancer mortality overall, and increased cancer incidence and mortality in current smokers.

• The association between increased pre-diagnostic lymphocyte counts and cancer risk was attenuated after excluding incident lung cancer cases.

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