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Inverse association of eosinophil count with colorectal cancer incidence: Atherosclerosis Risk in Communities Study

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Abstract

Background—Allergic conditions are associated with reduced risk of several malignancies. We hypothesized that blood eosinophil count, a marker for allergic disorders, is inversely associated with the risk of colorectal cancer (CRC) in the Atherosclerosis Risk in Communities (ARIC) prospective cohort. To our knowledge, the association between blood eosinophil count and cancer risk has not been investigated before.

Methods—Relative eosinophil and total leukocyte counts were measured in blood at baseline. Absolute eosinophil counts were calculated by multiplying relative count by the total leukocyte count. Proportional hazards regression provided hazard ratios (HR) and 95% confidence intervals (CI) of CRC in relation to eosinophil count.

Results—From 1987–2006, 242 incident CRC cases (187 colon; 56 rectal) occurred in 10,675 initially cancer-free participants. In a multivariate-adjusted model, HRs were 1.0, 0.70 (95%CI, 0.50;0.98) and 0.58 (95%CI, 0.40;0.83) across tertiles of absolute eosinophil count (P-trend=0.003). A similar inverse association was observed for relative eosinophil count. Age, sex, race, or smoking status did not modify associations.

Conclusions and impact—We observed an inverse association between blood eosinophil count and CRC risk. This novel finding supports the hypothesis that allergies are protective for colorectal cancer, since an increased eosinophil count correlates with allergy in the developed world.

Keywords

eosinophils; allergy; colorectal cancer; cohort

The theory of tumor immunosurveillance suggests that allergic conditions could reduce cancer risk by enhancing the immune system's ability to detect and remove malignant cells (1, 2). A history of allergy has been associated with reduced risk of several malignancies, most consistently with cancers of the pancreas, brain, and childhood leukemia (1, 3). Most of the studies on colorectal cancer (CRC) also indicated a decreased risk associated with having allergies but results of other studies are inconsistent (2, 4–6). We previously reported that in the Iowa Women's Health Study, history of allergy was associated with a 25%

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decreased CRC risk, and risk was decreased by 42% for women with two or more allergic conditions (7), which is consistent with immunosurveillance having an important role in colorectal carcinogenesis (8).

Allergy is characterized by increased level of blood eosinophils -- granulocytes capable of killing pathogens and tumor cells *in vitro* (9). Several studies have shown that increased blood or tissue eosinophil counts are associated with better prognostic indicators of colorectal carcinoma *in vitro* and *in vivo* (9–12). To our knowledge, the association between blood eosinophil count and cancer risk has not been investigated before. We hypothesized that blood eosinophil count is inversely associated with CRC risk in the Atherosclerosis Risk in Communities (ARIC) prospective cohort. Investigating new mechanisms of colorectal carcinogenesis is important since CRC is the third most common malignancy and cause of death in the United States, and causes of CRC are incompletely known (13).

Methods

ARIC enrolled and followed 15,792 men and women aged 45–64 years in 1987–89 in four US communities: Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, Maryland. Local institutional review boards approved the ARIC protocol and all participants provided an informed consent.

The baseline and three follow-up visits included interviews, laboratory measurements, and clinic examinations (14–16). Participants were asked to report asthma; but information about other allergic conditions was not collected.

Total white blood cell (WBC) and relative eosinophil (i.e. number of eosinophils per 100 WBC) counts were measured at baseline (1987–89) and at Visit 2 (1990–92) in local hospitals using Coulter counters (17). Eosinophil counts were not measured in Washington County; thus, data from only three ARIC sites (NC, MN, MS) were used for this analysis. Incident cancers were ascertained for 1987–2006 by linkage to cancer registries and supplemented by hospital records (16, 18). Primary site, date of cancer diagnosis, and source of diagnostic information (e.g., a pathology report) were recorded.

Our main analysis utilized absolute eosinophil counts at baseline. Absolute eosinophil counts were calculated by multiplying relative counts by the total WBC count. Proportional hazards regression models were used to estimate the hazard ratios (HR) and 95% confidence interval (CI) of CRC in relation to eosinophil count. Person-years were calculated from the baseline examination date to the date of CRC diagnosis, death, loss to follow-up, or December 31, 2006, whichever occurred first. Two models were utilized: Model 1 adjusted for age, race, sex, and center, and Model 2 additionally adjusted for CRC risk factors in ARIC: education, body-mass index, smoking status, pack-years of smoking, alcohol use, diabetes, fibrinogen, and total WBC count. Further adjustment for aspirin and hormone replacement therapy did not markedly change the results, and these variables were not included into the final model.

In the analysis of CRC in relation to eosinophil count measured at Visit 2, person-years were calculated from the Visit 2 date (as a new baseline) until the date of CRC diagnosis, death, loss to follow-up, or December 31, 2006, whichever occurred first.

To examine associations of eosinophil count with colon and rectal cancers, we conducted a competing-risk survival analysis to explore whether parameter estimates for colon and rectal cancer were statistically different. We compared the sum of goodness-of-fit statistics ($-2 \times \log\text{-likelihood}$) for event-specific (colon and rectal cancers) models to that of the global model that does not distinguish between event types (19).

Results

At baseline, the mean age of 10,675 initially cancer-free participants was 53.9 years; 36% were African American, 64% were Caucasians; and 55% were women. Participants with higher absolute eosinophil levels were more likely to smoke, be less educated, have history of asthma and diabetes, and have higher WBC and fibrinogen levels (Table 1). During 174,999 person-years of follow-up in 1987–2006, 242 incident CRC cases (187 colon; 56 rectal) occurred.

In age- and multivariate-adjusted models, eosinophil count was inversely associated with CRC incidence. HRs across tertiles were 1.0, 0.70, and 0.58 (P -trend=0.003) in Model 2 (Table 2). The inverse association was consistent across the three ARIC centers. The associations held among never smokers and among non-asthmatics. There was no effect modification by age, sex, race, or smoking status. Since absolute eosinophil count is a component of the total WBC count, we repeated the analysis after adjustment for the total WBC minus eosinophil count, but this did not change our findings. Additionally, we reran Model 2 using relative eosinophil count categorized into tertiles, and the inverse association persisted. The inverse association was observed for colon cancer, but not rectal cancer. However, after conducting a competing risk analysis, we failed to reject the null hypothesis that the estimates for rectal and colon cancers were identical ($p>0.05$) (19). Thus, there was insufficient statistical evidence to conclude that estimates for colon and rectal cancer were different.

To exclude a potential effect of preclinical CRC on the eosinophil count, we excluded CRC cases that occurred within five or ten years of follow-up, but the association remained. The association held after excluding ARIC participants with an acute response, i.e. those with clinically elevated eosinophil levels (>300 cells/mL) (20). Further, the inverse association also held in the subset of 6,767 participants who also had eosinophils measured at Visit 2. The eosinophil counts at two visits were correlated (Spearman's $r=0.47$). Finally, for comparison, we examined associations of eosinophil count with lung and breast cancers but no inverse associations were observed.

Discussion

To the best of our knowledge, this is the first study showing that circulating eosinophil count is inversely associated with CRC risk. Several previous studies, but not all, reported high blood and tissue eosinophil counts to be associated with better CRC prognosis (9–12).

It is not clear whether the association between eosinophils and colorectal carcinogenesis is causal. Eosinophils are innate immune leukocytes linked to type 2 immune responses, including asthma and allergy. In healthy people, eosinophils account for 1–3% of peripheral-blood leukocytes and they are present mainly in tissues of gastrointestinal mucosa (21). In patients with allergic diseases, eosinophils accumulate in blood and other tissues. Absolute eosinophil counts are closely linked to immunoglobulin E (IgE) levels and are correlated with severity of allergic disease (22).

Under stimuli, eosinophils may produce and rapidly release over 30 cytokines with preferential secretion of cytokines promoting type 2 immunity (interleukins IL-4) (23). They may participate in immune surveillance by acting synergistically with macrophages and releasing immunoregulatory cytokines responsible for antitumor responses (11, 24, 25). Further, in vitro and in vivo studies demonstrated that eosinophils may produce granule proteins that are highly tumor-cytotoxic (26, 27). Both of these mechanisms may explain an inverse association of eosinophil count with colorectal cancer. Alternatively, it has been

shown that eosinophils may directly recognize CRC cells and induce their death by releasing cytotoxic granzyme A (11).

The strengths of our study are that it is a large prospective cohort with a long and almost complete follow-up, with detailed information about confounding variables and standardized methods of measuring biomarkers. A limitation is that the eosinophil count could reflect some acute disease occurring at the time of blood collection rather than the average eosinophil count over time. However, similar associations of CRC with eosinophil measures at two visits lend credibility to our results.

If, in fact, eosinophils inhibit CRC development and act through immunoregulation, our findings may corroborate an inverse association of allergy with incident CRC, since allergy is the most common cause for an increased eosinophil count in the developed world.

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Table 1

Prevalence of characteristics across tertiles of eosinophil count in 10,675 cancer-free participants, at baseline (1987–89), ARIC.

Characteristics Mean or prevalence (%)	Eosinophil count (cells/mL)		
	≤70	71–176	≥177
Age at baseline (y)	53.7	54.0	54.0
Race (% White)	72.0	57.7	62.9
Sex (% Male)	44.4	41.6	49.2
BMI (kg/m ²)	27.3	27.8	27.9
Education (more than high school) (%)	52.1	46.1	46.5
Current smokers, (%)	21.1	26.7	34.5
Current alcohol intake, (%)	65.2	51.1	54.1
Aspirin (%)	45.2	45.0	45.4
Diabetes (%)	9.9	12.2	13.8
Asthma (%)	4.5	5.9	9.2
Current HRT ^a , (%) (for women)	22.5	19.9	20.9
WBC ^b count (×10 ³ cells/mL)	5.7	5.8	6.7
Fibrinogen (mg/dL)	296	304	311

^aHRT – history of hormone replacement therapy

^bWBC – white blood cell

Table 2

Hazard ratios (HR) of colorectal cancer (CRC), colon cancer, and rectal cancer in relation to eosinophil count at baseline in ARIC, 1987–2006

Eosinophil count, cells/mcl	Number of CRC	Person-years	Hazard ratio (95%CI)			
			CRC Model 1 ^a	CRC Model 2 ^b	Colon cancer Model 2 ^b	Rectal cancer Model 2 ^b
≤70	96	59,004	1.0	1.0	1.0	1.0
70–176	84	59,310	0.81 (0.59;1.12)	0.70 (0.50;0.98)	0.74 (0.51;1.07)	0.54 (0.25;1.17)
≥177	62	56,685	0.64 (0.46;0.91)	0.58 (0.40;0.83)	0.49 (0.32;0.75)	0.90 (0.45;1.79)
<i>P-trend</i>			0.01	0.003	0.001	0.85

^aModel 1-adjusted for age, race, sex, and ARIC center

^bModel 2 -- Model 1, additionally adjusted for education, BMI, smoking status and pack-years of smoking, alcohol, diabetes, WBC count and fibrinogen.