Research Article

Cancer Epidemiology, Biomarkers & Prevention

Inverse Association of Eosinophil Count with Colorectal Cancer Incidence: Atherosclerosis Risk in Communities Study

Anna E. Prizment[1], Kristin E. Anderson[1,2], Kala Visvanathan[3], and Aaron R. Folsom[1,2]

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 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 HRs and 95% CIs of CRC in relation to eosinophil count.

Results: From 1987–2006, 242 incident CRC cases (187 colon and 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 CRC, as an increased eosinophil count correlates with allergy in the developed world. *Cancer Epidemiol Biomarkers Prev; 20(9); 1861–4. ©2011 AACR.*

Introduction

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% decreased CRC risk, and risk was decreased by 42% for women with 2 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 because 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 to 64 years in 1987–1989 in 4 U.S. communities: Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD. Local institutional review boards approved the ARIC protocol, and all participants provided an informed consent.

The baseline and 3 follow-up visits included interviews, laboratory measurements, and clinical examinations (14–16). Participants were asked to report asthma, but information about other allergic conditions was not collected.

Authors' Affiliations: [1]Division of Epidemiology and Community Health, School of Public Health; [2]University of Minnesota Masonic Cancer Center, University of Minnesota, Minneapolis Minnesota; and [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Corresponding Author: Anna E. Prizment, Division of Epidemiology and Community Health, 1300 2nd Street South, Suite 300, University of Minnesota, Minneapolis, MN 55455. Phone: 1-612-626-0250; Fax: 1-612-624-0315; E-mail: prizm001@umn.edu

doi: 10.1158/1055-9965.EPI-11-0360

Total white blood cell (WBC) and relative eosinophil (i.e., number or eosinophils per 100 WBC) counts were measured at baseline (1987–1989) and at visit 2 (1990–1992) in local hospitals by using Coulter counters (17). Eosinophil counts were not measured in Washington County; thus, data from only 3 ARIC sites (NC, MN, and 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 HRs and 95% 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 (HRT) 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*log-likelihood) for event-specific (colon and rectal cancers) models to that of the global model that does not distinguish between event types (19).

Table 1. Prevalence of characteristics across tertiles of eosinophil count in 10,675 cancer-free participants, at baseline (1987–1989), ARIC

Characteristics mean or prevalence (%)	Eosinophil count (cells/μL)		
	≤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 (%; for women)	22.5	19.9	20.9
WBC count ($\times 10^3$ cells/μL)	5.7	5.8	6.7
Fibrinogen (mg/dL)	296	304	311

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 and 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).

Table 2. HRs of CRC, colon cancer, and rectal cancer in relation to eosinophil count at baseline in ARIC, 1987–2006

Eosinophil count, cells/μL	Number of CRC	Person-years	HR (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)
P_{trend}			0.01	0.003	0.001	0.85

[a]Model 1 adjusted for age, race, sex, and ARIC center.

[b]Model 2 adjusted for age, race, sex, ARIC center, education, BMI, smoking status, pack-years of smoking, alcohol, diabetes, WBC count, and fibrinogen.

The inverse association was consistent across the 3 ARIC centers. The associations held among never-smokers and among nonasthmatics. There was no effect modification by age, sex, race, or smoking status. Because 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. In addition, we reran model 2 by 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 ($P > 0.05$; ref. 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 5 or 10 years of follow-up, but the association remained. The association held after excluding ARIC participants with an acute response, that is, those with clinically elevated eosinophil levels (>300 cells/μL; ref. 20). Furthermore, 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% to 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 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 (IL-4; ref. 23). They may participate in immune surveillance by acting synergistically with macrophages and releasing immunoregulatory cytokines responsible for antitumor responses (11, 24, 25). Furthermore, *in vitro* and *in vivo* studies showed 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 CRC. 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, as allergy is the most common cause for an increased eosinophil count in the developed world.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions. Cancer incidence data have been provided by Maryland Cancer Registry, Center of Cancer Surveillance and Control, Department of Health and Mental Hygiene, 201 W. Preston Street, Room 400, Baltimore, MD 21201. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund and the National Program of Cancer Registries (NPCR) of the Centers for disease control and Prevention (CDC) for the funds that helped support the availability of the cancer registry data.

Grant Support

The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

A.E. Prizment was supported as a postdoctoral fellow by the National Cancer Institute (T32CA132670).

Received April 14, 2011; revised June 2, 2011; accepted July 1, 2011; published OnlineFirst July 8, 2011.

References

1. Turner AR. Epidemiological evidence: IgE, atopy, and solid tumors. In: Penichet ML, Jensen-Jarolim E, editors. Cancer and IgE. London: Spinger Science; 2010. p. 47–77.

2. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 2005;60: 1098–111.

3. Martínez-Maza O, Moreno AD, Cozen W. Epidemiological evidence: IgE, allergies, and hematopoietic malignancies. In:Penichet ML, Jensen-Jarolim E, editors. Cancer and IgE. London: Springer Science; 2010. p.79–136.
4. Merrill RM, Isakson RT, Beck RE. The association between allergies and cancer: what is currently known?Ann Allergy Asthma Immunol 2007;99:117–9.
5. Sherman PW, Holland E, Sherman JS. Allergies: their role in cancer prevention. Q Rev Biol 2008;83:339–62.
6. Vojtechova P, Martin RM. The association of atopic diseases with breast, prostate, and colorectal cancers: a meta-analysis. Cancer Causes Control 2009;20:1091–105.
7. Prizment AE, Folsom AR, Cerhan JR, Flood A, Ross JA, Anderson KE. History of allergy and reduced incidence of colorectal cancer, Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 2007;16:2357–62.
8. Pages F, Galon J, Fridman WH. The essential role of the *in situ* immune reaction in human colorectal cancer. J Leukoc Biol 2008;84:981–7.
9. Sanderson CJ. Interleukin-5, eosinophils, and disease. Blood 1992;79:3101–9.
10. Fernndez-Aceero MJ, Galindo-Gallego M, Sanz J, Aljama A. Prognostic influence of tumor-associated eosinophilic infiltrate in colorectal carcinoma. Cancer 2000;88:1544–8.
11. Legrand F, Driss V, Delbeke M, Loiseau S, Hermann E, Dombrowicz D, et al. Human eosinophils exert TNF-α and granzyme A-mediated tumoricidal activity toward colon carcinoma cells. J Immunol 2010;185:7443–51.
12. Nielsen HJ, Hansen U, Christensen IJ, Reimert CM, Brunner N, Moesgaard F. Independent prognostic value of eosinophil and mast cell infiltration in colorectal cancer tissue. J Pathol 1999;189:487–95.
13. American Cancer Society, Cancer facts & figures 2010. Atlanta: American Cancer Society; 2010.
14. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687–702.
15. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 1997;96:1102–8.
16. Prizment AE, Anderson KE, Visvanathan K, Folsom AR. Association of inflammatory markers with colorectal cancer incidence in the Atherosclerosis Risk in Communities (ARIC) study. Cancer Epidemiol Biomarkers Prev 2011;20:297.
17. Duncan BB, Schmidt MI, Offenbacher S, Wu KK, Savage PJ, Heiss G. Factor VIII and other hemostasis variables are related to incident diabetes in adults. The Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 1999;22:767–72.
18. Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. Cancer 2006;107:28–36.
19. Singer JD, Willett JB. Applied longitudinal data analysis. New York: Oxford University Press; 2003. p. 586–96.
20. Fauci AS, Braunwald E, Kasper DL, et al. Harrison's principles of internal medicine. 17th ed. New York: McGraw-Hill Professional; 2009.
21. Rothenberg ME. Eosinophilia. N Engl J Med 1998;338:1592–600.
22. Dhar S, Malakar R, Chattopadhyay S, Dhar S, Banerjee R, Ghosh A. Correlation of the severity of atopic dermatitis with absolute eosinophil counts in peripheral blood and serum IgE levels. Indian J Dermatol Venereol Leprol 2005;71:246–9.
23. Spencer LA, Szela CT, Perez SA, Kirchhoffer CL, Neves JS, Radke AL, et al. Human eosinophils constitutively express multiple Th1, Th2, and immunoregulatory cytokines that are secreted rapidly and differentially. J Leukoc Biol 2009;85:117–23.
24. Cormier S, Taranova A, Bedient C, Nguyen T, Protheroe C, Pero R, et al. Pivotal advance: Eosinophil infiltration of solid tumors is an early and persistent inflammatory host response. J Leukoc Biol 2006;79:1131–9.
25. Simson L, Ellyard JI, Dent LA, Matthaei KI, Rothenberg ME, Foster PS, et al. Regulation of carcinogenesis by IL-5 and CCL11: a potential role for eosinophils in tumor immune surveillance. J Immunol 2007;178:4222–9.
26. Munitz A, Levi-Schaffer F. Eosinophils: 'new' roles for 'old' cells. Allergy 2004;59:268–75.
27. Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, Capron M, et al. AllergoOncology: the role of IgE-mediated allergy in cancer. Allergy 2008;63:1255–66.