HHS Public Access

Author manuscript

Cancer Epidemiol. Author manuscript; available in PMC 2018 February 21.

Published in final edited form as:

Cancer Epidemiol. 2016 October ; 44: 65–70. doi:10.1016/j.canep.2016.07.012.

Inflammatory Biomarkers, Aspirin, and Risk of Colorectal Cancer: Findings from the Physicians' Health Study

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Abstract

Background—Chronic inflammation has been implicated in colorectal carcinogenesis. However, the associations between plasma inflammatory markers and risk of colorectal cancer have been inconsistent.

Methods—In a nested case-control study in the Physicians' Health Study, we prospectively investigated the associations of plasma C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor receptor 2 (TNFR-2) with risk of colorectal cancer, and whether aspirin modified these associations among 268 colorectal cancer patients and 446 age- and smoking-matched controls.

Results—In multivariate-adjusted models, plasma levels of CRP, IL-6 and TNFR-2 were not significantly associated with risk of colorectal cancer, although a positive trend was observed for TNFR-2 ($RR_{highest\ vs.\ lowest\ quartile}$=1.55; 95% CI=0.95–2.54; P_{trend}=0.05). We observed a statistically significant association between elevated TNFR-2 levels and colorectal cancer risk in

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Disclosures: None

the placebo arm ($RR_{highest\ vs.\ lowest\ tertile}$=1.77; 95% CI=1.02–3.06; P_{trend}=0.02), but not in the aspirin arm (P_{trend}=0.72). However, the interaction between TNFR-2 and aspirin was not statistically significant ($P_{interaction}$=0.34).

Conclusion—Plasma inflammatory markers were not significantly associated with colorectal cancer risk among men, though there was a statistically non-significant positive trend between TNFR-2 and colorectal cancer risk. More studies are required to understand the relationship between the role of TNFα pathway, aspirin, and colorectal cancer risk.

Keywords

CRP; IL-6; TNFR-2; colorectal cancer; aspirin

1. Introduction

Inflammation has been implicated in carcinogenesis of many cancer types including colorectal cancer[1]. Considerable experimental, epidemiologic, and clinical data suggest that chronic inflammation including inflammatory bowel disease plays an important role in colorectal carcinogenesis[2,3]. Long-term aspirin and nonsteroidal anti-inflammatory drug use reduce the risk of colorectal cancer[4,5].

Several prospective epidemiologic studies have evaluated the association between plasma inflammatory markers and colorectal cancer risk with mixed results[6]. Among published prospective studies of circulating C-reactive protein (CRP), some studies reported a significant association between CRP and colorectal cancer risk[7–10], whereas the remaining studies were null[11–19]. The majority of studies investigated IL-6 did not find a significant association with colorectal cancer risk[9,12,13,17,20]. Two prospective studies of tumor necrosis factor receptor 2 (TNFR-2) showed inconsistent results. One study showed a significant association with risk of colorectal cancer in women[12]; the study found a significant reduction of colorectal cancer risk by anti-inflammatory drugs (aspirin and NSAIDs) in persons with high baseline levels of TNFR-2. Another study in men did not observe a significant association with colorectal cancer risk[17]. Both studies were limited by the fact that self-reported use of aspirin and NSAIDs was used.

To further elucidate the link between these three inflammatory biomarkers and incident colorectal cancer risk, we conducted a case-control analysis using data from the Physicians' Health Study, a randomized trial of aspirin and beta-carotene in US male physicians. Besides evaluating the overall associations of the biomarkers, we specifically tested the hypothesis that inflammatory biomarkers were associated with an increased risk of colorectal cancer only among non-aspirin users (placebo group), which is based on the rationale that anti-inflammatory activities of aspirin may have a mitigating effect on the association between inflammation and colorectal carcinogenesis.

2. Materials and Methods

2.1. Study population

This is a prospective study nested in the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of aspirin (325 mg every other day) and beta-carotene (50 mg on alternate days) among 22,071 US male physicians 40–84 years of age in 1982[21]. Participants were excluded if they had a history of myocardial infarction, stroke, transient ischemic attack, cancer (except non-melanoma skin cancer), current renal or liver disease, peptic ulcer, gout, or current use of a vitamin A or beta-carotene supplement. The aspirin component of the trial was terminated in 1988 primarily because of a significant reduction in the risk of total myocardial infarction among those in the aspirin group[21]. After the termination of the aspirin component of the trial, the beta-carotene component of the trial continued uninterrupted.

Before randomization, kits for blood sampling were sent to all participants with instructions to have their blood drawn into the EDTA tubes. Each blood collection kit contained vacutainer tubes, cold packs for mailing, and prepaid shipping packs. The participants were requested to fractionate the blood by centrifugation to collect both plasma and whole blood. The samples were placed on cold packs, and sent to investigators by overnight courier within 24 hours of being drawn. Upon receipt, specimens were divided into aliquots, and stored at −82 °C. Blood samples from 14,916 (68%) of the participants between 1982 and 1984 before randomization were received. Information regarding height, weight, physical activity, alcohol intake, multivitamin use, smoking habit, and history of diabetes was obtained by self-administered questionnaires at baseline. The frequency of intake of seafood and dairy food was obtained on the 12-month follow-up questionnaires.

Cases were identified by annual follow-up questionnaires and verified by the PHS Endpoints Committee using medical records. Among those who provided blood samples, we identified 268 case patients who were diagnosed with colorectal cancer between the date of blood draw and July 31, 2000. For each case subject, we matched approximately two controls on age (±1 year for younger participants and ±5 years for older participants) and smoking status (never, past, or current). Eligible controls were those who were free of colorectal cancer at the time of cases diagnosed, and who had provided a blood sample at baseline. For 91 cases, we were able to identify only one appropriate control. Therefore, a total of 268 cases and 446 controls were included in our analysis.

2.2. Laboratory Assessment

Stored plasma from prospectively collected samples from each case and control subject was thawed and assayed for CRP, IL-6, and TNFR-2 at the Boston Children's Hospital laboratory. CRP levels were measured using a high-sensitivity immunoturbidimetric assay (Denka Seiken Co, Tokyo, Japan). The IL-6 and TNFR-2 levels were measured using a commercially available enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN). The median time between collection of blood and case diagnosis was 8.9 years (range 0.1 – 17.5 years). Case-control pairs were assayed in adjoining wells, with blinding of laboratory personnel as to case-control status. In addition, we included 10% of samples as

pooled quality control randomly distributed across plates. The median coefficients of variation were 2.3% for CRP, 4.5% for IL-6, and 6.5% for TNFR-2.

2.3. Statistical Analysis

We compared baseline characteristics between case subjects and control subjects using paired t test for log-transformed CRP, IL-6, and TNFR-2, and the Cochran-Mantel-Haenszel test for categorical variables. We examined the correlations between plasma CRP, IL-6, TNFR-2, and factors related to colorectal cancer risk (age, smoking status, body mass index, alcohol intake, and intake of seafood and dairy food) using partial Spearman correlations among the control group after adjusting for age and smoking status. Relative risk for colorectal cancer and corresponding 95% confidence intervals (95% CIs) were estimated using conditional logistic regression. Quartile cut points for each biomarker were based on the distribution of concentrations among controls. In multivariate analyses, we adjusted for potential confounders including randomized aspirin assignment (yes or no), body mass index (<23, 23–24.99, 25–26.99, and ≥27 kg/m^2), alcohol intake (≤1 time/week, 2–6 times/week, ≥1 time/day), physical activity (<1 time/week, 1–4 times/week, ≥5 times/week), multivitamin use (never, past, current use), seafood and dairy food intake (quartile). Tests for trend across quartiles were conducted by using the median value for each category of plasma biomarker as a continuous variable in the regression model. Additional analyses were performed according to cancer site (colon vs. rectum). Furthermore, we conducted an analysis after excluding incident cases diagnosed within the first two years of follow-up to eliminate possible influence of undiagnosed cancer on levels of plasma inflammatory markers.

We assessed potential effect modifications by estimating the relative risks from conditional logistic regression models cross-tabulating inflammatory markers with aspirin assignment (yes or no), BMI (<25, ≥25 kg/m^2), alcohol intake (≤1, >1 time/week), physical activity (<2, ≥2 times/week), smoking status (never, ever smoker), and seafood intake (<2, ≥2 servings/week). To test for multiplicative interactions, we used the conditional logistic models with multiplicative interaction terms including the median level of each tertile of biomarker and ordinal categories of those variables. To test for trend across tertiles, we fit the unconditional models using the median values for each category of plasma biomarker for the variables except matching factor because stratification by these variables would break the matching of case-control pairs.

All analyses were performed by using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina). All statistical tests were two-sided. $P<0.05$ were considered statistically significant.

3. Results

The baseline characteristics of the 268 colorectal cancer cases and 446 matched controls are presented in Table 1. The mean age at diagnosis of colorectal cancer was 67.8 years. Plasma levels of CRP were not significantly different between cases and controls (P=0.31), but the age and smoking-adjusted median plasma levels of IL-6 (P=0.02) and TNFR-2 (P=0.049) were significantly higher among cases than controls. Persons who subsequently developed

colorectal cancer consumed more alcohol and less dairy food. No significant differences were observed for other variables.

Table 2 shows the Spearman correlation coefficients between plasma inflammatory markers, alcohol intake, aspirin assignment, seafood and dairy food intake among controls after adjusting for age and smoking status. Plasma inflammatory biomarkers were positively correlated with each other. Age was positively correlated with all three inflammatory markers; the Spearman correlations were r=0.18 for CRP (P=0.0002), r=0.33 for IL-6 (P<0.0001), and r=0.31 for TNFR-2 (P<0.0001). After adjusting for age and smoking status, BMI was positively correlated with CRP (r=0.32, P<0.0001) and IL-6 (r=0.25, P<0.0001). Alcohol intake was inversely correlated with TNFR-2 (r=−0.17, P<0.0003), and dairy food intake was negatively correlated with plasma IL-6 levels (r=−0.10, P=0.04). Physical activity was inversely correlated with all inflammatory biomarkers; CRP (r=−0.13, P=0.01), IL-6 (r=−0.12, P=0.02), and TNFR-2 (r=−0.10, P=0.03).

Table 3 shows the main associations between baseline plasma inflammatory markers and colorectal cancer risk. Results of age- and smoking-adjusted models (via matching) were similar to multivariable adjusted results. Overall, we found no statistically significant associations of plasma levels of CRP, IL-6 and TNFR-2 with risk of colorectal cancer, although we observed a nonsignificant positive trend for TNFR-2 (P_{trend}=0.05) in the multivariate-adjusted model. Results were similar when we excluded cases diagnosed within the first two years after blood draw to reduce the potential influence of undiagnosed colorectal cancer on levels of biomarkers (supplemental table 1). In addition, no significant associations were seen when we stratified the analysis by colon or rectal cancer (supplemental table 2).

To test the hypotheses that TNFR-2 is associated with risk of colorectal cancer among non-users of aspirin, we evaluated the association between plasma inflammatory markers and colorectal cancer risk by aspirin versus placebo. We found that higher plasma TNFR-2 level was significantly associated with an increased risk of colorectal cancer risk only among men in the placebo group ($RR_{highest\ vs.\ lowest\ tertile}$ =1.77; 95% CI=1.02–3.06; P_{trend}=0.02), but not among men assigned to aspirin (P_{trend}=0.72), although the interaction was not statistically significant (Table 4). In addition, a positive association with higher TNFR-2 level was also observed among those who drink alcohol more than once per week (P_{trend}=0.02), though no significant interaction between the two variables was observed. There was no apparent modification of the association between TNFR-2 and colorectal cancer risk by other variables (i.e., seafood intake and physical activity, data not shown). No apparent modification of associations by aspirin was seen for plasma CRP and IL-6.

4. Discussion

Overall, in this large prospective nested case-control study, we found no statistically significant associations between plasma levels of CRP, IL-6, and TNFR-2 and subsequent risk of colorectal cancer, though there was a statistically non-significant positive trend between TNFR-2 and colorectal cancer risk.

Accumulating evidence suggests that chronic inflammation plays an important role in the development of colorectal carcinoma. Chronic inflammation may promote colorectal carcinogenesis through production of reactive oxygen and nitrogen species, enhanced survival and proliferation of preneoplastic cells, and increase in vascular permeability[1]. One prior study, the Nurses' Health Study, has shown a significant association between TNFR-2 level and colorectal cancer risk in women (RR=1.67, 95% CI=1.05–2.68, P_{trend}=0.03)[12]. We did not observe a significant association between plasma TNFR-2 level and colorectal cancer risk, though there was a positive trend with a similar magnitude of risk estimates in comparison to the data from the Nurses' Health Study (RR=1.55, 95% CI=0.95–2.54, P_{trend}=0.05). The Health Professionals Follow-up Study, an ongoing prospective cohort composed of male health professionals, also showed no significant association between TNFR-2 level and colorectal cancer risk. Further investigation will be needed to elucidate whether gender modifies the association between TNFR-2 and colorectal cancer.

In our study, higher TNFR-2 was significantly associated with colorectal cancer risk among individuals in the placebo group (highest vs. lowest tertile RR=1.77; 95% CI=1.02–3.06; P_{trend}=0.02), but not in the aspirin group (P_{trend}=0.72). This may suggest that aspirin exerts its carcinoprotective effect via blocking TNFα pathway. Supporting this explanation, it has been shown that blocking TNFα in mice reduces colorectal carcinogenesis associated with chronic colitis[22]. However, it should be noted that the interaction between TNFR-2 and aspirin was not significant in the current study, and whether aspirin modifies the association between TNFR-2 and colorectal cancer requires further study.

The null association between plasma CRP level and colorectal cancer risk observed in the present study is in line with the majority of previous studies[11–16,18,19]. The totality of the current evidence, as summarized in previous meta-analyses, suggests that CRP is weakly associated with an increased risk for colorectal cancer[23,24]. Our null association between plasma IL-6 level and colorectal cancer risk was consistent with conclusions from most previous published prospective studies[9,12,13,25], and meta-analyses[24,25]. In one study, IL-6 levels were associated with colorectal cancer risk, but the association did not remain significant after further adjustment for insulin[20]. Of note, in the Health Professionals Follow-up Study, there was a significant association of IL-6 with colorectal cancer among lean men17, which was not observed in this study. Lastly, data from the prospective CLUE II cohort suggest that there is a significant association between IL-6 levels and risk of colon cancer[25]. While our study did not confirm this finding, more prospective research is required to determine whether plasma IL-6 levels are associated with colon cancer risk.

The major strengths of this study include its nested design in a prospective randomized aspirin trial with relatively large sample size, a high follow-up rate, and long follow-up time. These strengths allowed us to specifically assess the effect modification by aspirin. Pre-diagnostic measurement of inflammatory markers minimized the potential influence of existing cancer. Prospectively collected detailed data on lifestyle risk factors for colorectal cancer permit control for potential confounding factors.

This study has limitations. As in any observational study, residual confounding may still exist although we have adjusted known colorectal cancer risk factors. Second, one single

measurement of inflammatory markers may not represent a person's inflammatory status during the development of colorectal cancer. One of the concerns is that plasma inflammatory markers not only reflect chronic inflammation, but also acute phase response. To address this issue, we did an additional analysis after excluding participants with CRP level > 10 mg/L, and the null association between CRP and colorectal cancer risk remained. Third, the level of inflammatory markers was measured during the run-in period when aspirin was given to all participants, which could have affected inflammatory marker levels. Moreover, the aspirin trial was only conducted for five years (1982–1987) and, after that, over 70% of the study participants took aspirin[26]. Therefore, these would have significantly attenuated the true association that we would observe in this study.

5. Conclusions

Baseline CRP and IL-6 were not associated with colorectal cancer risk in this prospective cohort after adjustment for risk factors for colorectal cancer. There was a statistically non-significant positive trend between TNFR-2 and colorectal cancer risk and we found a significant association in men who were in the placebo group during the 5-year aspirin trial, though the interaction between TNFR-2 and aspirin was not significant. More prospective observational studies are required to fully understand the relationship between the role of TNFα pathway, aspirin, and colorectal cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Haiyan Zhang, Virginia Piaseczny, and Eunjung Kim for their assistance in data management and technical assistance. The authors are also indebted to the participants in the Physicians' Health Study.

Grant Support

This study was supported by Grant Numbers CA42182, CA097193, CA019894, U54CA155626 from the National Cancer Institute, by Grant Numbers HL26490 and HL34595 from the National Heart, Lung, and Blood Institute, and a grant (019894) from the National Cancer Institute of Canada. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Heart, Lung, and Blood Institute. This work was also supported by National Institute of Health grants R01 CA137178 (to A.T.C.). A.T.C. is a Damon Runyon Cancer Foundation Clinical Investigator.

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Highlights

- In this nested case-control study of the Physicians' Health Study, a randomized trial of aspirin, we prospectively investigated the associations of plasma C-reactive protein, interleukin-6, and tumor necrosis factor receptor 2 (TNFR-2) with future risk of colorectal cancer, and whether aspirin modified these associations among 268 colorectal cancer patients and 446 age- and smoking-matched controls.
- Plasma inflammatory markers were not significantly associated with colorectal cancer risk among men, though there was a statistically non-significant positive trend between TNFR-2 and colorectal cancer risk.
- There was a statistically significant association between elevated TNFR-2 levels and colorectal cancer risk only in the placebo arm, but not in the aspirin arm, though the interaction between TNFR-2 and aspirin was not significant.
- These findings contribute to a growing body of evidence indicating that chronic inflammation is implicated in colorectal carcinogenesis, and more specifically, TNFR-2 may serve as a useful biomarker for increased risk of colorectal cancer. Further research is needed to confirm these findings.

Table 1

Baseline characteristics of study participants in the Physician's Health Study (PHS)

Baseline characteristics	Cases (n =268)	Controls (n =446)	P-value*
Mean age at randomization ± SD (y)	59.3 (8.8)	57.4 (8.1)	Matched
Smoking status, no. (%)			Matched
Never	105 (39)	188 (42)	
Past	139 (52)	219 (49)	
Current	24 (9)	39 (9)	
Mean age at diagnosis ± SD (y)	67.8 (8.8)	.	.
CRP (mg/L), median (IQR)	1.12 (0.56–2.32)	1.03 (0.50–2.11)	0.31
IL-6 (pg/mL), median (IQR)	1.28 (0.92–2.03)	1.10 (0.80–1.79)	0.02
TNFR-2 (pg/mL), median (IQR)	2453 (2027–2847)	2293 (1945–2722)	0.049
BMI, no. (%)			0.16
<23 kg/m^2	50 (19)	116 (26)	
23–24.9 kg/m^2	90 (33)	144 (32)	
25–26.9 kg/m^2	77 (29)	114 (26)	
27 kg/m^2	51 (19)	72 (16)	
Aspirin assignment, no. (%)	133 (50)	230 (52)	0.61
Diabetes, no. (%)	11 (4)	11 (2)	0.47
Multivitamin use, no. (%)			0.93
Never	169 (63)	281 (63)	
Past	43 (16)	69 (16)	
Current	56 (21)	94 (21)	
Vigorous exercise, no. (%)			0.46
<1 time per week	76 (28)	118 (26)	
1–4 times per week	143 (53)	259 (58)	
≥5 times per week	49 (18)	69 (16)	
Alcoholic intake, no. (%)			0.01
≤1 time per week	79 (30)	182 (41)	
2–6 times per week	103 (38)	139 (31)	
≥1 time per day	86 (32)	125 (28)	
Seafood intake ≥2–4 servings/week, no. (%)	54 (20)	115 (26)	0.06
Dairy food intake > 1 serving/day, no. (%)	114 (43)	221 (50)	0.04

*P values were calculated using the Mantel-Haenszel test for categorical variables and the paired t test for log transformed plasma CRP, IL-6, and TNFR-2.

IQR: Inter-quartile range.

Table 2

Partial Spearman correlation coefficients between CRP, IL-6, TNFR-2, BMI, and aspirin assignment and lifestyle risk factors among controls*

Variable	CRP	IL-6	TNFR-2	Age	Smoking	BMI	Alcohol intake	Seafood intake	Dairy food intake	Physical activity
CRP	1.000	0.50	0.25	0.18	0.06	0.32	−0.01	−0.04	0.04	−0.13
		<0.0001	<0.0001	0.0002	0.23	<0.0001	0.89	0.41	0.38	0.01
IL-6		1.00	0.20	0.33	0.10	0.25	−0.03	−0.004	−0.10	−0.12
			<0.0001	<0.0001	0.05	<0.0001	0.60	0.94	0.04	0.02
TNFR-2			1.000	0.31	−0.05	0.06	−0.17	−0.04	0.05	−0.10
				<0.0001	0.33	0.23	0.0003	0.47	0.30	0.03

*Age and smoking status (ever smoking vs. never smoking) were adjusted.

Table3

Relative risk of colorectal cancer according to quartiles of plasma CRP, IL-6, and TNFR-2 *

		Quartile of Biomarkers				P value for trend †
		Q1	Q2	Q3	Q4	
CRP						
	Median (mg/L) ‡	0.29	0.71	1.49	3.94	
	No. of cases/controls	60/111	59/111	76/111	72/110	
	Matching factor adjusted OR **	1.00 (referent)	0.94 (0.60–1.49)	1.20 (0.78–1.85)	1.07 (0.69–1.66)	0.72
	Multivariable adjusted OR §	1.00 (referent)	0.96 (0.59–1.56)	1.09 (0.68–1.75)	0.98 (0.61–1.58)	0.92
IL-6						
	Median (pg/mL)	0.65	0.95	1.32	2.70	
	No. of cases/controls	46/110	61/110	76/111	78/108	
	Matching factor adjusted OR	1.00 (referent)	1.30 (0.81–2.07)	1.49 (0.94–2.36)	1.46 (0.90–2.35)	0.29
	Multivariable adjusted OR §	1.00 (referent)	1.29 (0.79–2.11)	1.37 (0.84–2.24)	1.27 (0.75–2.13)	0.72
TNFR-2						
	Median (pg/mL)	1749	2136	2463	3097	
	No. of cases/controls	56/110	57/111	67/110	87/110	
	Matching factor adjusted OR	1.00 (referent)	1.01 (0.63–1.60)	1.19 (0.75–1.87)	1.49 (0.94–2.36)	0.06
	Multivariable adjusted OR §	1.00 (referent)	0.99 (0.61–1.61)	1.23 (0.76–1.99)	1.55 (0.95–2.54)	0.05

* Numbers in parenthesis are 95% CIs.

** Adjusted for age and smoking status

§ Adjusted for aspirin assignment (yes or no), body mass index (<23, 23–24.99, 25–26.99, and ≥27 kg/m^2), alcohol intake (≤1 time per week, 2–6 times per week, ≥1 time per day), physical activity (<1 time per week, 1–4 times per week, ≥5 times per week), multivitamin use (never, past, current use), and seafood and dairy food intake (quartile).

† Tests for linear trend were conducted using the median values for each quartile of biomarker.

‡ Medians were calculated among controls.

Table 4

Association of the risk of colorectal cancer with plasma TNFR-2 and aspirin assignment, BMI, and alcohol consumption*

	Plasma TNFR-2 tertiles						P value for trend†§
	T1		T2		T3		
	No. of case/control subjects	RR (95% CI)	No. of case/control subjects	RR (95% CI)	No. of case/control subjects	RR (95% CI)	
Aspirin assignment							
No	35/73	1.00 (referent)	37/70	1.11 (0.61–2.00)	62/71	1.77 (1.02–3.06)	0.02
Yes	40/74	1.16 (0.65–2.08)	38/77	1.03 (0.57–1.85)	55/76	1.44 (0.82–2.53)	0.72
$P_{interaction}$=0.34							
BMI							
<25 kg/m^2	47/92	1.00 (referent)	36/84	0.82 (0.47–1.42)	57/81	1.32 (0.80–2.18)	0.29
≥25 kg/m^2	28/55	1.01 (0.57–1.78)	39/63	1.17 (0.69–2.01)	60/66	1.69 (1.00–2.85)	0.08
$P_{interaction}$=0.52							
Alcohol intake							
≤1 time/week	22/48	1.00 (referent)	17/61	0.52 (0.24–1.16)	40/66	1.27 (0.65–2.47)	0.91
>1 time/week	53/99	1.08 (0.57–2.05)	58/85	1.41 (0.74–2.69)	76/79	1.90 (1.02–3.55)	0.02
$P_{interaction}$=0.68							

*Numbers in parenthesis are 95% CIs.

†Tests for linear trend were conducted using the median values for each tertile of biomarker.

§Adjusted for aspirin assignment (yes or no), body mass index <23, 23–24.99, 25–26.99, and ≥27 kg/m^2), alcohol intake (≤1 time per week, 2–6 times per week, ≥1 time per day), physical activity (<1 time per week, 1–4 times per week, ≥5 times per week), multivitamin use (never, past, current use), and seafood and dairy foods intake (quartile). Stratified variable was excluded from each multivariate model.