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A Peripheral Circulating T_H1 Cytokine Profile Is Inversely Associated with Prostate Cancer Risk in CLUE II

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Abstract

Background—T_H1 cytokines, such as IFNγ and TNFα, and potentially innate cytokines, such as IL6, can potentiate the immune response to tumor. Cytokines, such as IL1β, IL8, and IL10, may suppress anticancer immunity. Thus, we prospectively evaluated the association between peripheral-cytokine concentrations and prostate cancer.

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Methods—We conducted an age-race matched case–control study (268 pairs) of incident prostate cancer in CLUE-II. We measured plasma IFNγ, IL10, IL12p70, IL1β, IL6, IL8, and TNFα concentrations using an ultrasensitive multiplex kit. ORs and 95% confidence intervals (CI) were calculated using conditional logistic regression.

Results—The OR of prostate cancer decreased across quartiles of IFNγ (highest vs. lowest quartiles: OR, 0.49; 95% CI, 0.30–0.81; P_{trend} = 0.006), TNFα (OR, 0.56; 95% CI, 0.33–0.96; P_{trend} = 0.01), and IL6 (OR, 0.46; 95% CI, 0.26–0.79; P_{trend} = 0.007). Higher TNFα (OR, 0.28; 95% CI, 0.09–0.85; P_{trend} = 0.01) and IL6 (OR, 0.20; 95% CI, 0.06–0.67; P_{trend} = 0.003) concentrations were associated with lower Gleason sum ≥7 disease risk. Other cytokines were not as clearly associated with risk.

Conclusions—Men with a prediagnostic circulating T_H1 profile and higher IL6 may have a lower risk of prostate cancer, including aggressive disease. Whether this profile reflects (i) an intraprostatic immune environment in benign tissue that protects against prostate cancer, (ii) the immune milieu in response to a prostate adenocarcinoma that inhibits tumor growth and detectability, and/or (iii) a systemic immune profile that mediates the influence of modifiable factors on risk, warrants additional study.

Impact—Identifying specific inflammatory cytokines associated with prostate cancer may lead to improved prevention and treatment strategies.

Introduction

A better understanding of the etiology of prostate cancer may foster novel prevention and treatment strategies. Chronic inflammation, a causal factor for multiple cancers (1–5), has a purported role in the etiology of prostate cancer (6–8). Cytokines are important regulators of the immune response, including in cancer.

In the context of cancer, proinflammatory T_H1 cytokines, such as IFNγ, TNFα, IL12, and, to some extent, IL6, can drive antitumor immunity (9, 10). Conversely, T_H2 cytokines, such as IL4, IL5, and IL13, are associated with antibody production and with allergy and asthma (11, 12). In several cancer models, smoldering T_H2 inflammation has been associated with cancer progression (13). Finally, innate cytokines, such as IL1β and IL8, have also been associated with cancer progression (14, 15). Thus, the character of a cancer patient's immune response may be an important prognostic factor for disease-free survival. Whether the circulating cytokine profile influences prostate cancer risk is understudied.

In this study, we prospectively evaluated whether circulating concentrations of IFNγ, TNFα, IL12, IL10, IL1β, IL6, and IL8 are associated with prostate cancer incidence in the CLUE II cohort. On the basis of our prior genetic studies in CLUE II (16), we specifically hypothesized that men with higher circulating IL10 concentrations would have a lower risk of prostate cancer. For the other cytokines, the work was exploratory. Although most cytokines act locally (e.g., at the tissue level), we postulated that broad tendencies, including inherent, toward either a T_H1 or a suppressive profile might be reflected peripherally in circulation. To begin to address this postulation, we also evaluated the cross-sectional association between candidate SNPs and concentrations of inflammatory cytokines.

Materials and Methods

Study population

We conducted a nested case–control study in CLUE II, a community-based cohort study initiated in 1989 in Washington County, MD. A total of 32,898 men and women, one third of the adult population of the county at the time of recruitment, participated. Forty-one percent were men and 98% were white. Men who were free of a cancer diagnosis at baseline (except possibly for nonmelanoma skin cancer) before blood draw were eligible to be a case or control in this analysis. Participants completed a brief medical and exposure history and a food frequency questionnaire at baseline. Blood samples were collected at baseline, processed within 24 hours, and stored at −70°C. Follow-up questionnaires were mailed to study participants in 1996, 1998, and 2000. The Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD) approved this study.

Cases and controls

Prostate cancer cases were identified by linkage with the Washington County Cancer Registry, and starting in 1992, additionally by linkage with the Maryland Cancer Registry. Abstracted information included age, date, stage, and Gleason sum at diagnosis. Prostate adenocarcinoma was histologically confirmed after blood draw through December 2002 in 269 men. Prostate cancer cases were classified as clinically organ-confined (T1 or T2) or advanced (T3, T4, N+, M+, or fatal), and as low (Gleason sum < 7) or high (≥7) grade. A participant was eligible to be a control for a case if he was still alive at the date of the case's diagnosis and he did not have a subsequent cancer diagnosis. Controls were individually matched to cases by time since last meal, age and date of blood draw, and race.

Cytokines

Plasma cytokines were measured using the Meso-Scale Discovery (MSD; Gaithersburg, MD) Ultrasensitive Proinflammatory multiplex kit. The MSD multispot array was run according to the manufacturer's protocol with minor modifications. Calibration curves were prepared ranging from 2,500 pg/mL to 0.15 pg/mL. Plates were read using the MS2400 imager (MSD). Samples for each case and matched control were assayed adjacently, but in random order. Each participant sample was assayed in replicate. The percentage of replicates that had a concentration below the lower limit of detection (LOD) for IFNγ, TNFα, IL10, IL12, IL1β, IL6, and IL8 were 33.1%, 0.09%, 0.65%, 6.52%, 41.9%, 0.47%, and 0.09%, respectively. Mean replicate concentrations were used in the analysis irrespective of whether one or both values were below the LOD. With exception of IFNγ and IL1β, the replicate means for each cytokine were all above the LOD.

To determine assay reliability for the CLUE samples, we calculated the coefficient of variation (CV%) for each man's replicates when both had concentrations above the LOD. The mean CV%s for IFNγ, TNFα, IL10, IL12, IL1β, IL6, and IL8 were 14.9%, 3.8%, 9.7%, 10.8%, 19.7%, 8.0%, and 3.4%, respectively. Cytokine concentrations in frozen plasma (heparin) are generally stable (17, 18).

Covariates

Information collected at baseline included age, race, attained education level, smoking status, use of diabetes medications and prescription and over-the-counter aspirin and other NSAIDs in the past 48 hours, current height and weight, and weight at the age of 21 years. Previously, we genotyped SNPs in genes encoding cytokines (16).

Statistical analysis

The paired *t* test (or the Wilcoxon sign rank test) and the McNemar test were used to test for differences between cases and controls in continuous and categorical variables, respectively. Cytokine concentrations were right skewed. We transformed them using the natural logarithm to achieve normality. We estimated geometric mean cytokine concentration among white controls by cytokine genotype. The association between the cytokines and prostate cancer risk overall and by stage and grade was evaluated by quartile of each marker. Quartile cutpoints were determined from the distribution of the cytokine concentrations in the cases and controls combined. For IFNγ and IL1β, mean replicate concentrations below the LOD were assigned to the lowest quartile. Conditional logistic regression was used to calculate ORs and 95% confidence intervals (CI) taking into account the matching factors (matched analysis, Model 1), and smoking status and body mass index (BMI; multivariable-adjusted analysis, Model 2). To test for trend, a linear model was fit using the median concentration of each cytokine quartile. Stratified analyses were conducted for age (≥65 vs. 65 years; median) and BMI (<25 vs. ≥25 kg/m^2) using unconditional logistic regression adjusting for matching factors. Interaction terms were tested using the Wald test.

Results

Baseline characteristics

Mean baseline age was 64 years and 2.2% of participants were African American (Table 1). Cases and controls did not differ on family history of prostate cancer, attained education, marital status, BMI, smoking status, or use of aspirin or other NSAIDs. Cases were less likely to use diabetes medications than controls. Mean age at diagnosis was 70 years, 22% had advanced disease, and 31% had Gleason sum ≥7 disease. Mean time between blood draw and diagnosis was 5.5 ± 3.1 years.

Baseline plasma cytokine concentrations by variation in genes encoding cytokines

Although cytokines typically act locally, we postulated that the tendency, including genetic, to have a particular usual cytokine profile might be reflected in circulation. However, geometric mean cytokine concentrations did not differ by cytokine genotype in the white controls (Table 2).

Baseline plasma cytokine concentrations in prostate cancer cases and controls

Geometric mean concentrations of IFNγ and TNFα were lower in cases than controls (Table 3). There was no statistically significant difference in IL6, IL10, IL12p70, IL1β, or IL8 concentrations between cases and controls.

Association of T_H1 cytokines with prostate cancer risk

The OR of prostate cancer decreased with increasing IFNγ (highest vs. lowest quartiles: OR, 0.49; 95% CI, 0.30–0.81; P_{trend} = 0.006) and TNFα (OR, 0.56; 95% CI, 0.33–0.96; P_{trend} = 0.01) concentrations in the matched analysis (Table 4). Further adjustment for smoking status and BMI did not change the associations appreciably (Table 4). Mutual adjustment for IFNγ (P_{trend} = 0.05) and TNFα (P_{trend} = 0.09) slightly attenuated the association for these cytokines. IL12p70 concentration was not associated with prostate cancer risk (P_{trend} = 0.99).

Higher IFNγ concentration was inversely associated with organ-confined disease (highest vs. lowest quartiles: matched OR, 0.51; 95% CI, 0.25–1.02; P_{trend} = 0.05), but not advanced disease or grade (data not shown). Higher TNFα concentration was inversely associated with Gleason sum ≥7 disease (OR, 0.28; 95% CI, 0.09–0.85; P_{trend} = 0.01), but not Gleason sum <7 disease or stage (data not shown). IL12p70 concentration was not associated with prostate cancer stage or grade.

The magnitude of the inverse associations for IFNγ and TNFα was generally the same as overall after excluding cases diagnosed within 2 (N = 220, 82%) or 5 years (N = 126, 47%) of blood draw (Supplementary Table S1). The associations between the T_H1 cytokines and prostate cancer risk did not seem to be modified by age or obesity (all $P_{interaction} \geq 0.10$).

Association of the anti-inflammatory cytokine IL10 with prostate cancer risk

IL10 concentration was not associated with prostate cancer risk either in the matched- or multivariable-adjusted analysis (Table 4). Furthermore, IL10 concentration was not clearly associated with stage or grade (data not shown). The association between IL10 and prostate cancer risk was similarly null after excluding cases diagnosed within 2 or 5 years of blood draw (Supplementary Table S1). However, in normal weight men (BMI <25 kg/m^2), higher IL10 concentration was inversely associated with prostate cancer risk (versus lowest quartile: OR, 0.35; 95% CI, 0.19–0.66; P_{trend} = 0.14). In contrast, in overweight and obese men (BMI ≥25 kg/m^2), IL10 concentration was not associated with risk (OR, 1.32; 95% CI, 0.88–2.00; P_{trend} = 0.15; $P_{interaction}$ = 0.0007). The association between IL10 and prostate cancer was not modified by age ($P_{interaction} \geq 0.39$).

Association of the innate cytokines IL6, IL1β, and IL8 with prostate cancer risk

Higher IL6 concentration was inversely associated with prostate cancer risk in both matched (highest vs. lowest quartile: OR, 0.46; 95% CI, 0.26–0.79; P_{trend} = 0.007) and multivariable-adjusted (OR, 0.45; 95% CI, 0.26–0.78; P_{trend} = 0.005) analyses. Results were similar when excluding cases diagnosed within the first 2 years, but were marginally attenuated and nonsignificant after excluding cases diagnosed within 5 years of follow-up (Supplementary Table S1). Higher IL6 concentration was inversely associated with advanced (matched OR, 0.29; 95% CI, 0.09–0.93; P_{trend} = 0.02) and high-grade (matched OR, 0.20; 95% CI, 0.06–0.67; P_{trend} = 0.003) disease, but not clinically organ-confined or low-grade disease (data not shown).

Although not statistically significant, IL1β was possibly inversely associated with prostate cancer risk, including after excluding cases diagnosed within 2 years (matched OR, 0.70; 95% CI, 0.42–01.14; P_{trend} = 0.11) and 5 years (matched OR, 0.68; 95% CI, 0.41–1.12; P_{trend} = 0.10) of blood draw, and with high-grade disease (OR, 0.51; 95% CI, 0.21–1.23; P_{trend} = 0.13). IL8 concentration was not associated with prostate cancer risk or by stage or grade. Age and obesity did not modify the associations of IL6, IL1β, or IL8 with prostate cancer risk (all $P_{interaction} \geq 0.11$).

Discussion

In this prospective study, circulating cytokine concentrations indicative of a T_H1 type immune response, IFNγ and TNFα, were inversely associated with prostate cancer risk. Higher TNFα concentration was associated with a lower risk of high-grade disease. IL6, a cytokine indicative of an innate immune response, and which has been shown to be associated with antitumor T cells in melanoma (19), also was inversely associated with prostate cancer risk, especially advanced and high-grade disease. IL1β was also possibly inversely associated with prostate cancer risk. The other cytokines, including IL10, were not associated with risk. However, in normal weight, but not overweight/obese men, higher concentration of IL10, a suppressive, anti-inflammatory cytokine, was inversely associated with prostate cancer risk.

Our results support the hypothesis that T_H1 cytokines, including IFNγ and TNFα, may function to prevent tumor development. T_H1-type cytokines contribute to inflammatory reactions essential for effective responses against tumor cells (20). Animal models show that T_H1-type cytokines may serve a protective role against cancer (21). Kaplan and colleagues demonstrated that endogenously produced IFNγ in mice models formed the basis of a tumor surveillance system that controlled the development of tumors that were chemically induced and those that occurred spontaneously (21). In the study, IFNγ receptor-deficient mice developed chemically induced tumors more often and more quickly than wild-type mice. Very few epidemiologic studies have addressed this hypothesis for cancer in humans by measuring circulating T_H1 cytokine levels. A nested case–control study of 270 endometrial cancer cases and 518 matched controls reported that endometrial cancer risk was significantly higher in patients with higher prediagnostic TNFα concentration (22). The direction of this association is opposite from what we observed for prostate cancer. To our knowledge, no epidemiology study has evaluated the association between prediagnostic concentration of IFNγ or TNFα and prostate cancer.

We had expected that IL10 would be inversely associated with prostate cancer risk because of its anti-inflammatory actions and because we had previously observed that SNPs in the *IL10* promoter that led to greater IL10 production were inversely associated with prostate cancer in CLUE II (16). IL10 can affect the pathogenesis of prostate cancer by directly inhibiting production of proinflammatory cytokines, such as IL6, TNFα, IL8, or by indirectly inhibiting tumor invasion and metastasis (23, 24). Men with higher BMI had a higher IL10 level, a finding that is consistent with previous studies (25). In overweight and obese men, higher IL10 concentration was associated with greater prostate cancer risk, which may signify overproduction of IL10 due to greater adiposity; this may not, however,

reflect the inter-prostatic environment. In normal weight men, higher IL10 concentration was inversely associated with prostate cancer. Elevated IL10 level in normal weight men may be indicative of inflammatory stimuli from sources unrelated to adiposity. In normal weight men, prediagnostic circulating IL10 concentration may signify anti-inflammatory processes occurring at the prostate. These anti-inflammatory processes may serve an antitumorigenic role, resulting in lower future prostate cancer risk.

We also noted an inverse association and a possible inverse association for two of the innate immune response cytokines. For IL6, the inverse association was present, in particular, for advanced and for high-grade disease. Our results differ from those in the Physician's Health Study, which were null (26). IL6 seems to have divergent roles in early stage (i.e., prediagnostic) and late stage (i.e., prevalent prostate cancer). It is well established that patients with prostate cancer have elevated IL6 concentrations (8, 27), which may serve as a marker for advanced disease, and may mediate morbidity in these patients (27). Like many cytokines, IL6 is markedly elevated in obese people but in normal weight people, elevated concentrations may signify inflammatory stimuli from sources unrelated to adiposity (26, 28). Obesity did not modify the IL6 association in our study. In our study, IL1β seemed to be inversely associated with prostate cancer, although not statistically significant. To our knowledge, no studies have reported an association between prediagnostic levels of IL1β and prostate cancer incidence.

Although most cytokines act locally at the tissue level, we postulated that broad tendencies toward either a proinflammatory or suppressive profile, including inherent, might be reflected peripherally in circulation. To examine this hypothesis, we cross-sectionally evaluated the association between SNPs in genes encoding cytokines and circulating cytokine concentrations. The SNPs were selected because they were known or suspected to influence the production or function of the cytokines or were previously associated with other cancers (16). However, concentrations did not differ across genotype in the controls. A possible explanation includes that we measured cytokine concentrations only at one point in time, which may not be reflective of the usual blood concentrations. Results from other human studies reporting a potential association between these SNPs and cytokine concentration are conflicting (29–33).

Several factors should be considered when interpreting our findings. This is the first study, to our knowledge, to evaluate the association between prediagnostic cytokine profile and prostate cancer incidence. Important strengths of this study include a well-established community-based cohort with comprehensive outcome ascertainment. The cytokines were measured using an assay with relatively high sensitivity and precision. Degradation of the cytokines in stored plasma is unlikely to explain the results as cases and control were stored for the same length of time and were handled in the same manner to preserve comparisons. We were able to explore the possible influence of undiagnosed cancer on the findings; none was found.

There are some limitations to the study as well. The relatively small sample size limited the ability to conduct extensive subgroup analyses, especially for advanced prostate cancer. Inflammatory cytokines can be elevated for reasons unrelated to cancer. Noncancer illnesses

that can elevate cytokine concentration may cause an attenuation of the association between inflammatory cytokines and prostate cancer incidence. Also, the CV%s of IFNγ (14.9%) and IL1β (19.7%) were higher than for the other cytokines. Imprecision of their measurement may have attenuated their associations with prostate cancer. In addition, the study population was largely white, which precluded our ability to determine whether the findings are generalizable to other racial/ ethnic groups.

In summary, we found that men with a prediagnostic circulating cytokine profile consistent with a T_H1 immune response and also some cytokines involved in the innate immune response may have a lower future risk of prostate cancer, including aggressive disease. Whether circulating cytokine profile reflects (i) the intraprostatic immune environment in benign tissue that protects against the development of prostate cancer, (ii) the immune milieu in response to a yet undetected prostate adenocarcinoma that inhibits its growth and thus detectability, and/or (iii) a systemic immune profile that mediates the influence of modifiable factors on prostate cancer risk, warrants additional study. The IL10–obesity interaction also warrants further study. Identifying specific inflammatory cytokines that are associated with prostate cancer incidence may lead to improved prostate cancer prevention and treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of prostate cancer cases and controls, CLUE II

Characteristics	Cases	Controls	*P*
Number	268	268	
Mean age at blood draw (SD, y)	64 (9.0)	64 (9.0)	matched
African American (%)	2.2	2.2	matched
Family history of prostate cancer (%)	13.4	9.9	0.26
Mean attained education (SD, y)	12.3 (3.4)	12.1 (3.4)	0.40
Married (%)	88.4	85.5	0.33
Mean current BMI (SD; kg/m^2)	26.4 (3.5)	26.7 (3.2)	0.25
Cigarette smoking status (%)			
Never	39.9	38.4	0.72
Former	51.5	52.6	0.80
Current	8.6	9.0	0.88
Use of a diabetes medication in the past 48 hours (%)	2.6	5.6	0.07
Use of aspirin or other NSAIDs in the past 48 hours (%)	33.2	34.7	0.71

Table 2

Geometric mean cytokine concentration (pg/mL) among white controls by cytokine genotype, CLUE II

	Major/major allele		Minor/major allele		Minor/minor allele		
	N **(%)**	**Mean (95% CI)**	***N*** **(%)**	**Mean (95% CI)**	***N*** **(%)**	**Mean (95% CI)**	***P***
TNFα							
		GG		AG		AA	
rs1800629	335 (66.5%)	8.01 (7.55–8.49)	149 (29.5%)	7.60 (6.96–8.31)	20 (4.0%)	8.40 (6.60–10.69)	0.56
IL10							
		GG		AG		AA	
rs1800896	141 (27.4%)	2.61 (2.11–2.32)	249 (48.4%)	2.43 (2.07–2.86)	125 (24.3%)	2.76 (2.20–3.47)	0.66
		CC		AC		AA	
rs1800872	315 (61.4%)	2.43 (1.36–4.36)	179 (34.9%)	2.82 (2.33–3.41)	19 (3.7%)	2.43 (1.36–4.36)	0.42
IL1β							
		TT		CT		CC	
rs1143627	236 (48.5%)	0.34 (0.30–0.39)	188 (38.6%)	0.28 (0.24–0.33)	63 (12.9%)	0.28 (0.21–0.36)	0.12
IL8							
		TT		AT		AA	
rs4073	131 (25.7%)	20.1 (16.7–24.2)	267 (52.5%)	21.6 (19.0–24.5)	111 (21.8%)	19.6 (16.1–24.0)	0.69
IL6							
		GG		AG		AA	
rs1800797	178 (35.1%)	1.38 (1.25–1.52)	244 (48.1%)	1.36 (1.25–1.48)	85 (16.8%)	1.49 (1.29–1.73)	0.54
		GG		CG		CC	
rs1800796	461 (91.1%)	1.37 (1.29–1.46)	44 (8.7%)	1.54 (1.26–1.88)	1 (0.2%)	0.90 (0.24–3.42)	0.47
		GG		CG		CC	
rs1800795	175 (34.7%)	1.38 (1.24, 1.53)	247 (48.9%)	1.35 (1.24, 1.47)	83 (16.4%)	1.50 (1.30, 1.74)	0.48

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Table 3

Geometric mean concentration (pg/mL) of cytokines in prostate cancer cases and controls, CLUE II

Cytokine	Case (*n* = 268)	Control (*n* = 268)	*P*
IFNγ	0.72 (0.64–0.82)	0.92 (0.83–1.03)	0.004
IL10	2.53 (2.18–2.94)	2.59 (2.20–3.06)	0.82
IL12p70	2.64 (2.17–3.21)	2.72 (2.20–3.36)	0.84
IL1β	0.28 (0.24–0.32)	0.29 (0.25–0.34)	0.74
IL6	1.32 (1.23–1.43)	1.45 (1.33–1.58)	0.13
IL8	20.4 (18.0–23.2)	20.8 (18.3–23.7)	0.84
TNFα	7.50 (7.05–7.98)	8.27 (7.73–8.86)	0.04

Table 4

OR of prostate cancer by quartile[a] of cytokine concentration, CLUE II

Cytokine	Q1 (lowest)	Q2	Q3	Q4 (highest)	P_{trend}
IFNγ					
Median concentration (pg/mL)	0.41	0.72	1.01	2.12	
Case/controls	100/71	50/47	61/73	57/77	
Matched OR (95% CI)	1.00 (ref.)	0.73 (0.44–1.21)	0.58 (0.36–0.93)	0.49 (0.30–0.81)	0.006
Multivariable adjusted[b] OR (95% CI)	1.00 (ref.)	0.69 (0.41–1.17)	0.58 (0.36–0.93)	0.46 (0.27–0.76)	0.004
IL10					
Median concentration (pg/mL)	1.0	1.54	2.27	6.86	
Case/controls	64/70	74/60	60/74	70/64	
Matched OR (95% CI)	1.00 (ref.)	1.47 (0.86–2.51)	0.89 (0.52–1.51)	1.30 (0.77–2.21)	0.65
Multivariable adjusted[b] OR (95% CI)	1.00 (ref.)	1.49 (0.87–2.56)	0.86 (0.50–1.47)	1.28 (0.75–2.18)	0.72
IL12p70					
Median concentration (pg/mL)	0.67	1.40	2.87	11.12	
Case/controls	67/67	73/61	60/74	68/66	
Matched OR (95% CI)	1.00 (ref.)	1.17 (0.72–1.91)	0.82 (0.50–1.35)	1.01 (0.61–1.67)	0.99
Multivariable adjusted[b] OR (95% CI)	1.00 (ref.)	1.21 (0.73–1.99)	0.80 (0.48–1.33)	0.98 (0.59–1.63)	0.85
IL1β					
Median concentration (pg/mL)	0.16	0.30	0.39	0.87	
Case/controls	118/109	23/18	66/68	61/73	
Matched OR (95% CI)	1.00 (ref.)	1.21 (0.61–2.42)	0.88 (0.57–1.36)	0.76 (0.49–1.18)	0.20
Multivariable adjusted[b] OR (95% CI)	1.00 (ref.)	1.15 (0.57–2.32)	0.89 (0.57–1.39)	0.74 (0.48–1.17)	0.18
IL6					
Median concentration (pg/mL)	0.72	1.12	1.59	2.58	
Case/controls	76/58	66/68	72/62	54/80	
Matched OR (95% CI)	1.00 (ref.)	0.71 (0.44–1.16)	0.81 (0.48–1.36)	0.46 (0.26–0.79)	0.007
Multivariable adjusted[b] OR (95% CI)	1.00 (ref.)	0.72 (0.44–1.18)	0.81 (0.48–1.37)	0.45 (0.26–0.78)	0.005
IL8					
Median concentration (pg/mL)	6.63	12.7	25.8	73.1	

Cytokine	Q1 (lowest)	Q2	Q3	Q4 (highest)	P_{trend}
Case/controls	70/64	67/67	62/72	69/65	
Matched OR (95% CI)	1.00 (ref.)	0.90 (0.54–1.48)	0.79 (0.48–1.29)	0.94 (0.57–1.54)	0.92
Multivariable adjusted[a] OR (95% CI)	1.00 (ref.)	0.92 (0.55–1.53)	0.81 (0.49–1.33)	0.94 (0.57–1.54)	0.97
TNFα					
Median concentration (pg/mL)	4.68	6.45	8.35	13.3	
Case/controls	71/63	76/58	65/69	56/78	
Matched OR (95% CI)	1.00 (ref.)	1.10 (0.68–1.78)	0.78 (0.47–1.30)	0.56 (0.33–0.96)	0.01
Multivariable adjusted[b] OR (95% CI)	1.00 (ref.)	1.12 (0.69–1.82)	0.81 (0.48–1.35)	0.58 (0.36–0.99)	0.02

[a] Quartile cutpoints were determined from the distribution of the cytokine concentrations in the cases and controls combined. For IFNγ and IL1β, mean replicate concentrations below the LOD were assigned to the lowest quartile.

[b] Taking into account the matching factors, time since last meal, age and date of blood draw, and race, and adjusting for smoking status and BMI.