American Journal of Epidemiology
Vol. 177, No. 1
DOI: 10.1093/aje/kws359
Advance Access publication:
November 20, 2012

Original Contribution

Association Between Prediagnostic Biomarkers of Inflammation and Endothelial Function and Cancer Risk: A Nested Case-Control Study

Mathilde Touvier*, Léopold Fezeu, Namanjeet Ahluwalia, Chantal Julia, Nathalie Charnaux, Angela Sutton, Caroline Méjean, Paule Latino-Martel, Serge Hercberg, Pilar Galan, and Sébastien Czernichow

* Correspondence to Dr. Mathilde Touvier, Nutritional Epidemiology Unit, INSERM U557, Paris 13 University, 74 rue Marcel Cachin, F-93017 Bobigny, France (e-mail: m.touvier@uren.smbh.univ-paris13.fr).

Initially submitted July 11, 2011; accepted for publication January 6, 2012.

Experimental and prevalent case-control studies suggest an association between biomarkers of inflammation, endothelial function, and adiposity and cancer risk, but results from prospective studies have been limited. The authors' objective was to prospectively examine the relations between these biomarkers and cancer risk. A nested case-control study was designed within the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) Study, a nationwide French cohort study, to include all first primary incident cancers diagnosed between 1994 and 2007 ($n = 512$). Cases were matched with randomly selected controls ($n = 1,024$) on sex, age (in 2-year strata), body mass index (weight (kg)/height $(m)^2$; <25 vs. ≥25), and SU.VI.MAX intervention group. Conditional logistic regression was used to study the associations between prediagnostic levels of high-sensitivity C-reactive protein (hs-CRP), adiponectin, leptin, soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1, soluble E-selectin, and monocyte chemoattractant protein 1 and cancer risk. All statistical tests were 2-sided. Plasma sICAM-1 level was positively associated with breast cancer risk (for quartile 4 vs. quartile 1, multivariate odds ratio (OR) = 1.86, 95% confidence interval (CI): 1.06, 3.26; $P_{trend} = 0.048$). Plasma hs-CRP level was positively associated with prostate cancer risk (for quartile 4 vs. quartile 1, multivariate OR = 3.04, 95% CI: 1.28, 7.23; $P_{trend} = 0.03$). These results suggest that prediagnostic hs-CRP and sICAM-1 levels are associated with increased prostate and breast cancer risk, respectively.

breast neoplasms; case-control studies; C-reactive protein; intercellular adhesion molecule 1; neoplasms; prostatic neoplasms

Abbreviations: CI, confidence interval; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; OR, odds ratio; Q, quartile; SD, standard deviation; sICAM-1, soluble intercellular adhesion molecule 1; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; sVCAM-1, soluble vascular cell adhesion molecule 1.

Editor's note: *An invited commentary on this article appears on page 14.*

The identification of prediagnostic biomarkers associated with subsequent cancer risk is a key challenge. Markers of inflammation, adiposity, and endothelial adhesion may be good candidates (1–4). C-reactive protein (CRP), which is produced in the liver in response to elevated cytokine levels after an inflammatory stimulus, is a widely used systemic biomarker for diagnosing acute and chronic inflammation (5). White adipose tissue plays a critical role in the regulation of inflammatory processes, as an endocrine organ, and produces adipokines (6). Leptin is a proinflammatory adipokine inducing T helper 1 cells. Its serum level strongly correlates with proportion of body fat stores. Conversely, adiponectin production is decreased in obesity and generally acts as an antiinflammatory factor. Adhesion

Table 1. Baseline Characteristics of Cancer Cases and Controls, SU.VI.MAX Cohort, France, 1994–2007

	Breast Cancer Cases ($n = 218$ cases)			Prostate Cancer Cases ($n = 156$ cases)			Overall Cancer Cases ($n = 512$)			Controls ($n = 1,024$)			*P* Value[a]
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Age, years			49.2 (6.1)			54.9 (4.8)			51.4 (6.1)			51.5 (6.1)	0.9
Sex													1.0
Male							229	44.7		458	44.7		
Female							283	55.3		566	55.3		
Body mass index[b]													0.3
<25	164	75.2		74	47.4		314	61.3		628	61.3		
25–<30	37	17.0		67	43.0		150	29.3		323	31.5		
≥30	17	7.8		15	9.6		48	9.4		73	7.1		
Height, cm			162.8 (6.2)			173.4 (6.7)			167.6 (8.3)			166.7 (8.3)	0.05
Intervention group													1.0
Yes	109	50.0		73	46.8		258	50.4		516	50.4		
No (placebo)	109	50.0		83	53.2		254	49.6		508	49.6		
Smoking status													0.001
Never smoker	126	57.8		63	40.4		245	47.9		516	50.4		
Former smoker	46	21.1		75	48.1		175	34.2		392	38.3		
Current smoker	46	21.1		18	11.5		92	18.0		116	11.3		
Alcohol intake, g/day			9.2 (11.2)			24.1 (19.9)			16.6 (18.6)			14.9 (16.7)	0.06
Physical activity													0.2
Low	64	29.4		35	22.4		129	25.2		259	25.3		
Moderate	75	34.4		40	25.6		156	30.5		273	26.7		
High	79	36.2		81	51.9		227	44.3		492	48.1		
Educational level, years													0.3
<12	130	59.6		89	57.1		306	59.8		584	57.0		
≥12	88	40.4		67	43.0		206	40.2		440	43.0		
PSA level for men, ng/mL						3.6 (3.6)			2.9 (3.3)			1.3 (1.5)	<0.0001
PSA category for men, ng/mL													<0.0001
<3				96	61.5		164	71.6		425	92.8		
≥3				60	38.5		65	28.4		33	7.2		
Plasma hs-CRP level, mg/L			2.1 (4.3)			2.5 (5.1)			2.5 (5.9)			2.1 (4.5)	0.006
Plasma sICAM-1 level, ng/mL			247.0 (80.0)			245.2 (65.5)			253.2 (80.0)			240.3 (65.4)	0.005
Plasma sVCAM-1 level, ng/mL			689.5 (226.9)			682.5 (194.6)			689.0 (233.9)			683.8 (200.7)	0.8

Table continues

Table 1. Continued

	Breast Cancer Cases ($n = 218$ cases)			Prostate Cancer Cases ($n = 156$ cases)			Overall Cancer Cases ($n = 512$)			Controls ($n = 1,024$)			*P* Value[a]
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Plasma soluble E-selectin level, ng/mL			33.8 (14.7)			41.0 (15.3)			38.1 (16.2)			37.9 (15.1)	0.8
Plasma MCP-1 level, pg/mL			248.7 (159.4)			278.8 (85.9)			266.0 (129.2)			257.5 (113.8)	0.1
Plasma leptin level, ng/mL			13.0 (12.0)			5.3 (4.6)			9.6 (9.7)			9.8 (10.3)	0.6
Plasma adiponectin level, μg/mL			13.8 (9.0)			7.1 (3.7)			10.6 (7.7)			11.0 (8.7)	0.4

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; MCP-1, monocyte chemoattractant protein 1; PSA, prostate-specific antigen; sICAM-1, soluble intercellular adhesion molecule 1; SD, standard deviation; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; sVCAM-1, soluble vascular cell adhesion molecule 1.

[a] *P* value for the comparison between overall cancer cases and controls by Student's *t* test or χ^2 test where appropriate. Data for biomarker variables were log-transformed to improve normality. All statistical tests were 2-sided.

[b] Weight (kg)/height $(m)^2$.

molecules such as E-selectin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1, and the chemokine monocyte chemoattractant protein 1 (MCP-1) are important in cell–cell and cell–basement membrane interactions. They are also intimately involved in inflammatory reactions (7).

For all of these biomarkers, a role in carcinogenesis has been postulated, notably based on prevalent case-control studies that have reported higher serum/plasma levels of CRP (2), leptin (3), and soluble adhesion molecules (7–9) and lower levels of adiponectin (1) in patients with cancer compared with controls, for various cancer sites. Studies on single nucleotide polymorphisms in the genes of CRP (10, 11), adipokines (12–14), and soluble adhesion molecules (15–17) have also suggested that these markers may affect cancer risk. The prognostic use of these markers has also been demonstrated in many forms of cancer (18–21). However, few prospective studies published so far have provided relevant analyses to investigate the relations between these biomarkers and cancer risk, and where results exist they are conflicting (22–28).

Thus, our objective was to prospectively examine the relations between biomarkers of inflammation, adiposity, and endothelial function and development of cancer.

MATERIALS AND METHODS

Study population

The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study was a population-based, double-blind, placebo-controlled, randomized trial initially designed to assess the relation of daily antioxidant supplementation to the incidence of cardiovascular disease and cancer (29). A total of 13,017 subjects were enrolled throughout France in 1994–1995. The intervention study lasted 8 years, and follow-up for health events was maintained until July 2007. Subjects provided written informed consent, and the study was approved by the Ethical Committee for Studies with Human Subjects at the Paris-Cochin Hospital and the Commission nationale de l'informatique et des libertés.

Baseline data collection

At enrollment, all participants underwent a clinical examination and had anthropometric measurements taken by study nurses and physicians. They completed questionnaires on sociodemographic data, smoking, alcohol intake, and physical activity. A 35-mL venous blood sample was collected in Vacutainer tubes (Becton Dickinson, Rungis, France) from participants who had been fasting for 12 hours at the time of the visit. Blood samples were centrifuged immediately after blood draw, and plasma aliquots were then preserved in sodium heparin. Less than 1 hour after blood draw, plasma aliquots were stored at −20°C in dry ice for shipment to the central biobank (maximum 24 hours), where they were stored frozen in liquid nitrogen (−70°C). For male participants, total prostate-specific antigen level was measured by immunometry (Roche

Table 2. Odds Ratios for the Relations Between Biomarkers of Inflammation, Endothelial Function, and Adiposity and Overall Cancer Risk From Conditional Logistic Regression Analyses[a], SU.VI.MAX Cohort, France, 1994–2007

	No. of Cases	No. of Controls	Unadjusted[b] Results		Results From Multivariate Model[c]		Results From Multivariate Model Including All Studied Biomarkers	
			OR	95% CI	OR	95% CI	OR	95% CI
hs-CRP								
Q1	111	272	1	Reference	1	Reference	1	Reference
Q2	124	261	1.17	0.86, 1.60	1.18	0.86, 1.62	1.20	0.87, 1.66
Q3	119	265	1.13	0.82, 1.55	1.08	0.78, 1.49	1.10	0.78, 1.53
Q4	158	226	1.81	1.32, 2.48	1.78	1.28, 2.47	1.78	1.26, 2.52
P for trend			0.0006		0.002		0.004	
sICAM-1								
Q1	113	269	1	Reference	1	Reference	1	Reference
Q2	129	258	1.21	0.89, 1.64	1.23	0.90, 1.67	1.32	0.96, 1.82
Q3	118	265	1.05	0.77, 1.43	1.05	0.77, 1.45	1.09	0.78, 1.53
Q4	152	232	1.56	1.16, 2.11	1.48	1.09, 2.02	1.51	1.06, 2.14
P for trend			0.012		0.035		0.068	
sVCAM-1								
Q1	139	244	1	Reference	1	Reference	1	Reference
Q2	121	265	0.81	0.60, 1.08	0.83	0.62, 1.13	0.80	0.59, 1.10
Q3	116	266	0.76	0.56, 1.04	0.77	0.56, 1.05	0.70	0.50, 0.97
Q4	136	249	0.95	0.71, 1.27	0.99	0.73, 1.34	0.85	0.61, 1.18
P for trend			0.7		0.9		0.3	
Soluble E-selectin								
Q1	126	257	1	Reference	1	Reference	1	Reference
Q2	134	250	1.08	0.81, 1.45	1.09	0.81, 1.47	1.00	0.74, 1.36
Q3	113	272	0.85	0.63, 1.16	0.84	0.62, 1.14	0.79	0.57, 1.09
Q4	139	245	1.17	0.86, 1.58	1.14	0.83, 1.56	1.01	0.72, 1.42
P for trend			0.7		0.9		0.5	

Table continues

Diagnostics, Mannheim, Germany) using a specific antibody with a highly sensitive technique standardized to the reference Stanford material (30).

Cases ascertainment

Confirmed or suspected events were self-declared by subjects during the follow-up process. Investigations were conducted in all cases to obtain medical data from participants, physicians, and/or hospitals. All information was reviewed by an independent expert committee, and cases were validated by pathologic report and classified using the *International Classification of Diseases, Tenth Revision, Clinical Modification*.

Nested case-control study

Among the 890 first primary invasive incident cancer cases diagnosed between inclusion in the SU.VI.MAX cohort in 1994 and July 2007, 368 had missing data for body mass index (weight (kg)/height $(m)^2$; measured during the clinical examination) or for a prediagnostic blood sample at baseline and were not included in the present study. Ten cases were further excluded because no control was available in the cohort with the required matching criteria. For each cancer case, 2 controls were randomly selected from participants of identical sex, age (in 2-year strata), body mass index (<25 vs. ≥25), and intervention group, with complete follow-up and without cancer diagnosis by the end of follow-up.

Baseline plasma samples of the corresponding subjects were used to determine the levels of high-sensitivity CRP (hs-CRP), leptin, adiponectin, soluble ICAM-1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), soluble E-selectin, and MCP-1. Biomarkers' levels were determined with an enzyme-linked immunosorbent assay sandwich technique (R&D Laboratory Systems, Minneapolis, Minnesota). Three samples of known concentrations were tested in 30 separate assays to assess interassay precision. Three samples of known concentrations were tested 20 times on 1 plate to assess intraassay precision. The intraassay and interassay coefficients of variation were all less

Table 2. Continued

	No. of Cases	No. of Controls	Unadjusted[b] Results		Results From Multivariate Model[c]		Results From Multivariate Model Including All Studied Biomarkers	
			OR	95% CI	OR	95% CI	OR	95% CI
MCP-1								
Q1	119	261	1	Reference	1	Reference	1	Reference
Q2	130	258	1.11	0.82, 1.50	1.07	0.79, 1.46	1.03	0.75, 1.41
Q3	130	252	1.13	0.84, 1.53	1.09	0.80, 1.48	1.04	0.76, 1.42
Q4	133	253	1.16	0.85, 1.58	1.08	0.79, 1.48	1.03	0.74, 1.43
P for trend			0.3		0.6		0.6	
Leptin								
Q1	134	249	1	Reference	1	Reference	1	Reference
Q2	121	264	0.85	0.63, 1.16	0.82	0.60, 1.12	0.77	0.55, 1.06
Q3	126	258	0.91	0.67, 1.23	0.87	0.63, 1.20	0.82	0.58, 1.14
Q4	131	253	0.97	0.68, 1.38	0.84	0.56, 1.25	0.70	0.46, 1.07
P for trend			0.9		0.4		0.2	
Adiponectin								
Q1			1	Reference	1	Reference	1	Reference
Q2	135	248	0.83	0.61, 1.12	0.86	0.63, 1.17	0.87	0.63, 1.19
Q3	119	265	0.98	0.72, 1.33	1.04	0.76, 1.41	1.11	0.80, 1.52
Q4	134	251	0.88	0.65, 1.19	0.92	0.67, 1.26	0.92	0.66, 1.27
P for trend	124	260	0.6		0.9		1.0	

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; MCP-1, monocyte chemoattractant protein-1; OR, odds ratio; Q, quartile; sICAM-1, soluble intercellular adhesion molecule 1; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; sVCAM-1, soluble vascular cell adhesion molecule 1.

[a] Cutoffs for sex-specific quartiles were: hs-CRP—0.6, 1.1, 2.2 in men and 0.5, 0.9, 1.9 in women; sICAM-1—199.0, 243.8, 288.0 in men and 194.0, 232.0, 272.8 in women; sVCAM-1—532.6, 652.0, 786.0 in men and 538.0, 652.0, 800.0 in women; soluble E-selectin—41.5, 30.6, 51.4 in men and 23.6, 33.0, 42.9 in women; MCP-1—225.0, 267.0, 315.0 in men and 183.0, 222.0, 268.0 in women; leptin—2.4, 4.1, 6.6 in men and 5.9, 10.0, 17.0 in women; adiponectin—4.3, 6.4, 9.2 in men and 8.9, 12.0, 16.3 in women. All statistical tests were 2-sided.

[b] Cases and controls were matched by sex, age, body mass index, and SU.VI.MAX intervention group.

[c] Adjusted for sex, age, body mass index, height, SU.VI.MAX intervention group, alcohol intake, physical activity, smoking status, and educational level.

than 10%. Hs-CRP had the lowest intraassay coefficient of variation (1.6%), and MCP-1 had the highest (6.2%). Hs-CRP had the lowest interassay coefficient of variation (3.6%), and soluble E-selectin had the highest (9.1%). Thirty specimens were measured as blinded duplicates on separated plates and showed only small variations for the second decimal digit. Cases and matched controls were measured on the same plate, but the case/control status of each sample within a plate was not known by the investigator (blinded determination). Specimens with values below the detection limit were observed only for leptin, and they represented only 2.5% of the totality of biologic samples. These observations were handled by conferring on them the detection limit value indicated by the manufacturer. For the other analytes, no sample exhibited values below the detection limit.

Statistical analyses

The participants' baseline characteristics were compared between cases and controls using Student's *t* tests or χ^2 tests. Associations between biomarkers and incident cancer were examined with conditional logistic regression models and expressed as odds ratios with 95% confidence intervals. Associations of biomarkers with overall, breast, and prostate cancer risk were successively tested. Associations between each single biomarker and cancer risk were studied in nonadjusted and multivariate models. Multivariate models that simultaneously included all biomarkers were also fitted. For all models, the odds ratios for sex-specific quartiles and the odds ratios for a 1-standard-deviation (SD) increase in the corresponding biomarker (considered as a continuous variable) were both computed. Multivariate models were adjusted for sex, age, body mass index, height, SU.VI.MAX intervention group, alcohol intake, physical activity, smoking status, educational level, and baseline prostate-specific antigen level (for prostate cancer analyses only). Further adjustment for other site-specific classical risk factors was also tested: family history of breast cancer, number of children, use of hormone replacement therapy for menopause and menopausal status at baseline (in breast cancer analyses), and family history of prostate cancer (in

Table 3. Odds Ratios for the Relations Between Biomarkers of Inflammation, Endothelial Function, and Adiposity and Breast Cancer Risk From Conditional Logistic Regression Analyses[a], SU.VI.MAX Cohort, France, 1994–2007

	No. of Cases	No. of Controls	Unadjusted[b] Results		Results From Multivariate Model[c]		Results From Multivariate Model Including All Studied Biomarkers	
			OR	95% CI	OR	95% CI	OR	95% CI
hs-CRP								
Q1	52	112	1	Reference	1	Reference	1	Reference
Q2	55	109	1.09	0.68, 1.75	1.16	0.71, 1.88	1.30	0.77, 2.19
Q3	53	111	1.05	0.66, 1.67	0.93	0.57, 1.51	1.06	0.63, 1.79
Q4	58	104	1.24	0.75, 2.05	1.25	0.73, 2.14	1.40	0.79, 2.49
P for trend			0.5		0.7		0.4	
sICAM-1								
Q1	48	123	1	Reference	1	Reference	1	Reference
Q2	57	104	1.44	0.90, 2.32	1.47	0.90, 2.41	1.75	1.03, 2.98
Q3	49	116	1.07	0.67, 1.72	1.15	0.70, 1.89	1.43	0.83, 2.47
Q4	64	93	1.77	1.12, 2.81	1.57	0.97, 2.54	1.86	1.06, 3.26
P for trend			0.05		0.1		0.048	
sVCAM-1								
Q1	61	92	1	Reference	1	Reference	1	Reference
Q2	51	114	0.69	0.44, 1.08	0.72	0.46, 1.15	0.72	0.44, 1.17
Q3	50	123	0.61	0.38, 0.98	0.64	0.39, 1.04	0.56	0.33, 0.95
Q4	56	107	0.79	0.50, 1.25	0.84	0.51, 1.36	0.72	0.42, 1.24
P for trend			0.3		0.4		0.1	
Soluble E-selectin								
Q1	56	114	1	Reference	1	Reference	1	Reference
Q2	63	104	1.19	0.77, 1.84	1.25	0.80, 1.95	1.11	0.69, 1.79
Q3	45	116	0.80	0.50, 1.28	0.79	0.48, 1.28	0.72	0.42, 1.23
Q4	54	102	1.08	0.67, 1.74	1.02	0.61, 1.70	0.90	0.51, 1.60
P for trend			0.8		0.5		0.3	

Table continues

prostate cancer analyses). Two-way interactions between each biomarker and smoking status were explored, but no interaction was detected.

All statistical tests were 2-sided, and $P < 0.05$ was considered significant. All analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 512 incident cancer cases were diagnosed during follow-up: 218 breast cancers, 156 prostate cancers, and 138 other cancers (50 colorectal cancers, 32 thyroid cancers, 24 lung cancers, 20 skin melanomas, 8 esophagus cancers, and 4 stomach cancers). Thus, a total of 512 sets of 1 case and 2 matched controls were included for the current analyses. Median follow-up time was 6.5 years in cases and 13 years in controls. Characteristics of cancer cases and noncases are described in Table 1. Overall cancer cases were more frequently current smokers and had higher prostate-specific antigen levels at baseline (for men).

In multivariate models, plasma hs-CRP level (for quartile 4 (Q4) vs. quartile 1 (Q1), odds ratio (OR) = 1.78, 95% confidence interval (CI): 1.28, 2.47; *P* for trend = 0.002) and plasma sICAM-1 level (for Q4 vs. Q1, OR = 1.48, 95% CI: 1.09, 2.02; *P* for trend = 0.035) were associated with increased overall cancer risk (Table 2). When all biomarkers were entered simultaneously into a multivariate model, the association with hs-CRP remained statistically significant (*P* for trend = 0.004), but the association with sICAM-1 became borderline nonsignificant (*P* for trend = 0.068; Table 2).

Regarding findings on site-specific cancers, in the multivariate model including all biomarkers, sICAM-1 was significantly associated with increased breast cancer risk (for Q4 vs. Q1, OR = 1.86 (95% CI: 1.06, 3.26), *P* for trend = 0.048 (Table 3); for a 1-SD increase, OR = 1.26 (95% CI: 1.03, 1.53), *P* = 0.02 (data not tabulated)). Hs-CRP was significantly associated with increased prostate cancer risk when data were considered as quartiles (for Q4 vs. Q1, multivariate OR = 3.04, 95% CI: 1.28, 7.23; *P* for trend = 0.03) (Table 4), though this association was not detected when hs-CRP was coded as a continuous variable

Table 3. Continued

	No. of Cases	No. of Controls	Unadjusted[b] Results		Results From Multivariate Model[c]		Results From Multivariate Model Including All Studied Biomarkers	
			OR	95% CI	OR	95% CI	OR	95% CI
MCP-1								
Q1	52	114	1	Reference	1	Reference	1	Reference
Q2	54	110	1.08	0.68, 1.72	1.10	0.68, 1.79	1.04	0.63, 1.73
Q3	53	100	1.16	0.73, 1.85	1.25	0.77, 2.01	1.22	0.74, 2.00
Q4	59	112	1.17	0.73, 1.86	1.14	0.70, 1.85	1.09	0.66, 1.81
P for trend			0.5		0.5		0.5	
Leptin								
Q1	55	103	1	Reference	1	Reference	1	Reference
Q2	64	102	1.16	0.73, 1.83	1.09	0.67, 1.76	0.99	0.59, 1.65
Q3	51	116	0.80	0.51, 1.26	0.81	0.50, 1.33	0.75	0.44, 1.29
Q4	48	115	0.69	0.39, 1.20	0.64	0.34, 1.20	0.51	0.26, 1.02
P for trend			0.09		0.1		0.08	
Adiponectin								
Q1	58	110	1	Reference	1	Reference	1	Reference
Q2	48	119	0.77	0.49, 1.23	0.80	0.50, 1.30	0.83	0.50, 1.38
Q3	55	102	1.04	0.64, 1.68	1.12	0.68, 1.85	1.29	0.76, 2.21
Q4	57	105	1.04	0.65, 1.67	1.13	0.68, 1.87	1.15	0.67, 1.97
P for trend			0.6		0.4		0.3	

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; MCP-1, monocyte chemoattractant protein-1; OR, odds ratio; Q, quartile; sICAM-1, soluble intercellular adhesion molecule 1; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; sVCAM-1, soluble vascular cell adhesion molecule 1.

[a] Cutoffs for female-specific quartiles were: hs-CRP—0.5, 0.9, 1.9; sICAM-1—194.0, 232.0, 272.8; sVCAM-1—538.0, 652.0, 800.0; soluble E-selectin—23.6, 33.0, 42.9; MCP-1—183.0, 222.0, 268.0; leptin—5.9, 10.0, 17.0; adiponectin—8.9, 12.0, 16.3. All statistical tests were 2-sided.

[b] Cases and controls were matched by sex, age, body mass index, and SU.VI.MAX intervention group.

[c] Adjusted for age, body mass index, height, SU.VI.MAX intervention group, alcohol intake, physical activity, smoking status, and educational level.

(for a 1-SD increase, OR = 1.03, 95% CI: 0.82, 1.30; $P = 0.8$).

Further adjustment for other site-specific classical risk factors did not modify the findings. Sensitivity analysis excluding cases that were diagnosed during the first 2 years of follow-up (54 cases) did not modify the results, nor did sensitivity analyses excluding subjects with the highest hs-CRP values (>17.25 ng/mL (i.e., mean +3 SDs); 18 subjects) (data not shown).

DISCUSSION

Plasma hs-CRP level was associated with increased overall and prostate cancer risk in this prospective study. A positive association between plasma sICAM-1 level and risk of breast cancer was also observed, independently of other known risk factors. Growing evidence from mechanistic (31–33), genetic (10), and epidemiologic (2) studies points to a role of inflammation in carcinogenesis (34). Serum/plasma CRP level has been found to be elevated in patients with various malignancies (35). Elevated CRP is also a predictor of lower survival rates in patients with cancer after surgical resection (35). It has been suggested that inflammation creates a tissue microenvironment where the reactive oxygen and nitrogen species released by inflammatory cells could cause potentially malignant DNA alterations (31) and that some inflammatory cytokines and proteins in chronic inflammation promote tumor growth (36).

Consistent with our finding, prospective studies have shown a higher overall cancer risk in subjects with elevated prediagnostic serum CRP levels (2, 11, 22, 24, 37, 38). However, uncertainty remains as to whether this association is restricted to certain cancer locations and which cancer sites are of particular concern. Several studies have suggested that increased lung cancer risk is particularly associated with hs-CRP levels and could partly drive observations for overall cancer risk (11, 39). In our study, the number of lung cancer cases was insufficient to perform specific analysis for this location. In contrast, consistent with our findings of a null association between hs-CRP and breast cancer risk, a recent meta-analysis found similar results; those authors reported an odds ratio for breast cancer of 1.10 (95% CI: 0.97, 1.26) for a log unit increase in CRP level (24).

Table 4. Odds Ratios for Each Biomarker and Prostate Cancer Risk From Conditional Logistic Regression Analyses[a], SU.VI.MAX Cohort, France, 1994–2007

	No. of Cases	No. of Controls	Unadjusted[b] Results		Results From Multivariate Model[c]		Results From Multivariate Model Including All Studied Biomarkers	
			OR	95% CI	OR	95% CI	OR	95% CI
hs-CRP								
Q1	28	82	1	Reference	1	Reference	1	Reference
Q2	41	84	1.43	0.80, 2.56	1.76	0.84, 3.69	2.06	0.90, 4.71
Q3	35	83	1.23	0.66, 2.31	1.70	0.77, 3.75	1.83	0.75, 4.48
Q4	52	63	2.56	1.41, 4.65	2.52	1.18, 5.39	3.04	1.28, 7.23
P for trend			0.04		0.03		0.03	
sICAM-1								
Q1	39	82	1	Reference	1	Reference	1	Reference
Q2	43	82	1.10	0.65, 1.85	1.30	0.68, 2.52	1.19	0.56, 2.50
Q3	37	75	1.03	0.59, 1.82	1.33	0.64, 2.76	1.10	0.49, 2.47
Q4	37	73	1.07	0.62, 1.83	1.36	0.69, 2.69	1.00	0.43, 2.34
P for trend			0.9		0.4		0.8	
sVCAM-1								
Q1	35	72	1	Reference	1	Reference	1	Reference
Q2	39	79	1.02	0.58, 1.78	1.06	0.51, 2.20	0.85	0.36, 1.99
Q3	42	83	1.04	0.60, 1.81	1.05	0.50, 2.22	0.86	0.36, 2.07
Q4	40	78	1.05	0.61, 1.81	1.33	0.66, 2.71	1.16	0.50, 2.70
P for trend			0.8		0.4		0.6	
Soluble E-selectin								
Q1	43	72	1	Reference	1	Reference	1	Reference
Q2	37	83	0.77	0.45, 1.29	0.81	0.41, 1.59	0.66	0.31, 1.42
Q3	33	81	0.69	0.40, 1.20	0.80	0.41, 1.56	0.64	0.30, 1.35
Q4	43	76	0.97	0.56, 1.65	1.22	0.61, 2.43	0.84	0.38, 1.88
P for trend			0.8		0.6		0.8	

Table continues

In our prospective study, the positive association with hs-CRP was observed for prostate cancer risk. In contrast with our findings, previous results from prospective studies investigating the relation between CRP and prostate cancer (11, 22, 24, 28, 37, 38, 40–42) have been mostly nonsignificant, as was shown in a recent meta-analysis (24). However, most of these studies included few prostate cancer cases (fewer than 100) (24, 37, 38), did not measure CRP with a high-sensitivity assay (28, 38), or focused only on men aged 65 years and older (41). As for the remaining studies, results are conflicting. Three studies obtained nonsignificant results (11, 22, 40), but two of them were not specifically designed to explore cancer of the prostate (11, 22). In contrast, Stark et al. (42) observed that CRP level was positively associated with increased risk of prostate cancer (all grades) among normal-weight men and with increased risk of high-grade prostate cancer among all subjects. Thus, further large prospective studies are needed to better understand whether CRP levels are associated with incident prostate cancer. In a recent study, Meyer et al. (43) showed that persons who were homozygous for the variant allele of rs12757998 had both an increased risk of prostate cancer and increased CRP levels, suggesting a link between genetic variation in the *RNASEL* gene (encoding ribonuclease L) and prostate cancer risk, potentially mediated through inflammation. Regarding prognostic studies, CRP has been observed to be an adverse prognostic marker for men with castration-resistant prostate cancer (21). *CRP* haplotype is also associated with high prostate-specific antigen level as a marker of metastatic prostate cancer (44).

Several prevalent case-control studies have observed higher circulating levels of sICAM-1 in breast cancer cases compared with controls (7–9). Genetic studies showed that some single nucleotide polymorphisms on the *ICAM-1* gene were associated with increased breast cancer risk (16, 17, 45), although this point is debated (46). Higher levels of sICAM-1 were also associated with poorer clinicopathologic features (such as number of metastases and response to chemo-endocrine therapy) and poorer overall survival in a prognostic

Table 4. Continued

	No. of Cases	No. of Controls	Unadjusted[b] Results		Results From Multivariate Model[c]		Results From Multivariate Model Including All Studied Biomarkers	
			OR	95% CI	OR	95% CI	OR	95% CI
MCP-1								
Q1	36	73	1	Reference	1	Reference	1	Reference
Q2	49	78	1.27	0.74, 2.19	1.13	0.58, 2.22	1.10	0.51, 2.36
Q3	38	79	0.98	0.55, 1.74	0.87	0.42, 1.78	0.66	0.29, 1.50
Q4	33	82	0.83	0.47, 1.46	0.59	0.29, 1.21	0.52	0.24, 1.14
P for trend			0.3		0.09		0.07	
Leptin								
Q1	46	81	1	Reference	1	Reference	1	Reference
Q2	27	90	0.54	0.30, 0.96	0.47	0.22, 0.97	0.42	0.19, 0.95
Q3	42	74	1.02	0.59, 1.76	0.89	0.44, 1.77	0.88	0.41, 1.91
Q4	41	67	1.19	0.64, 2.22	0.69	0.27, 1.75	0.58	0.20, 1.68
P for trend			0.3		0.9		0.7	
Adiponectin								
Q1	37	74	1	Reference	1	Reference	1	Reference
Q2	39	84	0.92	0.54, 1.58	0.90	0.45, 1.80	0.78	0.37, 1.65
Q3	40	81	0.99	0.57, 1.71	1.38	0.69, 2.76	1.36	0.63, 2.94
Q4	40	73	1.10	0.64, 1.90	1.34	0.68, 2.61	1.18	0.56, 2.48
P for trend			0.7		0.3		0.1	

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; MCP-1, monocyte chemoattractant protein-1; OR, odds ratio; Q, quartile; sICAM-1, soluble intercellular adhesion molecule 1; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; sVCAM-1, soluble vascular cell adhesion molecule 1.

[a] Cutoffs for male-specific quartiles were: hs-CRP—0.6, 1.1, 2.2; sICAM-1—199.0, 243.8, 288.0; sVCAM-1—532.6, 652.0, 786.0; soluble E-selectin—41.5, 30.6, 51.4; MCP-1—225.0, 267.0, 315.0; leptin—2.4, 4.1, 6.6; adiponectin—4.3, 6.4, 9.2. All statistical tests were 2-sided.

[b] Cases and controls were matched by sex, age, body mass index, and SU.VI.MAX intervention group.

[c] Adjusted for age, body mass index, height, SU.VI.MAX intervention group, alcohol intake, physical activity, smoking status, educational level, and baseline prostate-specific antigen level.

study of metastatic breast cancer (20). However, to the best of our knowledge, our study is the first to have investigated the prospective association between prediagnostic level of sICAM-1 and breast cancer risk. The observed positive association is supported by mechanistic plausibility. Indeed, it has been demonstrated experimentally that sICAM-1 stimulates angiogenesis and neovascularization (47, 48), endothelial cell migration and differentiation (48), and tumor growth (49). In the present study, the association between studied biomarkers and breast cancer risk varied slightly between the model with each biomarker included separately and the model with all biomarkers included simultaneously, the association being stronger for sICAM-1 in the latter model. This probably results from the mechanistic interrelations between the studied biomarkers of endothelial adhesion, inflammation and adiposity. Indeed, it is known that leptin and adiponectin generally act as pro- and antiinflammatory factors, respectively (6), and that the synthesis of adhesion molecules (such as sICAM-1) is stimulated both by leptin and by proinflammatory cytokines (49, 50). The mechanistic synergy between all studied biomarkers is better taken into account in the model which included them all simultaneously. In our study, sICAM-1 was moderately associated with E-selectin, sVCAM-1, MCP-1, and hs-CRP, while its associations with leptin and adiponectin were weaker (Pearson correlation coefficients were 0.4, 0.3, 0.2, 0.2, 0.07, and 0.01, respectively; data not tabulated).

Strengths of our study included the use of multiple biomarkers, the nested case-control design, the reasonably large total number of cancers, and the strong priors. Some limitations should be acknowledged. First, a unique measurement of biomarkers at baseline was performed, and no indication was available regarding transient acute infection (cold, throat infection, etc.) concomitant to blood draw. For some biomarkers such as hs-CRP, although the probability of differential bias between cases and controls is low, this limitation could lead to an attenuation of the strengths of observed associations because of intraindividual variation (51). This may have limited our ability to detect an association between hs-CRP and breast cancer, but conversely, this limitation is unlikely to explain the observed relation between hs-CRP and prostate cancer risk, which was statistically significant despite the potential attenuation of odds ratios. Besides, information on intraclass correlation coefficients

over time is available in the literature for each studied biomarker measured in plasma samples. The reported intraclass correlation coefficients over time were relatively high (0.59 for hs-CRP, 0.86 for E-selectin, 0.62 for sVCAM-1, 0.64 for sICAM-1, 0.70–0.75 for MCP-1, 0.74–0.82 for leptin, and 0.81 for adiponectin), demonstrating that a single blood sample can be used in prospective epidemiologic studies for these biomarkers (52, 53).

Second, controls were selected among persons who had complete follow-up without cancer (and were alive) as of the study end date, without matching on follow-up time. Thus, odds ratios should not be directly extrapolated as rate ratios in our study, since the hypothesis of stability of the exposure distribution over time was probably not fully respected (54). In addition, this may have contributed to driving risk estimates away from the null if the studied biomarkers have causal deleterious effects on the risk of mortality. However, among subjects who did not develop cancer during follow-up in our cohort (i.e., potential controls), the mortality rate (1.1%) and the rate of loss to follow-up (5.2%) were relatively low, limiting the potential for bias.

Next, while the number of total cancers was reasonably large, the number of cancers at any given site was relatively small. This represents a limitation because of heterogeneity in associations by cancer site. In addition, there may be heterogeneity of association even within a cancer site (e.g., localized vs. advanced prostate cancer (42)), but the number of cases in the current study was too small to allow for such a stratified analysis.

Lastly, observed relations could be partly affected by unmeasured or residual confounding. However, a broad range of usual risk factors was accounted for, including specific adjustment factors depending on cancer location.

Our study adds to the current knowledge on inflammation-, adiposity-, and endothelial function-related pathways to development of cancer. For the first time, we have shown a prospective positive association between plasma sICAM-1 level and breast cancer risk. In addition, we observed a positive relation between prediagnostic hs-CRP level and prostate cancer risk, which provides new insights in a context of conflicting literature. Large prospective studies are needed to confirm the pertinence of these biomarkers in cancer risk prediction. If these results are confirmed in validation studies, this could lead to better identification of persons at risk of developing cancer and result in more efficiently targeted cancer screening campaigns.

ACKNOWLEDGMENTS

Author affiliations: Nutritional Epidemiology Unit, National Institute for Health and Medical Research (INSERM) U557/National Institute for Food and Agricultural Research (INRA)/National Academy for Engineering Studies (CNAM)/Paris 13 University, Bobigny, France (Mathilde Touvier, Léopold Fezeu, Namanjeet Ahluwalia, Chantal Julia, Caroline Méjean, Paule Latino-Martel, Serge Hercberg, Pilar Galan); Biochemistry Department, Jean Verdier Hospital, Bondy, France (Nathalie Charnaux, Angela Sutton); Cardiovascular and Bioengineering Team, INSERM U698, Paris 13 University, Bobigny, France (Nathalie Charnaux, Angela Sutton); and Department of Nutrition, Ambroise Paré Hospital, INSERM U1018, Epidemiology and Public Health Center (CESP), University Versailles St.-Quentin, Boulogne-Billancourt, France (Sébastien Czernichow).

This work was supported by grant 2007-1-SPC-3 from the French National Cancer Institute.

The funding sources had no role in the design, conduct, or reporting of this study.

Conflict of interest: none declared.

REFERENCES

1. Barb D, Williams CJ, Neuwirth AK, et al. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. *Am J Clin Nutr*. 2007;86(3):s858–s866.
2. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *J Epidemiol Community Health*. 2007;61(9):824–833.
3. Paz-Filho G, Lim EL, Wong ML, et al. Associations between adipokines and obesity-related cancer. *Front Biosci*. 2011;16(1):1634–1650.
4. van Kilsdonk JW, van Kempen LC, van Muijen GN, et al. Soluble adhesion molecules in human cancers: sources and fates. *Eur J Cell Biol*. 2010;89(6):415–427.
5. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805–1812.
6. Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. *Endocr Regul*. 2009;43(4):157–168.
7. O'Hanlon DM, Fitzsimons H, Lynch J, et al. Soluble adhesion molecules (E-selectin, ICAM-1 and VCAM-1) in breast carcinoma. *Eur J Cancer*. 2002;38(17):2252–2257.
8. Altomonte M, Fonsatti E, Lamaj E, et al. Differential levels of soluble intercellular adhesion molecule-1 (sICAM-1) in early breast cancer and benign breast lesions. *Breast Cancer Res Treat*. 1999;58(1):19–23.
9. Basoglu M, Atamanalp SS, Yildirgan MI, et al. Correlation between the serum values of soluble intercellular adhesion molecule-1 and total sialic acid levels in patients with breast cancer. *Eur Surg Res*. 2007;39(3):136–140.
10. Heikkila K, Silander K, Salomaa V, et al. C-reactive protein-associated genetic variants and cancer risk: findings from FINRISK 1992, FINRISK 1997 and Health 2000 studies. *Eur J Cancer*. 2011;47(3):404–412.
11. Siemes C, Visser LE, Coebergh JW, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. *J Clin Oncol*. 2006;24(33):5216–5222.
12. Kaklamani VG, Wisinski KB, Sadim M, et al. Variants of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes and colorectal cancer risk. *JAMA*. 2008;300(13):1523–1531.
13. Moore SC, Leitzmann MF, Albanes D, et al. Adipokine genes and prostate cancer risk. *Int J Cancer*. 2009;124(4):869–876.
14. Pechlivanis S, Bermejo JL, Pardini B, et al. Genetic variation in adipokine genes and risk of colorectal cancer. *Eur J Endocrinol*. 2009;160(6):933–940.
15. Chen H, Hernandez W, Shriver MD, et al. ICAM gene cluster SNPs and prostate cancer risk in African Americans. *Hum Genet*. 2006;120(1):69–76.
16. Han W, Kang SY, Kang D, et al. Multiplex genotyping of 1107 SNPs from 232 candidate genes identified an

association between IL1A polymorphism and breast cancer risk. *Oncol Rep*. 2010;23(3):763–769.
17. Kammerer S, Roth RB, Reneland R, et al. Large-scale association study identifies ICAM gene region as breast and prostate cancer susceptibility locus. *Cancer Res*. 2004;64(24):8906–8910.
18. Guadagni F, Roselli M, Martini F, et al. Prognostic significance of serum adipokine levels in colorectal cancer patients. *Anticancer Res*. 2009;29(8):3321–3327.
19. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol*. 2009; 27(21):3437–3444.
20. Zhang GJ, Adachi I. Serum levels of soluble intercellular adhesion molecule-1 and E-selectin in metastatic breast carcinoma: correlations with clinicopathological features and prognosis. *Int J Oncol*. 1999;14(1):71–77.
21. Prins RC, Rademacher BL, Mongoue-Tchokote S, et al. C-reactive protein as an adverse prognostic marker for men with castration-resistant prostate cancer (CRPC): confirmatory results. *Urol Oncol*. 2012;30(1):33–37.
22. Allin KH, Bojesen SE, Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. *J Clin Oncol*. 2009;27(13):2217–2224.
23. Chaturvedi AK, Caporaso NE, Katki HA, et al. C-reactive protein and risk of lung cancer. *J Clin Oncol*. 2010; 28(16):2719–2726.
24. Heikkila K, Harris R, Lowe G, et al. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. *Cancer Causes Control*. 2009;20(1):15–26.
25. Lukanova A, Soderberg S, Kaaks R, et al. Serum adiponectin is not associated with risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15(2):401–402.
26. Wei EK, Giovannucci E, Fuchs CS, et al. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. *J Natl Cancer Inst*. 2005;97(22):1688–1694.
27. Aleksandrova K, Jenab M, Boeing H, et al. Circulating C-reactive protein concentrations and risks of colon and rectal cancer: a nested case-control study within the European Prospective Investigation into Cancer and Nutrition. *Am J Epidemiol*. 2010;172(4):407–418.
28. Van Hemelrijck M, Jungner I, Walldius G, et al. Risk of prostate cancer is not associated with levels of C-reactive protein and other commonly used markers of inflammation. *Int J Cancer*. 2011;129(6):1485–1492.
29. Hercberg S, Galan P, Preziosi P, et al. The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*. 2004;164(21):2335–2342.
30. Stamey TA. Second Stanford Conference on International Standardization of Prostate-Specific Antigen Immunoassays: September 1 and 2, 1994. *Urology*. 1995;45(2):173–184.
31. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860–867.
32. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. *Mol Cancer Res*. 2006;4(4):221–233.
33. Schwartsburd PM. Chronic inflammation as inductor of pro-cancer microenvironment: pathogenesis of dysregulated feedback control. *Cancer Metastasis Rev*. 2003;22(1):95–102.
34. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001;357(9255):539–545.
35. Wang CS, Sun CF. C-reactive protein and malignancy: clinico-pathological association and therapeutic implication. *Chang Gung Med J*. 2009;32(5):471–482.
36. Philip M, Rowley DA, Schreiber H. Inflammation as a tumor promoter in cancer induction. *Semin Cancer Biol*. 2004; 14(6):433–439.
37. Il'yasova D, Colbert LH, Harris TB, et al. Circulating levels of inflammatory markers and cancer risk in the Health Aging and Body Composition cohort. *Cancer Epidemiol Biomarkers Prev*. 2005;14(10):2413–2418.
38. Trichopoulos D, Psaltopoulou T, Orfanos P, et al. Plasma C-reactive protein and risk of cancer: a prospective study from Greece. *Cancer Epidemiol Biomarkers Prev*. 2006;15(2):381–384.
39. Pine SR, Mechanic LE, Enewold L, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst*. 2011;103(14): 1112–1122.
40. Helzlsouer KJ, Erlinger TP, Platz EA. C-reactive protein levels and subsequent cancer outcomes: results from a prospective cohort study. *Eur J Cancer*. 2006;42(6):704–707.
41. Pierce BL, Biggs ML, DeCambre M, et al. C-reactive protein, interleukin-6, and prostate cancer risk in men aged 65 years and older. *Cancer Causes Control*. 2009;20(7):1193–1203.
42. Stark JR, Li H, Kraft P, et al. Circulating prediagnostic interleukin-6 and C-reactive protein and prostate cancer incidence and mortality. *Int J Cancer*. 2009;124(11): 2683–2689.
43. Meyer MS, Penney KL, Stark JR, et al. Genetic variation in RNASEL associated with prostate cancer risk and progression. *Carcinogenesis*. 2010;31(9):1597–1603.
44. Eklund CM, Tammela TL, Schleutker J, et al. C-reactive protein haplotype is associated with high PSA as a marker of metastatic prostate cancer but not with overall cancer risk. *Br J Cancer*. 2009;100(12):1846–1851.
45. Arandi N, Talei A, Erfani N, et al. Intercellular adhesion molecule-1 genetic markers (+241G/A and +469A/G) in Iranian women with breast cancer. *Cancer Genet Cytogenet*. 2008;183(1):9–13.
46. Cox DG, Hankinson SE, Hunter DJ. Polymorphisms in the ICAM gene locus are not associated with breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2006;15(1):178–179.
47. Byrne GJ, Ghellal A, Iddon J, et al. Serum soluble vascular cell adhesion molecule-1: role as a surrogate marker of angiogenesis. *J Natl Cancer Inst*. 2000;92(16):1329–1336.
48. Gho YS, Kleinman HK, Sosne G. Angiogenic activity of human soluble intercellular adhesion molecule-1. *Cancer Res*. 1999;59(20):5128–5132.
49. Gho YS, Kim PN, Li HC, et al. Stimulation of tumor growth by human soluble intercellular adhesion molecule-1. *Cancer Res*. 2001;61(10):4253–4257.
50. Curat CA, Miranville A, Sengenes C, et al. From blood monocytes to adipose tissue-resident macrophages: induction of diapedesis by human mature adipocytes. *Diabetes*. 2004;53(5):1285–1292.
51. Platz EA, De Marzo AM, Erlinger TP, et al. No association between pre-diagnostic plasma C-reactive protein concentration and subsequent prostate cancer. *Prostate*. 2004;59(4):393–400.
52. Lee SA, Kallianpur A, Xiang YB, et al. Intra-individual variation of plasma adipokine levels and utility of single measurement of these biomarkers in population-based studies. *Cancer Epidemiol Biomarkers Prev*. 2007;16(11):2464–2470.
53. Linkov F, Gu Y, Arslan AA, et al. Reliability of tumor markers, chemokines, and metastasis-related molecules in serum. *Eur Cytokine Netw*. 2009;20(1):21–26.
54. Knol MJ, Vandenbroucke JP, Scott P, et al. What do case-control studies estimate? Survey of methods and assumptions in published case-control research. *Am J Epidemiol*. 2008; 168(9):1073–1081.