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### ► **To cite this version:**

Mathilde Touvier, Léopold Fezeu Kamedjie, Namanjeet Ahluwalia, Chantal Julia, Nathalie Charnaux, et al.. Pre-diagnostic levels of adiponectin and soluble vascular cell adhesion molecule-1 are associated with colorectal cancer risk. *World Journal of Gastroenterology*, 2012, 18 (22), pp.2805 - 2812. <10.3748/wjg.v18.i22.2805>. <hal-02649500>

**HAL Id: hal-02649500**

**<https://hal.inrae.fr/hal-02649500v1>**

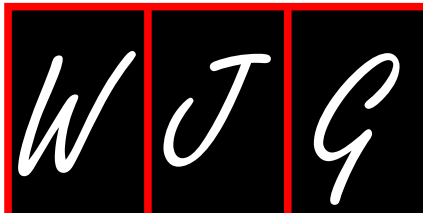
Submitted on 29 May 2020

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## Pre-diagnostic levels of adiponectin and soluble vascular cell adhesion molecule-1 are associated with colorectal cancer risk

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**Supported by** A grant from the French National Cancer Institute (Institut National du Cancer), No. INCa 2007-1-SPC-3

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Received: July 12, 2011 Revised: December 14, 2011

Accepted: March 10, 2012

Published online: June 14, 2012

**METHODS:** A nested case-control study was designed to include all first primary incident colorectal cancer cases diagnosed between inclusion in the SUPplémentation en VItamines et Minéraux AntioXydants cohort in 1994 and the end of follow-up in 2007. Cases ( $n = 50$ ) were matched with two randomly selected controls ( $n = 100$ ). Conditional logistic regression models were used to investigate the associations between pre-diagnostic levels of hs-CRP, adiponectin, leptin, soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1, E-selectin, monocyte chemoattractant protein-1 and colorectal cancer risk. Area under the receiver operating curves (AUC) and relative integrated discrimination improvement (RIDI) statistics were used to assess the discriminatory potential of the models.

**RESULTS:** Plasma adiponectin level was associated with decreased colorectal cancer risk ( $P$  for linear trend = 0.03). Quartiles of sVCAM-1 were associated with increased colorectal cancer risk ( $P$  for linear trend = 0.02). No association was observed with any of the other biomarkers. Compared to standard models with known risk factors, those including both adiponectin and sVCAM-1 had substantially improved performance for colorectal cancer risk prediction ( $P$  for AUC improvement = 0.01, RIDI = 26.5%).

**CONCLUSION:** These results suggest that pre-diagnostic plasma adiponectin and sVCAM-1 levels are associated with decreased and increased colorectal cancer risk, respectively. These relationships must be confirmed in large validation studies.

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**Key words:** Colorectal cancer; Adiponectin; Soluble vascular cell adhesion molecule-1; Nested case-control study;

### Abstract

**AIM:** To examine the relationships between pre-diagnostic biomarkers and colorectal cancer risk and assess their relevance in predictive models.

## Prospective study

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Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, Méjean C, Latino-Martel P, Hercberg S, Galan P, Czernichow S. Pre-diagnostic levels of adiponectin and soluble vascular cell adhesion molecule-1 are associated with colorectal cancer risk. *World J Gastroenterol* 2012; 18(22): 2805-2812 Available from: URL: <http://www.wjnet.com/1007-9327/full/v18/i22/2805.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i22.2805>

## INTRODUCTION

Colorectal cancer is the third most frequently diagnosed cancer worldwide, accounting for more than one million cases and 600 000 deaths every year<sup>[1]</sup>. The identification of pre-diagnostic biomarkers associated with subsequent colorectal cancer risk is a key challenge. Markers of adiposity, endothelial adhesion, and inflammation may be suitable candidates<sup>[2-5]</sup>. Adipose tissue is an endocrine organ that produces adipokines and plays a critical role in the regulation of inflammatory processes<sup>[6]</sup>. Leptin reflects body fat storage and acts as a pro-inflammatory adipokine. Conversely, adiponectin production is decreased in obesity and generally has anti-inflammatory properties. Adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-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<sup>[7]</sup>. C-reactive protein (CRP) is a widely used systemic biomarker for diagnosing acute and chronic inflammation<sup>[8]</sup>.

Previous cross-sectional studies suggest the potential involvement of these biomarkers in colorectal carcinogenesis, with higher blood levels of CRP<sup>[9]</sup>, leptin<sup>[10]</sup>, soluble adhesion molecules<sup>[11,12]</sup>, and lower levels of adiponectin<sup>[10,13]</sup> observed in patients with colorectal cancer compared to controls. The prognostic value of these markers has also been suggested by research with colorectal cancer patients<sup>[10,12]</sup>. However, few prospective studies have investigated the association between these biomarkers and colorectal cancer risk, and the current evidence is conflicting<sup>[14-19]</sup>. In addition, such studies did not evaluate the discriminatory capabilities of these biomarkers regarding colorectal cancer risk by contemporary statistical methods<sup>[20,21]</sup>.

Thus, our objectives were twofold: (1) to prospectively examine the relationships between biomarkers of adiposity, endothelial adhesion, and inflammation and development of colorectal cancer; and (2) to statistically compare the pertinence of models including these bio-

markers to standard models with known risk factors of colorectal cancer.

## MATERIALS AND METHODS

**Study population**

The SUPplémentation en Vitamines et Minéraux AntioXydants (SU.VI.MAX) study is a population-based, double-blind, placebo-controlled, randomized trial initially designed to assess the effect of a daily antioxidant supplementation on the incidence of cardiovascular disease and cancer<sup>[22,23]</sup>. A total of 13 017 subjects were enrolled in 1994-1995. The intervention study lasted 8 years, and follow-up of health events was maintained until July 2007. Subjects provided written informed consent and the study was approved by the Ethics Committee for Studies with Human Subjects at the Paris-Cochin Hospital, "Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale", No. 706 and the "Commission Nationale de l'Informatique et des Libertés", No. 334641.

**Baseline data collection**

At enrolment, all participants underwent a clinical examination and anthropometric measurements carried out by study nurses and physicians. The participants also completed questionnaires on socio-demographic data, smoking, alcohol intake and physical activity. A fasting venous blood sample was obtained. Plasma aliquots were immediately prepared and stored frozen in liquid nitrogen.

**Case ascertainment**

Confirmed or suspected cancer events were self-reported by subjects during the follow-up process. Investigations were conducted for all such events to obtain medical data from participants, physicians and/or hospitals. All information was reviewed by an independent expert committee and cancer cases were validated by pathological report and classified using the International Chronic Diseases Classification, 10th Revision, Clinical Modification.

**Nested case-control study**

All first primary incident colorectal cancer cases diagnosed between inclusion in the SU.VI.MAX cohort in 1994 and July 2007 were included in the present study. For each cancer case, two controls were randomly selected among the remaining participants with complete follow-up data and without cancer diagnosis by the end of follow-up. Cases and controls were matched for sex, age (by 2-year strata), body mass index (BMI,  $< \nu \geq 25$  kg/m<sup>2</sup>) and intervention group.

Baseline plasma samples of the selected subjects were used to determine the levels of highly-sensitive CRP (hs-CRP), leptin, adiponectin, soluble ICAM-1 (sICAM-1), soluble VCAM-1 (sVCAM-1), soluble E-selectin (sE-selectin) and MCP-1. Biomarker levels were determined with ELISA sandwich technique (R and D Laboratory Systems). Intra-assay (IACV) and inter-assay (IRCV) co-

**Table 1** Baseline characteristics of colorectal cancer cases and controls

	Cases (n = 50)		Controls (n = 100)		P value <sup>1</sup>
Age, yr	51.8	± 5.6	52.1	± 5.6	0.8
Gender					1.0
Men	28	56.0%	56	56.0%	
Women	22	44.0%	44	44.0%	
Intervention group					1.0
Yes	27	54.0%	54	54.0%	
No (placebo)	23	46.0%	46	46.0%	
BMI, kg/m <sup>2</sup>					1.0
< 25	24	48.0%	48	48.0%	
≥ 25	26	52.0%	52	52.0%	
Waist circumference, cm	88.2	± 12.9	82.2	± 12.1	0.01
Height, cm	169.3	± 7.1	167.8	± 8.5	0.3
Smoking status					0.9
Never smoker	23	46.0%	46	46.0%	
Former smoker	21	42.0%	40	40.0%	
Current smoker	6	12.0%	14	14.0%	
Alcohol intake, g/d	24	± 24.4	15.4	± 16.3	0.01
Physical activity					0.4
Low	10	20.0%	26	26.0%	
Moderate	18	36.0%	25	25.0%	
High	22	44.0%	49	49.0%	
Educational level, yr					0.9
< 12	30	60.0%	61	61.0%	
≥ 12	20	40.0%	39	39.0%	
Family history of colorectal cancer <sup>2</sup>					0.3
No	45	90.0%	84	84.0%	
Yes	5	10.0%	16	16.0%	
Plasma levels of biomarkers					
Adiponectin, µg/mL	9.0	± 4.7	10.9	± 7.5	0.2
Leptin, ng/mL	8.5	± 5.3	8.6	± 8.7	0.5
sVCAM-1, ng/mL	750.3	± 316.2	677.6	± 215.3	0.2
sICAM-1, ng/mL	249.7	± 80.3	247.8	± 67.3	0.9
sE-selectin, ng/mL	41.1	± 16.9	39.3	± 16.0	0.7
MCP-1, pg/mL	268.2	± 117.4	249	± 78.2	0.3
hs-CRP, mg/L	2.4	± 4.5	2.2	± 4.4	0.3

<sup>1</sup>P value for the comparison of cases and controls by Student *t* test or  $\chi^2$  test, as appropriate. Biomarker variables were log-transformed to improve normality. Values are mean ± SD or *n* % as appropriate. <sup>2</sup>In first degree relatives. BMI: Body mass index; hs-CRP: Highly sensitive C-reactive protein; sICAM-1: Soluble intercellular adhesion molecule-1; sVCAM-1: Soluble vascular cell adhesion molecule-1; sE-selectin: Soluble E-selectin; MCP-1: Monocyte chemoattractant protein-1.

efficients of variation were all < 10%. hs-CRP had the lowest (1.6%) and MCP-1 had the highest (6.2%) IACV, and hs-CRP had the lowest (3.6) and sE-selectin had the highest (9.1%) IRCV.

### Statistical analyses

The participants' baseline characteristics were compared between colorectal cancer cases and controls using Student's *t*-tests or  $\chi^2$  tests. Associations between biomarkers and incident colorectal cancer were examined with conditional logistic regression models and expressed as odds ratios (OR) with 95% confidence intervals (CI). The ORs for sex-specific quartiles and for a 1 standard deviation (SD) increase in the corresponding biomarker were com-

puted in unadjusted and multivariate models. Multivariate models were adjusted for age, sex, BMI, height, intervention group, alcohol intake, physical activity, smoking status, family history of colorectal cancer, waist circumference and educational level.

The improvement in colorectal cancer prediction performance attributed to the biomarkers was assessed with both the area under the receiver operating curves (AUC) and the more recently proposed statistical tool, the Relative Integrated Discrimination Improvement (RIDI)<sup>[21]</sup>. The latter measures the percentage of increased discrimination upon addition of another variable to the prediction model. The Bootstrap method was used to derive the 95% CI for the RIDI estimates, which were based on 1000 replications. The added prediction performance was determined separately for each biomarker identified as statistically significantly associated with cancer risk (in the logistic regression analyses step), and then for a combination of these biomarkers simultaneously. Tests of significance for AUC improvement were one-sided, as improvement in model fit was expected. All other statistical tests were two-sided, and *P* < 0.05 was considered significant. Analyses were performed with SAS software (v9.1, Cary, NC, United States).

## RESULTS

A total of 50 incident colorectal cancer cases were diagnosed during follow-up (30 colon and 20 rectal cancers). Each case was matched with two randomly selected controls; thus, 150 subjects were included in the analyses. Median follow-up was 6.5 years in cases and 13 years in controls. Baseline characteristics of cases and non-cases are presented in Table 1. Compared to controls, cancer cases had a higher waist circumference and a higher alcohol intake.

In multivariate models, a one SD change in plasma adiponectin level was associated with a decreased colorectal cancer risk [OR (95% CI) = 0.45 (0.22-0.91), *P* = 0.03]. This association was also observed when adiponectin was considered as quartiles (OR for Q4 vs Q1 = 0.11 (0.01-0.93), *P* for linear trend = 0.03) (Table 2).

Quartiles of plasma sVCAM-1 level were positively associated with increased colorectal cancer risk (*P* for linear trend = 0.02) (Table 2). This association was borderline non-significant when sVCAM-1 was coded as a continuous variable (*P* = 0.07).

Unadjusted models (matching factors only) showed similar results (data not shown). A sensitivity analysis excluding cases that were diagnosed during the first two years of follow-up (7 cases) did not modify the findings, nor did sensitivity analyses excluding subjects with high hs-CRP values (> 15.5 ng/mL, i.e., mean + 3SD, *n* = 3 subjects; data not shown).

Indicators of the predictive potential of colorectal cancer risk models (Table 3) showed improvement when adiponectin alone was included in the multivariate model

**Table 2 Odds ratios and 95% confidence intervals for quartiles of each biomarker level and colorectal cancer risk from multivariate conditional logistic regression models<sup>1</sup>**

	For a change in 1SD	Quartile1	Quartile2	Quartile3	Quartile4
<b>Adiponectin</b>					
OR	0.45	1 (ref)	0.83	0.42	0.11
95% CI	0.22-0.91		0.12-5.65	0.06-2.93	0.01-0.93
<i>P</i> for linear trend	0.03				0.03
<b>Leptin</b>					
OR	0.55	1 (ref)	0.19	2.22	0.29
95% CI	0.21-1.40		0.02-1.9	0.25-20.09	0.02-3.65
<i>P</i> for linear trend	0.2				0.6
<b>sVCAM-1</b>					
OR	1.69	1 (ref)	6.89	11.59	19.11
95% CI	0.96-2.98		0.72-66.4	0.64-209.81	1.4-261.27
<i>P</i> for linear trend	0.07				0.02
<b>sICAM-1</b>					
OR	0.74	1 (ref)	0.38	0.07	0.13
95% CI	0.40-1.40		0.04-3.23	0.01-0.76	0.01-1.93
<i>P</i> for linear trend	0.4				0.08
<b>sE-selectin</b>					
OR	0.95	1 (ref)	1.23	0.9	1.59
95% CI	0.49-1.81		0.13-11.49	0.1-8.14	0.16-15.62
<i>P</i> for linear trend	0.9				0.9
<b>MCP-1</b>					
OR	1.35	1 (ref)	1.67	1.02	2.02
95% CI	0.73-2.49		0.27-10.24	0.17-6.24	0.26-15.97
<i>P</i> for linear trend	0.3				0.4
<b>hs-CRP</b>					
OR	0.8	1 (ref)	0.73	2.22	1.53
95% CI	0.52-1.24		0.06-9.38	0.25-19.9	0.13-17.84
<i>P</i> for linear trend	0.3				0.6

<sup>1</sup>Adjusted for age, sex, body mass index, intervention group, alcohol intake, physical activity, smoking status, family history of colorectal cancer, waist circumference, height and educational level. *n* = 50 colorectal cancer cases and 100 controls. Cut-offs for sex-specific quartiles were: hs-CRP: 0.6, 1.2, 2.3 in men and 0.5, 0.9, 2.1 in women; sICAM-1: 198.7, 242.0, 287.4 in men and 193.0, 232.5, 286.0 in women; sVCAM-1: 539.0, 653.5, 798.6 in men and 523.0, 651.5, 875.7 in women; sE-selectin: 29.8, 42.5, 51.7 in men and 26.0, 36.3, 44.6 in women; MCP-1: 216.7, 263.5, 316.5 in men and 171.0, 212.0, 238.0 in women; Leptin: 3.1, 5.0, 8.2 in men and 5.4, 9.6, 15.4 in women; Adiponectin: 4.2, 6.6, 10.0 in men and 9.5, 13.9, 16.0 in women. OR: Odds ratio; CI: Confidence interval; hs-CRP: Highly sensitive C-reactive protein; sICAM-1: Soluble intercellular adhesion molecule-1; sVCAM-1: Soluble vascular cell adhesion molecule-1; sE-selectin: Soluble E-selectin; MCP-1: Monocyte chemoattractant protein-1; ref: Reference category.

(*P* for AUC improvement = 0.009). The RIDI statistic indicated a 12.2% (10.9-13.6) improvement. Improvement in the prediction of colorectal cancer risk was limited when sVCAM-1 only was introduced into the multivariate model (*P* for AUC improvement = 0.09), with 9.9% (8.7-11.0) improvement, as indicated by the RIDI statistic. Prediction was substantially improved when adiponectin and sVCAM-1 were simultaneously included in the multivariate model: *P* for AUC improvement was equal to 0.01, and the RIDI reached 26.5% (24.4-28.7).

## DISCUSSION

In this prospective study, pre-diagnostic plasma adiponectin level was associated with decreased colorectal cancer risk, independently of other known risk factors. On the contrary, plasma sVCAM-1 level was associated with increased colorectal cancer risk. Models including these two biomarkers showed significantly improved discriminatory capabilities compared to models including only established risk factors.

Lower levels of circulating adiponectin have been ob-

served in prevalent colorectal cancer cases compared to controls<sup>[10,13,24-26]</sup>. Single nucleotide polymorphism analyses have found that some variants of the adiponectin genes are related to either increased (rs822395, rs1342387) or decreased (rs266729) colorectal cancer risk<sup>[27]</sup>, although no association was detected in a recent study in the United Kingdom<sup>[28]</sup>. Another study suggested that variants of the adipokine genes may affect colorectal cancer risk in combination with variants in diabetes-related genes<sup>[29]</sup>. Studies with colorectal cancer patients showed that higher adiponectin levels were associated with a better prognosis<sup>[10,13,30]</sup>. It has been suggested that adiponectin may be used for estimation of advanced stage of cancer and for estimating risk of cancer recurrence<sup>[31]</sup>. However, to date, only three nested case-control studies have investigated the prospective association between adiponectin and colorectal cancer risk, showing inconsistent results<sup>[16-18]</sup>. Two studies did not find any associations; one of them included 381 male colorectal cancer cases<sup>[17]</sup> and the other included 306 colorectal cancer cases of both genders<sup>[16]</sup>. Consistent with our findings, the study of Wei *et al.*<sup>[18]</sup>, based on 179 male colorectal cancer cases, found an

**Table 3** Predictive potential of adiponectin and soluble vascular cell adhesion molecule-1 regarding colorectal cancer risk: Relative integrated discrimination improvement and improvement of area under the curve

	AUC	P value for AUC improvement	RIDI (%)	95% CI
Multivariate model <sup>1</sup>	0.89			
+ Adiponectin	0.98	0.009	12.2	10.9-13.6
+ sVCAM-1	0.92	0.09	9.9	8.7-11.0
+ Adiponectin + sVCAM-1	0.98	0.01	26.5	24.4-28.7

<sup>1</sup>Multivariate model was adjusted for age, sex, BMI, intervention group, alcohol intake, physical activity, smoking status, family history of colorectal cancer, waist circumference, height and educational level. Models including adiponectin and/or sVCAM-1 were compared to the multivariate model. *n* = 50 colorectal cancer cases and 100 controls. BMI: Body mass index; RIDI: Relative integrated discrimination improvement; AUC: Area under the receiver operating curve; sVCAM-1: Soluble vascular cell adhesion molecule-1; CI: Confidence interval.

inverse association between pre-diagnostic adiponectin levels and colorectal cancer risk. Circulating levels of adiponectin in those studies were comparable to the levels found in the present study. However, none of those three studies matched cases and controls on BMI. Adiponectin is strongly related to adiposity, which is, in turn, associated with an adverse effect on colorectal cancer development, especially in stathmin-positive patients, as recently shown by Ogino *et al.*<sup>[32]</sup>. Thus, matching on BMI is crucial and is a strength of our study compared to previous reports in the literature. Several mechanisms support the inverse relationship between adiponectin and colorectal cancer risk<sup>[33]</sup>. Adiponectin suppresses tumorigenesis in Apc(Min)(/+) mice<sup>[34]</sup> and also suppresses colonic epithelial proliferation *via* inhibition of the mammalian target of the rapamycin (mTOR) pathway under a high-fat diet<sup>[35]</sup>. It inhibits colorectal cancer cell growth through the AMP-activated protein kinase/mTOR pathway<sup>[36]</sup> and possibly the PI3K/Akt signal pathway<sup>[37]</sup>. Adiponectin also attenuates interleukin-6-induced colon carcinoma cell proliferation *via* STAT-3<sup>[38]</sup>.

Several case-control studies have observed higher circulating levels of sVCAM-1 in colorectal cancer cases compared to controls<sup>[11,12,39-41]</sup>. In addition, it has been suggested that the serum level of sVCAM-1 may be a valuable prognostic marker in colorectal carcinoma<sup>[12,42]</sup>, reflecting both tumour progression and metastasis<sup>[39]</sup>. For instance, Mantur *et al.*<sup>[11]</sup> observed a significant correlation of serum levels of sVCAM-1 with tumor, node, metastases (TNM) stage and lymph node involvement in colorectal cancer patients. Yamada *et al.*<sup>[43]</sup> observed a positive association between concentrations of sVCAM-1 and risk of post-operative colorectal cancer recurrence. Consequently, investigations have been conducted to test for the chemopreventive potential of some molecules (e.g., celecoxib) *via* down-regulation of VCAM-1 in the colon cancer cell line HT29<sup>[44]</sup>.

However, to the best of our knowledge, our study is the first to investigate the prospective association be-

tween pre-diagnostic levels of sVCAM-1 and colorectal cancer risk. The observed positive association is supported by a mechanistic plausibility. Indeed, it has been demonstrated experimentally that sVCAM-1 stimulates angiogenesis and neovascularization<sup>[45,46]</sup> and is negatively correlated with the degree of tumour differentiation<sup>[41]</sup>. Cell adhesion molecule expression has been demonstrated in endothelial cells of small vessels at the invasive margin of tumour cells involved in metastatic spread<sup>[47]</sup>. The association among immunohistochemical cell adhesion molecule expression, tumour vascularity and leukocyte infiltration suggests an important role for these molecules in host immune response and in tumour progression<sup>[48]</sup>.

Epidemiologic studies usually estimate the strength of the association between a biomarker and disease risk. Assessment of the discriminatory capabilities of a biomarker in predicting risk of the studied pathology is another approach that may lead to slightly different but complementary information<sup>[21]</sup>. To the best of our knowledge, no study has previously evaluated the discriminatory capabilities of hs-CRP, leptin, adiponectin, sICAM-1, sVCAM-1, sE-selectin and MCP-1 in predicting colorectal cancer risk, using *ad-hoc* statistical methods such as the novel RIDI statistic<sup>[21]</sup>. Indeed, the use of the traditional AUC method as a comparative measure of prediction between models has certain limitations<sup>[49]</sup>, and the complementary use of the novel RIDI statistic appears to be more sensitive and accurate<sup>[21]</sup>. Several factors are already known to influence colorectal cancer risk (e.g., age, smoking status, physical activity, *etc.*) and are usually included in predictive models. As shown in Table 3, the RIDI statistic suggests that when quartiles of adiponectin and quartiles of sVCAM-1 plasma levels are added to the model, the ability of the model to predict colorectal cancer risk is improved by 26.5%, compared to a model including only well-established risk factors (age, smoking status, *etc.*). Thus, our results suggest that adiponectin, and possibly sVCAM-1, should not be ignored as predictors of colorectal cancer risk. In addition, the improvement in the predictive potential was substantially increased when both biomarkers were simultaneously added to the model. This might result from the mechanistic interrelations between adiposity and endothelial adhesion, notably through an inflammation pathway<sup>[6,50,51]</sup>. Large prospective and validation studies are needed to confirm and better quantify the predictive performance of these biomarkers in colorectal carcinogenesis.

Strengths of our study include its prospective design, the simultaneous measurement of seven biomarkers in the same individuals and, to our knowledge, the first assessment of the discriminatory capabilities of these biomarkers for estimating colorectal cancer risk by the novel RIDI statistic.

Some limitations should also be acknowledged. Firstly, the number of cases was limited in this exploratory study. This may explain some of the null results observed; however, it is unlikely to explain the observed relationships between adiponectin, sVCAM-1 and colorectal cancer

risk, which were statistically significant despite the limited statistical power. These associations are consistent with our initial hypothesis and are supported by available mechanistic data. Secondly, a single measurement of biomarker levels (at baseline) was performed and no indication was available regarding transient acute infection (cold, throat infection, *etc.*) concomitant with the blood draws. For some biomarkers such as hs-CRP, although the probability of differential misclassification bias between cases and controls is low, this limitation might have led to an attenuation of the strengths of the observed associations due to intra-individual variation. This may have limited our ability to detect an association between hs-CRP and colorectal cancer. Finally, the observed relationships might have been partly affected by unmeasured or residual confounders, even though such a possibility is limited since a broad range of usual risk factors were accounted for in the statistical analyses.

Our study adds to current knowledge of adiposity- and endothelial adhesion-related pathways in the development of colorectal cancer. For the first time, we have shown a prospective positive association between plasma sVCAM-1 levels and colorectal cancer risk. In addition, we observed an inverse relationship between pre-diagnostic adiponectin levels and colorectal cancer risk, which provides new insights given the conflicting literature. Our results suggest that the inclusion of adiponectin and sVCAM-1 plasma levels in prediction models of colorectal cancer risk may improve their discriminatory capabilities. Large prospective studies are needed to confirm the pertinence of these biomarkers in colorectal cancer risk prediction. If confirmed in validation studies, these results could lead to improved identification of individuals at risk of developing colorectal cancer, which could result in well-targeted cancer screening campaigns.

## COMMENTS

### Background

Previous studies suggest an association between biomarkers of adiposity, endothelial adhesion and inflammation and colorectal cancer risk, but prospective data are limited and evaluation of predictive performance is lacking.

### Research frontiers

Previous cross-sectional and case-control studies have suggested the potential involvement of such biomarkers in colorectal carcinogenesis, with higher blood levels of soluble adhesion molecules and lower levels of adiponectin in patients with colorectal cancer compared to controls. The prognostic value of these markers has also been suggested. Studies on single nucleotide polymorphisms further indicate that these markers may affect cancer risk. However, few prospective studies have investigated the association between these biomarkers and colorectal cancer risk, often providing conflicting evidence.

### Innovations and breakthroughs

This work shows a prospective positive association between plasma soluble vascular cell adhesion molecule-1 (sVCAM-1) levels and colorectal cancer risk, which has not been investigated previously. In addition, the authors observed an inverse relationship between pre-diagnostic adiponectin levels and colorectal cancer risk, which provides new insights given the conflicting literature. The inclusion of adiponectin and sVCAM-1 plasma levels in prediction models of colorectal cancer risk improved their discriminatory capabilities.

### Applications

This study adds to current knowledge of adiposity- and endothelial adhesion-

related pathways in the development of colorectal cancer. If confirmed in large validation studies, these results could lead to improved identification of individuals at risk of developing colorectal cancer, which could result in well-targeted cancer screening campaigns.

### Terminology

Leptin reflects body fat storage and acts as a pro-inflammatory adipokine. Conversely, adiponectin production is decreased in obesity and generally has anti-inflammatory properties. Adhesion molecules such as E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and the chemokine monocyte chemoattractant protein-1 are important in cell-cell and cell-basement membrane interactions. C-reactive protein is a widely used systemic biomarker for diagnosing acute and chronic inflammation.

### Peer review

The authors describe the potential role of two biomarkers in the diagnosis of colorectal cancer using a prospective study cohort initiated almost 18 years ago. The availability of this cohort and the derived material is a major strength of the study; even though a limited number of cases developed and were available for analysis. The study design and analytical work is not questionable, and the statistical analysis is "state of the art".

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S- Editor Shi ZF L- Editor Logan S E- Editor Zhang DN