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Pre-diagnostic circulating resistin concentrations and mortality among individuals with colorectal cancer: Results from the European Prospective Investigation into Cancer and Nutrition study

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Abstract

Resistin is a protein involved in inflammation and angiogenesis processes and may play a role in the progression of colorectal cancer (CRC). However, it remains unclear whether resistin is associated with increased mortality after CRC diagnosis. We examined pre-diagnostic serum resistin concentrations in relation to CRC-specific and all-cause mortality among 1343 incident CRC cases from the European Prospective Investigation into Cancer and Nutrition cohort. For CRC-specific mortality as the primary outcome, hazard ratios (HRs) and 95% confidence intervals (95% CI) were estimated from competing risk analyses based on cause-specific Cox proportional hazards models and further in sensitivity analyses using Fine–Gray proportional subdistribution hazards models. For all-cause mortality as the secondary outcome, Cox proportional hazards models were used. Subgroup analyses were performed by sex, tumor subsite, tumor stage, body mass index and time to CRC diagnosis. Resistin was measured on a median of 4.8 years before CRC diagnosis. During a median follow-up of 8.2 years, 474 deaths from CRC and 147 deaths from other causes were observed. Resistin concentrations were not associated with

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For affiliations refer to page 1604

CRC-specific mortality ($HR_{Q4vsQ1} = 0.95$, 95% CI: 0.73–1.23; $P_{trend} = .97$; and $HR_{per\ doubling\ of\ resistin\ concentration} = 1.00$; 95% CI: 0.84–1.19; $P = .98$) or all-cause mortality. Results from competing risk (sensitivity) analysis were similar. No associations were found in any subgroup analyses. These findings suggest no association between pre-diagnostic circulating resistin concentrations and CRC-specific or all-cause mortality among persons with CRC, and the potential insignificance of resistin in CRC progression.

KEYWORDS

colorectal cancer, EPIC, mortality, pre-diagnostic, resistin, survival

What's new?

Previous studies suggested that obesity and inflammation are related to cancer progression, and resistin was proposed as an obesity biomarker involved in inflammatory processes in humans. However, it remained unclear whether resistin is associated with increased mortality after colorectal cancer diagnosis. In this study the authors examined the novel association between pre-diagnostic level of resistin and mortality in 1343 incident colorectal cancer patients. Resistin concentrations measured 4.8 years before diagnosis were not associated with mortality in individuals with CRC. These findings do not support the hypothesis that resistin may contribute to cancer progression.

1 | INTRODUCTION

Resistin is a protein produced by adipocytes discovered in rodent models and is consequently considered as an adipokine.[1] However subsequent human studies have shown that it is primarily produced and expressed by mononuclear cells (monocytes, macrophages and lymphocytes).[2] In rodents, resistin is related to obesity and insulin resistance,[1] whereas, in humans, resistin is purportedly involved in inflammation by creating a vicious circle,[3–6] and implicated in angiogenesis,[7] which both may be relevant for cancer promotion and progression.[8–10] For example, resistin induces pro-inflammatory cytokines in human peripheral blood mononuclear cells[5,6]; while, vice versa, stimulation of human macrophages with tumor necrosis factor-alpha significantly induced resistin protein expression[11]; furthermore, resistin could induce its own expression and secretion in macrophages suggesting the possibility of a positive feedback loop on resistin.[6]

Colorectal cancer (CRC) was the second most common cause of cancer death in 2020, with an estimated 1.8 million deaths worldwide.[12] The course of CRC is determined by complex systemic processes and accompanied by systemic inflammation, which is one of the common factors contributing to CRC deaths.[10] Obesity is an established risk factor for CRC, and studies suggest that pre-diagnostic obesity is also related to decreased survival in persons with CRC.[13–15] Obesity is also characterized by chronic low-grade systemic inflammation (CLGSI),[15] and by the infiltration of inflammatory cells into adipose tissues.[8] While some studies found higher resistin concentrations in patients with CRC as compared to controls,[16] findings from prospective studies, including our recent study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, suggest that pre-diagnostic resistin concentrations are not associated with risk of CRC.[17,18] In a recent Mendelian randomization study with substantial statistical power to

detect even weak associations, we found no association between genetically predicted levels of resistin and CRC risk.[19] However, this does not preclude the possibility that resistin may have an effect on CRC cancer progression and mortality, because inflammation[3–6] and angiogenesis,[7] in which resistin is involved, may contribute to advanced stages of the disease.[20,21] Indeed, a previous study reported that CRC patients whose tumor tissue specimens were strongly positive for resistin expression had slightly lower relapse-free survival and overall survival times compared to those without positive resistin expression, but these differences were not statistically significant.[22]

To our knowledge, the association between pre-diagnostic circulating resistin concentrations and mortality among CRC patients has not been investigated so far. However, as a consequence of the vicious circle of inflammation, resistin concentrations measured after CRC diagnosis may be difficult to interpret as they may be affected by the presence of tumors or by cancer treatment. In contrast, given the long-term reliability of circulating resistin concentrations in humans,[23,24] pre-diagnostic measurements may better reflect sustained resistin concentrations in a steady-state condition of inflammation. Therefore, we investigated whether higher pre-diagnostic resistin concentrations are associated with higher CRC-specific or all-cause mortality among individuals with CRC in the EPIC study.

2 | METHODS

2.1 | Study population and baseline data collection

The study population was derived from EPIC participants with first-incident CRC. EPIC is a large multicenter cohort study that included 519,978 participants enrolled between 1992 and 2000 in 23 centers

in 10 European countries (France, Greece, Germany, Italy, Spain, Denmark, Sweden, Norway, the Netherlands and the United Kingdom). Details of the EPIC study can be found elsewhere.[25] Briefly, at baseline, standardized lifestyle, dietary questionnaires and anthropometric data were collected from all participants. Blood samples were collected from 80% of the participants following a strict protocol, aliquoted into plastic straws and stored both locally at each study center and centrally at the International Agency for Research on Cancer (IARC) in the vapor phase of liquid nitrogen (at -196°C). Exceptions from this procedure were Sweden and Denmark, where blood samples were aliquoted into tubes. Since the central EPIC repository at IARC was not suitable for tube storage, these samples were only stored locally in freezers at -70°C (Sweden) and in nitrogen vapor at -150°C (Denmark).

2.2 | Cancer incidence follow-up

Follow-up for cancer incidence was based on a passive follow-up procedure utilizing regional or national population-based cancer registries (Italy, Spain, Denmark, Sweden, Norway, the Netherlands and the United Kingdom) or through an active follow-up procedure which combined several methods, including health insurance records, cancer and pathology registries and self-reporting from study subjects or their next-of-kin which were later verified through pathology reports and physicians (Germany, Greece and France). The active follow-up procedure has been described elsewhere.[26]

2.3 | Case ascertainment and selection for the current analysis

CRC cases were defined based on the International Classification of Diseases, 10th Revision (ICD-10).[27] Participants who were free of cancer at recruitment but later developed colon (C18.0–C18.7) or rectal cancer (C19–C20) with the availability of blood samples were included in the analysis. The current study included 1343 incident CRC cases to examine the association between pre-diagnostic resistin concentrations and mortality after CRC. The closure dates for complete follow-up for cancer incidence were between 2002 and 2012. Due to administrative issues, data from Greece and Norway were not included in the current study.

2.4 | Vital status follow-up

Information on vital status was also collected by a passive follow-up procedure through regional/national mortality registries in all countries except Germany and France, where data are collected by an active follow-up procedure as used for cancer incidence follow-up. The closure dates for vital status follow-up, which were either the date of death or the last date of contact, whichever occurred first, were ranged between 2009 and 2015 depending on the local country

and study center. The current study outcomes were CRC-specific mortality and all-cause mortality and they were determined by the underlying cause of death using the ICD-10.

2.5 | Resistin concentration measurements and exposure assessments

Resistin concentrations in serum were measured one time in baseline samples using Human Resistin enzyme-linked immunosorbent assay (ELISA) (BioVendor Laboratory Medicine, Inc; Brno, Czech Republic) according to the manufacturer's protocols. Samples were analyzed in 39-well microtiter plates. Mean interassay coefficients of variation (CV) (representing resistin levels' variance between plates/assays) for all quality controls were estimated by BioVendor and reported as 7.4% for the quality control high concentrations and 6.6% for the quality control low concentrations. The inter-assay CVs for the pooled sera used as the internal quality controls were <10.4%. The means of the intra-assay CVs (representing resistin levels' variance within an assay) were all <2.5%.

A study using three measurements of resistin per individual over 3–4 years revealed a high intraclass correlation coefficient (ICC) of 0.95, suggesting a high stability of resistin levels within a person.[24] Thus, the use of one measurement of resistin per individual is supported in epidemiological studies.[23,24]

2.6 | Baseline variables and prognostic factors

Data on prognostic factors were extracted from the medical records, including age at diagnosis, tumor subsite and tumor stage. Due to the utilization of different stage classifications among EPIC centers (including TNM staging, Dukes classification or the "localized/ metastatic/metastatic regional/ metastatic distant" categories), a harmonization procedure had been previously carried out to obtain a broad category for tumor stage (I, II, III and IV).[27] Data were collected from baseline questionnaires for age at recruitment, sex, body mass index (BMI), waist circumference, physical activity index, highest education level and smoking status. Moreover, all diet exposure, including consumed amounts of alcohol, dairy, fruit, red meat, processed meat, vegetables and dietary fiber was assessed by food frequency questionnaires or diet history logs.

Overall, information on tumor stage was missing in 13.3% of the participants. In the centers in France, Ragusa (Italy), Granada (Spain), Heidelberg (Germany) and Umeå (Sweden), data on tumor stage were completed for all participants. In contrast, these data were missing for all participants at the Oxford center (United Kingdom). In the other centers, the proportion of missing information on tumor stage ranged from 1.3% (Potsdam, Germany) to 30.8% (Varese, Italy). Information on waist circumference was missing in 5.6% of participants with all the missing data occurring in Umeå (Sweden).

2.7 | Statistical analysis

Study population characteristics were tabulated across quartiles of resistin concentrations (≤3.54; 3.55–4.37; 4.38–5.45; >5.45 ng/mL). A cumulative incidence function (CIF) of CRC-specific mortality was plotted using a Fine–Gray model,[28] with time from CRC diagnosis to death or last contact as the time metric. Gray's test was used to test for incidence function changes over the quantiles of resistin.[28]

The associations between pre-diagnostic resistin concentrations and CRC-specific (primary endpoint) and all-cause mortality (secondary endpoint) were examined using Cox proportional hazards regression models with PROC PHREG in SAS. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the primary endpoint were estimated from competing risk analyses based on cause-specific Cox proportional hazards models,[29] with non-CRC death serving as the competing event[29]; while HRs (95% CIs) for the secondary endpoint were derived from multivariable-adjusted Cox proportional hazards models. We fitted three models with time from the date of CRC diagnosis to date of death or date of last contact as the underlying time variable, stratified by country and adjusted for: age at CRC diagnosis (continuous), sex (men, women) (model 1); additionally adjusted for tumor subsite (colon or rectum), year of diagnosis (model 2); and additionally adjusted for baseline BMI (continuous) and residuals from linear models regressing waist circumference on BMI and height (residuals$_{(WC \sim BMI+Height)}$) to avoid multicollinearity (model 3). Model 3 was used as the final model in further analyses. Because data were missing for one covariate (residuals$_{(WC \sim BMI+Height)}$), which were assumed to be missing at random, missing data were imputed based on multiple imputation using chained equations to generate 20 imputed datasets using PROC MI in SAS. The results of the analyses of imputations were then combined using PROC MIANALYZE.

We also estimated risk of CRC-specific mortality according to resistin concentration using a restricted cubic spline cause-specific Cox proportional hazards regression analysis with knots at the 5th, 35th, 65th and 95th percentiles of the resistin distribution. To assess any deviation from linearity, we tested the significance of the spline term using likelihood ratio tests. No deviation from linearity was detected with $P = .89$ for the null hypothesis of linearity. However, due to non-normal distribution and the comparability of results, resistin concentrations were analyzed in quartiles as well as a continuous variable by base-2-log-transformed resistin, which corresponds to a doubling of resistin on its original scale. Adding non-linear terms to log-transformed resistin concentrations did not significantly improve the model ($P = .81$), suggesting that log-transformed resistin sufficiently captures the hazard function for risk of mortality after CRC. We found no violation of the Cox proportional hazards assumption (see the Supporting Information Methods section S1 for details).

The associations between resistin and mortality were further examined in subgroup analyses by sex (men, women), tumor subsite (colon, rectum), BMI (<30, ≥30 kg/m^2), tumor stage (I, II, III,

IV) and time from resistin measurement to CRC diagnosis (≤2 years, >2 to ≤8 years and >8 years). In these subgroup analyses, missing data for tumor stage were imputed by multiple imputation and HRs for each subgroup were estimated from model 3, excluding the subgroup-determining variable itself. Wald Chi-Squared tests were used to test interaction terms (and calculate P-values) between log-transformed resistin and covariates. In sensitivity analyses, we (a) re-estimated HRs and 95% CI for the primary endpoint again using the Fine-Gray proportional subdistribution hazards models as another competing risk model, (b) fitted all the models again after excluding extreme resistin levels (defined as concentrations of 1.5 times the interquartile range below the 25th percentile and above the 75th percentile),[30] (c) performed complete-case analyses and (d) additionally adjusted for tumor stage.

With a standard deviation of 0.52 for log-transformed resistin concentrations,[17] a sample size of 1343 participants, CRC-specific mortality of 0.35, a 5% probability of type I error and 80% power, the minimum detectable HR$_{per\ doubling\ of\ resistin\ levels}$ is 1.28, which represents the smallest effect size in the hazard ratio that our study can statistically distinguish from the null hypothesis. Further information on the rationales of model covariate selection, the implementation of multiple imputation and assessment of the proportional hazard assumption is provided in Data S1. All statistical tests were two-sided, and P-values <.05 were considered statistically significant. All analyses were performed by using SAS enterprise guide, version 8.3 (SAS Institute, Inc., Cary, North Carolina).

3 | RESULTS

Resistin was measured at a median of 4.8 years (25th–75th percentile, 2.6–7.0) before CRC diagnosis. Median follow-up time, defined as time from CRC diagnosis to the end of follow-up for vital status, was 8.2 years (25th–75th percentile, 2.1–12.2). Among 1343 CRC cases, 474 deaths from CRC and 147 deaths from other causes were observed. CRC cases in the upper compared to the lower quartiles of resistin levels were more likely to be women, have higher age at diagnosis, consume more dairy and fruit, less alcohol and processed meat (Table 1).

The unadjusted cumulative incidence functions of CRC-specific mortality over time were not significantly different among quartile groups at all time points ($P = .98$ from Gray's test [Figure S1]). Circulating resistin concentrations were not significantly associated with CRC mortality in the cause-specific Cox proportional hazards models. In the fully adjusted model (model 3): HR$_{Q2vsQ1}$: 0.98, 95% CI: 0.76–1.27; HR$_{Q3vsQ1}$: 0.96, 95% CI: 0.74–1.24; HR$_{Q4vsQ1}$: 0.95, 95% CI: 0.73–1.23; $P_{trend} = .97$; and HR$_{per\ doubling\ of\ resistin\ concentrations}$, 1.00; 95% CI: 0.84–1.19; $P = .98$ (Table 2). No substantial difference in HRs was observed among the three models. We also found no association between resistin concentrations and all-cause mortality (HR$_{Q4vsQ1}$: 0.99, 95% CI: 0.79–1.24; $P_{trend} = .87$; Table 2). There was

TABLE 1 Baseline characteristics according to quartiles of pre-diagnostic circulating resistin concentrations among CRC cases (N = 1343) in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

	Serum resistin concentrations (ng/mL)			
	Quartile 1 ≤3.54 N = 338	Quartile 2 3.55–4.37 N = 335	Quartile 3 4.38–5.45 N = 336	Quartile 4 >5.45 N = 334
Age at CRC diagnosis, years, mean (SD)	56.8 (6.5)	58.3 (6.6)	58.2 (7.1)	59.1 (7.4)
Women, %	46. 6	51.0	54.3	56.3
Tumor stage, n (%)[a]				
I	95 (28.1)	98 (29.3)	70 (20.8)	70 (21.0)
II	67 (19.8)	60 (17.9)	68 (20.2)	73 (21.9)
III	104 (30.8)	98 (29.3)	113 (33.6)	102 (30.5)
IV	36 (10.7)	36 (10.7)	39 (11.6)	35 (10.5)
Unknown	36 (10.7)	43 (12.8)	46 (13.7)	54 (16.2)
Tumor subsite, colon, n (%)	204 (60.4)	218 (65.1)	208 (61.9)	224 (67.1)
BMI, kg/m^2, mean (SD)	26.6 (3.8)	26.7 (3.9)	26.9 (4.5)	27 (4.2)
Waist circumference, cm, mean (SD)[b,c]	90.6 (12.6)	89.9 (12.6)	90.9 (13.5)	90.5 (12.4)
Diabetes at baseline, n (%)	30 (8.9)	27 (8.1)	28 (8.3)	24 (7.2)
Physically moderately active or active, sex-specific n (%)	185 (54.7)	160 (47.8)	170 (50.6)	159 (47.6)
University degree and higher education level, n (%)	51 (15.1)	69 (20.6)	63 (18.8)	53 (15.9)
Current smoking, n (%)	89 (26.3)	86 (25.7)	84 (25.0)	86 (25.7)
Alcohol consumption, g/d, median (P25–P75)[b,d]	13.5 (2.6–37.1)	9.1 (1.6–24.3)	9.5 (1.8–23.7)	5.1 (0.8–15.7)
Dairy consumption, g/d, median (P25–P75)[b,d]	247.6 (120.4–432.6)	289.2 (155.6–462.8)	284.3 (158.1–451.9)	314.5 (171.7–473.1)
Energy intake, kcal/d, median (P25–P75)[b,d]	2108 (1683–2521)	2108 (1683–2496)	2072 (1699–2480)	2055 (1694–2452)
Fish and shellfish consumption, g/d, median (P25–P75)[b,d]	29.7 (15.1–54.8)	27.7 (14.1–47.5)	27.8 (16.2–49.7)	25.4 (14.6–44.3)
Fruit consumption, g/d, median (P25–P75)[b,d]	158.5 (80.6–271.4)	187.7 (117.4–288.2)	186.8 (93.9–288.1)	196.8 (100.9–313.7)
Red meat consumption, g/d, median (P25–P75)[b,d]	53.8 (27.2–85.4)	44.4 (24.8–71.9)	48.3 (24.2–73.6)	47.1 (23.2–75.0)
Processed meat, g/d, median (P25–P75)[b,d]	26.5 (13.6–51.2)	26.1 (15.7–42.1)	25.2 (13.1–44.8)	25.0 (13.4–43.5)
Vegetable consumption, g/d, median (P25–P75)[b,d]	161.8 (104.8–244.6)	148.7 (98.5–225.0)	160.3 (111.4–227.4)	149.2 (99.3–235.8)
Dietary fiber intake, g/d, median (P25–P75)[b,d]	21.6 (17.2–27.2)	21.9 (16.8–27.2)	22.0 (18.1–27.2)	22.7 (18.0–27.9)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; P25, the 25th percentile; P75, the 75th percentile; SD, standard deviation.

[a]Missing rates of tumor stage in EPIC study centers range from 1.3% to 30.8%. No information is available about tumor stage for participants in the Oxford center (the United Kingdom).

[b]Among users only.

[c]Data on waist circumference were missing in 5.58% of the participants.

[d]Data on all other dietary variables were missing in 0.30% (4/1343) of the participants.

no significant association between resistin concentrations and CRC-specific mortality in subgroup analyses stratified by sex, tumor subsite, tumor stage, BMI and time to CRC diagnosis in cause-specific Cox hazards models (Figure 1).

The main results were not substantially different when using the Fine–Gray proportional subdistribution hazards models as the competing risk model (Table S1 and Figure S2A) when excluding extreme resistin levels (Table S2) or in complete-case analyses (Table S3). However, there was a statistically significant interaction between resistin and tumor stage in relation to CRC mortality in complete-case analyses with cause-specific Cox proportional hazards models (P = .02) (Figure S2B) (HRs (95% CI)

of CRC mortality for a doubling of resistin concentrations in persons with stage I, II, III and IV tumors were 0.63, 95% CI: 0.33–1.18; 0.83, 95% CI: 0.48–1.41; 0.91, 95% CI: 0.66–1.24 and 1.52, 95% CI: 1.05–2.19, respectively; $P_{interaction}$ = .02). This significant interaction was not observed in the complete-case analyses with Fine–Gray proportional subdistribution hazards models (Figure S2C).

Further adjustment of our main results for tumor stage did not alter the results in both imputation and complete case analysis (cause-specific hazards models, HR $_{Q4vsQ1}$: 0.93 (0.71–1.22); P-trend = .82; and HR$_{per doubling of resistin concentrations}$, 0.98 (0.81–1.19); P = .85 (data not shown)).

TABLE 2 Hazard ratios and 95% confidence intervals for CRC mortality and all-cause mortality according to pre-diagnostic circulating resistin concentrations.

Resistin category	Resistin quartile ranges, ng/mL	No. of participants[a]	Number of events	Number of competing events	Alive	Model 1[b] HR (95% CI)	P-value[f]	Model 2[c] HR (95% CI)	P-value[f]	Model 3[d] HR (95% CI)[e]	P-value[e,f]
CRC-specific mortality (Competing risk analysis with cause-specific hazard model)											
Quartile 1	≤3.54	338	119	31	188	Ref		Ref		Ref	
Quartile 2	3.55–4.37	335	120	27	188	1.02 (0.79–1.32)		1.00 (0.77–1.29)		0.98 (0.76–1.27)	
Quartile 3	4.38–5.45	336	118	44	174	0.99 (0.77–1.28)		0.97 (0.75–1.26)		0.96 (0.74–1.24)	
Quartile 4	>5.45	334	117	45	172	0.98 (0.75–1.27)	.99	0.96 (0.74–1.24)	.98	0.95 (0.73–1.23)	.97
Per doubling of resistin concentrations[g]		1343	474	147	722	1.02 (0.85–1.21)	.84	1.01 (0.84–1.20)	.94	1.00 (0.84–1.19)	.98
Overall mortality (Cox proportional hazards model)											
Quartile 1	≤3.54	338	150	—	188	Ref		Ref		Ref	
Quartile 2	3.55–4.37	335	147	—	188	0.97 (0.77–1.22)		0.95 (0.76–1.20)		0.94 (0.74–1.18)	
Quartile 3	4.38–5.45	336	162	—	174	1.07 (0.86–1.34)		1.05 (0.84–1.32)		1.03 (0.82–1.29)	
Quartile 4	>5.45	334	162	—	172	1.02 (0.81–1.28)	.85	1.00 (0.80–1.26)	.87	0.99 (0.79–1.24)	.87
Per doubling of resistin concentrations[g]		1343	621		722	1.04 (0.89–1.21)	.64	1.03 (0.88–1.20)	.74	1.01 (0.87–1.18)	.87

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio.

[a]Data of a covariate (residual$_{(WC \sim BMI+Height)}$) were missing in 75/1343 CRC patients and were imputed using the multiple imputation method.

[b]Model 1: Cause-specific Cox hazard model, or Cox proportional hazards model with time from CRC diagnosis to death or last contact (years) as the underlying time variable, stratified by country and adjusted for age at CRC diagnosis (continuous) and sex (male, female).

[c]Model 2: Model 1 with additional adjustment for year of CRC diagnosis (continuous) and tumor subsite (colon or rectum).

[d]Model 3: Model 2 with additional adjustment for BMI (kg/m^2) and residual$_{(WC \sim BMI+Height)}$ in a linear model with BMI.

[e]HRs and P-values from model 3 were estimated for each of the 20 imputed datasets, and combined into a pooled HR and pooled P-value.

[f]Where resistin was used as a categorical variable, p values were estimated from the test for trend across the quartiles of resistin.

[g]Models with continuous log-transformed resistin concentrations by log 2.

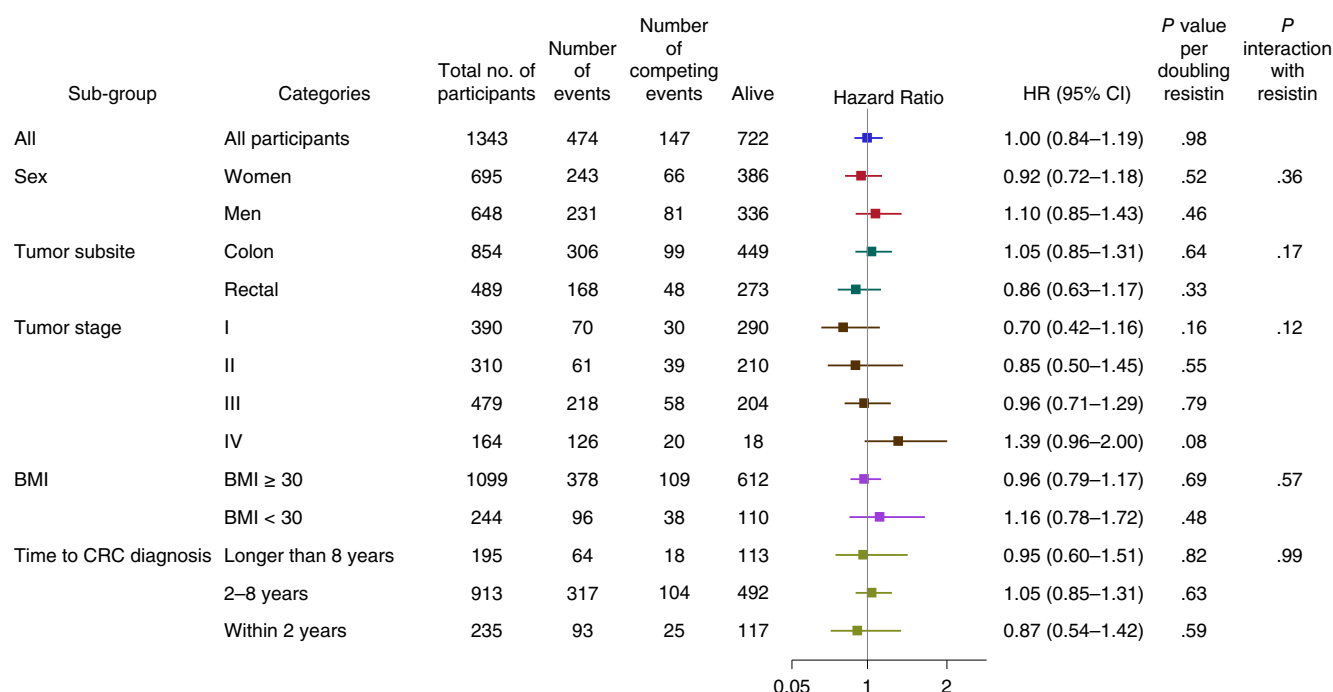**Association between circulating resistin concentrations and CRC-specific mortality**

Sub-group	Categories	Total no. of participants	Number of events	Number of competing events	Alive	Hazard Ratio	HR (95% CI)	P value per doubling resistin	P interaction with resistin
All	All participants	1343	474	147	722		1.00 (0.84–1.19)	.98	
Sex	Women	695	243	66	386		0.92 (0.72–1.18)	.52	.36
	Men	648	231	81	336		1.10 (0.85–1.43)	.46	
Tumor subsite	Colon	854	306	99	449		1.05 (0.85–1.31)	.64	.17
	Rectal	489	168	48	273		0.86 (0.63–1.17)	.33	
Tumor stage	I	390	70	30	290		0.70 (0.42–1.16)	.16	.12
	II	310	61	39	210		0.85 (0.50–1.45)	.55	
	III	479	218	58	204		0.96 (0.71–1.29)	.79	
	IV	164	126	20	18		1.39 (0.96–2.00)	.08	
BMI	BMI ≥ 30	1099	378	109	612		0.96 (0.79–1.17)	.69	.57
	BMI < 30	244	96	38	110		1.16 (0.78–1.72)	.48	
Time to CRC diagnosis	Longer than 8 years	195	64	18	113		0.95 (0.60–1.51)	.82	.99
	2–8 years	913	317	104	492		1.05 (0.85–1.31)	.63	
	Within 2 years	235	93	25	117		0.87 (0.54–1.42)	.59	

Hazard Ratio axis: 0.05   1   2

FIGURE 1 Association between resistin concentrations and CRC mortality in cause-specific Cox hazards models in subgroup analyses. BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio. Missing data of residual$_{(WC \sim BMI+Height)}$ (75/1343), and stage (254/1343) were assumed to be missing at random and were imputed using multiple imputation. The imputation model contained the variables included in the analysis model and auxiliary variables (all baseline lifestyle and dietary variables as in Table 1). Hazard ratios and 95% CIs refer to a doubling in resistin concentrations and were derived from cause-specific Cox hazards models (model 3) with time from CRC diagnosis to death or last contact (years) as the underlying time variable, stratified by country and adjusted for age at CRC diagnosis (continuous), sex (male, female), year of CRC diagnosis (continuous), tumor subsite (colon or rectum), BMI (kg/m^2) and residual$_{(WC \sim BMI+Height)}$. In each subgroup analysis, the subgroup-determining variable itself was excluded from the models. Hazard ratios and 95% CIs were estimated for each of the 20 imputed datasets, and combined into pooled values. P-values for the interaction of each variable with log-transformed resistin were estimated using Wald Chi-squared tests and presented as the median of the P-values from the 20 imputed data analyses.

4 | DISCUSSION

In our study, we found that pre-diagnostic resistin concentrations were not associated with CRC-specific or all-cause mortality risk among individuals with incident CRC. No association was found when performing subgroup analysis by sex, tumor subsite, tumor stage, BMI and time to CRC diagnosis.

To our knowledge, our study is the first to investigate the association between pre-diagnostic resistin concentrations and mortality in CRC patients. Therefore, we cannot compare our results directly to those of other published studies. The REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study investigated the association between baseline resistin concentrations and cancer mortality among community-dwelling adults in the United States and found no significant relationship with mortality due to obesity-related cancers (defined as breast, colorectal, kidney, pancreas, stomach, endometrial and esophagus cancer) or total cancer mortality.[31] However, in subgroup analyses, the study found a statistically significant association between higher resistin concentrations and risk of cancer mortality in Black (but not in White) participants.[31] In another study of 599 elderly Finnish patients with hypertension, resistin

concentrations at recruitment were significantly associated with all-cause mortality (HR$_{one\ standard\ deviation\ increment\ in\ log-resistin}$, 5.48, 95% CI: 1.10–27.25).[32] However, the findings of these studies are more difficult to interpret because resistin has been associated with cardiovascular disease (CVD) mortality in high-CVD-risk populations[33]; thus, any relationship of resistin with total mortality may be driven by risk of CVD mortality. Although case–control studies suggest that persons with CRC have higher resistin concentrations than controls,[16] we have previously found in a prospective study that in persons free of cancer at baseline resistin is not significantly associated with risk of incident CRC.[17] Findings from that prospective study are consistent with a previous case-cohort study within the Women's Health Initiative study,[18] and our recent Mendelian Randomization study.[19] Together with the results from the present analysis, evidence suggests that circulating resistin concentrations are neither related to risk of CRC nor mortality among persons with CRC.

In our study, we used the multiple imputation approach to impute the missing data in residuals$_{(WC \sim BMI+Height)}$ in all models and the missing data of tumor stage in subgroup analysis. Complete-case analyses were used for sensitivity analyses, however, they may not provide an unbiased estimate for the association since participants with missing

data for cancer stage also have higher levels of resistin than those with complete stage data. Furthermore, with the exception of a marginally significant association between resistin and CRC-specific mortality among people with stage IV CRC at diagnosis using a cause-specific hazard model, the main results of the complete-case analyses did not differ from analyses of the multiple-imputation data. The results were not replicated using sub-distribution hazard as an alternative competing risk model, suggesting that the marginally significant association may be due to chance. Nevertheless, the sample sizes of the subgroups were not large enough to ensure a reasonably precise point estimate. Future large sample studies should be implemented to substantiate the findings.

Measurements of resistin concentrations after CRC diagnosis ("post-diagnosis") could be influenced by systemic inflammatory reactions during the expansion of the tumor or by treatment (eg, surgery, chemotherapy and radiotherapy), leading to higher circulating resistin concentrations compared to healthy individuals as observed in case-control studies.[16] However, it is difficult to determine whether this increase is due to the expansion of the tumor or to the effects of the treatment. Ideally, to determine whether resistin is influenced by tumors, resistin should be measured at the time of CRC diagnosis, before any treatment or prescription is given to the patients. While this setting is difficult to protocol in clinical practice, a relatively large number of CRC patients were needed to estimate the effect, indicating the challenges in real-world implementation. Nevertheless, future studies employing this setting will provide more insights into the relationship being studied. In contrast, as the first study to investigate this relationship, the current study measured resistin at a median of 4.8 years before CRC diagnosis to avoid the aforementioned ambiguity. This can be considered a strength of our study. As such, resistin concentrations are not likely to be influenced by the tumor but rather reflect "steady-state conditions" of inflammation. This is supported by studies showing that resistin levels are stable within individuals over 3 years.[24] Although we cannot rule out that our analysis included persons with existing but not yet diagnosed CRC at baseline, in the subgroup analysis by time from baseline to CRC diagnosis (≤2 years, >2 to ≤8 years and >8 years), we found no difference in the association between resistin and CRC-specific mortality between these three groups. High resistin levels in the "steady-state" conditions could be caused by CLGSI, which many conditions may have triggered. Under CLGSI, C-reactive protein (CRP), an inflammatory marker, was not significantly associated with CRC mortality, as previously reported.[34] Of the conditions that trigger CLGSI, obesity is typical, as inflammation is initially induced in white adipose tissue and extends to other tissues and circulation, resulting in CLGSI.[35] Pre-diagnostic obesity was reported as a significant factor in the risk of death in patients with non-metastatic CRC.[14,36] However, in a previous study using EPIC data, we found no significant correlation between pre-diagnostic resistin and BMI (correlation coefficient = −0.02, P = .52),[17] but a weakly significant positive correlation with CRP concentrations in control participants (correlation coefficient = 0.12, P < .01).[17] The findings were consistent with several population-based studies that showed a significant but comparatively weak positive association

between resistin and BMI in humans (modest absolute value of correlation coefficients).[37–39] The null or least significant correlation between resistin and BMI as well as CRP might partially help explain the lack of association between resistin and CRC mortality in our study. Of note, CLGSI is not only caused by obesity, but also by other triggers such as chronic infections, physical inactivity, microbiome dysbiosis, westernized diet, social isolation, psychological stress, disrupted sleep and circadian rhythm disruption and xenobiotic exposure including tobacco smoking.[40] All inflammatory conditions are major determinants of circulating resistin concentrations.[8] Thus, many non-cancerous conditions could induce the "steady state conditions" of resistin, such as atherosclerosis,[8] non-alcoholic steatohepatitis,[8] inflammatory bowel disease,[41] low-grade and high-grade dysplasia adenoma.[42]

Our study has several strengths, including the prospective design, population data with a large sample size, pre-diagnostic exposure data, detailed outcome data extracted from medical records and a long follow-up period, which is reasonable for follow-up of CRC incidence and mortality after CRC. Further, we adjusted for several variables that may act as confounders or competing exposures. However, there were several limitations in our study. First, we acknowledge that the generalizability of the findings to different populations or ethnicities other than European is limited by the use of data from European countries only. Second, we had only a single measurement of resistin concentration available for each participant, and long-term storage of biosamples at −196°C may affect the stability of resistin, and biological fluctuations over time may dilute biomarker-disease associations. However, previous studies suggest that resistin concentrations are stable even when stored for long periods (roughly 3 years), thus, supporting the use of baseline resistin concentrations in long-term follow-up population studies.[23,24] In line with this, we found no correlation between resistin concentrations and storage time in our dataset (data not shown). Third, in our study, we relied on a single measurement of resistin while resistin levels may have changed in individuals whose resistin was measured closer to their CRC diagnosis. We do not have data for within-person variation of resistin concentrations in our study. However, we checked the scatter plot of resistin concentrations and time to CRC diagnosis which revealed no pattern deviating from a zero-slope line (Figure S3), suggesting that there is no significant change in resistin levels when measured further or closer to the time of CRC diagnosis. However, future studies with repeated resistin measurements are necessary to confirm this assumption. Fourth, we lacked data on other comorbidities that may be related to inflammation and to mortality, such as cardiovascular disease, inflammatory bowel disease and asthma, which might affect inflammatory pathways. Nevertheless, given that we found no significant association of resistin with all-cause mortality, which was driven by risk of CVD mortality, it is unlikely that non-adjustment for these potential confounders may have affected our results because such confounding, if anything, would be expected to bias relative risk estimates away from the null. Further, additional adjustments for all inflammatory and metabolic biomarkers (total cholesterol, triglycerides, low-density lipoprotein cholesterol, C-peptide, HbA1c and CRP) did not

substantially change the results (data not shown). Of note, there were 32%–40% missing data for these biomarkers in our dataset, thus, HRs estimated adjusted for all variables may have insufficient statistical power.

In conclusion, data from this prospective study suggest that pre-diagnostic resistin concentrations, measured around 5 years before diagnosis and assumed to be stable in the human body, are not associated with CRC survival. As the current study is the first prospective study on this topic, it warrants confirmation by large sample size prospective studies.

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AFFILIATIONS

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CONFLICT OF INTEREST STATEMENT

DATA AVAILABILITY STATEMENT

EPIC data are accessible by written request to and approval of the EPIC Steering Committee. Instructions and further information on the EPIC data access policy can be found here https://epic.iarc.fr/access/index.php. Further information and aggregated data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Informed consent was obtained from all participants involved in the study. The EPIC study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Review Board of the International Agency for Research on Cancer (IARC) and the ethical committees of the participating centers.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.