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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Statistical analysis

Model covariate selection

Several potential confounders were assessed as mutual causes of both baseline-resistin concentrations and CRC-specific mortality [1], by such definition, age at CRC diagnosis, and sex were defined as confounders. Year of diagnosis was used as a surrogate for possible changes in treatment regimens of CRC during the course of the study [2]. Because year of diagnosis and tumor subsites, were not related to pre-diagnostic resistin concentrations [3], while survival after CRC was different between colon and rectal cancer [4], and depended on year of diagnosis [4], they were considered as competing exposures and included in the model to improve precision [5]. Baseline body mass index (BMI) and waist circumference (WC) were positively associated with CRC-specific mortality in some studies [6], while no association was found in others [7, 8], and resistin was theoretically secreted from adipose tissue [9, 10], and thus could be considered as potential confounders. The relationship between tumor stage and pre-diagnosis resistin remains unclear, these factors could theoretically play a role as mediators or competing exposures in the link between resistin and CRC death, and thus were not included in the final model but were included in the sensitivity analysis. Other baseline lifestyle and dietary factors were not included as covariates in the final model since there has been little or no strong evidence of relationships between these factors and CRC survival or mortality [7, 8, 11]. Nevertheless, we also estimated a maximum 1.28% change in HRs between the final Cox model and the model with each of these variables additionally included, and <2% changes in HRs when including all baseline lifestyle and dietary variables (**Supplementary Table 4**).

Multiple imputation

In the current study, imputed data were used in the main analysis as one of the covariates (residuals from linear models regressing waist circumference and height on BMI ($\mathrm{residual}_{(\mathrm{WC}\sim\mathrm{BMI}+\mathrm{Height})}$) was missing following a missing at random assumption. The imputation model contained the variables included in the analysis model and auxiliary variables [12] including baseline lifestyle and dietary variables (included in Table 1). HRs, 95%CIs, and p-values of the association

were estimated for each of the imputed datasets and pooled based on Rubin's rule using PROC MIANALYZE in SAS. Pooled p-values for the test of trends across quartiles of resistin were derived as the median of the p-values from the imputed data, as it is suggested to have better power than other pooling methods [13].

Proportional hazards assumption

The proportional hazards assumption was tested using cause-specific Cox proportional hazards model [14]. First, we graphically evaluated Schoenfeld residuals taken from univariable Cox models over follow-up time and observed approximately zero slopes over time. Second, we included time-dependent explanatory covariates defined as interactions of a time-dependent covariate and the log of follow-up time and found that no time-dependent explanatory covariates contributed significantly to the models. The linear relationship between the log hazard and each covariate was assessed and held by observing each of the plots of the cumulative Martingale residuals against levels of the index covariate which all showed the absolute values of any residual were not much greater than 0. Thus, the use of Cox proportional hazards regression models was justified.

Supplementary Tables

Supplementary Table 1: (in addition to Table 2) Hazard ratios and 95% confidence intervals for colorectal cancer mortality according to pre-diagnostic circulating resistin concentrations in a sub-distribution hazard model (Fine and Gray model)

Resistin category	Resistin quartile ranges, ng/ml	No. of participants [a]	Number of events	Number of competing events	Alive	Model 1 [b]		Model 2 [c]		Model 3 [d]	
						HR (95%CI)	P value [f]	HR (95%CI)	P-value [f]	HR (95%CI) [e]	P-value [e,f]
CRC-specific mortality (Competing risk analysis with subdistribution hazard model)											
Quartile 1	≤ 3.54	338	119	31	188	Ref		Ref		Ref	
Quartile 2	3.55-4.37	335	120	27	188	1.04 (0.80 - 1.35)	0.95	1.02 (0.79 - 1.33)	0.93	1.01 (0.78 -1.31)	0.93
Quartile 3	4.38-5.45	336	118	44	174	0.98 (0.76 - 1.27)		0.96 (0.74 - 1.24)		0.95 (0.73 -1.23)	
Quartile 4	> 5.45	334	117	45	172	0.97 (0.74 - 1.26)		0.95 (0.73 - 1.24)		0.94 (0.72 -1.23)	
Per doubling of resistin concentrations [g]		1343	474	147	722	1.01 (0.84 - 1.21)	0.93	1.00 (0.83 - 1.19)	0.97	0.99 (0.83 -1.19)	0.91

a. Data of a covariate ($\mathrm{residual}_{(\mathrm{WC}\sim\mathrm{BMI+Height})}$) were missing in 75/1343 CRC patients and were imputed using the multiple imputation method.
b. Model 1: Cause-specific Cox hazard model, subdistribution 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 $\mathrm{residual}_{(\mathrm{WC}\sim\mathrm{BMI+Height})}$.
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 4 quartiles of resistin.
g. Models with continuous log-transformed resistin concentrations by log 2.

Supplementary Table 2: Hazard ratios and 95% confidence intervals for colorectal cancer mortality and all-cause mortality according to quartiles of pre-diagnostic circulating resistin concentrations excluding participants with extreme resistin levels (defined as concentrations of 1.5 times the interquartile range below the 25th percentile and above the 75th percentile)

Resistin Category	Resistin quartile ranges, ng/ml	No. of participants	Number of events	Number of competing events	Alive	Model 3	
						HR (95%CI)	P-value
CRC-specific mortality - **Competing risk analysis with Cause-Specific Hazard Model**							
Quartile 1	≤ 3.54	338	119	31	188	ref	
Quartile 2	3.55-4.37	335	120	27	188	0.98 (0.76 -1.27)	0.94
Quartile 3	4.38-5.45	336	118	44	174	0.96 (0.74 -1.24)	
Quartile 4	> 5.45	273	93	36	144	0.92 (0.70 -1.21)	
Per doubling of resistin concentrations *		1282	450	138	694	0.97 (0.78 -1.20)	0.76
CRC-specific mortality - **Competing risk analysis with Subdistribution Hazard Model**							
Quartile 1	≤ 3.54	338	119	31	188	ref	
Quartile 2	3.55-4.37	335	120	27	188	1.00 (0.77 -1.30)	0.88
Quartile 3	4.38-5.45	336	118	44	174	0.95 (0.73 -1.23)	
Quartile 4	> 5.45	273	93	36	144	0.91 (0.69 -1.21)	
Per doubling of resistin concentrations *		1282	450	138	694	0.95 (0.77 -1.18)	0.64
Overall mortality - Cox proportional hazards model							
Quartile 1	≤ 3.54	338	150	-	188	ref	
Quartile 2	3.55-4.37	335	147	-	188	0.93 (0.74 -1.18)	0.86
Quartile 3	4.38-5.45	336	162	-	174	1.03 (0.82 -1.29)	
Quartile 4	> 5.45	273	129	-	144	0.97 (0.76 -1.24)	
Per doubling of resistin concentrations *		1282	588	-	694	1.02 (0.85 -1.24)	0.82

Missing data of $\mathrm{residual}_{(\mathrm{WC}\sim\mathrm{BMI+Height})}$ (75/1343) were assumed to be missing at random and were imputed using multiple imputation. Hazard ratios (95% confidence interval) and p values were estimated from different Cox proportional hazards models 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), and BMI (kg/m^2) and $\mathrm{residual}_{(\mathrm{WC}\sim\mathrm{BMI+Height})}$. Hazard Ratios and 95%CIs were estimated for each of the 20 imputed datasets and combined into pooled values. * Models with continuous log-transformed resistin concentrations by log 2.

Supplementary Table 3: Hazard ratios and 95% confidence intervals for colorectal cancer mortality and all-cause mortality according to quartiles of pre-diagnostic circulating resistin concentrations in complete case analysis

Resistin Category	Resistin quartile ranges, ng/ml	No. of participants	Number of events	Number of competing events	Alive	Model 3	
						HR (95%CI)	P-value
CRC-specific mortality - **Competing risk analysis with** Cause-Specific Hazard Model							
Quartile 1	≤ 3.54	328	114	31	183	ref	
Quartile 2	3.55-4.37	308	110	26	172	1.00 (0.77 -1.31)	0.99
Quartile 3	4.38-5.45	317	112	44	161	0.98 (0.75 -1.28)	
Quartile 4	> 5.45	315	112	44	159	0.98 (0.75 -1.28)	
Per doubling of resistin concentrations *		1268	448	145	675	1.02 (0.85 -1.23)	0.79
CRC-specific mortality - **Competing risk analysis with Subdistribution Hazard Model**							
Quartile 1	≤ 3.54	328	114	31	183	ref	
Quartile 2	3.55-4.37	308	110	26	172	1.03 (0.79 -1.35)	0.97
Quartile 3	4.38-5.45	317	112	44	161	0.97 (0.74 -1.26)	
Quartile 4	> 5.45	315	112	44	159	0.98 (0.74 -1.28)	
Per doubling of resistin concentrations *		1268	448	145	675	1.02 (0.84 -1.22)	0.87
Overall mortality - Cox proportional hazards model							
Quartile 1	≤ 3.54	328	145	-	183	ref	
Quartile 2	3.55-4.37	308	136	-	172	0.94 (0.74 -1.19)	0.84
Quartile 3	4.38-5.45	317	156	-	161	1.05 (0.83 -1.32)	
Quartile 4	> 5.45	315	156	-	159	1.01 (0.80 -1.27)	
Per doubling of resistin concentrations *		1268	593	-	675	1.03 (0.88 -1.20)	0.73

Hazard ratios (95% confidence interval) and p values were estimated from different Cox proportional hazards models 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), and BMI (kg/m^2) and $\mathrm{residual}_{(\mathrm{WC}\sim\mathrm{BMI+Height})}$. In total, 75 cases missing in $\mathrm{residual}_{(\mathrm{WC}\sim\mathrm{BMI+Height})}$ were excluded before doing the complete case analysis. * Models with continuous log-transformed resistin concentrations by log 2.

88 **Supplementary Table 4**: Hazard Ratio changes when baseline lifestyle and dietary covariates were additionally added to the primary model (model 3).

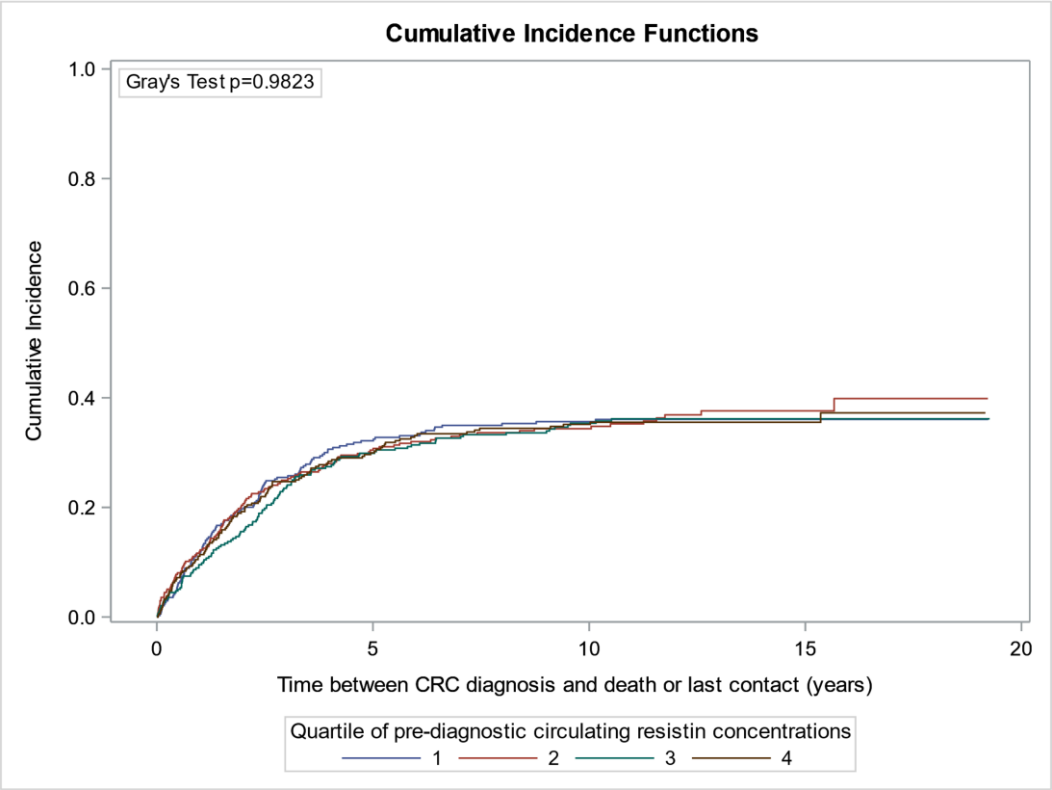
Competing risk analysis	Model	Hazard Ratio	95% Confidence Interval	Percentage change in HR compared with HR resulted from model 3
Cause-Specific Hazard Model	Model 3 *	0.99825	(0.83581 ; 1.19226)	Reference
Cause-Specific Hazard Model	Model 3 + Smoking status, (categorical)	0.99825	(0.83593 ; 1.19210)	0.00%
Cause-Specific Hazard Model	Model 3 + Red meat consumption, g/d	0.99828	(0.83598 ; 1.19208)	0.00%
Cause-Specific Hazard Model	Model 3 + Vegetable consumption, g/d	0.99797	(0.83557 ; 1.19192)	0.03%
Cause-Specific Hazard Model	Model 3 + Fruit consumption, g/d	0.99892	(0.83624 ; 1.19325)	0.07%
Cause-Specific Hazard Model	Model 3 + Processed meat, g/d	0.99752	(0.83521 ; 1.19136)	0.07%
Cause-Specific Hazard Model	Model 3 + Energy intake, Kcal/d	0.99927	(0.83700 ; 1.19299)	0.10%
Cause-Specific Hazard Model	Model 3 + Fish and shellfish consumption, g/d	0.99936	(0.83663 ; 1.19374)	0.11%
Cause-Specific Hazard Model	Model 3 + Diabetes at baseline (yes/no)	0.99978	(0.83721 ; 1.19392)	0.15%
Cause-Specific Hazard Model	Model 3 + Physical activity, sex-specific (categorical)	0.99667	(0.83398 ; 1.19109)	0.16%
Cause-Specific Hazard Model	Model 3 + Education level (categorical)	0.99543	(0.83310 ; 1.18940)	0.28%
Cause-Specific Hazard Model	Model 3 + Dietary fiber intake, g/d	1.00189	(0.83910 ; 1.19626)	0.36%
Cause-Specific Hazard Model	Model 3 + Dairy consumption, g/d	1.00229	(0.83911 ; 1.19721)	0.40%
Cause-Specific Hazard Model	Model 3 + Alcohol consumption, g/d	1.00918	(0.84302 ; 1.20809)	1.09%
Cause-Specific Hazard Model	Model 3+ All baseline lifestyle and dietary variables	1.00456	(0.83806 ; 1.20414)	0.63%
Subdistribution Hazard Model	Model 3 *	0.98982	(0.82598 ; 1.18616)	Reference
Subdistribution Hazard Model	Model 3 + Vegetable consumption, g/d	0.98972	(0.82584 ; 1.18611)	0.01%
Subdistribution Hazard Model	Model 3 + Red meat consumption, g/d	0.98915	(0.82547 ; 1.18530)	0.07%
Subdistribution Hazard Model	Model 3 + Processed meat, g/d	0.98912	(0.82528 ; 1.18549)	0.07%
Subdistribution Hazard Model	Model 3 + Fruit consumption, g/d	0.99074	(0.82646 ; 1.18768)	0.09%
Subdistribution Hazard Model	Model 3 + Energy intake, Kcal/d	0.99096	(0.82706 ; 1.18733)	0.11%
Subdistribution Hazard Model	Model 3 + Diabetes at baseline (yes/no)	0.99101	(0.82706 ; 1.18747)	0.12%
Subdistribution Hazard Model	Model 3 + Physical activity, sex-specific (categorical)	0.98833	(0.82435 ; 1.18493)	0.15%
Subdistribution Hazard Model	Model 3 + Smoking status, (categorical)	0.99132	(0.82763 ; 1.18738)	0.15%

Subdistribution Hazard Model	Model 3 + Fish and shellfish consumption, g/d	0.99143	(0.82735 ; 1.18806)	0.16%
Subdistribution Hazard Model	Model 3 + Education level (categorical)	0.98765	(0.82392 ; 1.18391)	0.22%
Subdistribution Hazard Model	Model 3 + Dairy consumption, g/d	0.99289	(0.82804 ; 1.19057)	0.31%
Subdistribution Hazard Model	Model 3 + Dietary fiber intake, g/d	0.99362	(0.82920 ; 1.19064)	0.38%
Subdistribution Hazard Model	Model 3 + Alcohol consumption, g/d	1.00259	(0.83362 ; 1.20580)	1.28%
Subdistribution Hazard Model	Model 3+ All baseline lifestyle and dietary variables	1.00000	(0.83021 ; 1.20451)	1.02%

(*) Hazard ratios (95% confidence interval) and p values were estimated from different Cox proportional hazards models with time from CRC diagnosis to death or last contact (years) as the underlying time variable, continuous log-transformed resistin concentrations by log 2, stratified by country, and adjusted for age at CRC diagnosis (continuous), sex (male, female), year of CRC diagnosis (continuous), and BMI (kg/m^2) and $\mathrm{residual}_{(\mathrm{WC\sim BMI+Height})}$. Missing data of $\mathrm{residual}_{(\mathrm{WC\sim BMI+Height})}$ (75/1343), education levels (44/1343), physical activity (87/1343), smoking status (11/1343), and all diet variables (4/1343) were assumed to be missing at random and were imputed using multiple imputation. Hazard Ratios and 95%CIs were estimated for each of the 20 imputed datasets and combined in pooled values.

Supplementary Figures

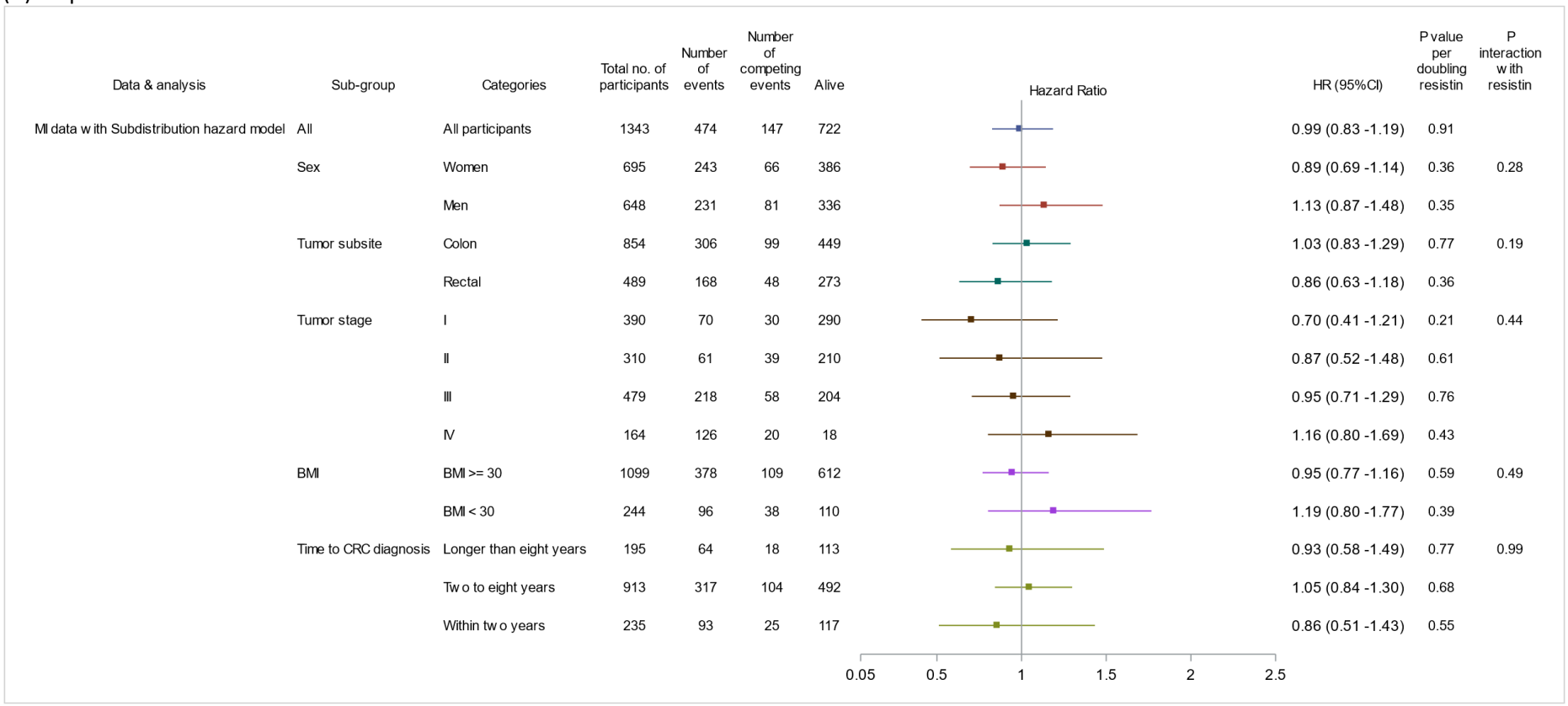
Supplementary Figure 1: Unadjusted cumulative Incidence functions (CIF) of CRC mortality according to resistin concentrations.



Unadjusted cumulative incidence function of CRC mortality from a Fine–Gray model, with time between CRC diagnostic and death or last contact as the time metric. Gray's test was used to test for incidence function changes over the quantiles of resistin [15].

Supplementary Figure 2: Association between circulating resistin concentrations and CRC mortality in subgroup analyses with Sensitivity analysis

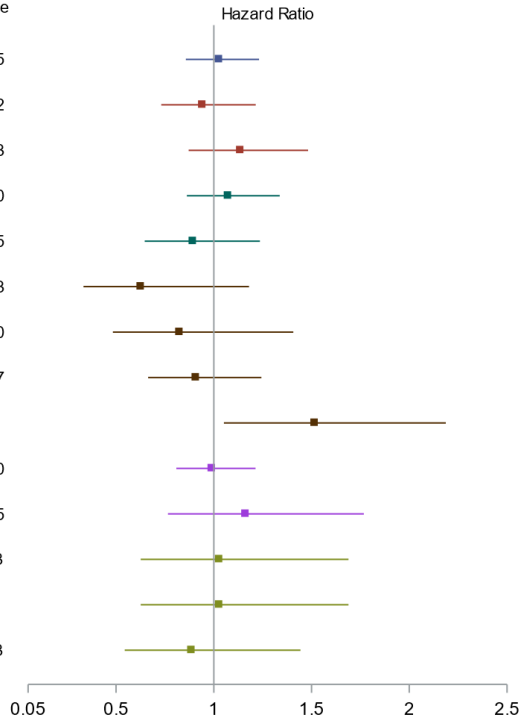
(A) Imputed data - Subdistribution hazards models



Missing data of $\text{residual}_{(\text{WC}\sim\text{BMI}+\text{Height})}$(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 were derived from Subdistribution 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), and BMI (kg/m^2) and $\text{residual}_{(\text{WC}\sim\text{BMI}+\text{Height})}$. In each subgroup analysis, the variable determining the subgroups itself was excluded from the models. Hazard Ratios and 95%CIs were estimated for each of the 20 imputed datasets and combined in pooled values. P-value for the interaction of each variable with log-transformed resistin was estimated by Wald Chi-Squared tests and presented as the median of the p-values from the 20 imputed data analyses.

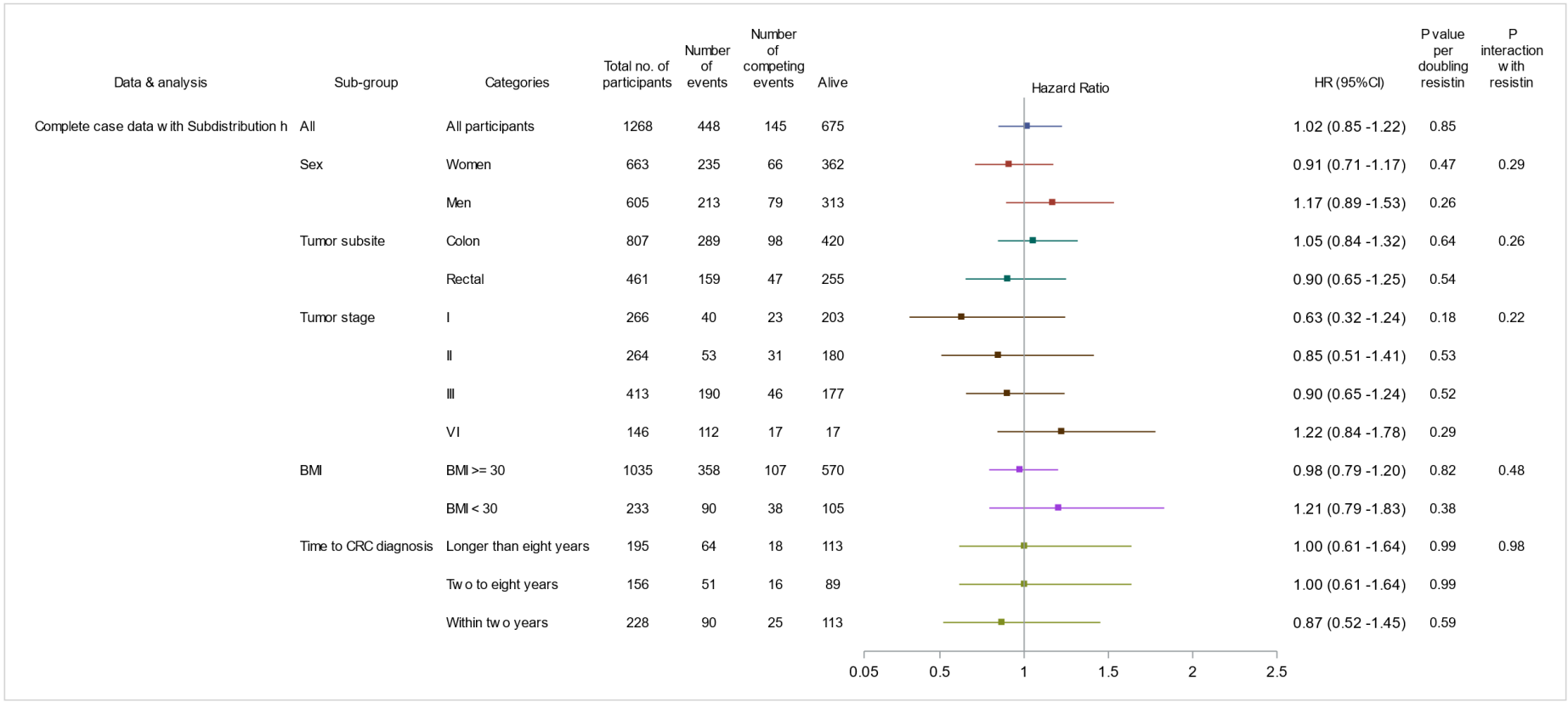
(B) Complete case analysis - Cause-specific Cox hazards models

Data & analysis	Sub-group	Categories	Total no. of participants	Number of events	Number of competing events	Alive	HR (95%CI)	P value per doubling resistin	P interaction with resistin
Complete case data with Cause-specific ha	All	All participants	1268	448	145	675	1.03 (0.86 -1.23)	0.77	
	Sex	Women	663	235	66	362	0.94 (0.73 -1.21)	0.65	0.39
		Men	605	213	79	313	1.14 (0.87 -1.48)	0.35	
	Tumor subsite	Colon	807	289	98	420	1.07 (0.86 -1.34)	0.53	0.23
		Rectal	461	159	47	255	0.89 (0.65 -1.24)	0.50	
	Tumor stage	I	266	40	23	203	0.63 (0.33 -1.18)	0.15	0.02
		II	264	53	31	180	0.83 (0.48 -1.41)	0.48	
		III	413	190	46	177	0.91 (0.66 -1.24)	0.55	
		IV	146	112	17	17	1.52 (1.05 -2.19)	0.03	
	BMI	BMI >= 30	1035	358	107	570	0.99 (0.81 -1.21)	0.93	0.56
		BMI < 30	233	90	38	105	1.16 (0.77 -1.77)	0.48	
	Time to CRC diagnosis	Longer than eight years	195	64	18	113	1.03 (0.63 -1.69)	0.91	0.96
		Two to eight years	156	51	16	89	1.03 (0.63 -1.69)	0.91	
		Within two years	228	90	25	113	0.89 (0.54 -1.44)	0.63	



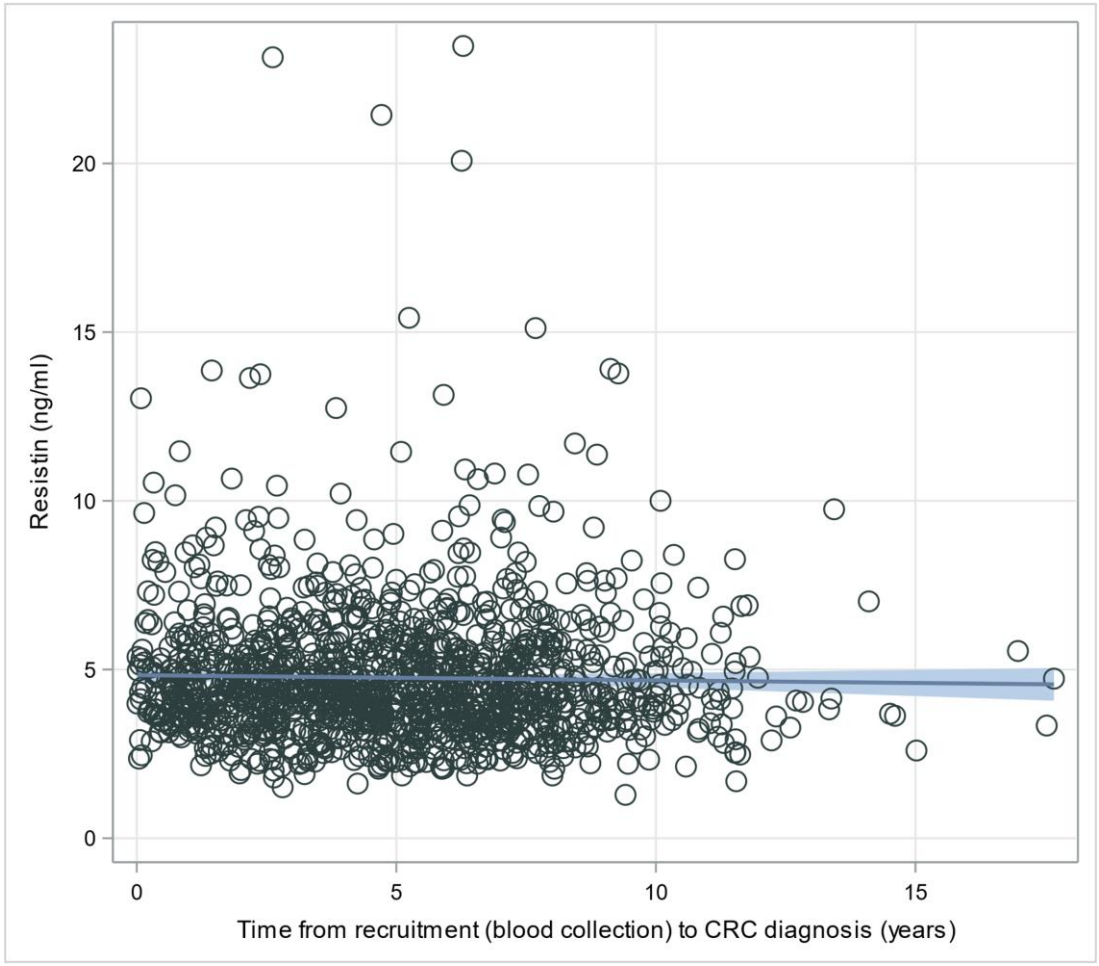
Participants with missing data of $\text{residual}_{(\text{WC}\sim\text{BMI}+\text{Height})}$ (75/1343) were excluded from all analyses, and participants with missing data in tumor stage (254/1343) were additionally excluded in the subgroup analyses by stage. Hazard Ratios and 95%CIs were derived from 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 $\text{residual}_{\text{WC}\sim\text{BMI}+\text{Height}}$. In each subgroup analysis, the variable determining the subgroups itself was excluded from the models. Hazard Ratios and 95%CIs were estimated for each of the 20 imputed datasets and combined in pooled values. P-value for the interaction of each variable with log-transformed resistin was estimated by Wald Chi-Squared tests and presented as the median of the p-values from the 20 imputed data analyses.

(C) Complete case analysis - Subdistribution hazard model



Participants with missing data of $\text{residual}_{(\text{WC}\sim\text{BMI+Height})}$ (75/1343) were excluded from all analyses, and participants with missing data in tumor stage (254/1343) were additionally excluded in the subgroup analyses by stage. Hazard Ratios and 95%CIs were derived from Subdistribution 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 $\text{residual}_{(\text{WC}\sim\text{BMI+Height})}$. In each subgroup analysis, the variable determining the subgroups itself was excluded from the models. Hazard Ratios and 95%CIs were estimated for each of the 20 imputed datasets and combined in pooled values. P-value for the interaction of each variable with log-transformed resistin was estimated by Wald Chi-Squared tests and presented as the median of the p-values from the 20 imputed data analyses.

Supplementary Figure 3: Scatter plot of resistin concentrations and time to CRC diagnosis



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