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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Supplementary materials & methods

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 (residual_{WC~BMI+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 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)

<table>
<thead>
<tr>
<th>Resistin category</th>
<th>Resistin quartile ranges, ng/ml</th>
<th>No. of participants (^a)</th>
<th>Number of events</th>
<th>Number of competing events</th>
<th>Alive</th>
<th>Model 1 (^b)</th>
<th>Model 2 (^c)</th>
<th>Model 3 (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P value (^f)</td>
<td>P value (^f)</td>
<td>P value (^f)</td>
</tr>
<tr>
<td>Quartile 1</td>
<td>(\leq 3.54)</td>
<td>338</td>
<td>119</td>
<td>31</td>
<td>188</td>
<td>Ref</td>
<td>1.04 (0.80 - 1.35)</td>
<td>1.02 (0.79 - 1.33)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>3.55 - 4.37</td>
<td>335</td>
<td>120</td>
<td>27</td>
<td>188</td>
<td>0.95</td>
<td>1.02 (0.79 - 1.33)</td>
<td>0.96 (0.74 - 1.24)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>4.38 - 5.45</td>
<td>336</td>
<td>118</td>
<td>44</td>
<td>174</td>
<td>0.98 (0.76 - 1.27)</td>
<td>0.95 (0.73 - 1.24)</td>
<td>0.97</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>&gt; 5.45</td>
<td>334</td>
<td>117</td>
<td>45</td>
<td>172</td>
<td>0.97 (0.74 - 1.26)</td>
<td>0.95 (0.73 - 1.24)</td>
<td>0.94</td>
</tr>
<tr>
<td>Per doubling of resistin concentrations (^e)</td>
<td>1343</td>
<td>474</td>
<td>147</td>
<td>722</td>
<td></td>
<td>1.01 (0.84 - 1.21)</td>
<td>1.00 (0.83 - 1.19)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

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

61 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).

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

63 d. Model 3: Model 2 with additional adjustment for BMI (kg/m\(^2\)) and residual\(_{(WC-BMI+Height)}\).

64 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.

65 f. Where resistin was used as a categorical variable, p values were estimated from the test for trend across the 4 quartiles of resistin.

66 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)

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

Missing data of residual \((WC_{\sim}BMI+Height)\) (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/m²) and residual \((WC_{\sim}BMI+Height)\). 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

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

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/m²) and residual (WC~BMI+Height). In total, 75 cases missing in residual (WC~BMI+Height) were excluded before doing the complete case analysis. * Models with continuous log-transformed resistin concentrations by log 2.
**Supplementary Table 4**: Hazard Ratio changes when baseline lifestyle and dietary covariates were additionally added to the primary model (model 3).

<table>
<thead>
<tr>
<th>Competing risk analysis</th>
<th>Model</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>Percentage change in HR compared with HR resulted from model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 *</td>
<td>0.99825</td>
<td>(0.83581 ; 1.19226)</td>
<td>Reference</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Smoking status, (categorical)</td>
<td>0.99825</td>
<td>(0.83593 ; 1.19210)</td>
<td>0.00%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Red meat consumption, g/d</td>
<td>0.99828</td>
<td>(0.83598 ; 1.19208)</td>
<td>0.00%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Vegetable consumption, g/d</td>
<td>0.99797</td>
<td>(0.83557 ; 1.19192)</td>
<td>0.03%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Fruit consumption, g/d</td>
<td>0.99892</td>
<td>(0.83624 ; 1.19325)</td>
<td>0.07%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Processed meat, g/d</td>
<td>0.99752</td>
<td>(0.83521 ; 1.19136)</td>
<td>0.07%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Energy intake, Kcal/d</td>
<td>0.99927</td>
<td>(0.83700 ; 1.19299)</td>
<td>0.10%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Fish and shellfish consumption, g/d</td>
<td>0.99936</td>
<td>(0.83663 ; 1.19374)</td>
<td>0.11%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Diabetes at baseline (yes/no)</td>
<td>0.99978</td>
<td>(0.83721 ; 1.19392)</td>
<td>0.15%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Physical activity, sex-specific (categorical)</td>
<td>0.99667</td>
<td>(0.83398 ; 1.19109)</td>
<td>0.16%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Education level (categorical)</td>
<td>0.99543</td>
<td>(0.83310 ; 1.18940)</td>
<td>0.28%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Dietary fiber intake, g/d</td>
<td>1.00189</td>
<td>(0.83910 ; 1.19626)</td>
<td>0.36%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + Alcohol consumption, g/d</td>
<td>1.00918</td>
<td>(0.84302 ; 1.20809)</td>
<td>1.09%</td>
</tr>
<tr>
<td>Cause-Specific Hazard Model</td>
<td>Model 3 + All baseline lifestyle and dietary variables</td>
<td>1.00456</td>
<td>(0.83806 ; 1.20414)</td>
<td>0.63%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 *</td>
<td>0.99825</td>
<td>(0.82598 ; 1.18616)</td>
<td>Reference</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Vegetable consumption, g/d</td>
<td>0.99872</td>
<td>(0.82584 ; 1.18611)</td>
<td>0.01%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Red meat consumption, g/d</td>
<td>0.98915</td>
<td>(0.82547 ; 1.18530)</td>
<td>0.07%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Processed meat, g/d</td>
<td>0.98912</td>
<td>(0.82528 ; 1.18549)</td>
<td>0.07%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Fruit consumption, g/d</td>
<td>0.99074</td>
<td>(0.82646 ; 1.18768)</td>
<td>0.09%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Energy intake, Kcal/d</td>
<td>0.99096</td>
<td>(0.82706 ; 1.18733)</td>
<td>0.11%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Diabetes at baseline (yes/no)</td>
<td>0.99101</td>
<td>(0.82706 ; 1.18747)</td>
<td>0.12%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Physical activity, sex-specific (categorical)</td>
<td>0.98833</td>
<td>(0.82435 ; 1.18493)</td>
<td>0.15%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Smoking status, (categorical)</td>
<td>0.99132</td>
<td>(0.82763 ; 1.18738)</td>
<td>0.15%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Fish and shellfish consumption, g/d</td>
<td>0.99143</td>
<td>(0.82735 ; 1.18806)</td>
<td>0.16%</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------</td>
<td>---------</td>
<td>---------------------</td>
<td>------</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Education level (categorical)</td>
<td>0.98765</td>
<td>(0.82392 ; 1.18391)</td>
<td>0.22%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Dairy consumption, g/d</td>
<td>0.99289</td>
<td>(0.82804 ; 1.19057)</td>
<td>0.31%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Dietary fiber intake, g/d</td>
<td>0.99362</td>
<td>(0.82920 ; 1.19064)</td>
<td>0.38%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3 + Alcohol consumption, g/d</td>
<td>1.00259</td>
<td>(0.83362 ; 1.20580)</td>
<td>1.28%</td>
</tr>
<tr>
<td>Subdistribution Hazard Model</td>
<td>Model 3+ All baseline lifestyle and dietary variables</td>
<td>1.00000</td>
<td>(0.83021 ; 1.20451)</td>
<td>1.02%</td>
</tr>
</tbody>
</table>

(*) 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/m²) and residual(WC-BMI+Height). Missing data of residual(WC-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

<table>
<thead>
<tr>
<th>Data &amp; analysis</th>
<th>Sub-group</th>
<th>Categories</th>
<th>Total no. of participants</th>
<th>Number of events</th>
<th>Number of competing events</th>
<th>Alive</th>
<th>Hazard Ratio</th>
<th>HR (95%CI)</th>
<th>P value per doubling resistin</th>
<th>P interaction with resistin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mi data w/ Subdistribution hazard model</td>
<td>All</td>
<td>All participants</td>
<td>1343</td>
<td>474</td>
<td>147</td>
<td>722</td>
<td></td>
<td>0.99 (0.83-1.19)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>Women</td>
<td>695</td>
<td>243</td>
<td>66</td>
<td>386</td>
<td></td>
<td>0.89 (0.69-1.14)</td>
<td>0.36</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>648</td>
<td>231</td>
<td>81</td>
<td>336</td>
<td></td>
<td>1.13 (0.87-1.48)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor subsite</td>
<td>Colon</td>
<td>854</td>
<td>306</td>
<td>99</td>
<td>449</td>
<td></td>
<td>1.03 (0.83-1.29)</td>
<td>0.77</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal</td>
<td>469</td>
<td>168</td>
<td>48</td>
<td>273</td>
<td></td>
<td>0.86 (0.63-1.18)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor stage</td>
<td>I</td>
<td>350</td>
<td>70</td>
<td>30</td>
<td>290</td>
<td></td>
<td>0.70 (0.41-1.21)</td>
<td>0.21</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>310</td>
<td>61</td>
<td>39</td>
<td>210</td>
<td></td>
<td>0.87 (0.52-1.48)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>479</td>
<td>218</td>
<td>58</td>
<td>204</td>
<td></td>
<td>0.95 (0.71-1.29)</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>164</td>
<td>126</td>
<td>20</td>
<td>18</td>
<td></td>
<td>1.16 (0.80-1.69)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>BMI &gt;= 30</td>
<td>1099</td>
<td>378</td>
<td>109</td>
<td>612</td>
<td></td>
<td>0.95 (0.77-1.16)</td>
<td>0.59</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI &lt; 30</td>
<td>244</td>
<td>96</td>
<td>38</td>
<td>110</td>
<td></td>
<td>1.19 (0.80-1.77)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to CRC diagnosis</td>
<td>Longer than eight years</td>
<td>195</td>
<td>64</td>
<td>18</td>
<td>113</td>
<td></td>
<td>0.93 (0.58-1.49)</td>
<td>0.77</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two to eight years</td>
<td>913</td>
<td>317</td>
<td>104</td>
<td>492</td>
<td></td>
<td>1.05 (0.84-1.30)</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Within two years</td>
<td>235</td>
<td>93</td>
<td>25</td>
<td>117</td>
<td></td>
<td>0.86 (0.51-1.43)</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>

Missing data of residual (WC~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 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/m²) and residual (WC~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.
(B) Complete case analysis - Cause-specific Cox hazards models

<table>
<thead>
<tr>
<th>Data &amp; analysis</th>
<th>Sub-group</th>
<th>Categories</th>
<th>Total no. of participants</th>
<th>Number of events</th>
<th>Number of competing events</th>
<th>Alive</th>
<th>Hazard Ratio</th>
<th>HR (95%CI)</th>
<th>P value per doubling resistin</th>
<th>P interaction with resistin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete case data with Cause-specific hazards</td>
<td>All</td>
<td>All participants</td>
<td>1268</td>
<td>448</td>
<td>145</td>
<td>675</td>
<td>1.03</td>
<td>(0.86-1.23)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Women</td>
<td>663</td>
<td>235</td>
<td>66</td>
<td>362</td>
<td></td>
<td>0.94</td>
<td>(0.73-1.21)</td>
<td>0.65</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>605</td>
<td>213</td>
<td>79</td>
<td>313</td>
<td></td>
<td>1.14</td>
<td>(0.87-1.48)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Tumor subsite</td>
<td>Colon</td>
<td>807</td>
<td>289</td>
<td>98</td>
<td>420</td>
<td></td>
<td>1.07</td>
<td>(0.86-1.34)</td>
<td>0.53</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Rectal</td>
<td>461</td>
<td>159</td>
<td>47</td>
<td>255</td>
<td></td>
<td>0.89</td>
<td>(0.65-1.24)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td>I</td>
<td>266</td>
<td>40</td>
<td>23</td>
<td>203</td>
<td></td>
<td>0.63</td>
<td>(0.33-1.18)</td>
<td>0.10</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>264</td>
<td>53</td>
<td>31</td>
<td>180</td>
<td></td>
<td>0.83</td>
<td>(0.48-1.41)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>413</td>
<td>190</td>
<td>46</td>
<td>177</td>
<td></td>
<td>0.91</td>
<td>(0.66-1.24)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>146</td>
<td>112</td>
<td>17</td>
<td>17</td>
<td></td>
<td>1.52</td>
<td>(1.05-2.19)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>BMI &gt;= 30</td>
<td>1035</td>
<td>358</td>
<td>107</td>
<td>570</td>
<td></td>
<td>0.99</td>
<td>(0.81-1.21)</td>
<td>0.93</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>BMI &lt; 30</td>
<td>233</td>
<td>90</td>
<td>38</td>
<td>105</td>
<td></td>
<td>1.16</td>
<td>(0.77-1.77)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Time to CRC diagnosis</td>
<td>Longer than eight years</td>
<td>195</td>
<td>64</td>
<td>18</td>
<td>113</td>
<td></td>
<td>1.03</td>
<td>(0.63-1.69)</td>
<td>0.91</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Two to eight years</td>
<td>156</td>
<td>51</td>
<td>16</td>
<td>89</td>
<td></td>
<td>1.03</td>
<td>(0.63-1.69)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within two years</td>
<td>228</td>
<td>90</td>
<td>25</td>
<td>113</td>
<td></td>
<td>0.89</td>
<td>(0.54-1.44)</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

Participants with missing data of residual(WC – 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 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/m²), and residual(WC – 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.
Complete case analysis - Subdistribution hazard model

Participants with missing data of residual \( (WC-BMI+Height) \) (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 residual \( (WC-BMI+Height) \). 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
Supplementary Reference