

Sex- and site-specific associations of circulating lipocalin 2 and incident colorectal cancer: Results from the EPIC cohort

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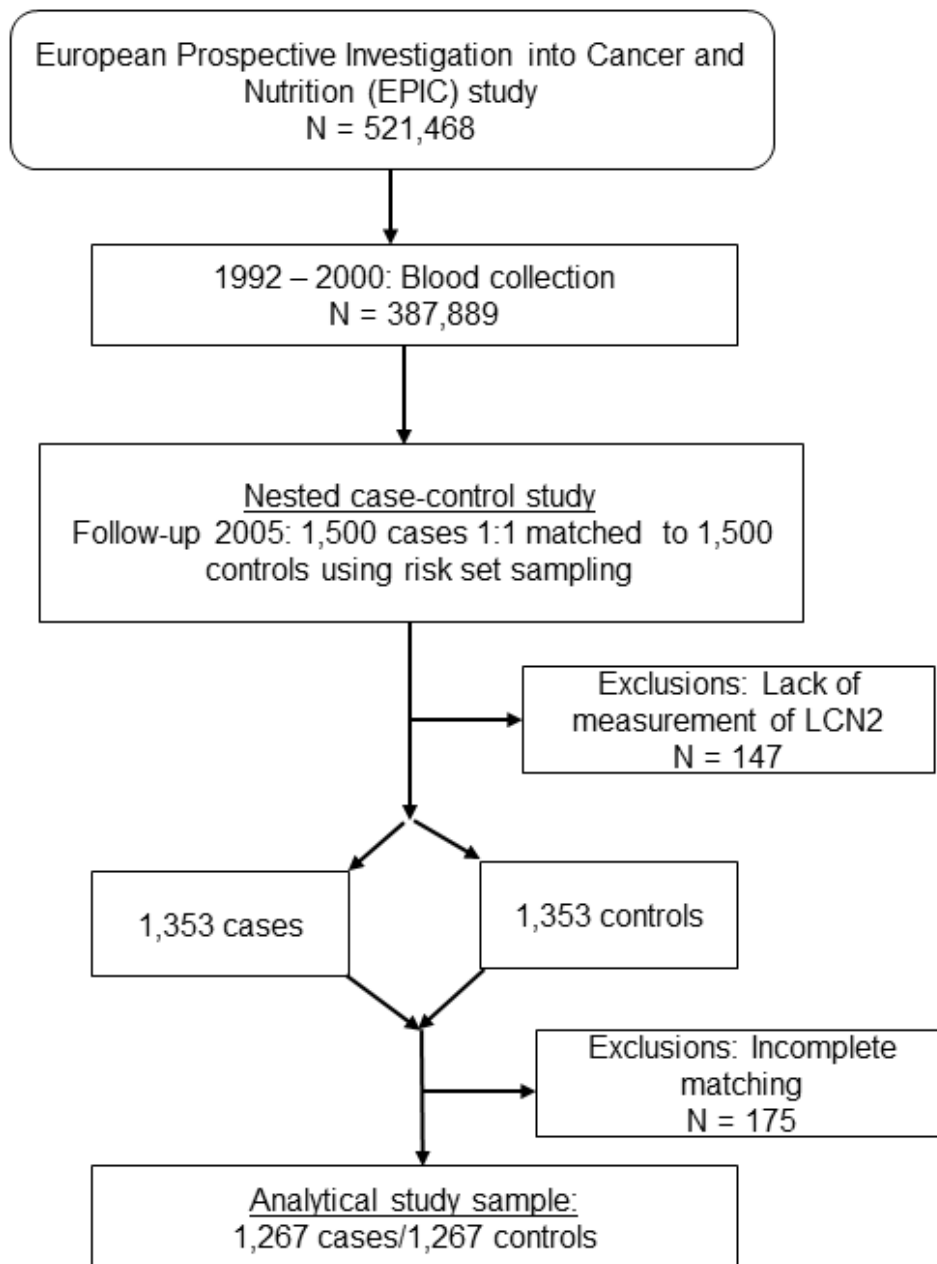


Figure S1. Flowchart of the nested case-control study in EPIC.

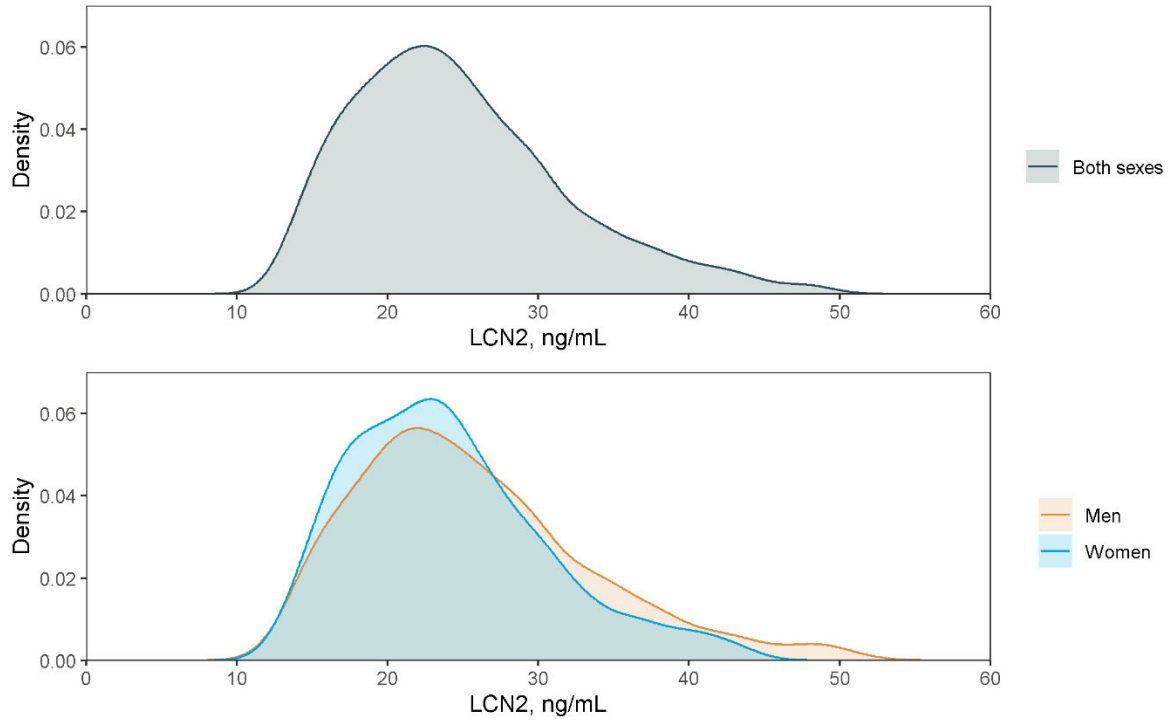


Figure S2a. Distribution of LCN2 concentration in control participants (n=1,267).

$p_{\text{difference by sex}}$ based on Wilcoxon's signed rank test: <0.001 .

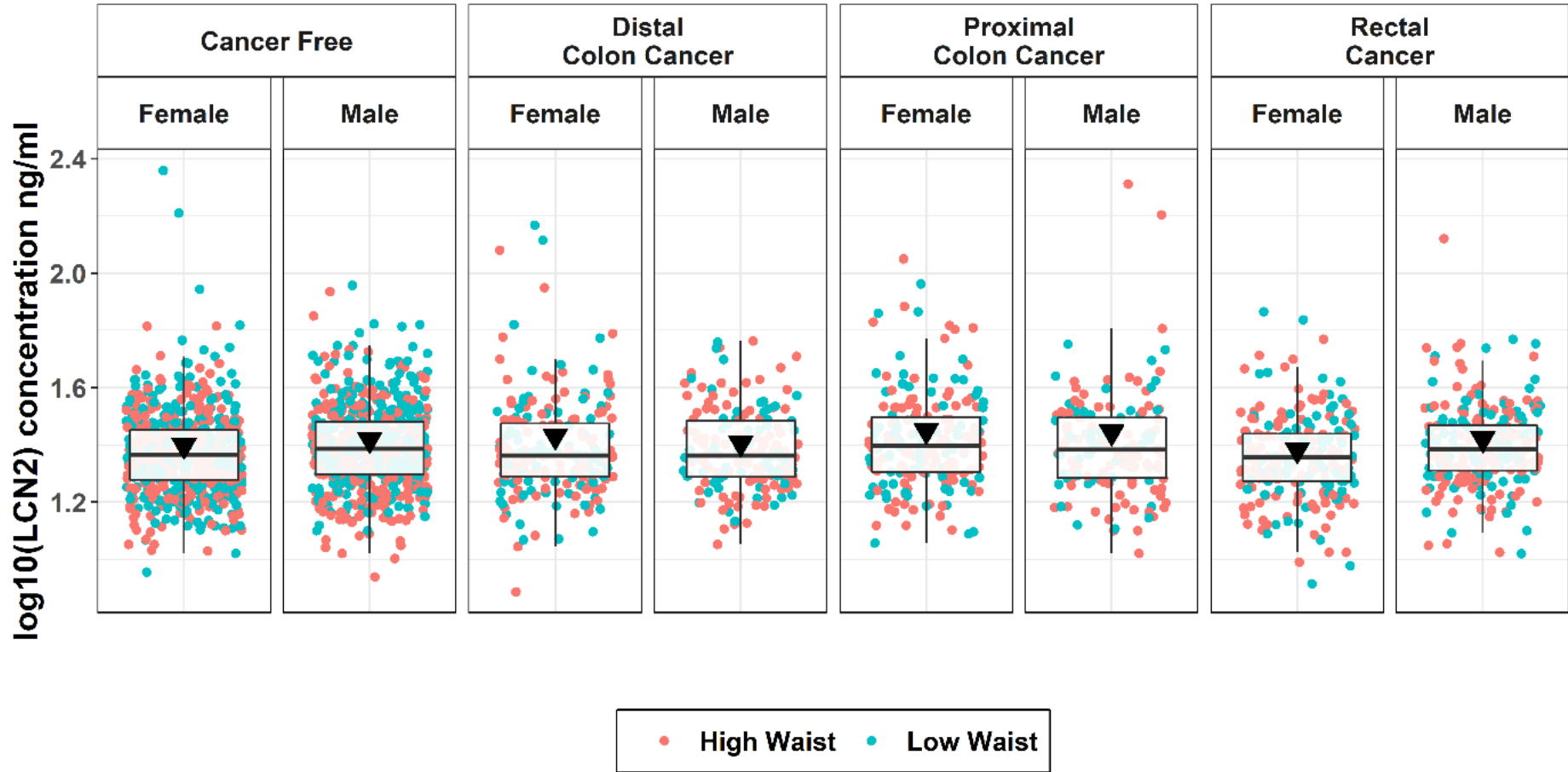


Figure S2b. Distribution of LCN2 concentration in all participants, stratified by sex and cancer status. The triangles mark each respective mean value.

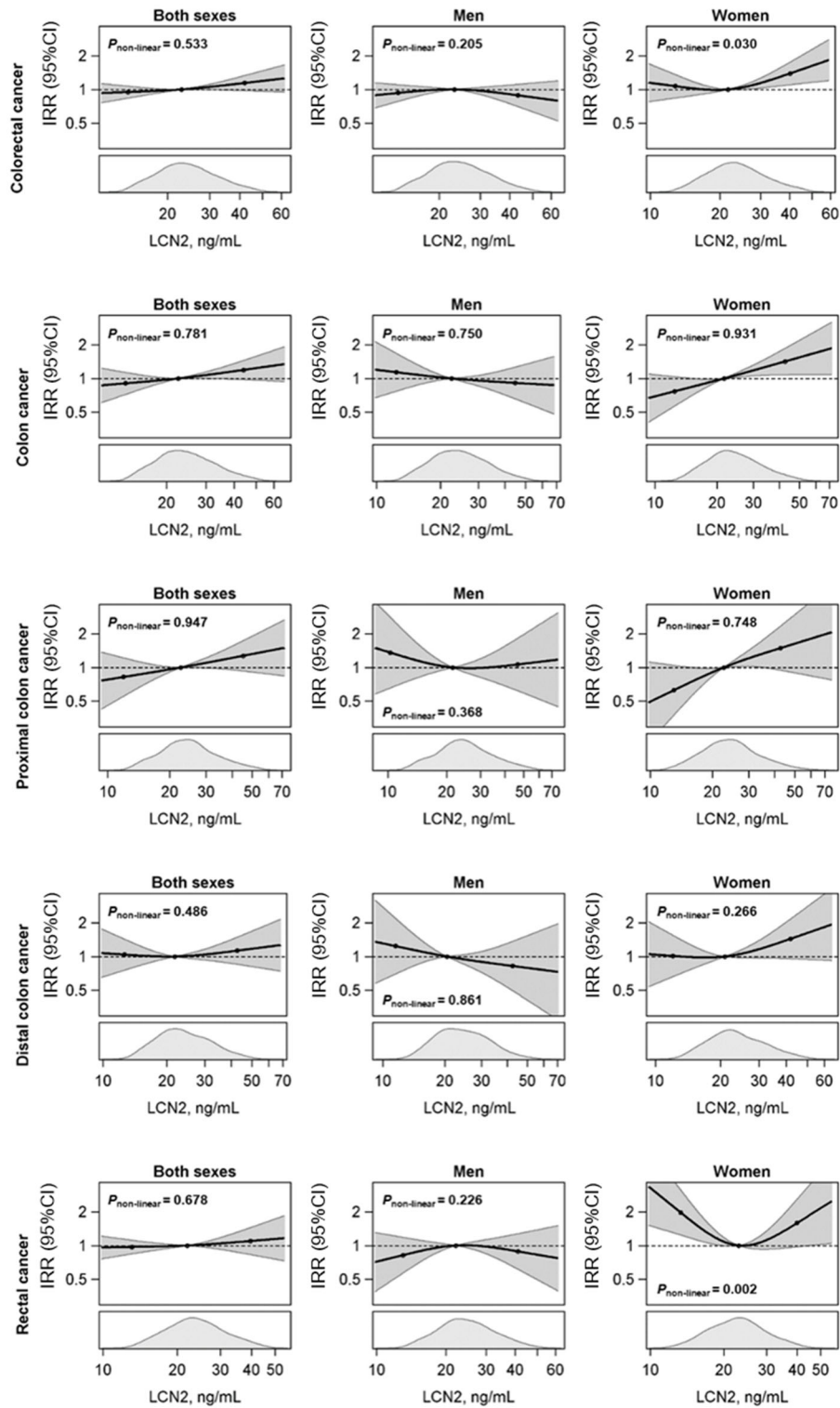


Figure S3. Incidence rate ratios (IRRs) and 95% confidence intervals for the association between LCN2 concentrations and colorectal cancer and subsites modelled with restricted cubic splines with 3 knots, overall and by sex.

Incidence rate ratios (IRRs) accounting for matching factors: age, sex, study center, follow-up time since blood collection, time of the day at blood collection and fasting status. Women were further matched by menopausal status, phase of menstrual cycle at blood collection, postmenopausal women were matched by hormone replacement therapy use. The model was further adjusted for smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference.

Table S1. Missing data by case and control status.

Characteristics	Cases (<i>N</i> = 1,267)		Controls (<i>N</i> = 1,267)	
	<i>N</i>	%	<i>N</i>	%
BMI	6	0.47	7	0.55
Waist circumference	70	5.52	67	5.29
Education	11	0.87	9	0.71
Physical activity	74	5.84	79	6.24
Diet	4	0.32	0	0.00
CRP	407	32.12	546	43.09
Non-HMW adiponectin	491	38.75	623	49.17
HDL cholesterol	408	32.20	547	43.17
ROM	402	31.73	550	43.41
Neopterin	395	31.18	699	55.17

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; HMW, high molecular weight; ROM, reactive oxygen metabolites.

Table S2. Spearman correlation of LCN2 and continuous covariates, partially adjusted for sex and age at blood collection. Confidence intervals were calculated with Fisher transformation.

Characteristics	Spearman ρ (95% confidence interval)
C-reactive protein	0.18 (0.12 – 0.23)
Non-HMW adiponectin	-0.10 (-0.16 – -0.05)
TNF alpha	0.26 (0.21 – 0.31)
HDL cholesterol	-0.16 (-0.21 – -0.11)
ROM	0.15 (0.09 – 0.20)
Neopterin	0.14 (0.09 – 0.19)

Abbreviations: HDL, high-density lipoprotein; HMW, high molecular weight; LCN2, lipocalin 2; ROM, reactive oxygen metabolites; TNF, tumor necrosis factor.

Table S3. Incidence rate ratios (IRRs)^a and 95% confidence intervals (95% CIs) of LCN2 quartile categories with colorectal cancer and subsites, overall, and by sex.

LCN2, ng/mL	LCN2 quartile categories (median (range))				<i>P</i> _{trend} ^b
	1 16.57 (7.7-19.2 ng/ml)	2 21.50 (19.2 – <23.6 ng/ml)	3 26.00 (23.6 – <29.0 ng/ml)	4 34.41 (29.0-228.3 ng/ml)	
Colorectal cancer					
Both sexes, <i>N</i> (cases/controls)	287/316	350/315	288/315	342/321	
IRR (95%CI)	1 (Ref.)	1.23 (0.97 – 1.56)	0.98 (0.77 – 1.25)	1.13 (0.88 – 1.45)	0.64
Men, <i>N</i> (cases/controls)	135/138	163/144	145/151	167/177	
IRR (95%CI)	1 (Ref.)	1.18 (0.82 – 1.69)	0.87 (0.60 – 1.26)	0.84 (0.58 – 1.20)	0.16
Women, <i>N</i> (cases/controls)	152/178	187/171	143/164	175/144	
IRR (95%CI)	1 (Ref.)	1.24 (0.89 – 1.72)	0.98 (0.70 – 1.37)	1.44 (0.99 – 2.09)	0.13
Colon cancer					
Both sexes, <i>N</i> (cases/controls)	179/196	215/199	171/191	226/205	
IRR (95%CI)	1 (Ref.)	1.25 (0.93 – 1.67)	1.01 (0.74 – 1.38)	1.24 (0.90 – 1.70)	0.33
Men, <i>N</i> (cases/controls)	88/78	90/87	79/89	97/100	
IRR (95%CI)	1 (Ref.)	1.03 (0.64 – 1.64)	0.69 (0.42 – 1.14)	0.72 (0.44 – 1.19)	0.19
Women, <i>N</i> (cases/controls)	91/118	125/102	92/102	129/105	
IRR (95%CI)	1 (Ref.)	1.54 (1.04 – 2.29)	1.30 (0.84 – 2.00)	1.85 (1.18 – 2.91)	0.02
Proximal colon cancer					
Both sexes, <i>N</i> (cases/controls)	75/75	82/89	86/92	98/85	
IRR (95%CI)	1 (Ref.)	0.94 (0.58 – 1.53)	1.01 (0.62 – 1.63)	1.19 (0.70 – 2.02)	0.45
Men, <i>N</i> (cases/controls)	38/28	33/39	35/38	40/41	
IRR (95%CI)	1 (Ref.)	0.43 (0.18 – 1.02)	0.49 (0.20 – 1.21)	0.43 (0.16 – 1.13)	0.17
Women, <i>N</i> (cases/controls)	37/47	49/50	51/54	58/44	
IRR (95%CI)	1 (Ref.)	1.43 (0.74 – 2.77)	1.50 (0.78 – 2.88)	2.14 (1.01 – 4.54)	0.06
Distal colon cancer					

Both sexes, <i>N</i> (cases/controls)	93/103	124/98	68/88	108/104	
IRR (95%CI)	1 (Ref.)	1.51 (1.00 – 2.28)	0.79 (0.49 – 1.27)	1.10 (0.70 – 1.73)	0.92
Men, <i>N</i> (cases/controls)	43/42	52/42	35/44	47/49	
IRR (95%CI)	1 (Ref.)	1.54 (0.75 – 3.13)	0.51 (0.24 – 1.11)	0.74 (0.36 – 1.54)	0.23
Women, <i>N</i> (cases/controls)	50/61	72/56	33/44	61/55	
IRR (95%CI)	1 (Ref.)	1.55 (0.88 – 2.74)	1.04 (0.52 – 2.08)	1.43 (0.76 – 2.69)	0.46
Rectal cancer					
Both sexes, <i>N</i> (cases/controls)	109/115	136/119	106/125	110/102	0.76
IRR (95%CI)	1 (Ref.)	1.15 (0.76 – 1.73)	0.81 (0.53 – 1.22)	1.03 (0.66 – 1.62)	
Men, <i>N</i> (cases/controls)	48/57	71/60	61/64	66/65	
IRR (95%CI)	1 (Ref.)	1.46 (0.81 – 2.61)	1.09 (0.59 – 2.02)	1.08 (0.59 – 1.97)	0.81
Women, <i>N</i> (cases/controls)	61/58	65/59	45/61	44/37	
IRR (95%CI)	1 (Ref.)	0.94 (0.49 – 1.79)	0.53 (0.28 – 0.98)	1.01 (0.45 – 2.23)	0.45

^a Multivariable-adjusted IRRs considering matching factors: age, sex, study center, follow-up time since blood collection, time of the day at blood collection and fasting status. Women were further matched by menopausal status, phase of menstrual cycle at blood collection; postmenopausal women were matched by hormone replacement therapy use. The model was further adjusted for smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference.

^b *P* values for trend were calculated with the Wald test on a multivariable-adjusted model with the sex-specific quartile categories modelled linearly as the sex-specific median of each category.

Table S4. Hazard Ratios (HR)^a and 95% confidence intervals (95% CIs) of LCN2 and CRC and subsites, excluding cases with a follow-up of <2 years (N_{cases}=231) and matched controls (N_{controls} = 231), stratified by sex and waist circumference.

Outcome	LCN2 log ₂				<i>P</i> _{interaction^b}
	Waist circumference				
	<94cm (men), <80cm (women)		≥94cm (men), ≥80cm (women)		
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	
Colorectal cancer, <i>N</i> (cases/controls)					
Both sexes	417/493		619/543		
	0.72 (0.64 – 0.81)	<0.01	1.22 (1.11 – 1.34)	<0.01	<0.01
Men	190/241		309/258		
	0.42 (0.35 – 0.51)	<0.01	0.96 (0.85 – 1.09)	0.56	<0.01
Women	227/252		310/285		
	0.81 (0.70 – 0.95)	<0.01	1.75 (1.49 – 2.06)	<0.01	<0.01
Colon cancer, <i>N</i> (cases/controls)					
Both sexes	261/316		394/339		
	0.80 (0.69 – 0.93)	<0.01	1.58 (1.40 – 1.78)	<0.01	0.03
Men	111/150		184/145		
	0.23 (0.17 – 0.30)	<0.01	1.237 (1.17 – 1.60)	<0.01	<0.01
Women	150/166		210/194		
	1.23 (1.01 – 1.50)	0.04	2.36 (1.93 – 2.89)	<0.01	<0.01
Proximal colon cancer, <i>N</i> (cases/controls)					
Both sexes	109/130		174/153		
	0.56 (0.44 – 0.72)	<0.01	2.96 (2.45 – 3.57)	<0.01	<0.01
Men	42/59		79/62		
	0.02 (0.01 – 0.04)	<0.01	0.92 (0.69 – 1.23)	0.58	<0.01
Women	67/71		95/91		

	0.88 (0.60 – 1.31)	0.55	5.94 (4.35 – 8.12)	<0.01	<0.01
Distal colon cancer, <i>N</i> (cases/controls)					
Both sexes	130/173 0.88 (0.69 – 1.13)	0.31	197/154 1.94 (1.61 – 2.34)	<0.01	<0.01
Men	56/82 0.12 (0.07 – 0.23)	<0.01	93/67 2.43 (1.83 – 3.21)	<0.01	<0.01
Women	74/91 2.37 (1.61 – 3.48)	<0.01	104/87 4.62 (3.06 – 6.96)	<0.01	<0.01
Rectal cancer, <i>N</i> (cases/controls)					
Both sexes	152/174 0.86 (0.70 – 1.07)	0.18	271/195 1.08 (0.91 – 1.29)	0.39	0.23
Men	77/89 1.02 (0.74 – 1.41)	0.91	120/108 0.94 (0.73 – 1.20)	0.61	0.31
Women	75/85 0.71 (0.51 – 0.98)	0.04	97/87 1.21 (0.90 – 1.62)	0.21	<0.01

^a Based on weighted Cox proportional hazard regression using inverse probability weighting to approximate the full cohort to evaluate the association of LCN2 with colorectal cancer risk per doubling of LCN2 concentration. HRs were adjusted for age, sex, study center, follow-up time since blood collection, time of the day at blood collection, fasting status, smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference. Women were additionally matched by menopausal status, and phase of menstrual cycle at blood collection; postmenopausal women by hormone replacement therapy use.

^b *P* values for interaction were calculated with the Wald-test for a multiplicative interaction term of LCN2 and the continuous waist circumference variable.

Table S5. Hazard Ratios (HR)^a and 95% confidence intervals (95% CIs) of LCN2 and CRC and subsites, excluding cases (N_{cases} = 53) and matched controls (N_{controls} = 53) with an LCN2 concentration below the 1st and above the 99th sex-specific LCN2 concentration-percentile, stratified by sex and waist circumference.

Outcome	LCN2 log ₂				<i>P</i> _{interaction} ^b
	Waist circumference				
	<94cm (men), <80cm (women)		≥94cm (men), ≥80cm (women)		
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	
Colorectal cancer, <i>N</i> (cases/controls)					
Both sexes	495/576 0.74 (0.65 – 0.83)	<0.01	719/638 1.46 (1.32 – 1.60)	<0.01	<0.01
Men	232/284 0.46 (0.38 – 0.55)	<0.01	352/300 1.29 (1.13 – 1.48)	<0.01	<0.01
Women	263/292 1.00 (0.84 – 1.20)	0.97	367/338 1.85 (1.60 – 2.14)	<0.01	<0.01
Colon cancer, <i>N</i> (cases/controls)					
Both sexes	309/360 0.92 (0.79 – 1.07)	0.28	450/399 1.61 (1.43 – 1.81)	<0.01	0.33
Men	136/170 0.35 (0.27 – 0.47)	<0.01	204/170 1.47 (1.23 – 1.75)	<0.01	<0.01
Women	173/190 1.48 (1.20 – 1.82)	<0.01	246/229 2.56 (2.13 – 3.08)	<0.01	<0.01
Proximal colon cancer, <i>N</i> (cases/controls)					
Both sexes	132/153 1.05 (0.83 – 1.33)	0.68	194/123 2.50 (2.06 – 3.04)	<0.01	<0.01
Men	54/71 0.10 (0.06 – 0.18)	<0.01	85/68 0.55 (0.39 – 0.76)	<0.01	<0.01
Women	78/82		109/105		

	2.95 (1.92 – 4.53)	<0.01	4.80 (3.61 – 6.39)	<0.01	<0.01
Distal colon cancer, <i>N</i> (cases/controls)					
Both sexes	152/189 0.76 (0.59 – 0.99)	0.04	227/190 2.60 (2.13 – 3.17)	<0.01	<0.01
Men	66/87 0.23 (0.12 – 0.44)	<0.01	104/83 2.87 (2.14 – 3.85)	<0.01	0.02
Women	86/102 2.85 (1.90 – 4.29)	<0.01	123/107 4.68 (3.25 – 6.76)	<0.01	<0.01
Rectal cancer, <i>N</i> (cases/controls)					
Both sexes	183/214 0.77 (0.63 – 0.96)	0.02	258/227 1.37 (1.16 – 1.62)	<0.001	0.093
Men	95/113 0.79 (0.58 – 1.07)	0.13	140/122 1.43 (1.11 – 1.85)	0.006	0.869
Women	88/101 0.59 (0.42 – 0.82)	<0.01	118/105 1.09 (0.83 – 1.43)	0.535	0.006

^a Based on weighted Cox proportional hazard regression using inverse probability weighting to approximate the full cohort to evaluate the association of LCN2 with colorectal cancer risk per doubling of LCN2 concentration. HRs were adjusted for age, sex, study center, follow-up time since blood collection, time of the day at blood collection, fasting status, smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference. Women were additionally matched by menopausal status and phase of menstrual cycle at blood collection; postmenopausal women by hormone replacement therapy use.

^b *P* values for interaction were calculated with the Wald-test for a multiplicative interaction term of LCN2 and the continuous waist circumference variable.

Table S6. Hazard Ratios (HRs)^a and 95% confidence intervals (95% CIs) of LCN2 and CRC and subsites, excluding cases (N_{cases} = 77) and matched controls (N_{controls} = 77) with missing covariates, stratified by sex and waist circumference.

Outcome	LCN2 log ₂				<i>P</i> _{interaction^b}
	Waist circumference				
	<94cm (men), <80cm (women)		≥94cm (men), ≥80cm (women)		
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	
Colorectal cancer, <i>N</i> (cases/controls)					
Both sexes	445/527		745/663		
	0.76 (0.68 – 0.85)	<0.01	1.38 (1.27 – 1.49)	<0.01	<0.01
Men	196/248		367/315		
	0.42 (0.35 – 0.51)	<0.01	1.20 (1.09 – 1.33)	<0.01	<0.01
Women	249/279		378/348		
	0.87 (0.76 – 0.99d)	0.04	2.01 (1.75 – 2.30)	<0.01	<0.01
Colon cancer, <i>N</i> (cases/controls)					
Both sexes	273/330		468/411		
	0.76 (0.67 – 0.88)	<0.01	1.66 (1.50 – 1.84)	<0.01	0.02
Men	111/147		213/177		
	0.25 (0.18 – 0.32)	<0.01	1.52 (1.32 – 1.76)	<0.01	<0.01
Women	162/183		255/234		
	1.04 (0.88 – 1.22)	0.63	3.09 (2.60 – 3.66)	<0.01	<0.01
Proximal colon cancer, <i>N</i> (cases/controls)					
Both sexes	119/135		198/182		
	0.76 (0.62 – 0.82)	0.01	3.05 (2.58 – 3.59)	<0.01	<0.01
Men	46/59		87/74		
	0.18 (0.11 – 0.29)	<0.01	1.24 (0.97 – 1.59)	0.09	<0.01
Women	73/76		111/108		

	1.15 (0.84 – 1.56)	0.38	6.91 (5.32 – 8.98)	<0.01	<0.01
Distal colon cancer, <i>N</i> (cases/controls)					
Both sexes	129/177 0.50 (0.39 – 0.64)	<0.01	239/191 2.29 (1.94 – 2.72)	<0.01	<0.01
Men	50/77 0.04 (0.02 – 0.07)	<0.01	111/84 2.13 (1.62 – 2.78)	<0.01	<0.01
Women	79/100 1.02 (0.73 – 1.42)	0.90	128/107 5.64 (4.18 – 7.61)	<0.01	<0.01
Rectal cancer, <i>N</i> (cases/controls)					
Both sexes	168/194 0.95 (0.78 – 1.15)	0.58	266/240 1.18 (1.03 – 1.35)	0.02	0.43
Men	83/99 0.85 (0.63 – 1.15)	0.29	146/130 1.15 (0.97 – 1.36)	0.11	0.75
Women	85/95 0.91 (0.68 – 1.22)	0.53	120/110 1.00 (0.78 – 1.29)	1.00	0.18

^a Based on weighted Cox proportional hazard regression using inverse probability weighting to approximate the full cohort to evaluate the association of LCN2 with colorectal cancer risk per doubling of LCN2 concentration. HRs were adjusted for age, sex, study center, follow-up time since blood collection, time of the day at blood collection, fasting status, smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference. Women were additionally matched by menopausal status and phase of menstrual cycle at blood collection; postmenopausal women by hormone replacement therapy use.

^b *P* values for interaction were calculated with the Wald-test for a multiplicative interaction term of LCN2 and the continuous waist circumference variable.

Table S7. Hazard Ratios (HRs)^a and 95% confidence intervals (95% CIs) of LCN2 and CRC and subsites, only including postmenopausal women cases (N_{cases} = 509) and matched controls (N_{controls} = 509), stratified by waist circumference.

Outcome	LCN2 log ₂				<i>P</i> _{interaction} ^b
	Waist circumference				
	<80cm	<i>P</i>	≥80cm	<i>P</i>	
	HR (95% CI)		HR (95% CI)		
Colorectal cancer, <i>N</i> (cases/controls)					
Women	201/227 0.81 (0.69 – 0.94)	<0.01	308/282 2.18 (1.85 – 2.57)	<0.01	0.12
Colon cancer, <i>N</i> (cases/controls)					
Women	132/148 0.89 (0.73 – 1.08)	0.23	216/196 3.52 (2.88 – 4.32)	<0.01	<0.01
Proximal colon cancer, <i>N</i> (cases/controls)					
Women	65/69 0.68 (0.46 – 1.01)	0.06	96/92 7.09 (5.03 – 9.98)	<0.01	<0.01
Distal colon cancer, <i>N</i> (cases/controls)					
Women	58/75 0.84 (0.57 – 1.24)	0.39	107/90 4.95 (3.48 – 7.05)	<0.01	<0.01
Rectal cancer, <i>N</i> (cases/controls)					
Women	70/78 1.04 (0.74 – 1.46)	0.84	91/83 0.97 (- 0.72 – 1.30)	0.84	0.03

^a Based on weighted Cox proportional hazard regression using inverse probability weighting to approximate the full cohort to evaluate the association of LCN2 with colorectal cancer risk per doubling of LCN2 concentration. HRs were adjusted for age, study center, follow-up time since blood collection, time of the day at blood collection, fasting status, smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference. Women were additionally matched by menopausal status and phase of menstrual cycle at blood collection; postmenopausal women by hormone replacement therapy use.

^b *P* values for interaction were calculated with the Wald-test for a multiplicative interaction term of LCN2 and the continuous waist circumference variable.

Table S8. Multivariable-adjusted hazard ratios^a (HRs) and 95% confidence intervals (95% CIs) for the association of LCN2 with colorectal cancer comparing high vs. low LCN2 levels based on a-priori defined cut-points.

LCN2 cut-points	≥50 ng/mL vs. <50 ng/mL		≥30 ng/mL vs. <30 ng/mL		≥25 ng/mL vs. <25 ng/mL	
	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value
Both Sexes	1.56 (1.33 - 1.82)	<0.001	1.10 (1.03 - 1.18)	0.005	1.00 (0.94 - 1.06)	0.906
Men	0.78 (0.61 - 0.99)	0.04	0.77 (0.70 - 0.85)	<0.001	0.87 (0.79 - 0.95)	0.002
Women	3.24 (2.55 - 4.13)	<0.001	1.46 (1.33 - 1.61)	<0.001	1.09 (1.00 - 1.18)	0.055

^a Based on weighted Cox proportional hazard regression using inverse probability weighting to approximate the full cohort to evaluate the association of dichotomized LCN2 values according to predefined cut-points with colorectal cancer risk. HRs were adjusted for age, study center, follow-up time since blood collection, time of the day at blood collection, fasting status, smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference. Women were additionally matched by menopausal status and phase of menstrual cycle at blood collection; postmenopausal women by hormone replacement therapy use.

Table S9. Multivariable-adjusted hazard ratios^a (HRs) and 95% confidence intervals (95% CIs) for the association of LCN2 with colorectal cancer comparing high vs. low LCN2 levels according to predefined cut-points, stratified by waist circumference categories.

	Waist circumference categories			
	<94cm (men), <80cm (women)		≥94cm (men), ≥80cm (women)	
	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value
	≥50 ng/mL vs. <50 ng/mL			
Both Sexes	1.11 (0.87 - 1.41)	0.413	2.18 (1.76 - 2.69)	<0.001
Men	0.73 (0.51 - 1.05)	0.092	1.14 (0.82 - 1.58)	0.443
Women	1.21 (0.83 - 1.77)	0.322	9.06 (6.43 - 12.76)	<0.001
	≥30 ng/mL vs. <30 ng/mL			
Both Sexes	0.83 (0.74 - 0.92)	0.001	1.45 (1.33 - 1.59)	<0.001
Men	0.57 (0.49 - 0.68)	<0.001	1.02 (0.90 - 1.16)	0.75
Women	0.84 (0.71 - 0.99)	0.044	2.31 (2.03 - 2.63)	<0.001
	≥25 ng/mL vs. <25 ng/mL			
Both Sexes	0.85 (0.77 - 0.94)	0.001	1.16 (1.07 - 1.25)	<0.001
Men	0.72 (0.62 - 0.83)	<0.001	0.98 (0.87 - 1.10)	0.682
Women	0.79 (0.69 - 0.91)	0.001	1.32 (1.17 - 1.49)	<0.001

^a Based on weighted Cox proportional hazard regression using inverse probability weighting to approximate the full cohort to evaluate the association of dichotomized LCN2 values according to predefined cut-points with colorectal cancer risk. HRs were adjusted for age, study center, follow-up time since blood collection, time of the day at blood collection, fasting status, smoking status, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish, and waist circumference. Women were additionally matched by menopausal status and phase of menstrual cycle at blood collection; postmenopausal women by hormone replacement therapy use.

Supplemental References

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