

Supplemental material

Relation between systemic inflammation and incident cancer in patients with stable cardiovascular disease

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Supplemental Table S1. Cancer diagnosis according to ICD-10 classification

Cancer group	Topography	Number	ICD-10 code
Colon/rectum	Colon, rectum	177	C18-C20
Lung	Lung, bronchus	226	C34
Breast	Breast	70	C50
Prostate	Prostate	188	C61
Urinary tract	Kidney, renal pelvis, ureter	52	C64-C66
	Bladder, or unspecified parts of urinary organs	57	C67-C68
Lymphoid/ hematopoietic	Hodgkin's disease	1	C81
	Non-Hodgkin's lymphoma	30	C82-C85
	Multiple myeloma	19	C88, C90
	Leukemia	32	C91-C96
Melanoma skin cancer	Melanoma of skin	52	C43
Other	Lip, oral cavity, pharynx	31	C00-C14
	Esophagus	36	C15
	Stomach	38	C16
	Small intestine	6	C17
	Liver and bile ducts, gallbladder	21	C22-C24, C26.9
	Pancreas	34	C25
	Nasal cavity, middle ear, accessory sinuses, larynx, trachea	26	C30-C33
	Bone and articular cartilage of limb	1	C40-C41
	Mesothelial and soft tissue	20	C45-C49
	Vulva or vagina	5	C51-C52
	Cervix uteri or corpus uteri	14	C53-C54
	Ovarium	5	C56-C57
	Penis or testis	5	C60,C62-C63
	Eye, brain, and other parts of central nervous system	8	C69-C72
	Thyroid gland	3	C73
	Ill-defined, secondary and unspecified sites	22	C76-C80

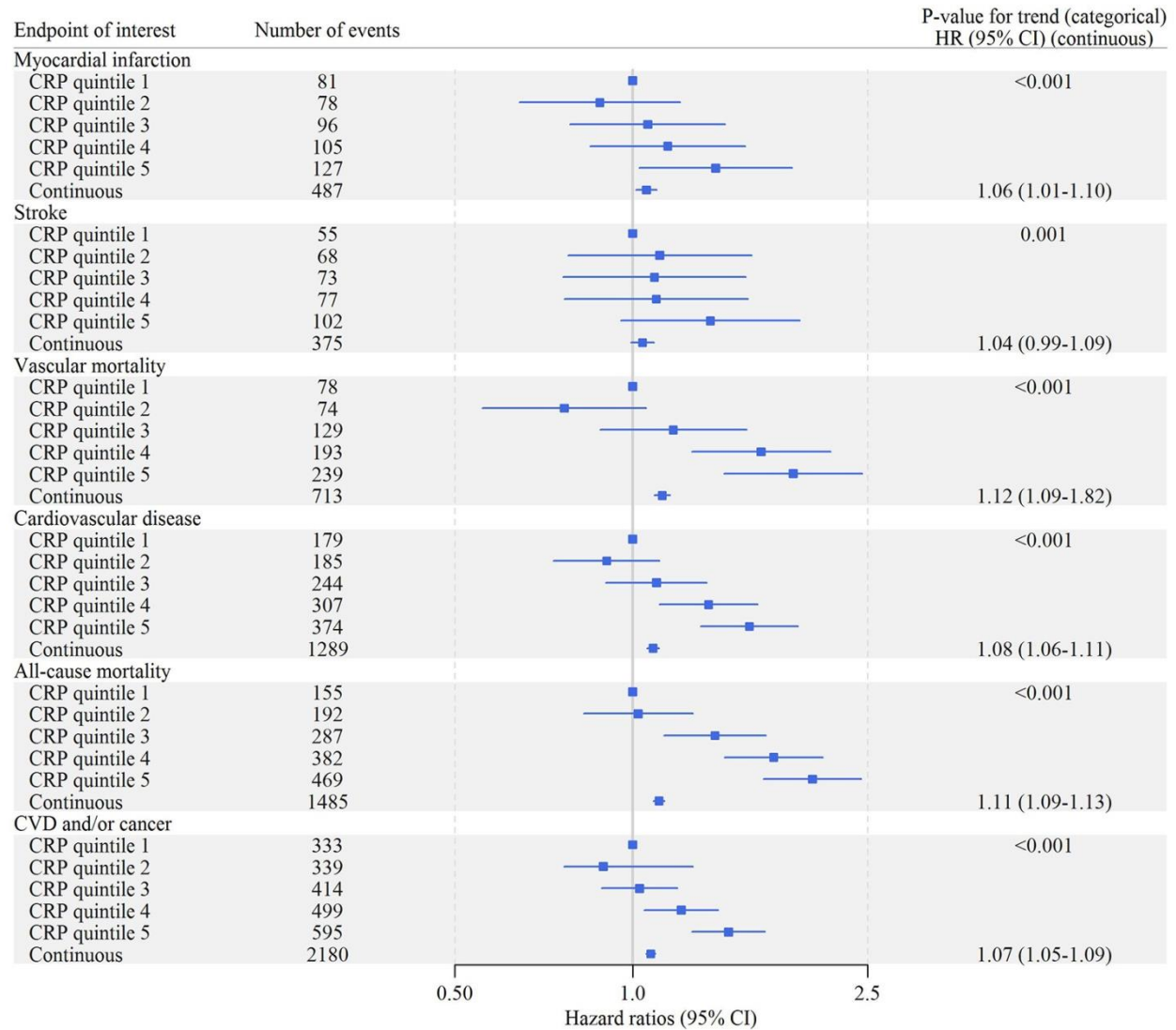
Supplemental Table S2. Tumor histopathology according to ICD-O-3 classification

Histopathology according to ICD-O-3 code	Number
800 Neoplasms, not further specified	60
801-804 Epithelial neoplasms, not further specified	83
805-808 Squamous cell neoplasms	117
809-811 Basal cell neoplasms	1
812-813 Papillomas and transitional cell carcinomas	61
814-838 Adenomas and adenocarcinomas	568
843 Mucoepidermoid neoplasms	1
844-849 Cystic, mucinous and serous neoplasms	42
850-854 Ductal and lobular neoplasms	79
855 Acinar cell neoplasms	9
856-857 Complex epithelial neoplasms	1
872-879 Nevi and melanomas	55
880 Tumors of soft tissue and sarcomas, not further specified	2
881-883 Fibrous neoplasms	1
885-888 Lipomatous neoplasms	1
889-892 Myxomatous neoplasms	2
893-899 Complex mixed and stromal neoplasms	4
905 Mesothelial neoplasms	11
906-909 Germ cell neoplasms	3
912-916 Tumors of blood vessels	1
918-924 Neoplasms of bone and cartilage	1
938-948 Gliomas	4
949-952 Neuroepithelial neoplasms	1
959-972 Hodgkin lymphomas and non-Hodgkin lymphomas	33
973 Plasma cell tumors	15
976 Immunoproliferative diseases	1
980-994 Leukemias	32
998 Myelodysplastic syndrome	1

Supplemental Table S3. Definitions of endpoint recurrent cardiovascular disease

Cardiovascular disease	Definition
Myocardial infarction	Myocardial infarction, fatal or non-fatal
Stroke	Cerebral infarction, fatal or non-fatal Intracranial hemorrhage, fatal or non-fatal Fatal stroke, undefined hemorrhage/infarction
Vascular mortality	Fatal stroke Fatal myocardial infarction Terminal heart failure Fatal rupture aneurysm abdominal aorta Sudden death Other vascular death
Cardiovascular disease	Any of the above

Supplemental Figure S1. Relation between CRP and recurrent cardiovascular disease risk.



Cardiovascular disease is defined as the occurrence of myocardial infarction, stroke, or vascular mortality. Models are adjusted for age, sex, smoking status, number of pack-years, body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. Continuous analyses represent hazard ratios per 1 mg/L higher CRP concentration.

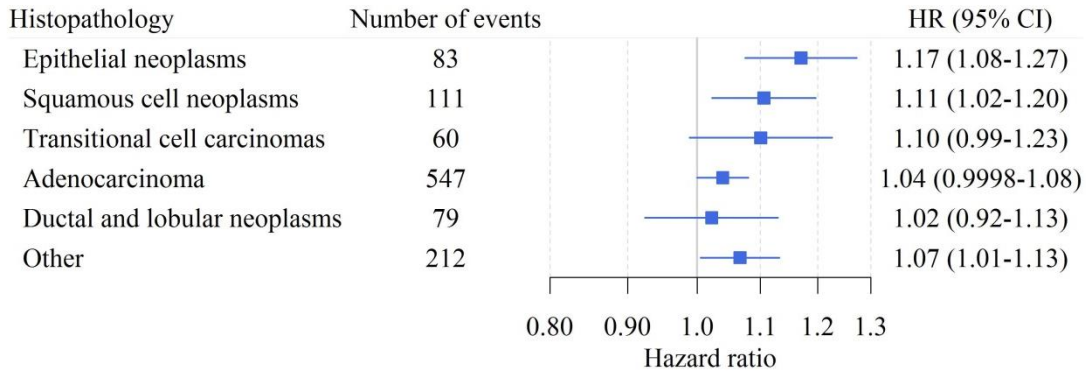
Supplemental Table S4. Relation between continuous CRP (1 mg/L higher) and risk of all lung cancers and for different histopathological diagnoses

Lung cancer Histopathological diagnosis	HR (95% CI)
All lung cancers	
Number of events	226
Model 1	1.20 (1.15-1.26)
Model 2	1.16 (1.10-1.22)
Small cell lung cancer (SCLC)	
Number of events	33
Model 1	1.25 (1.11-1.42)
Model 2	1.23 (1.08-1.40)
Non-small cell lung cancer (NSCLC) (including adeno-, squamous cell, and large cell carcinoma)	
Number of events	164
Model 1	1.19 (1.12-1.26)
Model 2	1.18 (1.11-1.25)
Adenocarcinoma	
Number of events	85
Model 1	1.19 (1.10-1.29)
Model 2	1.19 (1.09-1.29)
Squamous cell carcinoma	
Number of events	47
Model 1	1.20 (1.08-1.33)
Model 2	1.19 (1.07-1.33)
Large cell carcinoma	
Number of events	29
Model 1	1.18 (1.03-1.36)
Model 2	1.15 (0.99-1.33)

Model 1= Adjusted for age, sex; Model 2= Adjusted for age, sex, number of pack-years, body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. No adjustment for smoking status due to low number of lung cancer in non-smokers. HR=Hazard ratio; CI=confidence interval.

The relatively high percentage of large cell undifferentiated NSCLC is related to the fact that the SMART cohort started in 1996 and histopathological subdivision of NSCLC was not routinely determined yet.

Supplemental Figure S2. Relation between continuous CRP and incident cancer according to histopathology, irrespective of anatomical location of origin.



Hazard ratios are adjusted for age, sex, smoking status, number of pack-years, body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. Category other includes basal cell neoplasms, mucoepidermoid neoplasms, cystic, mucinous, and serous neoplasms, acinar cell neoplasms, fibrous neoplasms, lipomatous neoplasms, myxomatous neoplasms, complex mixed and stromal neoplasms, mesothelial neoplasms, germ cell neoplasms, tumors of blood vessels, bone and cartilage neoplasms, gliomas, neuroepithelial neoplasms, Hodgkin lymphomas and non-Hodgkin lymphomas, plasma cell neoplasms, leukemias, and myelodysplastic syndrome (Supplemental material Table S2).

Supplemental Table S5. Relation between continuous CRP (1 mg/L higher) and cancer risk, for all cancers and according to anatomical location, with separate adjustment for BMI and smoking.

Endpoint of interest	HR (95% CI)
Lung	
Number of events	226
Model 1	1.20 (1.15-1.26)
Model 1b (smoking adjusted)	1.14 (1.09-1.20)
Model 1c (body mass index adjusted)	1.22 (1.16-1.28)
Model 2	1.16 (1.10-1.22)
Colon/rectum	
Number of events	177
Model 1	1.06 (1.00-1.13)
Model 1b (smoking adjusted)	1.05 (0.99-1.12)
Model 1c (body mass index adjusted)	1.06 (0.995-1.13)
Model 2	1.05 (0.98-1.12)
Urinary tract	
Number of events	107
Model 1	1.10 (1.02-1.19)
Model 1b (smoking adjusted)	1.08 (0.997-1.17)
Model 1c (body mass index adjusted)	1.10 (1.01-1.19)
Model 2	1.08 (0.995-1.17)
Lymphoid/hematopoietic	
Number of events	82
Model 1	1.11 (1.01-1.21)
Model 1b (smoking adjusted)	1.11 (1.02-1.21)
Model 1c (body mass index adjusted)	1.11 (1.02-1.21)
Model 2	1.12 (1.02-1.22)
Breast	
Number of events/females	69/1828
Model 1	1.04 (0.94-1.15)
Model 1b (smoking adjusted)	1.05 (0.95-1.16)
Model 1c (body mass index adjusted)	1.05 (0.95-1.16)
Model 2	1.06 (0.96-1.17)
Prostate	
Number of events/males	188/5350
Model 1	0.95 (0.89-1.02)
Model 1b (smoking adjusted)	0.95 (0.89-1.03)
Model 1c (body mass index adjusted)	0.96 (0.89-1.03)
Model 2	0.96 (0.89-1.03)
All cancers	
Number of events	1072
Model 1	1.08 (1.05-1.11)
Model 1b (smoking adjusted)	1.06 (1.03-1.09)
Model 1c (body mass index adjusted)	1.08 (1.06-1.11)
Model 2	1.07 (1.04-1.09)

Model 1= Adjusted for age, sex; Model 1b= Adjusted for age, sex, smoking status, and pack-years of smoking. Model 1c= Adjusted for age, sex, and body mass index. Model 2= Adjusted for age, sex, smoking status, number of pack-years, body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. HR=Hazard ratio; CI=confidence interval; CVD=cardiovascular disease.

Supplemental Table S6. Relation between continuous CRP (1 mg/L higher) and cancer risk, stratified for smoking status.

	Never smokers N= 1587 HR (95% CI)	Former smokers N=3416 HR (95% CI)	Current smokers N=2175 HR (95% CI)	P-value for interaction Former vs never smokers	P value for interaction Current vs never smokers
Lung					
Number of events	9	93	124		
Model 1	1.18 (0.91-1.53)	1.28 (1.19-1.37)	1.06 (0.99-1.14)		
Model 2	1.16 (0.88-1.53)	1.26 (1.16-1.36)	1.08 (1.01-1.16)	0.51	0.56
Colon/rectum					
Number of events	33	94	50		
Model 1	1.21 (1.06-1.38)	1.07 (0.97-1.16)	0.97 (0.85-1.09)		
Model 2	1.19 (1.04-1.37)	1.05 (0.95-1.15)	0.95 (0.83-1.08)	0.07	0.01
Urinary tract					
Number of events	13	55	39		
Model 1	0.87 (0.62-1.22)	1.09 (0.97-1.22)	1.11 (0.98-1.25)		
Model 2	0.90 (0.64-1.26)	1.04 (0.92-1.18)	1.12 (0.99-1.26)	0.28	0.21
Lymphoid/hematopoietic					
Number of events	19	42	21		
Model 1	0.99 (0.79-1.25)	1.19 (1.06-1.33)	1.07 (0.90-1.27)		
Model 2	0.94 (0.73-1.21)	1.16 (1.03-1.32)	1.09 (0.91-1.29)	0.21	0.60
Breast					
Number of events/females	23/563	28/648	18/617		
Model 1	1.15 (0.97-1.35)	1.03 (0.89-1.20)	0.97 (0.80-1.18)		
Model 2	1.16 (0.98-1.38)	1.02 (0.87-1.20)	0.99 (0.81-1.22)	0.40	0.22
Prostate					
Number of events/males	34/1024	112/2768	42/1558		
Model 1	0.85 (0.69-1.07)	0.96 (0.88-1.06)	0.98 (0.86-1.12)		
Model 2	0.90 (0.72-1.12)	0.96 (0.87-1.06)	0.96 (0.83-1.10)	0.44	0.29
All cancers					
Number of events	182	539	351		
Model 1	1.05 (0.98-1.12)	1.09 (1.05-1.13)	1.05 (1.01-1.10)		
Model 2	1.05 (0.98-1.13)	1.07 (1.03-1.11)	1.05 (1.01-1.10)	0.59	0.99
CVD and/or cancer (Myocardial infarction, stroke, vascular mortality, or cancer)					
Number of events	360	1080	767		
Model 1	1.07 (1.02-1.12)	1.09 (1.07-1.12)	1.08 (1.05-1.11)		
Model 2	1.05 (1.00-1.11)	1.06 (1.03-1.09)	1.08 (1.05-1.11)	0.62	0.47

Model 1= Adjusted for age, sex; Model 2= Adjusted for age, sex, number of pack-years (for former and current smokers), body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function.
CRP=C-reactive protein; HR=Hazard ratio; CI=Confidence interval; CVD=cardiovascular disease.

Supplemental Table S7. Relation between continuous CRP (1 mg/L higher) and cancer risk after exclusion of diagnosis within 1, 2, and 5 year(s) after inclusion in the cohort

	Exclusion cancer diagnoses <1 year N=7076 HR (95% CI)	Exclusion cancer diagnoses <2 year N=6985 HR (95% CI)	Exclusion cancer diagnoses <5 year N=6701 HR (95% CI)
Lung			
Number of events	213	191	124
Model 1	1.19 (1.14-1.25)	1.20 (1.14-1.26)	1.19 (1.12-1.28)
Model 2	1.15 (1.09-1.21)	1.16 (1.09-1.23)	1.15 (1.07-1.23)
Colon/rectum			
Number of events	159	144	106
Model 1	1.07 (1.00-1.14)	1.05 (0.98-1.13)	1.04 (0.95-1.13)
Model 2	1.05 (0.98-1.12)	1.04 (0.96-1.12)	1.01 (0.92-1.11)
Urinary tract			
Number of events	83	78	50
Model 1	1.09 (1.00-1.19)	1.10 (1.00-1.20)	1.05 (0.93-1.18)
Model 2	1.10 (0.998-1.20)	1.10 (0.997-1.21)	1.03 (0.91-1.18)
Lymphoid/hematopoietic			
Number of events	74	64	43
Model 1	1.08 (0.98-1.19)	1.06 (0.95-1.18)	1.04 (0.91-1.19)
Model 2	1.08 (0.98-1.20)	1.08 (0.97-1.20)	1.05 (0.91-1.21)
Breast			
Number of events/females	60/1800	58/1780	44/1712
Model 1	1.06 (0.96-1.17)	1.08 (0.97-1.19)	1.07 (0.95-1.20)
Model 2	1.08 (0.98-1.20)	1.10 (0.99-1.22)	1.09 (0.97-1.23)
Prostate			
Number of events/males	171/5276	149/5205	92/4989
Model 1	0.96 (0.89-1.03)	0.97 (0.90-1.05)	0.91 (0.82-1.02)
Model 2	0.96 (0.89-1.04)	0.98 (0.90-1.06)	0.93 (0.83-1.04)
All cancers			
Number of events	970	879	595
Model 1	1.08 (1.05-1.11)	1.07 (1.05-1.11)	1.06 (1.02-1.10)
Model 2	1.06 (1.03-1.09)	1.06 (1.03-1.09)	1.04 (1.00-1.08)
CVD and/or cancer (Myocardial infarction, stroke, vascular mortality, or cancer)			
Number of events	2078	1987	1703
Model 1	1.10 (1.08-1.12)	1.10 (1.08-1.12)	1.10 (1.08-1.12)
Model 2	1.07 (1.05-1.09)	1.07 (1.05-1.09)	1.07 (1.05-1.09)

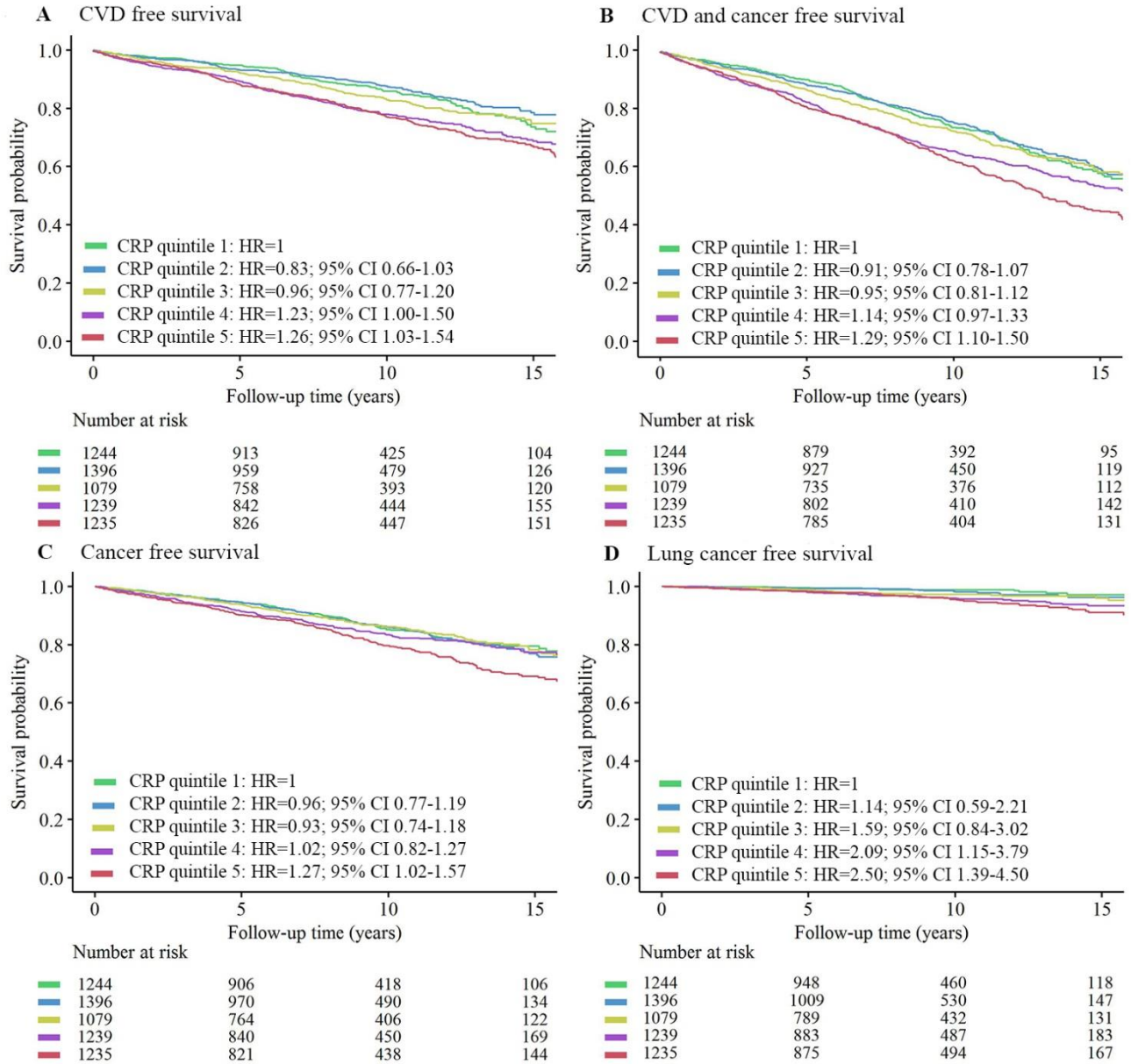
Model 1= Adjusted for age, sex; Model 2= Adjusted for age, sex, smoking status, number of pack-years, body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. CRP=C-reactive protein; HR=Hazard ratio; CI=Confidence interval; CVD=cardiovascular disease.

Supplemental Table S8. Relation between continuous CRP (1 mg/L higher) and cancer risk stratified for cardiovascular disease at baseline

	Coronary artery disease (CAD)	Cerebrovascular disease (CeVD)	Peripheral vascular disease (PAD)	P-value for interaction	P-value for interaction
	N= 3931 HR (95% CI)	N=1904 HR (95% CI)	N=1343 HR (95% CI)	CeVD vs CAD	PAD vs CAD
Lung					
Number of events	89	49	88		
Model 1	1.30 (1.20-1.40)	1.16 (1.04-1.30)	1.06 (0.98-1.15)		
Model 2	1.28 (1.18-1.38)	1.16 (1.03-1.31)	1.04 (0.95-1.13)	0.13	0.56
Colon/rectum					
Number of events	98	46	33		
Model 1	1.08 (0.99-1.19)	1.10 (0.98-1.24)	1.03 (0.90-1.18)		
Model 2	1.04 (0.94-1.15)	1.09 (0.96-1.23)	1.04 (0.91-1.19)	0.97	0.20
Urinary tract					
Number of events	53	23	31		
Model 1	1.08 (0.95-1.22)	1.10 (0.93-1.30)	1.07 (0.93-1.22)		
Model 2	1.10 (0.96-1.25)	1.05 (0.87-1.26)	1.06 (0.93-1.22)	0.98	0.30
Lymphoid/hematopoietic					
Number of events	42	15	25		
Model 1	1.07 (0.93-1.23)	0.95 (0.75-1.22)	1.17 (1.02-1.35)		
Model 2	1.10 (0.95-1.27)	0.97 (0.75-1.25)	1.16 (1.00-1.34)	0.21	0.17
Breast					
Number of events/females	31/728	21/720	17/380		
Model 1	1.08 (0.93-1.26)	1.05 (0.88-1.25)	0.94 (0.77-1.14)		
Model 2	1.07 (0.90-1.26)	1.05 (0.88-1.27)	0.96 (0.79-1.18)	0.45	0.75
Prostate					
Number of events/males	110/3203	47/1184	31/963		
Model 1	0.95 (0.86-1.06)	1.01 (0.89-1.15)	0.91 (0.78-1.07)		
Model 2	0.97 (0.87-1.08)	1.01 (0.88-1.17)	0.89 (0.76-1.05)	0.65	0.21
All cancers					
Number of events	540	261	271		
Model 1	1.10 (1.05-1.14)	1.06 (1.01-1.12)	1.05 (1.00-1.10)		
Model 2	1.08 (1.04-1.13)	1.06 (1.00-1.12)	1.04 (0.99-1.09)	0.39	0.99
CVD and/or cancer (Myocardial infarction, stroke, vascular mortality or cancer)					
Number of events	1053	546	591		
Model 1	1.11 (1.08-1.14)	1.08 (1.05-1.12)	1.07 (1.03-1.10)		
Model 2	1.08 (1.05-1.11)	1.06 (1.02-1.10)	1.06 (1.03-1.09)	0.97	0.17

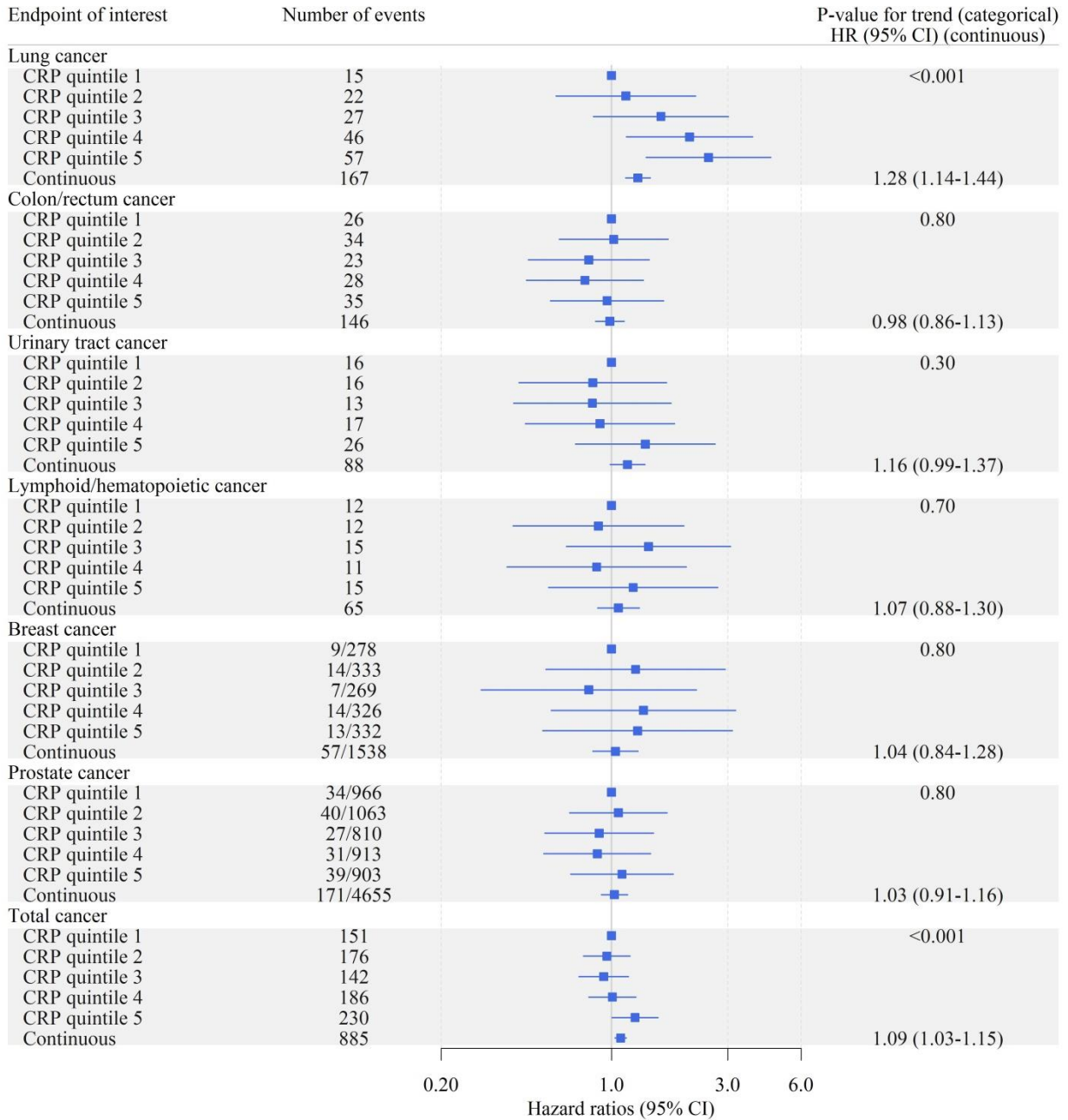
Model 1= Adjusted for age, sex; Model 2= Adjusted for age, sex, number of pack-years, smoking status, body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. CRP=C-reactive protein; HR=Hazard ratio; CI=confidence interval; CVD=cardiovascular disease.

Supplemental Figure S3 Survival curves in CRP quintiles for recurrent cardiovascular disease, combined endpoint, total cancer, and lung cancer (only patients with CRP concentration ≤ 5 mg/L)



Hazard ratios are adjusted for age, sex, body mass index, smoking status, pack-years of smoking, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. Quintile 1: CRP 0.49 (range 0.10-0.64); Quintile 2: CRP 0.90 (range 0.64-1.20); Quintile 3: CRP 1.50 (range 1.20-1.85); Quintile 4: CRP 2.35 (range 1.85-2.98); Quintile 5: CRP 3.80 (range 2.98-5.00).

Supplemental Figure S4. Relation between CRP and incident cancer, according to anatomical location of origin (only patients with CRP concentration ≤ 5 mg/L)



Hazard ratios are adjusted for age, sex, smoking status, number of pack-years, body mass index, LDL cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. Analyses for breast and prostate cancer were performed in subgroups of women and men respectively. Number of events per number of women or men in CRP quintiles are given. Continuous analyses represent hazard ratios per 1 mg/L higher CRP concentration. Quintile 1: CRP 0.49 (range 0.10-0.64); Quintile 2: CRP 0.90 (range 0.64-1.20); Quintile 3: CRP 1.50 (range 1.20-1.85); Quintile 4: CRP 2.35 (range 1.85-2.98); Quintile 5: CRP 3.80 (range 2.98-5.00).