C-Reactive Protein and Risk of Lung Cancer

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ABSTRACT

Purpose

Chronic inflammation could play a role in lung carcinogenesis, underscoring the potential for lung cancer prevention and screening. We investigated the association of circulating high-sensitivity C-reactive protein (CRP, an inflammation biomarker) and *CRP* single nucleotide polymorphisms (SNPs) with prospective lung cancer risk.

Patients and Methods

We conducted a nested case-control study of 592 lung cancer patients and 670 controls with available prediagnostic serum and 378 patients and 447 controls with DNA within the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (N = 77,464). Controls were matched to patients on age, sex, entry year, follow-up time, and smoking. We measured CRP levels in baseline serum samples and genotyped five common *CRP* SNPs.

Results

Elevated CRP levels were associated with increased lung cancer risk (odds ratio [OR], 1.98; 95% CI, 1.35 to 2.89; *P*-trend < .001 for fourth quartile [Q4, ≥ 5.6 mg/L] v Q1 [< 1.0 mg/L]). The CRP association did not differ significantly by histology, follow-up time, or smoking status, but was most apparent for squamous cell carcinomas (OR, 2.92; 95% CI, 1.30 to 6.54), 2 to 5 years before lung cancer diagnosis (OR, 2.33; 95% CI, 1.24 to 4.39), and among former smokers (OR, 2.48; 95% CI, 1.53 to 4.03) and current smokers (OR, 1.90; 95% CI, 1.06 to 3.41). Although *CRP* SNPs and haplotypes were associated with CRP levels, they were not associated with lung cancer risk. Ten-year standardized absolute risks of lung cancer were higher with elevated CRP levels among former smokers (Q4: 2.55%; 95% CI, 1.98% to 3.27% v Q1: 1.39%; 95% CI, 1.07% to 1.81%) and current smokers (Q4: 7.37%; 95% CI, 5.81% to 9.33% v Q1: 4.03%; 95% CI, 3.01% to 5.40%).

Conclusion

Elevated CRP levels are associated with subsequently increased lung cancer risk, suggesting an etiologic role for chronic pulmonary inflammation in lung carcinogenesis.

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INTRODUCTION

Smoking is the major risk factor for lung cancer, the most common cancer worldwide.¹ Nonetheless, smoking is neither necessary nor sufficient for lung cancer development,¹ underscoring the influence of additional cofactors. Experimental as well as epidemiologic studies support a role for chronic pulmonary inflammation in lung carcinogenesis.²⁻⁴ Inflammatory lung conditions such as chronic obstructive pulmonary disease,⁵⁻⁸ elevated serum levels of pro-inflammatory cytokines,⁹⁻¹¹ and polymorphisms in inflammation-related genes¹²⁻¹⁵ have all been linked with increased lung cancer risk.

Notably, elevated levels of C-reactive protein (CRP), a systemic marker of chronic inflammation, have been associated with increased lung cancer risk in several retrospective and a few pro-

spective studies.^{9-11,16,17} However, previous prospective investigations have included only modest numbers of lung cancers (42 to 255 cases), thus precluding a precise estimation of risk overall and especially among subgroups defined by smoking status or lung cancer subtype. An alternative approach to evaluating the role of CRP in lung carcinogenesis is through investigating the relationship of lung cancer risk with *CRP* genetic polymorphisms, which are associated with variation in circulating CRP levels.¹¹ Parallel assessments of both *CRP* genotypes and circulating CRP levels would help characterize the role of genetic versus environmental influences involved in CRP-related lung cancer risk. Only one previous study has evaluated lung cancer risk in relation to *CRP* genotypes.¹¹

Understanding the role of chronic inflammation in lung cancer etiology could have relevance

for prevention as well as screening of populations at high risk for lung cancer. This prospect is underscored by the utility of CRP measurement in cardiovascular disease risk stratification, where it is used to help target chemopreventive intervention (eg, with statin therapy).¹⁸⁻²⁰ In the current nested case-control study within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, we investigated the association of lung cancer with circulating prediagnostic CRP levels and *CRP* genotypes. We also calculated absolute risks of lung cancer across circulating CRP levels to evaluate the utility of this marker in lung cancer risk stratification.

PATIENTS AND METHODS

Study Design

The PLCO study, a randomized trial aimed at evaluating the efficacy of screening in reducing cancer mortality, recruited approximately 155,000 men and women age 55 to 74 years from 1992 to 2001.²¹ Screening for lung cancer among participants in the intervention arm included a chest x-ray at baseline followed by either three annual x-rays (for current or former smokers at enrollment) or two annual x-rays (for never smokers); participants in the control arm received routine health care.²¹ Screening-arm participants provided data on sociodemographic factors, smoking behavior, anthropometric characteristics, medical history, and family history of cancer, as well as blood samples annually for the first 6 years of the study (baseline [T0] and T1 through T5).²² Lung cancers were ascertained through annual questionnaires mailed to the participants, and positive reports were followed up by abstracting medical records or death certificates. Follow-up in the trial as of July 2009 was 96.7%.

We conducted a nested case-control study within the screening arm of the PLCO trial. As of December 31, 2004, 898 lung cancers were diagnosed among the 77,464 participants. Patients were excluded because of missing baseline questionnaire, previous history of any cancer, diagnosis of multiple cancers during follow-up, missing smoking information at baseline, missing consent for utilization of biologic specimens for etiologic studies, or unavailability of serum or DNA specimens. Thus, we included 626 lung cancer patients in this case-control study.

Controls were individuals free of cancer at the time of a case's lung cancer diagnosis. Controls were individually matched to lung cancer patients on age at enrollment (55 to 59, 60 to 64, 65 to 69, and 70 to 74 years), sex, year of random assignment, follow-up time since enrollment, and smoking status at enrollment (never, former, or current smoker). Current and former smokers were matched on cumulative amount of smoking (0 to 29, 30 to 39, 40 to 49, and 50+ pack-years), with additional matching for time since quitting (< 15 years and ≥ 15 years) for former smokers. We matched never smoker controls to patients using a 3:1 ratio to enhance statistical power, whereas former and current smoker controls were matched to patients using a 1:1 ratio.

Laboratory Methods

High-sensitivity CRP was measured in baseline (T0) serum samples using a chemiluminescent immunoassay (Diagnostic Products Corporation, Los Angeles, CA). We assessed single nucleotide polymorphisms (SNPs) at five loci within the *CRP* gene (rs1417938, rs1800947, rs1205, rs2808630, and rs3093077) as part of a Golden Gate assay (Illumina, San Diego, CA). These SNPs were chosen on the basis of their high pair-wise linkage disequilibrium (ie, tag SNPs with $r^2 > 80\%$) with other common SNPs in the *CRP* region, spanning 20 kb upstream to 10 kb past the downstream polyA tail. The five SNPs tag five of eight bins in the *CRP* region.²³ Four of the *CRP* SNPs (rs1417938, rs1800947, rs3093077, and rs1205) have been shown to be associated with differences in CRP levels.^{24,25} Of 399 patients and 467 controls with available DNA, genotyping was successful for 378 patients and 447 controls. We observed high reproducibility for serum CRP measurements across replicate samples ($n = 90$ [six replicates each from 15 individuals]), with 93.3% concordance across CRP quartiles and an intraclass correlation coefficient of 99.4%. Likewise, concordance was 100% for *CRP* genotyping across 23 pairs of

duplicates. Our analyses of circulating CRP levels included 592 patients and 670 controls, whereas the *CRP* SNP analyses included 378 patients and 447 controls. Data on both CRP levels and *CRP* genotypes were available for 345 patients and 402 controls.

Statistical Analyses

Data collected on the baseline questionnaire were used for all analyses. We used conditional logistic regression to estimate odds ratios (ORs) for the relationship of lung cancer risk with CRP levels. CRP levels were classified into quartiles on the basis of distribution among controls. Using the lowest quartile (Q1) as the reference, we assessed ORs for the second (Q2), third (Q3), and fourth (Q4) quartiles; we also treated the CRP quartiles as an ordinal variable to assess trends in risk. In addition to the matching variables, these models included adjustment for race/ethnicity, level of education, body mass index (BMI) at enrollment, regular use of aspirin/ibuprofen, family history of lung cancer, history of heart disease, and history of emphysema/bronchitis.

Associations of individual SNPs with lung cancer were evaluated using unconditional logistic regression, unadjusted and adjusted for the factors listed above. We inferred haplotype frequencies using the expectation-maximization algorithm²⁶ and assessed associations with lung cancer using unconditional logistic regression.

We conducted separate analyses for never, former, and current smokers and across lung cancer histologies (adenocarcinoma [AC], squamous cell carcinoma [SCC], small-cell carcinoma, large-cell carcinoma, and other/unknown histologies). We also conducted analyses stratified by time interval between serum sampling and lung cancer diagnosis/control selection (ie, follow-up time, classified as < 1, 1 to 2, 2 to 5, and ≥ 5 years).

We used linear regression to examine associations with CRP levels (log-transformed) among controls. These analyses considered questionnaire data and *CRP* genotypes and haplotypes as potential predictors.

We calculated standardized 10-year lung cancer absolute risks and risk differences across CRP quartiles among former and current smokers using a weighted Cox regression model.^{27,28} These absolute risk calculations were restricted to 58,220 screening-arm participants who were eligible for selection into our case-control study and were standardized to the screening-arm cohort's joint distribution of age, sex, year of random assignment, and smoking status (duration and intensity of smoking for current and former smokers, and time since quitting for former smokers). Additional details are presented in the Appendix (online only). All statistical tests were two-sided, and P values < .05 were considered statistically significant.

RESULTS

Table 1 lists the characteristics of 592 patients and 670 controls with available serum and 378 patients and 447 controls with available DNA. By virtue of matching, patients and controls had similar distributions of age at enrollment, sex, and smoking behavior. For subjects with available serum, no significant differences were observed between patients and controls for race, BMI, regular use of aspirin/ibuprofen, or history of heart disease. Compared with controls, patients more often had lower educational attainment ($P = .017$), a personal history of bronchitis/emphysema ($P < .001$), and a family history of lung cancer ($P = .004$). Similar differences, albeit at a lower significance level, were observed among subjects with available DNA, and patients were significantly more likely to have a family history of lung cancer. All *CRP* SNPs conformed to the Hardy-Weinberg equilibrium among controls.

Individuals with CRP values in the highest quartile had a two-fold increased risk of lung cancer when compared with individuals having CRP levels in the lowest quartile (OR, 1.98; 95% CI, 1.35 to 2.89; Table 2), and a significant trend for increasing risk with increasing CRP levels was observed (P -trend < .001). In contrast, none of the five *CRP* SNPs was associated with lung cancer risk (Table 2). Of the

Table 1. Characteristics of Lung Cancer Patients and Controls From the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Characteristic	With Available Serum					With Available DNA				
	Controls (n = 670)		Patients (n = 592)		P*	Controls (n = 447)		Patients (n = 378)		P*
	No.	%	No.	%		No.	%	No.	%	
Age at enrollment, years					—†					—†
≤ 59	120	17.9	112	18.9		88	19.7	80	21.2	
60-64	188	28.1	164	27.7		129	28.8	106	28.0	
65-69	215	32.1	197	33.3		147	32.9	128	33.9	
70-74	147	21.9	119	20.1		83	18.6	64	16.9	
Sex					—†					—†
Female	234	34.9	186	31.4		177	39.6	131	34.7	
Male	436	65.1	406	68.6		270	60.4	247	65.3	
Smoking status					—†					—†
Never smoker	117	17.5	39	6.6		98	21.9	30	7.9	
Former smoker	317	47.3	317	53.5		217	48.6	217	57.4	
0-29 Pack-years and quit for < 15 years	30	4.5	30	5.1		21	4.7	23	6.1	
0-29 Pack-years and quit for ≥ 15 years	65	9.7	65	11.0		49	11.0	44	11.6	
30-39 Pack-years and quit for < 15 years	48	7.2	48	8.1		32	7.1	30	7.9	
30-39 Pack-years and quit for ≥ 15 years	21	3.1	21	3.5		16	3.6	17	4.5	
40-49 Pack-years and quit for < 15 years	18	2.7	18	3.0		15	3.3	14	3.7	
40-49 Pack-years and quit for ≥ 15 years	13	1.9	13	2.2		8	1.8	11	2.9	
50+ Pack-years and quit for < 15 years	103	15.4	103	17.4		64	14.3	66	17.5	
50+ Pack-years and quit for ≥ 15 years	19	2.8	19	3.2		12	2.7	12	3.2	
Current smoker	236	35.2	236	39.9		132	29.4	131	34.7	
0-29 Pack-years	49	7.3	49	8.3		32	7.1	26	6.9	
30-39 Pack-years	73	10.9	73	12.3		40	8.9	39	10.3	
40-49 Pack-years	18	2.7	18	3.1		9	2.0	11	2.9	
50+ Pack-years	96	14.3	96	16.2		51	11.4	55	14.6	
Race/ethnicity					.114					.386
White	610	91.0	522	88.2		407	91.0	338	89.4	
Black	29	4.3	43	7.3		20	4.5	27	7.1	
Hispanic	6	0.9	10	1.7		7	1.6	4	1.1	
Asian/Pacific Islander	25	3.7	17	2.9		13	2.9	9	2.4	
Education					.017					.172
High school graduate or less	216	32.2	233	39.4		155	34.7	148	39.2	
College or more	454	67.8	359	60.6		292	65.3	230	60.8	
Body mass index at enrollment					.143					.255
< 18.5	4	0.6	8	1.4		2	0.4	4	1.0	
18.5-24.9	216	32.2	217	36.7		140	31.3	121	32.0	
25.0-29.9	313	46.7	253	42.7		211	47.2	162	42.9	
≥ 30	126	18.8	109	18.4		88	19.7	88	23.3	
Missing	11	1.7	5	0.8		6	1.3	3	0.8	
Regular use of aspirin or ibuprofen					.584					.248
Yes	437	65.2	381	64.4		300	67.1	242	64.0	
No	233	34.8	210	35.5		147	32.9	136	36.0	
Missing	0	0.0	1	0.1		0	0.0	0	0.0	
History of bronchitis/emphysema					< .001					.073
Yes	72	10.8	111	18.8		47	10.5	62	16.4	
No	586	87.4	458	77.3		392	87.7	300	79.4	
Missing	12	1.8	23	3.9		8	1.8	16	4.2	
History of heart disease					.804					.329
Yes	96	14.3	93	15.7		55	12.3	62	16.4	
No	561	83.7	470	79.4		383	85.7	300	79.4	
Missing	13	2.0	29	4.9		9	2.0	16	4.2	
Family history of lung cancer					.004					.012
Yes	74	11.0	103	17.4		49	11.0	67	17.7	
No	568	84.8	451	76.2		384	85.9	288	76.2	
Missing	28	4.2	38	6.4		14	3.1	23	6.1	

NOTE. Of the 626 patients and 716 controls included in this study, serum specimens were available for 592 patients and 670 controls, and DNA specimens were available for 378 patients and 447 controls. Results are shown separately for subjects with available serum or DNA specimens. *P* values in boldface are statistically significant at *P* < .05.

**P* values are from conditional logistic regression models. Models included adjustment for study matching factors: age at enrollment, sex, year of random assignment, follow-up time in study in years, and smoking status (never smokers, former smokers matched on pack-years of smoking and time since quitting, and current smokers matched on pack-years of smoking). Subjects with missing values were excluded from the *P* value calculation.

†Matching variable. The distributions do not appear identical in the table because the case:control ratio varies according to smoking status.

Table 2. Association of Lung Cancer Risk With Circulating CRP Levels and *CRP* Genotypes

CRP Level and Genotype	Controls*		Patients*		OR	95% CI†	<i>P</i> -Trend	Adjusted OR	95% CI‡	<i>P</i> -Trend
	No.	%	No.	%						
CRP, mg/L							< .001			< .001
≤ 1.0	168	25.1	106	17.9	1.00			1.00		
1.1-2.7	176	26.3	136	23.0	1.26	0.88 to 1.80		1.22	0.83 to 1.78	
2.8-5.5	167	24.9	150	25.3	1.41	1.00 to 1.98		1.54	1.08 to 2.21	
≥ 5.6	159	23.7	200	33.8	1.95	1.38 to 2.75		1.98	1.35 to 2.89	
rs1417938							.952			.880
AA	221	49.4	186	49.2	1.00			1.00		
AT	177	39.6	149	39.4	1.00	0.74 to 1.34		1.04	0.76 to 1.42	
TT	49	11.0	42	11.1	1.01	0.64 to 1.60		1.00	0.62 to 1.63	
rs1800947							.677			.456
GG	399	89.3	335	88.6	1.00			1.00		
CG	46	10.3	40	10.6	1.03	0.66 to 1.62		1.16	0.72 to 1.88	
CC	2	0.4	3	0.8	1.78	0.29 to 10.73		1.50	0.22 to 9.94	
rs1205							.960			.667
CC	204	45.7	167	44.2	1.00			1.00		
CT	188	42.2	168	44.8	1.09	0.81 to 1.46		1.12	0.82 to 1.54	
TT	54	12.1	40	10.7	0.90	0.57 to 1.42		1.02	0.63 to 1.67	
rs2808630							.527			.652
TT	242	54.1	206	54.5	1.00			1.00		
CT	172	38.5	153	40.5	1.04	0.78 to 1.39		1.05	0.77 to 1.41	
CC	33	7.4	19	5.0	0.67	0.37 to 1.22		0.72	0.38 to 1.34	
rs3093077							.813			.570
TT	375	83.9	316	83.6	1.00			1.00		
GT	70	15.7	59	15.6	1.00	0.68 to 1.45		0.87	0.57 to 1.31	
GG	2	0.4	3	0.8	1.77	0.29 to 10.69		1.07	0.16 to 7.14	

NOTE. Values in boldface are statistically significant at $P < .05$. Numbers do not add up to total owing to missing values.

Abbreviations: CRP, C-reactive protein; OR, odds ratio.

*Analyses for circulating CRP levels included 592 patients and 670 controls. Analyses for *CRP* genotypes included 378 patients and 447 controls.

†ORs were calculated using conditional logistic regression (CRP levels) or unconditional logistic regression (*CRP* single nucleotide polymorphisms [SNPs]). ORs for CRP levels were adjusted for matching factors: age at enrollment, sex, year of random assignment, follow-up time in study, and smoking status. ORs for *CRP* SNPs were not adjusted for any factors.

‡Adjusted ORs included adjustment for matching factors (CRP/SNP associations adjusted for age, sex, and smoking status) and additionally for race, level of education, body mass index at enrollment, regular use of aspirin/ibuprofen, family history of lung cancer, history of heart disease, and history of emphysema/bronchitis.

five *CRP* SNPs, four SNPs formed haplotype blocks, and these haplotypes were also unrelated to lung cancer (Appendix Table A1, online only).

In analyses stratified by histology (Fig 1A), elevated CRP levels (Q3 and Q4) were associated with increased risk of SCC lung cancers (eg, Q4 v Q1: OR, 2.92; 95% CI, 1.30 to 6.54; P -trend = .008), but not lung ACs (Q4 v Q1: OR, 1.34; 95% CI, 0.83 to 2.17; P -trend = .172). Elevated CRP levels were also associated with increased risk of small-cell carcinomas (Q4 v Q1: OR, 3.03; 95% CI, 1.04 to 8.83; P -trend = .040). However, this difference across subtypes was not statistically significant (P value for difference in slopes = .361). The mean time between serum sampling and subject selection was 3.36 years (standard deviation, 2.59). The relationship of CRP with lung cancer did not vary significantly by follow-up time (Fig 1B; P -interaction = .581), although the association appeared strongest in the period 2 to 5 years before lung cancer diagnosis (Q4 v Q1: OR, 2.33; 95% CI, 1.24 to 4.39).

Elevated CRP levels were associated with increased lung cancer risk among former smokers (Fig 1C; Q4 v Q1: OR, 2.48; 95% CI, 1.53 to 4.03; P -trend = .001) and current smokers (Q4 v Q1: OR, 1.90; 95% CI, 1.06 to 3.41; P -trend = .019), but not among never smokers. However, the difference across smoking strata was not statistically significant (P -interaction = .589). For former smokers, elevated CRP

levels were associated with increased lung cancer risk among individuals who quit smoking for < 15 years (Q4 v Q1: OR, 2.70; 95% CI, 1.47 to 4.95) as well as among those who quit for > 15 years (OR, 2.17; 95% CI, 0.94 to 5.01).

Among controls (Table 3), CRP levels varied significantly by age and were higher among current smokers, Hispanics, individuals with a high BMI, and among individuals with a family history of lung cancer. CRP levels increased with cumulative amount of smoking and smoking intensity but were unrelated to time since quitting among former smokers.

CRP levels were significantly associated with *CRP* SNPs rs1800947 (decreased levels for CC or CG v GG genotype; P -trend = .016), rs1205 (decreased levels for TT or CT v CC genotype; P -trend = .008), and rs3093077 (increased levels for GG or GT v TT genotype; P -trend = .003; Table 3). Likewise, CRP levels differed across haplotypes formed by four SNPs: rs1417938, rs1800947, rs1205, and rs2808630 (Appendix Table A1). Compared with the most common haplotype (TGCT), haplotypes AGTT and ACTT were associated with lower CRP levels, whereas haplotype AGCT was associated with higher CRP levels. The individual *CRP* SNPs rs1417938, rs1800947, rs1205, rs2808630, and rs3093077 accounted for 0.5%, 1.4%, 2.5%, 0.4%, and 2.6%, respectively, of the total variability in circulating CRP levels (Appendix Table A2, online only).

Fig 1. Association of circulating C-reactive protein (CRP) levels with lung cancer risk across (A) lung cancer histologies (squamous cell carcinomas [SCCs; $n = 126$ lung cancers], adenocarcinomas [ACs; $n = 269$], small-cell carcinomas [$n = 75$], large-cell carcinomas [$n = 36$], and cancers of other/unknown histologies [$n = 86$]), (B) follow-up time (< 1 year [$n = 128$ lung cancers], 1 to 2 years [$n = 70$], 2 to 5 years [$n = 238$], and 5+ years [$n = 156$]), and (C) smoking strata (never smokers [$n = 39$ lung cancers], former smokers [$n = 318$], and current smokers [$n = 236$]). Odds ratios (ORs) and 95% CIs were estimated in conditional logistic regression models, and by virtue of matching, incorporated adjustment for age, sex, year of random assignment, follow-up time, and smoking (see Patients and Methods for details). ORs and 95% CIs are shown for the second (Q2), third (Q3), and fourth (Q4) quartiles compared with the first quartile (Q1). *P*-trend values for ORs across CRP quartiles are shown. *P*-heterogeneity values are shown for the association of CRP quartiles (treated as an ordinal variable with 1 *df*) with risk of specific lung cancer histologic subsites (A), as well as for the multiplicative statistical interaction between CRP levels and follow-up time (B) and cigarette smoking (C) on lung cancer risk.

Standardized absolute risks of lung cancer over 10 years of follow-up across CRP quartiles among former and current smokers are shown in Table 4. For former smokers, the 10-year absolute risk was 2.55% (95% CI, 1.98% to 3.27%) among individuals with CRP levels ≥ 5.6 mg/L versus 1.39% (95% CI, 1.07% to 1.81%) among those with CRP levels of < 1.0 mg/L (risk difference, 1.15%; 95% CI, 0.41% to 1.89%). For current smokers, the 10-year absolute risk was much higher among individuals with CRP levels ≥ 5.6 mg/L compared with those with CRP levels of < 1.0 mg/L (absolute risk, 7.37%; 95% CI, 5.81% to 9.33% v 4.03%; 95% CI, 3.01% to 5.40%; risk difference, 3.33%; 95% CI, 1.24% to 5.42%).

DISCUSSION

This study is the largest to date to evaluate the association of serum CRP levels and *CRP* genotypes with prospective lung cancer risk. Elevated CRP levels were associated with increased lung cancer risk, and risk rose steadily with increasing CRP levels. Likewise, we ob-

served clear separation in 10-year lung cancer absolute risks across CRP quartiles among former and current smokers. In contrast, although significantly associated with differences in CRP levels, SNPs in the *CRP* gene were not related to lung cancer risk.

Our observations that elevated CRP levels were associated with a two-fold increased risk of lung cancer are consistent with previous smaller prospective studies.^{9-11,17} Because we tightly controlled for smoking through matching, it is unlikely that the CRP associations are explained entirely by smoking. Notably, CRP levels were also elevated among former smokers and were associated with increased lung cancer risk even among those who had quit smoking for up to 15 years. Nonetheless, cigarette smoke itself can lead to pulmonary inflammation,^{4,29} and we found high CRP levels among current smokers in relation to the amount smoked. It is possible that, despite similar tobacco exposures, elevated CRP levels may identify those individuals with a heightened inflammatory response to tobacco smoke and thus at highest lung cancer risk.

Table 3. Predictors of Circulating CRP Levels Among Controls

Characteristic	No. of Patients	Geometric Mean CRP Level (mg/L)	P*
Age at enrollment, years			.013
≤ 59	120	1.94	
60-64	186	2.08	
65-69	208	2.65	
70-74	144	1.92	
Sex			.217
Female	233	2.25	
Male	425	2.01	
Smoking status			.023
Never smoker	116	1.80	
Former smoker	312	2.12	
Current smoker	230	2.53	
Former smoker			.012
0-29 Pack-years and quit for < 15 years	30	1.71	
0-29 Pack-years and quit for ≥ 15 years	65	1.54	
30-39 Pack-years and quit for < 15 years	47	2.23	
30-39 Pack-years and quit for ≥ 15 years	21	2.66	
40-49 Pack-years and quit for < 15 years	18	2.14	
40-49 Pack-years and quit for ≥ 15 years	13	2.25	
50+ Pack-years and quit for < 15 years	99	2.96	
50+ Pack-years and quit for ≥ 15 years	19	3.07	
Current smoker			.011
0-29 Pack-years	47	2.30	
30-39 Pack-years	71	2.08	
40-49 Pack-years	17	4.08	
50+ Pack-years	95	3.28	
Current smokers by smoking intensity, cigarettes per day			.023
≤ 10	35	2.17	
11-20	88	2.44	
21-40	94	3.30	
40+	13	4.80	
Race/ethnicity			.006
White	599	2.40	
Black	29	2.64	
Hispanic	6	2.89	
Asian/Pacific Islander	24	1.12	
Education			.172
High school graduate or less	212	2.26	
College or more	446	2.00	
BMI at enrollment			< .001
< 18.5	4	1.33	
18.5-24.9	214	1.45	
25.0-29.9	305	2.24	
≥ 30	124	3.31	
Regular use of aspirin or ibuprofen			.262
No	230	2.00	
Yes	428	2.21	

(continued in next column)

Table 3. Predictors of Circulating CRP Levels Among Controls (continued)

Characteristic	No. of Patients	Geometric Mean CRP Level (mg/L)	P*
History of bronchitis/emphysema			.157
No	574	2.07	
Yes	72	2.50	
History of heart disease			.087
No	551	2.08	
Yes	94	2.56	
Family history of lung cancer			.004
No	558	2.08	
Yes	72	3.05	
rs1417938			.138†
AA	200	2.19	
AT	158	2.53	
TT	44	2.66	
rs1800947			.016†
GG	359	2.47	
CG	42	1.71	
CC	1	0.69	
rs1205			.008†
CC	186	2.57	
CT	167	2.44	
TT	48	1.51	
rs2808630			.451†
TT	218	2.39	
CT	151	2.45	
CC	33	1.87	
rs3093077			.003†
TT	337	2.23	
GT	63	3.10	
GG	2	13.20	

NOTE. Serum specimens were available for 658 controls, DNA specimens were available for 447 controls, and both serum and DNA specimens were available for 402 controls. The number of controls with available serum is different from that in Table 1 owing to the exclusion of instances of multiple selections for controls who were selected more than once (n = 12 controls; 10 controls selected two times, and one control selected three times) owing to sampling with replacement. P values in boldface are statistically significant at $P < .05$. Numbers do not add up to total owing to missing values.

Abbreviations: CRP, C-reactive protein; BMI, body mass index.

*P values from linear regression models that incorporated age, sex, race, and smoking.

†P values for trend across categories; not adjusted for any factors.

In addition to smoking, several factors could lead to chronic pulmonary inflammation, including chronic lung infections with microorganisms such as mycobacteria or *Chlamydia pneumoniae*; particulate matter such as asbestos or silica; and lung conditions such as asthma, idiopathic pulmonary fibrosis, and pulmonary scarring.⁴ Indeed, all of these factors have been associated with increased lung cancer risk.^{4,30,31} A chronic inflammatory response to these insults could result in increased cellular turnover and accumulation of reactive oxygen species which, in turn, could act as promoters to amplify the mutagenic effects of cigarette smoke.³²

One limitation is that, although serum CRP levels reliably indicate the presence of chronic inflammation, CRP is not a specific marker for inflammation in the lung. While elevated CRP levels to some extent could arise from nonpulmonary inflammatory conditions, we nonetheless observed nonsignificantly elevated CRP levels

Table 4. Standardized 10-Year Absolute Risks of Lung Cancer Across CRP Quartiles Among Former and Current Smokers

CRP Levels (mg/L)	Absolute Risk (%)	95% CI	Standardized Absolute Risk Difference (%)	95% CI
Former smokers				
≤ 1.0	1.39	1.07 to 1.81	Reference	
1.1-2.7	1.79	1.38 to 2.31	0.39	−0.17 to 0.96
2.8-5.5	1.94	1.52 to 2.49	0.55	−0.06 to 1.16
≥ 5.6	2.55	1.98 to 3.27	1.15	0.41 to 1.89
Current smokers				
≤ 1.0	4.03	3.01 to 5.40	Reference	
1.1-2.7	5.18	3.92 to 6.83	1.14	−0.51 to 2.79
2.8-5.5	5.64	4.39 to 7.22	1.60	−0.17 to 3.37
≥ 5.6	7.37	5.81 to 9.33	3.33	1.24 to 5.42

NOTE. Absolute risks were standardized to the distributions of the following variables in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial's screening-arm cohort: age, sex, year of random assignment, smoking duration and intensity, and time since quitting (for former smokers). Abbreviation: CRP, C-reactive protein.

among individuals with a history of bronchitis or emphysema. Furthermore, elevated systemic CRP levels have been shown to be associated with incident chronic obstructive pulmonary disease^{33,34} as well as progression of dysplastic lung lesions,³⁵ indicating that systemic CRP levels can partly reflect aspects of pulmonary inflammation that are relevant in lung carcinogenesis.

Consistent with previous studies,^{11,17} elevated CRP levels were significantly associated with risk of lung SCCs and small-cell cancers but not ACs, although this difference across lung cancer subtypes was not statistically significant. Notably, the number of lung ACs in our study was higher than lung SCCs, arguing against differences in statistical power as a potential explanation for the null association with ACs. The reasons for these differential associations of CRP levels across lung cancer histologies are unclear and warrant further investigation.

Although CRP genotypes were associated with systemic CRP levels, little of the variation in CRP levels was explained by CRP SNPs, and we found that CRP genotypes did not predict lung cancer risk. These observations contrast with results from a previous study showing a significant association of CRP SNP rs1205 with increased lung cancer risk.¹¹ Nonetheless, the absence of an association of CRP SNPs with lung cancer risk parallels recent observations for cardiovascular disease.^{24,25,36} Our data suggest that circulating CRP levels are determined by both genetic and environmental factors.²⁴ The lack of association between CRP genotypes and lung cancer highlights the predominance of environmental factors in determining CRP-related lung cancer risk. Nevertheless, we note that our results do not discount the possibility that variations in other genes could modulate chronic inflammation in ways relevant for lung cancer.

Given the accruing evidence for a significant association of circulating CRP levels with lung cancer, we calculated standardized absolute risks of lung cancer as a preliminary approach to evaluating the utility of CRP in lung cancer risk stratification. The discrimination in absolute risks that we observed indicates that CRP measurements may aid in identifying former and current smokers at highest lung cancer risk. It remains to be seen whether the addition of CRP to lung cancer risk prediction models, which currently include standard risk factors such as age, sex, and smoking behaviors,³⁷⁻³⁹ would afford

improvements in risk prediction, akin to recent observations for cardiovascular disease.¹⁸⁻²⁰ Additionally, differential associations across lung cancer histologies will have to be considered in risk prediction.

The strengths of our study include the assessment of CRP genotypes and circulating CRP levels in conjunction, highly standardized procedures for data collection and disease ascertainment, and careful control for a range of potential confounding factors. Furthermore, although reverse causality cannot be ruled out, it is unlikely, given the use of prediagnostic specimens, our observation that CRP levels were elevated up to 5 years before lung cancer diagnosis, and the aggressive clinical course of most lung cancers. We also note the limitations of our study. We used systemic CRP level as a marker of pulmonary inflammation, but elevated CRP levels can arise from several nonpulmonary processes. Additional studies are needed to investigate the correlation of systemic inflammatory markers such as CRP with local lung inflammation. Similarly, the process of inflammation encompasses several pathways, and a more comprehensive evaluation of inflammatory markers is required to further characterize the role of chronic inflammation in lung carcinogenesis. Despite the large number of lung cancers in our study, some subgroup analyses were based on small numbers and should therefore be interpreted with caution. Finally, because our absolute risk estimates do not account for competing mortality, these values do not represent the observed proportion of individuals developing lung cancer.

In conclusion, we found that elevated CRP levels were associated with significantly increased risk of lung cancer, suggesting an etiologic role for chronic inflammation in lung carcinogenesis. Our key observation was that elevated CRP levels preceded lung cancer diagnosis by several years. The separation in lung cancer absolute risks across circulating CRP levels among former and current smokers provides preliminary evidence for the utility of CRP measurements in lung cancer risk stratification. These results also highlight the possibility that interventions targeting pulmonary inflammation may be effective in reducing lung cancer risk.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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