Supplementary Table 1. Distribution of characteristics of participants enrolled in the NCI-MD study during 1998–2003*

Characteristic	Case patients			Control subjects		
	All enrolled 1998-2003 (N = 346) No. (%)	With cytokine results (N = 270) No. (%)	P	All enrolled 1998-2003 (N = 381) No. (%)	With cytokine results (N = 296) No. (%)	P
Age, y Mean (SD)	66.9 (10.2)	66.6 (10.0)	.72†	65.5 (10.2)	65.2 (10.4)	.71†
Sex						
Men	172 (49.7)	142 (52.6)	.48‡	183 (48.0)	148 (50.0)	.61‡
Women	174 (50.3)	128 (47.4)		198 (52.0)	148 (50.0)	
Smoking status						
Never	26 (7.5)	22 (8.2)	.97‡	110 (29.0)	86 (29.2)	.98‡
Former quit ≤15 y	77 (22.3)	57 (21.1)		92 (24.3)	68 (23.1)	
Former quit >15 y	83 (24.1)	63 (23.4)		102 (26.9)	82 (27.8)	
Current	159 (46.1)	127 (47.2)		75 (19.8)	59 (20.0)	
Pack-years, mean (SD)§	46.6 (26.0)	47.8 (26.4)	.59†	39.4 (30.3)	39.7 (31.3)	.92†
Smoking duration, y, mean (SD)§	40.6 (13.0)	40.5 (12.8)	.93†	33.9 (15.3)	33.3 (15.5)	.67†
Education ‖						
High school or less	184 (59.0)	146 (60.1)	.79‡	174 (52.3)	127 (49.8)	.56‡
Some college or higher	128 (41.0)	97 (39.9)		159 (47.8)	128 (50.2)	
Regular aspirin or ibuprofen use ‖						
No	224 (65.1)	174 (64.7)	.91‡	197 (51.7)	145 (49.0)	.48‡
Yes	120 (34.9)	95 (35.3)		184 (48.3)	151 (51.0)	
BMI, kg/m² ‖						
<26.5	99 (28.6)	74 (27.4)	.74‡	71 (18.6)	52 (17.6)	.72‡
≥26.5	247 (71.4)	196 (72.6)		310 (81.4)	244 (82.4)	
History of heart disease ‖						
No	258 (75.2)	204 (76.1)	.80‡	282 (74.0)	217 (73.3)	.84‡
Yes	85 (24.8)	64 (23.9)		99 (26.0)	79 (26.7)	
History of emphysema or bronchitis ‖						
No	265 (77.0)	204 (75.8)	.73‡	290 (76.1)	225 (76.0)	.98‡
Yes	79 (22.0)	65 (24.2)		91 (23.9)	71 (24.0)	
Family history of lung cancer ‖						
No	282 (82.0)	221 (82.2)	.95‡	326 (85.6)	253 (85.5)	.97‡
Yes	62 (18.0)	48 (17.8)		55 (14.4)	43 (14.5)	
Histology ‖						

AC	121 (41.2)	105 (42.9)	.94‡	–	–
SCC	61 (20.8)	53 (21.6)		–	–
NSCLC, NOS	75 (25.5)	59 (24.1)		–	–
Other	37 (12.6)	28 (11.4)		–	–
Tumor stage‖					
I	146 (72.6)	104 (71.2)	.77‡	–	–
II-IV	55 (27.4)	42 (28.8)		–	–

* – = Not applicable; NCI-MD = National Cancer Institute-Maryland study; y = year; SD = standard deviation; BMI = body mass index; AC = adenocarcinoma; SCC = squamous cell carcinoma; NSCLC, NOS = non small cell lung cancer, not otherwise specified.

† *P* values were calculated using a two-sided Student *t* test.

‡ *P* values were calculated using a two-sided χ^2 test.

§ Excludes individuals who had never smoked.

‖ Numbers do not add to 100% of total because of missing information.

Supplementary Table 2. Quality control metrics for raw data for cytokine measurements*

Category	Interleukin-6		Interleukin-8	
	NCI-MD	PLCO	NCI-MD	PLCO
Intra-Plate				
Spearman's correlation coefficient†	0.99	0.84	0.87	0.92
P‡	<.001	<.001	<.001	<.001
Inter-Plate				
Spearman's correlation coefficient†	0.81	0.78	0.86	0.76
P‡	<.001	<.001	<.001	<.001
Average limit of detection (pg/mL) §	0.40	0.11	0.12	0.10
Samples below detection limit (%)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Coefficient of variation % (mean, pg/mL)‖				
Low	46 (1.6)	33 (15.2)	36 (16.3)	48 (16.2)
Medium	8 (49)	27 (110)	10 (269)	22 (118)
High	8 (1024)	15 (1066)	10 (1087)	1 (1190)

* Quality control was tested by analyzing the correlation of duplicate samples within plates (intra-plate) and across plates (inter-plate). NCI-MD = National Cancer Institute-Maryland study; PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial.

† A Spearman's correlation test was performed.

‡ *P* values were based on a two-sided Gaussian approximation.

§ The detection limit for each plate was determined based on linearity of standard curve.

‖ The coefficient of variation was calculated for laboratory controls (low, medium and high) included on each plate.

Supplementary Table 3. Association of interleukin-6 and interleukin-8 serum levels with lung cancer across NCI-MD control groups*

Cytokine level	No. of case patients	No. of population control subjects	OR (95% CI)†	P_{trend}‡	No. of hospital control subjects	OR (95% CI)†	P_{trend}‡
IL-6							
1st Quartile§	27	51	1.00 (referent)	3.3×10^{-7}	22	1.00 (referent)	.001
2nd Quartile	30	45	1.20 (0.55 to 2.62)		30	0.84 (0.38 to 1.87)	
3rd Quartile	83	31	3.61 (1.73 to 7.53)		43	1.58 (1.18 to 4.72)	
4th Quartile	130	31	4.97 (2.43 to 10.17)		43	2.36 (1.18 to 4.72)	
Low IL-6‖	57	96	1.00 (referent)	1.4×10^{-7}	52	1.00 (referent)	.001
High IL-6	213	62	3.92 (2.36 to 6.52)		86	2.17 (1.34 to 3.61)	
IL-8							
1st Quartile§	34	47	1.00 (referent)	.006	27	1.00 (referent)	.03
2nd Quartile	57	37	1.78 (0.85 to 3.72)		37	1.22 (0.61 to 2.42)	
3rd Quartile	96	34	3.70 (1.82 to 7.50		40	1.98 (1.03 to 3.81	
4th Quartile	83	40	2.31 (1.14 to 4.68)		34	1.83 (0.93 to 3.61)	
Low IL-8‖	91	84	1.00 (referent)	.002	64	1.00 (referent)	.02
High IL-8	179	74	2.18 (1.34 to 3.54)		74	1.70 (1.09 to 2.63)	

* NCI-MD = National Cancer Institute-Maryland study; IL-6 = interleukin-6; IL-8 = interleukin-8; OR = odds ratio; CI = confidence interval.

† Multivariable unconditional logistic regression analysis adjusted for age (continuous), gender, smoking pack-years (continuous), smoking status (never, former quit ≤ 15 years, former quit >15 years, current).

‡ P values were calculated using a two-sided Wald χ^2 statistic.

§ Quartiles (25%, 50%, 75%) were based on serum IL-6 and IL-8 cut-off levels among controls in NCI-MD study (IL-6, 1.4, 2.1, 3.8 pg/mL; IL-8 7.0, 10.8 and 28.5 pg/mL).

‖ Serum IL-6 and IL-8 levels were dichotomized into ≤ the median vs > the median among controls in the NCI-MD study (IL-6, 2.1 pg/mL; IL-8 10.8 pg/mL).

Supplementary Table 4. Association of interleukin-6 and interleukin-8 serum levels with lung cancer in the NCI-MD study and with lung cancer risk in the PLCO study, adjusted for potential confounding*

Cytokine and level	NCI-MD				PLCO			
	Adjustment 1† OR (95% CI)	P_{trend}‖	Adjustment 2‡ OR (95% CI)	P_{trend}‖	Adjustment 1† OR (95% CI)	P_{trend}‖	Adjustment 2§ OR (95% CI)	P_{trend}‖
IL-6								
1st Quartile¶	1.00 (referent)	5.9×10^{-6}	1.00 (referent)	1.1×10^{-5}	1.00 (referent)	.03	1.00 (referent)	.04
2nd Quartile	0.85 (0.42 to 1.72)		0.87 (0.43 to 1.76)		1.09 (0.73 to 1.63)		1.09 (0.72 to 1.63)	
3rd Quartile	2.02 (1.07 to 3.84)		2.06 (1.08 to 3.91)		1.16 (0.78 to 1.74)		1.14 (0.76 to 1.72)	
4th Quartile	3.01 (1.62 to 5.61)		2.95 (1.58 to 5.50)		1.52 (1.03 to 2.25)		1.49 (1.00 to 2.22)	
IL-8								
1st Quartile¶	1.00 (referent)	4.7×10^{-4}	1.00 (referent)	4.7×10^{-4}	1.00 (referent)	.02	1.00 (referent)	.05
2nd Quartile	1.31 (0.66 to 2.62)		1.39 (0.69 to 2.80)		0.96 (0.64 to 1.45)		0.93 (0.62 to 1.41)	
3rd Quartile	3.41 (1.82 to 6.41)		3.42 (1.81 to 6.46)		1.19 (0.80 to 1.78		1.18 (0.79 to 1.76	
4th Quartile	2.52 (1.35 to 4.69)		2.59 (1.38 to 4.86)		1.46 (1.00 to 2.14)		1.37 (0.93 to 2.02)	

* IL-6 = interleukin-6; IL-8 = interleukin-8; OR = odds ratio; CI = confidence ratio; NCI-MD = National Cancer Institute-Maryland study; PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial.

† Multivariable unconditional logistic regression adjusted for age (continuous), gender, smoking pack-years (continuous), smoking status (never, former quit ≤ 15 years, former quit >15 years, current), heart disease (no, yes), family history of lung cancer (no, yes), body mass index (continuous), education (high school or less, more than high school), regular use of aspirin or ibuprofen (yes, no).

‡ Same model as "Adjustment 1" in NCI-MD study, and additionally adjusted for chronic bronchitis, emphysema, adult asthma, asbestosis, tuberculosis, pneumonia, lupus, and arthritis (all categorized as yes vs no).

§ Same model as "Adjustment 1" in PLCO study, and additionally adjusted for chronic bronchitis (yes, no) and emphysema (yes, no).

‖ P values were calculated using a two-sided Wald χ^2 statistic.

¶ Quartiles (25%, 50%, 75%) were based on serum IL-6 and IL-8 cut-off levels among controls in NCI-MD study (IL-6, 1.4, 2.1, 3.8 pg/mL; IL-8 7.0, 10.8 and 28.5 pg/mL) and PLCO study (IL-6, 2.7, 4.0, 6.6 pg/mL; IL-8, 13.1, 17.4, 23.3 pg/mL).

Supplementary Table 5. Serum interleukin-6 and interleukin-8 levels as predictors of demographic and clinicopathologic features*

| | IL-6 | | | | IL-8 | | | |
| | NCI-MD | | PLCO | | NCI-MD | | PLCO | |
Characteristic	Median level (pg/mL)	*P*†‡	Median level (pg/mL)	*P*†‡	Median level (pg/mL)	*P*†‡	Median level (pg/mL)	*P*†‡
Age, years								
<65	2.0	.58	3.9	.06	9.0	.13	17.0	.15
≥65	2.2		4.3		12.0		17.6	
Gender								
Male	2.2	.75	4.0	.17	11.8	.42	17.4	.19
Female	2.1		3.9		10.1		17.5	
Smoking status								
Never	1.6	.006	3.7	.003	8.3	.005	16.0	.30
Former quit >15 years	2.0		3.8		13.1		18.1	
Former quit ≤15 years	2.5		3.6		10.2		17.6	
Current	3.8		4.6		12.7		17.3	
Education								
High school or less	2.4	.09	4.4	.03	11.3	.12	18.6	.05
College or higher	2.0		3.7		9.9		16.8	
Regular aspirin or Ibuprofen use								
No	2.2	.43	3.8	.27	9.7	.17	17.3	.70
Yes	2.1		4.0		11.1		17.4	
BMI, kg/m^2								
<26.5	1.8	.04	3.9	.02	11.2	.41	18.7	.001
≥26.5	2.2		4.3		10.5		16.4	
History of heart disease								
No	2.0	.24	4.1	.76	8.9	2×10^{-4}	17.2	.07
Yes	2.6		3.7		19.5		18.1	
History of Emphysema/bronchitis								
No	1.9	.71	3.9	.56	9.7	.24	17.4	.09
Yes	2.8		4.3		11.3		18.1	

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Family history of
Lung cancer

No	2.8	.19	3.9	.42	9.8	.09	17.4	.49
Yes	2.1		5.2		12.7		17.8	

* NCI-MD = National Cancer Institute-Maryland study; PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial; IL-6 = interleukin-6; IL-8 = interleukin-8.

† Linear regression models among control subjects incorporating age, gender, and smoking for NCI-MD and PLCO, and additionally year of randomization and years in study for PLCO.

‡ *P* values were based on a two-sided Gaussian approximation.

Supplementary Table 6. Standardized 10-year absolute risks of lung cancer across interleukin-8 and C-reactive protein levels among former and current smokers*

Category	Absolute risk, % (95% CI)	Standardized absolute risk difference (95% CI)†
Former smokers		
Low IL-8 and low CRP‡	1.26 (0.84 to 1.89)	1.00 (referent)
High IL-8 and low CRP or low IL-8 and high CRP	1.53 (1.16 to 2.02)	0.27 (-0.42 to 0.97)
High IL-8 and high CRP	3.18 (2.15 to 4.68)	1.92 (0.57 to 3.27)
Current smokers		
Low IL-8 and low CRP	3.17 (1.93 to 5.20)	1.00 (referent)
High IL-8 and low CRP or low IL-8 and high CRP	6.42 (4.85 to 8.46)	3.25 (0.90 to 5.59)
High IL-8 and high CRP	8.01 (5.77 to 11.05)	4.83 (1.84 to 7.83)

* IL-8 = interleukin-8, CRP = C-reactive protein; CI = confidence interval.

† Absolute risks were standardized to the distributions of the following variables in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial's screening-arm cohort: age, sex, year of randomization, smoking duration and intensity, and time since quitting (for former smokers).

‡ Low vs high IL-8 and CRP levels were dichotomized by the median values among control subjects (IL-8, 17.4 pg/mL; CRP, 2.7 mg/mL).