# Prospective evaluation of C-reactive protein, smoking and lung cancer death in the Third National Health and Nutrition Examination Survey

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**Abstract.** Chronic inflammation plays an important role in lung carcinogenesis. Few prospective studies have examined associations between lung cancer, serum C-reactive protein (CRP), a measure of systemic inflammation, and inflammatory lifestyle factors, such as smoking and obesity. This study prospectively examined the relationship between CRP and lung cancer death and its interrelationships with several lifestyle factors. Baseline data on smoking and other lifestyle variables were collected for 8,950 participants in the Third National Health and Nutrition Examination Survey (NHANES III: 1988-1994). Baseline CRP levels were measured in serum samples by nephelometry. Mortality status was ascertained through probabilistic record matching using the National Death Index through 2006. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) for CRP and lung cancer death, with adjustment for smoking and other variables. During 18 years of follow-up, 219 individuals died from lung cancer. Multivariate regression models revealed a dose-response effect for elevated CRP and risk of lung cancer death when adjusting for age, gender, BMI and smoking. Compared to individuals with CRP <3 mg/l, lung cancer death was significantly associated with elevated levels of CRP: HR=1.63 (95% CI=1.15-2.26) for 3-7 mg/l and HR=2.44 (95% CI=1.81-3.45) for CRP >7 mg/l, P-trend <0.0001). The risk of lung cancer death for smokers increased 9-fold in adjusted models (P<0.0001). When stratified by gender and smoking status the effects of CRP were similar for smokers and males but did not reach statistical significance for females and non-smokers. This study supports a dose-dependent relationship between lung cancer death and CRP for males and smokers, but additional efforts are needed to better elucidate these relationships in women and non-smokers. The results suggest that CRP may emerge as a valuable tool in identifying high-risk subgroups of smokers for lung cancer prevention strategies.

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## Introduction

Lung cancer is the leading cause of cancer mortality in both men and women, accounting for ~28% of all cancer deaths. Approximately 221,200 new lung cancer cases and 158,040 deaths have been estimated to occur in 2015 (1). While the 1-year relative survival rate of lung cancer increased from 37% in 1975-1979 to 43% in 2003-2009, which is primarily due to improved surgical techniques and therapies, the 5-year survival rate remains very low at only 17% (averaged across all stages) (1). The continued low survival rate is primarily due to the lack of effective early detection methods for lung cancer, and because the disease is usually in the advanced stages by the time it is diagnosed (2,3). Overall, lung cancer incidence and mortality rates in the United States have modestly decreased in recent decades due to reduced smoking levels, improved screening techniques, chemoprevention, and treatment methods for lung cancer (4,5).

Although tobacco is the most critical risk factor for lung cancer development, evidence suggests that other environmental exposures, such as radon, asbestos, and dietary and lifestyle variables may also contribute to risk (3,6). However, the evidence for many of these factors has not been conclusive (6).

Based on past evidence, we propose that many factors contributing to cancer risk may interact within a complex network of inflammatory processes to mediate lung carcinogenesis (7-10). In addition to tobacco, environmental/occupational exposures, combined with inherited susceptibility variants, may impact carcinogen metabolism or inflammatory processes to modulate risk among smokers (11-15).

This study sought to examine the potential of a biomarker of systemic inflammation, serum C-reactive protein (CRP), to predict the risk of lung cancer death in a large prospective

cohort. CRP, which is an acute-phase protein that displays a rapid and distinct rise in its plasma concentration in response to acute inflammation, infection and tissue damage, has been examined in studies as a marker of chronic inflammatory states (16-18). Most critically, CRP has been reported to be elevated in epidemiologic studies, in some studies marking the presence of prevalent cancer (19), but also associated with an increased risk of future cancer in otherwise healthy individuals (16,20-22).

There have only been a few large, prospective studies that have focused on CRP and its relationship to lung cancer risk or mortality (20,23,24), but other studies have been modest in statistical power (14,25,26). This study sought to prospectively examine the relationship between CRP and lung cancer death, as well as the interrelationships with other lifestyle factors. It was hypothesized that increased levels of CRP would exhibit a positive relationship with lung cancer death and that the ability of CRP to predict poor outcomes in men and women would be enhanced by controlling for smoking status, obesity and demographic factors.

## Materials and methods

The data obtained for this study were from the National Health and Nutrition Examination Survey III (NHANES III), which was conducted by the National Center for Health Statistics (NCHS) (27). The NHANES III study used a complex, multi-stage, stratified sample of civilian, non-institutionalized persons aged two months or greater. NHANES III was conducted from October 1988-1994 in two phases. In NHANES III, 39,695 persons were selected over the six years, and, of those, 33,994 (86%) were interviewed in their homes. All interviewed persons were invited to mobile examination centers (MECs) for a medical examination. A detailed description of design specifications and methods can be found elsewhere (27).

For the present study, data from NHANES III participants were used to prospectively examine the association between CRP and lung cancer death. The criteria for inclusion in this study were: a) age ≥40 years and b) study participants were cancer-free when they began the study (i.e., they had never been told by a doctor that they had cancer, with the exception of non-melanoma skin cancer). This prospective study followed cancer-free individuals from the time of entry into the NHANES III study until death or December 1, 2006.

### *Measures*

*Household Adult Questionnaire*. The NHANES III Household Adult Questionnaire included all data collected during the household interviews for adults aged ≥17 years. Demographic and lifestyle data, such as age, sex, race, education, smoking and history of cancer, were obtained from the Household Adult Questionnaire. Interviews were conducted by field staff, who received intensive initial training and formal retraining, which continued throughout the study to ensure high skill levels. The data collection system was automated in phase 2, during which interviews were conducted using CAPI (computer-assisted personal interview). Details on survey instruments and forms, training manuals and data collection procedures are published elsewhere (27).

*MEC physical examination*. Blood and urine specimens were obtained at the MEC within one month of the interview, where several lab tests and measurements were performed, including anthropometric body measurements, X-rays and electrocardiography. While some of the blood and urine analyses were performed in the MEC laboratory, most were conducted by contract laboratories (28). For those who could not visit the MEC, a limited home examination was conducted.

*CRP analysis*. CRP was measured in serum samples by nephelometry and stored at -70˚C within 2 months of collection. CRP levels were analyzed using a fully automated Behring Nephelometer Analyzer System (Behring Diagnostics, Inc., Somerville, NJ, USA). Additional details about the specific methods for quantifying CRP are provided elsewhere (21).

*Ascertainment of mortality through National Death Index Linkage*. The outcome measure for this prospective study was death from lung cancer, which was ascertained through a record linkage process with mortality data from the National Death Index (NDI). The NHANES III database was linked with NDI mortality records through December 31, 2006, which resulted in a follow-up time for mortality that ranged from 6 to 12 years (29,30). This linkage was performed through probabilistic matching using social security number, first, middle and last name, year/day of birth, and additional fields described elsewhere (30). Mortality status could also be ascertained if the death certificate was received directly from NCHS and matched with an NHANES III survey record based on a participant's name and other linkable information, such as occupation (31). The underlying cause of death was established from ICD-9 codes through 1998 and ICD-10 codes for 1999-2000, but the final cause of death was determined by the ICD-10 codes after adjusting for changes between the coding systems. At the end of the follow-up period, 3,384 adult NHANES III participants were determined to be deceased through the NDI linkage process (30).

### *Statistical analysis*

*Descriptive statistics*. Descriptive statistics were displayed for all variables, with frequencies and percentages shown for discrete variables and means and standard deviations (SDs) displayed for continuous variables. Tests of statistical significance were also shown, with Chi-square tests performed for discrete variables and t-tests performed for continuous variables. The level of statistical significance was $\alpha$=0.05.

*Regression analysis*. Cox proportional hazards regression analysis was performed to assess the relationship between CRP levels and the study outcome of time to lung cancer death. Effects were quantified by estimating hazard ratios (HRs) and associated P-values from univariate and multivariate regression models. Regression models were developed to examine the relationship between CRP and lung cancer death, as well as covariate factors, with a dichotomous indicator variable denoting whether the person died (dead=1, not dead=0, i.e., right censored). CRP was classified into 3 levels: <3 mg/l, 3-7 mg/l and >7 mg/l, based on cutpoints previously defined in the literature (32,33). Graphical checks of the data and covariates revealed that the proportional hazards assumption

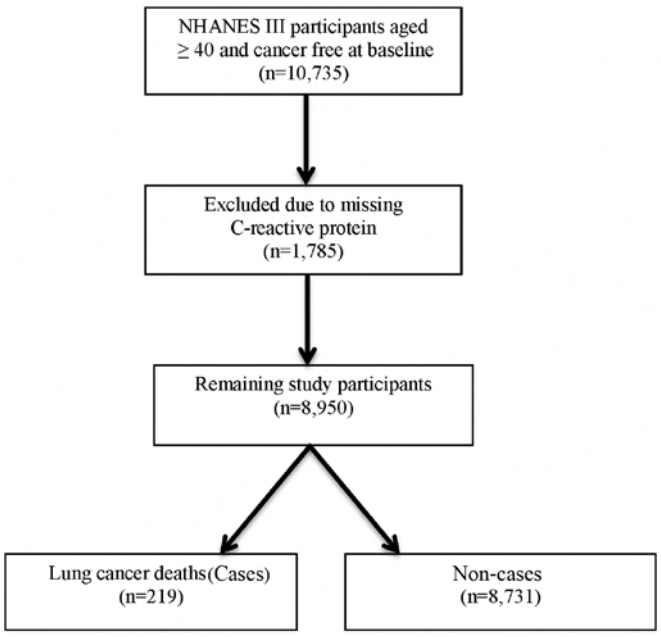


Figure 1. Study recruitment. The total eligible participants and total remaining after exclusions stratified by lung cancer death status is shown.

was met. Fig. 2 shows that the hazards by CRP levels were proportional.

The effect of demographic and other risk factors on the relationship between inflammation and lung cancer death was assessed from the following factors: age (years), gender (male, female), race (white, African American/other), education (<high school, ≥high school), smoking status (ever smoked ≥100 cigarettes, never smoked), pack-years (number of packs smoked per day times number of years smoked), BMI (kg/m$^2$), and waist-hip ratio (WHR). All analyses were conducted using SAS 9.3.

## Results

*Participants*. Out of 10,735 participants who met the eligibility criteria for inclusion (age ≥40 and cancer-free at baseline), a total of 1,785 participants did not have a measurement for CRP, and were, therefore, excluded, providing a total of 8,950 participants for analysis in this study (Fig. 1). There were 219 deaths from lung cancer over the follow-up period of 218 months. The total follow-up time for lung cancer deaths was 199 months and for the remaining cohort was 218 months.

*Demographic, lifestyle and anthropometric characteristics*. Demographic characteristics of participants at baseline are displayed in Table I. Over half of the participants in this study were female (51.9%), but two-thirds of the lung cancer deaths occurred in males (P<0.001). Over 70% of participants in the study cohort were white and almost one-fourth were black. Over half of participants had a high school education or greater, with over half of lung cancer deaths not having a high school education. The mean age at baseline for the entire cohort was 61 years, but those who died of lung cancer were older (64.7 versus 61.0 years, P<0.001).

Anthropometric and lifestyle risk factors are also shown in Table I. Upon examining BMI by established categories that define obesity (34), it was evident that those who died of lung cancer were significantly less likely to be classified as overweight or obese compared to the remaining cohort (P<0.001).

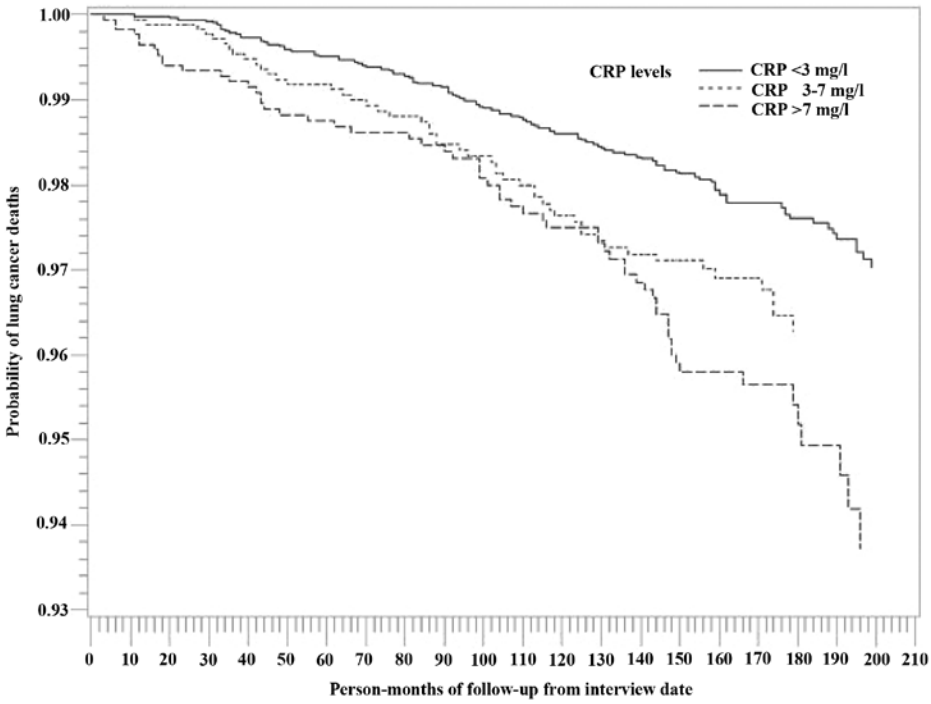


Figure 2. Probability of lung cancer survival by C-reactive protein (CRP) levels. The probability of surviving lung cancer by the 3 levels of CRP examined in this study is shown. Those with the lowest levels of CRP (<3 mg/l) had the highest probability of survival and those with the highest CRP levels (>7 mg/l) had the lowest probability of survival.

Table I. Demographic and clinical characteristics of participants.

| Variable | Lung cancer deaths (cases) (N=219) n (%) | Non-cases (N=8,731) n (%) | Total (N=8,950) n (%) |
|---|---|---|---|
| Gender[b] | | | |
| Male | 144 (65.7) | 4,161 (47.7) | 4,305 (48.1) |
| Female | 75 (34.3) | 4,570 (52.3) | 4,645 (51.9) |
| Race | | | |
| White | 154 (70.3) | 6,402 (73.3) | 6,556 (73.3) |
| African American | 62 (28.3) | 2,091 (24.0) | 2,153 (24.1) |
| Other | 3 ( 1.4) | 238 (2.7) | 241 (2.7) |
| Education | | | |
| <High school | 113 (52.1) | 4138 (47.7) | 4,251 (47.5) |
| ≥High school | 104 (47.9) | 4,529 (52.3) | 4,699 (52.5) |
| Age[b] | | | |
| 40-49 years | 20 (9.1) | 2,378 (27.2) | 2,398 (26.8) |
| 50-59 years | 39 (17.8) | 1,676 (19.2) | 1,715 (19.2) |
| 60-69 years | 84 (38.4) | 2,024 (23.2) | 2,108 (23.6) |
| 70-79 years | 61 (27.9) | 1,497 (17.2) | 1,558 (17.4) |
| ≥80 years | 15 (6.9) | 1,156 (13.2) | 1,171 (13.1) |
| Mean ± SD | 64.7±10.0 | 61.0±14.0 | 61.0±14.0 |
| Body mass index (BMI)[b] | | | |
| <18.5 underweight | 7 (3.2) | 190 (2.2) | 197 (2.2) |
| 18.5-24.9 normal | 100 (45.7) | 2,740 (31.4) | 2,840 (31.7) |
| 25.0-29.9 oveweight | 74 (33.8) | 3,366 (38.6) | 3,440 (38.4) |
| >30 obese | 38 (17.4) | 2,435 (27.9) | 2,473 (27.6) |
| BMI (kg/m$^2$) Mean ± SD[c] | 25.7±4.6 | 27.6±5.6 | 27.6±5.6 |
| Waist-hip ratio Mean ± SD[a] | 0.96±0.1 | 0.95±0.1 | 0.95±0.1 |
| Smoking status[c] | | | |
| Ever smoked ≥100 cig | 202 (92.2) | 4,705 (53.9) | 4,907 (54.8) |
| Former | 84 (38.4) | 2,845 (32.6) | 2,929 (32.7) |
| Current | 18 (53.8) | 1,860 (21.3) | 1,978 (22.1) |
| Never smoked | 17 (7.8) | 4,026 (46.1) | 4,043 (45.2) |
| Pack-years (Mean ± SD)[a] | 24.3±23.4 | 18.5±20.6 | 18.8±20.8 |
| CRP levels[b] | | | |
| CRP<3 mg/l | 108 (49.3) | 5,297 (60.7) | 5,405 (60.4) |
| CRP 3-7 mg/l | 50 (22.8) | 1,747 (20.0) | 1,797 (20.1) |
| CRP >7 mg/l | 61 (27.9) | 1,687 (19.3) | 1,748 (19.5) |
| Mean ± SD[a] | 6.4±7.9 | 5.4±9.0 | 5.4±9.0 |

[a]P<0.05; [b]P<0.001; [c]P<0.0001.

The mean BMI at enrollment was slightly lower for those who had lung cancer deaths versus the remaining cohort (25.7 and 27.6, respectively, P<0.0001). The mean WHR was slightly higher for lung cancer deaths versus those who did not die of lung cancer (0.96 and 0.95, respectively; P=0.04).

While almost 55% of all participants had ever smoked >100 cigarettes in their lifetime, a large majority (92.2%) of those who died of lung cancer had ever smoked (P<0.0001). Of those, almost 54% were current smokers at baseline compared to only 21% of the remaining cohort. Males were also more likely to smoke than females (63 versus 37%, respectively, not shown). Those who died of lung cancer also had a significantly higher number of mean pack-years smoked (24.3 versus 18.5; P<0.05).

Mean CRP levels were significantly higher at enrollment for those who subsequently died of lung cancer versus the

Table II. Cox proportional hazards regression overall model of CRP and lung cancer.

| Multivariate | Cases n (%) | Controls n (%) | HR (95% CI) |
|---|---|---|---|
| CRP <3 mg/l[a] | 108 (49.3) | 5,297 (60.7) | - |
| CRP 3-7 mg/l | 50 (22.8) | 1,747 (20.0) | 1.63 (1.15-2.26) |
| CRP >7 mg/l | 67 (27.9) | 1,687 (19.3) | 2.44 (1.81-3.45) |
| Smoker (ever vs never) | 202 (92.2) | 4,705 (53.9) | 9.83 (5.65-15.59) |
| BMI (kg/m$^2$) | 219 (100.0) | 8,731 (100.0) | 0.92 (0.89-0.95) |

[a]P-trend <0.0001. [b]Models were also adjusted for age (HR=1.05; 95% CI=1.04-1.06) and gender (male vs female) (HR=1.37; 95% CI=1.03-1.82).

remaining cohort (P<0.05). When examining CRP by the previously employed cutoff values of low, moderate and high CRP levels (<3, 3-7, >7 mg/l), those who died of lung cancer had higher overall CRP levels. Over half (50.7%) of all lung cancer deaths had a CRP level of 3 or greater compared to only 39.3% the remaining cohort, which was statistically significant (P<0.001).

The overall survival graph by CRP levels is shown in Fig. 2. The overall survival probabilities decreased from 1.0 at study start to ~0.97, 0.96 and 0.94, respectively, for the lowest to highest CRP levels at the end of follow-up. Therefore, the group with the lowest CRP levels had a higher probability of survival by the end of the study.

*Regression analysis*. The results of the Cox proportional hazards regression analyses are shown in Tables II and III. Table II shows that individuals with CRP levels 3-7 mg/l had

Table III. Cox proportional hazards regression stratified models of CRP and lung cancer death by smoking status and gender.[a]

| Ever smokers | Cases n (%) | Controls n (%) | HR (95% CI)[b] |
|---|---|---|---|
| CRP <3 mg/l | 99 (49.0) | 2,801 (59.5) | - |
| CRP 3-7 mg/l | 44 (21.8) | 970 (20.6) | 1.54 (1.08-2.20) |
| CRP >7 mg/l | 59 (29.2) | 934 (19.9) | 2.58 (1.85-3.61) |
| BMI (kg/m$^2$) | 200 (100.0) | 4,690 (100.0) | 0.91 (0.89-0.95) |
| **Never smokers** | **Cases n (%)** | **Controls n (%)** | **HR (95% CI)** |
| CRP <3 mg/l[c] | 9 (52.9) | 2,496 (62.0) | - |
| CRP 3-7 mg/l | 6 (35.3) | 777 (19.3) | 2.46 (0.87-7.26) |
| CRP >7 mg/l | 2 (11.8) | 753 (18.7) | - |
| BMI (kg/m$^2$) | 17 (100.0) | 4,011 (100.0) | 0.96 (0.99-1.00) |
| **Males** | **Cases n (%)** | **Controls n (%)** | **HR (95% CI)[b]** |
| CRP <3 mg/l | 68 (47.2) | 2,740 (65.9) | - |
| CRP 3-7 mg/l | 34 (23.6) | 779 (8.7) | 1.89 (1.26-2.90) |
| CRP >7 mg/l | 42 (29.2) | 642 (15.5) | 3.04 (2.25-4.92) |
| Smoker (ever vs never) | 136 (94.4) | 2,963 (71.2) | 6.39 (3.10-13.00) |
| BMI (kg/m$^2$) | 142 (100.0) | 4,154 (100.0) | 0.89 (0.86-0.93) |
| **Females** | **Cases n (%)** | **Controls n (%)** | **HR (95% CI)** |
| CRP <3 mg/l | 40 (56.0) | 2,557 (56.0) | - |
| CRP 3-7 mg/l | 16 (21.3) | 968 (21.2) | 1.26 (0.62-1.99) |
| CRP >7 mg/l | 19 (25.3) | 1,045 (22.9) | 1.40 (0.66-2.21) |
| Smoker (ever vs never) | 66 (88.0) | 1,742 (38.1) | 12.51 (6.25-25.52) |
| BMI (kg/m$^2$) | 75 (100.0) | 4,547 (100.0) | 0.96 (0.92-1.01) |

[a]HR, hazard ratio; CRP, C-reactive protein; BMI, body mass index; models were also adjusted for age and gender. [b]P-trend <0.0001 for males and smokers. [c]CRP in never smokers was dichotomized as CRP <3 mg/l and CRP ≥3 mg/l.

a 1.63 times higher risk of lung cancer death compared to the reference group (CRP <3 mg/l), which was statistically significant (95% CI=1.15-2.26). Individuals with CRP >7 mg/l had 2.44 times the risk of dying from lung cancer, which was also statistically significant (95% CI=1.81-3.45). A dose-response effect was observed for higher CRP levels and lung cancer death, even when adjusting for other factors such as smoking (P-trend <0.0001). Notably, the HRs for CRP and lung cancer were adjusted for the dominant lung cancer risk factor of smoking, for which the HR was 9.83, which revealed a greatly increased risk of lung cancer death (95% CI=5.65-15.59).

Due to the powerful effect of smoking in this study and the fact that the majority of men (63%) were smokers, the models were stratified according to smoking and gender. Table III shows the multivariate model by smoking status (ever versus never smoked). For ever smokers, the HRs for CRP revealed a statistically significant dose-response effect (P-trend <0.0001), with higher levels of CRP indicating a higher risk of lung cancer death, similar to the results in Table II (HR=1.54 and 2.58 for CRP 3-7 mg/l and CRP >7 mg/l, respectively). For never smokers, individuals with CRP >3 mg/l (CRP was dichotomized due to the small sample size), were at increased risk (HR=2.46, 95% CI=0.87-7.26), but the estimate did not reach statistical significance.

The results for males were similar to those of smokers, although the HRs were higher (1.89 and 3.04 for CRP 3-7 mg/l and CRP >7 mg/l, respectively), with a dose-response effect (P-trend <0.0001). The HR estimates for females, however, were not significant at either level of CRP. Interestingly, the HR for female smokers was statistically significant (HR=12.51; 95% CI=6.25-25.52) and was double that of males (HR=6.39; 95% CI=3.10-13.00).

The results for BMI showed a reduced risk of lung cancer death (HR=0.92; 95% CI=0.89-0.95) in the overall model (Table II). In the stratified models (Table III), the results for BMI revealed the lowest HR for males, which was statistically significant (HR=0.89; 95%CI=0.86-0.93). The BMI for ever smokers was slightly higher but still statistically significant (HR=0.91; 95%CI=0.89-0.95). The BMI HRs for females and never smokers were not statistically significant.

## Discussion

Our prospective study examined the interrelationships between CRP, lifestyle risk factors and risk of lung cancer death. CRP is an acute-phase protein that is produced in the liver and whose main biologic function is to recognize pathogens and damaged cells in the host, as well as to mediate their elimination by recruiting the complement system and phagocytic cells (17). CRP is suggested as a prognostic factor for the risk of several cancers (35), including lung cancer (14,20,24) and chronic lung disease (18,36). We hypothesized that CRP concentrations may provide an integrative biomarker of inflammatory responses of the host to tobacco and other environmental factors, which may predict those at greater risk of death from lung cancer.

We observed a significant 2.4-fold positive association between baseline CRP concentrations and subsequent risk of lung cancer death. Furthermore, a significant dose-dependent relationship emerged. Our study supports earlier findings indicating a positive association between CRP and lung cancer. In a prospective study by Allin *et al* (24), a 2-fold increased risk of lung cancer was observed among incident cases with a similar dose-response relationship. Chaturvedi *et al* (20) and Shiels *et al* (23) also observed a 2- to 3-fold increased risk of CRP and incidence of lung cancer with a dose-response effect. A meta-analysis of 6 prospective studies of CRP and incident lung cancer found a lower risk ratio of 1.32, but the authors indicated that considerable heterogeneity across studies may have been related to differential effects in the different populations, and there may also have been residual confounding factors (19). Of note is that previous studies did not assess other potential modulating factors of CRP, such as obesity and other lifestyle factors.

The interrelationships between tobacco use and CRP were investigated in the regression analysis. Past studies show that lung cancer risk is clearly related to smoking (37,38), which is consistent with the result of our multivariate model showing a 9-fold increased risk of lung cancer for those who had ever smoked versus never smoked. Allin *et al* (24) did not report the HRs for smoking and Chaturvedi *et al* (20) and Shiels *et al* (23) controlled for smoking through matching. When stratified by smoking, the HR remained similar to that of smokers, but did not reach statistical significance, which may have been due to the smaller sample of non-smokers. This finding warrants further investigation, however, since others have shown that there may be different mechanisms in smokers versus non-smokers (39).

When the multivariate model was stratified by gender, the relationship between CRP and lung cancer death showed differential effects. While a strong positive relationship between CRP and lung cancer death remained for males, the effect was weakened and not significant for females. Interestingly, the HR for smoking in females was twice that of males (12.51 versus 6.39). CRP, however, was not shown to be statistically significant for females, which suggests that lung cancer in females in this study may have been more related to carcinogens in tobacco smoke than inflammation (as measured by CRP), whereas the results for males showed that lung cancer appeared to be related to both smoking and inflammation. Khera *et al* (40) investigated CRP differences between males and females and observed that females tended to have higher CRP levels than males. They proposed that different cutoff levels may be useful in studies assessing CRP and health outcomes based on gender, but future research is needed. We conclude that the interrelationships between tobacco, smoking, markers of inflammation and risk of cancer in men and women may differ and warrant further investigation.

Obesity emerged as a significant factor with regards to lung cancer death in this study, demonstrating a protective effect for males and smokers but not always for females and non-smokers. One reason for this occurrence may be that smoking is associated with reduced BMI and males were more likely to smoke than females in this study. Past studies assessing obesity and lung cancer have primarily shown a protective effect, but many studies have not stratified between males and females (39). This issue should, therefore, be further investigated in future studies. Another difference in the stratified models was that the HR for BMI was not statistically significant for non-smokers, and only approached significance for females. It is known that smokers tend to be leaner than non-smokers, which

may explain why BMI was no longer significantly related to lung cancer death in non-smokers. Male smokers also tend to be leaner than female smokers, which may explain why the protective BMI did not quite reach statistical significance for females. Others have noted that smoking may mask the effect of BMI (41). Also, since males were more likely to smoke in this study, and smoking is usually correlated with other inflammatory factors, such as increased CRP and decreased BMI, further studies are needed to specifically examine the differences between males and females, and to determine which mechanisms may be causing these differential results. Possible assessments include environmental exposures, histologic differences, and biological or genetic factors (39).

The primary strength of this study was the novelty of examining the CRP-lung cancer relationship and associations with lifestyle factors in the NHANES cohort, which is a large national probability sample. Our results are, therefore, more likely to be generalizable to the US population. NHANES was a well-planned and executed study that included a detailed plan, well-trained staff and implemented many quality control methods in the data collection phase in order to ensure high quality data and a consistent data collection process. CRP and other study data were obtained from blood draws that were analyzed by an independent lab; anthropometric data were obtained through physical exams conducted at baseline versus self-report.

There were also several limitations in this study. Several variables, including demographic/lifestyle data, were based on participant recall. The surveys were primarily done in person, however, using computer-assisted techniques, with standard cards, pictures and other probing methods used to help participants recall each data item as accurately as possible. Self-reported smoking in NHANES was previously shown to accurately reflect smoking status (42). The lack of high-sensitivity assays to measure CRP limited the lower threshold of CRP that could be detected and, therefore, limited the number of strata we could use for the analysis. Our study outcome of lung cancer death versus lung cancer incidence was another limitation, but since lung cancer has a short survival time, our results are believed to be reasonably similar to what lung cancer incidence data would have produced. Also, the outcome ascertainment for lung cancer death was not histologically confirmed, but was obtained through a death certificate linkage process. This could have led to misclassification since individuals with lung cancer may have died of other causes. As a result, we may have missed some of the lung cancer cases. Death certificates also do not reflect histology, so we could not conduct any histology analyses.

In conclusion, several important results emerged from this study, which can be used to make recommendations for reducing the risk of lung cancer death. First, this study supports the concept that a higher concentration of CRP, particularly in those who smoke, may identify a group at particularly high risk of developing lung cancer. Most critically, our study supports that the CRP-lung cancer relationship is quantitatively dose-dependent and CRP may serve as a biomarker in prevention studies, particularly for men exposed to tobacco smoke. Yet additional efforts are necessary to better elucidate the relationships in women and non-smokers. While effective interventions to quit smoking are greatly needed, CRP may emerge as a valuable tool to identify particularly high-risk subgroups of smokers for lung cancer prevention strategies.

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