Lung Cancer Death Rates in Lifelong Nonsmokers

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Background: **Few studies have directly measured the age-, sex-, and race-specific risks of lung cancer incidence and mortality among never tobacco smokers. Such data are needed to quantify the risks associated with smoking and to understand racial and sex disparities and temporal trends that are due to factors other than active smoking.** ***Methods:*** **We measured age-, sex-, and race-specific rates (per 100 000 person-years at risk) of death from lung cancer among more than 940 000 adults who reported no history of smoking at enrollment in either of two large American Cancer Society Cancer Prevention Study cohorts during 1959–1972 (CPS-I) and 1982–2000 (CPS-II). We compared lung cancer death rates between men and women and between African Americans and whites and analyzed temporal trends in lung cancer death rates among never smokers across the two studies by using directly age-standardized rates as well as Poisson and Cox proportional hazards regression analyses. All statistical tests were two-sided.** ***Results:*** **The age-standardized lung cancer death rates among never-smoking men and women in CPS-II were 17.1 and 14.7 per 100 000 person-years, respectively. Men who had never smoked had higher age-standardized lung cancer death rates than women in both studies (CPS-I: hazard ratio [HR] = 1.52, 95% confidence interval [CI] = 1.28 to 1.79; CPS-II: HR = 1.21, 95% CI = 1.09 to 1.36). The rate was higher among African American women than white women in CPS-II (HR = 1.43, CI = 1.11 to 1.85). A small temporal increase (CPS-II versus CPS-I) in lung cancer mortality was seen for white women (HR = 1.25, CI = 1.12 to 1.41) and African American women (HR = 1.22, CI = 0.64 to 2.33), but not for white men (HR = 0.89, CI = 0.74 to 1.08). Among white and African American women combined, the temporal increase was statistically significant only among those aged 70–84 years (*****P*****<.001).** ***Conclusions:*** **Contrary to clinical perception, the lung cancer death rate is not higher in female than in male never smokers and shows little evidence of having increased over time in the absence of smoking. Factors that affect the interpretation of lung cancer trends are discussed. Our novel finding that lung cancer mortality is higher among African American than white women never smokers should be confirmed in other studies. [J Natl Cancer Inst 2006;98:691–9]**

Approximately 85%–90% of all lung cancer deaths in the United States are caused by active cigarette smoking *(1)*. The remaining 10%–15% represent between 17 000 and 26 000 deaths annually *(2)*, a number that would rank among the six to eight most common fatal cancers in the United States if considered as a separate category *(3,4)*. An estimated 15 000 lung cancer deaths caused by factors other than active cigarette smoking occur in lifelong non-smokers; the rest are combined with and statistically indistinguishable from the much larger number caused by cigarette smoking among current and former smokers. Known causes of lung cancer other than cigarette smoking include secondhand smoke, active smoking of other tobacco products, and exposure to other carcinogens such as asbestos, radon, radiation therapy, combustion products, and various other exposures in occupational, environmental, and/or medical settings.

Information on lung cancer risk among lifelong nonsmokers is needed to understand racial and sex disparities in incidence and mortality, to determine whether lung cancer occurrence has changed over time because of factors other than active smoking, and to quantify the risks associated with smoking. Such information also helps to inform ongoing scientific debates, such as whether women are more susceptible to lung cancer than men in the presence *(5–7)* or absence *(5,8)* of current cigarette smoking and whether factors other than active smoking contribute to the disparity in lung cancer risk between African Americans and whites *(9–11)*.

Despite the need for these data, it is surprisingly difficult to obtain reliable and precise measurements of lung cancer risk among lifelong nonsmokers. Smoking histories are not collected routinely by population-based cancer registries or on death certificates; smoking information that is available from next of kin or hospital records is incomplete and often unreliable. Studies published in the early 1960s estimated age- and sex-specific lung cancer death rates in never smokers from a 10% sample of U.S. deaths in 1958 and 1959 and from interviews of selected households *(12,13)*. However, the age categories were broad, the smoking information was collected from next of kin, and the number of never smokers was estimated indirectly. Three large cohort studies have reported age-specific death rates from lung cancer in never-smoking men and women *(14–17)*, but did not present data separately for African Americans, and in some reports *(18–20)* combined the results for occasional and never smokers. Analyses from the Multiethnic Cohort *(21)* demonstrate that most of the difference in lung cancer risk between African Americans and whites is attributable to different smoking practices, but there were too few cancers among never-smokers in this cohort to measure race-, sex-, and age-specific incidence rates precisely in persons who never smoked. Smaller cohort studies and all case–control studies typically report only the relative risk of lung cancer in smokers compared with that in never smokers.

In this study we examined age-, sex-, and race-specific death rates from lung cancer among more than 940 000 white and African American adults who reported no history of tobacco use

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when enrolled in either of two large American Cancer Society (ACS) studies. The Cancer Prevention Study I (CPS-I) began in the fall of 1959 and ended follow-up in July 30, 1972. The Cancer Prevention Study II (CPS-II) began in the fall of 1982 and has ongoing follow-up of mortality. The analyses of CPS-II in our paper are based on 20 years of follow-up, increasing the number of lung cancer deaths among never smokers from less than 440 in previous reports *(15,16,22)* to 1498 here. The massive size and similar methods of enrollment and follow-up of these cohorts provide a unique longitudinal perspective on changes in lung cancer mortality in relation to smoking over the last 50 years.

Subjects and Methods

Study Population

The CPS-I and CPS-II cohorts have been described at length elsewhere *(23)*. Briefly, 1 million participants in CPS-I *(16,18,24,25)* and 1.2 million in CPS-II *(16,22,25–28)* were recruited by ACS volunteers in the falls of 1959 and 1982, respectively. Volunteers contacted their friends, neighbors, and acquaintances and requested that all household members aged at least 30 years complete a questionnaire if at least one household member was aged 45 years or older *(24)*. CPS-I encompassed 25 states; CPS-II encompassed 50 states, the District of Columbia, Puerto Rico, and Guam. Participants in both studies were older, more educated, and more likely to be married and middle class than the general U.S. population *(24)*. Whites made up 97% and 93% of CPS-I and CPS-II, respectively. Informed consent to participate in CPS-II was implied by the return of the self-administered questionnaire. All aspects of the CPS-II study protocol have been reviewed and approved by the Emory University institutional review board (IRB), and the protocol is renewed annually. Active follow-up of the CPS-I cohort ended in 1972; closed studies are exempt from IRB approval.

Follow-up

For the entire 12 years of CPS-I and the first 6 years of CPS-II, ACS volunteers made personal inquiries to determine vital status and the date and place of all deaths of the study cohort members. Follow-up began at the midpoint of the month of enrollment and ended with the subject's death, loss to follow-up, or end of follow-up—whichever occurred first. Reported deaths were verified from death certificates *(29)*. During vital status follow-up through July 30, 1972, 17.9% of CPS-I participants were identified as deceased, 69.6% as alive, 7.3% as lost to follow-up, and 5.2% as having follow-up truncated in 1965 due to the inability of the ACS unit to continue the study. CPS-II follow-up continued from 1988 through December 31, 2000, using automated linkage with the National Death Index. National Death Index linkage also identified deaths among the 21 704 participants who were lost to follow-up between 1982 and 1988 *(29)*. As of December 31, 2000, 28.1% of CPS-II participants were deceased and 71.7% were alive. Follow-up was truncated on September 1, 1988, for 0.2% of CPS-II participants because of insufficient data to link with the National Death Index. In all analyses, the endpoint was lung cancer coded as the underlying cause of death from the death certificate. In CPS-I, this endpoint corresponded to International Classification of Diseases (ICD)-7 (codes 162–163); in CPS-II it corresponded to ICD-9 (code 162) for deaths occurring in 1982–1998 and to ICD-10 (codes C–33 and C–34) for deaths occurring thereafter.

Smoking Information

Participants in both studies reported their smoking status and other medical, demographic, and lifestyle characteristics on a four-page questionnaire that they completed at enrollment *(26)*. In CPS-I, lifelong nonsmoking was defined by a negative response to the questions "Do you now smoke?" and "If you do not smoke cigarettes now, did you ever smoke cigarettes regularly?" Men were asked the same questions with respect to pipes and cigars. In CPS-II, lifelong nonsmokers were defined as persons who reported never smoking one or more cigarettes, cigars, or pipes daily for at least 1 year's time. Information on changes in smoking status was collected in CPS-I in 1961, 1963, 1965, and 1972. No updated information on smoking was collected during follow-up of the entire CPS-II cohort. However, updated information was collected on a subset of 184 000 CPS-II participants who were reenrolled in the CPS-II Nutrition Cohort in 1992–1993 *(30)*.

Rate Analyses

We calculated age-specific and age-standardized lung cancer death rates (per 100 000 person-years at risk) by attained age among lifelong nonsmokers in both cohorts, on the basis of smoking information provided at enrollment and the underlying cause of death as coded from the death certificate. Age-specific rates are presented for each stratum of age (5-year groupings from ages 35–84 years), sex, and race only for groups with at least five lung cancer deaths. No data are presented for people aged 85 years or older, because of greater diagnostic uncertainty at older ages *(31)*. Smoothed age-specific rates were calculated by using Poisson regression *(32)*. Age-standardized death rates were calculated by using the combined age distribution of CPS-I and CPS-II as the standard population. The corresponding rates standardized to the year 2000 age standard would be 25%–35% lower. Mantel–Haenszel tests of statistical significance for a change in age-specific rates from CPS-I to CPS-II used the broader age groupings 35–54, 55–69, and 70–84 years; all statistical tests were two-sided. $P<.05$ was considered statistically significant.

Adjustment for Covariates

Cox proportional hazards modeling was used to adjust for a slightly different set of covariates in the two studies. We assessed the appropriateness of the Cox proportional hazards model for each cause of death by plotting log(-log) survival curves of each sex, race, and study subgroup against survival time. Although there was some instability in the survival curves among African American participants, the log(-log) survival curves for all subgroups were essentially parallel, suggesting that the proportional hazards assumption was met and that the model was appropriate. We considered hazard ratios to depict statistically significant difference in mortality rates if the 95% confidence interval (CI) excluded 1.0. All multivariable analyses adjusted for single year of age at enrollment. Minimally adjusted models were stratified by sex or race as appropriate. Further adjustments were made for education (less than high school, high school graduate, some college, college graduate, and missing), and current employment (yes, no, or missing). Analyses limited to CPS-II also adjusted for type of employment (blue collar, white collar, missing, or housewife), self-reported asbestos exposure (yes or no), indices of vegetable or dietary fat consumption (quartiles), and spousal smoking in 1982 (never, current, former or unknown status, and years of exposure). Indicator variables were used for all independent variables.

Sensitivity Analyses

We conducted sensitivity analyses to determine whether changes in smoking status during follow-up or greater losses to follow-up during the last 2 years of CPS-I (1970–1972) could affect our results. In CPS-I we compared the lung cancer death rate among the 460 941 persons (90 570 and 370 371 women) who reported no regular smoking on all questionnaires with the rate among the 476 895 subjects (Table 1) who reported no history of tobacco use at baseline, regardless of their responses to later surveys. In CPS-II we examined the information on smoking provided in 1992–1993 among 75 745 persons in the CPS-II Nutrition Cohort who reported no history of regular smoking in 1982 *(23)*. We also evaluated the potential effects of differential losses to follow-up in CPS-I by comparing the age-standardized death rate from lung cancer during follow-up through 1970 with that through 1972.

Results

Table 1 shows the number of people in each cohort at baseline, the percentage excluded for various reasons, and the number and demographic characteristics of lifelong nonsmokers included in the analyses. Each cohort included more than 460 000 lifelong nonsmokers who were aged 35–84 years. In both studies, the numbers of never smokers and lung cancer deaths was greater in women than men and in whites than in African Americans. CPS-II included more than 20 000 African Americans who had never smoked, 44% of the total number of African American participants in this cohort. More than 40% of never smokers in CPS-I but only 13% of those in CPS-II had less than a high school education.

We determined the number of lung cancer deaths within each stratum of age (5-year periods), sex, race, and study and calculated the observed and smoothed age-specific death rates for strata with at least five deaths (Table 2). The lung cancer death rates increased with age in both CPS-I and CPS-II in all subgroups in which age-specific rates could be measured in both cohorts; the age-related increase was greater in men than women (Fig. 1, A). Among women, the age-related increase in lung cancer deaths was greater in CPS-II than in CPS-I, particularly for those aged 70 years and above (Fig. 1, B). Age-specific rates could not be calculated for African Americans in most age groups in either cohort because of low numbers.

We then calculated the age-standardized death rates from each study and the corresponding hazard ratios (HRs), adjusted for age and either race or sex or age and multiple covariates (Table 3). We used hazard ratios to compare the lung cancer death rates in men with those in women, in African Americans with those in whites, and in CPS-II with those in CPS-I.

Table 1. Demographic characteristics of lifelong nonsmokers in CPS-I and CPS-II*

	CPS-I (1959–1972)		CPS-II (1982–2000)	
Characteristic	Men	Women	Men	Women
No. of people in baseline cohort	456 487	594 544	508 318	676 270
Exclusions, %				
Current smokers	32	25	20	18
Former smokers	10	4	27	18
Ever pipe/cigar smokers	33	0	20	0
Unquantifiable smoking data	4	4	7	10
Race other than white or African American	1	1	2	2
Not aged 35–84 years	<1	<1	<1	<1
No. of people in analysis	94 041	382 854	122 563	341 643
White	91 895	373 064	118 045	325 703
African American	2146	9790	4518	15 940
Person-years of follow-up among those aged 35–84 years	1 016 767	4 265 328	1 924 424	5 433 700
White	995 507	4 162 830	1 856 070	5 187 474
African American	21 260	102 499	68 354	246 226
Lung cancer deaths among those aged 35–84 years	188	517	433	1065
White	185	504	411	1001
African American	3	13	22	64
Mean age at baseline, y	56	55	57	57
White	56	55	57	57
African American	54	53	56	56
Education, %				
<High school	43	42	12	14
High school graduate	17	24	19	32
Some college	16	20	23	28
College graduate	23	13	45	25
Asbestos exposure, %	NA	NA	5.2	1.5
Spousal smoking, %				
Never smoker	74	18	64	22
Currently smokes cigarettes only	11	19	8	10
Formerly smoked cigarettes only	4	7	14	19
Currently smokes >1 type tobacco	0	16	0	6
Formerly smoked >1 type tobacco	0	6	0	7
Unknown smoking status	2	2	5	3
Spouse not in study	10	31	12	32

*NA = data not available; percents may not sum to 100 because of missing values.

Table 2. Age-, sex-, and race-specific lung cancer death rates among lifelong nonsmokers in CPS-I (1959–1972) and CPS-II (1982–2000)

	CPS-I								CPS-II									
	White						African American		White						African American			
	Men			Women			Men	Women	Men			Women			Men	Women		
Age, y	Deaths	Rate*	Rate†	Deaths	Rate*	Rate†	Deaths	Deaths	Deaths	Rate*	Rate†	Deaths	Rate*	Rate†	Deaths	Deaths	Rate*	Rate†
35–39	0	–	2.7	0	–	1.9	0	0	1	–	1.5	1	–	2.0	0	0	–	3.1
40–44	3	–	3.9	3	–	2.6	0	0	1	–	2.3	0	–	2.9	0	0	–	4.5
45–49	3	–	5.5	15	3.6	3.7	1	0	5	(5.1)	3.5	6	(2.1)	4.1	0	0	–	6.4
50–54	12	7.7	7.9	28	4.4	5.3	0	4	9	(4.8)	5.5	32	6.3	5.9	2	3	–	9.1
55–59	21	10.8	11.3	52	7.0	7.5	0	1	19	7.0	8.5	57	7.8	8.6	2	5	(14.5)	12.9
60–64	30	17.3	16.3	91	13.2	10.6	2	3	48	14.2	13.2	118	13.3	12.4	1	4	–	18.3
65–69	39	28.8	23.3	93	16.4	15.0	0	1	65	19.8	20.5	152	17.2	17.9	4	10	26.4	26.1
70–74	24	24.3	33.4	77	18.3	21.2	0	3	93	34.4	31.8	230	29.9	25.8	3	19	57.6	37.1
75–79	31	49.4	47.8	88	33.1	30.0	0	0	84	44.0	49.3	211	36.3	37.2	7	19	74.9	52.8
80–84	22	71.2	68.5	57	42.1	42.5	0	1	86	80.3	76.5	194	52.8	53.7	3	4	–	–
Total	185			504			3	13	411			1001			22	64		

*Rates are per 100 000 person-years and are shown for cells with five or more deaths (rates based on five to nine deaths are in parentheses).
†Rates are per 100 000 person-years and were smoothed by using Poisson regression *(17)*.

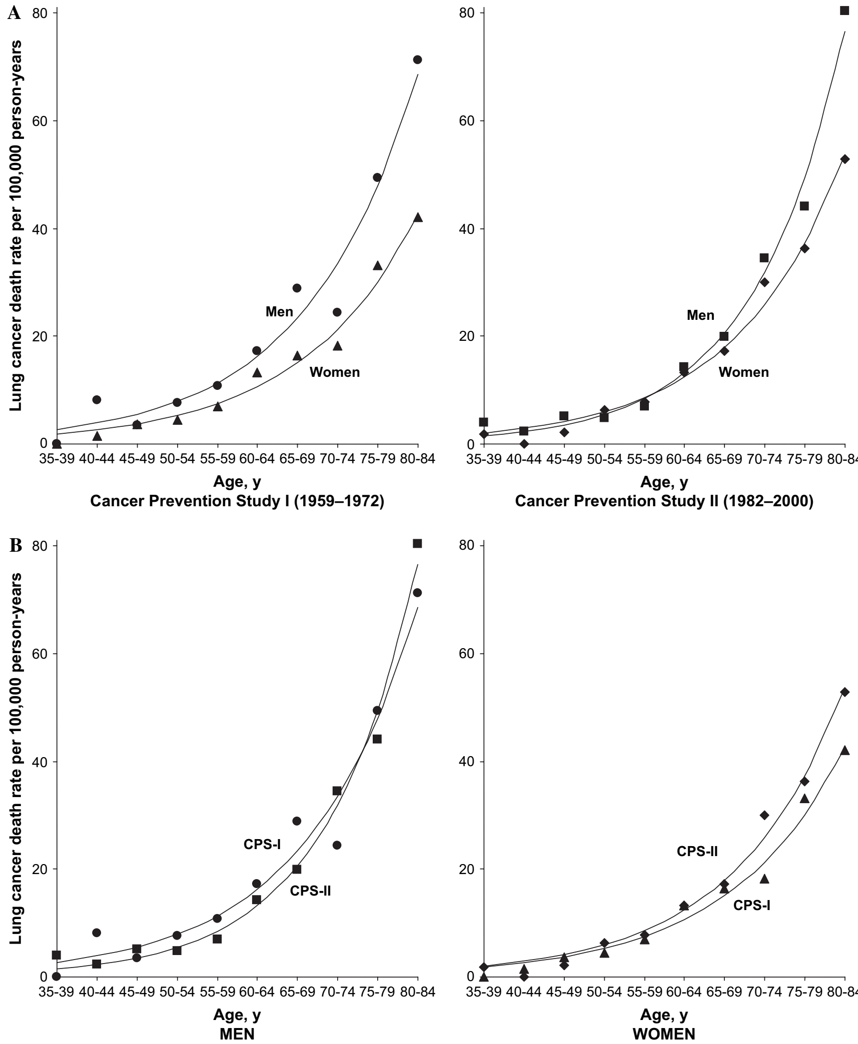

Fig. 1. Age- and sex-specific lung cancer death rates among white lifelong nonsmokers in American Cancer Society Cancer Prevention Study (CPS-I) (1959–1972) and CPS-II (1982–2000). Observed rates in CPS-I men (**circles**), CPS-I women (**triangles**), CPS-II men (**squares**), and CPS-II women (**diamonds**). Trend lines were smoothed by using Poisson regression. **A**) Rates of men versus women, stratified by study. **B**) Rates between studies, stratified by sex.

Rates in Men Versus Women

Lung cancer death rates were higher in men than in women at all ages in CPS-I and at 60 years and older in CPS-II (Fig. 1, A). Although the difference between lung cancer death rates among men and women was statistically significant in both studies, it narrowed substantially from CPS-I (HR = 1.52, 95% CI = 1.28 to 1.79) to CPS-II (HR = 1.21, 95% CI = 1.09 to 1.36), based on rates adjusted for single year of age at enrollment (Table 3). The absolute rate of dying from lung cancer (standardized to the age distribution of CPS-I and CPS-II study participants using 5-year age categories), per 100 000 person-years, was 18.7 in CPS-I men, 12.3 in CPS-I women, 17.1 in CPS-II men, and 14.7 in CPS-II women. The associations were only slightly attenuated after adjustment for other covariates, such as education, vegetable intake, and type of employment (Table 3). The convergence of the sex-specific rates from CPS-I to CPS-II reflects an increase in the death rates among women aged 70–84 years ($P<.001$) and a decrease in the death rates in men aged 35–69 years in CPS-II compared with CPS-I (Table 2, Fig. 1, B).

Rates in African Americans Versus Whites

Among never smokers in CPS-II, the age-adjusted lung cancer death rate was statistically significantly higher in African American men than in white men (HR = 1.58, 95% CI = 1.03 to 2.42) and in African American women than in white women (HR = 1.43, 95% CI = 1.11 to 1.85) (Table 3). These associations were weakened after adjustment for other covariates, so that only the hazard ratio for African American women compared with white women remained statistically significantly different in CPS-II (HR = 1.43, 95% CI = 1.10 to 1.85) (Table 3). The hazard ratios for African Americans versus whites in CPS-I was smaller and not statistically significant among women (HR = 1.18, CI = 0.68 to 2.05); it could not be evaluated among men because of low numbers (Table 3). The absolute rates of dying from lung cancer (standardized to the age distribution of CPS-I and CPS-II study participants using 5-year age categories) were 16.8 in white CPS-II men, 27.3 in black CPS-II men, 14.4 in white CPS-II women, 21.3 in black CPS-II women, 12.3 in white CPS-I women, and 14.2 in black CPS-I women.

Analyses Relating to Temporal Trend

The lung cancer death rate, adjusted for single year of age at enrollment, was higher in CPS-II than in CPS-I among white women (HR = 1.25, 95% CI = 1.12 to 1.41) and black women (HR = 1.22, 95% CI = 0.64 to 2.33) but not white men (HR = 0.89, 95% CI = 0.74 to 1.08) (Table 3). The temporal trend could not

Table 3. Comparison of age-standardized, sex-, and race-specific lung cancer death rates and hazard ratios (HRs) among lifelong nonsmokers for ages 35–84 years in CPS-I (1959–1972) and CPS-II (1982–2000)

Comparison group	Age-standardized rate (95% CI)*	HR (95% CI)†	HR (95% CI)‡
Women and men			
CPS-I			
All women	12.3 (11.3 to13.4)	1.00 (Referent)	1.00 (Referent)
All men	18.7 (16.0 to 21.3)	1.52 (1.28 to 1.79)	1.47 (1.21 to 1.79)
White women	12.3 (11.2 to 13.3)	1.00 (Referent)	1.00 (Referent)
White men	18.7 (16.0 to 21.4)	1.53 (1.29 to 1.81)	1.49 (1.22 to 1.83)
CPS-II			
All women	14.7 (13.7 to 15.6)	1.00 (Referent)	1.00 (Referent)
All men	17.1 (15.4 to 18.8)	1.21 (1.09 to 1.36)	1.21 (1.05 to 1.40)
White women	14.4 (13.4 to 15.3)	1.00 (Referent)	1.00 (Referent)
White men	16.8 (15.1 to 18.5)	1.21 (1.08 to 1.36)	1.20 (1.04 to 1.39)
African American women	21.3 (15.8 to 26.7)	1.00 (Referent)	1.00 (Referent)
African American men	27.3 (15.5 to 39.1)	1.30 (0.80 to 2.11)	1.38 (0.79 to 2.41)
African American and white subjects			
CPS-I			
White women	12.3 (11.2 to 13.3)	1.00 (Referent)	1.00 (Referent)
African American women	14.2 (6.4 to 21.9)	1.18 (0.68 to 2.05)	1.13 (0.65 to 1.97)
CPS-II			
White men and women	15.0 (14.1 to 15.8)	1.00 (Referent)	1.00 (Referent)
African American men and women	22.5 (17.5 to 27.5)	1.47 (1.18 to 1.83)	1.43 (1.14 to 1.79)
White men	16.8 (15.1 to 18.5)	1.00 (Referent)	1.00 (Referent)
African American men	27.3 (15.5 to 39.1)	1.58 (1.03 to 2.42)	1.43 (0.92 to 2.22)
White women	14.4 (13.4 to 15.3)	1.00 (Referent)	1.00 (Referent)
African American women	21.3 (15.8 to 26.7)	1.43 (1.11 to 1.85)	1.43 (1.10 to 1.85)
CPS-I and CPS-II subjects			
White			
CPS-I men	18.7 (16.0 to 21.4)	1.00 (Referent)	
CPS-II men	16.8 (15.1 to 18.5)	0.89 (0.74 to 1.08)	
CPS-I women	12.3 (11.2 to 13.3)	1.00 (Referent)	
CPS-II women	14.4 (13.4 to 15.3)	1.25 (1.12 to 1.41)	
African American			
CPS-I women	14.2 (6.4 to 21.9)	1.00 (Referent)	
CPS-II women	21.3 (15.8 to 26.7)	1.22 (0.64 to 2.33)	

*Rates are per 100 000 person-years and are age-standardized to the combined CPS-I and CPS-II population. CI = confidence interval.

†Hazard ratios are adjusted for single year of age and race or sex as appropriate.

‡Hazard ratios in CPS-I are adjusted for single year of age at enrollment, education (less than high school, high school graduate, some college, college graduate, and missing), vegetable intake (quartiles), and current employment (yes, no, or missing). Hazard ratios in CPS-II are adjusted for single year of age at enrollment, education (<high school, high school graduate, some college, college graduate, and missing), vegetable intake (quartiles), dietary fat consumption (quartiles), asbestos exposure (self-reported, yes or no), spousal smoking in 1982 (never, current, former or unknown status, and years of exposure), current employment (yes, no, or missing), and type of employment (blue collar, white collar, housewife, or missing).

be evaluated in black men because of insufficient numbers in CPS-I. The increase from CPS-I to CPS-II among white women (Table 2, Fig. 1, B) was statistically significant only in those aged 70–84 years ($P<.001$). Among white men, the age-specific lung cancer death rates decreased from CPS-I to CPS-II among never smokers aged 50–69 years (Table 2, Fig. 1, B).

Sensitivity Analyses

We examined the extent to which the misclassification of smoking status or differential losses to follow-up from 1970–1972 in CPS-I might bias the results. In CPS-I, 3.5% of the 487 696 participants who reported no history of regular smoking at baseline indicated some use of tobacco on a later survey. No difference in the age-standardized lung cancer death rate (13.5 deaths per 100 000) was observed with or without the exclusion of persons with discordant smoking histories. Similarly, no difference in the lung cancer death rate among CPS-I never smokers was observed whether follow-up was truncated in 1970 or in 1972. In CPS-II, only 0.3% of the 75 745 persons who reported no history of regular smoking in 1982 indicated ever having smoked at least 100 cigarettes when enrolled in the CPS-II Nutrition cohort in 1992–1993.

Discussion

Our principal findings were that the lung cancer death rate among never smokers was higher in men than women, was higher in African American women than white women, and showed little evidence of increasing over time. These two large prospective studies provide more precise estimates of age- and sex-specific lung cancer mortality among contemporary never smokers than previous reports *(15,16,22)*, especially for African Americans *(21)*. Extending the follow-up of CPS-II never smokers to 20 years increases the number of lung cancer deaths in this subgroup by more than threefold over previous reports *(15,16,22)*. Our data help to inform at least three ongoing controversies about lung cancer, namely, whether susceptibility to develop or die from the disease differs by sex and/or race and whether lung cancer occurrence has changed over time because of factors other than cigarette smoking.

Our finding that male lifetime nonsmokers had higher lung cancer death rates than female never smokers contradicts the widely held view that "women who have never smoked are more likely to develop lung cancer than men who have never smoked" *(8)*. However, our results are consistent with previously published data from several other studies that are smaller or have shorter follow-up *(13,14,33–38)*. On average, the age-standardized death rate from lung cancer in these studies is approximately 25% higher in men than in women who have never smoked *(7)*. The difference by sex is partly attributable to a greater frequency of diagnostic errors for women than for men, resulting in an underestimation of lung cancer occurrence, especially during the era of CPS-I *(39)*. Cechner et al. *(39)* conducted an autopsy study at the University Hospital of Cleveland between 1948 and 1973 and reported that 41.0% of lung cancers identified in women at autopsy were never diagnosed clinically, compared with 25.0% in men. Missed diagnoses were partly offset by a greater proportion of false positives (metastases from extrapulmonary tumors misdiagnosed as primary lung cancer) in women (14.5%) than men (7.8%), yet the net effect of diagnostic error was to underestimate the rate in women by approximately 10% compared with men. Other autopsy studies have reported more frequent missed diagnoses in older women and among never smokers *(40,41)*. Diagnostic error has become less common over time *(42)* because of advances such as the introduction of thin-needle aspiration *(43)* and computerized tomography *(44)* in the 1980s, making it possible to biopsy tumors in the periphery of the lung without open-chest surgery. Improved diagnosis of lung cancer in older patients may explain the increase in lung cancer death rates among older women in CPS-II. Improved diagnosis, together with narrowing of the sex difference in relative survival *(4,45)* contribute to the smaller difference in lung cancer death rates between men and women in CPS-II than that observed in CPS-I.

Even if lung cancer incidence rates were identical in male and female never smokers, the death rates would differ because of the slightly higher relative survival in women than men with lung cancer. One-year relative survival remains higher in women (41.3%) than men (38.3%) with lung cancer in the 1975–2002 National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) registries *(4)*, even though the difference has narrowed over time. For these reasons it is not possible to determine whether lung cancer incidence in women who have never smoked is equal to or lower than that of men who have never smoked. However, it is unlikely that the actual incidence or death rate in women is higher than that in men who have never smoked.

Paradoxically, however, our findings with respect to sex are not incompatible with the clinical perception that "women outnumber men among lung cancer patients who have never smoked" *(5)*. A distinction should be made between the number of people who develop a disease and the average probability (risk) that an individual will develop the disease, as measured in a population of specified size (100 000 persons), period (per year), and age. Many more women than men aged 60 years and older have never smoked, as indicated by census data *(46)* and population-based surveys of smoking behavior *(47)*. Approximately 16.2 million women and 6.4 million men in the United States, aged 60 years or older, have never smoked. The female predominance of never having smoked increases with age, such that women outnumber men in this group by a factor of 1.7, 2.2, and 3.3 at ages 55–64, 65–74, and 75 years and above, respectively. It is not surprising, therefore, to find "a substantially higher proportion of lifetime nonsmokers among all lung cancer cases in women (33% worldwide) than men (3.9% worldwide)" *(48)*, given the greater longevity of women and their later uptake of smoking than men during the 20th century.

Diagnostic error is unlikely to account for the higher lung cancer death rates among African American than white never smokers. In fact, racial differences in diagnostic accuracy would, if anything, underestimate the disparity in lung cancer mortality between black and white lifelong nonsmokers in CPS-II *(39)*. Cechner et al. *(39)* found a higher percentage of false-positive diagnoses in autopsies of white (10.4%) than black (6.7%) patients and found a lower percentage of false negatives (27.1% versus 30.4%, respectively). We observed a widening of the disparity between black and white women from CPS-I to CPS-II, a 20-year interval during which diagnostic accuracy improved. Although we were unable to measure lung cancer mortality among black men who had never smoked in CPS-I, the magnitude of the racial disparity in men in CPS-II was similar to that in women.

To our knowledge, CPS-II is the largest study to measure lung cancer risk prospectively among many African American never smokers. Eighty-six lung cancer deaths occurred during the 18-year follow-up of over 20,000 black never-smokers, more than twice the number in the next largest study *(21)*. In the Multiethnic cohort *(21)*, lung cancer incidence was 29% higher among African American than white women who had never smoked, and nine percent higher in African American than in white men. However, the rates were based on only seven and 31 lung cancers in African American men and women respectively, and in neither sex was the difference statistically significant *(21)*. A smaller case–control study *(10)* compared lung cancer risk among African American with white never smokers and found no difference in risk between African American and white women or in men of all ages but higher lung cancer risk in African American than white men aged 40–54 years (OR = 8, 95% CI = 2.0 to 32.8). Other studies that have examined racial differences in lung cancer risk have measured only the risks associated with smoking *(49–51)*, differences in smoking practices *(52)*, and/or differences in risk in the general population *(4)*.

Compared with white men, black men in the general population have had higher death rates from lung cancer since the mid-1960s *(53)*, although the difference has decreased since 1990 *(45)*. Reasons for the racial disparity in lung cancer seen in the general population are poorly understood, although most of the difference is seen in current and former smokers *(21)*. African American men have slightly higher smoking prevalence than whites *(54)*, smoke cigarettes with higher machine-measured tar levels, have higher levels of blood cotinine *(55)*, and have more difficulty quitting *(52)*. However, black men smoke fewer cigarettes per day and begin smoking at an older age than do white men *(49)*. The racial difference that we observed among lifelong nonsmokers implicates more factors besides cigarette smoking. Contributing factors could include unequal access to treatment for early-stage lung cancer, differences in diet and/or exposure to environmental carcinogens, differences in the prevalence of tuberculosis *(56,57)*, and potential differences in biologic susceptibility.

Contrary to reports based on indirect evidence *(58,59)* or comparisons that include smokers *(60)*, we find little evidence that lung cancer rates have increased over the last 40 years in nonsmokers. The age-specific death rates among never-smoking women increased statistically significantly from CPS-I to CPS-II only for those aged 70–84 years, ages at which death certificate information is least accurate *(39)* and would be most affected by diagnostic improvements from CPS-I to CPS-II. Among men, we observed no difference in the age-standardized lung cancer death rate from CPS-I to CPS-II, and the age-specific death rate decreased rather than increased for those aged 50–69 years. Temporal changes in exposures such as ambient air pollution and domestic exposure to radon gas *(61)* would be expected to affect men and women equally, although the decrease in occupational exposures to lung carcinogens would affect men more than women. Historically, the exposure of women to environmental tobacco smoke *(62,63)* increased as more women moved into the workforce outside the home. Indoor air pollution from cooking with unventilated stoves is an important cause of lung cancer among never-smoking women in some countries such as China *(64)*, but not in the United States.

Limitations of our study are that we cannot determine whether the higher death rates among men than women and African Americans than whites reflect differences in disease incidence, survival, or diagnostic error. Age-specific rates are based on small numbers of lung cancer deaths at younger ages (younger than 45 years) in whites and at all ages in African Americans; stable estimates could not be made for other racial or ethnic groups and data on them were therefore not included.

Strengths of our study are its size, prospective design, long-term follow-up, and ability to adjust the hazard ratio estimates in CPS-II for many factors known to influence lung cancer risk. Extending the follow-up of CPS-II more than triples the number of lung cancer deaths observed among never smokers compared with previous reports *(15,16,22)* and provides the first detailed information on African Americans who have never smoked.

In summary, our findings provide reassuring evidence against the hypotheses that lung cancer risk is higher among women than men who have never smoked and that risk may be increasing over time because of factors other than tobacco smoking. However, our findings suggest that never-smoking African American women, and possibly African American men, may have higher lung cancer mortality than never-smoking whites. Whether this conclusion represents a real difference in disease incidence or the combination of poorer survival and greater diagnostic error (particularly false positives) in African Americans than whites should be examined in future studies.

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Notes

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