Smoking vs Other Risk Factors as the Cause of Smoking-Attributable Deaths

Confounding in the Courtroom

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Context The surgeon general estimates that more than 400 000 deaths are attributable to smoking annually in the United States. The tobacco industry has criticized the surgeon general's estimates because they do not control for the lower educational and socioeconomic status of modern-day smokers.

Objective To determine whether controlling for education, occupation, race, alcohol consumption, and various dietary factors, in addition to age and sex, substantially alters the relative and attributable risk estimates associated with tobacco smoking.

Design, Setting, and Participants Nationwide American Cancer Society prospective cohort study of 974 150 US adults aged 30 years or older, enrolled in 1982 and followed up through 1988. (The same study is used for the surgeon general and Centers for Disease Control and Prevention [CDC] estimates of smoking-attributable deaths in the United States.)

Main Outcome Measures Death from each of the chronic diseases considered in the CDC's estimate of smoking-attributable mortality (cancers of the lung, oropharynx, larynx, esophagus, pancreas, kidney, bladder, and cervix; ischemic heart disease, arterial disease, and other heart conditions; stroke; chronic obstructive pulmonary disease; and other respiratory conditions). Estimates adjusted for multiple covariates were compared with those adjusted for age only among current and former vs never smokers.

Results Adjusting for multiple covariates slightly decreased the relative and attributable risk estimates for current smoking in both men and women, but slightly increased the estimates for former smoking in women. Multivariate adjustment decreased the overall estimate of deaths attributable to smoking in the United States by approximately 1%, from 401 109 to 396 741 per year.

Conclusions Our study suggests that federal estimates of deaths caused by smoking are not substantially altered by adjustment for behavioral and demographic factors associated with smoking beyond the current adjustment for age and sex.

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THE US SURGEON GENERAL attributes to cigarette smoking approximately 400 000 deaths annually, approximately one fifth of all deaths that occur in the United States.[1] Tobacco industry defendants criticize these estimates,[2,3] arguing that the Centers for Disease Control and Prevention's (CDC's) method of estimating "smoking-attributable" deaths[4,5] adjusts for age and sex, but fails to consider the lower socioeconomic and educational status and associated dietary, occupational, and other risk factors of modern smokers,[6-13] thereby exaggerating the burden of mortality attributed to smoking.

We examined the impact of adjusting the relative and attributable risk estimates associated with smoking for other demographic and behavioral correlates of smoking aside from age and sex. We first assessed the effect of multivariate adjustment on relative risk (RR) estimates associated with current and former smoking in a large prospective American Cancer Society study begun in 1982,[14-16] the same cohort that provides the RR estimates used by the CDC to calculate deaths attributable to smoking in the United States.[4,5,17] We then used the CDC computer program Smoking-Attributable Mortality, Morbidity, and Economic Costs 3.0 (SAMMEC 3.0)[4] to measure the extent to which smoking-attributable deaths may be overestimated or underestimated because of factors associated with smoking.

Our analyses also illustrate the concept of confounding, a term derived from the Latin verb *confundere*, "to mix together." Epidemiologists use the technical term *confounding* to signify a distortion of the apparent association between a factor and disease risk, brought about by the former being associated with other factors that influence (cause or prevent) the condition being studied.[18] More general definitions of confounding include "To mix up or confuse—to confound one's enemy, to confound truth and lies."[19] The 2 meanings may coexist in legal and public relations battles regarding tobacco.[20]

METHODS

Study Population

The Cancer Prevention Study II (CPS-II) is a nationwide prospective mortality study of nearly 1.2 million US adults, aged 30 years or older, that began in 1982.[14-16] Enrollees were asked by an American Cancer Society volunteer to complete a confidential, 4-page mailed questionnaire on tobacco and alcohol use, diet, and other factors potentially

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affecting mortality. The present analyses include 974 150 people (370 037 men and 604 113 women) who at enrollment reported either never smoking or currently or formerly smoking cigarettes only. We restricted analyses to persons who provided complete information on smoking and excluded men who had ever smoked pipes or cigars (TABLE 1). The mean age at the time of enrollment was 57 years. Study participants are more likely than the general US population to be college-educated, married, middle-class, and white (TABLE 2).[16]

Vital Status Follow-up. Deaths were ascertained from the month of enrollment through August 1988 via personal inquiries by the volunteers in September 1984, 1986, and 1988. During these 6 years, 8.6% of the men and 4.7% of the women participants died, and 1.8% and 2.3%, respectively, were lost to follow-up (Table 1). Death certificates were successfully obtained for 97.3% of deceased persons; from these the underlying cause of death was coded according to an abbreviated version of the *International Classification of Diseases, Ninth Revision* (*ICD-9*).[21] We based our analyses on 6 rather than 4 years of follow-up (as used by the CDC)[4,5,22] to maximize the number of deaths available for analysis, especially in lifelong nonsmokers, while minimizing misclassification of exposure due to active smokers quitting smoking during more prolonged follow-up.

End Points. Our analyses considered deaths in which the underlying cause was coded to any of the chronic diseases included in the CDC estimates of smoking-attributable mortality.[4,5] Deaths due to cancer included malignancies of the trachea, bronchus, or lung (n=4847), cancers of the lip, oral cavity, or pharynx (n=289), esophagus (n=290), pancreas (n=1107), larynx (n=91), uterine cervix (n=82), urinary bladder (n=375), and kidney and other urinary tract (n=484). Because of the small number of cancers of the oropharynx, larynx, and esophagus among lifelong nonsmokers, we combined these sites into upper aerodigestive tract malignancies (n=670) (Table 1). Circulatory disease deaths included ischemic heart disease (n=14 685), arterial disease (n=1223), other heart conditions (n=5514), and cerebrovascular diseases (n=3539). Respiratory deaths included chronic obstructive pulmonary disease (COPD) (n=1884) and other respiratory diseases (n=1146). We did not consider deaths from smoking-related pediatric diseases, burns, or environmental tobacco smoke. To parallel the RR estimates used in the CDC SAMMEC 3.0 software[4] we included persons who reported prevalent cancer at the time of enrollment.

Classification of Smoking Behavior. The information on smoking provided in 1982 was used to categorize respondents into: (1) current cigarette smokers who reported smoking cigarettes at least once a day for 1 year or more and had never smoked other tobacco products; (2) former cigarette smokers who met the above criteria but who reported having stopped smoking

Table 1. Selected Characteristics of the Cancer Prevention Study II at Baseline and End of Study*

	No. (%)	
	Men	Women
Vital status at end of study		
Total persons	508 576	676 526
Alive	455 546 (89.6)	629 145 (93.0)
Dead	43 730 (8.6)	32 084 (4.7)
Lost to follow-up	9300 (1.8)	15 297 (2.3)
Excluded from analytic cohort		
Incomplete/unclassifiable smoking data	36 939 (7.3)	72 413 (10.7)
Men who ever smoked pipes or cigars†	101 600 (20.0)	NA
Total excluded	138 539 (27.3)	72 413 (10.7)
Baseline smoking status of analytic cohort‡		
Total persons	370 037	604 113
Current cigarette smoker	101 887 (20.0)	126 794 (18.7)
Former cigarette smokers	140 988 (27.7)	121 802 (18.0)
Lifelong nonsmoker	127 162 (25.0)	355 517 (52.6)
Vital status of analytic cohort		
Alive	331 103 (89.5)	566 926 (93.8)
Dead	30 069 (8.1)	27 157 (4.5)
Lost to follow-up	8865 (2.4)	10 030 (1.7)
Total deaths in analysis (*ICD-9* code[s])		
Malignant neoplasms		
Upper aerodigestive tract (140-149, 150, 161)§	455 (1.5)	215 (0.8)
Trachea, bronchus, lung (162)	3136 (10.4)	1711 (6.3)
Pancreas (157)	520 (1.7)	587 (2.1)
Cervix uteri (180)		82 (0.3)
Urinary bladder (188)	267 (0.9)	108 (0.4)
Kidney, other urinary (189)	276 (0.9)	208 (0.8)
Cardiovascular conditions		
Ischemic heart disease (410-414)	8947 (29.8)	5738 (21.1)
Other heart conditions (390-398, 401-405, 415-417, 420-429)‖	2835 (9.4)	2679 (9.9)
Stroke (430-438)	1528 (5.1)	2011 (7.4)
Arterial disease (440-448)	727 (2.4)	496 (1.8)
Respiratory conditions		
COPD (490-492, 496)	1200 (4.0)	684 (2.5)
Other respiratory (010-012, 480-487, 493)	599 (2.0)	547 (2.0)

*The baseline questionnaire was administered in fall 1982; 6-year follow-up ended on August 31, 1988. See the "Methods" section for details. NA indicates not applicable; *ICD-9*, *International Classification of Diseases, Ninth Revision*; and COPD, chronic obstructive pulmonary disease.
†Women were not questioned about pipe or cigar smoking.
‡Smoking status percentages based on overall cohort before exclusions.
§Cancers of the oropharynx, esophagus, and larynx combined.
‖Rheumatic fever, hypertension, pulmonary circulation disease, and other forms of heart disease combined.

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before 1982; and (3) lifelong nonsmokers who reported never having smoked any tobacco product.[14] No further information on smoking was collected for the overall cohort after 1982. Although the vital status of participants continues to be followed, we based the present analyses on the first 6 years of follow-up to minimize misclassification of current smokers who may have quit during follow-up. A repeat survey of 185 000 CPS-II participants in 1992-1993 found that approximately half of those who smoked when enrolled in 1982 reported no longer smoking 10 years later (data not shown).

Statistical Methods

Estimation of Relative Risk. Cox proportional hazards methods[23] were used to estimate the hazard ratio (HR) (corresponding to the RR) and 95% confidence intervals associated with current or former smoking in men and women separately, first adjusting only for age, and later for multiple other covariates. All multivariate models adjusted for age at enrollment within 1 year, race (white vs nonwhite), education (3 levels), marital status, "blue collar" employment in most recent or current job, and total weekly consumption of vegetables and citrus fruit.[23] For cardiovascular end points, statistical models also adjusted for any current aspirin use or alcohol consumption, body mass index (calculated as weight in kilograms divided by the square of height in meters), physical activity in work or play (4 levels), and weekly consumption of fatty foods.[24] For lung cancer and COPD the analyses controlled for a history of occupational asbestos exposure. Analyses of uterine cervical cancer controlled for age at menarche (4 levels), number of live births (5 levels), oral contraceptive use (yes/no), and menopausal status (6 levels). People with missing data on 5 factors were assigned to the most commonly reported category; thus, an additional 1.3% were classified as high school graduates, 1.5% as moderate exercisers, 0.4% as white, 0.5% as married, and 2.0% of men and 3.7% of women as unemployed. Persons reporting eating 3 or fewer servings of vegetables per week due to incomplete answers were classified as missing data on vegetable consumption. The imputation of missing covariates had negligible effect on the RR estimates.

We assessed the validity of the proportional hazards assumption by graphing Kaplan-Meier curves[25] and by testing the statistical significance of an interaction term between smoking and year of follow-up. $P<.05$ was considered statistically significant.

Table 2. Characteristics of Persons in 1982 Reporting Never, Current, or Former Smoking

	Men			Women		
	Never (n = 127 162)	Current (n = 101 887)	Former (n = 140 988)	Never (n = 355 517)	Current (n = 126 794)	Former (n = 121 802)
Demographic Characteristics						
Age, mean (SD), y	57.0 (11.0)	54.8 (9.4)	58.3 (9.5)	57.7 (11.5)	53.7 (9.8)	55.2 (10.1)
White race, %	94.0	92.9	96.2	93.3	93.0	95.8
Education, %						
≤High school	32.1	43.2	36.9	47.5	45.5	34.3
Some college/vocational	23.3	29.9	28.9	28.1	32.9	33.8
≥College	44.6	26.9	34.2	24.4	21.5	32.0
Married, %	93.5	92.5	95.8	76.0	73.9	80.0
Employed, age-adjusted %	75.2	69.7	71.3	45.1	46.1	45.0
Blue collar work, age-adjusted %	26.1	30.7	26.2	9.3	9.5	7.0
Dietary Characteristics*						
Vegetable intake, %						
Lowest quintile	17.6	29.1	18.4	20.3	27.4	14.7
Highest quintile	23.3	13.8	22.4	20.2	16.0	26.6
Fat intake, %						
Lowest quintile	20.4	18.6	20.7	20.5	21.1	17.4
Highest quintile	18.9	23.6	18.4	20.4	19.5	19.4
Current alcohol drinker, %	39.1	59.1	56.1	26.0	48.8	51.0
Vitamin use in last month, %						
A	8.6	6.4	7.7	9.1	8.0	10.4
C	24.8	18.9	23.1	26.4	25.3	31.0
E	16.8	13.3	17.8	19.5	17.9	22.8
Aspirin, any current use, %	55.2	55.4	56.3	59.8	59.1	63.0
Other Characteristics						
Physical activity, none or slight, %	21.7	27.9	24.1	25.2	28.4	28.3
Body mass index, mean (SD), kg/m^2	25.9 (3.4)	25.4 (3.5)	26.1 (3.4)	25.0 (4.6)	23.7 (4.2)	24.6 (4.5)
Asbestos exposure, %	5.2	7.7	7.1	1.5	1.6	1.9

*Quintiles of vegetable and citrus fruit intake and an index of total fat intake were determined in men and women separately, based on the overall cohort.[24]

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Estimation of Attributable Risk. Deaths attributable to smoking were estimated using the SAMMEC 3.0 software, which uses RR (or HR) estimates from CPS-II to calculate the attributable fraction of deaths due to smoking among current and former smokers for 19 disease categories.[4,5] These are combined with population-based prevalence data on current, former, and never smoking in the United States in 1990,[4,26] and with the total number of deaths in each of the 19 smoking-related disease categories.[27] We assessed the potential impact of confounding on deaths attributed to smoking by entering first the age-adjusted and then the fully adjusted RR estimates from CPS-II.

RESULTS

Men and women who currently smoked cigarettes when enrolled in CPS-II were on average 3 to 4 years younger than lifelong nonsmokers, somewhat less educated, and apt to report lower consumption of vegetables but more regular alcohol consumption (Table 2). The demographic differences between current and never smokers were small. Male current smokers were slightly less likely to be currently employed, more likely to have held a blue collar job and to report ever being exposed to asbestos, more likely to consume a diet higher in fat, not to take vitamin supplements, and to be less active (Table 2). Some of these associations were reversed among female former smokers. Women who had stopped smoking were more educated than the never smokers and more likely to be married and to consume vegetables, alcoholic beverages, and vitamin supplements (Table 2).

Adjusting for the small demographic and behavioral differences between smokers and lifelong nonsmokers produced only minor changes in the HR estimates associated with smoking (TABLE 3). Adjustment caused the HR estimates associated with ischemic heart disease and lung cancer (which together constitute approximately half of smoking-attributable deaths in the United States)[5] to decrease by 9% and 5%, respectively, in male current smokers, and by 5% and 0% in female current smokers. Multivariate adjustment had the opposite effect in formerly smoking women, increasing the HR estimates between smoking and ischemic heart disease, COPD, and cancers of the lung, upper aerodigestive tract, bladder, and cervix (Table 3). Adjustment for the alcohol consumption of smokers also increased the HR between smoking and cardiovascular deaths,[28] partially offsetting the impact of the lower educational status, less frequent vegetable consumption, and physical inactivity of smokers. The proportional hazards assumption was not violated in any of these statistical models.

TABLE 4 illustrates the change in the number of deaths attributed to smoking when fully adjusted rather than age-adjusted HR estimates from CPS-II are used. The total estimate of smoking-attributable disease deaths among US adults decreases from 401 109 to 396 741, approximately 1%. The net change is correspondingly small in the 3 subcategories of neoplastic, cardiovascular, and respiratory diseases. Reasons for the negligible change in smoking-attributable mortality when adjusted for multiple correlates of smoking are discussed below.

We also compared the age- and sex-adjusted estimates of smoking-attributable deaths when calculated based on the CPS-II HR estimates from 4 rather than 6 years of follow-up. The estimated total deaths attributable to smoking in adults, again excluding pediatric diseases, deaths from burns, and environmental tobacco smoke, was 421 711 based on the 4-year follow-up and 401 109 based on 6-year follow-up. Most of this 4.9% decline was attributable to lower risk of cardiovascular death among former smokers over the 6-year follow-up.

COMMENT

Our principal finding is that after adjusting for age, further adjustment for behavioral and socioeconomic differences between smokers and nonsmokers minimally affects the RR estimates associated with smoking and has even less impact on the estimates of smoking-attributable deaths. These findings are important because they are based on the same large prospective study[14-16] and attributable risk calculation methods[4] that the CDC uses to estimate deaths due to smoking in the United States.[1,5,17,22] Our results suggest that the current federal estimates of smoking-attributable mortality[5,22] are not seriously biased by other demographic or behavioral factors associated with smoking, after controlling for age.

Most previous large prospective studies of smoking conducted between 1950 and 1980 predated the development of computers and statistical software programs that could adjust simultaneously for multiple covariates in very large data sets.[29-33] Only 4 such studies in the United States have, to our knowledge, reported both multivariate- and age-adjusted RR estimates associated with active smoking.[34-37] In none of these did adjustment for factors other than age and sex substantially alter the RR estimates. Our analyses go further by demonstrating that the small changes in the RR after multivariate adjustment result in even smaller changes in smoking-attributable deaths. Our findings complement those of Malarcher et al,[37] who reported that the smoking-attributable fraction underlying the CDC estimates was robust compared with alternative approaches for estimating RR.[38]

Several considerations explain why adjusting for socioeconomic and behavioral factors that have become associated with contemporary smoking only minimally changes the estimates of RR and smoking-attributable deaths. First, the smokers and lifelong nonsmokers are more similar with respect to socioeconomic and educational status in our study than in the contemporary United States. In fact, the cohort is more homogeneous than is the overall US population, reflecting the demographic characteristics of American Cancer Society volunteers at the time. Many CPS-II smokers began

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Table 3. Estimated Hazard Ratios in Current and Former Smokers for Death Due to Selected Smoking-Related Diseases*

	Hazard Ratio (95% Confidence Interval)			
	Men		Women	
Disease Category	Current	Former	Current	Former
Malignant neoplasms				
Upper aerodigestive tract	(n = 228)	(n = 189)	(n = 101)	(n = 47)
Age only	9.3 (6.5-13.1)	4.3 (3.0-6.1)	6.8 (4.9-9.4)	2.8 (1.9-4.1)
Full model	8.1 (5.7-11.7)	4.4 (3.1-6.3)	6.0 (4.3-8.5)	3.0 (2.0-4.5)
Trachea, bronchus, lung	(n = 1781)	(n = 1231)	(n = 1014)	(n = 387)
Age only	23.6 (19.6-28.3)	8.7 (7.2-10.4)	12.8 (11.2-14.6)	4.6 (3.9-5.4)
Full model	21.3 (17.7-25.6)	8.3 (6.9-10.0)	12.5 (10.9-14.3)	4.8 (4.1-5.6)
Pancreas	(n = 193)	(n = 188)	(n = 163)	(n = 126)
Age only	2.4 (1.9-3.0)	1.2 (0.9-1.5)	2.3 (1.9-2.8)	1.6 (1.3-1.9)
Full model	2.2 (1.7-2.8)	1.2 (1.0-1.5)	2.2 (1.8-2.8)	1.6 (1.3-1.9)
Cervix uteri			(n = 24)	(n = 15)
Age only			1.7 (1.0-2.8)	1.1 (0.6-2.0)
Full model			1.5 (0.9-2.6)	1.4 (0.8-2.6)
Urinary bladder	(n = 93)	(n = 120)	(n = 24)	(n = 23)
Age only	3.3 (2.3-4.7)	2.1 (1.5-2.9)	2.5 (1.5-4.1)	1.9 (1.2-3.1)
Full model	3.0 (2.1-4.3)	2.0 (1.4-2.8)	2.4 (1.5-4.1)	2.0 (1.2-3.3)
Kidney, other urinary	(n = 100)	(n = 117)	(n = 44)	(n = 37)
Age only	2.5 (1.8-3.5)	1.7 (1.3-2.4)	1.4 (1.0-1.9)	1.0 (0.7-1.5)
Full model	2.5 (1.8-3.6)	1.8 (1.3-2.4)	1.5 (1.0-2.1)	1.2 (0.8-1.7)
Cardiovascular conditions				
Ischemic heart disease				
All ages	(n = 2772)	(n = 3689)	(n = 1161)	(n = 860)
Age only	2.0 (1.9-2.1)	1.3 (1.3-1.4)	2.1 (1.9-2.2)	1.3 (1.2-1.4)
Full model	1.9 (1.8-2.1)	1.3 (1.2-1.4)	2.1 (2.0-2.3)	1.4 (1.3-1.5)
35-64 y	(n = 1668)	(n = 1493)	(n = 560)	(n = 227)
Age only	2.6 (2.4-2.9)	1.6 (1.5-1.7)	2.9 (2.6-3.3)	1.2 (1.0-1.4)
Full model	2.6 (2.4-2.9)	1.6 (1.4-1.7)	3.2 (2.8-3.6)	1.4 (1.2-1.7)
≥65 y	(n = 1050)	(n = 2195)	(n = 600)	(n = 633)
Age only	1.6 (1.4-1.7)	1.2 (1.1-1.3)	1.7 (1.6-1.9)	1.3 (1.2-1.4)
Full model	1.5 (1.3-1.6)	1.2 (1.1-1.2)	1.7 (1.6-1.9)	1.4 (1.3-1.5)
Other heart disease, all ages	(n = 527)	(n = 694)	(n = 489)	(n = 399)
Age only	2.0 (1.8-2.2)	1.2 (1.1-1.4)	1.7 (1.5-1.9)	1.2 (1.0-1.3)
Full model	1.8 (1.6-2.0)	1.2 (1.1-1.3)	1.7 (1.5-1.9)	1.3 (1.2-1.4)
Stroke				
All ages	(n = 476)	(n = 551)	(n = 423)	(n = 257)
Age only	2.1 (1.9-2.4)	1.1 (1.0-1.2)	2.3 (2.0-2.6)	1.2 (1.0-1.3)
Full model	1.7 (1.5-2.0)	1.1 (0.9-1.2)	2.2 (2.0-2.5)	1.3 (1.1-1.5)
35-64 y	(n = 231)	(n = 128)	(n = 224)	(n = 72)
Age only	2.9 (2.3-3.7)	1.1 (0.8-1.4)	3.9 (3.2-4.8)	1.3 (1.0-1.7)
Full model	2.4 (1.8-3.0)	1.0 (0.8-1.4)	3.8 (3.1-4.7)	1.5 (1.1-2.0)
≥65 y	(n = 244)	(n = 423)	(n = 198)	(n = 185)
Age only	1.8 (1.6-2.2)	1.1 (1.0-1.3)	1.7 (1.5-2.0)	1.1 (1.0-1.3)
Full model	1.5 (1.2-1.8)	1.0 (0.9-1.2)	1.6 (1.4-1.9)	1.2 (1.0-1.4)
Arterial disease	(n = 279)	(n = 302)	(n = 149)	(n = 61)
Age only	4.1 (3.3-5.1)	2.0 (1.6-2.4)	3.9 (3.1-4.8)	1.3 (1.0-1.7)
Full model	3.9 (3.1-4.9)	1.9 (1.5-2.3)	3.8 (3.1-4.8)	1.4 (1.0-1.8)
Respiratory conditions				
Chronic obstructive pulmonary disease	(n = 422)	(n = 700)	(n = 303)	(n = 238)
Age only	12.2 (9.5-15.7)	8.4 (6.7-10.6)	12.8 (10.3-15.8)	8.0 (6.4-9.9)
Full model	10.8 (8.4-13.9)	7.8 (6.1-9.8)	12.3 (9.9-15.2)	8.9 (7.1-11.1)
Other respiratory diseases	(n = 63)	(n = 116)	(n = 109)	(n = 71)
Age only	2.0 (1.6-2.6)	1.5 (1.2-1.8)	2.2 (1.8-2.8)	1.2 (0.9-1.5)
Full model	1.9 (1.5-2.4)	1.4 (1.2-1.7)	2.2 (1.7-2.8)	1.2 (0.9-1.5)

*Hazard ratio from Cox regression corresponds to relative risk. Never smokers are the comparison group (hazard ratio = 1.0 for all comparisons). Numbers in parentheses (n =) under "Current" and "Former" indicate the number of deaths.

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Table 4. Deaths Attributable to Smoking-Related Diseases in Adults*

	Estimated Deaths, No.					
	Men		Women		Total	
Disease Category	Age-Adjusted	Full Model	Age-Adjusted	Full Model	Age-Adjusted	Full Model
Malignant neoplasms						
Upper aerodigestive tract†	12 104	11 928	3338	3259	15 442	15 187
Trachea, bronchus, lung	81 074	80 336	36 159	36 176	117 233	116 512
Pancreas	3287	3035	3121	3018	6408	6053
Cervix uteri			577	677	577	677
Urinary bladder	3398	3202	983	1000	4381	4202
Kidney, other urinary	2434	2541	223	426	2657	2967
Total Neoplastic Deaths	**102 297**	**101 042**	**44 401**	**44 556**	**146 698**	**145 598**
Cardiovascular conditions						
Ischemic heart disease						
Age 35-64 y	24 219	24 219	7043	8039	31 262	32 258
Age ≥65 y	32 101	30 101	28 165	31 875	60 266	61 976
Other heart diseases	24 448	21 939	15 225	17 446	39 673	39 385
Stroke						
Age 35-64 y	3580	2826	3564	3615	7144	6441
Age ≥65 y	6874	3187	7393	8140	14 267	11 327
Arterial disease	10 891	10 434	6300	6414	17 191	16 848
Total Cardiovascular Deaths	**102 113**	**92 706**	**67 690**	**75 529**	**169 803**	**168 235**
Respiratory conditions						
Chronic obstructive pulmonary disease‡	40 161	39 544	25 556	25 834	65 717	65 378
Other respiratory diseases§	11 530	10 169	7361	7361	18 891	17 530
Total Respiratory Deaths	**51 691**	**49 713**	**32 917**	**33 195**	**84 608**	**82 908**
Deaths From All Causes	**256 101**	**243 461**	**145 008**	**153 280**	**401 109**	**396 741**

*Based on age-adjusted and fully adjusted Cox estimates from Cancer Prevention Study II and US smoking prevalence and mortality, 1990.
†Includes lip, oral cavity, pharynx, larynx, and esophagus.
‡Includes bronchitis, emphysema, and chronic airway obstruction.
§Includes pneumonia, tuberculosis, asthma, and influenza.

tobacco use around World War II, and much of their smoking preceded the era when cigarette smoking became a behavior of the disenfranchised. The socioeconomic homogeneity of the cohort strengthens, rather than weakens, our ability to control for certain extraneous factors that might affect the survival of smokers.

Second, not all of the behaviors with which smoking was associated in our study were detrimentally associated with survival. CPS-II smokers did report less physical activity and lower dietary consumption of vegetables and fruit, both of which were associated with higher cardiovascular death rates in our study. However, smokers also reported more regular consumption of alcohol, which was associated with lower cardiovascular mortality.[28] Adjusting for all of these factors in combination produces a smaller net change in the RR estimates for cardiovascular mortality in CPS-II than would be expected if only selected factors were considered separately.

Third, the effect of multivariate adjustment among former smokers, especially in women who have stopped smoking, is to decrease the estimate of smoking-attributable deaths, partly offsetting the increase in the estimate that occurs among male current smokers. The higher educational status and healthy behavior of women who have quit smoking contrast sharply with the characteristics of male current smokers. It also can be argued that some of the factors that we controlled for in these analyses should not have been because they represent adverse effects of smoking and/or intermediates in the causal pathway. For example, both physical inactivity and low body mass index can be caused by smoking or smoking-related diseases. Controlling for these may cause attributable risk calculations to underestimate the true burden of disease caused by smoking.

CONCLUSIONS

Adjusting for the lower educational and socioeconomic characteristics of modern-day smokers had little impact on the relative or attributable risks associated with smoking. The absence of evidence of epidemiologic confounding may help resolve at least one aspect of the ongoing tobacco debate.

REFERENCES

1. *Reducing the Health Consequences of Smoking: 25 Years of Progress: A Report of the Surgeon General*. Washington, DC: Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1989.
2. Levy R, Marimont R. Lies, damned lies, & 400,000 smoking-related deaths. *Regulation*. 1998;21:24-29.
3. Sterling TD, Rosenbaum WL, Weinkam JJ. Risk attribution and tobacco-related deaths. *Am J Epidemiol*. 1993;138:128-139.
4. *Smoking-Attributable Mortality, Morbidity, and Economic Costs* [SAMMEC] version 3.0 [computer software and documentation]. Atlanta, Ga: Centers for Disease Control and Prevention; 1996.

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5. Cigarette smoking-attributable mortality and years of potential life lost—United States, 1990. *MMWR Morb Mortal Wkly Rep*. 1993;42:645-649.
6. Subar AF, Harlan LC. Nutrient and food group intake by tobacco use status: the 1987 National Health Interview Survey. *Ann N Y Acad Sci*. 1993;686:310-321.
7. Subar AF, Harlan LC, Mattson ME. Food and nutrient intake differences between smokers and nonsmokers in the US. *Am J Public Health*. 1990;80:1323-1329.
8. Zondervan KT, Ocke MC, Smit HA, Seidell JC. Do dietary and supplementary intakes of antioxidants differ with smoking status? *Int J Epidemiol*. 1996;25:70-79.
9. Midgette AS, Baron JA, Rohan TE. Do cigarette smokers have diets that increase their risks of coronary heart disease and cancer? *Am J Epidemiol*. 1993;137:521-529.
10. Cade JE, Margetts BM. Relationship between diet and smoking: is the diet of smokers different? *J Epidemiol Community Health*. 1991;45:270-272.
11. Escobedo LG, Anda RF, Smith PF, Remington PL, Mast EE. Sociodemographic characteristics of cigarette smoking initiation in the United States: implications for smoking prevention policy. *JAMA*. 1990;264:1550-1555.
12. Zhu BP, Giovino GA, Mowery PD, Eriksen MP. The relationship between cigarette smoking and education revisited: implications for categorizing persons' educational status [published erratum appears in *Am J Public Health*. 1997;87:168]. *Am J Public Health*. 1996;86:1582-1589.
13. Wagenknecht LE, Perkins LL, Cutter GR, et al. Cigarette smoking behavior is strongly related to educational status: the CARDIA study. *Prev Med*. 1990;19:158-169.
14. Thun M, Day-Lally C, Myers D, et al. Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959 through 1965) and II (1982 through 1988). In: Shopland D, Burns D, Garfinkel L, Samet J, eds. *Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control: Smoking and Tobacco Control*. Bethesda, Md: National Institutes of Health; 1997:305-382. Monograph 8. NIH publication 97-4213.
15. Thun MJ, Day-Lally CA, Calle EE, Flanders WD, Heath CW Jr. Excess mortality among cigarette smokers: changes in a 20-year interval. *Am J Public Health*. 1995;85:1223-1230.
16. Garfinkel L. Selection, follow-up, and analysis in the American Cancer Society prospective studies. In: *Selection, Follow-up, and Analysis in Prospective Studies: A Workshop*. Washington, DC: Government Printing Office; 1985:49-52. National Cancer Institute monograph 67. NIH publication 85-2713.
17. Smoking-attributable mortality and years of potential life lost—United States, 1984. *MMWR Morb Mortal Wkly Rep*. 1997;46:444-451.
18. Last JM. *A Dictionary of Epidemiology*. 2nd ed. Oxford, England: Oxford University Press; 1988.
19. *Webster's II New College Dictionary*. Boston, Mass: Houghton Mifflin; 1995:237.
20. Cohen J. Tobacco money lights up a debate. *Science*. 1996;272:488-494.
21. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977.
22. *Smoking and Health in the Americas*. Atlanta, Ga: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1992. DHHS publication 92-8419.
23. Cox DR. Regression models and life-tables. *J R Stat Soc*. 1972;34:187-220.
24. Thun MJ, Calle EE, Namboodiri MM, et al. Risk factors for fatal colon cancer in a large prospective study. *J Natl Cancer Inst*. 1992;84:1491-1500.
25. Kleinbaum D. *Survival Analysis: A Self-Learning Text*. New York, NY: Springer-Verlag; 1996.
26. National Center for Health Statistics. *Health, United States, 1995*. Hyattsville, Md: Public Health Service; 1996.
27. Deaths from 282 selected causes by age, race, and sex: United States, 1990. In: *Vital Statistics of the United States, 1990—Vol 2: Mortality*. Part A. Washington, DC: Government Printing Office; 1994:312-371. DHHS publication 95-1101. Table 1-27.
28. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly US adults. *N Engl J Med*. 1997;337:1705-1714.
29. Doll R, Hill A. Lung cancer and other causes of death in relation to smoking. *BMJ*. 1956;2:1071-1081.
30. Hammond EC, Horn D. Smoking and death rates: report on forty-four months of follow-up of 187,783 men. *JAMA*. 1958;166:1159-1172, 1294-1308.
31. Hammond E. Smoking in relation to the death rates of one million men and women. In: Haenszel W, ed. *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Rockville, Md: US Dept of Health, Education, and Welfare; 1966:127-204. National Cancer Institute Monograph 19.
32. Doll R, Gray R, Haafner B, Peto R. Mortality in relation to smoking: 22 years' observations on female British doctors. *BMJ*. 1980;280:967-971.
33. Kahn H. The Dorn study of smoking and mortality among U.S. veterans: report on eight and one-half years of observation. In: Haenszel W, ed. *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. Rockville, Md: US Dept of Health, Education, and Welfare; 1966:1-125. National Cancer Institute Monograph 19.
34. Friedman GD, Dales LG, Ury HK. Mortality in middle-aged smokers and nonsmokers. *N Engl J Med*. 1979;300:213-217.
35. Kawachi I, Colditz G, Stampfer M, et al. Smoking cessation and decreased risks of total mortality, stroke and coronary heart disease incidence among women: a prospective cohort study. In: Shopland D, Burns D, Garfinkel L, Samet J, eds. *Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control: Smoking and Tobacco Control*. Bethesda, Md: National Institutes of Health, National Cancer Institute; 1997:531-564. Monograph 8. NIH publication 97-4213.
36. LaCroix AZ, Lang J, Scherr P, et al. Smoking and mortality among older men and women in three communities. *N Engl J Med*. 1991;324:1619-1625.
37. Malarcher AM, Schulman J, Epstein LA, et al. Methodologic issues in estimating smoking attributable mortality in the United States. *Am J Epidemiol*. In press.
38. Weinkam JJ, Rosenbaum WL, Sterling TD. Computation of relative risk based on simultaneous surveys: an alternative to cohort and case-control studies. *Am J Epidemiol*. 1992;136:722-729.

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