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Smoking and Lung Cancer in Women: Findings in a Prospective Study

Lawrence Garfinkel[1] and Steven D. Stellman[2]

Department of Epidemiology and Statistics, American Cancer Society, New York, New York 10036

ABSTRACT

Lung cancer rates in relation to smoking habits were studied in a cohort of 619,225 women traced over a 4-yr period (1982 to 1986). A total of 1,006 lung cancer deaths was recorded. The standardized mortality ratio (SMR) for women smokers was 12.7 for current smokers and 4.8 for exsmokers. For those women without a history of chronic diseases, the SMR rose to 17.6 for current smokers. The SMRs rose with the number of cigarettes smoked per day to 22.0 for women who smoked 31 or more per day. SMRs also increased with depth of inhalation; this increase was independent of the number smoked per day. SMRs also increased by duration of smoking and decreased with cessation of smoking. Mortality ratios for lung cancer in women ranged from about 2 to 1 to 3 to 1 in studies carried out in the 1950s and 1960s. As women have begun to smoke earlier in life, smoke more cigarettes a day, and inhale more deeply, we are now observing much higher SMRs in women with lung cancer, similar in magnitude to those seen in men in the earlier studies.

INTRODUCTION

Studies of lung cancer in the 1960s and 1970s among nonsmoking and smoking women found relative risk ratios much lower than in men. For example, the Surgeon General's Report on Women (1) showed relative risk ratios in 3 prospective studies ranging from 2.6 to 4.5. These included the American Cancer Society's 25-state study (2), the British physician study (3), and the Swedish study (4). Hirayama reported a relative risk of lung cancer in women in his prospective study of 3.67 for smokers of 1 to 19 cigarettes a day and 5.26 for smokers of 20+ cigarettes a day (5). The 1971 Surgeon General's report summarized the findings of 16 retrospective studies in women carried out in the 1950s and 1960s (6). The relative risk for smokers of developing lung cancer ranged from 0.2 to 6.8. Half of these studies had relative risks of 2 to 3. In Wynder and Stellman's large case control study for cases collected in the 1970s, the relative risk was 7.8 (7). In the study of Akiba *et al.* (8) of Japanese women, the odds ratio for lung cancer in female smokers was 2.4. Men, on the other hand, had risk ratios for lung cancer in the three prospective studies of 8.2, 10.1, and 14.0 (1). In 30 retrospective studies in men in the 1950s and 1960s, the relative risks of lung cancer ranged from 1.2 to 36.0. Ten of these studies had relative risks of 9 or greater (6).

The major reason for the difference in these risk ratios would appear to be in the many parameters which describe lifetime exposure. Women in those studies started smoking later in life, smoked fewer cigarettes per day, and inhaled less deeply than men. Smoking patterns of women have changed over time and women, particularly those over age 50, have much more exposure to tobacco products now than they did in the past. In 1980, Doll *et al.* stated that female smokers born after the first World War were more likely to have started smoking young and to describe themselves as inhalers. They predicted that, when these women progressed into their 60s and 70s, the absolute effects of smoking a given number of cigarettes on mortality may turn out to be about the same as those observed in men (9).

The data from the American Cancer Society's Cancer Prevention Study II have been used to test whether differences in lung cancer risk ratios for women smokers have increased in the 1980s.

SUBJECTS AND METHODS

The study has been described previously (10). In 1982, 77,000 volunteers enrolled 1.2 million men and women in a prospective study by asking them to complete a confidential 4-page questionnaire. In addition to smoking, the questionnaire included questions on dietary and drinking habits, occupational exposures, medicines and vitamins, menstrual and reproductive history, and many other questions. Enrollment of subjects took place in all 50 states, the District of Columbia, and Puerto Rico. Enrollment was in family groups, with at least one person above the age of 45 in each family. All family members 30 yr or older were asked to complete the questionnaire.

Every second year the volunteer researchers are given a list of the persons they enrolled and asked to check if they are alive or dead, and if dead, the data and place of death. Copies of death certificates are obtained from state health departments and are subsequently coded according to an abbreviated version of the International Classification of Diseases (ICD-9). Follow-up on cancer cases is made through cancer registries, physicians, or hospitals to verify the primary site of cancer reported on death certificates and histological diagnosis, if any.

Subjects in the study have now been traced through 2 follow-ups or 4 yr of experience. At the close of the second follow-up, 98.5% of the subjects had been traced, alive or dead. The results shown pertain to the 619,925 women successfully traced and for whom it was possible to classify smoking habits as never smoked regularly, current smoker, or exsmoker. Smoking habits in this paper always refer to those reported by subjects at the time of enrollment.

Relative risks of lung cancer are expressed as SMRs.[3] Lung cancer rates in nonsmokers in each 5-yr age group are applied to the person-years of each smoking group to obtain expected numbers of deaths. Expected deaths are summed over age groups. The SMR is the observed divided by the expected number of deaths.

RESULTS

During the first 4 yr of follow-up, there were 18,367 deaths reported among these 619,925 women or 3.0% of the total. This group accumulated 2,446,435 person-years, giving a crude death rate of 750.8×10^{-5}; after adjustment to the 1970 age distribution of United States White females, the rate was 887.0. Among the same cohort there were 1,006 lung cancer deaths reported, giving a crude rate of 41.1 per 100,000 population and an age-adjusted rate of 34.6. Lung cancer thus accounted for 5.5% of all deaths among women enrolled in CPS-II.

The distributions of age, person-years, and smoking habits are presented in Table 1. Nonsmokers make up an increasingly higher percentage of women at older ages, while the percentage of current smokers decreases with age. The proportion of exsmokers is relatively unvarying (21 to 24%) up to age 69. Two factors contribute to the decreasing prevalence of smoking

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[1] To whom requests for reprints should be addressed at American Cancer Society, 1180 Avenue of Americas, New York, NY 10036.

[2] Present address: Division of Biostatistics and Epidemiologic Research, New York City Department of Health, New York, NY 10013.

[3] The abbreviations used are: SMR, standard mortality ratio; CPS, Cancer Prevention Study; T/N, tar/nicotine.

Table 1 *Distribution of age, person years, and smoking habits in CPS-II female study population*

Age group	No. of women	Never smoked regularly (%)	Current smoker (%)	Former smoker (%)	Person-years
30–39	32,579	51.8	27.3	20.9	130,020
40–44	45,694	50.3	25.9	23.8	182,312
45–49	93,496	51.1	25.7	23.2	372,470
50–54	106,812	52.5	24.3	23.2	424,903
55–59	107,244	54.3	22.6	23.0	425,386
60–64	90,064	58.0	19.8	22.2	355,594
65–69	66,175	60.2	17.2	22.6	259,391
70–74	41,848	66.7	13.3	20.0	162,374
75–79	22,031	75.7	9.0	15.3	84,091
80–84	9,074	83.2	6.0	10.8	33,603
85+	4,908	90.2	3.4	6.4	16,291
Total	619,925				2,446,435

Table 2 *Expected and observed lung cancer deaths and SMRs according to smoking habit and history of chronic illness*

History of heart disease, stroke, or cancer	Never smoked regularly	Former smoker	Current smoker
Yes			
No. of women	52,104	22,757	17,562
O[a]	86	155	137
E	86.0	31.7	21.1
SMR	1.0	4.9	6.5
No			
No. of women	298,546	114,152	114,804
O	88	107	433
E	88.0	27.6	24.6
SMR	1.0	3.9	17.6
Total			
No. of women	350,650	136,909	132,366
O	174	262	570
E	174.0	54.6	45.0
SMR	1.0	4.8	12.7

[a] O, observed; E, expected (based upon age-specific rates in nonsmokers with the same history).

habit with advancing age: selective mortality among smokers and a secular trend toward greater likelihood of smoking in younger birth cohorts. The exsmoking rate is 4 times that of a comparable group of women in Cancer Prevention Study I who completed a questionnaire 23 yr before CPS-II started (10). Table 1 shows a higher percentage of exsmokers than current smokers at every age group after age 50 to 54.

Smoking History

The SMRs are presented in Table 2 according to smoking history and whether or not there was a history of chronic illness, defined as a history of heart disease, stroke, or cancer. The SMR among all subjects was 12.7 for current smokers and 4.8 for exsmokers. Among women who were initially healthy at the time of enrollment, the SMRs were 17.6 for current smokers and 3.9 for exsmokers. These findings are based upon over 100 observed deaths in each smoking stratum. The SMRs among current smokers with a history of chronic illness at enrollment are lower, because the baseline rate among nonsmokers in this group is relatively higher.

Cigarettes Smoked per Day

The SMRs for specific groupings of number of cigarettes smoked per day by current smokers are given in Table 3, for women without history of chronic disease, and for all women. Whether or not history of illness is considered, a powerful dose-response effect is evident. Even women who smoke half a pack a day or less have a risk 5.5 to 7.5 times that of nonsmokers.

Table 3 *Expected and observed lung cancer deaths and SMRs according to number of cigarettes smoked per day by current smokers and by history of chronic illness*

History of heart disease, stroke, or cancer	Never smoked regularly	No. of cigarettes/day, current smokers				
		1–10	11–19	20	21–30	31+
No history						
O[a]	88	51	48	159	81	65
E	88.0	6.8	3.1	7.9	3.0	2.3
SMR	1.0	7.5	15.6	20.3	27.4	28.7
All women						
O	174	69	63	203	106	89
E	174.0	12.5	5.6	14.3	5.2	4.0
SMR	1.0	5.5	11.2	14.2	20.4	22.0

[a] O, observed; E, expected (based upon age-specific rates in nonsmokers with the same history).

Table 4 *Observed and expected lung cancer deaths and SMRs among women with no history of chronic illness, according to depth of inhalation*

	Never smoked regularly	Current smokers, inhalation			
		Do not inhale	Slight	Moderate	Deep
O[a]	88	25	72	252	84
E	88.0	3.6	4.7	13.7	2.6
SMR	1.0	6.9	15.2	18.5	31.9

[a] O, observed; E, expected (based on age-specific rates in nonsmokers).

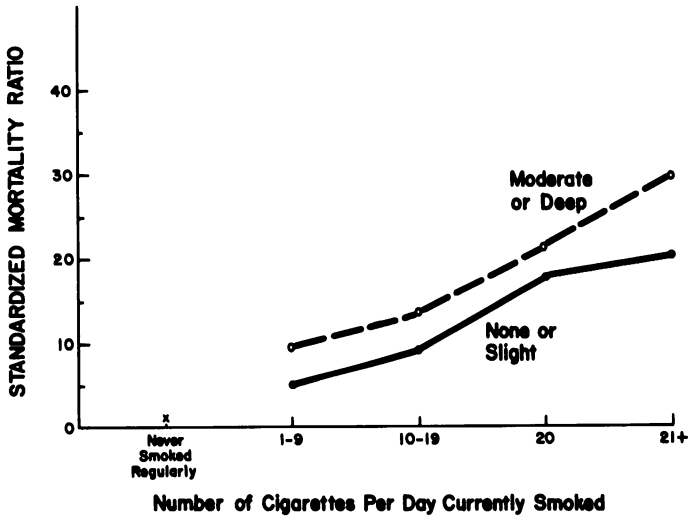

Fig. 1. Lung cancer mortality ratios in women by depth of inhalation and number of cigarettes smoked per day.

Furthermore lung cancer death rates in pack-and-a-half per day smokers rose 22-fold among all women and nearly 30-fold among women with no previous history of chronic illness (based on 65 deaths in that category).

Inhalation

The SMRs for current smokers rose with the stated level of inhalation (none, slight, moderate, deep), as shown in Table 4 for women with no history. Inhalation is a fairly subjective measure and has not consistently been found to be related to lung cancer death rates in other studies. In our population, depth of inhalation is strongly correlated with number of cigarettes smoked per day, so that it is conceivable that inhalation might merely be a proxy for quantity. Therefore, the SMR for lung cancer is shown in Fig. 1 according to both inhalation and quantity currently smoked. In the figure, the categories "do not inhale" and "inhale slightly" have been combined with each other, because the quantity-specific SMRs were practically identical in those two categories. For the same reason, the categories

"inhale moderately" and "inhale deeply" were also combined. It is apparent that quantity smoked and inhalation depth are independent risk factors for lung cancer.

Duration

The number of years that current smokers have smoked cigarettes is correlated with age, so that adjustment for age tends to result in adjustment for duration as well. Table 5 shows the SMRs for lung cancer according to both duration and quantity currently smoked. Only three deaths occurred to women who had smoked for 20 yr or less. For smokers of specific numbers of cigarettes per day, the SMR increases dramatically with the number of years smoked. The SMR for pack-and-a-half-or-more smokers increased from 18.9 (duration, 21 to 30 yr) to 38.8 (41 to 70 yr).

Smoking Cessation

Table 6 shows the SMRs for former smokers according to the number of years since they last smoked cigarettes and by amount last smoked. The distinction between ratios for all women and for those without a history of chronic illness is quite important. Smokers often quit as a result of developing symptoms of a life-threatening disease or immediately following diagnosis. This phenomenon is evidenced by the rise in the SMR for all women within the first 2 yr following cessation (from 10.3 to 13.6 in light smokers, and from 21.1 to 32.4 in heavy smokers), in contrast to a drop among women without a history of chronic disease (from 14.5 to 8.9 in light smokers, and from 27.5 to 24.0 in heavy smokers). The SMRs do not fall completely to 1.0, even after 16 yr, but the number of deaths among exsmokers without history of chronic illness is too few to determine reliably the number of years of cessation required for a woman's risk to fall to that of a nonsmoker.

Table 5 *Observed and expected lung cancer deaths and SMRs among women with no history of chronic illness, according to number of cigarettes per day currently smoked and number of years of smoking habit*

Duration of smoking habit (yr)	No. of cigarettes/day, current smokers				
	1–10	11–19	20	21–30	31+
21–30					
O[a]	3	3	16	9	7
E	1.0	0.4	1.2	0.5	0.4
SMR	2.9	6.7	13.6	18.4	18.9
31–40					
O	18	22	59	36	27
E	2.3	1.1	3.1	1.4	1.1
SMR	7.9	19.2	19.2	26.5	25.3
41–70					
O	29	23	83	36	30
E	2.9	1.4	3.3	1.0	0.8
SMR	10.0	17.0	25.1	34.3	38.8

[a] O, observed; E, expected (based on age-specific rates in nonsmoking women).

Tar Yield of Current Cigarette

One important goal of CPS-II is to evaluate the possible influence of machine-rated tar yields on risks of lung cancer and other diseases. In CPS-I a decrease of about 40% was observed in women who smoked cigarettes which were then considered "low T/N" (11). At that time (the early 1960s), low T/N cigarettes contained up to 17 mg of tar, whereas "high T/N" cigarettes yielded at least 27 mg of tar. Other studies since then have led to the general impression that higher tar yields are related to higher risks of lung cancer (12).

Assessment of a relationship between tar yield and lung cancer risk is complicated by a number of factors: (*a*) the sales-weighted average yield has been steadily dropping for many years, in high T/N brands as well as low, so that today's "high" brands may be more like earlier "low" or "medium" brands; (*b*) most smokers in this study took up the habit when average yields were much higher than they are now, and therefore have smoked cigarettes spanning a wide range of yields; (*c*) very low or "ultra" low cigarettes which debuted in the early 1980s may not have been smoked for sufficient periods of time to show an effect; (*d*) low T/N cigarettes may be flavored by untested additives which also affect the risk of lung cancer.

In view of this complexity, a more thorough analysis of lung cancer risk in relation to cigarette yield is planned and will be published separately. Nevertheless, even two simplified analyses, one based upon yield of the cigarette smoked at time of enrollment in this study and the other upon the number of years subjects smoked filter cigarettes, both show differential risks.

Current Cigarette Yield. We also classified the tar and nicotine yield of the cigarettes women in CPS-II smoked. In a previous study (10), 13.9% of women enrolled in CPS-II reported currently smoking cigarettes which had less than 6.0 mg of tar, and 37.7% reported currently smoking cigarettes with 6.0 to 11.9 mg of tar. Only 3.6% smoked cigarettes with 20.2 mg or more of tar (most of these were nonfilter cigarettes).

A logistic regression model was developed in which the tar yield of the cigarette currently smoked was a continuous variable, together with categorical variables: age (5-yr groups); number of cigarettes smoked per day (none, 1 to 9, 10 to 19,

Table 6 *Expected and observed lung cancer deaths and SMRs among former smokers, according to years of smoking cessation and number of cigarettes smoked at time of cessation*

History of heart disease, stroke, or cancer	Never smoked regularly	No. of cigarettes/day	Current smokers	Former smokers after the following yr of smoking cessation				
				Up to 2	3–5	6–10	11–15	16+
No history								
O[a]	88	1–20	258	17	15	12	7	19
E	88.0		17.8	1.9	1.9	3.1	3.7	13.3
SMR	1.0		14.5	8.9	7.8	3.9	1.9	1.4
O		21 or more	146	14	7	9	2	4
E			5.3	0.6	0.5	0.7	0.8	1.1
SMR			27.5	24.0	13.0	12.4	2.7	3.6
All women								
O	174	1–20	335	52	33	20	21	41
E	174.0		32.4	3.8	3.9	6.1	7.0	26.0
SMR	1.0		10.3	13.6	8.4	3.3	3.0	1.6
O		21 or more	195	39	23	17	6	9
E			9.2	1.2	1.1	1.5	1.5	2.3
SMR			21.2	32.4	20.3	11.4	4.1	4.0

[a] O, observed; E, expected (based on age-specific rates in nonsmokers with the same history).

Table 7 *Age-specific and age-standardized lung cancer rates per 100,000 for nonsmokers and cigarette smokers in CPS-I and CPS-II*

	CPS-I						CPS-II, 1982–86	
	1960–64		1965–68		1969–72			
	NS[a]	Smokers	NS	Smokers	NS	Smokers	NS	Smokers
35–39								
40–44	–[c]	7.2	3.5	15.1	3.6	8.3	–	8.7
45–49	6.0	13.9	3.4	20.1	1.6	30.2	2.5	34.3
50–54	5.2	16.9	7.7	28.9	3.0	32.0	5.7	56.4
55–59	7.4	16.3	8.0	31.5	5.9	40.1	6.1	102.4
60–64	14.4	47.5	12.3	36.6	14.5	84.0	9.9	148.7
65–69	16.1	27.8	15.2	77.5	17.8	99.4	15.4	228.2
70–74	19.4	72.0	21.8	53.5	22.1	87.9	29.7	255.0
75–79	37.3	23.4	30.4	81.4	36.4	108.2	24.5	364.1
80–84	48.5	–	47.4	39.2	40.9	112.8	48.9	341.5
85+	53.6	–	44.5	–	59.5	152.6	72.8	377.8
No. of deaths	176	106	186	181	205	278	174	570
Age standardized rate[b]	11.68	23.86	12.41	36.51	12.19	54.01	12.12	130.39
Relative risk		2.04		2.94		4.47		10.76

[a] NS, nonsmokers.
[b] Adjusted to the United States female population, 1970.
[c] –, No deaths in age group.

Table 8 *Distribution of smoking exposure variables in women, at time of enrollment, by age group: CPS-I (1959) and CPS-II (1982)*

	% of current smokers who smoke at least 20 cigarettes/day		Mean inhalation index[a]		Mean age began smoking	
Age group	CPS-I (1959)	CPS-II (1982)	CPS-I (1959)	CPS-II (1982)	CPS-I (1959)	CPS-II (1982)
35–39	47.9	62.9	2.84	2.98	21.57	18.27
40–44	46.5	64.4	2.80	2.95	22.26	18.76
45–49	44.6	63.2	2.72	2.92	22.70	19.43
50–54	42.7	62.4	2.56	2.87	25.30	20.04
55–59	39.9	61.0	2.34	2.78	28.63	20.81
60–64	36.3	58.4	2.13	2.70	30.80	21.65
65–69	31.9	53.1	1.96	2.61	32.23	22.09
70–74	26.7	47.1	1.82	2.45	32.70	24.33
75–79	23.8	45.1	1.75	2.25	33.27	27.38
80 and up	17.6	35.0	1.71	2.03	32.68	32.50

[a] Do not inhale, 1; inhale slightly, 2; inhale moderately, 3; inhale deeply, 4.

20, 21 to 30, 31 or more); and inhalation (none, slight, moderate, deep). The outcome variable was 1 (died of lung cancer within 4 yr) or 0 (otherwise). Former smokers were excluded. After adjustment for age, quantity, and inhalation, the exponentiated coefficient for tar yield was exp(0.03075) = 1.031 ($P < 0.01$). Under this model, the lung cancer risks for women smoking cigarettes with machine-rated yields of 5, 10, 15, and 20 mg of tar would be 1.17, 1.36, 1.59, and 1.85 times those of nonsmokers, respectively. In particular, doubling the tar yield would be equivalent to an increased risk of about 40%, independently of amount smoked or depth of inhalation.

Years Smoked Filter Cigarettes. Those women who currently smoked cigarettes and who had smoked for at least 20 yr were also classified by the proportion of their smoking lifetimes during which they had used filter cigarettes. This fraction ranged from 0% (nonfilter smokers only) to 100% (filter smokers only). After adjustment for age and quantity smoked per day, the standardized mortality ratio for women who smoked filters for 40% of their smoking lifetime or less was 1.51 compared to women who smoked filter cigarettes only (95% confidence interval, 1.29, 1.75).

Some have suggested that low-tar-yield smokers tend to smoke more cigarettes or inhale more deeply (13–15). Our data suggest that compensation may have some small effect in increasing the number of cigarettes smoked by ultra-low-tar-yield smokers, but does not fully compensate for the total tar inhaled. Depth of inhalation is lowest in low-tar-yield smokers and highest in high-tar-yield smokers (10).

DISCUSSION

The predicted increase in the SMR for smokers with lung cancer is borne out in this study. The SMR of 12.7 for lung cancer is similar to those found in men in prospective studies carried out in the 1960s and 1970s. Table 7 shows how the ratios in smokers increased over the years. The table shows age-specific rates and age-standardized lung cancer mortality ratios in three 4-yr periods of time in Cancer Prevention Study I (the American Cancer Society 25-state study) (2) and for the 4-yr period in Cancer Prevention Study II. The age-standardized lung cancer rate in nonsmokers remained the same for the 26-yr period covered by the two studies (11.68 in 1960 to 1964, 12.41 in 1965 to 1968, 12.19 in 1969 to 1972, and 12.12 in 1982 to 1986). The rate among cigarette smokers, however, rose from 23.86 per 100,000 in 1960 to 1964 to 130.39 per 100,000 in 1982 to 1986, a more than 5-fold increase. Relative risks increased from 2.04 in 1960 to 1964 to 2.94 in 1965 to 1968 to 4.47 in 1969 to 1972 to 10.76 in 1982 to 1986. Smoking exposures changed dramatically between CPS-I and CPS-II (Table 8). The percentage who smoked 20 or more cigarettes a day was 20% higher in CPS-II then in CPS-I, especially in women of ages 50 to 79. The age at which women began smoking decreased considerably in the later study to an 8- to 10-yr difference in women between ages 55 and 79, and the index of inhalation was also higher at each age for women enrolled in CPS-II compared to CPS-I. The observed increases in lung cancer risk related to these dosage factors evidently far outweighs the much smaller ameliorative effect of reduced tar/nicotine yield over the same time period.

The decrease in lung cancer SMRs in exsmokers parallels the finding in men and is an encouraging aspect for the control of lung cancer. Despite the study increase of age-standardized lung cancer rates in women, so many smokers have quit that we are starting to see a drop in rates in women under 45 and a leveling off of rates in women 45 to 54. This phenomenon has been observed in age-specific rates in men. This presages a day in the not too distant future when we shall see a reversal in the overall lung cancer rates in men, followed some years later by a downturn in the lung cancer rate in women.

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