Association Between Smoking and Leukemia in Two American Cancer Society Prospective Studies

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The association between smoking and leukemia in men and women was analyzed from the data of two prospective studies. Myeloid leukemia was positively associated with smoking in men in both studies (standardized mortality ratios [SMR], 2.44 and 1.32; $P < 0.05$), but not with smoking in women. Lymphatic leukemia showed no elevation in risk in men and women in both studies. Animal studies suggest a real biologic difference in leukemogenic effect between the sexes, but further analyses are needed to characterize the smoking effect of leukemia in women. *Cancer* 65:2356–2360, 1990.

TOBACCO SMOKE contains at least four groups of chemicals that are known to cause leukemia in experimental animals: urethane, nitrosamines, benzene, and radioactive compounds. The latter two also have been shown to cause cancer in humans.[1] On the basis of laboratory tests, the amount of benzene in the smoke of one cigarette ranges from 10 to 75 μg, which corresponds to a dose of up to 3 mg for a smoker of 2 packs per day.[2]

The biologic plausibility of a leukemogenic effect of tobacco smoking in humans has been reviewed recently.[2,3] Up to now, however, while evidence suggests an association, firm conclusions of a causal relationship cannot be derived from the epidemiologic studies alone.[4]

A positive association between cigarette smoking and risk of adult leukemia among men has been suggested by two US prospective studies,[5,6] but was not confirmed by a cohort study of British doctors.[7] That study found a negative trend in the "cancer of bone marrow and reticuloendothelial system" mortality rate with increased cigarette smoking. The study of US veterans[6] subdivided leukemia deaths according to cell type: smokers had significantly higher mortality rates of acute and chronic lymphatic leukemia and chronic myeloid leukemia, the latter type showing the strongest dose–response relationship with the amount of smoking. The US veterans study has been updated to 26 years of follow-up information with essentially the same results.[8]

Currently, four case–control studies have addressed this problem. Three of them[9–11] have shown an increased odds ratio for myeloid leukemia. No positive relationship between smoking and lymphatic leukemia was found in the Third Cancer National Survey study,[9] and a nonsignificant twofold increase in the risk of lymphatic leukemia was reported in the case–control analysis nested in a study of a cohort of Harvard and Pennsylvania State Universities alumni.[10] In another study the odds ratio for acute myelocytic leukemia was 1.78, and this increase was statistically significant.[11] A further study, which was based on a nonsystematic ascertainment of cases in several US hospitals,[12] failed to find any association with smoking when comparing lymphatic or myeloid leukemia patients with neoplastic control subjects, excluding cancers known to be related to smoking. When these patients were compared with nonneoplastic control subjects, however, a negative association with total leukemias, as well as with all major subtypes, was found. It should be noted that all of these case–control studies had too few patients from each subtype to derive stable risk estimates.

Risk of leukemia associated with smoking among women was addressed by three case–control studies only.[9,11,12] In all cases, the results of these analyses agreed with those for men.

In this analysis, we study the risk of death from total, lymphatic, and myeloid leukemia in relation to smoking habit among more than 2 million US men and women enrolled in two large American Cancer Society (ACS) prospective studies.

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Accepted for publication December 19, 1989.

Materials and Methods

This analysis is based on two large prospective studies carried out by the ACS: Cancer Prevention Study I and II (CPS I and CPS II). CPS I was started in 1959 when 68,116 ACS volunteers enrolled more than 1,000,000 subjects 30 years of age and older from 25 US states. These enrollees completed a 4-page questionnaire on exposure to known or suspected cancer risk factors. Subjects were classified as current or former cigarette smokers, or cigar and pipe smokers who did not smoke cigarettes. They were classified by the current number of cigarettes smoked per day (CPD). Subjects in CPS I were observed each year until 1965. The death certificates of deceased subjects were collected from state health departments and further information on cancer deaths was requested from doctors or hospitals. Two further observations were conducted in 1971 and 1972 to establish the 1965 to 1971 mortality experience of the cohort, but information on leukemia deaths that occurred in the latter period was not checked by hospital or doctor records; therefore, we were unable to classify these deaths by cell type and they are not reported in this article. More detailed information about study design, as well as detailed results on overall and cause-specific mortality in relation to cigarette smoking, has been previously published, including a limited analysis of overall leukemia risk associated with cigarette smoking.[5]

CPS II was similar in design to CPS I: 77,000 ACS volunteers enrolled more than 1,200,000 subjects 30 years of age and older in 1982 from every state in the US. Enrollees completed a 4-page questionnaire. This questionnaire was different from the one used in CPS I, and the vital status of subjects was checked by volunteers in 1984, 1986, and 1988. More detailed questions on smoking habits were asked of subjects enrolled in CPS II, as compared with CPS I. However, only basic information on smoking status and number of CPD was used in this analysis for the sake of comparability between the two studies. Because only a small portion of death certificates for deceased subjects identified in 1988 were available when this analysis was done, mortality data for only the first 4 years of follow-up (1982 to 1986) were used.

For this analysis, subjects were classified as never smokers or current cigarette smokers. They were further divided into 1 to 19 and 20+ CPD smokers, ex-cigarette smokers, and, for men only, cigar and/or pipe smokers. Cigar and/or pipe smokers who also smoked cigarettes were classified as cigarette smokers and the number of cigars or pipefuls smoked was not included in CPD calculations. Subjects with missing data on smoking habits were excluded from the analysis. Deaths from lymphatic leukemia (International Classification of Diseases, 9th Revision [ICD9 code 204]), myeloid leukemia (ICD9 code 205), and other and unspecified leukemias (ICD9 codes 206 to 208) were considered.

The number of expected deaths was obtained by applying the 5-year age group specific mortality rate of the reference category (nonsmokers) to the denominator (person years) of the corresponding age group in the exposed categories, and summing over all age groups. The ratio of observed to expected deaths is the standardized mortality ratio (SMR). Ninety-five percent confidence intervals were calculated according to the approximated formula proposed by Rothman and Boice.[13]

Results

The analysis was based on the mortality rates of 437,197 men and 588,148 women enrolled in CPS I, and of 489,696 men and 622,488 women enrolled in CPS II.

TABLE 1. Subjects in the Analysis by Study, Sex, Smoking Habits, and Age Group

	CPS I		CPS II	
	Men (%)	Women (%)	Men (%)	Women (%)
Age group (yr)				
30–44	13.4	21.9	7.1	12.8
45–54	42.3	37.9	33.2	32.3
55–64	27.8	24.2	35.7	31.7
65–74	12.9	12.0	19.0	17.3
75+	3.5	4.0	5.0	5.8
Total	100.0	100.0	100.0	100.0
Smoking habits				
Nonsmoker	22.7	67.4	26.0	57.1
Cigarette smoker	65.6	32.6	64.1	42.9
Current cigarette	48.3	27.0	22.5	20.6
1–19 a day	14.9	15.3	5.8	8.0
20+ a day	33.4	11.7	16.7	12.5
Ex-cig. smoker	17.4	5.6	41.6	22.3
Cigar/pipe smoker	11.6	—	9.9	—
Total	100.0	100.0	100.0	100.0
No. of subjects	437,197	588,148	489,696	622,488
Person years	2,387,252	3,318,242	1,867,375	2,398,772

The age distribution of subjects in the two studies is shown in Table 1. CPS II subjects were older than CPS I subjects. The proportions of never smokers, cigarette smokers, and cigar and/or pipe smokers among men were approximately 25%, 65%, and 10%, respectively, in both CPS I and CPS II. The latter, however, had a higher proportion of ex-cigarette smokers and fewer current cigarette smokers (Table 1). Among women, the proportions of nonsmokers and 1 to 19 CPD current smokers decreased between CPS I and CPS II, whereas the proportion of heavy smokers increased slightly and the proportion of ex-smokers increased from 6% to 22% (Table 1). More detailed comparisons of smoking habits in CPS I and CPS II have been published previously.[14]

During the first 6 years of CPS I follow-up, 477 men and 339 women died of leukemia. During the first 4 years of CPS II follow-up, there were 327 leukemia deaths among men and 235 among women (Table 2). The proportion of lymphatic leukemia deaths ranged between 25% and 28% in both studies and both sexes, whereas the proportion of myeloid leukemia deaths was approximately the same between the sexes, but increased from approximately 30% in CPS I to approximately 50% in CPS II. The other and unspecified category was 41% in men and 45.4% in women, reflecting a large proportion of unspecified cell types (Table 2).

Tables 3 and 4 show smoking-related leukemia SMR by sex and study. Men from both CPS I and CPS II who smoked cigarettes had a higher leukemia mortality rate than nonsmokers. However, the increase was limited to myeloid leukemia and to the other and unspecified category. Cigar and/or pipe smokers showed an insignificantly increased SMR in CPS I only (Table 3). Current smokers had higher SMR than ex-smokers. A trend was present among current smokers according to amount, and the increase was highest for myeloid leukemia deaths (Table 3). Ex-smokers in CPS II was the only group with a discordant result, as it showed a higher SMR for lymphatic than myeloid leukemia.

SMR in women were different from those in men. CPS I women who smoked had an SMR for all leukemia lower than 1, and their mortality rate for myeloid leukemia was the lowest (SMR = 0.61; $P < 0.05$). CPS II women who smoked showed an increase in total leukemia mortality rate that was not significant (it was lower than that in men, with higher SMR for lymphatic leukemia) (Table 4). Analyses by current and ex-smoker status and the amount of smoking did not show any consistent pattern. The low SMR for myeloid leukemia in CPS I women was partially due to a deficit in the mortality rate among ex-smokers. The increased SMR for lymphoid leukemia in CPS II women was explained by a high mortality ratio (1.94) among ex-smokers (Table 4).

Discussion

This analysis supports the hypothesis of an association between tobacco smoking and the risk of myeloid leukemia in men. The increased risks are close to those reported in another prospective study.[6] No association between smoking and leukemia was present in women.

Both CPS I and CPS II were prospective studies based on selected populations. However, internal comparisons are not likely to be affected by selection bias. In fact, CPS I was one of the most important studies in the establishment of a causal relationship between tobacco smoking and cancer from several organs in humans.[1,15] The completeness of smoking data and observations was high in both studies. Only a small proportion of CPS I and CPS II subjects were excluded from this analysis because of missing data on smoking. Follow-up information was more than 97% complete in both studies. It has been reported previously that the ACS study cohorts are select populations with respect to socioeconomic status, race, and condition of health.[16] The death rate for CPS I was low in the first year of follow-up, and never reached more than 80% of the US rates. It is doubtful that selection could have had more than a slight effect on the SMR in this study because all comparisons were internal.

Some subjects may have changed their smoking habits during the course of the study. However, subjects with leukemia were not more likely than other subjects to have stopped before their illness occurred. Nondifferential misclassification produces a bias toward the null: therefore, it cannot explain a positive result. Although there were larger numbers in this study than in any of the case-control studies, the number of cases by 5-year age groups in some subgroups of smoking categories were small and subject to some sampling variation. This variability was not great, especially in the older age groups where most of the deaths occurred.

The positive association between tobacco smoking and myeloid leukemia risk in men may be due, in part, to confounding factors (*i.e.*, occupational exposure to benzene or radioactive materials). No information on such exposures was available in CPS I. In CPS II, questions on occupational exposure to "chemicals, acids, solvents" and "X rays and radioactive materials" were in the questionnaire. Smokers were more likely to report exposure to chemicals and solvents, but not to radiation, than nonsmokers.[17] Further analysis showed slight differences in leukemia rates by race and socioeconomic status. However, these differences were too small to explain a twofold increase in risk.

In interpreting the SMR shown in this analysis, it is valuable to have two studies to see if findings are consistent. CPS I was conducted in 25 states and CPS II was conducted in all 50 states. There may have been a few people enrolled in both studies, but this would have been rare. The average age at enrollment in CPS I was 47 years. These subjects were 23 years older in 1982 when CPS II began, so that only a small proportion of CPS I enrollees were eligible for enrollment in CPS II.

In addition to the prospective study that found a relationship with myeloid leukemia in men, three of the four case-control studies also reported this association. The US veterans study also found an increased risk of lymphatic leukemia with smoking, but only one of the three case-control studies found an increased risk, which was not significant. Our study showed a slight, but not statistically significant, increased risk (more in CPS I than in CPS II). The other and unspecified types of leukemia showed an increased risk in men both in CPS I and CPS II. This category consisted of approximately 41% of all leukemia cases in CPS I. Few of these cases were specified as monocytic or other types, and the great majority were not specified as to type (many could have been myeloid leukemias). This may be the reason for the high SMR.

A relationship of smoking to myeloid leukemia in women was found in two of the three case-control studies.

TABLE 2. Number of Leukemia Deaths by Study and Sex

	CPS I				CPS II			
	Men		Women		Men		Women	
Leukemia deaths	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Total	477	100.0	339	100.0	327	100.0	235	100.0
Lymphatic	130	27.3	86	25.4	93	28.4	59	25.1
Myeloid	150	31.4	99	29.2	147	45.0	124	52.8
Other and unspecified	197	41.3	154	45.4	87	26.6	52	22.1

TABLE 3. Standardized Leukemia Mortality Ratios* by Smoking Status and Study for Males

	History of cigarette smoking	Current cigarette			Ex-cigarette smokers	Cigar/pipe smokers
		Total	1–19 a day	20+ a day		
CPS I						
All leukemia	1.46†	1.50†	1.32†	1.61†	1.36†	1.19
Lymphatic	1.02	0.91	0.77	0.99	1.25	1.12
Myeloid	2.44†	2.54†	2.25†	2.87†	2.23†	1.51
Other and unspecified	1.58†	1.79†	1.53†	1.95†	1.18	1.07
CPS II						
All leukemia	1.38†	1.45†	1.55†	1.41†	1.35†	1.03
Lymphatic	1.24	0.76	0.94	0.68	1.44†	1.23
Myeloid	1.32†	1.72†	1.65	1.75†	1.17	0.85
Other and unspecified	1.70	1.89†	2.17*	1.75	1.63†	1.14

* Nonsmokers are the referent category

† $P < 0.05$.

TABLE 4. Standardized Leukemia Mortality Ratios* by Smoking Status and Study for Females

	History of cigarette smoking	Current cigarette			Ex-cigarette smokers
		Total	1–19 a day	20+ a day	
CPS I					
All leukemia	0.79	0.77	0.77	0.76	0.91
Lymphatic	0.80	0.86	0.87	0.83	0.56
Myeloid	0.61†	0.66	0.61	0.74	0.36
Other and unspecified	0.94	0.82	0.88	0.75	1.44
CPS II					
All leukemia	1.19	1.00	1.12	0.91	1.34†
Lymphatic	1.52	0.92	0.67	1.13	1.94†
Myeloid	1.27	1.18	1.45	0.98	1.33
Other and unspecified	0.79	0.69	0.79	0.61	0.88

* Nonsmokers are the referent category.

† $P < 0.05$.

Our analysis showed an increased risk, which was not significant, in CPS II, but no added risk in CPS I. One reason for this may be that 61% of the women smokers in CPS II smoked 20 or more cigarettes a day and only 43% of the women smokers in CPS I smoked 20 or more cigarettes a day (see Table 1).

Also, there is some evidence from animal experiments that smoking is associated with a leukemogenic effect in male mice but not in female mice. Harris and Negroni[18] found that leukemia or lymphosarcoma developed in 70 of 100 male C57DL mice and 44 of 100 female C57DL mice, whereas among control mice the disease developed in 53 males and 60 females. This suggests a smoking-induced effect in males, but a smoking-inhibiting effect in females. Cowdry *et al.*[19] reported that leukemia developed in four of 51 mice in a group of female Swiss mice treated with a 50% acetone suspension of "tar." In 47 control mice, nine leukemias developed. In groups consisting of 150 female mice exposed to x-ray, 12 leukemias developed in those also exposed to tar. In those exposed to x-ray alone, 30 leukemias developed. These results suggest a negative effect of smoking and leukemia in female mice. Therefore, our results may reflect a true biologic difference. However, further epidemiologic studies are needed to document this.

REFERENCES

1. U.S. Department of Health, Education and Welfare. Smoking and Health. A Report of the Surgeon General. DHEW publication no. 79-50066.
2. Hoffman D, Brunnemann KD, Hoffman I. Significance of benzene in tobacco carcinogesis. In: Mehlman MA, ed. Benzene: Occupational and Environmental Hazards Scientific Update. Princeton, NJ: Princeton Scientific Publ., 1989; 99–112.
3. Austin H, Cole P. Cigarette smoking and leukemia. *J Chron Dis* 1986; 39:417–421.
4. Wald N. Smoking and leukemia. *Br Med J* 1988; 297:638.
5. Hammond EC. Smoking in relation to death rates of one million men and women. In: Haenszel W, ed. Epidemiological Approaches to the Study of Cancer and Other Diseases. Bethesda, MD: National Cancer Institute, 1966; 127–204.
6. Kinlen LJ, Rogot E. Leukemia and smoking habits among United States veterans. *Br Med J* 1988; 297:657–659.
7. Doll R, Peto R. Mortality in relation to smoking: 20 years observations on male British doctors. *Br Med J* 1976; 2:1525–1536.
8. McLaughlin JK, Hrubec Z, Linet MS, Heineman EF, Blot WS, Fraumeni JF Jr. Cigarette smoking and leukemia. *J Natl Cancer Inst* 1989; 81:1262–1263.
9. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. *J Natl Cancer Inst* 1977; 58:525–547.
10. Pallenbarger RS Jr, Wing AL, Hyde RT. Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas and leukemias. *J Natl Cancer Inst* 1978; 60:89–92.
11. Severson RK. Cigarette smoking and leukemia. *Cancer* 1987; 60: 141–44.
12. Kabat GC, Augustine A, Hebert JR. Smoking and adult leukemia: A case-control study. *J Clin Epidemiol* 1988; 41:907–914.
13. Rothman KJ, Boice JD. Epidemiologic Analysis with a Programmable Calculator. Washington, D.C.: U.S. Dept. of Health, Education and Welfare, 1973.
14. Stellman SD, Garfinkel L. Smoking habits and tar levels in a new American Cancer Society prospective study of 1.2 million men and women. *J Natl Cancer Inst* 1986; 76:1057–1063.
15. U.S. Department of Health, Education and Welfare. Smoking and Health. A Report of the Advisory Committee to the Surgeon General. Washington, D.C.: U.S. Pub. Health Serv. Publ. 1103, 1964.
16. Garfinkel L. Selection, Followup, and Analysis in the American Cancer Society Prospective Studies. Bethesda, MD: National Cancer Institute. NIH Publ. No. 85-2713, 1985.
17. Stellman SD, Boffetta P, Garfinkel L. Smoking habits of 800,000 American men and women in relation to their occupations. *Am J Ind Med* 1988; 13:43–58.
18. Harris RJC, Negroni G. Production of lung carcinomas in C57BL mice exposed to a cigarette smoke and air mixture. *Br Med J* 1967; 4: 637–641.
19. Cowdry EV, Cronin ger A, Solaric S, Suntzeff V. Combined action of cigarette tar and beta radiation on mice. *Cancer* 1961; 14:344.

Significant Changes in the Distribution of Histologic Types of Lung Cancer

A Review of 4928 Cases

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The histopathologic data for lung carcinoma were review ed in 4928 patients between 1964 and 1985. The analysis of this data indicate that lung cancer is increasing in our region. Squamous carcinoma remains t he most frequent type in men, followed by adenocarcinoma. Small cell carcinoma a the second most frequent type in women, after adenocarcinoma. Small cel l carcinoma has increased over the past years and may become the most common ty pe of lung cancer in women, a development that might result in increased nu mbers of deaths. Lung cancer data must be carefully analyzed in view of the im pact on selection of therapy, patient management, and education. *Cancer* 65: 2361–2367, 1990.

IN 1988 APPROXIMATELY 152,000 new cases of lung cancer will be diagnosed in the United States,[1] 100,000 cases in men and 52,000 in women. Lung cancer related deaths in 1988 will total an estimated 139,000, with 93,000 men and 46,000 women dying from the direct or indirect effects of the malignancy. By the 21st century, lung cancer cases are projected to progressively increase such that 300,000 new cases will be diagnosed in the year 2000.[2]

This continuing escalation of lung cancer cases results from varying degrees of increases in all four major histologic types of lung cancer, including adenocarcinoma, squamous cell (epidermoid) carcinoma, small cell carcinoma, and large cell (undifferentiated) carcinoma. These four histologic types in aggregate account for approximately 99% of all cases of primary lung cancer. Although squamous cell carcinoma has for many years been the most common histologic type, adenocarcinoma has been increasing in incidence in recent years, a trend which has been amply demonstrated in several reports.[2–4] This increasing incidence of adenocarcinoma is attributed to several factors: changes in the criteria for the histopathologic diagnosis of lung carcinoma; increasing incidence of lung cancer in women; and exposure to new environmental and occupational carcinogens.

Our observation of changing trends in the distribution of the histologic types of lung cancer in the middle to southern region of the United States over the last several years prompted our careful statistical review of these cases. The increasing incidence of lung cancer as compared with other types of cancer in our region is in line with national statistics. However, varying increases in certain histologic types of lung cancer in our region are documented and may portend important changes in the selection of specific therapy and in patient management and education.

Materials and Methods

Baptist Memorial Hospital in Memphis, Tennessee, is one of the world's largest private medical institutions and is a medical center for the mid-south, serving patients in its referral areas of Tennessee, Alabama, Mississippi, Arkansas, Missouri, and Kentucky. The hospital has 2053 beds and offers comprehensive medical, surgical, rehabilitative, subspecialty, pathologic, therapeutic, and consultative services for adult patients. Over the 22 years covered by this study, the proportion of women among patients admitted to the hospital has remained very stable (60% of admissions). The total number of admissions has not significantly changed over this time period. This institution thus provided data from a large number of lung cancer patients, and 4928 patients met the criteria for inclusion in our study. Each of these cases was initially

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Accepted for publication November 14, 1989.