J Chron Dis Vol. 39. No. 6. pp. 417–421, 1986
Printed in Great Britain

0021-9681/86 $3.00 + 0.00
Pergamon Journals Ltd

CIGARETTE SMOKING AND LEUKEMIA*

HARLAND AUSTIN and PHILIP COLE

Department of Epidemiology and the Comprehensive Cancer Center, University of Alabama in Birmingham, Birmingham, AL 35294, U.S.A.

(*Received in revised form* 10 *December* 1985)

INTRODUCTION

THE REPORT of the Surgeon General of the United States cites cigarette smoking as a major cause of cancers of the lung, larynx, oral cavity, and esophagus, and as a contributory factor in the etiology of cancers of the bladder, kidney, and pancreas [1]. It is also indicated in this report that cigarette smoking may be related to stomach and cervical cancer. Leukemia is not considered a tobacco-related cancer, although the report mentions that several epidemiologic studies have reported higher leukemia risks among smokers compared with non-smokers [2]. This evidence was judged inconclusive because no dose–response relationship between leukemia mortality and the amount smoked was found in these studies. This paper reviews briefly the epidemiologic evidence pertinent to an evaluation of the relationship between cigarette smoking and leukemia and suggests strategies for the further evaluation of this relationship.

EPIDEMIOLOGIC STUDIES

In a review of the epidemiology of leukemia, Alderson concluded that cigarette smoking was not an etiologic factor [3]. This conclusion was based on the lack of an association between smoking and deaths from Cancers of the blood and reticuloendothelial system in the prospective follow-up study of British male doctors [4]. However, there are several other epidemiologic studies which report data on cigarette smoking and leukemia. An appraisal of these studies suggests that Alderson's conclusion was premature.

Prospective follow-up studies

The results of three large prospective follow-up studies of cigarette smoking and leukemia mortality appear in Table I. Each of these studies is generally considered to have been well designed and well executed. In the British doctors study, there is a deficit of leukemia deaths among current or ex-smokers compared with non-smokers. Furthermore, among smokers there is an inverse relationship between leukemia mortality and the amount of tobacco smoked daily. On the other hand, in the two follow-up studies from the United States, there is an overall excess of leukemia mortality of about 50% among cigarette smokers compared with non-smokers. In the United States Veterans study, there is some evidence of a dose–response relationship among current smokers, but the trend is erratic and is not statistically significant (one-tailed p value = 0.19).

There are two other prospective follow-up studies relevant to an evaluation of the relationship between cigarette smoking and leukemia mortality. In a study of male labor

*Supported by grants from the National Cancer Institute (5-30-CA13148) and the American Petroleum Institute.

TABLE 2. THE RELATIVE INCIDENCE RATES OF ACUTE AND CHRONIC MYELOCYTIC LEUKEMIAS ACCORDING TO PACK-YEARS OF CIGARETTE SMOKING AND GENDER (THIRD NATIONAL CANCER SURVEY INTERVIEW STUDY)

	Chronic Myelocytic		Acute Myelocytic	
Pack-Years	Men	Women	Men	Women
<20	1.8[1,2] (2)[3]	0.8 (1)	1.6 (5)	1.6 (2)
20-39	—(0)	3.3 (2)	1.4 (3)	8.8 (4)
40+	3.2(5)	2.6 (1)	1.1 (4)	2.6 (1)
Total Cases	10	I2	27	23

[1]The reference value is 1 0 for non-smokers.
[2]Adjusted for differences between cares and controls in age and race.
[3]Number of cases in rhat category.

union members in California in which 30 leukemia deaths occurred, the relative rate (RR) of leukemia mortality for cigarette smokers compared with non-smokers was 1.3 [9]. In a Japanese follow-up study which included 33 male leukemia deaths. the RR of leukemia mortality for daily cigarette smokers compared with non-smokers or occasional smokers was 0.8 [IO]. However, these two latter studies are small and are not inconsistent with a small or moderate increase in leukemia risk attributable to cigarette smoking.

Case–control studies

Two case-control studies are also relevant to an evaluation of the relationship between cigarette smoking and leukemia. In the interview study from the Third National Cancer Survey, leukemia cases were reported according to chronicity and cell-type [11]. Controls in this study were persons with cancers of various sites which are not generally believed to be related to cigarette smoking. The RR's of acute and chronic myelocytic leukemia according to pack-years of cigarette smoking and gender are displayed in Table 2 (the referent category is non-smokers). The investigators reached the reasonable conclusion that there was a "suggestion" of a positive relationship between cigarette smoking and both types of myelogenous leukemia. There was no such positive relationship between cigarette smoking and lymphocytic leukemia.

Paffenbarger *et al.* followed about 50,000 men who had attended Harvard University or the University of Pennsylvania between 1916 and 1950 [12]. After 1.7 million person-years of observation, 27 and 41 men had died from lymphatic and myeloid leukemia, respectively. For each of these decedents, four controls were chosen from among classmates born in the same year and who were known to have survived the decedent case. The RR of lymphocytic leukemia for cigarette smokers compared with non-smokers was 1.3 (95% confidence limits: 0.5, 3.2), while for smokers of more than 10 cigarettes per day, this RR was 2.7 (0.7, 11.2). For myelocytic leukemia, the RR for all cigarette smokers compared with non-smokers was 2.4 (1.1, 5.3), while for heavy smokers, the RR was 3.6 (1.1, 11.4).

Interpretation of the epidemiologic studies

None of the studies described above was designed specifically to evaluate the relationship between cigarette smoking and leukemia. As a result, they have major limitations with respect to an evaluation of this hypothesis. For example, the follow-up studies did not distinguish the acute from the chronic forms of leukemia, nor did they distinguish among the various cell-types of leukemia. There is some evidence that the different forms of leukemia have different etiologies, and it is possible that cigarette smoking is related to one, or several, but not to all forms of the disease. To the extent that this is true. these studies would present an underestimate of a true positive association of smoking with some particular form or forms of leukemia. The case–control studies do not suffer this limitation, but they are small and obtained only sparse information on cigarette smoking.

Both the American Cancer Society and the U.S. Veterans studies suggest a small excess leukemia risk attributable to cigarette smoking. The inference that cigarette smoking causes leukemia is supported by the results of the two case–control studies. More

the other hand, other epidemiologic studies are suggestive of a positive association and we are not able to suggest any credible sources of bias which would explain the reasonably consistent positive effect seen in these studies. Although the epidemiologic evidence pertaining to the cigarette smoking–leukemia hypothesis is currently equivocal, it is our opinion that there is enough of a suggestion of a positive association to warrant further investigation.

The relationship .between cigarette smoking and leukemia might be clarified by more detailed analysis of existing data sources. As mentioned above, the reports of the prospective follow-up studies did not distinguish the various forms of leukemia. Experimental and epidemiologic evidence suggest that smoking is more likely to be related to AML rather than to other forms of leukemia. If these published reports could be re-analyzed to provide estimates of leukemia mortality rates according to form of leukemia and smoking status, much might be learned about the smoking–leukemia hypothesis. In particular. if it were found that AML is more strongly associated with smoking than are other forms of leukemia. the more specific inference that cigarette smoking is a cause of AML would be strengthened. It may be possible to evaluate the relationship between smoking and specific forms of leukemia in extant case-control studies. In future case-control studies of the leukemias. a moderately detailed history of cigarette smoking should be obtained. Until such data are available, it will m a i n speculative that cigarette smoking is a cause of leukemia.

REFERENCES

1. U.S. Department of Health Services: The health consequences of smoking. Cancer. A Report of the Surgeon General. Washington. D.C.: U.S. Govt. Print. Office, 1982. [DHHS (PHS) 82-50179]
2. U.S. Department of Health. Education, and Welfare: Smoking and Health, A Report to the Surgeon General, Washington. D.C.: U.S. Govt. Print. Office. 1979. [DHEW (PHS) 79-50066]
3. Alderson M: The epidemiology of leukemia. Adv Cancer Res 31: 1-76. 1980
4. Doll R, Peto R: Mortality in relation to smoking: *20* years observations on male British doctors. Br Med J 2: 1525–1536, 1976
5. Hammond EC: Smoking in relation to death rates of one million men and women. Natl Cancer Inst Monogr 19: 127-204. 1966
6. Hammond EC: A multiple factor analysis of the association between cigarette smoking and mortality. (Unpublished.) A paper read at a meeting of the American Association for the Advanament of Science on December 28. 1971
7. Kahn HA: The Dorn study of smoking and mortality among U.S. Veterans: Report on 8.5 years of observation. Natl Cancer Inst Monogr 19: 1-125, 1966
8. Rogot E Smoking and mortality among U.S. Veterans. J Chron Dis 27: 189-203. 1974
9. Weir JM. Dum JE: Smoking and mortality: A prospective study. Cancer 25: 105–112, 1970
10. Hirayarna T: Prospective studies on cancer epidemiology based on census population in Japan. In: Cancer Epidemiology, Environmental Factors. Bucalossi P, Veronesi U. Cascinelli N (Eds). Vol 3. Proc XI International Cancer Congress. Florence, October 20–26, 1974. Amsterdam: Exarpta Medica. 1975. pp. 26-36.
11. 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 58: 525–547, 1977
12. Paffenbarger RS, Wing AL. Hyde RT: Characteristia in youth predictive of adult-onset malignant lymphomas. melanomas, and leukemias: Brief Communications. J Natl Cancer Inst 60: 89-92. 1978
13. Kawamoto S, Kirschbaum IA, Taylor G: Urcthan and leukemogenesis in mice. Cancer Res 18: 725–729, 1958
14. Fiore-Donati L, Chieco-Bianchi L. DeBenedictis G *et al*: Leukaemogenesis by urethan in new-born Swiss mice. Nature 190: 278–279, 1961
15. Vesselinovitch SD, Mihailovich N: Significance of newborn age and dose of urcthan in leukemogenesis. Cancer Res 26: 1633–1636, 1966
16. Shisa H. Matsudaira Y. Hiai H *et al*: Origin of leukemia cells in mouse leukemia induced by N-butylnitrooourea. Gann 66: 3742. 1975
17. Odashima S: Leukemogenesis of N-nitrosobutylurea in the rat. I. Effect of various conantrations in the drinking water to female Donryu rats. Gann 61: 245–253, 1970
18. Hadjiolov D Thymic lymphoma and myeloid leukemia in the rat induced with ethylnitrosurea. Z Krebsforsch 77: 98–100, 1972
19. Newberne P Known or suspected chemical carcinogens in cigarette smoke. A report prepared for the American Petroleum Institute. (Unpublished.) October 24, 1983
20. Blanchard R L Concentrations of ^{210}Pb and ^{210}Po in human soft tissues. Health Phys 13: 625–632, 1967
21. Hill CR: Polonium-210 in man. Nature 208: 423–428, 1965
22. Holtzman RB. Ilcewicz FH: Lead-210 and Polonium-210 in tissues of cigarette smokers. Science 153: 1259–1260, 1966