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REVIEWS AND COMMENTARY

Smoking and Leukemia: Evaluation of a Causal Hypothesis

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Leukemia has not traditionally been recognized as a smoking-related malignancy. Until 4 years ago, there were no studies that were designed specifically to examine the relation between smoking and leukemia. Of the 21 studies that have considered this relation, 13 have been published within the past 4 years. The recent interest in this research question was stimulated by the review of the evidence by Austin and Cole in 1986(1), in which they suggested that there was some support for a causal relation between smoking and leukemia and called for more research. Although 14 additional studies have been published since then, there has been no formal reevaluation of the causal hypothesis. Because of the potential public health significance of a causal relation between smoking and leukemia and the availability of much recent data, it seems appropriate to review the studies at this time.

This paper evaluates the hypothesis that smoking is a cause of leukemia. First, the findings of the studies, taken as a whole, are evaluated. Second, the validity of the findings is evaluated in terms of the roles of chance, bias, and confounding. Third, the criteria for causal inference are considered. Finally, a conclusion is reached, and the implications for public health and future research are considered.

There are 21 published studies that have examined the relation between smoking and leukemia (2–22). Six of these have been updated by subsequent reports on the same populations and will not be considered separately (17–22). Of the remaining 15 (2–16), nine were case-control studies (2–10) and six were cohort studies (11–16). The most important features of the methodology of these studies are summarized in table 1.

EVALUATION OF FINDINGS OF EPIDEMIOLOGIC STUDIES

The findings of the 15 epidemiologic studies are summarized in table 2. With respect to leukemia in general, 10 of the studies found an elevated risk estimate for smoking; in eight of these studies, the elevated risk was statistically significant. Five studies found a decreased relative risk for smokers; in one, the decreased risk was statistically significant. An examination of the confidence intervals in table 2 suggests that

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Abbreviation: CI, confidence interval.

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TABLE 1. Summary of methodology of studies of smoking and leukemia

Study	Subjects	Size*
	Case-control studies	
Williams and Horrn (2)	Third National Cancer survey tumor registry; controls: incident cancer cases not related to smoking	172
Paffenbarger et al. (3)	Cohort of male Harvard and University of Pennsylvania alumni; controls: random sample of cohort survivors	96
Kabat et al. **(4)**	US hospitalized patients; controls: hospitalized noncancer patients and patients with cancer not related to smoking	539
Flodin et al. (5)	Swedish hospital tumor registries; controls: random population-based sample	111
Cartwright et al. (6)	Hospital hematology clinics, Yorkshire, England; controls: noncancer hospitalized patients	161
Severson et al. **(7)**	Washington State tumor registries, 3 counties; controls: random population-based sample	106
Spitz et al. (8)	Texas cancer referral center; controls: patients with cancer not related to smoking	241
Brownson et al. (9)	Missouri Cancer Registry; controls: patients with cancer not related to smoking	1,131
Brown et al. (10)	Iowa/Minnesota tumor registries, white males; controls: random state-rnatchied population sample	578
	Cohort studies	
Weir and Dunn (11)	Male California labor union members	30
Doll and **Peto** (12)	British male physicians	**43**
McLaughlin et al., (13)	Male US veterans	1,206
Garfinkel and Boffetta (1**4**)	National sample enrolled by American Cancer Society volunteers	1,378
Mills et al. (15)	California Seventh-day Adventists	**43**
Linet et al. (16)	Lutheran Brotherhood policyholders	**74**

* Number of leukemia cases

based on all of the studies, there is an elevated risk of leukemia in smokers, but the table is not entirely convincing. With respect to myeloid leukemia, however, the results are quite consistent. Of the 12 studies that examined myeloid leukemia specifically, eight found an elevated relative risk for smokers. Six of these risk estimates were statistically significant. An elevated relative risk of about 1.5 is consistent with all but two of the studies. Only three of the studies that found an elevated risk for myeloid leukemia considered acute and chronic myeloid leukemia separately (2, 9, 10). Two of these found an elevated risk for both acute and chronic myeloid leukemia (2, 10). The seven risk estimates that are available do not provide evidence of an elevated risk of lymphatic leukemia for smokers.

There appears, then, to **be** an elevated risk of leukemia in smokers that is most striking for myeloid leukemia but is not seen for lymphatic leukemia. An estimate of the magnitude of this risk can be obtained by pooling the study findings. Each individual study can be viewed as a stratum, and a weighted average of the stratum-specific risk estimates can be calculated. Using the Mantel-Haenszel method for pooling of uniform stratum-specific estimates (23), we determined pooled risk estimates for the case-control and cohort studies. Confidence intervals were determined by using the test-based method (24). For the cohort studies, the relative risk for all leukemia was 1.34 (95 percent confidence interval (CI) 1.15–1.56). For the four cohort studies that evaluated myeloid leukemia specifically, the

TABLE 2. Summary

Study
Williams and Horrn
Paffenbarger et al.
Kabat et al. (4)
Flodin et al. (5)
Cartwright et al. (6)
Severson et al. (7)
Spitz et al. (8)
Brownson et al. (9)
Brown et al. (10)
Pooled odds ratio
Chi-square, hom
Degrees of freed
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Weir and Dunn (11)
Doll and **Peto** (12)
McLaughlin et al. (1
Gatfinkel and Boffet
Mills et al. (15)
Linet et al. (16)
pooled relative risk
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* Risk estimates are lor r
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pooled relative risk
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leukemia it was 1.2
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TABLE 2. Summary of findings of studies of smoking and leukemia*

study	All leukemia		Myeloid leukemia		Lymphatic leukemia	
	Risk estimate†	95% CI‡	Risk estimate†	95% CI	Risk estimate†	95% CI
Case-control studies						
Williams and Horm (2)	1.89	1.38–2.5	2.09	1.18–3.71		
Paffenbarger et al. (3)	1.7	1.1–2.7	2.3	1.1–4.6	1.3	0.5–3.2
Kabat et al. (4)	0.87	0.73–1.04	0.99	0.76–1.28		
Flodin et al. (5)	0.71	0.4–1.2			0.71	0.4–1.2
Cartwright et al. (6)	0.6	0.4–0.96	0.6	0.4–0.96		
Severson et al. (7)	2.1	1.2–3.8	2.1	1.2–3.8		
Spitz et al. (8)	0.78	0.55–1.12	0.75	0.37–1.54	0.96	0.5–1.7
Brownson et al. (9)	1.14	1.00–1.30	1.45	1.18–1.78	0.98	0.8–1.2
Brown et al. (10)	1.4	1.1–1.9	1.3	0.9–1.9	1.5	1.0–2.1
Pooled odds ratio	1.09	1.01–1.19	1.23	1.08–1.39		
Chi-square, homogeneity	45		31			
Degrees of freedom	8		7			
p value	<0.01		<0.01			
Cohort studies						
Weir and Dunn (11)	1.32	0.40-4.37				
Doll and Peto (12)	0.73	0.50–1.07				
McLaughlin et al. (13)	1.28	1.13–1.45	1.51	1.15–1.98	1.09	0.9–1.4
Garfinkel and Boffetta (14)	1.41	1.26–1.57	1.50	1.25–1.79		
Mills et al. (15)	2.00	1.01–3.95	2.24	0.9–5.53		
Linet et al. (16)	1.1	0.6–1.9	0.8	0.3–1.7	1.4	0.5–3.5
Pooled relative risk	1.34	1.15–1.56	1.51	1.31–1.74		
Chi-square, homogeneity	9.15		5.1			
Degrees of freedom	5		3			
p value	0.11		0.17			

* Risk estimates are for never/ever smoking. When relative risks and confidence intervals are not given in the papers, they have been calculated from available data. For lymphatic leukemia. confidence intervals could not be calculated for several studies, and no results are reported for these studies.

† In the risk estimates column, odds ratios were reported for all case control studies, and relative risks were reported for all cohort studies.

‡ 95% CI, 95% confidence interval.

pooled relative risk was 1.51 (95 percent CI 1.31–1.74). For the case-control studies, the pooled odds ratio for all leukemia was 1.09 (95 percent CI 1.01–1.19), and for myeloid leukemia it was 1.23 (95 percent CI 1.08–1.39). While caution must be used in interpreting the results of this analysis because of nonuniform methodology in the studies (25) and statistical evidence for nonuniformity of risk estimates among the case-control studies (table 2), the analysis does provide a reasonable weighted average of the risk estimates. Moreover, there is statistical evidence for the homogeneity of risk estimates for all leukemias and for myeloid leukemia among the cohort studies (table 2). When the study findings are pooled, there is a fair degree of confidence that the relative risk of myeloid leukemia in smokers in the 12 studies is in the range of about 1.1–1.7. The pooled relative risk for all leukemias is lower (in the range of about 1.0–1.5).

Only nine of the 15 studies included females, and only four of these reported sex-specific results (table 3). The confidence intervals in three of these four studies are wide enough so that the differences in risk between males and females could be explained by chance.

THE ROLE OF CHANCE

One must consider whether the negative studies are inconsistent with the positive studies. In other words, were these studies

TABLE 3. Relation between smoking and myeloid leukemia: sex-specific findings*

Study	Male		Female	
	Risk estimate	95% CI†	Risk estimate	95% CI
Williams and Horm (2)	1.30	0.61–2.79	2.27	0.93–5.53
Kabat et al. (4)	0.97	0.6–1.4	0.87	0.6–1.3
Brownson et al. (9)	1.5	1.1–2.0	1.4	1.0–1.9
Garfinkel and Boffetta (14)	1.72	1.26–2.34	0.99	0.75–1.30

* Risk estimates are for never/ever smoking When relative risks and confidence intervals are not given in the papers, they havebeen calculated from available data
† 95% CI, 95% confidence interval

able to accept the null hypothesis of no association, rather than merely failing to reject it? The answer to this question can be obtained by calculating the power of each study to detect a given elevation of relative risk. Table 4 shows this evaluation of power. Calculations were based on formulas outlined by Hennekens and Buring **(26)** for case-control studies and Hulley and Cummings **(27)** for cohort studies. Only four of the studies had adequate power (greater than 0.80) to detect a relative risk of 1.5 for myeloid leukemia. Of the three studies that found a nonsignificant decreased myeloid leukemia risk for smokers, the power was 0.81 (4), 0.14 (8), and 0.16 (16). Thus, two of these negative studies do not have the power to accept the null hypothesis of no association between smoking and myeloid leukemia. As a result of low study power, the confidence intervals in these studies are quite wide, and they include a risk estimate of 1.5. The study by Kabat et al. (4) had adequate power to detect a relative risk of 1.5 for myeloid leukemia, and the study by Cartwright et al. (6) found a significant decreased risk of myeloid leukemia in smokers. These two studies, then. are the only ones not consistent with a moderately increased risk of myeloid leukemia for smokers.

TABLE 4. Power* of studies to detect relative risk of leukemia for ever smokers

Study	Power* to detect relative risk for:	
	All leukemia	Myeloid leukemia
Williams and Horm (2)	0.64	0.32
Paffenbarger et al. (3)	0.39	0.17
Kabat et al. (4)	0.99	0.81
Flodin et al. (5)	0.26	
Cartwright et al. (6)	0.45	**0.45**
Severson et al. (7)	0.31	
Spitz et al. (8)	0.53	0.14
Brownson et al. (9)	0.99	0.81
Brown et al. (10)	0.84	0.58
Weir and Dunn (11)	0.11	
Doll and Peto (12)	0.29	
McLaughlin et al. (13)	0.99	0.86
Garfinkel and Boffetta (14)	0.99	0.98
Mills et al. (15)	0.14	0.01
Linet et al. (16)	0.27	0.16

* Power to detect relative nsk = 1 5

THE ROLE OF BIAS

There are a number of biases that could have affected the risk estimates in the individual studies. This discussion will consider whether these factors could explain a consistently elevated risk estimate for myeloid leukemia.

The finding of an elevated odds ratio in two studies that used cancer controls (2, 9) and in three that used a population-based control sample (3, 7, 10) precludes the possibility that a single bias might explain the elevated odds ratios.

A major methodological problem in cohort studies is that of differential loss to follow-up. However, the possibility of differential losses to follow-up in the cohort studies cannot explain the consistent association between smoking and myeloid leukemia in the case-control studies. Moreover. follow-upwas noted to be at least 95 percent complete in three of the four cohort studies

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Risk timate	95% CI
2.27	0.93-5.53
3.87	0.6-1.3
1.4	1.0–1.9
0.99	0.75-1.30

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id myeloid leukemia. As study power, the confi- 1 these studies are quite nclude a risk estimate of Kabat et al. (4) had ade- etect a relative risk of 1.5 kemia, and the study by (6) found a significant de- yeloid leukemia in smok- tudies, then, are the only ent with a moderately in- f myeloid leukemia for

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hodological problem in co- that of differential loss to vever, the possibility of dif- to follow-up in the cohort explain the consistent asso- n smoking and myeloid leu- se-control studies. Moreover, noted to be at least 95 percent ree of the four cohort studies that reported on myeloid leukemia (11–13). Any differential losses in the remaining 5 percent of subjects are unlikely to alter the relative risk estimates significantly. In fact, the one cohort study that failed to find an elevated risk of myeloid leukemia in smokers had only 77 percent follow-up (16).

In general, the consistency of findings across a variety of research designs in the studies makes it difficult to invoke a single bias in explaining the findings.

The studies by Kabat et al. (4) and Cartwright et al. (6) deserve individual mention because they suffered from a methodological weakness not present in the other seven case-control studies. Cases were not sampled from a registry of incident leukemias. In the study by Kabat et al., cases were redefined from a population of hospitalized controls used in a previous study and represent only a fraction of the incident leukemia cases in these hospitals. In the study by Cartwright et al., cases were identified from hospital hematology clinics, and only 31 percent were alive to be interviewed. Selection bias due to the use of nonincident surviving cases may explain why these studies are inconsistent with the others. Smoking rates in surviving (prevalent) leukemia cases are likely to be lower than those in incident cases. This bias would result in an underestimate of the true odds ratio.

When these two studies are excluded from the analysis, the pooled odds ratio for myeloid leukemia in the case-control studies is 1.48 (95 percent CI 1.26–1.72). These risk estimates are almost identical to those for the cohort studies. Thus, selection of nonrepresentative cases and controls in two studies may explain the inconsistency between the pooled risk estimates for the case-control and cohort studies.

In addition to bias within the individual studies, the possibility of selective publication of positive results (publication bias) must be considered (28–30). The likelihood of publication bias was evaluated in two ways. First, the analysis was restricted to studies that were not designed specifically to examine the relation between smoking and leukemia. These studies reported on the relation between smoking and multiple causes of mortality (2, 11–14) or between leukemia and a wide range of potential risk factors (2, 3, 6). Publication bias is less likely for nonspecific studies because they examine a wide range of potential associations, and it is less plausible that a negative result for any one specific relation would lead to nonpublication. Of these nonspecific studies, four of five found a positive association between smoking and myeloid leukemia, and five of seven found a positive association between smoking and all leukemia. It is unlikely that publication bias explains the preponderance of positive findings in these studies.

Second, graphic analysis of the relation between effect size and study size has been suggested as a method to assess the likelihood of publication bias (30–32). In the absence of publication bias, when effect size is plotted against sample size (or standard error) in a funnel graph (33), a pyramid pattern with the apex at the true effect size should be obtained. Publication bias tends to skew the pyramid by creating a gap in the area of negative studies with small sample size (31, 32). A funnel plot of the 15 published studies of smoking and leukemia (figure 1) produced a pyramid shape with apex corresponding to a relative risk of about 1.3 and no gap in the lower left-hand comer of the pyramid. While this analysis does not rule out the possibility of publication bias, it provides further evidence that it is unlikely to explain the preponderance of positive findings in the 15 studies.

THE ROLE OF CONFOUNDING

There are several known confounding variables that must be considered in evaluating the relation between smoking and leukemia. These are age, sex, race, socioeconomic status, and exposure to known leukemogens. Age and sex are controlled for in all 15 studies. The remaining variables are now considered in terms of the direction and

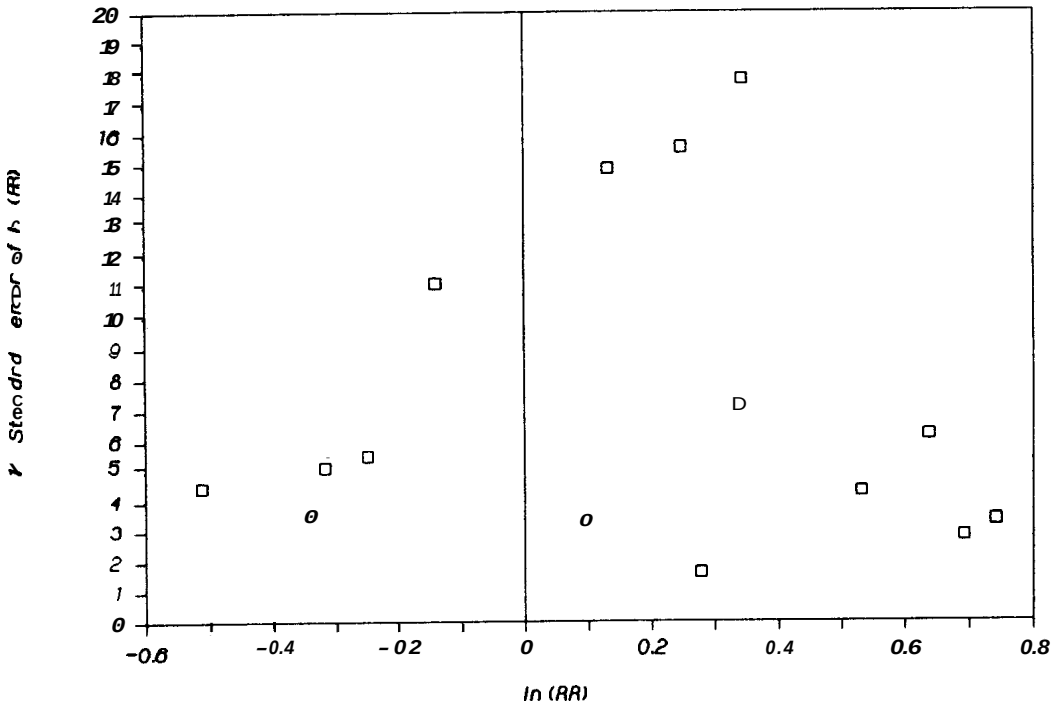


FIGURE 1. Funnel plot of relative risk (on a logarithmic scale) according to the inverse of standard error of lognormal relative risk (ln RR) calculated for 15 published studies of smoking and leukemia.

magnitude of effect they would have on the risk estimates.

Race

Only five of the positive studies were controlled for race. Leukemia is more common among whites than among nonwhites **(34).** Blacks are more likely to be smokers than are whites **(35).** Thus, confounding by race would result in an underestimate of the relative risk for current smoking and leukemia.

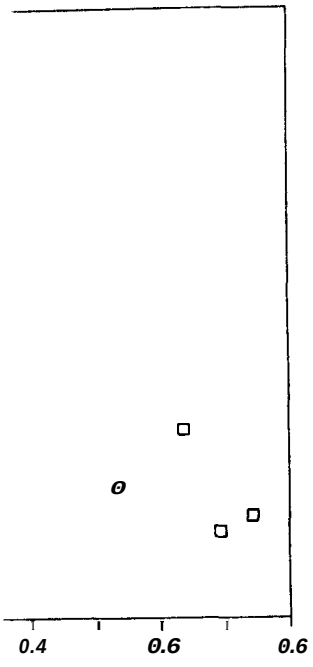
Socioeconomic status

Education and/or income levels were controlled for in five of the positive studies. There is a slight positive association of leukemia **with** higher **socioeconomic** status *(2).* There is a small negative association between both education and income and smoking **(35).** Thus, confounding by socioeconomic status would result in an underestimate of the relative risk of leukemia in smokers.

Exposure to known leukemogens

The major known environmental risk factors for leukemia are exposure to benzene, ionizing radiation, and chemotherapeutic agents **(34).** Only one of the studies controlled for these variables. Severson et al. (7) found no substantial change in the odds ratio or dose-response relation when analysis was restricted to subjects with no reported exposure to these agents. There is certainly a potential for confounding by exposure to known leukemogens, and this confounding would result in an overestimate of the relative risk. First, smokers are at increased risk of cancer at several sites and may be more likely than nonsmokers to be exposed to chemotherapeutic agents. Second, smokers are slightly more likely to report occupational exposure to chemicals. Stellman et al. (36) found that **54** reported occupational compared with **46** per and **52** percent of ever no difference in exposu ation. The relative risks ciated with occupation; have generally been in **(34).** Using these data greatest potential mag confounding on the rela the cohort studies. To bt assumed that all person cupational chemical ex to benzene, and a relati kemia in benzene-exp **used.** If there were no tween smoking and leuk trol for the effects of t under these conditions **in** the detection of a r **1.06.** Even under the r tions, the magnitude of posure to known leu small.

Confounding by know unlikely to explain the c between smoking and Confounding by an however, could explain risk in the range of **1.5.** clinical trial could elim of confounding. Nevertl the likelihood that con known factor explains t must be made. There mogeneity of the subj studies. Paffenbarger e male Harvard and Univ nia alumni. Weir and Du male labor union meml cupations. McLaughlir **only** male US veterans insurance in **1953.** Mil **only** California Sever **The** homogeneity of within many of the studi likelihood that confoun **factor** explains the obs



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ire to chemicals. Stellman et al. (36) found that 54 percent of smokers reported occupational chemical exposure compared with 46 percent of nonsmokers and 52 percent of ever smokers. There was no difference in exposure to ionizing radiation. The relative risks for leukemia associated with occupational benzene exposure have generally been in the range of 1.5–3.0 (34). Using these data, we estimated the greatest potential magnitude of effect of confounding on the relative risk estimates in the cohort studies. To be conservative, it was assumed that all persons who report any occupational chemical exposure are exposed to benzene, and a relative risk of 3.0 for leukemia in benzene-exposed workers was used. If there were no true association between smoking and leukemia, failure to control for the effects of exposure to benzene under these conditions would have resulted in the detection of a relative risk of only 1.06. Even under the most extreme conditions, the magnitude of confounding by exposure to known leukemogens is quite small.

Confounding by known variables, then, is unlikely to explain the observed association between smoking and myeloid leukemia. Confounding by an unknown factor, however, could explain a consistent relative risk in the range of 1.5. Only a randomized clinical trial could eliminate the possibility of confounding. Nevertheless, a judgment of the likelihood that confounding by an unknown factor explains the observed relation must be made. There is a remarkable homogeneity of the subjects in many of the studies. Paffenbarger et al. (3) studied only male Harvard and University of Pennsylvania alumni. Weir and Dunn (11) studied only male labor union members in high-risk occupations. McLaughlin et al. (13) studied only male US veterans with government life insurance in 1953. Mills et al. (15) studied only California Seventh-Day Adventists. The homogeneity of cases and controls within many of the studies argues for a small likelihood that confounding by an unknown factor explains the observed association.

CRITERIA FOR CAUSAL INFERENCE

Consistency of association

There is a good deal of consistency in the epidemiologic studies. In fact, for myeloid leukemia, all but two of the studies are consistent with a relative risk of about 1.5 for ever smokers.

Strength of association

This criterion is not met by the studies. The relative risk for myeloid leukemia in ever smokers appears to be about 1.5. This is low enough that confounding by some unrecognized variable could potentially explain the observed association. This does not rule out a causal relation, however, as the true relative risk could be quite small.

Dose-response relation

Six of the nine studies that looked for a dose-response relation between intensity of smoking and leukemia risk found one (7, 9, 13–16). This relation was statistically significant in five of these (7, 9, 13, 15, 16).

Decreased risk after removal from exposure

The one study that examined this question (7) found a linear trend of decreasing risk with increasing number of years since smoking was stopped. In addition, the elevated risk was present only for smokers who inhaled into the chest.

Biologic plausibility

There are several lines of evidence for the plausibility of a causal relation between smoking and leukemia.

Animal studies. Several studies have demonstrated the induction of hematopoietic tumors in animals by tobacco smoke. Keast et al. (37) found an elevated incidence of lymphocytic lymphomas in smoke-exposed mice. DiPaolo and Levin (38) found a greatly increased incidence of lymphomas in smoke condensate-treated mice.

Cytogenetic studies in humans. Numerous studies have documented an increased frequency of cytologic changes in peripheral blood lymphocytes of smokers (38). Specifically, an increased frequency of chromosomal aberrations, sister chromatid exchanges, and micronuclei have been found. Most recently, Bridges et al. (39) found an increased frequency of thioguanine-resistant mutants in circulating T lymphocytes of smokers.

Leukemogens in cigaretie smoke. At least three chemical leukemogens (benzene, urethane, and nitrosamines) are present in tobacco smoke **(1).** In addition, the concentration of lead-210, a radioactive leukemogen, has been demonstrated to be significantly increased in the bones (40) and soft tissues (41) of smokers.

CONCLUSION

Based on the existing epidemiologic data; the analysis of the roles of chance, bias, and confounding; and the criteria for causal inference, it appears that smoking causes myeloid leukemia.

A causal relation between smoking and leukemia has important public health implications. With a relative risk of 1.5 for myeloid leukemia in ever smokers and the Centers for Disease Control and Prevention estimate of a 55.8 percent prevalence of ever smoking (35), the population attributable risk is 22 percent. Since the causes of leukemia are largely unknown, this would make smoking the leading known cause of leukemia. Leukemia should be added to the list of smoking-related diseases, and efforts to prevent leukemia should include appropriate attention to the role of smoking.

Since there are insufficient data to rule out the possibility that smoking causes lymphatic leukemia and to separate out the effects of smoking on acute versus chronic myeloid leukemia, future studies should be designed specifically to determine the effects of smoking on cell-specific leukemia risk.

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