

Letter to the Editor

Correspondence re: Lawrence A. Loeb *et al.* Smoking and Lung Cancer: An Overview. *Cancer Res.*, 44: 5940-5958, 1984.

The position paper of Loeb *et al.* asserts that it "... summarizes the overwhelming evidence that tobacco smoking is the cause of 30 to 40% of deaths from cancer. The focus is on lung cancer..." Their paper would have been more balanced and complete had they discussed alternatives to the causal interpretation of positive associations and described studies that have aimed to discriminate between them.

Given an established association between a habit such as smoking and a disease such as lung cancer, the rules of scientific inference oblige us to evaluate the following possibilities: hypothesis 1, the smoking, or something closely connected with it such as means of ignition, causes the disease (the "causal hypothesis"); hypothesis 2, the disease, or an associated pre-disease condition such as dysplasia or carcinoma *in situ*, causes the smoking (the "converse causal" hypothesis); hypothesis 3, a third factor, such as constitution, causes or predisposes both to the habit and to the disease (the "common cause" hypothesis); and hypothesis 4, because they are not mutually exclusive, any combination of hypotheses 1 to 3 (the "mixed" hypothesis). Passey (1) and Herrold (2) found that the mean age of onset of lung cancer was effectively independent of both the age of commencing smoking and the level of smoking and hence it seems most unlikely that hypothesis 2 makes any appreciable contribution to the association between smoking and lung cancer in Western males. The common cause hypothesis (hypothesis 3) has been extremely difficult to reject (3, 4) and because the pertinent evidence is statistical in character, absolute rejection is unattainable.

We are therefore required in a rigorous analysis to estimate, under hypothesis 4, the relative contributions of hypotheses 1 and 3 to any overall association, complete with appropriate confidence intervals. As far as I am aware no one has succeeded in this task although statisticians of the eminence of Fisher (5), Brownlee (3), and Yerushalmy (6) have recognized the potential importance of hypothesis 3.

A different methodology is followed in the United States Surgeon General's reports on health and smoking and is endorsed by Loeb *et al.* Five poorly defined criteria for evaluating causal significance are adopted (7): (a) the consistency of the association; (b) the strength of the association; (c) the specificity of the association; (d) the temporal relationship of the association and (e) the coherence of the association. I have argued in Ref. 4 that "the criteria are not given adequate definition but unless they are so lax as to be meaningless we can only conclude that, in the context of lung cancer: (a) reported associations are inconsistent; (b) the reported strength of association ranges widely; (c) the association has no specificity [acknowledged also by the Surgeon General (7)]; (d) the temporal relationship shows many anomalies; and (e) because of (a) to (d), together with evidence relating, for example, to inhalation and to contradictions between experimental and epidemiological findings [references given], the association lacks coherence." The Surgeon General also asserts (7) that "the causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability." I submit that this heavy and repeated emphasis on subjective judgment is incompatible

with a scientific analysis. Furthermore, by treating the issue of causality on an all-or-none basis, the difficulties of evaluating hypothesis 4 in quantitative terms are evaded but not solved. I added in Ref. 4 that "Because not even one criterion is indisputably satisfied it follows that the Report, on its own terms, should have rejected the causal interpretation of the association between smoking and lung cancer... Does it then follow that the relation between smoking and lung cancer is wholly non-causal? In my view that inference would be as unjustified as the Report's own conclusion; on present evidence it seems very unlikely that the whole of the association observed, for example, in male Caucasoid populations should be attributed to causal effects of smoking but we cannot as yet rule out the possibility that some part should be."

Loeb *et al.* rightly direct attention to the importance of the temporal trends of smoking and lung cancer but fail to mention that in England and Wales the proportionate changes in mortality, both overall and from one 5-year period to another, were strikingly synchronous in the two sexes from 1901 to 1955 even though the post-1920 sharp rise in smoking by women lagged about 30 years behind that in men (4). Hence the enormous rises in recorded mortality from lung cancer were caused, in the main, by factors other than smoking; there seems little doubt that changes in diagnostic accuracy with better recognition of lung cancer following the advent of diagnostic X-rays constituted one such factor. Any increases that might reasonably be attributed to smoking would have been much too small to be detected against the overwhelming background of synchronous changes.

The randomized trial has been described by Feinstein (8) as the "gold standard" of epidemiology and, in principle, is one of the best methods available of evaluating hypotheses 1 and 3. Neither the method nor the results of such trials were mentioned by Loeb *et al.* However, in common with all other epidemiological methods, it falls short of the theoretical ideal. Randomized trials of the effects of quitting smoking have been successfully carried out (at considerable cost) but it remains possible that the act of quitting is followed by other changes, of a psychological, dietary, or other nature, that are carcinogenic or anticarcinogenic. Apart from this fundamental difficulty, which might be deemed to be of little consequence where lung cancer is concerned, and the statistical limitations necessarily imposed by finite numbers, we encounter a further barrier to hypothesis testing. We have no sound theory of the mechanism of tobacco carcinogenesis in humans that would enable us to predict cancer levels following the quitting of smoking. Observations of self-selected quitters have little or no value because such groups differ from self-selected continuing smokers in various ways before they abandoned the habit (9). Moreover, at 1-4 yr after quitting smoking the level of lung cancer is higher than that in the control continuing smokers (7) suggesting that the presence of the cancer, or a precancerous condition, sometimes caused the quitting.

In spite of the complications randomized intervention trials have one supreme advantage over case-control and prospective studies. They eliminate the bias of self-selection for quitting. Only one statistically significant difference in cancer incidence

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between randomized "normal care" and "intervention" groups has been reported thus far. Rose *et al.* (10) recorded 19 cases of cancer other than lung cancer in the normal care group and 41 in the intervention, low-smoking, group; in a test of the null hypothesis they quoted $P = 0.003$. On a causal hypothesis the lower rate of smoking in the intervention group (a self-reported average of 7.6 cigarettes a day below the normal care group) ought to have produced some reduction in the incidence of cancers over the 10-year period of the trial, although we have no reliable way of estimating how much. Hence the causal hypothesis of the association between smoking and cancers other than lung cancer is rejected at an even higher, although not calculable, level. The trend in the MRFIT study (11) was in the same direction (47 deaths in the intervention group of 6428 men and 41 in the usual care group of 6438) but did not approach statistical significance.

A more useful test of the causal/constitutional interpretations would be to combine the data from the Whitehall and MRFIT studies and to analyze the deaths and registrations for all types of cancer that associate appreciably with smoking in case-control and prospective studies of males in the United States and United Kingdom. The log-rank test would probably afford the best discrimination. Perhaps the organizers of the two trials could be persuaded to perform such an analysis on their data.

In the meantime, those of us with an inborn tendency to scepticism, and with an understanding of methodology that differs from that of the Surgeon General, find the "evidence that tobacco smoking is the cause of 30 to 40% of deaths from cancer" to be less than overwhelming.

Reply 1

We appreciate this opportunity to respond to Dr. Burch. We are gratified that he rejects his possible hypothesis 2, that cancer causes smoking. However, Burch still argues that the epidemiological data on smoking and cancer might be explained by hypothesis 1 (smoking causes cancer), hypothesis 3 (a third agent causes both smoking and cancer), or some combination of hypotheses 1 and 3.

We are gratified that Burch sees value in a temporal analysis of the effects of smoking on lung cancer. He cites his own work examining data from the United Kingdom (1) as evidence against hypothesis 1, that smoking causes cancer. Burch claims that the "synchronous" increase in lung cancer among both men and women, despite the temporal lag in tobacco smoking by women, suggests that these increases are due chiefly to improved diagnostic methods, not to smoking. Contrary to Burch's interpretation, a replot of his data on a linear scale shows more definitively that from 1930 to 1950, lung cancer rates among men rose more rapidly than rates among women. Moreover, Burch halted his analysis at 1955, just before lung cancer rates in men reached a plateau, while rates in women continue to rise to this day. If Burch is to argue that increases in lung cancer are due to improved methods of detection, he must assume that these methods contain a sex bias that decreases with time, a situation that strains credulity. Moreover, considering the rapid demise of patients with lung cancer, early detection is going to have little consequence on incidence. Thus, it appears that one of Burch's major reasons for rejecting hypothesis 1 crumbles quickly upon inspection.

With regard to the intervention trial studies, the following

References

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comments are relevant.

In the MRFIT study (3), subjects were placed into groups of "special intervention," who were advised to quit smoking and change diet; or "usual care," who received no such advice. However, all subjects were informed that they were considered "high-risk" for coronary heart disease. With time, both the "usual care" group and the "special intervention" group showed decreases in risk factors, such as serum cholesterol and cigarette smoking, and both groups experienced substantially lower mortality than had been anticipated. Thus, the information that they were considered "high risk" must have motivated some members of the "usual care" group to modify their habits. It therefore may be somewhat irrelevant to compare a group which was advised to stop smoking with a group that was not. More instructive is a comparison between those who continued to smoke with those who quit. Within both groups, "usual care" and "special intervention," coronary heart disease mortality rates were lower for quitters than for those who did not quit (lung cancer rates were not reported for smokers *versus* quitters).

Similar dynamics were observed in the study by Rose *et al.* (4). Smoking declined among the "usual care" group, perhaps due to notification of high risk, as well as among the "intervention" group. Within both groups, 10-year lung cancer mortality rates were lower for those who quit smoking after 1 year than those who continued smoking cigarettes. With regard to an observed higher number of non-lung cancers in the intervention group, the authors note that there was no site specificity and no relation to change in smoking habit; they thus consider the higher number "more likely to have been due to chance than to intervention." More important is the authors' concluding statement: "In our view the present policy of encouraging smokers