6th October, 1956.

Dear Todd,

I am enclosing a note on my reflections upon looking again at this smoking and cancer of the lung material.

I can take a train arriving 11.19 at Liverpool Street. It will be nice if you can arrange a car and some means of recognition.

Sincerely yours,
A Note on Some of the Evidence Produced in Relation to Tobacco Smoking and Cancer of the Lung

by Sir Ronald A. Fisher

It may not be premature for me to put down my reactions to the published work on smoking and lung cancer, most of which I had seen at the time of publication, but my memory of which has been refreshed by looking through some of this material again.

Doll and Bradford Hill, in confirmation of some previous workers, report that patients suffering from cancer of the lung include a larger proportion of cigarette smokers, and in particular of heavy cigarette smokers, than that found among the Control Groups chosen for comparison. Of course, such an apparent association deserves to be followed up by varied inquiries. Probably the most important of those actually carried out consists in classifying healthy persons of the appropriate age groups, according to their smoking habits, and ascertaining subsequently the incidence of lung cancer among deaths in these smoking classes. The improvement effected by this second mode of inquiry lies, I think, entirely in it providing a more appropriate Control Group, and not at all in any supposed bearing on the question of causation or contingency of the order in which the observations smoker/non-smoker, and cancer/non-cancer, are made.
In the transition from recognizing contingency to claiming causation, I would say that Doll and Hill have been both precipitate and careless. The transition can be logically complete in the experimental sciences, and I think the authors concerned have been rash in speaking as though the association observed was logically equivalent to an experiment in which so many thousand experimental subjects have been assigned to Treatment A, "no cigarettes", and so many thousand have been assigned to Treatment B, "20 cigarettes a day". From the point of view of experimental design, the observations must at this point be criticized severely in that there has been no randomization of the experimental material, such as is needed when dealing with flies or rats in drawing inferences of causation. The smoking classes are self-selected. No studies have been made as to what causes, external or internal, are effective in determining whether a subject shall be a non-smoker, a pipe smoker, a cigarette smoker, etc. We ought to be clearly and explicitly aware either of the principle causes in this field, or of our ignorance of what causes are in action. It would be frankly incredible to assert that these smoking classes are not systematically differentiated, at least in respect of genotype, if not also in respect of environmental exposures not irrelevant to the subsequent incidence of cancer. The importances of genotypic differences are, of course, familiar to
workers in cancer research with mice, and have been emphasized in Man by recent findings of the association of blood-group A with cancer of the stomach. In this case it happens that an easy serological test distinguishes the one class of genotypes from another, and the case makes it probable that any other genotypic separation, whether we can recognize it or not, would also be associated with different rates of cancer incidence.

In clinical trials generally, it would be too much to expect that the full rigour of the experimental sciences should always be attainable. When, however, it is not attained, or even attempted, this should be made clear in reporting the investigations, which may still be suggestive of real effects which will require other types of evidence to establish their reality. However, other types of evidence may have weight without being conclusive, and in the papers with which I am concerned, some efforts are made to supply such supplementation. Thus at an early stage Doll and Hill seem to claim a simple relationship between quantity of tobacco consumed, and frequency of lung cancer, and that the difference between pipe smokers and cigarette smokers could be ascribed, rather surprisingly, to the supposed fact that pipe smokers smoke less than cigarette smokers. I do not suppose there is evidence for this as a statement of fact, and it would seem to be admitted at a later stage that the
difference observed between pipe smokers and cigarette smokers is not to be explained on the simple quantitative basis originally proposed. The view that we were dealing with direct causation would have been supported by any such simple relationship, and it is by so much weakened when it is admitted that large differences appear which are not explained by this simple theory. In fact the supposition that there is any association at all between lung cancer and pipe smoking becomes questionable when it is remembered that the classification between pipe smokers and cigarette smokers is not sharp and mutually exclusive, but that some overlap must be admitted, that pipe smokers frequent the same places, e.g. railway smoking carriages, as cigarette smokers, and, even if they do not like cigarettes, can be induced by social convention, in restaurants, and theatre intervals, to take tobacco in a form which is really rather unsatisfying. The mild and insignificant degree of association found for pipe smokers may well arise secondarily from such casual admixture.

The second case in which support for the theory of causation might have been supplied by available data, lies in the temporal course of events, in which a very large increase in the incidence of lung cancer was, at first sight, thought to be capable of explanation in terms of an increase of the habit of smoking. This association, as often happens with those based on time
series, breaks down on examination at every point. It is questionable if there has been any increase in the habit of smoking among males, and it is among males that the greatest increase of lung cancer has been observed. There probably has been an increase of smoking among women in the last 50 years or so, and the increase of lung cancer has been very much less, both absolutely and relatively, in the female sex. One of the diagrams of Hill and Doll seems, if I understand it, to show the course of increase of lung cancer for men and women together, per unit number of population, along side the increase of the total importation of tobacco consumed by both men and women, and without allowance for increase in the adult consuming population. This seems to be quite uncritical and misleading. The course of change from year to year does not lend the support much needed for the theory of direct causation, any more than the comparison of tobacco consumed in different forms.

At one point Hill and Doll express themselves as unable to imagine any alternative to direct causation in explanation of the association which they have demonstrated. This at least shows that they do not think they have excluded such alternatives, and frankly, if they cannot imagine others, that they cannot have reflected much on associations found in other cases between quite irrelevant variables.

6th October, 1956.

(signed) Ronald A. Fisher.