

# SMOKING. THE CANCER CONTROVERSY: SOME ATTEMPTS TO ASSESS THE EVIDENCE

## THE AUTHOR

SIR RONALD A. FISHER has achieved a formidable reputation amongst statisticians for his pioneer work in this field during the past forty years. His particular achievement has been in the development of statistical methods appropriate to biological research. During his brilliant career in academic and research work many honours have come to him: he has been awarded the Royal, Guy, Darwin and Copley Medals of the Royal Society of which he is a Fellow; he is a Foreign Associate of the United States National Academy of Science, a Foreign Member of the Royal Swedish and Royal Danish Academies of Sciences, and a Foreign Member of the American Philosophical Society; he holds degrees from the Universities of Ames, Chicago, Harvard, Calcutta and Glasgow; he is a Fellow of Gonville and Caius College, Cambridge, and a former Arthur Balfour Professor of Genetics in the University of Cambridge; he has also been Galton Professor of Eugenics in University College, London.

It is appropriate that Sir Ronald Fisher should have written this pamphlet because to his scientific reputation he has added a reputation for frank and outspoken contributions to many statistical debates. This pamphlet is a fair-minded assessment of the value of the statistical evidence relating to the incidence of lung cancer in smokers.

## PREFACE

Scientists in many fields have felt the need for canons of valid inference, and these have been becoming available in what are, properly, experimental sciences, by the rapid development of interest and teaching in “The Design of Experiments”.

Unfortunately, it has become obvious that many teaching departments, with mathematical but without scientific qualifications, have plunged into the task of teaching this new discipline, in spite of harbouring gravely confused notions of the logic of scientific research.

If, indeed, the statistical departments engaged in university teaching, were performing their appropriate task, of clarifying and confirming, in the future research workers who come within their influence, an understanding of the art of examining observational data, the fallacious conclusions drawn, *from a simple association*, about the danger of cigarettes, could scarcely have been made the basis of a terrifying propaganda.

For this reason I have thought that the fallacies must be attacked at both of two distinct levels; as an experimental scientist, and as a mathematical statistician. The lecture on *The Nature of Probability* was to a non-mathematical audience, on the general question of the validity of inferences from facts available on lung cancer.

As the subject has developed during the last year or so, it has seemed important to reprint these letters and addresses strictly in order of their date.

RONALD A. FISHER

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### ALLEGED DANGERS OF CIGARETTE-SMOKING

Your annotation on “Dangers of Cigarette-smoking”<sup>\*</sup> leads up to the demand that these hazards “must be brought home to the public by all the modern devices of publicity”. That is just what some of us with research interests are afraid of. In recent wars, for example, we have seen how unscrupulously the “modern devices of publicity” are liable to be used under the impulsion of fear; and surely the “yellow peril” of modern times is not the mild and soothing weed but the original creation of states of frantic alarm.

A common “device” is to point to a real cause for alarm, such as the increased incidence of lung cancer, and to ascribe it urgent terms to what is possibly an entirely imaginary cause. Another, also illustrated in your annotation, is to ignore the extent to which the claims in question have aroused rational scepticism. The phrase “in the presence of the painstaking investigations of statisticians that are seen to have closed every loophole of escape for tobacco as the villain of the piece”, seems to be pure political rhetoric, even to the curious practice of escaping through loopholes. I believe I have seen the sources of all the evidence cited. I do see a good deal of other statisticians. Many would still fell, as I did about five years ago, that a good *prima facie* case had been made for further investigation. None think that the matter is already settled. The further investigation seems, however, to have degenerated into the making of more confident exclamations, with the

<sup>\*</sup>*British Medical Journal*, June 20, p. 1518.

studied avoidance of the discussion of those alternative explanations of the facts which still await exclusion.

Is not the matter serious enough to require more serious treatment?

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In the *Journal* of July 20 Dr. Robert N. C. McCurdy writes: “Fisher’s criticism<sup>†</sup> . . . would not be so unfair if he had specified what alternative explanations of the facts still await exclusion”. I had hoped to be brief. A few days later the B.B.C. gave me the opportunity of putting forward examples of the two classes of alternative theories which any statistical association, observed without the predictions of a definite experiment, allows—namely, (1) that the supposed effect is really the cause, or in this case that incipient cancer, or a pre-cancerous condition with chronic inflammation, is a factor in inducing the smoking of cigarettes, or (2) that cigarette smoking and lung cancer, though not mutually causative, are both influenced by a common cause, in this case the individual genotype.

The latter unexcluded possibility was known to Dr. McCurdy but he brushes it aside with abundant irony. Is he really persuaded that this is the way to arrive at scientific truth? Dr. McCurdy points out correctly that difference in the genotypic composition of the smoking classes—non-smokers, cigarette smokers, pipe smokers, etc., would not explain the secular change in lung cancer incidence. I have never thought that it would be charged with this task. Is it axiomatic that the differences between smoking classes should have the same cause as the secular change in incidence? Is there the faintest evidence to support this view? Indeed, Dr. McCurdy’s belief that cigarette smoking causes lung cancer would be more secure if he did not consider it with the *non-sequitur* that increase of smoking is the cause of increasing cancer of the lung. For at this point there appears one of those massive and

<sup>†</sup>*British Medical Journal*, July 6, p. 43.

recalcitrant facts which have been emerging through the smoke screen of propaganda. When the sexes are compared it is found that lung cancer has been increasing more rapidly in men relative to women. The absolute rate of increase is, of course, obscured by improved methods of diagnosis, and by the increased attention paid to this disease, but the relative proportionate changes in men and women should be free from these disturbances, and the change has gone decidedly against the men. But it is notorious, and conspicuous in the memory of most of us that over the last fifty years the increase of smoking among women has been great, and that among men (even if positive) certainly small. The theory that increased smoking is "the cause" of the change in apparent incidence of lung cancer is not even tenable in face of this contrast.

For the secular change, therefore. neither the smoking causation theory nor the theory of differential genotype will afford an explanation. For the contrast between cigarette smokers and non-smokers both are available; for the contrast between cigarette smokers and pipe smokers the first theory requires some special pleading, but this has never been lacking. The two circumstances (1) that heavy smokers show a greater effect than light smokers, and (2) that persons who have voluntarily abandoned smoking react like non-smokers or light smokers, are not independent experimental confirmation of the smoking theory. They are only reiteration of the main association to be explained. Any theory which explains this association may be expected to explain these facts also.

Differentiation of genotype is not in itself an unreasonable possibility. Indeed strains of mice if genotypically different almost invariably show differences in the frequency, age-incidence and type of the various kinds of cancer. In Man cancer of the stomach has been shown to be favoured by the gene for the blood group A. My claim, however, is not that the various alternative possibilities which have been excluded all command instant assent, or are going to be demonstrated. It is rather that excessive confidence that the solution has already been found is the main obstacle in the way of such more penetrating research as might eliminate some of them. I am sure it is useless to treat

the question as though it were a matter of loyalty to a political ideology or of forensic disputation. Statistics has gained a place of modest usefulness in medical research. It can derive and retain this only by complete impartiality, which is not unattainable by rational minds. We should not be content to be "not so unfair", for without fairness the statistician is in danger of scientific errors through his moral fault. I do not relish the prospect of this science being now discredited by a catastrophic and complacent howler. For it will be as clear in retrospect, as it is now in logic, that the data so far do not warrant the conclusions based upon them.

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*Sir Ronald Fisher*

SEVEN OR EIGHT years ago, those of us interested in such things in England heard of a rather remarkable piece of research carried out by Dr. Bradford Hill and his colleagues of the London School of Hygiene. We heard, indeed, that it was thought that he had made a remarkable discovery to the effect that smoking was an important cause of lung cancer. Dr. Bradford Hill was a well-known Fellow of the Royal Statistical Society, a member of Council, and a past president—a man of great modesty and transparent honesty. Most of us thought at that time, on hearing the nature of the evidence, which I hope to make clear a little later, that a good *prima facie* case had been made for further investigation. But time has passed, and although further investigation, in a sense, has taken place, it has consisted very largely of the repetition of observations of the same kind as those which Hill and his colleagues called attention to several years ago. I read a recent article to the effect that nineteen different investigations in different parts of the world had all concurred in confirming Dr. Hill's findings. I think they *had* concurred, but I think they were mere repetitions of evidence of the same kind, and it is necessary to try to examine whether that kind is sufficient for any scientific conclusion.

The need for such scrutiny was brought home to me very forcibly about a year ago in an annotation published by the British Medical Association's *Journal*, leading up to the almost shrill conclusion that it was necessary that every device

of modern publicity should be employed to bring home to the world at large this terrible danger. When I read that, I wasn't sure that I liked "all the devices of modern publicity," and it seemed to me that a moral distinction ought to be drawn at this point. There is the attitude of a man (may I say, I think it is an entirely rational attitude and one within his own competence to judge) who says, "There seems to be some danger—I can't assess whether it is infinitesimal or serious. This habit of mine of smoking isn't very important to me. I will give up smoking as a kind of insurance against a danger which I am quite unable to assess." That seems to me a perfectly rational attitude. What is not quite so much the work of a good citizen is to plant fear in the minds of perhaps a hundred million smokers throughout the world—to plant it with the aid of all the means of modern publicity backed by public money, without knowing for certain that they have anything to be afraid of in the particular habit against which the propaganda is to be directed. After all, a large number of the smokers of the world are not very clever, perhaps not very strong-minded. The habit is an insidious one, difficult to break, and consequently in many, many cases there would be implanted what a psychologist might recognize as a grave conflict.

If there is cause for fear, let there be warning. But there is no reason for this in the first rational response that I described—that does not require scientific proof that there is reason to fear. There is only the possibility that there is reason.

Before one interferes with the peace of mind and habits of others, it seems to me that the scientific evidence—the exact weight of the evidence free from emotion—should be rather carefully examined. I may say, I am not alone in this. I have been interested to note that leading statisticians in this country also—and I contact a good many statisticians both in my own country and here—are exceedingly skeptical of the claim

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that decisive evidence has been obtained. In the popular press, the matter seems to be argued, as always, a little off the simplest lines. For example, I find people saying, "These statisticians think this"—"These statisticians think that," or representing that this kind of evidence which has been produced has been attacked as being merely statistical. Now I should be the last person to attack evidence for being merely statistical, because for a great part of my work I have been concerned with the problem of *how* experimentation should be carried out, *how* reasoning processes should be applied to the data supplied by experimentation or by survey so as to give really conclusive answers.

Progress has been made during the last twenty-five years. A large part of the educated world, at least in the statistical field, has become aware that, by taking certain specific precautions, entirely unchallengeable conclusions can be obtained in the experimental field. The work was done primarily in agriculture, where problems of experimentation attracted the attention of leading agronomists at an early time. The key words which emerged in the course of these inquiries—replication, randomization, and control—are now widely understood.

We understand that replication is required for two purposes: it is necessary in order to add precision to our results by diminishing the error to which they are subject, and it is essential in a more important way, as supplying the only means of the estimation of such error.

Although replication is essential in this way, it is not sufficient without the added precaution of randomization, that is, the assignment of the different treatments—which may be manurial treatments, or different varieties of agricultural crops, or different methods of tillage—to the plots set aside for the purpose, in such way at random as to guarantee the validity of the experiment, and in particular of the estimate of error to which it is subject. This necessity for randomization was

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brought home to agriculturists largely because it was found that human judgment was very liable to err in this matter, that if one tries to think of numbers at random, one thinks of numbers very far from at random. If one tries to think of a card of an ordinary playing deck, it's well known (perhaps it's not so well known—it is known to me, at least) that red cards are thought of more readily than black cards, that odd numbers are thought of more readily than even numbers, and that the Queen of Diamonds is a hot favorite. This proclivity of the human mind affects any consciously guided choice or assignment of material. Agriculturists, at least, do not trust themselves to choose plots and say that they have been chosen at random. They use decks of cards or, more expeditiously, in recent years, some of these large collections of random sampling numbers which some of you may have seen at the ends of books of tables and perhaps wondered what on earth they can be for. They are in constant use in the design of experiments.

There is a logical aspect, too, of randomization which needs emphasis in this connection. Supposing we have an association—an observable and verifiable association—between two things. I remember Professor Udny Yule in England pointing to one which illustrates my purpose sufficiently well. He said that in the years in which a large number of apples were imported into Great Britain, there were also a large number of divorces. The correlation was large, statistically significant at a high level of significance, unmistakable. But no one, fortunately, drew the conclusion that the apples caused the divorces or that the divorces caused the apples to be imported. The early logicians would say that *post hoc* is not the same as *propter hoc*, or in other words—as it would be put in the early years of our century, when statisticians had had perhaps ten years' experience of the correlation coefficient as a means of research—that *correlation is not causation*. The fact is that if two factors, *A* and *B*, are associated—clearly, positively,

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with statistical significance, as I say—it may be that *A* is an important cause of *B*, it may be that *B* is an important cause of *A*, it may be that something else, let us say *X*, is an important cause of both. If, now, *A*, the supposed cause, has been randomized—has been randomly assigned to the material from which the reaction is seen—then one may exclude at a blow the possibility that *B* causes *A*, or that *X* causes *A*. We know perfectly well what causes *A*—the fall of the dice or the chances of the random sampling numbers, and nothing else.

But in the case where randomization has not been possible, these other possibilities lie wide open and should be excluded, or at least every effort should be made to exclude them, before we can assert that causation has been established. When I spoke to Bradford Hill in the early days of this affair, he was entirely unwilling to claim that causation had been proved. He said he didn't see what else it could be, but he was certainly unwilling to make the claim which is being made vociferously during the last year or two by committees reporting to the Medical Research Council in England, and to the American Cancer Society. Now, randomization is totally impossible, so far as I can judge, in an inquiry of this kind. It is not the fault of the medical investigators. It is not the fault of Hill or Doll or Hammond that they cannot produce evidence in which a thousand children of teen age have been laid under a ban that they shall never smoke, and a thousand more chosen at random from the same age group have been under compulsion to smoke at least thirty cigarettes a day. If that type of experiment could be done, there would be no difficulty.

The principles of experimentation—which, as I mentioned, were developed in the agricultural field, where the need for them was greater or more manifest—have spread, and spread rapidly and healthily, into the other experimental sciences. And I suppose during the last fifteen years a dozen important books have been written on the design of experiments, prin-

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cipally to make clear what these principles are in their particular applications in chemistry, physics, biology, or what you may will.

But the most difficult field for the application of these principles has always been the medical field. This is partly because you can do things to a rat or rabbit which may not be good for it, feeling that in a good cause you have a right to do so. But no one feels—and especially a medical man could not feel—that it is right to do things to a human being which probably will do him harm. Consequently, deliberate experimentation has not been very widely used in the medical field. There is a movement at the present time to organize clinical trials, let us say, of new drugs or of new antibiotics in such a way that an impartial judgment of comparing the new with the old may be obtained by hospital staffs. And that would involve applying the new and the old at random to some of the hospital patients. So long as no body of medical opinion can say with confidence that one is better than the other, or perhaps that in matters usually as complicated as this, for what cases one drug is the better and for what cases the other—so long as that state of ignorance remains, it would be perfectly fair, I think, to clear the air by such simple experimentation.

But manifestly we cannot experiment with the same freedom that is possible with agricultural animals and laboratory animals in other sciences. For lack of that, medical research has had to rely a good deal on uncontrolled experiments, uncontrolled observations; and of course from the time of Jenner onwards there were numerous cases where an observant (and also, I may say, an experimental) physician may be able to make out an exceedingly strong case. Jenner's work was not completely passive. And Dr. Snow, who studied and in the end quelled the occurrence of cholera in London, used a very large number of different types of inquiry in order to gain sufficient confirmation of his important con-

clusion, namely, that it was fecal contamination in the water supply that was responsible for the cholera, an opinion that is easy to take for granted at the present time, but which in the absence of any knowledge of the organisms concerned—or, indeed, knowledge that the disease *was* caused by an organism—was a considerable advance, just as Jenner's was also in the case of smallpox. Consequently, when inconclusive evidence is criticised on the grounds that it is inconclusive, it is not uncommon for medical men to defend it, perhaps with certain indignation, on the ground that in the past medical science has made notable advances primarily—not solely, never only, but primarily—by the observational method.

Now, in the sciences we also have cases in which experimentation is impossible. In astronomy, for example, experimentation, you might say, has only just begun. And in those sciences we must use what I may call *sidelights*.

Let me illustrate this possibility with a very few instances. The first reports of Hill and Doll made a very simple claim. They said that the additional amount of lung cancer observed in patients was proportional to the amount of tobacco they consumed. That simple conclusion was quite rapidly withdrawn, and it was admitted that tobacco consumed in the pipe or in the cigar did not appear to have so close an association with lung cancer as that consumed in the cigarette. And this was a puzzling thing. After all, tobacco is burned in all three cases. The effluvia, smoke, or aerosol from the burning tobacco passes into the mouth, partly into the throat, partly, indeed, into the lungs, in all three cases. It is not obvious—it is not what one would guess at first sight, it was not what Doll and Hill guessed at first—that the one sort of smoke should be comparatively or perhaps wholly innocuous and the other sort should have the effect of inducing the beginnings of a dreadful disease.

And now I must go back and recall just what the kind of evidence it was that Hill and Doll laid before us at the be-

ginning, and in what ways it has been extended by other evidence.

The first inquiry was to take about 1500 patients in a number of different hospitals who had been diagnosed as suffering from lung cancer. Of course the diagnosis is enormously aided in recent times by the use of radiology. The lung cancers can be perceived by their shadows when X-rays are passed through the lungs. Consequently there was good reason to think that these patients—although they were alive and had not been examined post-mortem—really were lung cancer cases. Arrangements were made to record their smoking habits and their smoking history: non-smokers, cigarette smokers, pipe smokers, estimates of the amount of daily consumption of tobacco in each case, and a number of other questions. A similar number, perhaps a few more, of non-cancer patients from the same hospitals received the same questionnaire, and the comparison between these two samples, one of them selected as being lung cancer cases and the other as being in hospitals from some other condition, was made of the classification by smoking habit. And it appeared from that that the cigarette smokers were more common among the sufferers from lung cancer than they were among other patients, and that within the cigarette smokers, heavy cigarette smokers were more common among the lung cancer patients than medium or light cigarette smokers.

The statement that consumers of tobacco in other forms were associated with lung cancer seems to have largely evaporated. I should say a word about it because it represents a common cause of error in statistical investigations, namely, the kind of error which flows from the difficulty of a perfect classification. Everyone can make a rough classification of cigarette smokers or pipe smokers or non-smokers, but there will be borderline cases. There are people who, though they may prefer a pipe when they have the opportunity, yet may be constrained by duress, such as in the intervals of a play when

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there is very little time, to smoke a cigarette. There are also distinguished and expensive restaurants, as well as aircraft, who don't like the customer to pull out a pipe. Consequently there is an overlap in the practices and habits of different people; there may not be exactly the same interpretation put on the questionnaire by all the different subjects; and, in fact, a good many pipe smokers may be classified as cigarette smokers, and vice versa. There is bound to be some mixture of the classes in any inquiry on a complicated question. And so the first results did seem to show some effect on pipe smokers and cigar smokers, but it is quite clear that the amount was much smaller than was at first thought, and certainly no more than might easily arise due to misclassification. At least it would be very foolish of anyone who wished to make a case for saying that cigarette smoking was a cause of lung cancer to bring in the evidence about pipe and cigar smoking.

When an unexpected discrepancy occurs, it is a common reaction (I won't say, a failing—it's part really of the scientific discussion which data deserves) to think up some reason for it. This, in effect, may be something like what the logicians would call a "special pleading." That is to say, the making of an assumption, which might be true, which might, indeed, not be true, but which, if true, would help to explain what is otherwise inexplicable. For example, the cigarette contains paper, or, rather, is contained by paper. One doesn't smoke paper much in pipes. There are, indeed, special papers supplied to pipe smokers who wish to enjoy their tobacco in that way. But most pipe smokers and, I suppose, all cigar smokers, do without paper. And it could be, therefore, that it's the consumption of paper that is the really dangerous practice. Then, also, it has been observed that the temperature at which the tobacco is burned is higher in the case of the cigarette than in the case of the pipe, and, it could be (though it certainly is not known to be) that burning at a higher temperature is a

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condition for producing something quite unknown, something quite unexplored, something quite hypothetical, in the tobacco smoke which would be capable of producing lung cancer. It is also known that the tobacco used as pipe tobacco and for cigars is more thoroughly fermented before use than is that used in cigarettes, or at least in the predominant source of cigarette tobacco, in Virginia. I think those who prepare the tobacco produced in Virginia are rather acutely aware, that the price per pound is high, there is loss of weight in fermentation, and it is as well not to lose 10 per cent more weight than is necessary. And so, on the whole, the Virginia tobacco is rather lightly fermented. You could imagine—you could claim even—as a special pleading, that it was the unfermented condition of the Virginia tobacco, largely used in cigarettes, that was responsible for the supposedly noxious fumes which the burning of such tobacco produces. Discussion is full of such things.

One of the first people in the United States that spoke to me on the matter, a lady, said, "Of course, cigarette smokers inhale; pipe smokers don't." And of course she laid her finger on an extremely important point. Cigarette smokers in this country, I believe, generally inhale. In England, some do and some don't. When I was a little boy, it was thought that smoking was all right and did you no harm, but inhaling was perhaps a perverse practice and might not do you any good. And so, at any rate my generation, and perhaps some decades of younger men, had a certain amount of warning against this particular practice. I imagine it is something like that that explains the difference in practice between the two countries.

Now, Doll and Hill, in their first inquiry—the one that I've gone over approximately—*did* include in their questionnaire, which was put both to the cancer patients and to the patients from other diseases, the question: "Do you inhale?" And the result came out that there were fewer inhalers among

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the cancer patients than among the non-cancer patients. That, I think, is an exceedingly important finding. I don't think Hill and Doll thought it an important finding. They said that probably the patients didn't understand what inhaling meant. And what makes it far more exasperating, when they put into effect an exceedingly important research, based on the habits of the medical profession, by asking about 60,000 doctors in Great Britain to register their smoking habits, and about 40,000 of them did so cooperatively, I am sorry to say that the question about inhaling was not in that questionnaire. I suppose the subject of inhaling had become distasteful to the research workers, and they just wanted to hear as little about it as possible. But it is serious because the doctors could have known whether they were inhalers or not; they could have known what the word meant; perhaps they would have consulted each other sufficiently to lay down a definition which the rest of us could understand. At any rate, there would have been no alibi if the question had been put to a body of 40,000 physicians.

So, our evidence about inhaling is embarrassing and difficult. There is no doubt that inhaling is more common among heavy cigarette smokers than among light cigarette smokers in Great Britain, where inhaling is not nearly a universal practice. There is no doubt that cancer is commoner among the heavy cigarette smokers than among the light cigarette smokers. Consequently, if inhaling had no effect whatever, you would expect to find more inhalers among the cancer patients than among the non-cancer patients. There would be an indirect correlation through the association of both with the quantity smoked. Now, of course, in what was reported everything was thrown together; and yet, in the aggregate data, it appeared that the cancer patients had the fewer inhalers than the non-cancer patients. It would look as though, if one could make the inquiry by comparing people who smoke the same number of cigarettes, there would be a

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negative association between cancer and inhaling. It seems to me the world ought to know the answer to that question.

Before I stop, in fact, I hope I shall make clear that there is a case for further research, and I shall only mention two areas which would seem to be profitable for investigation. I would stress the importance of what could be done comparatively easily with rather little expense, namely, to ascertain unmistakably what the facts are about inhaling. If inhaling is found to be strongly associated with lung cancer, it would be consonant with the view that the products of combustion, wafted over the surface of the bronchus, might induce a pre-cancerous and thence a cancerous condition. But if there is either no association at all or a negative association, we should have to reject altogether that simple theory of the causation of cancer. The subject is complicated, and I mentioned at an early stage that the logical distinction was between *A* causing *B*, *B* causing *A*, something else causing both. Is it possible, then, that lung cancer—that is to say, the pre-cancerous condition which must exist and is known to exist for years in those who are going to show overt lung cancer—is one of the causes of smoking cigarettes? I don't think it can be excluded. I don't think we know enough to say that it is such a cause. But the pre-cancerous condition is one involving a certain amount of slight chronic inflammation. The causes of smoking cigarettes may be studied among your friends, to some extent, and I think you will agree that a slight cause of irritation—a slight disappointment, an unexpected delay, some sort of a mild rebuff, a frustration—are commonly accompanied by pulling out a cigarette and getting a little compensation for life's minor ills in that way. And so, anyone suffering from a chronic inflammation in part of the body (something that does not give rise to conscious pain) is not unlikely to be associated with smoking more frequently, or smoking rather than not smoking. It is the kind of comfort that might be a real solace to anyone in the fifteen years of

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approaching lung cancer. And to take the poor chap's cigarettes away from him would be rather like taking away his white stick from a blind man. It would make an already unhappy person a little more unhappy than he need be.

For my part, I think it is more likely that a common cause supplies the explanation. Again, we do not know. I do not put forth any explanation as proved, but as requiring investigation. The obvious common cause to think of is the genotype. We are all different genotypes. I suppose in this nation there must be well over 150 million different genotypes. If one studies cancer in mice (and I suppose about half the mice of the world are kept to study cancer with), if one examines any of the many (and there are thousands) of inbred lines of mice (where we can get a hundred or two hundred individuals of the same genotype to study)—if you take, then, any two such lines of differing genotypes, they will, I believe, invariably be found to differ in the frequency, in the age incidence, and in the type of cancer which those mice suffer from. Consequently if there is any genotypic difference between the different smoking classes, we may expect differences in the type or frequency of cancer that they display.

That is the second line of research which I should like to advocate, a little bit more difficult than that which is concerned with inhaling, but certainly well within the capacity of modern methods in human genetics. It certainly could be ascertained, as a matter of fact, whether in the different smoking classes of nonsmokers, cigarette smokers, pipe smokers, cigar smokers (the minor classes, perhaps, of snuffers and chewers perhaps might not be sufficiently numerous, but in those first main four classes it could certainly be ascertained) whether there was evidence that they differed genetically. It wouldn't be a long shot to guess that they did. After all, we choose these things for ourselves. I know that there are families in which there would be some pressure on a growing boy or girl to be a nonsmoker because his father and mother

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firmly believe that smoking is an objectionable habit, or perhaps an irreligious habit. But most of us choose for ourselves, and even though one may have been exposed to opportunities—temptations, if you like—to smoke cigarettes from a fairly early boyhood, it is not uncommon to find people who never smoke anything but a pipe. Why? Because they are made that way. They are the sort of men who take to the pipe and don't take to cigarettes, just as there are other men who would never take to a pipe but constantly feel the need of cigarettes. It is not, then, a very long shot to guess that there is a genetic component which distinguishes the different smoking classes. And that is the second piece of research which I think is extremely urgent.

I have criticised the over-confidence shown at least in public utterances or published reports of anonymous committees on this subject, and I do not suppose that Bradford Hill, at least, is at all to blame for that overconfidence. The worst effect of that overconfidence, so far, is that it seems to have held back the various teams of workers. They are well supplied with money—the Medical Research Council is not stinting money on cancer research, and the American Cancer Society is obviously exceedingly well supplied with money. And yet, I think nothing but overconfidence that they had found the solution, that they had the game in the bag, could have prevented them from following up some of the other lines of inquiry which are much needed. I have said nothing, for example, so far of the very striking fact that at the same level of cigarette smoking, dwellers in towns have considerably more lung cancer than dwellers in the country. I don't know any extensive piece of research which has been set on foot to get to the bottom of that important difference.

The desire to make a strong sensation, to bring home the terrible danger to these passive millions, has led writers to stress the very alarming fact that lung cancer is a disease increasing, one of the few important diseases that are increasing

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in frequency. It is not so important in the United States as it is in England, but it is an important cause of death in both countries. It has been increasing over the last fifty years. It is frightening. But it shouldn't be used to frighten people.

The change over recent decades gives not the least evidence of being due to increasing consumption of tobacco. We can't tell much about the absolute magnitude of this secular change. It is certain that radiology has facilitated the detection of lung cancer enormously, that radiological apparatus and radiologists are much more abundantly available for our populations than they formerly were. I do not know that there are not remote and secluded communities where patients with lung cancer are not looked at by radiologists, but that proportion of our populations must be still decreasing. Again, the attention of the medical profession has been forcibly drawn to lung cancer, and it invariably happens that when the attention of the medical profession is drawn to any disease, that disease begins to take up more space in the official reports—it is more often seen and more often diagnosed with confidence; death certificates more often include that particular disease. Consequently it is not easy to say how much of the increase is real. I think part of it must be real, because there's no doubt that the populations concerned have been enduring or enjoying a very considerable increase in urbanization. The big metropolitan cities have been growing rapidly. In England, smaller towns have been running together into extensive masses called conurbations, like those of Clydeside or Merseyside or the Birmingham region. Even in the country, even in what used to be remote villages, there are motorbuses regularly which take the young men and women into cinemas perhaps six or eight miles away. You might say that the whole population during the last twenty, thirty, forty years has been becoming steadily urbanized, and as the urban rate for lung cancer is considerably greater than the rural rate, in my country as in yours, we must recognize here the possibility

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of one real cause of the increase in lung cancer. There may be others.

But the only good comparison we can make in respect of the time-change is that between men and women. The same apparatus, the same radiologists, the same physicians diagnose both men and women. Whatever effects improved apparatus may have, whatever effects an increased attention to the disease may have, will be the same in the two sexes. Whatever effects urbanization may have you would think might be the same in the two sexes. Consequently, we can, at least, inquire whether the rate of increase of lung cancer in men is the same, or greater, or less, than the rate of increase of lung cancer in women. For it is certainly true, I think in both our countries, that whereas the smoking habits of men have not changed very dramatically over the last fifty years, yet the smoking habits of women have changed a very great deal. And on making that comparison, it appears that lung cancer is increasing considerably more rapidly—absolutely and relatively—in men than it is in women, whereas the habit of smoking has certainly increased much more extensively in women than in men. There is, in fact, no reasonable ground at all to associate the secular increase in lung cancer as has been done with dramatic eloquence, I suppose as part of the campaign of bringing home the terrible danger, just as though it was impossible that statistical methods of inquiry should supply a means of checking that very rash assumption.

And so I should like to see those two things done, one immediately and quickly: an inquiry into the effects of inhaling, and secondly, a more difficult but certainly a possible task of seeing to what extent different smoking classes were genotypically conditioned. And I believe that only overconfidence, if it is allowed to have its way, could prevent those further inquiries from being made.

THE NATURE OF PROBABILITY

Sir Ronald Fisher<sup>1</sup>

IT IS NO SECRET—it is a fact that I have stressed particularly in a recent book of mine on scientific inference<sup>2</sup>—that grave differences of opinion touching upon the nature of probability are at present current among mathematicians. I should emphasize that mathematicians are expert and exceedingly skilled people at the particular jobs that they have had experience of—in particular: exact, precise deductive reasoning. In that field of deductive logic, at least when carried out with mathematical symbols, they are of course experts. But it would be a mistake to think that mathematicians as such are particularly good at the inductive logical processes which are needed in improving our knowledge of the natural world, in reasoning from observational facts to the inferences which those facts warrant. Now when we are presented, as we are at the present time in the 20th century and perhaps especially in this country, with grave differences of opinion of this sort among entirely competent mathematicians, we may reasonably suspect that the difficulty does not lie in the mathematics—or at least only incidentally or accidentally in the mathematics—but has a much deeper root in the semantics or an understanding of the meanings of the terms which are used.

It's not the first time that grave differences of opinion among mathematicians have occurred on this very question of probability. Looking over the history of the subject, I

<sup>1</sup> This paper represents the substance of an address given in November 1957 at Michigan State University.

<sup>2</sup> *Statistical Methods and Scientific Inference* (Edinburgh: Oliver and Boyd, 1956).

think we can say that a crucial set of circumstances occurred at an early period, in the 17th and 18th centuries, at the time when the interest of mathematicians in the area of probability hung upon the high social prestige of the recreation of gambling, and mathematicians were constantly being approached by persons of the highest social standing, worthy of every respect and service, in order to solve the knotty problems that arose in this recreation; and this activity was manifestly the mainspring of the interest of the galaxy of distinguished mathematicians who, at that period, gave their attention to the subject.

May I just mention a few names illustrative of that period: Pascal, Fermat, Leibnitz, Montmort (all of whom functioned principally in France), De Moivre and Bayes (in England), and Bernoulli (who didn't live quite in France because he was a member of a distinguished family of the town of Basel). And I am inclined to say that all of those founders of the mathematical theory of probability understood the meaning of the word in one way, and they had the great advantage of coming to an understanding of the word which they used in their work, in that they were brought frequently into contact with its practical applications in the real world.

Now one of the difficulties in the teaching of mathematics in the present century is the difficulty of representing in mathematical departments those arts, crafts, skills, and technologies to which statistics is now being actively applied. It would seem an almost impossible task to staff a mathematical department, to get even a representation of the immense variety of practical affairs in which mathematics or statistics is applicable and is now being used. That is a problem for the organizers of education.

My own problem is a much narrower one. I want to make clear what I mean by probability; I want to make clear, so far as I can, why it is that quite a number of mathematicians fall into what I consider to be manifest fallacies in this field.

† This article not address smoking, and so is omitted from this 2010 re-compilation.

Full article at <http://digital.library.adelaide.edu.au/coll/special//fisher/>

*Nature* **182** (1958 July 12), 108.

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## LUNG CANCER AND CIGARETTES

THE ASSOCIATION observable between the practice of cigarette-smoking and the incidence of cancer of the lung, to which attention has been actively, or even vehemently, directed by the Medical Research Council Statistical Unit, has been interpreted, by that Unit, almost as though it demonstrated a casual connection between these variables.

The suggestion<sup>§</sup>, among others that might be made on the present evidence, that without any direct causation being involved, both characteristics might be largely influenced by a common cause, in this case the individual genotype, was indeed rejected by one writer<sup>¶</sup>, although I believe that no one doubts the importance of the genotype in predisposing to cancers of all types.

It seemed to me that although the importance of this factor had been overlooked by the Unit in question, it was well within the capacity of human genetics, in its current state, to examine whether the smoking classes, to which human beings assign themselves, such as non-smokers, cigarette smokers, pipe smokers, cigar smokers, etc, were in fact genotypical differentiated, to a demonstrable extent, or whether, on the contrary, they appeared to be genotypical homogeneous, for only on the latter view could causation, either of the disease by the influence of the products of combustion, or of the smoking habit by the subconscious irritation of the postulated pre-cancerous condition, be confidently inferred from the association observed.

<sup>§</sup>Fisher, R. A., *Brit. Med. J.*, ii, 43, 297 (1957).

<sup>¶</sup>McCurdy, R. N. C., *Brit. Med. J.*, ii, 158 (1957).

The method of inquiry by which such differentiation can be recognized is the same as that by which the congenital factor has been demonstrated for several types of disease, namely<sup>||</sup>, the comparison of the similarities between monozygotic (one-egg) and dizygotic (two-egg) twins respectively; for any recognizably greater resemblance of the former may be confidently ascribed to the identity of the genotypes in these cases.

I owe to the generous co-operation of Prof. F. Von Verschuer and of the Institute of Human Genetics of the University of Munster the results of an inquiry into the smoking habits of adult male twin pairs on their lists.

The data so far assembled relate to 31 monozygotic and 31 dizygotic pairs, from Tubingen, Frankfurt and Berlin. Of the first, 33 pairs are wholly alike qualitatively, namely, 9 pairs both non-smokers, 22 pairs both cigarette smokers and 2 pairs both cigar smokers. Six pairs, though closely alike, show some differences in the record, as in a pair of whom one smokes cigars only, whereas the other smokes cigars and sometimes a pipe. Twelve pairs, less than one-quarter of the whole, show distinct differences, such as a cigarette smoker and a non-smoker, or a cigar smoker and a cigarette smoker.

By contrast, of the dizygotic pairs only 11 can be classed as wholly alike, while 16 out of the 31 are distinctly different, this being 51 per cent. as against 24 per cent. among the monozygotic.

The data can be rearranged in several ways according to the extent to which attention is given to minor variations in the smoking habit. In all cases, however, the monozygotic twins show closer similarity and fewer divergences than the dizygotic.

There can therefore be little doubt that the genotype exercises a considerable influence on the smoking and on the particular habit of smoking adopted, and that a study of twins on a comparatively small scale is competent to demonstrate the rather considerable differences which

<sup>||</sup>Von Verschuer, F., *Proc. Roy. Soc.*, **B**, **128**, 62 (1939).

must exist between the different groups who classify themselves as non-smokers, or the different classes of smokers. Such genotypical different groups would be expected to differ in cancer incidence; and their existence helps to explain such oddities as that pipe and cigar smokers should show much less lung cancer than cigarette smokers, while among the latter, the practice of inhaling is associated with less, rather than with more cancer of the lung.

Dr. Bradford Hill, while admitting that the evidence of association found by his Unit did not amount of proof of causation, has emphasized that he does not know what else it can be due to. The facts here reported do show, however, that the choice is not so narrow as has been thought.

*Nature* **182** (1958 July 12), 108.

*Nature* **182** (1958 August 30), 596.

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### CANCER AND SMOKING

THE CURIOUS ASSOCIATIONS with lung cancer found in relation to smoking habits do not, in the minds of some of us, lend themselves easily to the simple conclusion that the products of combustion reaching the surface of the bronchus induce, though after a long interval, the development of a cancer. If, for example, it were possible to infer that inhaling cigarette smoke was a practice of considerable prophylactic value in preventing the disease, for the practice of inhaling is rarer among patients with cancer of the lung than with others.

Such results suggest that an error has been made of an old kind, in arguing from correlation to causation, and that the possibility should be explored that the different smoking classes, cigarette smokers, cigar smokers, pipe smokers, etc., have adopted their habits partly by reason of their personal temperaments and dispositions, and are not lightly to be assumed to be equivalent in their genotypic composition. Such differences in genetic make-up between those classes would naturally be associated with differences of disease incidence without the disease being causally connected with smoking. It would then seem not so paradoxical that the stronger fumes of pipes or cigars should be so much less associated with cancer than those of cigarettes, or that the practice of drawing cigarette smoke in bulk into the lung would have apparently a protective effect.

A letter of mine in *Nature*\*\* included a brief first report of some data on the smoking habits of twins in Germany kindly supplied by Prof. v. Verschuen. What was evident in these data, which concerned only

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\*\*Fisher, R. A., *Nature*, 108 (1958).

males, was that the smoking habits of monozygotic, or one-egg, twins were clearly more alike than those of twins derived from two eggs. The monozygotic twins are identical in genotype and the clear difference in these data gave *prima facie* evidence that among the many causes which may influence the smoking habit, the genotype is not unimportant.

Unfortunately, considerable propaganda is now being developed to convince the public that cigarette smoking is dangerous, and it is perhaps natural that efforts should be made to discredit evidence which suggests a different view. Assumptions are put forward which, *if true*, would show my inference from von Verschuen's data not indeed to be false but at least to be inconclusive. I may refer to an anonymous writer "Geminus" in the *New Scientist*<sup>††</sup>, who supports in this way "what is rapidly becoming an accepted truth—that smoking can cause lung cancer".

If it could be assumed as known facts (a) that twins greatly influence each other's smoking habits, and (b) that this influence is much stronger between monozygotic than between dizygotic twins, then an alternative explanation would be afforded for the result I have emphasized. The assumptions can be supported by eloquence\*, but they should, for scientific purposes, be supported by verifiable observations.

Since my letter was written, however, I have received from Dr. Eliot Slater, of the Maudsley Hospital (London, S.E.5), some further data, the greater part of which concern girl twins, and in this way supply a valuable supplement to Verschuer's data, and in which, moreover, a considerable number of pairs were separated at or shortly after birth.

For the resemblance in smoking habits, these female pairs give:

	<i>Alike</i>	<i>Unlike</i>	<i>Total</i>
Monozygotic	44	9	33
Dizygotic	9	9	18

<sup>††</sup>"Geminus", *New Scientist*, 4, 440 (1958).

So far, there is only a clear confirmation of the conclusion from the German data that the monozygotic are much more alike than the dizygotics in their smoking habits. The peculiar value of these data, however, lie in the subdivision of the monozygotic pairs into those separated at birth and those brought up together. Those are:

	<i>Alike</i>	<i>Unlike</i>	<i>Total</i>
Separated	23	4	27
Not separated	21	5	26

Of the 9 cases of unlike smoking habits, only 4 occur among the 27 separated at birth. It would appear that the small proportion unlike among these 53 monozygotic pairs is not to be ascribed to mutual influence.

There is nothing to stop those who greatly desire it from believing that lung cancer is caused by smoking cigarettes. They should also believe that inhaling cigarette smoke is a protection. To believe this is, however, to run the risk of failing to recognize, and therefore failing to prevent, other and more genuine causes.

\* The quotation from "Geminus" was too short to do justice to the techniques of "modern publicity". The two paragraphs which follow deserve careful reading. They show how a simple assumption, which *might* have been true (though the first factual evidence at once showed it not to be) is progressively built up into confident assertions that both my method and my results were erroneous; and as it is built up, so it is progressively ornamented.

The public should not think that publicity, even if supported by the Ministry of Health, is always aimed at *improving* public knowledge.

"But things are not really as simple as this. Comparisons of identical and non-identical twins are unimpeachable when they are used to assess the inevitability of purely physiological characteristics, but the habit of smoking is not necessarily physiological at all. And in the formation of psychological attitudes towards smoking, one would expect that identical twins would be more likely to go along with each other than would non-identical twins. For one thing they must constantly be reminded of

their identity by all those around them, and they are bound eventually to be blessed with a conviction that they ought always to do similar things. This, after all, is what society expects of them.

“Such a correlation of all kinds of habits might easily account for Sir Ronald Fisher’s results. So it is too much to say that these imply the inheritance of smoking and of a susceptibility to lung cancer may be jointly inherited. There is therefore no support for the corollary that those who are going to die of lung cancer will do whether they smoke or not. I hope that heavy smokers will not seek some kind of solace in this latest smoke-screen between them and what is rapidly becoming an accepted truth—that smoking can cause lung cancer.”

*Nature* **182** (1958 August 30), 596.

*Smoking: The Cancer Controversy*, Edinburgh: Oliver and Boyd 1959, pp. 45–47.

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### INHALING

WHEN, several years ago, it appeared that a verifiable association could be established between smoking and cancer of the lung, and before there was any reason to doubt the simple theory that the products of combustion could so act on the surface of the bronchus as to induce the growth of a cancer, it was natural to seek the powerful confirmation of this theory which would be obtained if those practising inhalation of cigarette smoke appeared with much higher frequency among the cancer patients than among those suffering from other conditions.

The failure of Hill and Doll’s retrospective inquiry to supply such corroboration took these workers by surprise, and at first they could scarcely believe the question had been understood. The investigators who actually questioned the patients, however, seem to have had no doubt of this; and the statisticians had the embarrassing choice between frankly avowing that one striking and unexpected result of their enquiry was clearly contrary to the expectations of the theory they advanced, or to take the timid and unsatisfactory course of saying as little about it as possible.

It has taken some years, therefore to elicit the tables below,

TABLE 1  
*Maximum daily cigarettes*

		1–4		5–14		15–24		25–49		>49	
		I	N	I	N	I	N	I	N	I	N
Men	Cancer	7	17	141	67	133	63	96	78	21	24
	Control	17	21	162	80	157	44	74	44	16	7
Women	Cancer	3	3	7	8	7	5	5	3	0	0
	Control	2	10	2	7	6	0	0	0	1	0

(I=Inhaler, N=Non-inhaler)

which are a reconstruction of the original observations. I have asked for, and have now obtained, confirmation that these are the actual counts originally made. Certain pipe and cigar smokers were originally included on the basis of total tobacco consumed, and I have not been able to secure their removal.

The women are too few to be discussed further; for each of the five tables for men, we may ask how many of the inhalers would have shown cancer, if the proportion had been the same as that among the non-inhalers.

TABLE 2

Cigs. <i>per diem</i>	Expected	Observed	Deficiency
1-4	10.737	7	3.737
5-14	138.380	142	-3.620
15-24	153.095	133	20.095
25-49	109.119	96	13.119
> 49	33.260	21	12.260
Total	444.591	399	45.591

If, following the method of the Medical Research Council, these differences were ascribed to inhalation as a cause, then inhalers may congratulate themselves of reducing the cancer incidence by over 10 per cent., using a very simple, and even enjoyable, method of prevention. This is indeed an under-estimate, for pipe smokers seldom inhale, and have a low cancer incidence, so that their inclusion has lowered the apparent advantage of inhaling<sup>‡‡</sup>.

To test the significance of this apparent protection due to inhaling, we must recognize the effects of random sampling not only due to the limited number of inhalers, but equally of the non-inhalers with whom they are compared. This is conveniently done by reducing the deficiency in the ratio of the non-inhalers to the total.

No particular importance need be attached to the test of significance. It disposes at about the 1 per cent. level the hypothesis that inhalers and non-inhalers have the same cancer incidence. Even equality would be a fair knock-out for the theory that smoke in the lung causes cancer. The fact, however, and it is a fact that should have interested Hill and Doll in 1950, is that inhalers get fewer cancers. and the difference is statistically significant.

TABLE 3

Cigs. <i>per diem</i>	Reduced deficiency	Sampling variance
1-4	2.290	3.49
5-14	-1.947	24.60
15-24	10.174	19.54
25-49	5.301	17.10
>49	3.485	3.75
Total	20.299	68.48
Standard error	8.274	

<sup>‡‡</sup>See Note [lower down the page]

Should not these workers have let the world know, not only that they had discovered the cause of lung cancer (cigarettes), but also that they had discovered the means of its prevention (inhaling cigarette smoke)? How had the M.R.C. the heart to withhold this information from the thousands who would otherwise die of lung cancer?

Those who refuse the jump from association to causation in the case of cigarette smoking will not be tempted to take it in the case of inhaling; but the M.R.C. and its Statistical Research Unit think this argument is valid in the first case. Can they refuse to admit it in the second?

NOTE: Data from which 78 have been removed as they did not smoke cigarettes, but which still include mixed smokers of pipes and cigarettes give the enhanced effect expected and show apparent "protection" of about 13 per cent.

*Smoking: The Cancer Controversy*, Edinburgh: Oliver and Boyd 1959, pp. 45-47.