

intrinsically important and a powerful support for a more statistical notion, is not essential for the latter.

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- ¹ Cornfield J, Haenszel W, Hammond EC, Lilienfeld AM, Shimkin MB, Wynder EL. Smoking and lung cancer: recent evidence and a discussion of some principles. *J Natl Cancer Inst* 1959;**22**:173–204. Reprinted *Int J Epidemiol* 2009;**38**:1175–91.
- ² Cochran WG. The planning of observational studies of human populations (with discussion). *J R Stat Soc A* 1965;**128**:234–66.

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Commentary: ‘Smoking and lung cancer’—the embryogenesis of modern epidemiology

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The reading of paper by Cornfield *et al.*¹ on ‘Smoking and Lung Cancer’ is a real treat to anyone who is interested in the roots of causal reasoning in today’s epidemiology. It is surprising how much was already known: basic notions about confounding, selection and other biases, genetic influences, misclassification, the nature of observational evidence and the threshold for action when evidence is not perfect. All these ideas are present in the paper—not with their present-day names, but with a clear exposé about the concepts in crisp language, as they pertained to the 1950s debate on smoking and lung cancer. These ideas still figure as essential topics for discussion in today’s textbooks. A reading of the paper makes clear how much modern epidemiology was formed by the discussions about smoking and lung cancer. In this commentary, I have tried to elucidate key aspects of the paper, to indicate how they still lead to debate in the 21st century—50 years after the original publication.

A sensitivity analysis that still reverberates

The magnitude of the excess lung-cancer risk among cigarette smokers is so great that the

results cannot be interpreted as arising from an indirect association of cigarette smoking with some other agent or characteristic, since this hypothetical agent would have to be at least as strongly associated with lung cancer as cigarette use; no such agent has been found or suggested.¹

This conclusion of the paper rests on an algebraic derivation in an appendix and is what the paper is often remembered for nowadays. Although conceptually simple, it represented a gigantic leap forward, and might be seen as the starting point of all sensitivity analyses.² The notion that large relative risks can be convincing by themselves is still very much alive.³ However, over the past few decades, the concept has often been reversed, to shed doubt on ‘small relative risks’, which led to statements that only relative risks >3 would be credible.⁴ That is not what the original said. The paper proposed that it is difficult to think of potential confounders to explain a 9-fold relative risk of smoking on lung cancer incidence because a potential confounder should be even more strongly associated with smoking. That does not mean that such confounders cannot exist, but that it is difficult to come up with likely candidates to explain away a large relative risk. For small relative risks more candidate confounders can be imagined, which in turn does not mean that the association is in fact confounded.⁵ Smaller relative risks may need more epidemiologic evidence, from repeated studies trying

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to tackle potential bias and confounding, as well as additional evidence from other lines of research, e.g. experimental evidence about biologic mechanisms.⁶

The original argument went beyond the sensitivity analysis for unknown confounder(s). Two corollaries followed in the paper. The first was: 'If two uncorrelated agents, A and B, each increase the risk of a disease, and if the risk of the disease in the absence of either agent is small (in a sense to be defined), then the apparent relative risk for A, r , is less than the risk for A in the absence of B'. In plain language, by the authors themselves: 'The presence of other real causes thus reduces the apparent relative risk'. As the authors explain, smoking has a lower relative risk for coronary heart disease than for lung cancer, which means that for coronary heart disease 'other causes of great importance must be present, as is manifested by the high mortality from this disease among non-smokers.' These ideas have been refined in the sufficient cause model that has influenced epidemiology since the 1980s: a strong cause, in terms of a large relative risk, is one that plays a role in a large fraction of cases, whereas a weak cause only in a smaller fraction.^{7,8} The second corollary was 'If a causal agent A increases the risk for disease I and has no effect on the risk for disease II, then the relative risk of developing disease I, alone, is greater than the relative risk of developing disease I and II, combined, while the absolute measure is unaffected'. The main original example was the difference in relative risk of smoking between epidermoid (spinocellular) lung cancer and adenocarcinoma—the first being much larger than the second. In analyses that lumped these tumours, the overall relative risk of smoking became less, whereas the risk difference remained similar.

The corollaries were linked to the concept of 'specificity' of causal effects, and to the idea that relative risk estimations would directly show such specificity. These ideas led to principles that investigators still use in designing studies: to quantify a potential causal effect investigators focus as much as possible on a precise definition of the aspect of the exposure that is likely to be causal and on the exact disease for which a cause and effect relation is assumed. Such a strategy is likely to show the clearest signal.

However, these same corollaries have projected epidemiology into protracted discussions about what is exactly meant by 'specificity of causal effects' and what is the corresponding 'right' measure of risk. It has been alleged that Cornfield *et al.* preferred the relative risk over the risk difference, in order to get rid of the seeming anomaly that smoking was linked to several diseases, amongst others, coronary heart disease.⁸ At the time this was much debated: critics argued that it seemed impossible that many diverse diseases might be linked causally to one agent and that this pointed to alternative explanations. The authors argued that the relative risk for lung cancer was 9-fold, and for coronary disease 1.7-fold, which

permitted them to focus on lung cancer. Nowadays, it is universally accepted that smoking also causes cardiovascular disease, and the wisdom of the original statements with its emphasis on the relative risk that would show specificity of effects is therefore doubted. Still, the original argument, in the face of knowledge as it was in the 1950s, was more subtle and at the time perfectly reasonable. By focusing on the relative risk of smoking for lung cancer, they could point out how high it was and how difficult to explain away. They did not discard the possibility that smoking causes coronary disease: they pointed to the diverse effects of the 1952 London Fog, and to the fact that tobacco smoke is a complex substance consisting of many combustion products. Wittily they added: 'A universe in which cause and effect always have one-to-one correspondence with each other would be easier to understand, but it obviously is not the kind we inhabit.'

The whole episode acted as a boomerang on the criterion of 'specificity' of cause and effect, as it was mentioned in the 1964 US Surgeon's General *Smoking and Health*, and in 1965 in Austin Bradford Hill's 'criteria' for causality. In later discussions, the smoking example almost became a counterexample against the necessity of 'specificity' because of the universal acceptance that smoking also causes cardiovascular disease. The discussion was revived in 2002 by Weiss, who traced the history of the concept of specificity of a cause to Yerushalmy, Palmer and Berkson.⁹ One of Weiss's examples was about sigmoidoscopy screening: distal colonic lesions would not be seen by sigmoidoscopy, so a seeming protection from advanced distal colon cancer by screening would lend credibility to some non-causal effect. The discussion was continued in the 2008 third edition of *Modern Epidemiology*, with the conclusion that specificity and non-specificity of predicted associations might be helpful if each can be logically deduced from either causal or non-causal hypotheses—as in the sigmoidoscopy example.⁸ Perhaps, we should also distinguish the principle of 'specificity' in setting up studies, vs the argument of 'specificity' in thinking about causality.

Real-life causal reasoning

The consistency of all the epidemiologic and experimental evidence also supports the conclusion of a causal relationship with cigarette smoking, while there are serious inconsistencies in reconciling the evidence with other hypotheses which have been advanced.¹

We are so accustomed these days to knowing for sure that smoking causes lung cancer, without thinking any more about the original debates, that we tend to forget how the paper constitutes an acute real-life example of causal reasoning amidst a controversy—in

a sense, 'frozen in time'. The paper illustrates how very diverse types of arguments played a role.

The authors discuss case-control and cohort studies (called retrospective and prospective at the time) with all issues of selection bias, information bias, misclassification and confounding. None of these is called by its present-day name, but the discussion is highly sophisticated and gives arguments and counterarguments that would hold in any of today's analytic epidemiologic papers.

However, the authors do more. They integrate the analytic epidemiology with other types of evidence: epidemiological, clinical and experimental. For example, time trends are discussed in depth with their strengths and weaknesses. One piece of evidence that the increase in lung cancer over calendar time was real, and not a reflection of greater awareness or better diagnostic procedures, was a study from Denmark with data from a tuberculosis screening clinic (an active public health institution in the middle of the previous century), in which a steep increase in lung cancer was found despite unchanged referral practices and unchanged diagnostic procedures. The authors also integrated findings from autopsy series and pathology specimens: about time trends in autopsy series, and about findings of metaplasia and 'carcinoma *in situ*' in the bronchial mucosa of smokers. Finally, they discussed animal experiments about the carcinogenicity of tar (condensed smoke). They not only included these non-epidemiologic studies as some additional reference, but also discussed strengths and weaknesses and the interpretation in almost the same detail as the analytic epidemiologic studies. The data from the time trends, from the autopsy series and from the animal experiments were important arguments because of their inconsistency with the 'constitutional hypotheses' (Fisher's proposal that some common genetic link would cause both lung cancer and a craving for smoking). Indeed, to rebut the constitutional hypothesis, these data were stronger than analytic epidemiology. Epidemiology cannot logically solve the constitutional hypothesis—except in an imaginary randomized trial in which tens of thousands of youngsters would be divided in two groups, one obliged to smoke a pack a day for a lifetime and others forbidden to do so. One epidemiologic alternative would be a study of monozygotic twins discordant for smoking: it took up to 1996 until a twin study with sufficient numbers was published as evidence against the constitutional hypothesis¹⁰—about four decades after the hypothesis was rendered unlikely by the Cornfield *et al.* article. Interestingly, a genetic variant of a nicotine receptor has recently been shown to be associated with smoking dependence—e.g. women with this variant have more difficulty quitting smoking when pregnant.¹¹ However, that is not the same as proof of the constitutional hypothesis, since it remains to be seen

whether this variant, or some genetic material close to it on the chromosome, is in itself conducive to lung cancer, irrespective of smoking.

The way in which causality is argued in the paper is an important lesson for today's epidemiology that is focused on direct acyclic graphs (DAGs), counterfactual and component cause reasoning. However much these ideas and techniques may clarify and refine the concepts of confounding and selection, they remain within the realm of analytic studies and do not directly lead to integration with other types of evidence. The paper shows how the final assessment of causality did not solely rely on analytic epidemiologic studies, not even in the discussion about confounding or bias: knowledge external to epidemiology was necessary to solve epidemiologic problems. The inverse is equally true, of course: basic science investigations about mutagens in tobacco smoke or mutational hotspots in DNA of bronchial epithelial cells only have meaning in the light of epidemiologic knowledge.¹²

The style of rebuttal of rivaling hypotheses is exemplary. Perhaps unwittingly, the authors follow time-honoured examples of great argumentations and dialogues, like Galileo's, who showed that in order to rebut, one first needs to explain the rival hypothesis as completely and thoroughly as possible and then impassively list and describe the counterarguments.¹³ Much space is devoted to explain rival hypotheses, weigh them on their merits, explain the arguments and counterarguments, and only thereafter the authors assess whether the rival hypothesis can be rebutted completely or only partially.

'Doubt is our product'

Unquestionably there are areas where more research is necessary, and, of course, no single cause accounts for all lung cancer. The information already available, however, is sufficient for planning and activating public health measures.¹

The interpretation section of the paper is timelessly important because of its message that complete knowledge of a causal process is not necessary for action. The authors address the unknowns and the partially unknowns: they are aware that no specific biologic mechanism is known (it still is not!) and that there are interesting epidemiologic questions still to solve, but at the same time they stand firm that the evidence suffices for action. They show their thought processes when writing: '... if the findings had been made on a new agent, to which hundreds of millions of adults were not already addicted, and one which did not support a large industry, skilled in the arts of mass persuasion, the evidence for the hazardous nature of the agent would be generally regarded as beyond dispute'. The paper is clairvoyant about the type of discussion that would come to dominate

later controversies. Its reasoning pre-empts later attempts by the tobacco industry, and by others like the chemical or pharmaceutical industry, to sow doubt on epidemiologic findings by striking a 'hyper-scientific' pose, i.e. by not wanting to accept any form of practical causality as long as scientific causality is not known in all detail¹⁴—which allows these companies to forestall action forever. This strategy of the tobacco and the chemical industry was described by Ong and Glantz,¹⁵ and it was never better summarized than in a 1969 statement by a tobacco industry executive, as found in the *Tobacco papers* that became publicly available after litigations in the USA: 'Doubt is our product ... since it is the best means of competing with the "body of fact" that exists in the minds of the general public. It is also the means of establishing a controversy'.¹⁶ Periodically, the chemical industry tries to revive this tactic, also in the 21st century, by proposing to fix the ills of observational epidemiology in the name of better science.¹⁷

Finally, the authors of the paper are listed alphabetically. Some justice may have been done by the alphabet by having Jerome Cornfield as the first author. In 1971 he published a paper similar in tone and style about another controversy with powerful industrial interests: on a randomized trial that showed that glucose-lowering drugs might increase the risk of myocardial infarction in patients with diabetes.¹⁸ (A topic that has been highly controversial again recently, be it with another drug.¹⁹) That article, like the *Smoking and Lung Cancer* paper, shows the same dispassionate explanation of all arguments and comes to an equally firm conclusion. In both papers there is a hint of Bayesianism in reasoning about rivaling hypothesis and how the data are more consistent with one hypothesis than with the other. The 1971 paper proposed a novel solution—a stratification by a 'confounder score', before the term was even coined. Perhaps Cornfield did not only give us the odds ratio, the logistic regression and the stratification by a confounder score, but also demonstrated how to reason about epidemiologic data in the midst of a controversy—a quality that that was clearly and affectionately remembered in a series of papers dedicated to his memory.²⁰

Conflict of interest: None declared.

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