Epidemiology Review

Causality in Epidemiology

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Abstract

This article provides an introduction to the meaning of causality in epidemiology and methods that epidemiologists use to distinguish causal associations from non-causal ones. Alternatives to causal association are discussed in detail. Hill's guidelines, set forth approximately 50 years ago, and more recent developments are reviewed. The role of religious and philosophic views in our understanding of causality is briefly discussed.

Keywords: Association, bias, cause, confounder, regression

Cite the article as: Kamangar F. Causality in Epidemiology. *Arch Iran Med*. 2012; **15(10):** 641 – 647.

Introduction

Epidemiologic studies have made major contributions to the discovery of the causes of disease and health, some example of which are shown in Table 1. But what do we mean by a cause in epidemiology? How do we establish causality? How certain are we that the studied factor causes the disease of interest? Answering these questions is the subject of this article.

In this article, we discuss the following topics:

1) the meaning of cause in epidemiology;
2) association versus causality;
3) alternatives to causality when associations are observed;
4) Hill's causality criteria;
5) two case studies;
6) the strengths and limitations of epidemiologic studies in establishing causality;
7) more recent developments in analyzing causality in epidemiology;
8) probabilities and causation;
9) religion and causation;
10) philosophy and causation.

1. The meaning of cause in epidemiology

A factor causes a disease if it increases ***the probability*** of the occurrence (incidence) of that disease. For example, "smoking causes lung cancer" means that smoking increases the incidence of lung cancer; lifetime risk of lung cancer is 17% in male smokers versus 1% in male non-smokers.[1]

Probability, in relative frequency terms, is a number assigned to a population, not to a single individual. The choice of probability in our definition is partly because often we cannot unequivocally establish the cause in a single individual – thus we need to resort to probability in a population – and partly because it is consistent with the nature of public health.

Let's first discuss the difficulty of identifying the cause in a single individual. Assume that a 68-year-old man diagnosed with lung cancer wants to know why he got this cancer. Was it because he smoked for 5 years, between ages 30 and 35? Was it because during his college years he lived in a basement and might have been exposed to radon? Was it because he was exposed to passive smoking when he rented a home with three smoker friends? Or was it due to other reasons, as each year there are thousands of people around the world who get lung cancer and have not been exposed to any of the above-mentioned factors. The only way to know is to go back in time, change one of those factors, and see what happens. But this is counterfactual; nobody can do that, and the cause remains a mystery. One can only make good guesses.

It might be possible, however, to identify the causes of a reversible outcome (e.g., migraine headaches, asthma attacks, or seizures) in an individual using cross-over studies. If the number of asthma attacks substantially increase in a certain person any time he eats strawberries, then he might conclude with reasonable certainty that strawberries cause his asthma attacks. This is particularly true if the attacks happen after eating strawberries under a variety of circumstances, for example, when he eats strawberries during both the summer time and winter time and the same thing happens. If so, one could be more certain that the causative problem is strawberry not factors that are associated with it (e.g., other seasonal berries) that may act as confounders. However, this is not the general case. As mentioned above, we often need to resort to probabilities, certainly so if the outcome is not reversible.

Now let's discuss the consistency of probability with the nature of public health. Public health deals with the health of a society, not an individual. Compared to a scenario that all people in the society smoke, a complete ban of smoking reduces the percentage of individuals who will ever get lung cancer from 17% to 1%. This is a great benefit to the health of the society.

2. Association versus causality

When a factor causes a disease, it increases its probability. Smoking substantially increases the lifetime incidence of lung cancer, human papillomavirus dramatically increases the risk of cervical cancer, and *H. pylori* increases the risk of stomach cancer. These are all examples of causes.

This leads to thinking that when our studies show that in the presence of an exposure (E), the risk of a disease (D) is increased, E should be a cause of D. However, this is not necessarily correct. Increased risk of a disease in the presence of an exposure is called

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Accepted for publication: 9 September 2012

Table 1. Epidemiologic studies have contributed to identifying several hundred causes of diseases. Some salient examples are shown below.

Health outcome	Cause
Cardiovascular diseases	Tobacco smoking High LDL cholesterol High blood pressure Obesity Diabetes
Lung cancer	Tobacco smoking Asbestos Radon
Cervical cancer	Human papillomavirus
Gastric cancer	*H. pylori*
Esophageal cancer (squamous type)	Tobacco smoking Alcohol consumption
Liver cancer	Hepatitis B virus Hepatitis C virus Aflatoxin
Stroke	High blood pressure Diabetes
Diabetes	Obesity

a positive association between E and D. However, as described below, an association doesn't necessarily imply a causal relationship, because there are other alternative situations in which associations can happen. The next section describes these alternatives.

3. Alternatives to causality when associations are observed

When a study shows an association between the exposure E and the disease D, i.e., when the risk of D is increased or decreased in the presence of E, there are at least five explanations. Association can be due to random variation, bias, confounding, reverse causality, and finally causality (Figure 1). Before concluding that E causes D, the other four alternatives should be ruled out.

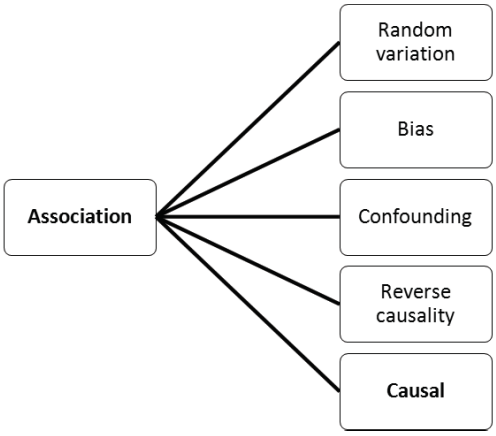

Figure 1. Alternatives to a causal association include random variation, bias, confounding, and reverse causality.

3.1. Random variation

An association between an exposure and an outcome may occur in one or more studies solely due to random variation (also known as luck or chance). For example, a cohort study may report an association between eating oranges and higher risk of depression. However, it might have been just by coincidence that those who ate more oranges in that cohort study were also more likely to be depressed, whereas in reality (i.e., if we study all people, not just that cohort) there may be no association between eating oranges and depression.

We use statistical significance tests and 95% confidence intervals to judge whether an association is due to random variation. Since most studies consider *P*-values less than 0.05 as statistically significant, there is a 5% chance that any statistically significant association may be due to chance (type I statistical error). However, the proportion of results reported in medical and public health literature that are due to random variation is substantially higher than 5%. Researchers analyze the data in many different ways to find significant results; authors are more likely to include their statistically significant results in their papers and to submit them for publication; and journals editors and reviewers are more likely to be interested in significant findings.[2–4] These are all reasons for higher publication rates of statistically significant findings, a phenomenon that has been termed publication bias.[4] The British economist and Nobel Laureate Ronald Coase is quoted to have said: "If you torture the data long enough, they will confess".

3.2. Bias

Bias is a systematic error in design, conduct, analysis, or reporting the results of a study. Various biases in a study may also result in associations that are not causal. Detailed descriptions of definition and types of biases in epidemiologic studies have been provided in articles[5] and textbooks.[6] Here we suffice to provide one example of bias to show how it results in a non-causal association.

Example 1: In a case-control study, investigators interviewed mothers of individuals with schizophrenia (as cases) and mothers of healthy volunteers (as controls) for obstetric complications.[7] Mothers of schizophrenic patients were more likely to report obstetric complications. However, reviewing hospital records showed no difference in such complications comparing case and control groups. The researchers concluded that the apparent association between obstetric complications and risk of schizophrenia was due to reporting (recall) bias; mothers of cases simply recalled or reported such events more, while there was no difference.

3.3. Confounding

Confounding factors (confounders) are variables that are associated with both the exposure and outcome of the study but are not in the pathway between the exposure and outcome. A detailed discussion of the definition, methods to identify, and methods to address confounding has been provided in a previously published article.[8] Here, we provide one example to show how a confounding factor may result in a non-causal association.

Example 2: Ginseng, an herb mainly cultivated in China and

Korea, is often used for medicinal purposes. Some people believe that it can strengthen the body and prevent diseases. A cohort study that investigated the association of ginseng with gastric cancer in China found that, contrary to initial expectations, ginseng increased the risk of gastric cancer by 40% (relative risk of 1.40).[9] However, the investigators realized that ginseng was not the cause of gastric cancer. The apparent association was because of age, which was a confounder in this study. Older people were more likely to use ginseng and they were more likely to develop gastric cancer, thus age was associated with both the exposure and the outcome (Figure 2).

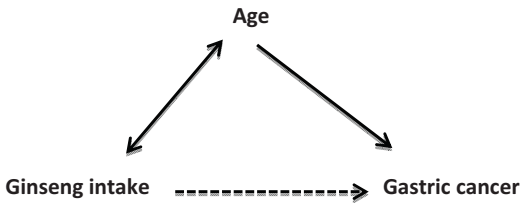

Figure 2. Increased risk of gastric cancer associated with ginseng intake is explained by age.

3.4. Reverse causality

When an association is shown between two factors, sometimes it is difficult to establish which one caused the other. See two examples below.

Example 3: Many studies have shown that job loss is associated with poor health and some researchers strongly believe that job loss leads to poor health. However, some researchers show evidence that it is not job loss that leads poor health.[10] It may rather be that poor health leads to low job functionality and hence losing ones job.

Example 4: The results of a cohort study showed an almost doubling of risk of death in opium users.[11] Before concluding that chronic opium use causally increases the risk of death, one needs to examine whether reverse causality may explain the association. It may be that people who had manifestations of chronic diseases (such as chest pain) used opium to alleviate their pain, thus the association between opium use and death might have been due to reverse causality.

3.5. Causal associations

When all of the above explanations for an association are excluded, a causal association may be concluded. For example, we are now almost sure that tobacco smoking causes lung cancer, or that human papillomavirus causes cervical cancer. The process of establishing causality is similar to establishing guilt in a court: when we exclude all the other possibilities beyond reasonable doubt, we are satisfied that the exposure causes the outcome. Section 4 shows what evidence we need to establish causality.

4. Hill's causality criteria

Sir Austin Bradford Hill, an eminent British biostatistician and epidemiologist, set forth a number of guidelines to help us determine whether or not an association should be considered as causal.[12] These guidelines, later named "Hill's causality criteria", have been widely used in epidemiology to establish causality. It is important to note that except for correct temporal sequence, perhaps none of these are necessary to establish causality. However, each one provides a clue, and when most of these points can be established, causality is very likely. Below, we discuss Hill's criteria.

4.1. Strength of association

The first criterion that Bradford Hill suggested was strength of association, by which he meant a relatively high relative risk for the association between exposure and outcome. Examples of extremely strong associations include the association between human papillomavirus and cervical cancer (relative risk of approximately 160[13]) and smoking and lung cancer (over 50-fold for very heavy smokers[14]).

Very strong associations help in ruling out some of the alternatives to causality (Section 3) in favor of a real causal association. A very strong association with a narrow confidence interval around the estimated relative risk is very unlikely to have happened due to random variation. It is unlikely to have happened due to confounding or bias either. Confounders should be more strongly associated with the outcome and exposure to cause an apparent association.[8] If the relative risk for association between HPV and cervical cancer is 160, then the confounder should be even more strongly associated with cervical cancer; there is no evidence for the presence of such a strong confounder. Notwithstanding these facts, causal relationships may still be believable with relatively small relative risks, too. For example, large double-blind, randomized trials have shown that taking β-carotene supplements increases the risk of lung cancer only slightly (relative risk of approximately 1.2[15,16]) but because of the strength of design of these studies, even such relatively weak associations are acceptable.

4.2. Consistency of association

This criterion refers to getting the same result when repeating the study under different circumstances. For example, when the Surgeon General of the United States declared in 1964 that tobacco smoking causes lung cancer, results from at least 29 retrospective and 7 prospective studies had nearly all shown an increased risk of lung cancer in relation to smoking.[17] When the results are repeated in a variety of circumstances, they are unlikely to have been due to random variation, a certain bias, or confounding. Therefore, consistency helps in refuting alternative explanations in favor of a real causal association. Nevertheless, consistency is neither necessary nor sufficient to establish causality. For example, studies may consistently find an association between short-term job loss and poor health yet it may be difficult to establish that job loss causes poor health, as the association may be due to reverse causality.

4.3. Temporality

Temporality refers to the temporal sequence of the studied exposure and the outcome. Which one came first? This criterion helps substantially in distinguishing causality from reverse causality. In Example 3, if we show that poor health happened only after job loss, and not before it, we can more readily establish that job loss caused poor health. Likewise, in Example 4, if we show that opium use was initiated well before the signs and symptoms of major chronic diseases started, we can more strongly reason that opium caused diseases leading to death.

4.4. Dose-response gradient

If the probability of the outcome is increased with increasing exposure to the risk factor, there is a dose-response relationship between the risk factor and the outcome. This is true for many

causes of diseases. For example, the longer and the more intensely one smokes tobacco, the more likely it is that one would get lung cancer.[14] Likewise, increasing exposure to alcohol consumption increases the risk of esophageal squamous cell carcinoma in a dose-response manner.[18]

Showing dose-response helps in attenuating the possibility of the presence of random error, confounding, and bias. This is because unless the confounder also increases in a dose-response manner in relation to the exposure and outcome, it is unlikely that we see a dose-response association between a confounded exposure and the outcome.

4.5. Biologic plausibility

If we know the mechanism through which the exposure can cause the outcome, we can infer causality on more solid grounds. Consider the association between smoking and lung cancer. A great deal is now known about chemical agents in tobacco smoke, such as polycyclic aromatic hydrocarbons, which after activation in the body can react with DNA, form adducts, cause mutations, and lead to cancer formation.[19] Likewise, we know how HPV can cause cervical cancer. The HPV E6 oncogene results in the production of a protein that ultimately destructs p53 protein, a tumor suppressor.[20] This in turn leads to higher rates of mutation and lower rates of apoptosis, leading to formation and maintenance of cancerous cells.

Although biologic plausibility is important, Hill believes that we cannot demand this to show causation. Proposing biologically plausible mechanisms depends on the scientific knowledge of the day. Hill recounts the example of higher risk of scrotal cancer in chimney sweeps. In 1775, Percival Pott, an eminent surgeon of his time, found that nearly all cases of scrotal cancer were among chimney sweeps.[21] The relative risk for the association between working as a chimney sweep and scrotal cancer has been estimated to be as high as 200.[22] At the time, nothing was known about the carcinogens in soot, so there was no way to know whether this association is biologically plausible. Nevertheless, this extremely strong association could not have been explained by random variation, bias, confounding, or reverse causality. When all other options are eliminated, causality is the only remaining explanation.

4.6. Analogy

If previously established causal analogues to the association under study exist, it may be easier to accept a causal relationship. For example, when it was found that tobacco smoke caused lung cancer, it was easier to accept that it could cause bladder cancer too. Likewise, since we knew that hepatitis B virus could cause liver cancer, it was not difficult to accept that hepatitis C virus could also cause liver cancer. While analogy is not a strong reason for causality, it does help.

4.7. Experiments

Large-scale randomized experimental studies are extremely effective in eliminating the possibility of confounding and in reducing bias. As such, results of experimental studies are given prime consideration in judging causality. For example, although only a few large-scale, randomized studies have shown an association between taking β-carotene supplements and higher risk of lung cancer,[23] and the relative risks have been quite small (approximately 1.2[15,16]), it is now widely accepted that β-carotene supplements can cause lung cancer.

4.8. Coherence

Coherence refers to compatibility of the presumed causal effect with the rest of our knowledge. For example, we know that in 1900 lung cancer was a rare disease in the United States.[24] Rates of this cancer started increasing only 20 years after the mass marketing of cigarettes. This makes it easier to accept the causal association between smoking and lung cancer.

4.9 Specificity

By specificity, Hill meant one cause for one effect. However, this criterion can be easily discarded today. One exposure can cause many outcomes, and one outcome may be caused by many exposures. For example, tobacco smoking causes a multitude of diseases, including laryngeal cancer, lung cancer, esophageal cancer, bladder cancer, coronary heart diseases, and cerebrovascular diseases, to name a few. Likewise, coronary heart disease can be caused by smoking, high cholesterol, high blood pressure, and a number of other exposures. So why did Hill suggest this criterion? Perhaps because in the 1950s, when he started thinking about causality, particularly of a causal relationship between smoking and lung cancer, it was when infectious agents were the best known causes of diseases, and the relationships in infectious diseases are usually one to one (e.g., *Treponema pallidum* and syphilis).

5. Two case studies

In this section, we review two case studies: tobacco smoking and esophageal adenocarcinoma (widely accepted as a cause), and alcohol consumption and esophageal adenocarcinoma (generally thought not to be cause).

5.1. Tobacco smoking and esophageal adenocarcinoma

Dozens of studies have examined the association between tobacco smoking and esophageal adenocarcinoma. The Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON) included data from studies that had a large enough number of esophageal adenocarcinoma cases and were either cohort studies (2 studies) or population-based case-control studies (10 studies) to examine this association in detail. Nearly all 12 studies showed an increased risk (consistency). The overall odds ratio for this association was approximately 2-fold (moderately strong). When data were examined by pack-years of smoking, compared to never-smokers, relative risk increased from 1.25 for those who had used less than 15 pack-years to 2.71 for those who had used more than 45 pack-years of tobacco (dose-response). There are many biologic reasons why smoking can cause cancer, e.g., its effects leading to *P53* mutations (biologic plausibility). Study participants had on average started using tobacco when they were 17 years old but received cancer diagnosis several decades later (temporality). Tobacco smoking can cause many other cancers, including esophageal squamous cell carcinoma (analogy). There are no experimental studies of tobacco smoking and esophageal adenocarcinoma but most of the existing studies adjusted for a number of confounders, and the results remained strong. Trends of the rise of smoking do not necessarily predict the rise in incidence of esophageal adenocarcinoma, but this is not incoherent with what we know about this cancer. This cancer has several other known and unknown risk factors.

5.2. Alcohol consumption and esophageal adenocarcinoma

BEACON investigators also analyzed the results of these studies for alcohol consumption in relation to esophageal adenocarcinoma.[25] In contrast to smoking, the results were not consistent across studies, with some showing increased risk for certain alcoholic

beverages, while others showed no association. The odds ratio for the association between drinking even very large amounts of alcohol (≥ drinks per day) and esophageal adenocarcinoma was 0.97, and there was no dose-response. These negative findings pointed to no association, and hence no causal relationship.

6. The strengths and limitations of epidemiologic studies in establishing causality

Epidemiologic study designs vary in their strengths in establishing causality, partly because they differ in their strength in fulfilling Hill's guidelines.

Large-scale randomized, double-blind, controlled trials are the strongest study designs. Large sample size minimizes the possibility of random variation. Because the distribution of the exposure is determined at random, no factor is associated with the exposure. Thus there is no factor that is associated with both the exposure and the outcome, and hence no confounding exists. Since these studies are prospective in nature – study participants receive the exposure before the outcome – temporality is established; in other words, reverse causality is unlikely. Making the study randomized, double-blind, and controlled all reduce the possibility of biases. Since this type of study minimizes the possibility of random variation, confounding, reverse causality, and bias, if an association is seen it is likely to be causal.

Observational studies, such as cohort and case-control studies, are subject to confounding and several biases. For example, cohort studies may be subject to bias due to loss to follow-up, or case-control studies may be subject to recall bias. Therefore, their results are slightly more difficult to interpret as causal. However, we strongly rely on observational studies, as randomized trials are not feasible to investigate most associations.

7. More recent developments

Hill developed his guidelines on causality during the 1950s and early 1960s, when he was trying to infer whether certain workplace exposures could be health hazards and whether smoking could cause lung cancer. They have been useful enough that, after 50 years, we still use some of them to show that an exposure has a causal relationship to an outcome. Nevertheless, much has been done since then to improve our ability to establish causal connections.

Regression models are now widely used to control for confounders. Observational studies remain important sources of information in epidemiology, but their results are highly subject to confounders. To deal with this problem, several regression models have been developed in the past few decades. Jerome Cornfield, in addition to his many other contributions,[26,27] developed odds ratios and logistic regression in the 1950s to 1960s and applied the results to epidemiologic studies (including those of the Framingham Study[28]), which opened the way for better handling of confounders when the outcomes was binary. Future developments extended the use of logistic regression to ordinal outcomes and non-ordinal categorical outcome with more than two categories. Sir David Cox developed his proportional hazards model regression in 1972,[29] which paved the way for dealing with confounders in time-to-event analyses. Use of these methods became popular only after computer power became more available to handle the extremely involved mathematical calculations, i.e., mostly after 1985.

The use of Directed Acyclic Graphs (DAGs) is becoming increasingly common for causal inference in epidemiology. They help in conceptual understanding and identifying confounding and bias. The idea was initially developed by computer and artificial intelligence scientists, such as Pearl,[30] but it was later adopted by other fields, such as epidemiology and economics. DAGs, as their name implies, are graphs and that have a direction from the cause to the effect (e.g., from smoking to lung cancer, and not the other way) and are not cyclic (only one-sided). To make a causal DAG, the common cause of any pair of the variables in the graph should also be present in the graph. For example, if we study the association between smoking and lung cancer, any variable that is a common cause of both smoking and lung cancer should also be in the graph. If none exists, we are done. However, if we add a third variable, then any variable that causes this third variable and the other variables (smoking or lung cancer) should be added, and so on and so forth. Therefore, the use of DAGs requires prior expert knowledge, and not all experts may agree on which variables should be added to the graph. Also, these graphs are mostly qualitative rather than quantitative, and do not address random variability. So, although their use provides some insight, it does not solve all problems. Also their use may result in a more uniform nomenclature in epidemiology that stems from the structure of the relationship of variables. For example, certain forms of selection bias may also be called confounding, and both can be addressed using adjustment methods, however, different terminology may confuse the researchers. Using DAGs, we will see that these two differently named problems are in fact one, and therefore could be named similarly. The common use of DAGs in epidemiology is a relatively recent phenomenon. In 2000, for example, teaching DAGs was not part of the curriculum of doctoral epidemiology students at Johns Hopkins University School of Public Health and Hygiene or most other prominent schools of public health. Likewise, there was no chapter on DAGs in the 2nd edition of Modern Epidemiology, which was published in 1998.[31] It was only in the 3rd edition of the book, published in 2008, when a chapter on DAGs was added.[32] Nevertheless, the insight provided by these graphs is now making it a common tool for understanding causal relationships.

Counterfactual-based approaches have been used in the past three decades to derive methods for causal inference. These methods that originated in statistics and were developed by Donald Rubin and other statisticians are powerful statistical tools but are often cumbersome and difficult to understand. Partly because of the novelty of the methods, and partly because of their difficulty, as of yet they are not as commonly used in epidemiology as the other methods mentioned above. However, there is intensive ongoing research and education in this field, and the use of these methods may become common in the not-so-distant future.

8. Probabilities in causal inference and prediction

Why do we need to use probabilities, complex study designs, and complex statistical methods in epidemiology? After all, without any of these methods, we develop some understanding of cause and effect from the time we are born. At early ages, we learn that crying expedites our being fed, clicking a switch turns on the light, dropping a stone causes it to fall, and pushing an object makes it move. However, most of these examples refer to nearly one-to-one and instant relationships between cause and effect (e.g., dropping and falling of the stone). However, in epidemiology and medicine, unfortunately there is a long lag between cause and effect (e.g., between the time one picks up smoking and the time one gets lung cancer), and the relationship is not one-to-one, partly due to the effect of other factors and partly due to luck.

So we often need to leave aside our simple intuition and resort to more complex probabilistic methods. The downside of using these probabilistic methods is that they are difficult to understand, and the rationale for using them is difficult to communicate to lay people. When the people, who are the consumers and voters, don't understand the debate, they get confused and may lose their trust. For example, scientific data are against the hypothesis that vaccines cause autism, yet there are many people who are still hesitant about vaccinating their children, fearing that pharmaceuticals producing the vaccines are trying to silence the scientists who identified the problem! Fortunately, however, science has gained enough respect among people that when scientists understand the issue, and repeat their conclusions to people many times, most of the population accepts the consensus.

Some may attribute the probabilistic nature of causality to our current ignorance and hope that there will be one day, when our scientific knowledge is vastly greater, that we can find causes much more easily, and that we predict with accuracy whether or not a person will get a disease, e.g., cancer. While I am not sure about the former (finding causes), I believe there is good evidence that the latter (predicting with accuracy) may never happen. There are theoretical grounds from physics that certainty may not be possible,[33] and from computer science that exact predictions in tremendously complex situations may not be feasible.[34] There is also empirical evidence from studying humans to show this. Identical twins share almost their entire genetic code and a considerable part of their intrauterine and childhood environment, yet the concordance of cancer occurrence in monozygotic twins is far from perfect.[35] In a Nordic cohort, of 248 monozygotic brothers who were diagnosed with lung cancer, for example, only 15 were concordant for lung cancer and 233 were not.[35] Indeed, the concordance rate between monozygotic twins for any type of cancer is usually 0.1 or less.[35] More convincing data come from studying natural history of cancers in single individuals and using our knowledge of biology. A woman shares with herself the entire genetic code and environmental exposures. Yet it happens often that one breast develops cancer whereas the other one does not. Indeed, several years after development of cancer in one breast, risk of contralateral breast cancer is still far from certain, even when contralateral prophylactic mastectomy is avoided.[36] More broadly, according to our current knowledge of cancer biology, most cancerous tumors are monoclonal. Only one cell out of millions or billions found in an organ develops into a full-blown tumor, whereas the adjacent cells, which should be identical in many ways, do not. All of this evidence points to impossibility of predicting cancer in an individual person with certainty. In one of his last articles,[37] Sir Richard Doll seems to have expressed a similar belief: "*…only a relatively small proportion of people are victims of a particular type of cancer even if heavily exposed to known chemical carcinogenic agents … the fact that only, say, 20% of heavy cigarette smokers would develop lung cancer by 75 years of age does not mean that 80% are genetically immune to the disease … whether an exposed subject does or does not develop cancer is largely a matter of luck.*"

9. Religion and causation

Our philosophy and religious views influence on our understanding and acceptance of causes. People have long known that there is a chain of causation. They may ask, for example, what causes lung cancer? The answer to a biologist may be mutations in *P53* gene. An epidemiologist may ask what causes that? The answer: smoking. A behavioral scientist may ask what caused that person to pick up smoking? These questions may go on, until we seek "an ultimate" cause, and for many people that would be "the Will of God". One might ask how this is relevant to public health? I believe it is very relevant. I have seen many people take no or little action about their health for two reasons. Being confused by the probabilistic (and not completely one-to-one) nature of the occurrence of outcomes and believing in the Will of God as the ultimate cause, many decide to take no action, for example not to undergo screening for cervical cancer. However, they miss the point that although health outcomes are not certain, they are not completely random either. Also, they miss the point that although most religions attribute outcomes to the Will of God, they also encourage people to take actions. Such discussions may help people take actions in the right direction. If we eliminate smoking, we can reduce the lifetime incidence of lung cancer from 17% to 1%, and that is a step in the right direction.

10. Philosophy and causation

The question "What is a cause?" has a long history among philosophers. Over the past few decades, epidemiologists have enthusiastically studied and debated different philosophical views on causation, not only those of centuries ago, but also those of the 20th century's philosophers of science, such as Popper, Kuhn, and Feyerabend.[38–41] Epidemiologists have done so partly as an intellectual exercise and partly in the hope that this knowledge will help them expedite the rate of discovering causes. In my view, thus far the most important use of these philosophical debates has been the intellectual stimulation; it has not been a major help with more rapid discoveries. Whereas it is interesting to read about Kuhn's philosophy of science (e.g., normal science and scientific revolutions), it has made little impact on finding the causes of diseases. For the past 100 years, we have believed in the existence of cells, molecules, atoms, the power of microscopes, etc. Whereas in 500 years this may undergo a revolution, such that we completely lose faith in the presence of an entity called atom, it has little bearing on our today's research.

However, these deliberations have at times resulted in adoption or development of some useful concepts or models. For example, a causality model hat is somewhat interesting and helps in better understanding some parts of epidemiology is the "sufficient cause model".[42] A sufficient cause is a collection of a number of events (component causes) that need to come together for an outcome to happen. For example, for Anna-Maria to die of liver cancer, she must have skipped vaccination against HBV, get HBV from sharing needles with an HBV-infected college classmate, not have health insurance to get tested and treated in time, etc. All of these need to happen for her to die of liver cancer. Which one is a cause? The answer is: "each and every of them". If we could reverse only one of these steps, e.g., she had received the vaccine, she would have not got liver cancer. Learning this concept facilitates learning some aspects of epidemiology better. For example, we understand why the sum of individual attributable risks could be much higher than 100%. If A and B are both needed for Y to happen (Figure 3), then the risk of Y attributable to A is 100%, and the risk attributable to B is also 100%, as when either of these is eliminated, Y is completely eliminated. In Figure 3, U is a collection of other unknown agents, which as mentioned earlier may be knowable or unknowable.

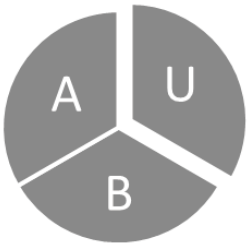

Figure 3. Factors A and B, in addition to a number of unknown factors (collectively called U) are needed for Y to happen. A, B, and U are called component causes, which together make a sufficient cause.

Summary and conclusions

Epidemiologists have significantly contributed to the discovery of numerous causal relationships. Nevertheless, establishing each causal relationship has been a monumental task, usually requiring many studies to show consistency of the association and to rule out other potential possibilities, including random variation, bias, confounding, and reverse causality. Ruling out other explanations still remains the key.

Guidelines developed by Hill and others, although neither sufficient nor necessary, have helped us over the past 50 years in differentiating between causal and non-causal relationships, and they remain relevant today. Since then, advances have been made to our methodology, including the introduction and popularization of regression techniques, DAGs, and counterfactual models. With the advancement of technology and statistical techniques, we are nearly certain that more and more causes of diseases will be discovered, however, it might be impossible for us to know it all, or to predict with certainty the occurrence of an outcome in a single individual. Such uncertainties should not deter us from taking steps in the right direction. Reduced cigarette consumption has already resulted in lower risk of lung cancer in American men,[43] and vaccination against HBV in Taiwan led to a significant reduction in risk of liver cancer.[44] Efforts should continue to find more couses, and to communicate our findings in a simple and understandable way to the public.

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