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Causality Phenomenon: Is an Exposure Really the Cause of a Disease?

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Abstract:

Background: Studies are carried out to determine association between a particular exposure and an outcome of interest. The results of these studies showing statistically significant relationships does not imply cause and effect relationship. Consumers of research outputs are more likely to accept the validity and reliability of research findings where causal relationship is determined. Objective: To elaborate on the criteria for consideration before a relationship between an exposure and an outcome can be considered to be causative. Literature Search Strategy: The search terms used were exposure, outcome, independent variable, dependent variable, causation, causality, association, and relationship in various combinations. Titles and abstracts of articles containing various combinations of the search terms were retrieved from medline via PUBMED, Cochrane library, Google Scholar, and Web of science with no year or language limits. Grey literature was also searched for relevant articles. Full papers of relevant articles were critically reviewed. Results: It is evident in scientific literature that the statistically significant relationships we derive from probability values (p - values) and confident intervals does not imply cause and effect relationship. Causal relationship is a complicated process. It is justifiable to consider component cause, sufficient cause and necessary cause in this regard. There is also the need to utilize the Bradford Hills criteria of causation in making a decision on causality. Conclusion: Once a cause and effect association has been established in studies beyond any reasonable doubt, action can be taken to change public policy, legislation, health education, clinical practice, or the direction of research.

Keywords:

Exposure, Outcome, Cause, Effect, Relationship, Bradford Hills, P Value, Confidence Interval

1. Introduction

Majority of the studies carried out aim to determine an association between a particular exposure and an outcome of interest. For example, a study aimed to investigate the association between male circumcision and HIV infection [1]. The aim is to achieve results that would influence clinical practice or health policy positively [2]. We seek to determine the relationship between dependent and independent

variables [2]. The results of these studies showing statistically significant relationships does not imply cause and effect relationship. Probability values (p - values) and confident intervals were used as estimates to obtain statistically significant associations, between exposure and outcome variables [3]. These results are based on uncertainties and probabilities with defined level of confidence and error. We cannot, therefore, prove causality because of these uncertainties.

Since study samples are taken from the population, we hope that the results we obtain from the analysis of the sample data will be a reflection of the truth in the general population. To achieve this, it is important that the relationship obtained is not by chance, biased or a result of confounding [4]. We need to ensure that the association is real. At times we take decisions on these results. Consumers of research outputs are more likely to accept the validity and reliability of research findings where causal relationship is determined [2].

As an illustration, a study showed that Peptic ulcer disease is associated with Helicobacter pylori infection beyond chance, bias and confounding [5]. In what circumstances can we confidently say the infection causes the disease? What criteria should we base our decision on?

2. What Do We Mean by An Event Causing Another Event?

In health, the causal relationship between an exposure and a disease is not as simple as we might be tempted to think. The causal phenomenon is not a one – to – one relationship such that every time the cause is present, the effect will manifest. It is a complicated process.

Literature has shown that not all individuals exposed to contaminated food came down with food poisoning [6]. In a household, not all close contacts of a patient with pulmonary tuberculosis will have the disease [7]. Infection depends on individual immunity level, dose of agent and overall level of health [7].

Rothman defined a cause as [8]:

"An event, condition or characteristic {or a combination of these factors} that plays essential role in the occurrence of disease"

This definition is better appreciated by the understanding of the following concepts [9].

A sufficient cause is a factor or more usually a combination of several factors that will inevitably produce disease.

A component cause is a factor that contributes towards the disease causation but is not sufficient to cause disease on its own.

A necessary cause is any agent or component cause that is required for the development of a given disease, the absence of which the disease cannot occur.

The tubercle bacilli is a part of the sufficient cause for tuberculosis. Other factors include immunity, load of bacilli and state of general health [10]. The tubercle bacilli is also a necessary cause because without it, there is no clinical tuberculosis. Low level of immunity is a component cause of tuberculosis, but alone cannot cause disease.

In practice, we often deal with component causes in the aetiology of disease. An exception to this rule is physical injury from physical and chemical agents like road traffic accidents and acid burns.

In disease prevention we do not need to determine the exact nature of the sufficient cause or all the possible component causes of disease. If any one of the component causes is identified and removed, the other components may not be sufficient to cause disease. Thus, prevention can be effective particularly in a large proportion of the population at risk. The significance of this is that among the component causes, identification of a modifiable cause that is associated with a large population attributable risk; that is one which causes a large number of cases of disease will give the greatest benefit in terms of public health [11].

If we consider the causes of ischaemic heart disease, the following are component causes; low intake of fruits and vegetables, overweight and obesity, smoking, physical inactivity and hypertension [12]. The modification of one or more of these factors depending on the context will results in varying degrees of reduction in the occurrence of ischaemic heart disease.

In lung cancer, smoking is a component in most sufficient causes [13]. However, not all smokers develop lung cancer. Smoking therefore is not a sufficient cause on its own but requires other factors for example weakened DNA – repair capacity to complete a sufficient cause. Similarly, since lung cancer can develop in non – smokers, we can presume that there is at least one sufficient cause that does not have personal smoking as a component cause.

How do we evaluate causation?

Several guidelines are available in the evaluation of causation. The one proposed by Sir Austin Bradford Hill (1965) [14]. helps us to decide whether an exposure could be considered to cause a disease or an intervention is effective in preventing or treating disease. These criteria are not absolute requirements to be met before causality is established. The elements of Bradford Hill criteria are discussed below:

2.1. Temporal Precedence

For an exposure to cause a disease, it must precede the development of the disease. If agent “A” like Salmonella typhi is believed to cause a disease, Typhoid fever, then it is clear that agent "A" must necessarily always precede the occurrence of the disease. This is the only absolutely essential criterion for causation.

In some instances there may be a challenge in differentiating between the exposure and the disease particularly for diseases of slow development. Does chronic stress lead to chronic hypertension or does cigarette smoking lead to development of lung cancer? Does a particular environmental pollutant promote the development of chronic obstructive pulmonary disease or the disease have already developed before exposure to the environment?

This temporal problem may not arise often when we are faced with acute medical conditions, but it certainly needs to be remembered. Thus, studies where the determination of temporal progression between the two variables is endured are more likely to be accepted at establishing causation [15].

2.2. Strength of Association

This is defined by the size of the association as measured by appropriate statistical tests (Odds ratio or Risk ratio). The stronger the association, the more likely it is that the relation of an exposure and a disease is causal. For example, a study on smoking showed that the death rate from cancer of the lung in cigarette smokers is about ten times the rate in non-smokers and the rate in heavy cigarette smokers is about thirty times as great [13].

It is suggested that an effect size (Odds ratio or Risk ratio) greater than 2 is moderately strong and an effect greater than 5 is strong [15,16]. Results of studies showing small associations could be due to chance, bias or confounding and therefore, less indicative of causation.

Recently, strength is no longer interpreted as simply the magnitude of an association. The knowledge on the multiple aetiopathogenesis of disease has shown that some risk factors are small in magnitude yet statistically strong. As a result, the use of statistical significance—not the magnitude of association—is now accepted as a determining factor for judging the strength of an observed association, and thus its potential causality [16].

2.3. Dose-Response Relationship or Biological Gradient

An increasing amount of exposure increases the risk of disease. If a dose-response relationship is present, it is strong evidence for a causal relationship [15,17]. At the same time, if a specific factor is the cause of a disease, the incidence of the disease should decline when exposure to the factor is reduced or eliminated. The dose in practical terms is related to level and duration of exposure.

A study among nurses in the US [18] showed that risk of Type 2 Diabetes Mellitus (T2DM) increased dramatically with increasing body size particularly with women with Body Mass Index (BMI) greater than $25kg/m^2$. Those with BMI >35 were 60 times at higher risk of T2DM than those with BMI <22.

The fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds immensely to the simpler evidence that cigarette smokers have a higher death rate than non-smokers [13]. However, the absence of a dose-response relationship does not rule out a causal relationship. A threshold may exist above which a relationship may develop. In addition, we have evidence in modern studies that more complex dose–response relationships may exist. In fact, most dose–response curves are non-linear and the shapes can vary in shape according to the study methods [19]. Furthermore, individual susceptibility and synergistic or antagonistic effects of cumulative exposures can make some biological gradients even more difficult to characterize [16].

2.4. Consistency

When many epidemiologic studies carried out in different locations and populations, with different study methods, show consistent association between variables in hypothesis tests, decision on causal relationship is strengthened [16]. Statistically significant single studies cannot provide enough ground to prove causation due to challenges to internal validity. As appropriate as this criterion is in determining causal relationships, data integration by meta-analysis has introduced another paradigm into the meaning of consistency. Combining data from several studies using meta-analysis can increase statistical power, provide insight into the nature of relationships among

variables, and increase generalizability of results more rigorously than less quantitative review methods [20].

Lack of consistency on its own does not rule out causality. When several studies give different results on the relationship between variables (heterogeneity), careful interrogation of the results may show variations in study design, differences in exposure or genetic makeup [16].

2.5. Biological Plausibility

Acceptance of causality is empowered when the association between the variables agrees with currently accepted understanding of pathological processes. Peptic ulcer disease was initially ascribed to gastric hyperacidity. The understanding of the role of Helicobacter pylori infection in the aetiopathogenesis of peptic ulcer disease has changed this paradigm [21]. This may not be the case in some instances, as the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd.

2.6. Specificity

This is established when a single agent causes one specific disease. This is considered by some to be the weakest of all the criteria proposed by Hill. In this regard, we attempt to specifically define exposures as an actual dose of a chemical, physical, or biological agent [16]. Exposure to asbestos leads to asbestosis. When specificity of an association is found, it provides additional support for a causal relationship.

Current research outputs examine diseases in relation to a variety of complicated multiple aetiological and risk factors. Causality is most often found to be multiple. The diseases attributed to cigarette smoking, for example, do not meet this criteria. However, absence of specificity does not negates a causal relationship. Therefore, it is necessary to examine specific causal relationships within a larger systemic perspective.

3. Experiment

Results of experiments in animals and intervention studies in humans could be utilized to determine causality. In epidemiological studies, intervention to reduce or eliminate exposure leading to reduction or cessation of disease risk, provides strong evidence for causal inference. Thalidomide is no longer given to pregnant women because it causes birth defects [21].

Dietary advice and drugs are given to lower cholesterol levels to prevent heart disease [16]. Recent advances in knowledge show that many diseases result from multiple exposures and complex aetipatogenesis [20]. While, determination of causality based on specificity is important in the choice of specific therapeutic interventions - It is justifiable in many cases to approach disease prevention with multiple attention to several risk factors.

3.1. Analogy

In some circumstances it would be fair to judge by analogy. Hill implied that when there is strong evidence of a causal relationship between a particular agent and a specific disease, researchers should be more accepting of weaker evidence that a

similar agent may cause a similar disease [14,16,23]. Some modern epidemiologists have argued that a lack of analogy does not preclude causation, but simply implies a lack of creativity on the researcher's part [24]. Tools that are available for researchers for seeking analogy include disease progression pattern, common risk factors and confounders, and biological mechanisms of action [16].

3.2. Coherence

A cause – effect interpretation should not conflict with the known facts. The association should be compatible with existing theory and knowledge [14]. In other words, it is necessary to evaluate claims of causality within the context of the current state of knowledge within a given field and in related fields. This has been viewed as being similar to biological plausibility in that the cause-and-effect story should make sense with all knowledge available to the researcher, and this criterion has not changed greatly since its inception [16]. However, new findings of research at conflict with existing knowledge and practice should not be seen as automatically false. They may serve as tools for re – appraisal of current accepted beliefs and principles.

3.3. Practical Perspective to Evaluating Causality

In 2001, a group pooled data from 12 studies to evaluate the relationship between H. pylori and stomach cancer [25]. The odds ratio from all 12 studies was 2.4 (95% CI 2.0-2.8).

3.4. So Could the Relation be Causal?

The association was quite strong and also consistent across these studies. In all the studies, the blood samples were collected before the diagnosis of cancer, suggesting that the infection precedes cancer. Since someone is either infected or not infected, it is not possible to look for a dose – response relationship. The association appears to be fairly specific for stomach cancer. Further experimental evidence comes from studies that have shown that H. pylori infection induces cancer in some animal models. A relation is also biologically plausible. This is because the bacterial infection directly affects the stomach, where the cancer occurs. As a result, there is enough evidence for the widely accepted conclusion that H. pylori infection is indeed a cause of stomach cancer.

4. Conclusions

The Bradford Hill Criteria remain one of the most cited concepts in health research and are still upheld as valid tools for aiding causal inference [26]. Depending on the situation, the decision on causality based on Hills criteria varies between being clear cut to being controversial. It is imperative to note that these elements do not provide infallible hard and fast checklist of evidence that determines cause and effect postulation. These elements should be regarded as a framework for the evaluation of causality.

Globally, changes are taking place in epidemiologic research. These changes have implications on Hills criteria. There is need for this criteria to involve principles of data integration and meta-analysis [16]. This would enable researchers to have a more expansive view of causation. Data integration and meta – analysis can enhance the application of the Bradford Hill Criteria in a causal analysis by: allowing for more scrutiny in study designs; providing new tools to demonstrate consistency, specificity,

and plausibility of associations; integration of homogeneous studies to determine temporality and dose–response; clarifying conflicting epidemiologic findings to determine coherence; and promoting the proposal and testing of new mechanistic hypotheses [16].

Once a cause and effect association has been established beyond any reasonable doubt, action can be taken to change public policy, legislation, health education, clinical practice, or the direction of research.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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