

Nutritional Epidemiology Methods and Interpretation Criteria

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Introduction

Today, it is common to hear daily media reports of studies relating human diet to a number of chronic diseases. This interest is not new. Throughout human history different philosophies and beliefs have existed about the relationship of foods, diets and lifestyles to health. The diversity of dietary practices in cultures around the world eloquently speaks to that fact. Yet after Sir Richard Doll reported that as many as 30% of human cancers are directly related to diet and lifestyle, there has been intense activity to identify the relationships.

In an era of instant and mass communication, we seem to be bombarded with views and reports about the definitive word on diet and health. Overall, the media does a fairly good job of reporting. They commonly include the limitations of the studies and the fact that they are expressions of risk probability. Since foods are heterogeneous, complex in terms of their composition and their contribution to the overall diet, ascribing an individual food component or food as “good” or “bad” is fraught with difficulty. But in our American culture we expect to be able to distill the complex into simple essentials that can be acted upon. So if tens or hundreds of factors are related to a disease, we expect there will be a top two or three, that if dealt with, can result in a practical solution that leads to prevention or a cure. Developing this hierarchy of relationships among diet, lifestyle and disease utilizes epidemiological research.

For participants in the social debate about diet and disease, it is crucial to understand the strengths and limits of epidemiology.

Epidemiology as a Scientific Discipline

Modern epidemiology is the branch of medicine that deals with the study of the causes, distribution and control of disease frequency in human populations. Historically, epidemiology began as the study of epidemics of infectious disease. Essentially, epidemiology looks for patterns of disease based on time, location, exposure and populations characteristics such as gender, race, genetics, lifestyle etc.

There are several types of epidemiological studies, each with their own strengths and weaknesses. Ecologic/descriptive studies are the simplest and least persuasive type. In these studies, the broad characteristics, such as average per capita consumption of a food and standard disease rates in different countries or cultures are compared and examined for trends. Ecologic studies characterize differences between large and diverse populations by simple generalizations and can help formulate hypotheses. However, they cannot control for hidden or potential confounding factors.

Case-control studies focus on individuals and provide stronger evidence for an association than ecologic studies. “Recalled” past diets of individuals diagnosed with a disease (cases) are compared to those of individuals without the disease (controls) in a retrospective case-control study. Data is typically collected by surveys or questionnaires. Many researchers rely on this type of study because of lower cost, smaller sample size and ability to study many potential factors. However, such retrospective studies are subject to recall bias and unavailable or incomplete data. There may also be questions regarding adequacy of the “control” group in being truly matched with all the cases for factors that can confound relationships.

Prospective or cohort studies, on the other hand, are considered to provide more definitive information and are the most persuasive epidemiological study design. They also represent the latest in the reports that we hear about today. Many large studies using volunteers are underway and the information in these respective databases is continually being analyzed for associations. The study groups are often identified by the acronym names such as NHANES I and II (National Health and Nutrition Exami-

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nation), AARP (American Association of Retired People), EPIC (European Prospective Investigation into Cancer) etc. In these studies, a cohort (group) of individuals, who do not yet have a specific disease, are selected and followed over a period of time while collecting specific information regarding diet, lifestyle and other factors related to the development of the disease. It is important to appreciate the difficulty associated with this method in terms of measuring diet, long term follow-up (often for decades), and the fact that diets are not static and methods to measure and account for dietary change over many years of time are minimal. Prospective studies are also very costly due to the time and large numbers of subjects.

Beyond epidemiological study, conducting human, randomized clinical intervention studies may be desirable to confirm or refute the existence of associations and provide very strong evidence for causality. However, these studies are often simply impractical to conduct.

Epidemiological results are expressed in term of relative risks, hazard ratios, or odds ratios, which while computationally different, represent the factor of increased or decreased likelihood that a person or population with a certain exposure will have on a health outcome. For example, an odds ratio equal to 1.5 for heart attacks comparing a dietary consumption of “x” gm/day above the baseline in a study would mean a 50% increase in likelihood of heart attacks for those that consume that specific dietary item. An odds ratio of 0.8 would mean a 20% decreased likelihood. Additionally, confidence intervals around these associations that include 1.0 indicate no statistical significance. This is one area where the natural human desire to report an “almost effect” can cause publication of reports that use terms such as “directional but not significant” followed by extensive discussion about the findings as if they were significant.

There is an ever increasing body of published studies covering the same diet-disease relationships, but on different population groups, with slightly different methods, or over different time frames. Often there is a mixture of case-control and cohort studies with both no significant findings and significant relationships with varying magnitudes of association. Summary techniques called meta analyses and data pooling have been utilized to improve statistical power and consolidate multiple studies in an attempt to better consolidate the body of research. In a meta analysis, the average results of individual studies are combined using normalizing statistical procedures. In essence, this results in an “average of averages” result.

Pooling combines all of the primary data from individual studies and then statistical analysis is performed on the larger data set. It is more difficult to pool data compared to a meta-analysis as it requires access to raw data and needs common factors collected in the same data units from multiple studies.

Bradford Hill Criteria

The eminent British biostatistician A. Bradford Hill published a seminal paper in 1965 offering a number of interpretation criteria that are useful when interpreting such “number crunching” studies. These criteria have become a *de facto* standard to evaluate epidemiological research and are very relevant to the public discussion of diet and disease. A short discussion of each follows.

Strength of Association

The stronger the relationship, between the independent variable (the risk factor) and the dependent variable (the disease), the less likely the relationship is due to an extraneous variable (a confounder). The relative risk of smokers developing lung cancer is around 10 (*i.e.* 10-fold higher risk than for non-smokers). The relative risks associated with consumption of grains containing mycotoxins and liver cancer is around 6. These are two examples of strong associations.

By contrast, modest relative risks on the order of 2 or less, which are common for most diet-disease associations, should be viewed with skepticism due to the likelihood of many confounders. This interpretive “designation” was recognized in 1994 when the National Cancer Institute publicly indicated that relative risks of less than 2 were not strong enough to use for public policy. Weak relative risk associations of 1.5 or less should be considered with even more caution. However, organizations seem to indicate a general willingness to promote public health policies based on such limited associations.

Temporality

The exposure must precede the disease by a reasonable amount of time, *i.e.* a cause must precede an effect in time. While this seems obvious, it is easy and common to discount. Again smoking over a period of years will raise lung cancer risk. Eating an excess of calories over those expended, ultimately results in higher body weight.

Consistency

Multiple observations of an association, with different people under different circumstances and with different measurement instruments, increase the credibility of a causal finding. Different methods (*e.g.* ecological, cohort and case-control studies) should produce the same conclusion. The relationship should also generally hold true for different groups of people (in males and females, in different populations on different continents). This standard is greatly debated because consistency is in the eye of the beholder. Some view six of ten studies with a significant relationship as consistent, while others view this as an inconsistency. For some factors, gender differences would be obvious, but for others they are difficult to biologically justify.

Theoretical Plausibility

It is easier to accept an association as causal when there is a rational and theoretical basis for such a conclusion as supported by known biological mechanisms and other facts. While our knowledge of physiology is vast, there is still much that is unknown about the complex interactions of ingested foods and metabolism. *In vitro* mechanistic studies can often be misleading. Often epidemiologists, while extremely skilled in statistical methods, are not as well informed about toxicology, physiology, metabolism, medicine, food composition and manufacturing. This results in inappropriate application of plausibility hypotheses to their data. One example is the common attribution of nitrite in cured meats as a potential underlying reason for associations between cured meat and cancers. However, the endogenous production of nitrite is now known to be many fold higher than what is consumed from cured meats, hence this is highly unlikely.

Coherence

A cause-and-effect interpretation for an association is clearest when it does not conflict with what is known about the variables under study and when there are no plausible competing theories or rival hypotheses. In other words, the association must be coherent with other knowledge. The conclusion that smoking causes lung cancer, based on epidemiologic, laboratory animal, pharmacokinetic, clinical and other biological data, showed that all available facts stuck together as a coherent whole. A weak but significant finding that high meat consumption is related to death from automobile accidents is likely due to chance or confounded by covariates to meat consumption.

Specificity in the Causes

In the ideal situation, an effect has only one cause. In other words, showing that an outcome is best predicted by one primary factor adds credibility to a causal claim. But in many cases this is not the norm. High consumption of one food or nutrient can be covariate with low consumption of another food. How does one determine which of the two is more important?

Other non-dietary confounders must be considered. For example, chronic *Helicobacter pylori* infection is a strongly suspected risk factor for gastric cancer. Since 1980, when viral causes of cancer were considered improbable, medical thought has now evolved where today at least eight cancer sites are considered to have strong viral contributions. Vitamin D and mineral metabolism may be important factors in colorectal cancer. Correction of a mild potassium, calcium and magnesium deficiency can lower blood pressure to a similar extent as dietary sodium reduction. Nutritional epidemiological studies that fail to account for these types of effects in the data interpretation should be viewed with caution.

Dose-Response Relationship

There should be a direct biological gradient between the risk factor (the independent variable) and subject's status on the disease variable (the dependent variable). Many dietary epidemiological studies report a significant trend for dose response, but on closer examination, the data is highly inconsistent. The data may only span a very narrow range of intake or conversely such a wide range of intake that upper intakes are representative of a grossly unbalanced diet. Relative risks may sometimes decline to non-significant levels with higher intake, or one quartile of intake has a high enough calculated risk to skew the overall result. Such data patterns need to be considered as part of the consistency criterion.

Experimental Evidence

Any related research (animal, *in vitro*, etc.) that is based on designed and controlled experiments will make a causal inference more plausible. This must be tempered with the understanding that animals are not people. Results from programs such as the National Toxicology Program (NTP) are often very useful. While NTP studies have confirmed that components of tobacco or wood smoke, and nitrosamines are carcinogenic in laboratory animals, nitrite does not appear to cause cancer based on these gold standards of toxicological assays.

Analogy

Sometimes a commonly accepted phenomenon in one area can be applied to another area. This is an obtuse criterion and analogy is considered to be a weak form of evidence.

Summary

Bradford Hill developed his list of "criteria" that continues to be used today. When using them, it is critical to recognize Hill's own advice:

"None of these nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis... What they can do, with greater or less strength, is to help answer the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

In making the link between diet and human cancer risk, most scientific publications, discussion and media attention have focused on data from epidemiological studies, but it is important to understand clearly that associations between dietary components, specific foods (or food groups) and chronic disease are rarely sufficient to establish cause and effect relationships. The results of epidemiological investigations must also be confirmed through other types of supportive studies (animal studies, metabolic studies, human clinical intervention trials, etc.) before persuasive causal relationships can be firmly established.

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