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Noel S. Weiss

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Standing on the shoulders of Austin Bradford Hill: The refinement of “specificity” as a consideration in causal inference

Noel S. Weiss

nweiss@uw.edu

Department of Epidemiology
University of Washington
Seattle, WA, USA 98195

I began my study of epidemiology in 1968, just a few years after Bradford Hill (and his American counterparts) outlined sets of guidelines to assist in inferring the causes of disease. At that time both Bradford Hill and the Americans had as a focus of their thinking the example of cigarette smoking and lung cancer. Both invoked the notion of the specificity of the association: for example, the Americans argued (U.S. Public Health Service, 1964) that “on an intuitive basis...when a given characteristic is found to be associated with one, or at most a few diseases, then the evidence for a causal relationship is more convincing.” However, they also acknowledged that “it would not be surprising to find that the diverse substances in tobacco smoke could produce more than a single disease”, and Bradford Hill (Hill, 1965) said that “we must not overemphasize the importance of the characteristic [i.e. specificity].” So, while the notion of specificity as a consideration when seeking to infer cause and effect was mentioned by Bradford Hill in his 1965 article, that mention came with qualifications.

After completing my academic training in epidemiology, I sought a career in academia, and was fortunate to find a position at the University of Washington where I could immediately (and for the next 45 years!) indulge my passion for the teaching of the principles and methods of epidemiology. For a number of years I would discuss the guidelines for causal inference in class, mentioning specificity, but always downplaying its importance. I would say something like, “the fact that cigarette smoking predisposes to emphysema, bladder cancer, coronary heart disease, etc. should not in any way detract from the inference that cigarette smoking predisposes to the development of lung cancer”.

Then, around the year 2000, I was reading a document prepared by one of our doctoral students in which she was addressing a possible causal influence of the presence of bacterial vaginosis in the acquisition of HIV infection. I remember gently chastising her for taking into account the notion of specificity, reminding her that this often was not a useful guideline. No more than two days following this conversation I received an article from my colleague, Victoria Holt, on a topic of mutual interest, the potential etiologic role of ovarian endometriosis in the development of ovarian cancer. That article reported a several-fold increase in the incidence of ovarian cancer associated with the presence of ovarian endometriosis, but no corresponding increased risk associated with endometriosis that affected only pelvic structures other than the ovary. I wrote a message to Victoria thanking

her for the paper, and added that because of the strength and specificity of the association, I suspected that a causal link was present.

Yes, I used the word “specificity”! Startled that I had done so, I began to search my memory for other instances in which I had invoked the notion without actually using the term. They were not hard to find. Here are two examples:

- In 1992, I had joined Joe Selby and others at Northern California Kaiser Permanente in publishing the results of a case-control study of fatal colorectal cancer in relation to a history of screening sigmoidoscopy (Selby et al., 1992). We reported that a considerably lower proportion of fatal cases of rectal and distal colon cancer than controls had previously undergone screening, but that no similar association was present for fatal cases whose tumor had arisen beyond the reach of the sigmoidoscope. The specificity of this association, as well as its large magnitude, led to the widespread acceptance of the results as indicative of genuine secondary prevention.
- In my teaching on clinical epidemiology, for some years I had featured a study using Medicaid data (Ray et al., 1997), which examined the occurrence of hip fracture among persons using psychoactive drugs. An increased risk of 50 to 80% was seen among current users of antipsychotic, tricyclic antidepressant, and long half-life hypnotic or anxiolytic agents. However, the question of confounding loomed - were people who took these drugs inherently prone to falls and/or fractures? One piece of evidence in support of a causal relation came from the specificity of the association - there was no increased risk of fracture associated with the use of short half-life hypnotic or anxiolytic agents, just as would have been predicted based on the relatively brief impact these agents might have on motor function.

Soon thereafter, I wrote an article (Weiss, 2001) to describe my new appreciation of the concept of specificity as a guide to causal inference, and went on to modify my classroom teaching accordingly. And yes, I offered an apology to the graduate student! On each of the several times we have encountered one another in the nearly 20 years since that time, we have shared a good laugh recalling this episode.

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