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Cervical Cancer Risk Factors 1966–2006: Causation or Correlation?

Cervical cancer is a major cause of mortality and morbidity in both the developed and developing worlds. It is caused by the human papillomavirus (HPV), and the major focus of recent prevention strategies has been centred on a program of vaccination directed against it. Cervical cancer has long been known to have risk factors resembling those of an infectious disease. For example, women with low age at first intercourse, low socioeconomic status, a high number of sexual partners or a large number of children tend to have higher rates of cervical cancer than the general population. Conversely, membership of various racial, religious and cultural groups, circumcision of male sexual partners and regular use of barrier contraception appear to reduce the risk of developing the disease.

Before the recognition of HPV's causal role in the development of cervical cancer this group of complex socio-biological factors tended to complicate the search for causes. While they played an important heuristic role in the search for causal infectious agents, evidence arising from studies of these factors suggested that a different virus, herpes simplex, was really the cause of the disease. Why were these factors so difficult to analyse? At least some of this difficulty resulted from their complex relationship to cervical cancer. For instance, having a large number of sexual partners is a positive risk factor for the development of the disease. Does this increased risk result solely from the increased chance of contracting HPV that frequent sexual contact produces? Alternatively, does the increased risk result from increased exposure to some other agent that acts synergistically with HPV to cause the disease? Or does it, perhaps, cause the disease directly through some other means? Perhaps the number of sexual partners a woman has is not causally related to her risk of developing cervical cancer at all. Perhaps it is just correlated with one or other causal factor. Finally, perhaps the causal situation is even more complex, with promiscuity acting as both cause and correlate of cause.

Given this complex situation, I'll review the attempts made to unpick causation and correlation for this type of risk factor, focusing on the period 1966–2006. This covers the period between the widespread recognition that the risk factors for cervical cancer resembled those of an infectious disease to the introduction of a vaccine against HPV.

This historical discussion is intended to support a bottom-up philosophical thesis: that causation in medicine is supported by both mechanistic and statistical evidence. A similar suggestion has recently been made by Russo and Williamson (2007), who described causation in medicine as monistic and epistemic, supported by both mechanistic and statistical evidence. However, their account does not develop what is meant by statistical or mechanistic evidence, nor indeed does it describe how the two distinct types of evidence might interact. Using the example given above, I therefore intend to develop this account of causation. In particular, I intend to discuss the following points:

First, how well is Russo and Williamson's thesis supported by the historical case? For instance, did the evidence used in resolving these causal difficulties actually fall into

mechanistic and statistical classes? I will argue that this was, in fact, the case. In general, mechanistic evidence arose from *in vitro* interventionist investigation of the nature and properties of pathophysiological entities. Statistical evidence, on the other hand, arose from population-level observational studies of these properties *in vivo*.

Second, how best to think of mechanistic evidence in this context? I will argue that the account of Machamer, Darden and Craver (2000) is best suited for this task. They characterise mechanisms as interlevel, productive communities of entities performing activities. I will show that this activity-entity dualism is essential to a discussion of these complex causal situations. In particular, if we permit entities to have multiple potential activities we can elegantly conceptualise the manifold possibilities of different outcomes from within one overarching mechanism, describing a situation where complex physiological and pathophysiological scenarios are entwined.

Third, how to give an account of the functional role of statistical evidence in this example? I will do this using a technique closely related to Salmon's account of Statistical Relevance (Salmon, 1984: 36–47). Ideally, we should be able to determine the conditional probability of the instantiation of a particular part of a mechanism given its causal antecedents. This seems to be the best reflection of the way that epidemiological statistical evidence is constructed. For instance, many studies have been conducted looking at the relative risk of developing a disease given the presence or absence of particular variables, and these risks are generally summarised by giving the probability of a disease developing conditional on these particular antecedents.

I then intend to show that, for both empirical and conceptual reasons, each type of evidence alone is inadequate. Finally, therefore, I will give an account of the manner in which these two types of evidence interact, and suggest that we can give at least an empirically adequate account of causation in medicine as a result. Of particular interest is both the manner in which statistical evidence allows us to deal with the difficulties of a purely mechanistic account and the possible resolution of difficulties with a statistical relevance-type account by using features of mechanism. With reference to the first, I will attempt to describe how statistical relevance allows us to describe which potential activities within our mechanism actually occur in particular circumstances – that is, to make a selection between potential activities on the basis of their antecedents. With reference to the second, we may be able to approach both reference class difficulties and partition homogeneity by conditioning our data epistemically, based on the features of the relevant mechanism.

In conclusion, I will present an historical example of the empirical resolution of causal difficulties in cervical cancer. This example will inform my philosophical thesis: that causation in medicine requires the consideration of both mechanistic and statistical evidence. I will develop this thesis by giving an account of both mechanistic and statistical evidence, by describing their interaction, and by relating issues within the philosophical case to the historical.

Machamer, P., Darden, L. & Craver, C. 2000. "Thinking about Mechanisms," *Philosophy of Science*. **67**(1): 1–25.

Russo, F. & Williamson, J. 2007. "Interpreting Causality in the Health Sciences," *International Studies in the Philosophy of Science*. **21**(2): 157–70.

Salmon, W. 1984. *Scientific Explanation and the Causal Structure of the World*. Princeton: Princeton University Press.