Public Health Classics

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. Michael Thun reviews the early studies on the relationship between tobacco smoking and lung cancer, with special reference to the 1950 paper by E.L. Wynder & E.A. Graham, which is reproduced by permission of the American Medical Association.

When truth is unwelcome: the first reports on smoking and lung cancer

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1950 should have been a very bad year for the tobacco companies. Five case–control studies published within a nine-month period reported that cigarette smoking was associated with lung cancer in men (*1*–*5*). In retrospect, the strength of the association in the two largest and most influential of these studies — by Ernest Wynder & Evarts Graham in the *Journal of the American Medical Association (JAMA)* (*1*), reproduced below, and by Richard Doll & Austin Bradford Hill (both of whom were later knighted for their work) in the *British Medical Journal* (*2*) — should have been sufficient to evoke a much stronger and more immediate response than the one that actually occurred (*6*). Had the methods for calculating and interpreting odds ratios been available at the time, the British study would have reported a relative risk of 14 in cigarette smokers compared with never-smokers, and the American study a relative risk of nearly 7, too high to be dismissed as bias.

The medical and scientific communities were notably resistant to the idea that smoking caused lung cancer (*7*, *8*), despite these publications. Doctors and scientists were as unreceptive as the general public, because most of them smoked (*6*). Doll has observed that "the ubiquity of the habit … had dulled the collective sense that tobacco might be a major threat to health" (*8*). Thus, an intriguing dimension of the impact of these early studies is the manner in which persistence and the accumulation of scientific evidence ultimately prevailed, despite the formidable resistance against it.

Remarkably, Ernest Wynder was still a medical student when he began interviewing lung cancer patients at Belleview Hospital in 1948, while a summer student at New York University. At the time he had never heard of the field of epidemiology and had no training in statistics (*7*). His motivation for beginning the study was anecdotal: he had witnessed the autopsy of a man who proved to have lung cancer, and whose widow later reported that her husband smoked two packs of cigarettes a day.

When Wynder returned to medical school at Washington University, St Louis, he recruited an unlikely but influential ally in Evarts Graham. Dr Graham was a distinguished thoracic surgeon, chair of the Department of Surgery, and a heavy smoker. He was initially unconvinced of the need for a study of smoking and lung cancer. His senior associate, Thomas Burford, echoed this scepticism, pronouncing that "smoking was not a cause of lung cancer" while puffing on his cigarette. Nevertheless, Evarts allowed Wynder to interview patients with lung cancer and other diseases on the surgical wards, and later provided him with letters of introduction to other surgeons and contacts at the American Cancer Society (ACS) so that the study could be extended to other areas of the United States (*7*). Wynder employed what was at the time a novel epidemiological study design, the case–control study.

Wynder was not alone in experiencing resistance to the new methodology, as well as to the disturbing hypothesis that smoking might cause lung cancer. Levin et al. completed a smaller study of smoking and cancer and submitted the manuscript to *JAMA* shortly before Wynder & Graham submitted theirs. The journal was hesitant to publish the paper by Levin and his co-workers because of the unfamiliar study design and preliminary nature of the data (*9*, *10*). On receipt of the much larger study with similar design and findings, and with the internationally respected Graham as co-author, *JAMA* decided to publish both papers in the same issue (*1*, *3*).

In the United Kingdom, Doll & Hill — who were also smokers — were doubtful that cigarette smoking was an important cause of lung cancer when they began their case–control study in 1948 (*8*). They noted that the combustion products from coal were more potent as carcinogens than was tobacco condensate when painted on the skin of mice (*8*). They initially expected that the large increase in lung cancer mortality in the United Kingdom and the United States was more likely to have resulted from the widespread tarring of roads and exhaust from motor vehicles than from cigarette smoking. Nevertheless, given the size of their study and that of Wynder & Graham, the completeness of follow-up, and care in measuring smoking histories, Doll was surprised at the "great reluctance on the part of most cancer research workers, physicians, and scientists to accept our conclusions" (*8*).

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The results of the early case–control studies were viewed as provocative rather than conclusive. Their most immediate consequence was to stimulate the formation of several large prospective studies to determine whether the findings could be replicated. Doll & Hill initiated the British Doctors' Study (*11*), while in the United States Cuyler Hammond & Daniel Horn at ACS began the Hammond–Horn Study (*12*), followed closely by Cancer Prevention Study I (*13*) and the United States Veterans' Study (*14*, *15*). These large cohort studies rapidly confirmed the relationship between tobacco smoking and lung cancer and added heart disease, stroke, chronic lung disease, other cancers and shortening of survival to the list of deleterious effects from smoking.

Whereas Doll & Hill were at the centre of epidemiological research conducted at the Medical Research Council, a focal point for epidemiologists interested in chronic diseases, Wynder pursued a multidisciplinary approach to study the carcinogenicity of tobacco combustion products in experimental studies. Using a cigarette-smoking machine designed by Graham, he extracted tobacco smoke condensate under conditions that simulated human smoking habits. He then demonstrated that prolonged topical application of this (for an average of 71 weeks) induced papillomas and histologically proven carcinomas in approximately half of various strains of mice (*16*, *17*). These experiments effectively negated the criticisms of earlier experimental studies by Roffo and others that the temperature at which the tobacco was burned was outside the usual temperature of a burning cigarette. They also demonstrated that prolonged exposure was needed to produce a high tumour yield (*18*–*21*).

The paper reproduced here remains the most famous of Wynder's 750 peer-reviewed papers, and has been reprinted twice previously as a landmark article (*22*, *23*). Graham successfully quit smoking in 1951 but died of lung cancer in 1957 (*24*). His wisdom was an extraordinary match with Wynder's great energy, self-confidence and perseverance. When Graham saw the final draft of the manuscript, he reportedly said, "You are going to have many difficulties. The smokers will not like your message. The tobacco interests will be vigorously opposed. The media and the government will be loath to support these findings. But you have one factor in your favour. What you have going for you is that you are right" (*25*). ■

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