Use of Cancer Incidence Data in Identification of Cancer Causation

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This paper discusses the use of cancer incidence data in identification of cancer causation. Selective descriptive and analytical epidemiological studies were reviewed. These examples were taken primarily from Denmark, where the possibilities for epidemiological research are good due to the existence of many exposure and disease registers. Descriptive studies are still needed for a better understanding of cancer. Analytical studies of individual risk factors today often show relative risks of only 1.5 to 2, and these are difficult to translate into preventive recommendations. Epidemiology still remains the best available tool for identification of risk factors. — Environ Health Perspect 104(Suppl 3):639–641 (1996)

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Background

Epidemiology has favorable conditions in countries with stable populations and good registers. Denmark benefits from a long tradition in this field. Deaths, births, and marriages have been systematically recorded for more than 300 years. All causes of death and all new cancer cases have been registered, beginning in 1943.

Important observations from the first years of cancer registration in Denmark were the hook on the incidence curve for breast cancer among women around the age of menopause (1) and the 4-fold difference in incidence of cervical cancer between poor inner-city and affluent neighborhoods of Copenhagen (2).

In the late 1960s, cancer incidence data became available from populations throughout the world (3,4). These data showed wide variations in the incidence of different cancer sites. For example, the rate of stomach cancer for men in Japan was close to five times the rate in the United States, and the rate of colon cancer for men in the United States was close to seven times the rate in Japan. Based on these data, a theoretical overall cancer incidence rate was calculated by adding the lowest observed rates for each cancer site. The observed overall cancer incidence rates for men throughout the world in the 1960s were between 3 and 15 times this theoretical rate (5). This led Higginson and Muir to their famous statement that “the significance of these observations, indicating that 80 to 90% of cancers are due to external factors and are thus theoretically preventable, is obvious” (5).

Descriptive Epidemiology

Today, simple descriptive studies are still needed to solve the mystery of many cancer diseases. Such studies would not be possible without the routinely collected data on cancer mortality and cancer incidence.

As pointed out recently by Beral et al. (6), the worldwide decline in cervical cancer incidence and mortality predates the introduction of screening; even though infection with certain types of human papilloma virus (HPV) is the main cause of cervical cancer, “it seems unlikely that a decline in the prevalence of HPV infection over time is the main reason for the overall decline in cervical cancer” (6). These declining trends in cervical cancer can be illustrated based on mortality data alone.

Testicular cancer is a disease that is increasing, and in-depth case-control studies have failed to identify major risk factors apart from cryptorchidism, which can only explain 10% of the cases. The major improvements in the treatment of testis cancer patients imply that mortality data are of little value in studies of disease etiology. The long-time series on testis cancer incidence from the countries around the Baltic Sea have proved valuable in showing a highly puzzling east–west gradient; there is a low rate in Finland, Poland, and the Baltic countries; an intermediate rate in Sweden; a higher rate in Norway, Saarland, and the former German Democratic Republic; and a world record in Denmark (7).

Comparison of mortality and incidence trends can also reveal patterns that are not so easily understood. From 1960 onward the breast cancer incidence in Denmark has almost doubled, whereas the breast cancer mortality has remained relatively stable. These diverging trends have developed prior to the introduction of mammographic screening, and although improvements in breast cancer therapy have taken place, they are unlikely to explain the difference (8). It is an advantage here to have data going back to the 1940s. A recent analysis based on the U.S. SEER (Surveillance, Epidemiology, and End Results data covers the periods 1975 to 1979 to 1987 to 1991; diverging trends between the incidence and the mortality in this period in the United States are more likely to be explained by early detection (9).

The importance of classic studies of social class distributions should also be stressed. Recent studies have shown that the social class gradient in lung cancer is modified but remains when controls for differences in smoking habits are used (10).

Analytical Epidemiology

Analytical epidemiological studies have been decisive for the identification of all the known carcinogens. This is clearly illustrated with the example of asbestos and lung cancer. The first case reports on this topic were published in the 1930s (11–13), but uncertainty about a causal association remained until results were available from analytical epidemiological studies in the 1960s (14–16).

The conditions for analytical epidemiological studies are particularly good in the Nordic countries where personal identification numbers are used in all public and in many private registers. An example from Denmark of a study concerning environmental risk factors is a nationwide cohort
study linking records from the 1970 census, the Central Population Register, the National Death Register, and the National Cancer Register. Based on this linked register, for example, an excess risk of leukemia has been observed among persons in occupations/industries probably exposed to magnetic fields continuously higher than the background level. Of 1.3 million economically active men in 1970, 18,000 men were classified as exposed according to codes assigned by two independent experts. During a 17-year follow-up period, 39 incident leukemia cases were diagnosed in this group in which 23.80 cases were expected (standardized incidence ratio [SIR], 1.64; 95%CI, 1.20–2.24) (17).

The combination of registers also makes it possible to collect cancer incidence data for workers from many small and closed workplaces. An example is a study from the reinforced plastics industry in which boats and similar products were made in workshops that often existed for only a few years and where less than 10 persons were employed at the time. The study included 54,000 men identified from a combination of data from the Institute of Occupational Health air measurements records, the Work Inspection Service, the Danish Plastics Association, the Unskilled and Semiskilled Workers Union, the Local Environment Authorities, the Industry Register in the Central Bureau of Statistics, telephone books, the National Custom and Tax Administration, the Supplementary Pension Fund, the Central Population Register, the National Death Register, and the National Cancer Register. Air monitoring data showed the average exposure level to styrene to have been 180 ppm in 1964 to 1970, 88 ppm in 1971 to 1975, and 43 ppm in 1976 to 1988. Men first employed in 1964 to 1970 had an excess risk of leukemia based on 30 incident cases (expected number [exp] 19.53; SIR, 1.54; 95%CI, 1.04–2.19), whereas no excess risk was observed among men first employed after 1970 (observed [obs], 12; exp, 14.86; SIR, 0.81; 95%CI, 0.42–1.41) (18).

**Limits of Epidemiology**

The examples above clearly illustrate that good registers by themselves do not enable us to overcome the limits of modern epidemiology. After combining all these data sources, the studies often end up with relative risks of about 1.5 to 2. In a recent interview in *Science* (19), Richard Doll, Dimitrios Trichopoulous, Marcia Angell, and Robert Temple all said that relative risks of 3 to 4 were required for them to trust new findings. This statement has later been modified by Trichopoulous (20). But the general problem remains: with relative risks of 1.5, epidemiologists are unable to give the public a clear answer—and they might even scare people unnecessarily.

Relative risks of 3 to 4 are rare in cancer epidemiology today. At the same time, epidemiological research is potentially hampered by the concern about data confidentiality (21), and on the experimental side of cancer research, major breakthroughs in the understanding of the role of mutations in genes for tumor development are reported (22–24). The priority questions are therefore pertinent in cancer research today.

**What to Do with the 1.5 Relative Risks?**

Many of the 1.5 relative risk studies address important environmental and occupational pollutants such as formaldehyde, trichloroethylene, diesel exhaust, etc. To assess the safety of such exposures remains an important task. Epidemiology has limitations, but so have experimental studies. In classification of chemicals, the arguments inevitably arise that epidemiological data cannot be trusted because not all potential confounders have been controlled for, and animal data cannot be trusted due to potential interspecies differences. But conclusions are needed in practical life.

A framework for decisions on carcinogenicity has been established in the monograph program of the International Agency for Research on Cancer (IARC). Today, systematic IARC evaluations of the consistency in the overall epidemiological and experimental evidence provide the best method of preventing the public from being frightened by press releases from single or conflicting studies. In a systematic evaluation, one study forms only a part of the basic work needed to determine whether a given exposure can be considered carcinogenic, probably carcinogenic, or possibly carcinogenic.

It is, however, a real problem when the evaluation of the epidemiology cannot result in a clear-cut answer. Epidemiology studies on formaldehyde, for example, were summarized as showing "limited evidence in humans," despite the fact that 14 cohort studies and 23 case–control studies were available (25). For the moment, one must accept that that is the way things are.

Evaluations of epidemiological and experimental data translate into classification and labeling (26), and further into regulations for marketing, workplace exposure, drinking water limits, etc. Sander Greenland has recently been quoted as saying that

There is nothing sinful about going out and getting evidence, like asking people how much do you drink and checking breast cancer records.... The sin comes in believing a causal hypothesis is true because your study came up with a positive result, or believing the opposite because your study was negative (19).

Making interpretations and evaluations, even in the best possible way, is clearly "sinful" business, but there is no point in collecting data without using them.

The deadlock of observational epidemiology will probably only be overcome when the studies can in some way be supplemented with molecular techniques. At present, there are many limitations for the use of biomarkers in exposure assessment in epidemiology (27), and the results from traditional epidemiology are necessary to guide the use. As pointed out by Bosch et al. (28) concerning the studies of HPV and cervical cancer, "the historical evidence based on questionnaires and appropriate study designs was extensive and had established the likely role of a sexually transmitted agent."

The IARC evaluations have traditionally covered chemicals but have recently been extended to include hepatitis viruses, HPV, and other infections like schistosomiasis. Today, there is clearly a need to extend the program to include evaluations of common medical procedures such as vasectomy (29–30) and induced abortion (31).

**Conclusion — Optimizing Data Generation**

The availability of cancer incidence data from populations throughout the world was invaluable for the understanding of cancer as a primarily preventable disease. Descriptive studies are still needed for a better understanding of cancer. Analytical studies of individual risk factors often show relative risks of only 1.5 to 2. These moderately elevated relative risks are difficult to translate into preventive recommendations; however, epidemiology remains the best available tool for identification of risk factors.

Furthermore, almost one in three persons in developed countries today will develop cancer. The care and treatment of cancer patients are therefore major economic burdens. In Denmark, with a population of 5.1 million, 15,000 new cancer
patients start on curable treatment every year, and 8,000 new patients are referred directly to palliative treatment and pain relief (32). Besides the need for cancer incidence data for identification of cancer causes, there is also a demand for cancer incidence data for health-care planning. The availability of many registers does not only affect the possibilities for research but also the possibilities for data generation.

In Denmark, a plan has recently been published by the Ministry of Health for generation of cancer incidence data primarily from computerized hospital records (33).

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