Review

The clinical relevance of epidemiology: An overview

C. La Vecchia¹,² & S. Franceschi³

¹Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy; ²Institute of Social and Preventive Medicine, University of Lausanne, Switzerland; ³Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano (PN), Italy

Summary. Epidemiology is one of the areas of medical research which by definition should have immediate clinical implications, since its inferences are based on and apply to humans and should in theory be directly transferable to clinical and preventive measures. However, interchange of information has not always been easy, and this has constituted a substantial drawback to both the epidemiologist and the clinician. This review paper will provide some points for discussion, with special emphasis on cancer epidemiology and aspects of specific interest to the clinician, i.e., quantification and risk assessment for primary prevention and cost/benefit evaluation for secondary prevention and cancer treatment. Quantitative assessment is of major importance for the oncologist in at least three areas: cancer trends (descriptive epidemiology), cancer risks (analytical epidemiology), and preventive and therapeutic measures (clinical epidemiology).

Cancer trends

Cancer trends have been reviewed for several developed countries, and there is general agreement that, with the notable exception of the tobacco-related cancer epidemic, no systematic or generalized upward trend has been observed for any of the major cancer sites over the last few decades in the middle-aged population [1-4]. Some controversy has arisen from the fact that a few specific cancer sites such as brain, prostate or myeloma, have apparently increased in the elderly [5, 6]. These sites, however, are among those that most accurately reflect improved diagnostic procedures and certification, and, therefore, most of the apparent increases may be artefactual, as is confirmed by inspection of trends in selected geographical areas with high standards of cancer registration [7-10]. Indeed it is important to remember that many factors contribute to creating the impression of a 'cancer epidemic': cancer has become more common as a cause of death in relative terms chiefly due to the prevention and cure of certain other diseases and, in absolute numbers, because of the larger present relative proportion of elderly people. Last but not least, cancer has become a highly political issue.

In order to avoid misjudgements, clinicians should keep a few basic rules in mind when interpreting cancer trends from either clinical series or local and national statistics.

Firstly, the importance of age-standardization of cancer rates cannot be overemphasized: if total neglect of this procedure is rare, insufficient allowance in a number of datasets for changes in the age distribution of a population (e.g., variations in the open-ended extreme categories, such as 75 or 80 and above) is still a matter of concern.

Secondly, cancer incidence rates are not always better than mortality rates. Although incidence data distinguish more reliably among the different types of cancer and are not affected by trends in the curability of particular types, they are affected by the strong tendency over the past two or three decades to register more accurately new cases and (especially recently) by the registration of more and more lumps that are histologically cancer but biologically benign. Cure rates are obviously subject to many of the same biases that affect estimation of incidence rates and, in addition, are likely to be influenced by anticipation of diagnoses (and hence delayed deaths). Nor is adjustment for cancer stage a possible remedy: if, by means of a more sophisticated search for cancer cells, formerly 'localized' cancers are now recognized as disseminated ones, for instance as a consequence of random biopsies, etc., stage-adjusted survival rates are going to be inflated to an even greater extent than crude cure rates [1].

The main theoretical reason for skepticism about the real existence of any consistent increase in cancer rates, however, is the lack of upward trends in the young. Most carcinogens, in fact, tend to affect cancer rates in the young before influencing trends in the elderly, since: (i) younger generations are more prone to adopt new habits, or be exposed to new risk factors and, (ii) changes in relative risks in the young are more easily detectable, since the underlying rates are generally lower [11, 12]. This phenomenon, usually described as 'cohort effect', was extremely clear for the rise and fall in the tobacco-related lung cancer epidemic, but was also observed for other neoplasms whose incidence...
and mortality have changed appreciably, such as stomach cancer, which has substantially declined over recent decades.

Theoretically again, this cohort pattern should be more evident for carcinogens acting on the first stages of the process of carcinogenesis (‘initiators’), and could be obscured for late-stage carcinogens or promoters. An important example of the latter type of effect was the epidemic of endometrial cancer induced by exogenous oestrogens. The impact of promoters on the relative change of rates is similar in different age (and baseline risk) groups. Still, since menopausal replacement oestrogens were more frequently used by younger women, also in this instance the impact was greater in peri-menopausal than in older women [13].

Thus, a clear indication emerges as to the central role of past and current trends in the young to predict the likelihood of future trends. This empirical approach can be extended to the use of age, period and cohort models to project trends in the near future [14].

When these models were applied to Swiss cancer mortality data [15] (Fig. 1) a steady decline in rates was predicted for females. Rates may well be downwards in males, too, subject to a reduced exposure to the single major risk factor, tobacco smoking. Thus, the objective of a 15% reduction in cancer rates by the year 2000, proposed by the ‘Europe Against Cancer’ Programme of the Commissions of the European Communities [16], appears reasonable for this as well as most other Western European countries, although in Southern Europe it may be somewhat delayed by the past unfavourable trends in colorectal and breast cancer mortality, which are still observed in older generations.

Although this perspective appears possible for cancer rates and hence individual risks, it does not imply, as previously discussed, a reduction in absolute numbers of cancer cases or deaths, which are largely influenced by the changing age structure of the popula-

Cancer risks

In a global strategy of cancer control, oncologists must have a quantitative appreciation of major risk factors for cancer, and strategies for reducing cancer mortality. The oncologist may appear to be involved essentially in treating patients, but his cultural role and influence are in fact much broader, and in this sense he represents a central figure in any effort to reduce cancer incidence and mortality.

Various estimates have been made and, although based on different assumptions and baseline data, they concur that tobacco, which is responsible for 25% to 35% of all cancer deaths, is the single most important avoidable risk factor for cancer [1, 17, 18]. The second preventable single cause of cancer is alcohol consumption, which accounts for approximately 3% of cancer deaths in North America and Northern Europe [1], but may reach 5% to 8% in France and a few other Southern European countries [19, 20]. Other established factors are occupational exposure to asbestos and other carcinogens, exposure to ionizing and non-ionizing (sunshine) radiation, environmental pollution, and obesity. Each of these individual factors probably accounts for only 1% to 4% of all cancer deaths and some of them comprise a wide variety of exposures. Still, the proportion of cancer deaths avoidable through intervention to eliminate known risk factors now approaches 40% even excluding factors such as diet, whose role in cancer aetiology is probable, but difficult to precisely define and hence exploit as a basis for intervention guidelines [21].

The clinician’s role may well be even more important, although very difficult, in the vast new field of so-called ‘weak associations’. Whereas relative risks for smoking and lung cancer or alcohol consumption and cancer of the mouth are on the order of 10 to 20 or more, the relative risks in the case of weak associations (generally defined as below 2) leave open the possibility that the finding is a consequence of study biases and confounders. Examples are the widely debated association between smoking and cervical cancer, and alcohol use and breast cancer.

Study problems cannot only artefactually raise relative risks (if that were so, a conservative attitude would be sufficient) but also reduce associations due, essentially, to the diluting influence of misclassification. Physician can help the general public to find their way through the present mass of information on cancer prevention without losing sight of the target of health as a whole. For instance, weak and/or uncertain causes of cancer which are strong risk factors for other disorders such as cardiovascular diseases, do not necessarily
require further demonstration in order to be tackled for preventative purposes.

In terms of clinical and preventive implications, quantification remains a key issue. Thus, the potential impact of present knowledge of cancer causes should be appreciated in its absolute and comparative terms by anyone involved in cancer control. Improved cancer treatment over the last few decades has enabled us to make considerable progress, but unfortunately mainly in instances of relatively rare cancers. Major advancements have been observed, for instance, in the treatment of Hodgkin's disease, whose mortality in Western (but not Eastern) Europe has been approximately halved over the last three decades (Table 1) [22]. This corresponds to the avoidance of at least 3000 (and probably as many as 4000) deaths per year in Western Europe.

Improvements have also been achieved in the treatment of testicular cancer [23], childhood neoplasms, choriocarcinoma and several types of leukaemias. However, the observation that potentialities offered by newer treatments are not adequately available in all geographic areas highlights the importance and urgency of assuring the delivery and utilization of efficacious treatments in various areas of the world [22, 23].

Appropriate application of currently available therapies is certainly a priority, but on a public health scale the impact in terms of reduced cancer mortality is probably of the order of 1% to 2% [24, 25], and will probably reach only 4% or 5%, even assuming some improvement in the cure of breast cancer, the widespread tumour for which the most promising advances appear to be forthcoming [26].

Only further research and a new generation of therapies can make possible appreciable progress beyond this level, but even in the most optimistic perspective, improvement in these percentages will be difficult to achieve before the first decades of the new century. Thus, any prospects for cancer control on a population level before the year 2000 rely largely on prevention, which consequently should be given a top-priority position by clinicians and, specifically, oncologists.

**Intervention studies (clinical epidemiology)**

Epidemiological methods also have an important role in establishing criteria for conducting and assessing studies of cancer detection and prevention as well as treatment.

### Table 1. Death certification rates* (and numbers of deaths) from Hodgkin's disease in selected European countries. 1955–59 and 1985–88.

<table>
<thead>
<tr>
<th>Country (yr)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (No of deaths per year)</td>
<td>Rate (No of deaths per year)</td>
</tr>
<tr>
<td><strong>Western Europe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>2.37 (93)</td>
<td>1.15 (54)</td>
</tr>
<tr>
<td>Belgium</td>
<td>2.39 (127)</td>
<td>1.18 (40)</td>
</tr>
<tr>
<td>Denmark</td>
<td>2.35 (30)</td>
<td>0.79 (29)</td>
</tr>
<tr>
<td>Finland</td>
<td>1.88 (249)</td>
<td>1.01 (30)</td>
</tr>
<tr>
<td>France</td>
<td>1.62 (138)</td>
<td>0.75 (261)</td>
</tr>
<tr>
<td>W. Germany</td>
<td>2.08 (572)</td>
<td>0.99 (397)</td>
</tr>
<tr>
<td>Greece (1965–69)</td>
<td>1.86 (87)</td>
<td>1.21 (81)</td>
</tr>
<tr>
<td>Ireland</td>
<td>2.08 (32)</td>
<td>1.37 (26)</td>
</tr>
<tr>
<td>Italy</td>
<td>2.37 (615)</td>
<td>1.16 (420)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2.08 (118)</td>
<td>0.96 (86)</td>
</tr>
<tr>
<td>Norway</td>
<td>1.89 (37)</td>
<td>0.72 (21)</td>
</tr>
<tr>
<td>Spain</td>
<td>1.06 (155)</td>
<td>0.82 (178)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.97 (88)</td>
<td>0.59 (38)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1.90 (53)</td>
<td>1.16 (51)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1.99 (570)</td>
<td>0.85 (299)</td>
</tr>
<tr>
<td><strong>Eastern Europe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria (1965–69)</td>
<td>1.45 (68)</td>
<td>1.02 (57)</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>2.75 (192)</td>
<td>1.54 (133)</td>
</tr>
<tr>
<td>E. Germany (1975–79)</td>
<td>1.39 (132)</td>
<td>1.33 (127)</td>
</tr>
<tr>
<td>Hungary (1970–74)</td>
<td>1.06 (65)</td>
<td>1.25 (80)</td>
</tr>
<tr>
<td>Poland (1960–64)</td>
<td>1.62 (312)</td>
<td>1.56 (399)</td>
</tr>
<tr>
<td>Romania (1965–69)</td>
<td>1.15 (116)</td>
<td>1.15 (138)*</td>
</tr>
<tr>
<td>Yugoslavia (1960–64)</td>
<td>1.14 (100)</td>
<td>1.53 (193)</td>
</tr>
</tbody>
</table>

* Age-standardized rates on the world standard population.

a 1980–84.
Before discussing opportunities of screening in specific cancer sites, certain issues relevant to the justification for screening, which are particularly subject to misunderstanding, should be mentioned. Firstly, a distinction must be drawn between screening and early diagnosis: whereas early diagnosis depends on the patient's seeking advice, in a screening programme the organizers take the initiative and thus assume responsibilities different from those of the physician whose help a patient has sought.

The basic reason for the adoption of a screening programme is that diagnosis in the asymptomatic phase increases the chances of cure as compared with the best standard of clinical diagnosis. A likely benefit from a screening test must not only be clearly demonstrated, but also set against its disadvantages. For instance, the improved prognosis of some cases of cancer detected by screening must be set against the longer morbidity of cases whose prognosis is unaltered, the less radical treatment of some early cases against the overtreatment of borderline, potentially non-evolving abnormalities, the reassurance of those with negative test results against the false reassurance of those with false negative results, and the financial and human burden produced by false positive results [27, 28].

In the field of secondary prevention, the Pap smear has certainly had a major impact on the control of cervical neoplasia. Although the magnitude of such an impact did not require a prospective controlled trial, quantitative assessment of the role of cervical screening came from retrospective epidemiological studies [29, 30], which indicated that over 90% of invasive cervical cancers could be avoided by regular screening at three-year intervals for women between 35 and 65 years of age. Shorter intervals, or screening of younger women, was deemed unjustified on a cost-benefit analysis [30].

Evaluation of other screening procedures has required more accurate instruments, and only for mammographic screening for breast cancer is there now evidence of a reduction in mortality. Any cost-benefit analysis for colon cancer screening is highly unreliable, and this is regrettable since the basic technology (occult blood screening) has long been available. Identification of high-risk groups, including subjects with previous adenomatous polyps of the large intestine, or the appropriate deletion of chromosome 5, could also be a realistic prospect, but given the small numbers of such individuals this would yield only a small number of cases [28].

Similar problems of evaluation and cost-benefit analysis apply to screening for other common neoplasms, including prostate, endometrium or bladder, and should lead to a less emotional but more rational and carefully quantitative approach to cancer screening, which is likely to remain a central (and increasingly important) tool for cancer control in the foreseeable future. It is, nonetheless, worth noting that also in the 1990 Workshop of the UICC Project on Evaluation of Screening for Cancer, screening for colorectal cancer and its precursors was thought not to be justified as public health policy, (although to be considered in experimental settings), while screening for prostate cancer on a large scale was claimed to be contraindicated, given the likelihood of overtreatment [27].

Identification and evaluation of therapeutic advances is another field of clinical epidemiology which requires critical inter-disciplinary consideration. In the past, new technology has led to major advances in the treatment of leukaemias, other lymphoid neoplasms and germ cell tumours, whose demonstration did not require controlled trials [31]. A similar approach applied to other neoplasms and measures, however, was not only unproductive but caused substantial loss of time, information and credibility (in addition to human lives). Also for breast cancer, for which data on therapeutic advances are now substantial, convincing evidence was provided only by a systematic overview (meta-analysis) of all published and unpublished trials. This led to the quantification, beyond reasonable doubt, of improved long-term survival following chemotherapy and anti-oestrogen treatment [26].

For a number of reasons, including the relative rarity of each individual neoplasm and the need for long-term follow-up, large-scale clinical trials for cancer have turned out to be far more difficult than for myocardial infarction, for which simple, large trials have provided quantitative evidence of moderate but important therapeutic advantages [32, 33]. Nonetheless, there is a rationale and scope for simple, large-scale clinical trials of common cancers whenever there are reasonable indications of possible therapeutic gain, particularly since most cancer patients are now treated outside of controlled schemes, using non-systematic approaches, which are often unreasonable [34].

Perspectives for epidemiology

This article is focused on the clinical environment, and consequently attempts to outline possible areas of common interest and cooperation for clinicians and epidemiologists. In the long run, this is certainly one of the most important areas of development for epidemiology, but other perspectives of this young, relatively simple discipline which required only limited resources should also be briefly examined.

This 'first-generation' epidemiology led to the discovery of primary causes, such as tobacco, alcohol and asbestos, of disease and death, and this had major public health impact. Less obvious or less strong associations, however, require more sophisticated study designs and methods. Some of them have aroused considerable interest over the past decade, and will probably represent lines of further development, including:

1. evaluation and assessment of dietary instruments, to clarify the role of complex components of diet in cancer risk [35, 36];
2. 'biochemical epidemiology', i.e., analysis of sera
or other biological materials to identify markers of risk and disease;

(3) molecular biology, particularly for defining and quantifying genetic components, but also for a better understanding of viral and chemical carcinogenesis [37].

These and other perspectives will probably render epidemiology considerably more complex, and require large investments of human and material resources. Nonetheless, cancer epidemiology will almost certainly not lose any of its major areas of activity such as analysis of distribution and trends of cancer rates in populations, as a means of establishing determinants and their ultimate control. Consequently, relatively simple approaches such as analysis of vital statistics, cancer registration schemes and risk factor surveillance will probably retain their basic role and importance because of their clinical and public health implications for the general public.

Acknowledgments

This work was conducted within the framework of the National Research Council (CNR), Applied Projects ‘Oncology’ (Contract No. 87.01544.44), and Prevention and Control of Disease Factors, and with the contribution of the Italian Association for Cancer Research, the Italian League against Tumours, Milan, and Mrs A. Marchegiano Borgomaneiro. Table 1 was produced by F. Lucchini and F. Levi, Vaud Cancer Registry. The authors wish to thank Mrs J. Baggott, Mrs. M. P. Bonifacio, and the G. A. Pfeiffer Memorial Library for editorial assistance.

References


Received 5 February 1991; accepted 6 February 1991.

Correspondence to:
Carlo La Vecchia, M.D.
Istituto di Ricerche Farmacologiche 'Mario Negri'
Via Eritrea 62
I-20157 Milano
Italy