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Contribution of epidemiology to etiological research on cancer

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Zusammenfassung: Beitrag der Epidemiologie zur Erforschung der Aetiologie der malignen Tumoren

Die Epidemiologie, das heisst das Studium der Verteilung der Bestimmungsfaktoren und der Frequenz der Krankheiten beim Menschen, hat zwei wichtige Beiträge zur Erforschung der Aetiologie der malignen Tumoren geleistet. Erstens, sie hat die Wichtigkeit der Umgebungsfaktoren und dadurch die potentiellen Möglichkeiten der primären Praevention der malignen Tumoren aufgezeigt. Zweitens, sie förderte die Kenntnisse über grundlegende Mechanismen dieser Krankheit zu erwerben. Nach einem kurzen Überblick der Methode der Risikofaktorenidentifikation und nach der Erwähnung der wichtigsten Ursachen der malignen Tumoren, werden drei Aspekte in Bezug auf die Karzinogenese epidemiologisch behandelt. Die Theorie der Karzinogenese in mehreren Entwicklungsstufen; die Dosis-Wirkung-Beziehung und die Interaktion zwischen zwei Risikofaktoren. Diese drei Aspekte zeigen die Übereinstimmung der erhaltenen Resultate durch die biologische und epidemiologische Arbeitsweise. Schliesslich wird eine laufende Forschungsarbeit über die vermutete Karzinogene in gleichartigen alkoholischen Getränken als Beispiel eines möglichen Vorteils der Zusammenarbeit zwischen Biologen und Epidemiologen erwähnt.

Résumé: Contribution de l'épidémiologie à la recherche sur l'étiologie des tumeurs malignes

L'épidémiologie, c'est-à-dire l'étude de la distribution des déterminants et de la fréquence des maladies chez l'homme, a apporté deux types de contributions majeures à la recherche de l'étiologie du cancer. Premièrement, elle a fait la démonstration de l'importance des facteurs de risque environnementaux et par là du potentiel de prévention primaire du cancer. Deuxiémement, elle a favorisé l'acquisition de connaissances sur les mécanismes fondamentaux de cette maladie. Après une brève revue de la méthode d'identification des facteurs de risque et l'énoncé des principales causes du cancer, trois aspects relatifs à la carcinogénèse sont envisagés du point de vue épidémiologique: la théorie de la carcinogénèse à étapes multiples, la relation dose-effet et l'interaction entre deux facteurs. Ces trois aspects mettent en évidence la cohérence entre résultats obtenus par les approches biologique et épidémiologique. Enfin, une recherche en cours sur les carcinogenes suspectés dans les congénères des boissons alcooliques est citée comme une illustration du bénéfice potentiel d'une collaboration entre épidémiologistes et biologistes.

Introduction

Epidemiology differs from other medical sciences by the scale of its field of observation. Biology focuses more and more on molecular structures, whereas the epidemiological approach relies on the observation of populations. It is the science of disease frequency.

For an epidemiologist, the knowledge of etiology is mainly assimilated to the identification of risk factors, i.e. the variables statistically associated with the advent of a disease. An etiological factor is not always a sufficient cause as such. It is frequently a component of a sufficient cause in the complex network resulting in cancer.

Numerous risk factors have been discovered by epidemiological research (see tab. 1). In a recent textbook of cancer epidemiology, a

section deals with the most important causes of cancer (Schottenfeld and Fraumeni 1982). One chapter is specifically devoted to each determinant subject to modification and to the familial predisposition mentioned on table 1. This list illustrates the ordinary approach of cancer etiology by epidemiologists. In fact, as shown in this paper, some epidemiological results contribute to the acquisition of knowledge on fundamental mechanisms of cancer. However, the identification of the risk factors subject to modification and the demonstration of the potential of primary prevention doubtlessly represent the main contribution of epidemiology in the fight against cancer.

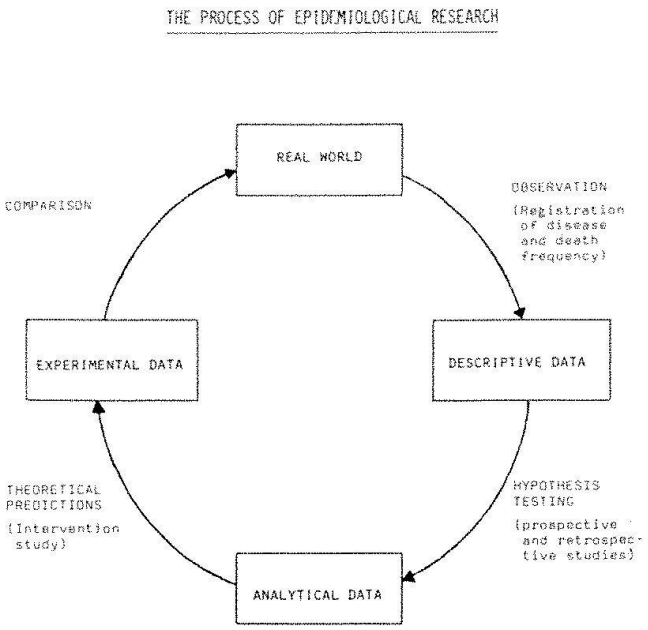

Fig. 1. The process of epidemiological research.

The epidemiological method

There are many definitions of epidemiology. Mac Mahon, in 1970, has given a concise description which fits well to the process of research in this field: "Epidemiology is the study of the distribution of disease and the search for the determinants of disease frequency in man". The successive steps of epidemiological research are illustrated on figure 1. The observation of the complex real world based on a cancer registry gives the frequency distribution of cancer. About 80 tumor registries have been selected by the International Agency against Cancer to be published in a fundamental descriptive work: "Cancer incidence in Five Continents" (Waterhouse 1982). Three of them are in operation in the French speaking part of Switzerland. The quality of their data is regularly checked by the International Agency for Research on Cancer.

The descriptive data can suggest some hypotheses concerning the determinants. This is where analytical epidemiology, as described on table 2, plays its part. If the quality of data is sufficient, a conclusion is possible by testing the statistical association between the suspected agent and cancer. Most causes have been found that way.

The effect of modification of one or more risk factors can then be introduced into a model and tested by experimental epidemiology. Basically, there are two possibilities; either one diminishes or one increases the risk in an intervention group to be compared to a reference group. Few results could be obtained by the reduction of a risk factor: numerous practical problems including ethical preoccupations preclude a wide utilisation of this method. On the other hand, catastrophes like the bombing of Hiroshima and Nagasaki or the present introduction of cigarette smoking in Africa are particularly productive from an epidemiological point of view!

Table 1. The main determinants of cancer

Subject to modification	Not subject to modification
— Tobacco	— Sex
— Alcohol	— Age
— Ionizing radiation	— Familial predisposition
— Drugs	
— Occupation	
— Air and water pollution	
— Diet	
— Viruses	
— Parasites	

Contribution of epidemiology to the comprehension of cancer mechanisms

The complementary approach of biology and epidemiology on etiological research will be illustrated here with respect to 3 fields: 1)

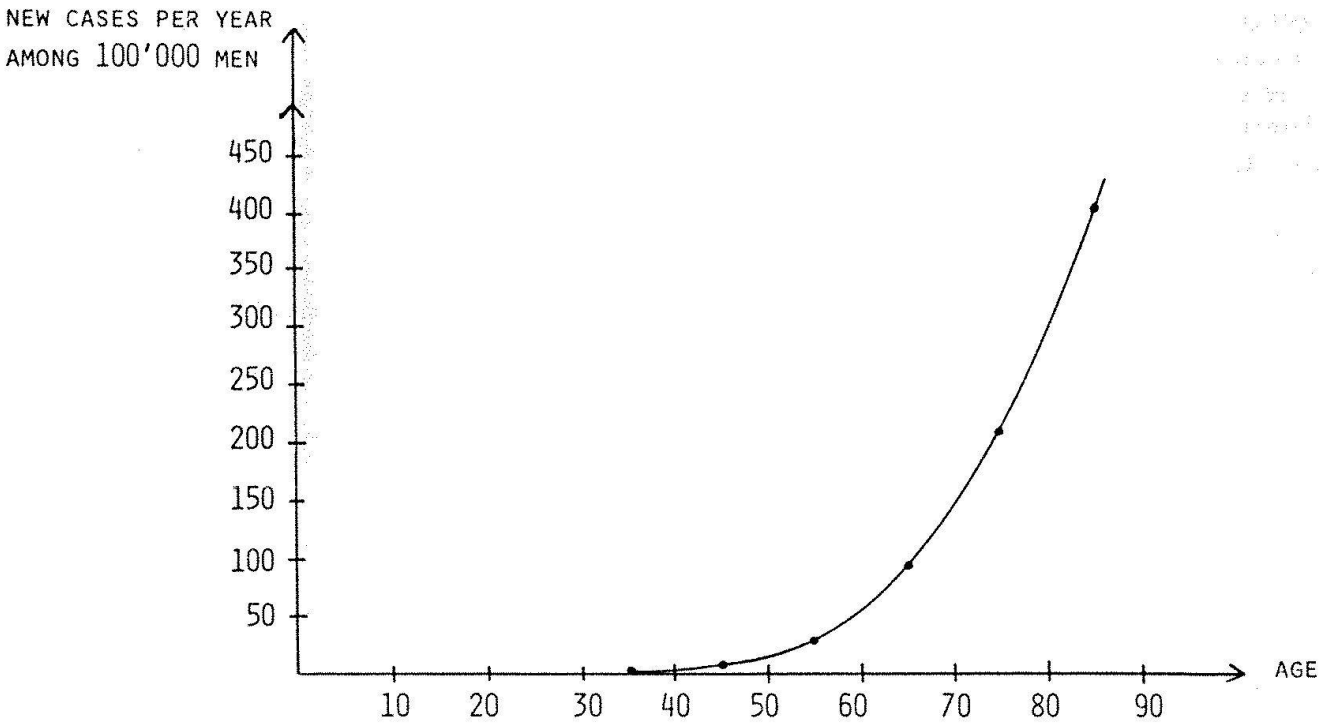

Fig. 2. Incidence of cancer of the stomach – male population – Vaud 1974–1978.

the multi-stage theory of carcinogenesis, 2) the dose-effect relation of one factor, and, 3) the interaction between two factors.

1. The multi-stage theory of carcinogenesis

This theory has been proposed by H.G. Muller (1951) and C.O. Nordling (1953). It derives from a basic epidemiological observation. The increase of cancer mortality to the 5th or 6th power of age (fig. 2) illustrates this phenomenon for stomach cancer in the Canton of Vaud. This theory presupposes that a cell originates a cancer after a certain number of transformations. Armitage and Doll (1957) have formulated the following hypothesis: each transformation occurs according to a specific transition rate at each stage. The resulting models are often too complex for a valid interpretation of the differences between prevision and observation. In a review on this subject, Peto (1977) points out the distortions introduced in such comparisons by the time trends, the inaccuracies of registration and by the multiple etiologies. Under these circumstances, the utility of this theory is somewhat questionable for cancer etiology. It is so general that it could be applied to all etiological situations. A model including fewer parameters would present more instructive features. Moolgavkar and Venzon (1979) have demonstrated that a two-stage model can explain a graph as shown on figure 2. The two-step model corresponds to the well admitted concepts of initiation and tumor promotion as defined by biologists.

Table 2. Analytical epidemiology (prospective and retrospective studies)

1. Distribution of N people according to exposure and outcome:

		Cancer (outcome) present	absent	total
Factor under investigation (exposure)	present	FC	$F\bar{C}$	F
	absent	$\bar{F}C$	$\bar{F}\bar{C}$	$\bar{F}$
	Total	C	$\bar{C}$	N

2. Definitions
Prospective study: F and $\bar{F}$ people are selected according to their exposure
Retrospective study: C and $\bar{C}$ people are selected according to the outcome variable

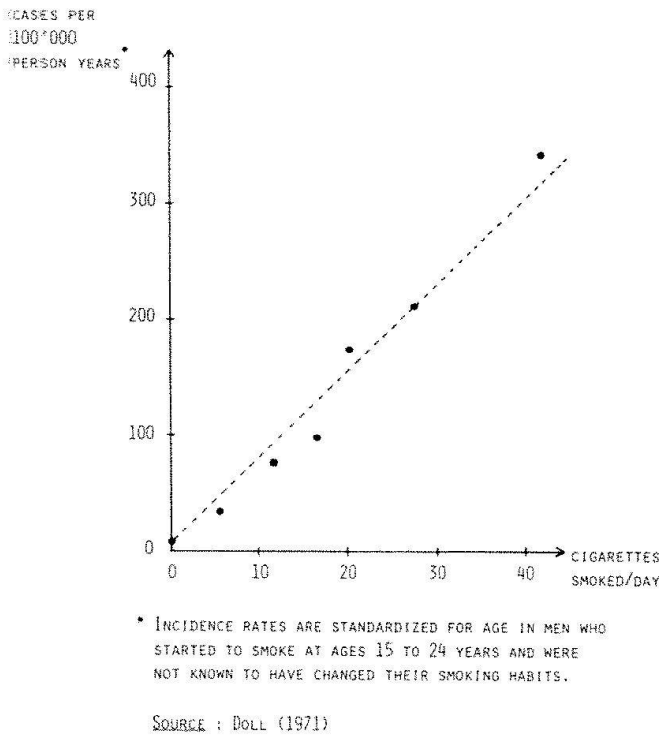

Fig. 3. Incidence rate of bronchial carcinoma versus rate of cigarette smoking.

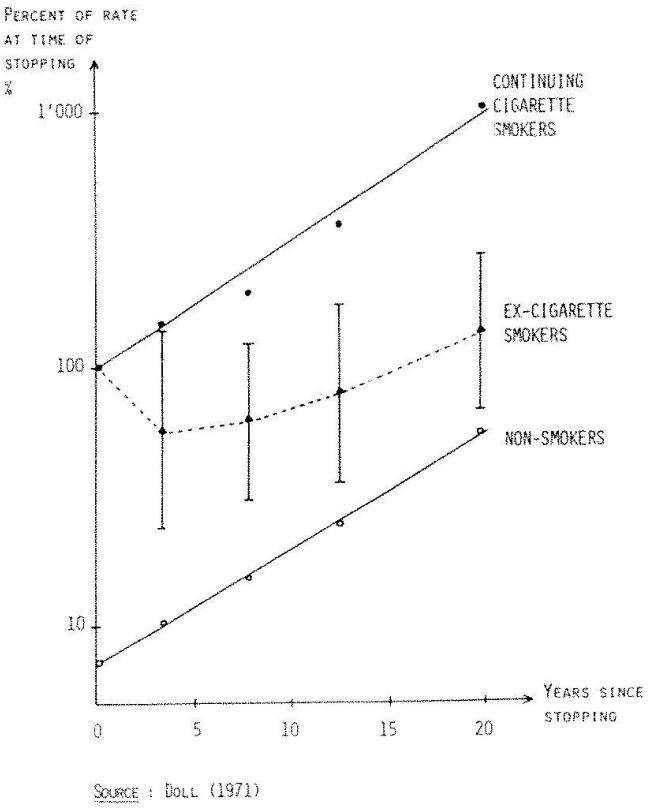

Fig. 4. Incidence rate of bronchial carcinoma versus time since cigarette smoking was stopped, compared with rates in continuing smokers and non-smokers.

2. Relationship between dose and effect

Analytical epidemiology gives a large importance to the dose-response relationship in order to interpret the causality envolved in the statistical association between an investigated factor and the disease. When a factor has been recognized as a cause, the function relating to the intensity of exposure with the frequency of the disease affords further elements suggesting possible mechanisms of cancer appearance.

The large tobacco consumption in countries where epidemiology acquired its experience and reputation is doubtlessly the main determinant of the study of bronchial carcinoma. As shown on the graph, figure 3, with a constant exposure time, the simple proportionality between tobacco consumption and the frequency of bronchial carcinoma can be observed. The same rule is observed for ionizing radiations with a reasonable dose and leukemia (Brown 1976 and Upton 1977) as well as for ultraviolets and skin cancer (Cutchis 1975). This relation is compatible with the fact that only one transition rate is affected by tobacco consumption. Moreover, if comparing cancer evolution of smokers and ex-smokers, one can suppose that tobacco consumption only interferes at the last stage of tumor development. As shown on the graph, figure 4, if the curb for ex-smokers does not increase, it does not attain the curb of non-smokers.

In the field of ionizing radiations, Land and Norman (1978) have analysed the distribution of induction periods for several cancers. They conclude by supposing that for two-stage models, radiations only affect the first stage for lung and breast cancer because of the long induction period, whereas the second stage is affected for chronic granulocytic leukemia for which the latent period is short. Furthermore, epidemiological observations have not yet revealed all new and unexpected elements; the graph, figure 5, shows the dose-effect relationship of ionizing radiations. The first part of the curb has been documented in detail by observations made on survivors of the Hiroshima and Nagasaki

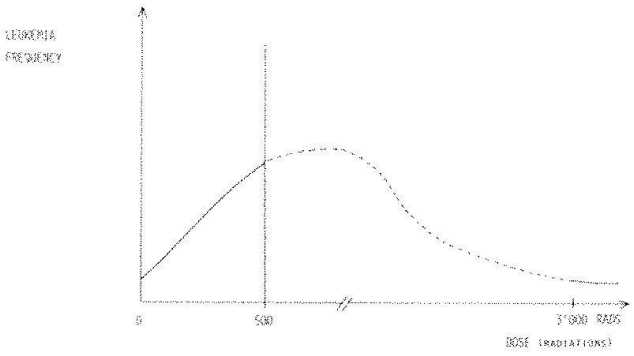

Fig. 5. Ionizing radiations and leukemia.

bombings (National Research Council 1980); in order to resist to more than 500 rads, the dose must be spread over a long period of time. It is precisely this which happens with cancer treatment. It has been proven that the rate of leukemia on strongly radiated patients does not increase. Moreover, it seems that lymphoma is more scarce on strongly radiated patients. One can thus presume that epidemiological data are an illustration of the "killing effect" described in vitro.

3. Interaction between two factors

The relative risk obtained for the combination of two factors at several exposure levels is the result of the mechanism in cancer etiology.
The data given by Rothman and Keller (1972) shown on table 3 are compatible with a multiplicative model as opposed to an additive one. This type of interaction can be observed for the combination of an exposure to asbestos and to tobacco (Saracci 1977). The multiplication of effects of two carcinogens is compatible with a multi-stage model where each one interferes at a different stage of the causal process. A proportional effect is thus obtained at each level of a factor.

Table 3. Relative risk of oral cancer according to level of exposure to smoking and alcohol.

		Smoking (Cigarette equivalent/day)		
		0	<20	40+
Alcohol (ml/day)	0	1.00	1.52	2.43
	11.8–45.8	1.60	4.36	8.21
	45.8+	2.33	4.13	15.5

Source: Rothman and Keller (1972)

Potential profits of a better cooperation between epidemiologists and biologists

The identification of substances responsible for cancer on man can largely benefit of cooperation between epidemiologists and biologists. Certain epidemiological data allow us to suppose that congeners of certain alcoholic drinks can engender cancer of the upper digestive tract. In order to test this hypothesis and to identify risk engendering drinks, the epidemiological approach is doubtlessly the right one (Junod and Pasche 1978). By questioning patients with tumors and alcoholics on the type of drinks they use, it is possible to select a limited number of wines and alcohols.
The detection of carcinogenic substances can then benefit of the biological methods used, such as the identification of mutagenic properties of these drinks on certain bacterial strains (Ames 1973). A study of this type is presently being carried out in Lausanne and will allow, within short, to determine the existence and the nature of drinks containing carcinogenes.

Conclusion

The principal result of epidemiology on cancer etiology is doubtlessly the demonstration of the importance of environmental factors in its largest meaning. Higginson and Muir (1977) have reexamined epidemiological data justifying the fact that 80% of human cancers have an environmental origin. This is not, however, a reason to minimise the importance of the acquisition of knowledge in the mechanisms of cancer, but there is no doubt that such a result could have an influence on primary cancer prevention. Even if this exceeds fundamental research it nevertheless concerns all those who fight against cancer.

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