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Susceptibility to Cancer: Some Examples from Epidemiology

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No population in the world is known to be resistant to canser development, but there seems to be differences between individuals in susceptibility to cancer development following exposure to environmental carcinogenic risk factors

The age dependency of cancer may be interpreted both with regard to carcinogenic exposure and resistance to tumour development. Studies of migrant populations have pointed both to the fact that apparent resistance to cancer in certain populations is spurious, and to characteristic susceptibility to certain tumour types as for instance nasalpharangyal cancer and skin cancer. "Host factors" - either genetically in origin or environmentally induced - may be responsible for differences in susceptibility.

It is concluded that there is abundant epidemiological evidence of the role of environmental factors in cancer causation, and that possible interactions between tumour-producing and risk modifying factors should be further exploited.

(Key Words: Epidemiology, Canceroccurrence, Host, Environment)

INTRODUCTION

Epidemiology has its basis in comparisons, and to an epidemiologist the concept of tumour resistance or rather tumour susceptibility are thus relative quantities. In individuals cancer development is - for all we observe an all or none phenomenon,i.e. some individuals develop cancer and some do not. When looking at populations none is known to be "resistant" to cancer development, and the ovserved differences in cancer incidence has led to the widely accepted suggestion that many - if not most - cancers are caused by environmental factors in the widest sense of the word (7). Although the study of the occurrence of cancer in human populations has mainly concentrated on the search for risk factors, there is an increasing awareness of the existence of differences in susceptibility to tumour development between populations. Epidemiology may thus provide some clues to the answer of the important question of: Why do not all individuals exposed to carcinogenic risk factors develop cancer?

STUDIES OF POPULATIONS

Relationship to age

One of the strongest, but often overlooked associations in cancer is that with age. In Denmark the risk of lung cancer development is thus approximately 500 times higher in men aged 80 than in men aged 25, indeed an increase in risk which is seldom if ever seen in relation to environmental carcinogens.

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Various types of age-curves exist (13). The incidence of cancer of the cervix uteri increases from young age to reach a plateau around the age of 40-50 in most Western cancer countries, Fig. 1. This type of curve is also seen for cancer of the liver in Africa. One interpretation of this relationship between age and cancer is that a stimulus which disappears from the environment or loses potency in early age makes the incidence rise and then flatten out. Secondly, it might be that a limited number of susceptible individuals in the population get the disease as a result of a universally present stimulus and that the disease therefore decreases in incidence as the susceptibles have been removed from the population at risk or, thirdly, individuals in the population may develop resistance to tumour development with increasing age. Whatever the explanation the aetiology proposed must be in consonance with the various epidemiological features of the disease including its age relationship.

A second type of curve, which by far is the most common, is characterized by a regular continuing increase in cancer incidence with age. Most gastrointestinal cancers, like cancer of the stomach and colon, and respiratory tract cancers, like cancer of the lung, follow this pattern, Fig. 2, which probably results from exposure to carcinogens that are constantly acting. If this is true one consequence of this age-pattern would be that the pool of susceptibles does not diminish with increasing age so as to influence cancer occurrence.

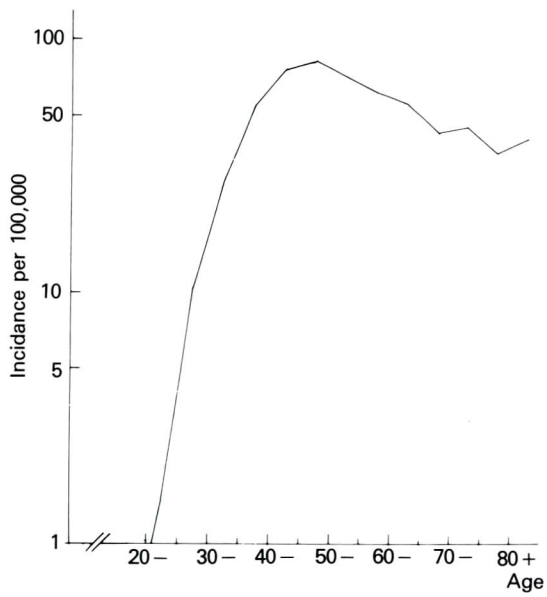

Fig. 1 Age-specific incidence of cancer of the cervix uteri in Denmark 1968 – 1972.

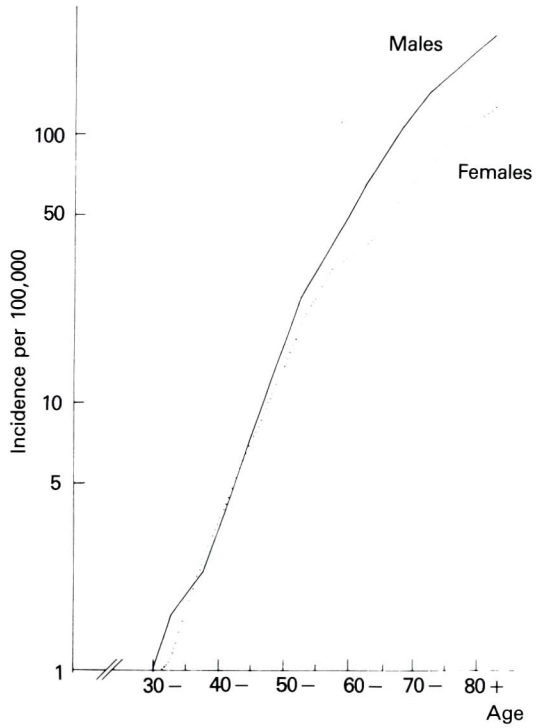

Fig. 2 Age-specific incidence of cancer of the rectum in Denmark 1968—1972.

Variation in cancer risks

Geographic differences - Two distinct features emerge from the geographic variation in cancer occurrence: First, there are marked geographical differences in cancers of specific sites, and secondly the variation in risk of cancer of all sites is relatively limited. Table 1 shows the risk of developing cancer of all sites (skin excluded) in selected populations around the world, based on data from Cancer Incidence in Five Continents (5). In Addition to the age-standardized rates per 100.000, table 1 also shows that 15—30% of all persons in any given population will develop cancer before their 75th birthday provided they live till that age.

Differences also exist within countries. Within a small country like Denmark with its homogenous population there are marked geographic variations in cancer incidence from east to west for example cancer of the lung, (9), as well as between urban and rural areas for all cancer and for cancer of specific sites (2).

Special exposure groups - The study of cancer incidence in human populations has provided sufficient evidence to correct the misconception that the sum of the cancer experience is constant. In other words the risk of one cancer type does not automatically occur at the expense of other cancers, and the apparent resistance to tumour development in 75% of the population is not absolute.

Already the geographic comparisons of total cancer incidence showed that this is not true and numerous examples from cohort studies of for ex-

Table 1 Variation in the incidence of cancer of all sites for selected populations

Cancer Registry	Males		Females	
	Incidence [a] per 100,000	Cummulative incidence 0–74 years (%)	Incidence per 100,000	Cummulative incidence 0–74 years (%)
Africa–Asia:				
Nigeria, Ibadan	79.5	8.5	107.0	10.9
India, Bombay	141.0	14.0	120.5	12.0
Israel, All Jews	218.3	22.1	231.6	22.4
Japan, Miyagi	184.7	19.9	127.7	13.2
America:				
Canada, Manitoba	255.0	25.0	226.6	22.0
Colombia, Cali	167.7	16.5	211.0	20.4
USA, Connecticut	285.9	28.3	238.1	23.3
Europe:				
Denmark	216.3	22.0	219.1	21.1
Norway	195.8	20.1	183.4	18.2
Spain, Zaragoza	186.0	18.9	133.2	13.6
UK, Birmingham	240.2	25.0	182.9	18.4

[a]Standardized to World population source (13).

ample occupational groups amplify this showing defferences between exposed and unexposed persons. Among Danish Brewery Workers, followed up during the period 1943–1972, increased risks were thus noted for cancer of the pharynx, oesophagus, larynx and liver. The risk of other cancers, except for non-melanoma cancers of the skin in this heavy beer-drinking group was that expected on the basis of the general population rates (8).

The most spectacular example was provided by Williams: (17), who showed that exposure to betanaphthylamine for more than five years resulted in a virtually 100% attack rate of bladder cancer in occupationally exposed men.

Studies of migrants

Studies of migrant populations have contributed elegantly to the clarification of our understanding of international differences in cancer incidence. The most extensive studies have been concerned with Japanese migrants to the united States, who migrate from a high incidence area of stomach cancer to the low incidence United States. Gradually the risk of stomach cancer development approaches that of white U.S. citizens (4). In contrast cancer of the colon is low in Japan and high in the United States; after a few generations the migrants move from low to high risk of colon cancer. Studies of migrants in various countries have confirmed these results. Thus an apparent resistance to tumour development is spurious and the studies of migrants support the role of environmental factors in cancer causation.

Migrant studies have also provided examples of persistently high incidences of certain cancers, pointing to the role of genetic factors in causation.

Cancer of the nasal pharynx, a rare tumour in most parts of the world, is known to be high among Chinese in particular the Cantonese from the Southern part of the Peoples Republic of China. Cancer of the nasopharynx

remains high also after migration of Cantonese to Singapore or to the United States (15) and certain chinese genotypes are now suspected as being of importance in increasing the susceptibility to naso-pharyngeal cancer development (14).

Both melanoma and non-melanoma skin cancers are influenced by individual susceptibility related to skin colour, and thus to genetics. Persons of light complexion are at higher risk when exposed to an equal "dose" of ultraviolet light (15).

"HOST FACTORS"

The study of the epidemiology of cancer provides many examples of the environmental origin of malignant neoplasms, and some indications of differences in susceptibility which may be of a genetic or environmental origin.

Such observations of a general nature provide only indications of associations, which must be explored further to make progress from using terms like "host factors" to explain why every heavy cigarette smoker does not develop cancer of the lung. A number of recent discoveries point to a role both of the environment, particularly diet, and genetics in modifying the risk of cancer following carcinogenic exposure.

Vitamin A—Following the observation that vitamin A deficiency increases the tumour yield in experimental animals exposed to carcinogens, Bjelke (1) in his prospective cohort study of Norwegian men was able to show that at any level of cigarette smoking Vitamin A intake protects against lung cancer i.e. at a given level of exposure, those individuals with a high intake of Vitamin A had a lower risk of cancer than those with a low intake of the same vitamin.

These results were confirmed by subsequent epidemiological studies, and recently Hirayama (4) in his large prospective cohort study of some 250,000 Japanese drew the attention to a possible protective effect against a number of cancers by the consumption of "green-yellow vegetables".

Dietary fibre—Whereas Vitamin A may be thought to act at the cellular level other environmental factors may be accompanied by a modification of risk of tumour development possibly by influencing the formation or action of carcinogens. Dietary fibre has thus been proposed to protect against colon cancer and although this hypothesis is still controversial some evidence of protection has been provided from case-control studies (12) and from international comparisons (6).

More recently Graham et al's (2) study of colon cancer patients and controls suggested a protective effect of cruciferous vegetables, the indoles of which are believed to inhibit tumour-formation by the induction of aryl hydrocarbon hydroxylase (= AHH) activity in the gut (3).

Enzyme systems—In parallel with this development Kellermann (16) suggested that the genetically determined inducibility of AHH determines the susceptibility to the development of cancer of the lung in tobacco smokers. When examining bladder cancer patients and controls Lower *et al.* (11) found the genetically determined acetyltransferase activity to differ, suggesting that the risk of these tumours carries a genetic component related to the handling of environmental carcinogens. Although much more work needs to be done in this field new perspectives have been opened in shedding light on

the problems of why some and not others are "resistant" to tumour development following carcinogenic exposure.

CONCLUSION

Epidemiology has provided ample evidence that environmental factors in the widest sense of the word are important determinants of cancer. Thus something like 30% of all male cancers in the developed part of the world is theoretically preventable by eliminating risk factors like cigarette smoking, exposure to sunlight, alcohol drinking, occupational hazards and pollutants of the general environment.

Present knowledge opens the way for primary prevention of cancer by eliminating environmental exposures. Further research is needed to solve the problems of risk modification and epidemiology may provide clues to factors which should be studied in individuals in close collaboration with investigators from other fields of cancer research. Undoubtedly such efforts will ultimately lead to establishing a broader basis for intervention to prevent individuals from developing cancer.

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