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SYMPOSIUM ON 'NUTRITION AND CANCER'

Nutrition and cancer: evidence from epidemiology

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This paper begins by commenting on trends in cancer, and some of the major known causes of cancer in the world. Though there have been many suggestions that diet may influence the risk of malignant disease, the evidence is somewhat diffuse. The paper indicates two different ways of studying the problem: (1) looking for variation in incidence or mortality from the disease, including collation studies relating variation in incidence or mortality to variation in various environmental indices, and (2) specific studies on patients or subjects, collecting detailed results in order to identify variation in risk of cancer.

Due to limitations of space, no consideration is given to agents added to food in manufacture, preparation, or cooking. Contamination, such as by mycotoxins, is also not covered.

What are the trends in cancer?

Results for England and Wales, and also for the United States, for the present century show that over all there has been a slight increase in mortality from malignant disease in males, and a slight decrease in females. When one excludes the impact of lung cancer (predominantly due to smoking) the over-all trend is a decline in all other malignancies for both sexes. However, examining some specific sites there is variation in the trend, with some showing a predominant increase and others a predominant decrease during this century. There are two main conclusions that can be drawn from these results; there has not been an explosion in cancer in the present century and the corollary of this is that recent changes in the environment (in particular the production and use of chemicals) have not obviously resulted in a more carcinogenic environment than existed at the beginning of the century.

What are the known causes of cancer?

Genetic predisposition to cancer exists for many specific sites, though is only responsible for a very small contribution to the over-all risk of developing cancer.

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For example, subjects with polyposis coli have a very high risk of cancer of the colon, but this probably accounts for only about one in 200 people in the total population developing such cancers (Bussey, 1975).

It is generally assumed that perhaps 90% of the variation in risk of malignant disease stems from specific environmental factors (Lancet, 1978). A major cause of malignant disease in western society (and to a lesser extent in developing countries) is smoking. At the present time about a third of the male cancer deaths in England are due to smoking, with a lower proportion in women (Doll & Peto, 1976; Doll *et al.* 1980). Apart from this specific major influence there are a number of particular occupational hazards that have been identified, some many years ago, others more recently. Though these may have a major impact on those exposed to a particular hazard, it is important to emphasize that they contribute a relatively small increment to the over-all toll of malignant disease. In a recent review of this topic (Higginson & Muir, 1979) it was suggested that 'lifestyle' was a particular determinant of risk of malignant disease. The remainder of this presentation attempts to identify the nutritional component within over-all 'lifestyle'.

Searching for variation in incidence and mortality

There are four rather different aspects to this: incidence and mortality may be examined between countries, within countries, over time, or in different sub-groups of the population. Probes such as this are highly dependent on the quality of the data (Alderson, 1977).

Oesophageal cancer has wide variation across the world, with a belt of high mortality stretching from parts of Africa, through the Middle East, into China. It is one of the sites of malignancy with the greatest international variation and, in Northern Iran, major variation within one country. Because there is considerable interest in the relationship between nutrition and gastrointestinal tract cancer we now turn to the trends in mortality of these cancers in this country. During the present century there was a modest rise in age-specific mortality from oesophageal, stomach, colon, and rectal cancer in England and Wales. A peak was reached in the 1930s, and since that time there has been a decline. This was perhaps most marked for stomach cancer, but also showed for the others. Colon and, to a lesser extent oesophageal and rectal cancer, show an increase in mortality in more recent times.

The above descriptive statistics are background to considering causation. A more specific examination is provided by looking at the mortality or incidence of malignant disease in sub-groups of the population. In America a number of studies have been carried out on Mormons and Seventh-Day Adventists. These have shown that the mortality from all malignant disease and certain specific sites is lower in the comparison with the rest of the population (Enstrom, 1978; Phillips, 1975).

The other source of sub-groups of a general population with different patterns of behaviour are migrants. A number of studies have been done in America on Japanese immigrants (Haenszel & Kurihara, 1968), the foreign born (Haenszel, 1961), Poles (Staszewski & Haenszel, 1965) and Chinese (King & Haenszel, 1973).

Halevi *et al.* (1971) reported on the mortality of migrants to Israel. Such studies aid in a search for variation in mortality from specific cancers and a first tentative probe of the types of aetiological factor that might be responsible. They have the disadvantage of confounding between a number of quite different potential aetiological factors, variation in validity of the mortality data (especially if international comparisons are made) and the results are often based upon relatively small numbers of deaths.

Collation studies. These relate incidence of mortality at international or national level to various indices of environment. For example, international mortality statistics for breast cancer in women and crude estimates of *per capita* intake of various nutrients including fat. This has shown (Alderson, 1977) a fairly close relationship between these two measurements and closer association than for any other nutrient. At the national level Enstrom (1977) using results from America demonstrated a high correlation of rectal cancer with variation in beer consumption by State. Obviously, in considering such studies, care needs to be given to consideration of the validity of the environmental data.

Studies on patients or healthy subjects

Case-control studies deliberately collect specific items of information for patients with malignant disease and appropriate controls in order to test particular hypotheses. Perhaps intermediate between such a study and a collation study are detailed investigations of individuals at known variation in risk of malignant disease (assuming that samples of the population at high risk and low risk can be identified and should be similarly exposed to variation in a particular aetiological factor as are the patients developing cancer in these populations). An extension of such studies are major prospective studies where information is traditionally collected from healthy subjects who are then followed up over many years to identify those developing or dying from malignant disease. In general, the planned design of such studies should ensure that results are valid for the various aetiological factors being investigated. Considering the topic of this paper, it is unfortunate that valid information on past diet is extremely difficult to collect.

The following notes have been listed in order of the cancer site involved, adhering to the International Classification of Disease.

Oesophageal cancer. Collation studies and case-control studies have indicated that in certain populations excess alcohol intake is associated with risk of oesophageal cancer (Tuyns, 1970; Tuyns *et al.* 1977). However, this is by no means the sole or major determinant. The case-control study in France has shown a multiplicative effect of smoking and alcohol. Also the very high risk population in Iran are teetotallers. Detailed case-control studies mounted in Iran have failed to identify specific nutritional factors responsible for variation in risk, though in general terms the high risk population are poor people living on a diet predominantly of bread (Cook-Mozaffari *et al.* 1979).

Stomach cancer. A number of case-control studies have failed to identify any consistency in dietary factors associated with excess of stomach cancer. However,

the one consistent finding has been that controls have an increased intake of green and fresh vegetables (Haenszel *et al.* 1972). The specific protective factor has yet to be identified, though this certainly seems an issue worth pursuing. There have been suggestions that nitrosamine intake or formation may be related to variation in risk of stomach cancer, but this specific range of chemicals are discussed further in bladder cancer.

Colo-rectal cancer. Collation studies indicate that excess fat, meat, or fibre intake may be related to risk of this cancer. However, there is considerable dispute about the specific role of these various factors, and case-control studies have done nothing to clarify this issue nor the role of faecal bacteria (Higginson, 1966; Wynder *et al.* 1969; Haenszel *et al.* 1973; International Agency for Research on Cancer, 1977).

Liver cancer. Patients with liver cancer have a higher prevalence of liver cirrhosis, and the cirrhosis may be secondary to excess alcohol intake. However, prospective studies of individuals consuming excess alcohol have produced conflicting findings. The malignant disease mortality is not increased to the extent that case-control studies would have suggested (Lancet, 1980).

Pancreatic cancer. There is no clear dietary aetiological factor identified, though there is a definite relationship with smoking (Doll & Peto, 1976).

Lung cancer. Though smoking is of overriding importance in generation of this cancer there is some recent evidence (Lee, unpublished results) that subjects regularly consuming vitamin A in various forms have a lower risk of lung cancer. There have been suggestions that vitamin A intake might reduce the risk of a number of other cancers (Smith & Jick, 1977).

Breast cancer. Though collation studies have indicated the relationship with fat intake at national level, case-control studies have failed to identify any clear nutritional variation (Kelsey, 1979). de Waard (1975) has advocated high risk in obese women, though this is disputed by other workers (Miller *et al.* 1978).

Uterus—body. There is a high international correlation between mortality and fat consumption. The disease is also associated with early menarche, late menopause, maturity onset diabetes, hypertension, and obesity. Doll (1979) pointed out that these are all conditions that are enhanced by excess consumption of fat.

Bladder cancer. The long-term consumption of artificial sweeteners (in various forms) was postulated as being a risk factor. However, Hoover & Strasser (1980) in reporting the preliminary findings of a large case-control study showed no evidence of increased risk with regular sweetener consumption. Various case-control studies have produced conflicting results, with more recent studies suggesting there is no particular hazard. Other work has identified increased coffee consumption as a risk factor, in addition to the known occupational and smoking effects (Cole, 1971).

Bladder cancer was one of the sites where nitrosamine production was identified as a risk factor. However, a recent case-control study of patients with bladder cancer, with schistosomiasis, living in a bilharzia area without urinary disease, with other cancers, and normal subjects showed no variation in nitrosamine

content (International Agency for Research in Cancer, 1978). The suggestion had been that increased nitrate consumption had resulted in the excretion of nitrites in the urine and production of nitrosamines in the bladder. Though there is in vitro evidence that such chemical production can occur, there is no adequate human evidence that variation in nitrate, nitrite, or nitrosamine intake influences the risk of bladder cancer (see Alderson, 1980 for brief review).

Prostate. The mortality from prostate cancer has been increasing in a number of western countries and collation studies indicate an association with increased fat intake exists. However, no case-control studies have adequately identified specific variation in diet, though Rotkin (1977) reported increased intake of foods with appreciable lipid and cholesterol content.

Thyroid cancer. Williams *et al.* (1977) have suggested that either natural or added iodine when in excess in the diet may have an impact on the incidence of papillary cancer of the thyroid. This is a particular example where without special review of the pathology it is very difficult to study such information at population routine level. No case-control study appears to have been done to assess variation in iodine intake in cases and controls.

Hodgkin's Disease. This is one of the malignancies of which there is very little known about the specific aetiology. A case-control study of Hodgkin's Disease developing on long-term follow-up of entrants to Harvard and the University of Pennsylvania led to suggestions that obesity and coffee intake may be associated with increased risk, but no detailed studies on this have been published (Paffenbarger *et al.* 1977).

Conclusions

Excess alcohol consumption is the main nutritional agent linked to risk of cancer (oral cavity, pharynx, oesophagus, liver). There is some evidence that adequate intake of vitamins A and C are associated with lower risk of cancer. The evidence of hazard from excess intake of fat and coffee is less complete, but suggests that the 'prudent diet' may be preferable to the food now generally consumed in western society.

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