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An overview of the epidemiological evidence linking diet and cancer

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There is now uniform agreement among oncologists that the incidence of cancer is determined, in large part, by factors in the environment and aspects of behaviour that are capable of modification or avoidance. It is agreed, too, that by such means the age-specific incidence of the disease in middle and old age could be reduced by some 80–90%. That the percentage should be so high should not be surprising, when it is borne in mind that we now know about fifty causes of human cancer that are responsible, between them, for about 40% of all the cancers that occur annually throughout the world, while in this country tobacco alone is responsible for about one-third of all cancer deaths. It may be surprising, however, that diet is also commonly suggested to be responsible for about 30–70% of the total, when so few aspects of diet have been established as causes of the disease.

This value of 30–70% is, in fact, a guess based partly on the knowledge that the diet of experimental animals has a major influence on the incidence of cancer produced by treatment with a variety of laboratory carcinogens, and partly on the simplistic belief that what you put into your mouth and pass into or through the digestive tract is likely to play a large part in the production of cancers of the corresponding organs which, in Britain, are responsible for 30% of all cancers.

That up to 70% has been thought to be possibly attributable to diet should not, however, be surprising when it is borne in mind that the production of cancer is a process, the progress of which may be influenced by many factors, and that the avoidance of each factor individually can have the same final effect. We can, therefore, properly say that two factors may each be separately responsible for (say) 80–90% of the risk of developing a particular type of the disease, while the avoidance of both will have little more effect than the avoidance of one. Examples include smoking and exposure to asbestos in the production of cancer of the lung, smoking and the consumption of alcohol in the production of cancers of the mouth, pharynx, and oesophagus, and infection with hepatitis B virus and the consumption of aflatoxin in the production of cancer of the liver. It is quite possible, therefore, that dietary modification could help to reduce the incidence of cancers that are now known to be due to tobacco, occupational hazards, viral infection, ultra-violet light, and ionizing radiation, even if these hazards continued

Table 1. *Established dietary causes of cancer*

Sufficient consumption to cause:	
(a) obesity	Endometrium, gall-bladder
(b) rapid growth in childhood	Breast
Food contaminated with aflatoxin	Liver
Salted fish as eaten in S. China	Nasopharynx
Alcohol	Mouth, tongue, pharynx, oesophagus, larynx, liver

to exist unchanged. This should not, of course, be an excuse for not reducing hazards that are capable of control, particularly when many of them can be controlled more easily and at less social expense than would be involved by major changes in the national diet. It does, however, explain how we can talk about diet being responsible for up to 70% of the risk of cancer when more than 30% is certainly attributable to other causes.

Suggestive evidence that some aspects of diet are causes of human cancer is plentiful; but firm evidence to implicate any specific factor sufficiently strongly to give public advice about its avoidance is still very limited, despite the great interest that has been shown in the subject over the last 20 years. This may be because it is so difficult to obtain quantitative evidence about the relevant dietary habits of individuals (which are likely to be the habits many years before the onset of the disease), or because we have been insufficiently precise in the definition of the hypotheses we seek to test, or (most probably) because of a combination of the two. The detailed evidence relating to most of the factors of interest is, in consequence, complex. Much of it will be presented in papers dealing with specific components of the diet and, in the present review, I shall attempt only a broad outline, filling in some of the gaps not covered by other speakers and offering suggestions about the way epidemiological research into dietary causes of cancer may develop in the future.

ESTABLISHED CAUSES

Obesity. Consider first the few established causes listed in Table 1. That obesity, which is so closely associated with cancers of the endometrium and gall-bladder, is a direct cause of endometrial cancer is clear, as adipose tissue is the main source of oestrogen after the menopause and the disease is produced by the action of oestrogen unopposed by other hormones; but just how it relates to gall-bladder cancer is still a matter for conjecture. The association with obesity might, in fact, be better regarded as coincidental, excess energy causing obesity by one mechanism and cancer of the gall-bladder by another. I have not, you will note, associated obesity with any other type of cancer, although it has been related at times to several, including cancer of the breast. In this case, the relationship is certainly complex, obesity possibly being protective before the menopause, when it may be associated with irregular periods, but definitely increasing the fatality of the disease later in life, even if it doesn't increase its incidence. What is certain, however, is that the high-energy diet of the developed world causes an increased risk of the disease by accelerating growth in childhood, by advancing menarche, and possibly by increasing the size of the breast.

Table 2. *Risk of nasopharyngeal cancer in Chinese by consumption of salted fish (after Yu et al. 1985)*

Malaysia*		Hong Kong† aged under 35 years	
Frequency of consumption in childhood	Relative risk	Frequency of consumption aged 10 years	Relative risk
Never	1·0	Rare	1·0
Less than daily	2·8	Monthly less than weekly	16·0
Daily	17·4	Weekly or more often	34·0

* 100 cases and 100 controls.
† 200 cases and 200 controls.

Aflatoxin. That aflatoxin is an important factor in the production of hepatoma has tended to be forgotten since the discovery of the role of the hepatitis B virus, which, when persistently present, may increase the risk of the disease 100-fold or more. The close correlation between the incidence of the disease and the amount of aflatoxin in the diet within countries, the occurrence of high rates of infection in some areas with relatively low risks of the disease, the potency of aflatoxin as a liver carcinogen in many species of animals, and the presence of enzymes in human livers that can convert aflatoxin to its carcinogenic metabolite make it difficult to believe that it is not also an important factor in the production of the disease in humans.

Chinese salted fish. Third, there is the role of the salted fish that is so characteristic of the diet of the Southern Chinese, whether resident in China, Hong Kong, Singapore, or Malaysia. The association has long been suspected; but it is only within the last few years that case–control studies have demonstrated the closeness of the association and, in particular, the importance of consumption early in life, which is illustrated by the findings of Yu *et al.* (1985) in Table 2. The association is so strong and the results obtained so consistent that even without the knowledge that nitrosamines have been detected in the fish and that rats fed on the fish have developed nasal and paranasal carcinomas (Huang *et al.* 1978*a,b*; Yu *et al.* 1989) I should have no doubt that consumption of the fish caused the disease. We may note, however, that in a recent study in Guangzhou, Yu *et al.* (1988) found only a twofold increase in incidence in people who had eaten the fish weekly at about 10 years of age compared with that in those who ate it rarely. This apparently disturbing observation can be explained, as Yu *et al.* (1988) point out, by the fact that the consumption of the fish has been more common in S. China than in Hong Kong, where traditional diets have changed with increasing economic prosperity, if one postulates, as it is only reasonable to do, that some substantial degree of misclassification occurs when dietary histories are taken many years after the event. If this is the true explanation of the differential findings in relation to the consumption of salted fish in different Chinese populations, it provides a warning of the hazard of interpreting the findings of case–control studies in developed countries that fail to demonstrate significant increases in relative risk associated with the consumption of common components of food.

Alcohol. Last, there is alcohol, which is responsible for perhaps 3% of fatal cancers in Britain and 10% in France, causing, in conjunction with smoking, a high proportion of all

Table 3. *Suspected causes of cancer*

Fat	Micronutrients*
Meat	Vitamins
	Trace elements
Fibre and resistant starch*	Non-nutrient chemicals
	Natural components†
Vegetables*	Additives
Fruit*	Contaminants
Specific foods*	Products of food preparation

* Regarded as protective, hence causative when deficient.
† Noxious or protective.

cancers of the mouth, tongue, pharynx, oesophagus, and larynx, and, via the production of cirrhosis, a small proportion of cancers of the liver. This subject is examined in detail by Dr. Tuyns, who has contributed more than anyone else to our knowledge of it, and I will add only two further points. First, the trends in the incidence of those diseases that the International Agency for Research on Cancer (1988) has accepted are caused by alcohol, cannot all be easily explained by the trends in the consumption of alcohol and tobacco and there is reason to think that some other major factor is also involved, possibly also nutritional and similar in nature to that which seems to be responsible for the enormously high incidence of oesophageal cancer in parts of Asia (see, for example, McLaughlin *et al.* 1988). Second, alcohol may also contribute to the production of two other types of cancer: alcohol increasing the risk of cancer of the breast, possibly by an effect on the metabolism of steroids in the liver, and beer (but not other types of alcohol) contributing to the production of cancer of the rectum, possibly because of its content of nitrosamines. The findings, which have been reviewed recently by the International Agency for Research on Cancer (1988), are not all consistent, but they are sufficiently suggestive to encourage further investigation.

SUSPECTED CAUSES

Other dietary factors that have been suspected of causing cancer are legion, including in this category deficiencies of factors that protect against cancer when present in the diet in suboptimal amounts. For convenience I have classified them under the broad heads shown in Table 3. As a classification, it leaves something to be desired, as some factors (e.g. nitrates and salt) could be classed under two or more heads; but it serves to illustrate the wide variety of the components of diet that have, for one reason or another, been thought to affect the risk of the disease.

Laboratory studies

Some components have come to attention as a result of laboratory experiments, which have shown them to be carcinogenic in animals or mutagenic in vitro (such as quercitin, a precursor of which is present in tea, or the polycyclic aromatic hydrocarbons in smoked or grilled food). Except, however, for aflatoxin, which has been referred to as an established cause, and some of the micronutrients that will be discussed later, the epidemiological evidence to connect any of them with any particular type of cancer is

weak. The best, perhaps, relates to bracken fern (*Pteridium aquilinum*), which may cause three times the risk of oesophageal cancer in the Japanese who eat it daily compared with that in those who avoid it (Hirayama, 1979). Methods of food preservation could be important, and I will refer to them later in relation to cancer of the stomach, but I know of no worthwhile evidence to suggest that any additives, other than those used for preservation, or any contaminant of food, such as pesticide residues, which have given rise to so much public concern, have been responsible for any hazard large enough to be detectable. The specific evidence has, however, not always been sought with the attention to detail that is desirable and I look forward to hearing the items to which Professor Ames and Professor Preussmann think epidemiologists should pay special attention and whether, perhaps, they think that fungal metabolites, comparable to aflatoxin, could be responsible for the extremely .high incidence of oesophageal cancer in parts of China and the 200-fold increase in the incidence of renal pelvis cancer in the Balkan villages afflicted by Balkan nephropathy.

Correlation studies

Other suspected causes, some of which could be responsible for a high proportion of the common cancers of the developed world, have come to attention as a result of correlation studies between disease incidence or mortality and consumption per head on a national scale or as a result of exploratory case–control studies, in which enquiry has been made about a wide range of past dietary habits of individuals with and without the disease.

Correlation studies constitute very weak evidence of a causal relationship. Even when correlations are as strong as they are between fat consumption and cancers of the breast, colon, rectum, prostate, ovary, and endometrium they do no more than constitute a basis for formulating a hypothesis. For these diseases the correlations are equally strong with the gross national product and, on this basis, any other aspect of life in a developed country could also be regarded as a potential cause.

The closest correlation is with cancer of the breast and, for this disease, Prentice *et al.* (1988) have shown that confounding with many other items of diet can be ruled out, the regression coefficients for fat energy being little changed, if at all, when non-fat, protein, alcohol, and carbohydrate energy, retinol, and β-carotene were allowed for, while none of these factors were related significantly to breast cancer after allowance had been made for energy from fat. Significant proportions of the variation in incidence of breast cancer could be attributed to energy from both saturated and polyunsaturated fats, but not to energy from monounsaturated fat. Weak though such evidence is for establishing a causal relationship, it provides a good basis for estimating the quantitative relationship with fat that might be anticipated within communities and it would give strong support for the idea that fat was a cause, if it was found to be associated with the disease in studies of individuals.

Case–control and cohort studies

Case–control, and even the more expensive, time-consuming, but generally more reliable, cohort studies have proved extremely difficult to interpret, particularly when the items of interest have been common foodstuffs, partly because the presence of a

cancer may alter a subject's diet and appreciation of food, partly because the variation in diet within a community may be relatively small, and partly because of the imprecision of quantification of items of diet by any of the methods suitable for large-scale use that are currently available, which dilutes a strong relationship and makes a weak relationship impossible to detect. If we assume, as the correlation studies suggest, that a 60% reduction in energy from fat would reduce the risk of breast cancer by three-quarters and we use the results of the validation studies of Willett *et al.* (1987) to adjust for the inaccuracy of food records, we can calculate, according to Prentice *et al.* (1988), that the risk of breast cancer in American women whose food records put them in the topmost quintile of fat consumption would be 33% higher than that in women in the lowest quintile. Few of the published studies, however, are likely to be based on dietary histories as accurate as those in the validation study of Willett *et al.* (1987) and I doubt whether we shall be able to reach a definite conclusion about the role of fat without an intervention study with random allocation of diets.

Somewhat stronger evidence relates the consumption of meat to cancers of the large bowel, for they are not only correlated internationally almost as closely as the consumption of fat and cancer of the breast, but they have also been associated more consistently in studies of individuals (see La Vecchia *et al.* 1988; Willett, 1989). The separation from fat consumption is, however, difficult and investigators have been unable to agree whether the association is specific for colon cancer, rectal cancer, or both. The question should be settled by reference to vegetarians, but there is surprisingly little information available for them. Seventh Day Adventists in California, more than half of whom eat meat less than weekly, have had half the mortality of US whites from cancers of the colon and rectum (Phillips & Snowdon, 1985), but there was no increase in risk in the meat eaters among the Adventists, while Kinlen (1982) found that the mortality from these diseases was about the same in British nuns, irrespective of whether they belonged to strict vegetarian orders or not, and was, in both groups, slightly higher than that in British women in general.

Not all case–control studies have been as unsatisfactory as those related to fat and meat. They have provided good evidence of the importance of three of the four factors that are regarded as established causes, failing only in regard to aflatoxin, the consumption of which by individuals has proved exceptionally difficult to quantify. They have also drawn our attention to the possible effects of vegetables and fruit in protecting against cancer of the stomach, of vegetables and especially cruciform vegetables in protecting against cancer of the large bowel, and of vitamin A and β-carotene in protecting against a multiplicity of cancers in different organs. Fifty-four studies have provided information about the last, forty-nine of which yield evidence of protection, with a median relative risk of 0·62 for high consumers compared with low.

The potential value of case–control studies is also illustrated by the findings in relation to gastric cancer, which have been steadily accumulating over several decades. Information extracted by my colleague David Forman (1989) from the epidemiological literature relating to the consumption of fresh fruit and vegetables that have been published in the last 5 years are summarized in Table 4. The odds ratios are based on different definitions of high and low consumption in each series, but the consistency with which the values for high consumption are materially below 1·00 and the high proportion that are statistically significant make it difficult not to believe that the investigators have identified something of importance in relation to the aetiology of the disease, provided,

Table 4. *Fresh fruit and vegetable intake in case–control studies of gastric cancer 1985–89 (after Forman, 1989)*

Country	No. of subjects (cases/controls)	Adjusted odds ratio	
		Fresh fruit	Vegetables
China	564/1131	0·6*	0·4*
Italy: 1	1016/1159	0·6*	0·6*
2	206/474	0·6	0·3*
UK: 1	95/190	0·6	0·3*
2	149/1934	0·4*	—
Poland	110/110	0·3*	0·6
USA: White	194/195	0·5*	0·9
Black	197/195	0·3*	0·5
Canada	246/246	0·8*	0·8*
Greece	110/110	0·8*	0·7*

* $P < 0.005$ for analysis in original report.

Table 5. *Preserved foods and salt intake in case–control studies of gastric cancer 1985–89 (after Forman, 1989)*

Country	No. of subjects (cases/controls)	Adjusted odds ratio	
		Preserved food	Fondness for salt
China: 1	564/1131	1·4	1·4
2	241/241	1·5*	—
Japan	93/186	2·0*	2·6*
Italy: 1	1016/1159	1·4*	1·4*
2	206/474	1·6*	1·5
France	163/1976	—	1·8*
UK	95/190	—	6·9*
USA: White	50/60	—	1·2
Black	50/60	—	1·3
	197/195	2·0*	—
Canada	246/246	2·2*	—

* $P < 0.05$ for analysis in original report.

that is, that the presence of the disease has not led to persistent under-reporting of consumption. That there should have been general under-reporting is, however, unlikely because of the findings summarized in Table 5, which show that gastric cancer patients consistently reported a higher consumption of some other foods, particularly preserved foods and salt.

Whether the temporal increase in the consumption of vegetables and fresh fruit (which has not been great in the UK) and the decrease in the consumption of preserved and

salted foods are sufficient to account for the extraordinary reduction in the incidence of gastric cancer throughout the world, as much as 70% in some countries since 1950 and 80% in women under 45 years of age in England and Wales since 1930, is open to doubt. We can, however, confidently advise an increased consumption of the former, as green vegetables may well be protective against some other types of cancer and there is no suggestion that either fruit or vegetables do any harm.

Whether the switch to refrigeration as the main means of preserving food and the use of antioxidants have been specifically beneficial in themselves or whether they have produced an effect by causing a reduction in the use of nitrite and other chemical preservatives is unclear, as we still do not know the mechanism by which the disease is produced. The idea that most gastric cancers are due to the formation of carcinogenic nitrosamines in vivo is attractive; but the epidemiological evidence from correlation studies relating the disease to exposure to nitrites and nitrates (which can be converted to nitrites in vivo) is confused and it seems unlikely that the nitrate content of food and water can be a rate-limiting factor, except perhaps in the most extreme situations. The best evidence, to my mind, would be provided by observation of the health of nitrate fertilizer workers in whom exposure to nitrates is not confounded with any other specific component of the diet. The observations currently available are too few to be conclusive; but such as they are they fail to indicate any specific hazard attributable to nitrates *per se* (Al-Dabbagh *et al.* 1986).

Use of physiological and biochemical markers

To obtain more definitive evidence about the role of dietary factors in the aetiology of the common cancers of the world than we have been able to do previously, epidemiologists will, I think, increasingly need to seek objective physiological or biochemical markers of the effect of consumption of different types of food. We would still be a long way from being able to give confident advice about the role of saturated fat in determining the risk of myocardial infarction, if we had been limited to dietary histories and had not been able to show, first, the correlation between blood lipid levels and the risk of the disease in individuals and, second, by experiment, the way the levels could be reduced by reducing the amount of saturated fat in the diet. No such relationship has been observed between lipid levels and the risk of breast cancer and this, to my mind, weighs heavily against the idea that the amount of saturated fat in the diet is specifically important in producing this type of cancer.

Serum banks. A big step forward was taken when it became a practical possibility to store thousands of samples of serum for many years and to analyse them subsequently after the individuals from whom they had been taken had been followed up, thus enabling comparisons to be made between the blood levels of different constituents in people who developed the disease of interest and in randomly selected samples matched for the date of serum collection, and the sex, age and survival of the individuals to the dates of onset of those who developed cancer.

Some of the results of eleven such studies relating to micronutrients are summarized in Table 6. This shows the mean values of the serum levels of β-carotene, vitamin E, and selenium in people who developed cancer expressed as percentages of the level of the controls who did not. The levels were generally lower in the future cancer patients, particularly in the case of β-carotene, but the differences were small and seldom

Table 6. *Levels of serum β-carotene, vitamin E, and selenium predictive of cancer in cohort studies*

| Country | Reference | Type of cancer | Serum level in people who develop cancer expressed as a percentage of the level in controls | | |
			β-carotene	Vitamin E	Se
USA	a	All types	—	92	96*
	b	Five types	82*	100	99
	c	Lung	87*	88*	103
		Colon	96	92	96
UK	d	All types	90*	98	—
	e	Breast	72	78	—
Finland	f		—	98	88*
	g		—	—	95
	h		89	97	97
Netherlands	i	All types	—	85*	96
Sweden	j		—	90	95
Switzerland	k		76	94	—

a, Willett *et al.* (1983, 1984); b, Nomura *et al.* (1985, 1987); c, Menkes *et al.* (1986), Schober *et al.* (1987); d, Wald *et al.* (1987); e, Wald *et al.* (1984); f, Salonen *et al.* (1985); g, Virtamo *et al.* (1987); h, Knekt *et al.* (1988), Knekt (1988); i, Kok *et al.* (1987a,b); j, Fex *et al.* (1987); k, Stähelin *et al.* (1984).
* $P<0.05$.

statistically significant, while no differences were observed at all in the serum retinol. From these studies it seems that β-carotene is more likely to be an effective prophylactic agent than retinol and is probably also more effective than vitamin E and Se, either singly or combined.

The substantial evidence now available in relation to β-carotene will be discussed in detail by Professor Wald and I want now only to draw attention to four general points that affect the interpretation of information of this type. Two are well known. First, there is the possibility that early and undetected disease may affect the serum levels, so that we need to examine separately the results for people who develop cancer more than (say) 2 years after the serum was collected. Second, there is the possibility of confounding, the level of the chemical of interest being linked with that of another that may be the agent of aetiological importance. The third and fourth points tend to be overlooked more often. One is the fact that small differences in the mean values can hide substantial differences associated with extreme values. Failure to appreciate the importance of this misled some of the early critics of the idea that cigarette smoking caused lung cancer, who pointed out that the average amounts smoked by lung cancer patients and controls were not very different. This was due, of course, to the fact that in the early 1950s the great majority of men smoked much the same amounts and the important role of cigarette smoking was evident only when one separated the relatively few who smoked very heavily and those who had never smoked at all. The other point was drawn to our attention recently by Richard Peto in relation to the significance of blood pressure readings and serum cholesterol as predictors of stroke and myocardial infarction: that is,

that the true quantitative relationship between the measured physiological variable and the risk of the related disease is much stronger than that observed on the basis of a single set of observations, because of the combined effects of measurement error and short-term physiological variation. This is demonstrated by the information collected in a large Finnish cohort study, which provided for repeat measurements of serum cholesterol after 1 year. With the second set of data it was possible to relate the risk observed, not to the mean value in each decile of cholesterol level as initially recorded, but to the mean of the repeat measurements for all individuals in each of the original deciles, thus, eliminating the various chance effects that had caused individuals to be classified in the more extreme groups. The results obtained with the repeat samples doubled the estimated increase in risk per unit dose and brought the results of cohort studies into line with those obtained from international correlations.

Markers of metabolism in the large bowel. Physiological markers of another sort may enable us to elucidate the role of dietary fibre in the prevention of cancers of the large bowel. Great enthusiasm for the concept of a protective role of fibre was engendered by Burkitt's exposition of the striking difference in the incidence of colorectal cancer and other diseases of the large bowel between populations in Africa and the developed countries of the West, and a similar difference in the amount of cereal consumed that had been depleted of fibre by refining; but it began to fade when case–control studies failed to show a consistent deficiency in the consumption of fibre associated with the appearance of cancer of the large bowel in individuals within a population. It was gradually realized, however, that the definition of fibre originally employed in epidemiological studies might not reflect the characteristics of physiological importance. What matters, from the point of view of colonic and rectal disease, may be the amount of material that reaches the large bowel that is capable of digestion by the bacterial flora and this, it appears, may include a substantial proportion of the intake of starch, which had not been classified as fibre as it could be digested by the enzymes of the small intestine. Evidence of the amount of metabolism that takes place in the large bowel can, however, be obtained directly as colonic fermentation is anoxic and produces butyric acid, thus reducing the pH of the faeces and causing hydrogen to be exhaled in the breath. Two findings lead me to think that this new approach may provide strong enough evidence for us to make firm recommendations about the desirability of eating more starchy and unrefined foods: namely, the lower faecal pH that has been reported for populations at low risk of colorectal cancer compared with that reported for high-risk populations and the higher concentrations of H_2 resulting from colonic fermentation that Thornton *et al.* (1987) have found in the breath of controls than in that of patients with colonic adenomas. I look forward to hearing from Dr. Bingham whether I have been unduly naïve in attaching importance to these findings or insufficiently optimistic.

Another possible approach is to measure the amount of mutagens in the faeces. This seemed to be very promising when fecapentaenes were identified and found to be particularly abundant in the faeces of North American populations; but, despite being effective mutagens, fecapentaenes were not obviously carcinogenic in animals (Ward *et al.* 1988) and have proved to be significantly less abundant in the faeces of patients with colorectal cancer than in controls (Schiffman *et al.* 1989*b*). Assessment of the amount of mutagenicity of faeces is highly dependent on the methods used for extraction and assay and there is, as yet, no general agreement on the most appropriate methods to use. Other mutagens are less abundant, but Schiffman *et al.* (1989*a*) have recently

reported that a higher proportion of faecal samples from patients with colorectal cancer contain non-fecapentaene mutagens than of samples from controls and this certainly deserves further investigation, particularly as cooked meats seem to be a source of the type of mutagenicity (TA98) observed (for references see Schiffman *et al.* 1989*a*).

Metabolism of galactose. A fourth type of biochemical marker that has been used in the study of dietary causes of cancer has been reported by Cramer *et al.* (1989), who examined the role of galactose and galactose-1-phosphate uridyltransferase (*EC* 2.7.7.32), the erythrocyte enzyme responsible for the metabolism of galactose, in the aetiology of ovarian cancer. The idea that galactose might play a part was suggested by the occurrence of hypergonadotropic hypogonadism in girls afflicted with galactosaemia. In a case–control study of some 250 cases of ovarian cancer in white women in the USA, Cramer *et al.* (1989) found that women with ovarian cancer, in addition to exhibiting an excess of all the known causes of ovarian cancer (low parity, high level of education, and non-use of oral contraception), also exhibited a small excess consumption of yoghurt and cottage cheese, two of the principal sources of lactose, and hence of galactose, in the diet. The finding was remarkable, however, only when taken in conjunction with a below average concentration of the transferase in the individual's erythrocytes, the relative risk being increased to 2·2 in women who consumed more than the median amounts of lactose daily and had less than the mean amount of transferase in their erythrocytes compared with that in women who consumed less lactose and had more transferase. These findings cannot now be accepted as indicating a causal relationship; but if they prove to be repeatable they may justify recommending the avoidance of lactose-rich foods in women with low transferase activity.

CONCLUSION

In the present review, I have attempted to show how it is conceptually possible for dietary modification to reduce the age-specific incidence of cancer by as much as 70%, even though we know that other factors cause more than 30%. I did not give a value for the contribution that the few aspects of diet that are known to cause cancer might make to the incidence of the disease in this country, but I doubt if their total avoidance would reduce it by more than 5%. Whether the many suspected factors could bridge the gap, if all proved to be causes of the disease, is still a matter for conjecture; but we could envisage a further reduction of 33% if, for example, an increased consumption of fruit, green vegetables, fibre and resistant starch reduced the risks of gastric and colorectal cancer by three-quarters, a reduction in the consumption of fats halved the incidence of cancer of the breast and reduced the risk of cancers of the ovary and prostate by one-third, and an increased consumption of micronutrients, including in particular β-carotene, reduced the risk of other epithelial cancers by one-quarter, reductions which would, in all cases, still leave incidence rates higher than they are or have been until recently in some other developed countries.

Not all these aspects of diet will prove to be causes of disease, but several, I am confident, will. How we can become certain enough about their effects to provide people with adequate information for them to make a sensible balance of the benefits and risks of particular ways of life still, unfortunately, presents a difficult problem for nutritionists of all sorts. Epidemiologists may not be able to do much more, by themselves, without the formulation of new hypotheses as a result of laboratory experiments; but there is

good reason to believe that joint studies, using biological markers of dietary habits, should enable many of our current hypotheses to be confirmed or rejected.

In some instances, however, we may have to resort to intervention studies with random allocation. This is a daunting prospect. An American attempt to test the value of reducing dietary fat proved too difficult and has been abandoned, but a trial of the prophylactic value of β-carotene has been successfully mounted by Hennekens & Eberlein (1985) with the collaboration of 20 000 American doctors and we should see some useful results within 5 years. I doubt if there are any similar trials we can launch in Britain until we can get clear indications of specific compounds that can be prescribed medicinally; but it might be possible to attempt interventions on a less ideal scientific basis in volunteers.

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