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Diet in the Aetiology of Cancer: a Review

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INTRODUCTION

THREE MEETINGS of the European School of Oncology Task Force on Diet, Nutrition and Cancer have been held. A report on our first meeting has been published [1]. In this review we update our previous conclusions on the scientific evidence on dietary factors in the aetiology of cancer, and present our recommendations for dietary modifications to reduce the incidence of cancer.

DIETARY FACTORS AND CANCER RISK

Dietary fat

Of all dietary factors believed to affect cancer incidence, dietary fat has attracted most interest. This is in part due to the strong correlations noted in international data between the incidence of or mortality from certain cancer sites and estimated population intake of dietary fat, and in part because of observations from animal experimental models. The international correlation studies cannot be used to infer causality, but they are useful in raising hypotheses. They may also provide some indication of the range of an effect, which may be difficult to determine within a country if dietary patterns are relatively homogeneous. Alternatively, animal models have been developed specifically to explore mechanisms potentially relevant to a hypothesis and, therefore, cannot be used to confirm the validity of that hypothesis [1].

We have, therefore, placed most emphasis in this review on the results of case–control and cohort studies. Unfortunately, many of the reported studies were based on inadequate dietary methodology, often with a very indirect assessment of dietary fat intake. This has led to much inconsistency, with studies with weak dietary methodology tending to show weak associations or negative findings. Further, the case–control studies provide estimates of fat intake which relate to current or recent diet, and which, therefore, only imperfectly, if at all, reflect diet at the relevant time period for cancer induction. The fact that fat intake is highly correlated with calories makes the evaluation of the association with cancer of each of the two specific factors uncertain, unless analytical methods that specifically address this issue are used [2].

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For breast cancer, some epidemiological studies have provided evidence that dietary fats are a determinant [1]. The association is probably not a simple linear one, since there may be no exposure–effect relationship at high levels of intake. This may be the reason that differences in effect have been difficult to determine in many high risk populations with relatively homogeneous fat intake. Further, when the questionnaire is self-administered, or when in cohort studies less detail can be collected than is possible in case–control studies, there may be much misclassification of fat intake. However, a number of observations suggest that fatty acid composition may be relevant, and that excess saturated fat intake is important in increasing risk. A combined analysis of 12 case–control studies has shown a significant effect of total and, perhaps particularly saturated fat in increasing risk in postmenopausal women [3], while a study in the Netherlands showed a positive association with total fat intake, which did not appear to be attributable to the degree of saturation of the fat [4]. Results have been reported from a large case–control study in Denmark involving 1457 cases and 1304 controls [5]. A significant trend of increasing breast cancer risk with increasing fat intake was found ($P < 0.001$). Compared to the lowest quartile, the top quartile was associated with a 45% increase in risk [relative risk (RR)1.45, 95% confidence interval (CI)1.17–1.80]. Willett [6] has criticised this study because it was not possible to control the analyses for total energy intake. A case–control study of postmenopausal breast cancer in Western New York found no association with fat intake, whether studied in terms of quantity or the proportion of total calories derived from fat [7]. However, a suggestive effect of fat in increasing breast cancer risk was found in a case–control study in Australia, especially when those patients who admitted changing their diet after diagnosis were excluded [8]. In addition, moderate effects of butter, oils and total fats used as "seasonings" in increasing breast cancer risk was found in a large hospital-based case–control study in Italy, with 2663 cases and 2344 controls admitted for acute conditions [9]. The relative risk for high intake of total seasoning fat was 1.4 (95% CI 1.2–1.7). Further, re-analysis of data from a case–control study in Hawaii suggested that women with both a high intake of foods rich in fat and animal protein, and with a large body size are at increased risk for breast cancer [10].

A cohort study based on over 56 000 women enrolled in the National Breast Screening Study in Canada has shown an effect of fat calories in increasing risk, with a protective effect for non-fat calories, with a relative risk of 1.35 for total fat intake (95% CI 1.00–1.82) [11]. A possible reason this study showed a positive effect, while a cohort study of 90 000 American nurses was negative [12], is suggested by the analysis of a cohort study of 34 388 postmenopausal women from Iowa [13]. In this study, a similar effect to the Canadian study was found when the data were analysed using the method used in that study [2], but the

absence of an effect when the data were analysed by the method used in the American nurses study. The difference in the two methods of analysis relates to the approach used to control for the effect of energy. In the method used in the Canadian study, the effect of fat calories is analysed in a model also containing other non-fat calories. In the method used in the American nurses study, the effect of fat calories is included in the model with all calories. Thus, in the latter method, fat calories are included twice, possibly producing an effect equivalent to over-matching. In addition, as nurses may be more aware of the potential effect of diet on health than general population groups, their reported intakes could reflect more what they would anticipate other health professionals to expect of them, rather than their true intake. Another cohort study of Norwegian women has shown a positive association between frequency of meat intake and breast cancer risk, and a protective effect from consumption of poached fish, though not for overall frequency of fish consumption [14].

There is some evidence that prostate cancer is associated with high intake of foods rich in animal fat [1]. This was reinforced by a study in Utah which showed associations with dietary fat especially for older (age 68–74 years) males with "aggressive" tumours [15]. In Hawaii, the attributable risk for saturated fat intake (with the lowest quartile of consumption as the base level) was estimated to be 13% [16].

We originally concluded that epidemiological studies do not provide unequivocal evidence for a causal role of dietary fat intake in the aetiology of colorectal and kidney cancer. However, the evidence did not rule out a role for dietary fat since the risk factors identified in terms of food, nutrients, dietary habits and their consequences are all associated, to a considerable extent, with high fat intake [1]. Although there has been no new evidence relating to dietary fat and renal cancer, for colorectal cancer the evidence that has appeared has largely strengthened the dietary fat hypothesis. For rectal cancer, for example, in a case–control study in Western New York, risk increased with increasing intake of kilocalories and fat, with the risk for fat in males persisting after adjustment for kilocalorie intake [17]. This was similar to the findings from a previously reported study of colon cancer by the same group [18]. Further, a study conducted in the Peoples Republic of China and in Chinese living in Western North America, has shown a significant effect of dietary fat in increasing risk of colon cancer in North American Chinese, and a lesser effect in China [19]. This is precisely the type of effect that could have been anticipated from the changes in incidence of colon cancer among Chinese migrants to North America. Further strength to the dietary fat hypothesis has come from a cohort study of American nurses, with a significant effect of total fat and meat in increasing risk [20]; a study in male health professionals, where saturated fat intake was positively associated with the risk of colorectal adenomas [21]; and a case–control study of colorectal cancer in Greece, where increased risk was found among those with a high dietary fat intake and low serum cholesterol [22]. However, no effect for fats but increased risk for total calories and dietary cholesterol was found in a case–control study of colorectal cancer in a Mediterranean-type population [23]. Similarly, in a case–control study in Los Angeles, total energy intake was associated with significantly increased risk in both sexes [24]. In men, total fat and alcohol intake were responsible for the calorie effect, in women, no individual source of calories was associated independently with risk. Further, in a case–control study in Stockholm, increased risk was largely seen for those with a high consumption of burnt or pyrolised meat [25]. There is a possibility that previous studies implicating dietary fat had neglected food processing methods in assessing risk; however, authors who find an effect of dietary factors in increasing risk may have considered, and even analysed food processing, but not reported the findings as they were negative. This could just be an example of negative publishing bias, though in order to be certain, future studies of dietary fat and other factors in colorectal cancer aetiology should consider and report on the results of the analysis of food processing methods.

For ovarian cancer, there have been several studies reported since our original review, but the findings are still contradictory. One study was conducted in Utah, finding no evidence of risk associated with increased fat intake [26]. A positive study was conducted in China with 172 case–control pairs. A significant ($P < 0.01$) dose–response relationship was found between intake of fat from animal sources and risk of ovarian cancer, but plant fat was not associated with increased risk [27]. A study in Western New York was conducted to evaluate a hypothesis that milk consumption increased the risk of ovarian cancer because of an association of lactose with ovarian failure [28]. An increased risk was found for consumers of whole milk relative to reduced fat milk. The authors, however, attributed their findings to the fat content of milk rather than lactose consumption. This conclusion was criticised [29], and defended [30], and a fourth study was interpreted as in favour of the lactose rather than the dietary fat hypothesis [31]. It would seem that further study, needing more complete dietary enquiry, is required to resolve this controversy.

There are some suggestions, from international correlation studies, that lung cancer risk is associated with increased dietary fat intake [32, 33]. A re-analysis of data from a case–control study in Hawaii suggests that the attributable risk for lung cancer in males for saturated fat intake (with the lowest quartile of consumption as the base level) is 23% [16].

Dietary cholesterol

Some of the early studies of breast and colon cancer showed an increased risk for consumption of dietary cholesterol, but these risks were usually substantially lower than those for total or saturated fat and were, therefore, largely ignored [34, 35]. More recent studies have found increased risks for dietary cholesterol in lung [36, 37] and bladder cancer [38]. Increased risk for lung cancer with increasing dietary cholesterol was confirmed in an analysis of the Western Electric Cohort Study [39]. The relative risk of lung cancer per 500 mg/day intake of dietary cholesterol was 1.9 (95% CI 1.1–3.4) after adjustment for cigarettes, age and intake of beta-carotene and fat. However, a study of bladder cancer failed to find an effect of dietary cholesterol, once saturated fat intake was taken into effect, which itself increased risk [40]. This raises the possibility that some studies which found an effect of dietary cholesterol but not a saturated fat effect may have failed to detect the latter because of an incomplete dietary enquiry, with insufficient data collected on saturated fat-containing foods. However, this does not seem to apply to recent studies of pancreas cancer. Thus, a case–control study in Australia, in which a detailed dietary enquiry was made, showed a significant effect of dietary cholesterol in increasing risk, with an estimated relative risk of 3.19 (95% CI 1.58–6.47) for the highest quartile of cholesterol intake relative to the lowest quartile, after adjustment for total energy, alcohol and tobacco usage [41]. Further, in a combined analysis of five case–control studies of pancreas cancer conducted in

Australia [41], Canada, the Netherlands and Poland, a consistent association with dietary cholesterol consumption was found, with a risk for the highest quintile of intake relative to the lowest of 2.68 (95% CI 1.72–4.17) [42].

Obesity

Obesity has been found to be associated with an increased risk of breast cancer in postmenopausal women, though there has been some inconsistency between the results of different studies [1, 7]. Some studies have suggested that abdominal fat deposits may be particularly associated with risk in postmenopausal women [43, 44]. In premenopausal women; obesity (as expressed by body mass index) appears to be protective, with a dose–response relationship [3, 45, 46]. The mechanism for this effect is somewhat obscure, though it has been suggested as possibly related to anovular cycles in heavily obese women [47]. In a re-analysis of data from an large international case–control study, the effect of a body mass index was evaluated in relation to an incidence rate function, with cases and controls from different countries grouped as high, moderate and low risk [48]. For postmenopausal women, increasing body mass index was associated with increasing breast cancer risk in women from all three groups of countries. For premenopausal women, however, increasing body mass index was associated with increasing breast cancer risk in moderate and low risk countries, but with decreasing breast cancer risk in high risk countries. The authors suggest these discrepancies may relate to different effects of central versus peripheral body fat, whose distributions may differ in low, moderate and high risk countries.

Body height is positively associated with premenopausal breast cancer [3]. In a cohort study of Norwegian women there was an inverse relation between body height and breast cancer in women under the age of 51, however, the association was restricted to women who were premenarchial in 1940–1945 [49].

Obesity has been consistently found to be a determinant of endometrial cancer, probably a causal one [1, 50].

There have been some studies that have suggested that obesity increases colon cancer risk. In a study of 52 539 men in Hawaii, with records linked to the Hawaii tumour registry, obesity in youth and middle age appeared to increase the risk of cancer of the sigmoid colon [51]. However, in a cohort study of American nurses, there was little overall relation of body mass with risk of colorectal cancer [52].

Body mass index has been found to be inversely associated with lung cancer risk [53]. Whether this association is due to leanness itself or another factor associated with leanness is not clear.

Calories and carbohydrate

Some studies have produced evidence of a positive effect of energy in increasing cancer risk, e.g. a study in Utah of colorectal cancer [54], a study of colon cancer in Los Angeles [24] and a study of colorectal cancer in Belgium, where oligosaccharides (largely sugars) were found as the major risk factor [55]. In animal studies, one of the most effective ways to reduce the overall incidence of cancer is by caloric restriction, and a similar mechanism may exist for some cancer sites in man. This possibility has been heightened by the findings from a Canadian study of pancreas cancer, in which the strongest effects were for calories, with carbohydrate calories contributing to the greatest extent in increasing risk, and with little or no effect for fat or protein calories [56]. A similar effect was found in the combined analysis of five case–control studies in which the Canadian study was included [42]. The relative risk for the highest versus lowest quintile of intake for carbohydrates was 2.57 (95% CI 1.64–4.03).

Fibre, fruits and vegetables

The evidence for a protective effect of dietary fibre *per se* is not strong [1]. Most of the methodological problems discussed above for epidemiological studies of dietary fat apply also to studies of dietary fibre. In addition, the methodology for assessment of dietary fibre has undergone marked changes in the past decade, without any final conclusion as to what constitutes dietary fibre, or in some instances, the components of dietary fibre that are potentially relevant in cancer aetiology. Thus, dietary data bases in the past were inadequate to provide estimates of dietary fibre intake, studies purporting to support the "dietary fibre hypothesis" being dependant on indexes of "fibre-rich foods". More difficult is the fact that a proportion of dietary starch reaches the colon where its physiological effect is the same as non-starch polysaccharide (fibre). For potatoes, for example, the starch is totally digested in the small bowel if the potatoes are eaten hot but behaves as fibre (i.e. is non-digested) if the potatos are eaten cold. These facts were not incorporated either in food tables or in diet questionnaires so it is quite unclear what is being measured in those studies purporting to make estimates of fibre intake. Hence, in the succeeding section, we place the term "fibre" in quotation marks to signify our lack of understanding of the associations reported.

Most of the studies reported until relatively recently related to colorectal cancer, and with few exceptions, no association was found for dietary "fibre" *per se* in case–control studies. Ecological studies have given inconsistent results. Animal studies have not been helpful in clarifying the possible relationship between "fibre" ingestion and colorectal cancer [1]. Nevertheless, in a combined analysis of 13 case–control studies of colorectal cancer, dietary "fibre" intake was found to be protective, with increasing protection with increasing estimated consumption of dietary "fibre" [57].

However, evidence is accumulating that the incidence of colorectal and other cancers (especially stomach and perhaps oesophageal cancer) is reduced in consumers of vegetables and fruit, whose consumption in the daily diet can, therefore, be encouraged without risk of undesirable side-effects [58]. For colon cancer, following a meta-analysis, Trock and colleagues [59] concluded that, "risk estimates based on vegetable consumption [odds ratio (OR) = 0.48] were only slightly more convincing than those based on an estimate of fiber intake (OR = 0.58), but the data do not permit discrimination between effects due to fiber and nonfiber effects due to vegetables." In one of the studies included in that meta-analysis, for example, the protective effect of vegetables with only low or moderate "fibre" content was stronger than that attributable to "fibre"-rich vegetables [60]. Further, in the study of rectal cancer in western New York (not included in the meta-analysis), there was a protective effect of "fibre" from vegetables, but not from "fibre" from grains, or from all foods (including "fibre" from vegetables and grains) [17]. In a case–control study of colorectal cancer in China, there was a strong protective effect of vegetables, especially green vegetables, chives and celery [61], while a protective effect of all sources of "fibre" (vegetables, fruits and grains) was found for colorectal adenomas in a cohort study of male health professionals [21]. In a study of colon cancer in Los Angeles, after adjustment for other dietary factors, crude "fibre" intake was significantly protective for the ascending colon but not for the distal colon [24].

For other sites of cancer, there is increasing evidence for a protective effect of some constituent of fruits and/or vegetables, even though for many of the sites the data available may have only permitted the analysis of a factor that should, on present evidence, be regarded as an index of consumption of plant foods. For breast cancer, for example, the combined analysis found evidence of a protective effect of "vitamin C" [3]. In the Canadian National Breast Screening Cohort Study, dietary "fibre" but not vitamin C intake was found to be protective [62]. Such data reflect evidence of a protective effect of vegetarianism for breast cancer risk [63] even though, within Seventh Day Adventists, the majority of whom are vegetarians, there appears to be no protective effect for breast cancer with increasing duration of membership of the church [64]. However, a case–control study of breast cancer in Australia found a protective effect of fruit consumption [8], while there was no evidence of a protective effect of dietary "fibre" in the nurses health study cohort [12].

For stomach cancer, several studies have found a protective effect of vitamin C [1], though in one study the vitamin C effect became non-significant when dietary fibre intake was included in the model [65]. However, fresh fruit, citrus fruits and raw vegetable intake were found to be protective in a large multicentre study in high and low risk areas of Italy [66], as was vitamin C in a further analysis of nutrient effects in that study [67]. Further, in a study in Germany [68], there were significant protective effects for fruits, including domestic and citrus fruits, and a dose–response relationship for the protective effect of vitamin C; in a case–control study in Spain, a protective effect of raw or cooked vegetables, non-citrus fruits and an index of vitamin C consumption was found [69]; in a study in Poland, consumption of vegetables and fruit was associated with a reduced risk, with a strong protective effect for consumption of radishes and onions [70]; in a case–control study in Belgium, protective effects of vegetables and fruits were found [71]; and in a case–control study in Italy, a protective effect of raw vegetables, citrus and other fruits and ascorbic acid was found on the risk of cancers of the gastric cardia [72]. These results are consistent with the temporal trends of stomach cancer, decreases having occurred in all populations with decreased consumption of salt-preserved and cured meats, and increased consumption of fruits and vegetables.

For oesophageal cancer, in a study in Uruguay, a clear protective effect was found for the consumption of fruits and vegetables with a dose–response relationship for fruits [73]. Similar effects have been found in a case–control study of oesophageal cancer in Argentina, in which, in an analysis of the effects of dietary items, intake of vegetables and fish was protective [74], and in an analysis of nutrients, increasing fibre intake was protective [75]. Increased risk from less frequent consumption of fruits and vegetables has also been found in a study of precancerous lesions of the oesophagus in China [76, 77].

For lung cancer, there has been an increasing tendency to ascribe protective effects to beta-carotene, though indices of consumption of beta-carotene are largely derived from estimated intake of various vegetables, while several studies have shown protective effects for vegetable consumption [1]. A study in Hawaii found a protective effect for vegetable consumption [78], and a study in Toronto failed to find a protective effect of beta-carotene, retinol or total vitamin A consumption, while a protective effect for nitrate ingestion was found, considered as an index of consumption of a number of vegetables [37]. Additional evidence has come from a study in Athens where a protective effect of high consumption of fruits but not from carotenoids was found [79]; from a cohort study of 34 198 Californian Seventh Day Adventists in which fruit consumption showed a strong, statistically significant protective effect for lung cancer, independent of smoking [80]; from a cohort study of 17 818 white male policy holders with the Lutheran Brotherhood Insurance Society which showed an inverse association of lung cancer mortality with intake of fruits, especially oranges [81]; from a case–control study of Yunnan tin miners who had increased risk of lung cancer with low consumption of yellow and light green vegetables [82]; and from a second study in Yunnan province where a protective effect of increased consumption of dark green leafy vegetables was found [83]. These studies were able to demonstrate a protective effect of vegetables after accounting for the effects of smoking. However, in a cohort study of 5080 men in a retirement community in California, adjustment for smoking almost abolished the protective effects of beta-carotene and vegetable consumption [84].

Protective effects of fruits and vegetables have been found for other cancer sites. Thus, for oral and pharynx cancer, protective effects have been found for fruit and vegetable consumption in a study in the United States [85] and in China [86], while in another study of pharyngeal cancer in the United States a protective effect of vitamin C derived from foods was found [87]. A strong protective and consistent effect of vegetables and fruits has also been found in a multicentre study of larynx and hypopharynx cancer, together with protective effects for indices of consumption of vitamins C and E [88]. The protective effects of fruits in this study were much stronger for citrus than other fruits, yet there was no protection for consumption of potatoes, casting doubt on the possibility that the protective effect of citrus fruits was due to the consumption of vitamin C. A study in Poland of larynx cancer also shows a protective effect of vegetable consumption together with a deleterious effect of poor nutrition generally [89], while a protective effect of fruits and some dark green/yellow vegetables was found in a study in China [90]. A study of pancreas cancer in Australia also showed a protective effect of nutrients derived from plant foods [41], as did a study in Minnesota [91], and the combined analysis of the five case–control studies of pancreas cancer (including the Australian study [41]). In the combined analysis [42], there were protective effects for estimated consumption of both dietary fibre (RR 0.45, 95% CI 0.30–0.63) and vitamin C (RR 0.53, 95% CI 0.38–0.76).

Alcohol

Of all dietary factors shown to increase the risk of cancer, the evidence is strongest for alcohol [1]. Although the largest risks relate to cancers shown to be increased by joint exposure to cigarette smoking (especially oral cavity, pharyngeal and oesophageal cancer, and the parts of the extrinsic larynx directly exposed to alcohol), the evidence is now conclusive that alcohol alone in high dosage increases the risk of these cancers. There has to be concern, therefore, over the fact that increases in incidence of cancers of these sites have been documented in many countries.

Alcohol consumption is also causally related to primary liver cancer, while the role of alcohol in increasing the risk of colon, rectal and breast cancer is still uncertain. The associations noted for the latter sites may reflect confounding with other causal factors.

For breast cancer, a number of studies have shown a positive

association and only a few have not [1]. In many of the positive studies, however, nutritional variables could not be fully evaluated, raising the possibility that alcohol consumption may be a marker of other factors which increase the risk of breast cancer [1]. One recent study in the U.S.A. has shown increased risk that was highest for alcohol consumption in early adult life [92], while in another in France a dose–response relationship was found with the highest risk (OR 3.5) for more than 17 drinks per week [93]. In a study in Northern Italy with very high consumption levels of alcohol in women, increased risk of breast cancer was found only at the highest levels of consumption (30+ g/day) [94], while in a study in Denmark, increased risk was found only for those age 50–59 with fat intake in the lowest quartile [95]. The findings from these studies raise the possibility that the increased risk found at surprisingly low levels of alcohol consumption in the U.S.A. nurses cohort study [96] and in a study in Australia [97] may have been due to overestimation of effect per unit of alcohol consumption because of underestimation of alcohol intake. Further, some large case–control studies reported recently have been negative for alcohol [98–100], raising the possibility of a positive reporting bias for some of the earlier studies, and thus an overestimation of effect in an earlier meta-analysis [101]. However, in a combined analysis of six previously conducted case–control studies (consisting of those among the 12 analysed for dietary fat effects [3] on which there was information on alcohol intake), there was an absence of an association with breast cancer for consumption levels up to 40 g of alcohol per day, and a highly significant association for drinkers of more than 40 g alcohol per day, with a risk compared to non-drinkers of 1.69 (95% CI 1.19–2.40) [102].

Colorectal cancer has also been associated with alcohol intake, especially rectal cancer and beer. A meta-analysis of 27 studies supports a weak association of alcohol with colorectal cancer, stronger for beer than other alcoholic beverages [103]. An analysis of two case–control studies conducted in Marseilles, France, one of colorectal cancer and one of adenomatous polyps of the colorectum showed an elevated risk for rectal cancer in male beer drinkers (relative risk 1.73, 95% CI 1.01–2.95) but not for colon cancer or polyps [104]. A case–control study of colon cancer in Los Angeles found that alcohol intake makes a significant contribution to the effect of calories in increasing risk in men [24].

One study has suggested that among heavy cigarette smokers, heavy alcohol consumption may increase the risk of lung cancer [105].

Other dietary factors

A host of studies have evaluated the effect of various vitamins, minerals, beverages and other dietary components on the risk of a number of cancer sites [1]. Although many have concluded that specific dietary factors (for example, beta-carotene or antioxidants such as vitamin C) may be protective against certain cancers, and have inferred that adding such factors to current diets may provide a more acceptable approach to cancer control than dietary change, current evidence does not justify such an approach. A major difficulty is that the majority of the studies with significant findings were derived from an incomplete assessment of dietary intake and, therefore, the investigators were unable to evaluate the possibility that the dietary factor considered was confounded by another more relevant dietary factor. Indeed, those few studies that have included complete dietary assessment have, in general, failed to show that the specific micronutrient under consideration (for example, beta-carotene or vitamin C) made an independent contribution once other factors were taken into account. However, several intervention trials currently in progress will eventually provide more precise information as to whether supplementation with some micronutrients will reduce cancer risk.

The evidence associating coffee, tea and artificial sweetener consumption with risk of a number of cancer sites suggested that no important or consistent increase in risk of any cancer site has yet been demonstrated following consumption of these items [1]. However, it has been pointed out by an IARC working group that there appears to be fairly consistent evidence of an increase in risk of bladder cancer with coffee consumption among non-smokers [106]. This led the working group to categorise the epidemiological evidence for coffee as *limited*. It is plausible that an increased risk of a weak carcinogen for the bladder may be easier to demonstrate in non-smokers than in smokers. However, the animal studies were assessed by the same working group as negative, while they noted a negative association in man for colon cancer. On balance, therefore, it would seem that the evidence does not allow a conclusion to be drawn on the causal nature of the association with bladder cancer, which could still be due to undetected confounding (such as with dietary fat intake or intake of dietary cholesterol).

Of other dietary factors, only for aflatoxin is there conclusive evidence of increase in cancer risk (though only for liver cancer) [1]. There is, however, some epidemiological evidence that excess nitrite and or salt consumption will increase the risk of stomach cancer [1, 65].

METHODOLOGICAL ISSUES IN THE INVESTIGATION OF DIET AND CANCER IN HUMANS

We have referred above to the methodological problems that have affected the investigation of dietary associations in human cancer, especially with regard to studies of dietary fat and fibre. The more complete the dietary questionnaire and the more care that is taken over the interview, the greater the precision of recording of diet. With good questionnaires, higher correlations are being reported with external measures of dietary consumption than tended to be reported previously, though there seems little doubt that substantial misclassification remains, accounting in part for the inconsistency sometimes seen as well as weak associations [107]. The ability to recall past diet has been demonstrated to be limited in a number of studies, with the diet recalled from the past being more reflective of current than past diet. Nevertheless, to the extent that individuals can recall past consumption patterns, it would seem preferable for them to attempt this in case–control studies rather than just recording diet prior to the onset of cancer symptoms. Further, under circumstances in a country where major dietary changes have occurred in the past, recall of past dietary patterns will be facilitated. In cohort studies, attempts are not usually made to recall past diet, suggesting that follow-up may have to be prolonged before such studies are able to detect an effect of dietary factors in the induction of incident cancer, especially if diet operates at the earlier stages of carcinogenesis.

A research issue (discussed further below) is the extent that biological markers can be developed to facilitate dietary enquiry. Studies of markers with relatively small numbers of individuals (because of the expense of marker studies) may advance the field more than larger and larger multicentre studies based on relatively poor and often different dietary instruments, that may be difficult to reconcile in an overview analysis.

A number of methodological factors should be taken into consideration when planning new research [1]:

(1) Use a dietary assessment method able to provide information on total energy intake and on all major nutrients, even if the focus of the study is on a particular nutrient.
(2) Adapt the method to local culture and local eating habits, such as eating pattern during the day, use of local casseroles and recipes.
(3) Adapt the dietary assessment method to the educational level of the subjects to be investigated, for example, self-administered questionnaires can substantially reduce the study cost but require that the subjects be able to read correctly, understand the questions, estimate frequency and amount of their food consumption, write the correct answers. Questionnaires administered by an interviewer, on the contrary, are more expensive but less dependent on subjects education.
(4) Test the repeatability and the relative validity of the proposed method under field conditions. Demonstration of repeatability (reliability) requires administering the instrument to the same subjects two or three times within a convenient time period. Relative validity can be demonstrated by comparing with an appropriate standard such as a more sophisticated method and/or a set of biochemical markers of diet.
(5) Adapt food composition tables to food locally consumed. Data on food composition may sometimes be available locally from institutions in charge of food analyses for administrative or health surveillance purposes. In addition, break down or pooling of food groups in the food table should be adapted to local dietary habits.
(6) Biochemical markers of nutrient intake should be used when appropriate and feasible to complement the information provided by other methods.
(7) Markers of individual genetic traits may enable sub-groups of subjects more or less susceptible to the health effects of particular dietary habits (e.g. differences in cholesterol metabolism, inherited risk of colon cancer, etc.) to be identified.
(8) Repeated measurements on the same subjects may be considered if the precision of the dietary assessment method or of a biological marker is not satisfactory.

THEORETICAL BASIS OF DIETARY RECOMMENDATIONS

We have conducted a detailed review of the ethical considerations that affect dietary recommendations, the quality of scientific evidence required in order to make recommendations for dietary change, the possibility that certain dietary changes might adversely affect the risk of some cancers and other diseases, the extent to which approaches to at risk individuals are feasible as distinct from mass population approaches, and also considered the ways by which dietary change may be affected. Our conclusions on these issues are as follows.

Ethical considerations

Dietary recommendations imply a promise of benefit to the individual who follows them that their disease risk will be reduced. Even if the evidence is very sound, it has almost invariably been derived from the experience of groups, with inferences based on probability, widely misunderstood by the public as applying to all individuals and, therefore, always to them. In general, the recommendations are presented as if all problems have been solved, and the public tends to be misled that the evidence is stronger than it may be, as the doubts and uncertainties that appear in the scientific literature are usually not presented out of fear that the public will not respond appropriately if they were. Further, recommendations are based on an understanding of the operation of risk factors, there is rarely evidence that following the recommendations will result in reduction in incidence of disease.

A conflict exists between the knowledge that is available, and the need (often in response to requests from the public) to provide some information. Concern that providing information based on incomplete knowledge may inhibit the conduct of research, and thus the acquisition of further knowledge, also has ethical implications, because it places scientists in the role of judge as to when information may be provided to the public, a role for which their training has not prepared them. As most research is conducted through funds provided directly or indirectly by the public, the public have a right to the information derived from such research, and have the right to have the information presented in such a way that they are in a position to come to their own judgement as to whether or not action by them is necessary. This implies that the information should be presented in such a way that the limits of scientific knowledge can be understood.

However, the ethics of imparting advice or recommendations by scientists, especially if it goes against established cultural norms, requires that the evidence for lack of hazard or unexpected adverse effect must be at least as strong as the evidence for the dietary change recommended. It is not acceptable that the overall effect on public health is beneficial if this results in detriment to some, even if outweighed by benefits to a larger number, unless those that could be affected adversely are identified and protected against such adverse effects.

It is incumbent upon those making recommendations that they put in place a mechanism to monitor the effect of the recommendations, so that corrective actions can be taken as soon as possible if they prove necessary, either because of an unanticipated adverse effect on disease rates, or a lack of the anticipated reduction in disease incidence within the relevant time period. It has to be recognised that the final evidence of disease causality will only come from a reduction in disease incidence following the relevant action, evidence that such changes are certain can not be expected in advance of making recommendations, otherwise all progress would cease.

Quality of scientific evidence

As implied above, to make recommendations for dietary modification requires strong evidence for the effect of a risk factor that is to be reduced or removed, or of benefit from a protective factor that is to be recommended, *and* strong evidence for the lack of an adverse effect of such a change. The strongest evidence in science comes from experiments, yet it seems unreasonable to expect every recommendation to be supported by evidence from randomised trials, particularly in the light of the expense of such trials, the selective nature of the population studied in many trials; the difficulty in conducting a trial over the time span necessary to see an effect (especially for interventions that affect the early stages of carcinogenesis), and the fact that most recommendations for cancer are congruent with those believed necessary to reduce the incidence of other chronic diseases, for which the evidence may be at least as strong as for cancer [58].

Although, in general, the criteria of causality widely accepted for other exposures in epidemiology should be expected to be applied to dietary causation before recommendations are made, their application should be tempered by a recognition of the fact that the strength of an association may be lower for dietary factors than that generally expected under other circumstances. There are two main reasons for this. The first is that in dietary enquiries one is rarely making a comparison between an exposed and a non-exposed group, rather the comparison is over gradients of different levels of exposure that may be relatively narrow within countries compared to the much larger ranges between countries. The second is the difficulty in quantifying many dietary exposures, and the problem of misclassification with the resulting attenuation of estimates of relative risk referred to above. For these reasons, more weight should be placed on the consistency of evidence in several studies and in different circumstances or countries, than on the strength of the relative risk, that may sometimes seem rather low, even though because of the widespread nature of exposure the attributable risk may be quite large. Indeed, for some dietary factors such as dietary fat and fruit and vegetable consumption, the proportion of all cancer affected may be very large, with the beneficial effects being seen over many cancer sites.

Although we do not regard it as necessary to insist on randomised trials in advance of making dietary recommendations, recommendations should not be regarded as inhibiting this type of research. Indeed, trials can benefit from dietary recommendations, because the intervention in the test group can be designed to be more extreme than that recommended to the general public, which then becomes the standard "treatment" applied to those allocated to the control group. Such a design will help to provide the scientific base for stronger recommendations in the future, if the degree of benefit from the more extreme treatment in the test subjects justifies this.

Nevertheless, to avoid confusing the public, it is important that dietary recommendations made for one condition are consistent with those made for another. In North America, there has been a major endeavour to ensure such consistency, in two major sets of recommendations in the United States [58, 108], as well as in Canada [109].

Competing risks

Given the reciprocal relationship in most populations between colon and stomach cancer, and between breast and cervix cancer, for example, it is reasonable to ask whether dietary modification designed to reduce the incidence of some cancers may increase the risk of other cancers of other diseases. Further, concern has been raised by some studies that show increased cancer incidence or mortality associated with low serum cholesterol, while there is a possibility that some individuals may be susceptible to the effects of increased fibre consumption and may fail to absorb iron or other minerals adequately.

Many of these issues were considered by a U.S. Committee [58], which concluded that there was no potential competing risk which raised major concern over any of their recommendations for dietary modification. For example, they pointed out that, in spite of the reciprocal relationship in most populations for colorectal and stomach cancer incidence, both appear to be reduced by the same protective factors (fruit and vegetable intake), which although the dietary factors that increase risk are different (dietary fat for colorectal cancer and nitrite for stomach cancer), they can both be reduced in a modern healthy or "prudent" diet.

More concern relates to the serum cholesterol issue, with over 20 reports published on a possible association with cancer risk [110, 111]. A negative association was found in slightly more than half of the studies, and where found was seen in men but not in women [58]. A preclinical cancer effect was considered to be the likeliest explanation in some but not all of these studies. For example, a study on a cohort of Norwegian women reported a negative relationship for serum cholesterol and breast cancer diagnosed before age 51, which was not seen in cases diagnosed in the first 2 years of follow-up [112]. However, the most persistent finding has been an increased risk of colon cancer among men with very low serum cholesterol levels [113]. Although confirmed in a follow-up of the cohort enrolled in the U.S. National Health and Nutrition Survey, male cases consumed more dietary cholesterol and a larger proportion of calories as saturated fat than controls [114]. Similarly, in a case–control study of colorectal cancer in Greece, risk was increased in those with a high dietary fat consumption and a low serum cholesterol [22]. The most plausible explanation for these findings is that persons with very low serum cholesterol levels may have reduced absorption of cholesterol from the colon, increased secretion of bile, and/or greater excretion of non-absorbed cholesterol in faeces [58,110]. Thus, low serum cholesterol may be a marker for a colonic milieu that increases the risk of colon cancer. If this is the case, dietary advice to reduce fat intake would be important for persons having naturally low serum cholestrol levels in spite of eating a high fat diet. Further, reassurance that a policy to reduce dietary cholesterol in a population by dietary modification is appropriate has come from a 25-year follow-up of the Finnish cohorts in the seven countries study [115]. Although all-cause mortality was higher in those with low serum cholesterol levels in the early years of follow-up, this trend was reversed with prolonged follow-up. The analysis suggested that low serum cholesterol, rather than being a cause of disease, is probably a marker for some other process that increases all cause mortality in the early years of follow-up.

Means to affect dietary change

In the past, the major approaches used to encourage good nutrition were a combination of public information and government regulation. Increasing interest by the public in disease prevention and a healthy life has resulted in the media and the food industry adding their contributions to the amount of information (and misinformation) disseminated, the latter heavily influenced by their commercial self-interest. Further players in some countries are the voluntary health agencies, with the Cancer Societies taking an increasing interest in dietary modification as a means to reduce cancer incidence. Unfortunately, some of the information disseminated may suffer from a lack of balance, or a failure to emphasise the priorities for action in accordance with the relative importance of the risk factor, in terms of the proportion of cancer that might be prevented by its modification. In this respect, in the dietary area the public is only now, in some countries, coming to appreciate that some "natural" constituents of diet, such as dietary fat, may be far more important than some perceived risks, such as food additives or pesticide residues, which may have a negligible effect on cancer incidence.

Insufficient knowledge is available on the best means to affect dietary change. That major changes are possible, however, has been demonstrated by the pilot studies that preceded the Women's Health Trial in the U.S.A. [116]. As a result of a structured intervention, involving individual counselling, diet-

ary fat intake was reduced in the intervention group from an average of 40% of energy intake at baseline to 26%, with only a slight increase 1 year after the intervention ended. It is important that research into effective but less expensive methods of achieving dietary change is pursued.

In every country, a partnership should develop between all health interests (including those concerned with heart disease, and other chronic diseases), government, the food industry, educationalists and the media to ensure that the appropriate information is disseminated and the appropriate action taken. The food industry is particularly important in this regard, to ensure that dietary choices can be made based on a suitable selection of food items correctly labelled as to their composition. Governments can often facilitate this process by regulation, though care has to be taken to avoid conflict within government between, for example, departments of agriculture and ministries of health. Government grants or subsidies have sometimes been made to promote the development of animal husbandry, encourage high fat content of meat, and encourage the provision of high fat milk and cream, even to schools. Governmental actions taken on economic grounds may also have adverse health effects. Thus, the agricultural policies of the EC have for some time encouraged the production of fat and alcohol. We note with concern that an increase in fat intake and, particularly, in saturated fat may specifically affect areas of southern Europe, where some dietary associated cancers are much lower in incidence than in northern or western Europe. Alternatively, the recently observed increase in alcohol consumption in central and northern Europe may lead to an increase in the incidence of cancers of the upper digestive tract in these areas. There is, therefore, a risk of a major increase in incidence of dietary associated cancers in Europe. National government policies should be directed to reducing dietary fat and alcohol consumption, as concluded, for example, in the recently implemented Action Programme Against Cancer of the European Community. Much might be achieved, for example, by moving away from high fat content of dairy products as implying high quality.

DIETARY RECOMMENDATIONS

Of the known causes of cancer, dietary factors collectively contribute to a large proportion of potentially preventable cancers. The challenge is to refine our present knowledge to the stage where appropriate and acceptable recommendations can be made on optimal dietary patterns. Such recommendations must be designed not only to reduce the incidence of cancer of most or several sites, but to prevent adverse changes in the rates of all cancers. At the same time, such recommendations must be compatible with those made for the prevention of other dietary associated diseases, especially cardiovascular disease. The recommendations that follow have been designed to ensure such compatibility. The Europe Against Cancer programme has accepted as an action the "development of nutritional recommendations against cancer adapted to each of the categories of participants concerned (action 16)" but has so far not adopted specific recommendations [117]. We feel those that follow could with advantage be adopted by that programme.

A. Population versus individual recommendations

Because of genetic differences plus acquired risk factors, certain individuals may be more likely to benefit from some types of dietary recommendations than others. However, our present state of knowledge does not enable us to identify these individuals. Although the weight of evidence which supports rcommendations for dietary change to control cardiovascular disease is stronger than it is for cancer, they may apply to different individuals within a population. For example, although there seems to be good evidence that an individual with a plasma cholesterol below 200 mg/dl is at relatively low risk for chronic ischaemic heart disease and might not, therefore, benefit from dietary modification to reduce the incidence of heart disease, this same individual, if consuming a standard high fat western European diet, may be at substantial risk for colorectal cancer. Thus, this individual might specifically benefit by reduction of dietary fat intake, and the other recommendations which follow which could, in this particular instance, result in the prevention of colorectal cancer, and thus result in an increase in his or her life expectancy. Studies which have purported to calculate average increases in life expectancy that might follow dietary change (e.g. [118]), in relation to cholesterol reduction and life expectancy, have in general failed to put across this concept. For those that benefit from dietary change, the effect will be substantially greater than the calculated increase in life expectancy for the average of a group identified by various risk characteristics, even when an average increase of life expectancy for the group may be a matter of only weeks or months. For the specific individual who benefits, the actual increase in life expectancy could be as great as 10–15 years. The average, of course, arises from the large numbers of individuals who will not benefit from this particular effect, though many of them could benefit from the reductions in risk for other diseases that may arise from the same dietary change. It is critical that this distinction is recognised both by professionals and by the public who have to make the decisions as to whether or not they will change their diet. It cannot be too strongly re-emphasised that our knowledge does not permit us to determine which of the public will benefit from the dietary recommendations. Each individual member of the public, who chooses to accept our recommendations, has a probability of benefit that for them could be very substantial indeed, or, because in practice they do not have a high risk of dying from any of the relevant diseases, they would receive little or no benefit. We emphasise this public health approach to disease prevention as distinct from the individual-based approach, which attempts to identify those individuals at high risk through some measured parameter, such as a high serum cholesterol level, and concentrate preventive measures on them. The individual-based clinical approach would, in general, result in a very minor reduction in overall disease risk in a population [119]. The general public health approach carries the potential for major reductions in disease incidence and mortality, as indeed appears to have been occurring in many countries, at least in part, from the widespread acceptance of recommendations for dietary change related to risk of chronic heart disease that were first promulgated some 15–20 years ago.

B. Specific dietary recommendations

1. *Reduce fat intake to less than* 30% *of total calories with no more than* 10% *of total calories from saturated fats*, 6–8% *as polyunsaturated fats, and the remainder as monounsaturated fats.* This recommendation is compatible with that of most authorities from countries with high rates of cardiovascular disease and diet-associated cancers, and is applicable for northern and western Europe as well as North America. For some Mediterranean populations, however, where the main constituent of fat is monounsaturated, and the rates of cardiovascular disease and diet associated cancers are lower, it may be appropri-

ate not to make such a recommendation, unless there are changes in the diet leading to a major increase in saturated and or polyunsaturated fat intake. For high risk populations, evidence does not, at present, exist as to the ideal level to which dietary fat should be reduced. However, 30% is approximately the base level for studies of diet and cancer in most populations, and is probably an achievable objective. Some believe that an appropriate objective should be 25%, largely because it has been demonstrated in several pilot studies that with individual dietary counseling, women can reduce their fat intake to approximately 20% of calories [116]. In addition, informed individuals, even in the absence of specific dietary counselling, can reduce their fat intake to the order of 25% providing they are aware of the appropriate dietary changes to make, such as choosing leaner meats, fish, eating poultry without skin, choosing low-fat dairy products, and in general, avoiding the use of added fat such as butter. Although the eventual target adopted may be 25% of calories, attempts to induce such a major shift at the present time may be unwise.

The epidemiological data, in general, support increased risk for saturated fat (thus our recommendations that no more than 10% of total calories should be saturated fat). Emphasising the sources of animal fat and dairy produce that should be reduced will help achieve this objective.

Although some cardiovascular disease epidemiologists have suggested substitution of polyunsaturated fat for saturated fat [120, 121], we accept the view that such an approach would be unwise as the animal experimental data suggest increased risk of some cancers following consumption of polyunsaturated fats of the omega-6 variety [58]. Hence our recommendation that consumption of polyunsaturated fats should be more than 8% total calories, which is approximately the present level of consumption. There is some evidence, especially from studies that show protective effects for some cancers from high fish intake, that increased consumption of omega-3 fatty acids may be beneficial. However, at this stage we would not recommend substitution of omega-6 fatty acids by omega-3, though we would advocate increased fish consumption in substitution for meats containing high levels of saturated fatty acids.

In northern and western Europe, reduction of consumption of some sources of saturated fat will inevitably result in reduction of monounsaturated fat, providing room for some increase in appropriate vegetable oils. This will not be the case for Southern Europe. A far better strategy will be to introduce approaches that will avoid an increase in saturated fat consumption which could follow a switch to the western or northern European dietary pattern.

2. *Consume a variety of vegetables and fruits (especially citrus fruits).* It is important to concentrate on the beneficial effects of vegetables and fruits in the light of the evidence presented earlier on their protective effects for many cancers, and the presence of vitamins and anticarcinogens in plant foods. We have not made a specific recommendation to increase whole grain and cereal product consumption as the evidence that they exert a protective effect is minimal. However, with reduction in dietary fat, in order to consume a diet adequate in calories, it will be necessary to increase the consumption of whole grain and cereal products, an action that is preferable to an increase in the consumption of sugars, in view of some evidence that sugars may increase the incidence of colon and other cancers. This recommendation will ensure adequate consumption of fibre-rich foods recognising that the full protective effect of the group of foods considered in this subsection may arise, not from fibre at all, but from either identified or non-identified components of the foods represented.

A U.S. committee [58] had a quantitative aspect to their version of this recommendation, six servings of vegetables or fruit a day, and five servings of whole grain and cereal products. We agree with these quantities, though we note that for some cultures in Europe, a considerable increase in fruit and vegetable consumption will be required to reach these levels.

3. *Adjust exercise and food intake to maintain healthy body weight.* The key to this recommendation is balance of energy intake to match energy expenditure, with increase of such expenditure in those who are mainly sedentary. Adherence to the recommendations above may well result in some loss of weight, as many individuals will find it difficult to completely substitute for reduced energy intake from fat with increase in fruits and vegetables (and whole grains and cereals). It is not clear whether the evidence that exercise reduces the risk of breast and colon cancer is due to reduction in relative importance of fat in the energy balance or whether exercise has an independent effect. However, it is increasingly clear that the balance of exercise and food intake is particularly important in controlling obesity, and hence should be recommended to lower the risk of obesity associated cancers.

4. *Avoid use of dietary supplements.* Our recommendations have been designed to ensure a balanced diet, the available evidence showing that with such a diet there will be adequate consumption of all vitamins, other essential micronutrients and minerals. There is, therefore, no need for dietary supplementation. Indeed, there is a danger that those members of the public who supplement their diet will derive false reassurance from such actions, may fail to follow our recommendations in other important respects and may, therefore, fail to derive the protection that the diet as recommended by us may provide.

Unfortunately, thre is a belief widely held by the public that if something is good, more is better. The fallacy of this belief is found in the risk of toxic effects from megadoses of some substances, such as vitamin A and selenium, and from the difficulty encountered in many studies in demonstrating any benefit from supplements. Without wishing to minimise the importance of toxicity from megadoses of vitamins, we re-emphasise that we regard a greater danger the fact that the wrong action may be taken by individuals by the supplementation approach. Taking a supplement but failing to reduce fat or consume adequate fruits and vegetables may place an individual at unnecessarily increased risk of disease, overwhelming any possible benefit that the supplement may have brought.

5. *Limit the use of salt and the consumption of salty, salt-preserved foods and nitrites.* Current salt intake in Europe approximates to 10 g/day, and a suitable target is of the order of 6 g/day. This will involve a considerable modification of intake for some, but it is an action especially to be stressed in parts of Europe where the stomach cancer incidence is still high, such as Portugal, parts of eastern Europe and parts of Italy. It is also an action that should be stressed for some manufactured foods, and some restaurants.

6. *If you drink alcoholic beverages, limit consumption to no more than the equivalent of two small drinks daily.* For some areas of Europe, this consumption level is considerably in excess of

current consumption for both men and women. However, in other areas it is desirable to promote moderation in consumption of alcohol as the evidence suggests that the adverse effects on cancer incidence are largely found at high consumption levels.

C. Age group to which recommendations are directed

These recommendations are directed to children from the age of 2, as well as adults of all ages. The applicability of these recommendations to children is important as for some cancers, perhaps particularly stomach and breast cancer, the effect of dietary risk factors may commence at an early age, i.e. in childhood and adolescence. Parents should, therefore, ensure that a correct dietary pattern is established early in life. This will also have beneficial effects later in helping to ensure more ready acceptance of the recommendations in adult life, as well as facilitating their general acceptance when they are applied to all members of the family.

D. Potential impact of dietary recommendations

The extent to which a factor increases the risk of a specific cancer in relation to individuals is normally determined by the relative risk. However, the extent to which a factor increases the amount of disease in the population is determined by the population attributable risk. Only certain studies enable population attributable risks to be determined, most specifically, population-based case–control studies. A few such estimates have been published, and other estimates can be derived from published data. Table 1 indicates approximate population attributable risks that have been gathered from various sources. In addition, the table lists the potentially preventable fraction of the relevant cancer derived from the registry with the highest incidence in the whole of Europe less the incidence in the registry with the lowest incidence in Europe, expressed as a percentage of the highest incidence registry. This approach is similar to that adopted by the IARC [122]. Caution has to be adopted in interpreting these numbers, especially those derived from population attributable risks, as it is unlikely that the whole population could be moved down to the lowest consumption levels. Rather, a shift down in the population distribution consumption could be expected [123]. However, if some members of the population shift to lower levels than the lowest currently experienced, this may offset, to some extent, the effect from those who remain at consumption levels well above the mean.

Included in Table 1, but in square brackets, are estimates of the effect of eliminating the effects of smoking, either alone in the case of lung, bladder, pancreas and kidney cancer, or jointly with alcohol in the case of oral, oesophageal and laryngeal cancer as well as estimated effects of the relevant dietary factors.

In some instances, the estimated benefits of dietary change derived from a case–control study are substantially less than those derived from comparisons of cancer incidence. This is particularly true for breast cancer. If dietary fat intake were to be reduced in some parts of western Europe from its present level of around 40% to somewhere midway between 30 and 25%, this would be similar to the current dietary fat intake of many parts of eastern Europe. On average, the incidence of breast cancer in eastern Europe is approximately half that of high risk countries of western Europe, with the maximum range, as in Table 1, of 75%. Thus, it could be anticipated that eventually a reduction of fat intake, if this was then followed by a reduction in breast cancer incidence, would reduce the incidence in much of western Europe by at least 50%. This is twice the effect that might have been anticipated from a reduction in dietary fat intake as determined by the estimated population attributable risk in a Canadian case–control study, if the average consumption was reduced to that of the lower tertile in that study [124]. However, this level of fat intake is of the order of 30% of calories and it is conceivable that the effect has been underestimated in the case–control study. Given this example, several of the estimates in the table may be conservative.

There are a number of barriers to achieving such effects in the population. The first is that sufficient individuals may not adopt

Table 1. Estimates of potential effects of dietary change on incidence of various cancers

Site	Action	Potential incidence reduction PAR	Potentially preventable
Oropharynx, oesophagus and larynx	[Eliminate smoking and] reduce alcohol, increase fruit and vegetable consumption	[90%] (89)	86%
Stomach	Reduce nitrite, cured meats and salt-preserved foods, increase fruit and vegetable consumption	68% (67)	74%
Colon and rectum	Reduce fat and increase vegetables	50% (35)	79%
Breast	Reduce fat and increase vegetables	27% (124)	75%
	Reduce obesity (postmenopausal women)	12% (124)	
Endometrum	Reduce obesity	30% (124)	82%
Ovary	Reduce fat	?	66%
Prostate	Reduce fat	?	81%
Kidney	[Eliminate smoking], reduce fat	[30%] (122)	98%
Lung	[Eliminate smoking], reduce fat and increase vegetables	[80%] (122)	76%
Bladder	[Eliminate smoking], reduce dietary cholesterol	[60%] (122)	73%
Pancreas	[Eliminate smoking], reduce calories, dietary cholesterol and increase vegetables	[50%] (42)	70%
Liver	Reduce alcohol	30% (122)	?

PAR, population-attributable risk. Square brackets are used when some of the benefit derives from eliminating smoking. Estimates for males except for breast, endometrium and ovary cancer. Citation source in parentheses. ? signifies no estimate of effect is available.

the manoeuver to result in the anticipated reduction in cancer incidence. The second is that the effect of the intervention may be somewhat delayed. However, the anticipated effect of dietary changes in influencing the incidence of colorectal cancer are relatively rapid; possibly an important effect could be detectable within 10–15 years. This anticipated early effect of dietary change when the factors affect the late stages of carcinogenesis may also be exhibited for sites with protective effects mediated through fruits and vegetables. For factors which affect early stage carcinogenesis, however, as may operate for stomach and breast cancer, there may be a substantial delay, with evidence for relatively slow changes in incidence after migration. For breast cancer, for example, cohort effects dominate changes in incidence. However, for both there could be beneficial effects from inhibitors of later stages of carcinogenesis. Nevertheless, it is conceivable that much of the benefit from the recommended action for stomach cancer may have already been achieved in some countries.

Determining the total impact of dietary factors on the incidence of cancer is difficult, as envisaged by the wide range of possible estimates derived by Doll and Peto [125], i.e. 10–70%. The calculations in the table, translated into an effect of total cancer incidence, suggest that of the order of at least 35% of cancer might eventually be prevented by dietary modification. This dietary modification, however, would probably have to affect a whole generation before such an impact would be envisaged, thus the full effect cannot be anticipated until well into the next century.

DIRECTIONS FOR RESEARCH

Detailed recommendations for research in relation to epidemiology, mechanisms of carcinogenesis, laboratory methods and various dietary constituents were published nearly a decade ago [126]. In many respects, these encompass the research agenda that still needs to be completed. Our adaptation of these recommendations are summarised below.

A. Identification of the foods and of the dietary macro- and microconstituents that alter the risk of cancer, and elucidation of their mechanisms of action.

Much work remains to be completed. The precise mechanism of action of many of the dietary factors that either increase or reduce cancer risk is still unclear. However, it is unclear how much epidemiology can contribute to this without innovative approaches to the use of biological markers (see below).

B. Improvement of the data base and the methodology for assessing human exposure to foods and dietary constituents that may alter the risk of cancer.

Innovative methods for dietary assessment are still required. The uncertainty relating to a possible protective effect of dietary fibre or other constituents of plants might be resolved by a better data base.

A limit may have been reached to the information that can be obtained from further case–control studies without new approaches to measuring exposure. More attention also needs to be devoted to the information collected in cohort studies.

C. Identification of markers of exposure and early indicators of the risk of cancer.

Improving our knowledge on the markers of genetic risks, as well as those related to an indication that individuals have had exposure to a specific dietary constituent that could increase their risk of cancer, might eventually enable focus on specific individuals for whom more extreme changes in diet than those recommended for the general population would be justified. This mandates collaboration between epidemiologists and molecular biologists in agreeing upon the biological samples to be collected, especially in cohort studies. There is a role for genetic/diet interactions and metabolic polymorphism. Molecular biology needs to be combined with good epidemiology design.

There is a conflict between better markers of exposure and larger numbers in epidemiology studies because of the high cost of the laboratory components of studies incorporating biological markers. Further research on the best ways to collect specimens and preserve them is required so that retrospective analyses can be done with more confidence. Higher priority is currently justified on smaller studies with better measures of exposure to reduce misclassification than on very large studies with less optimal instruments.

D. Determination and quantification of the adverse or beneficial effects of the foods and of the dietary macro- and microconstituents that affect the risk of cancer.

The quantitative nature of the relationship between many food constituents and cancer risk is still imperfectly understood. For example, the recommendation that dietary fat intake should be reduced to below 30%, with 25% as a reasonably achievable target, is to a large extent based on inferences and not data. Studies in populations that enable quantitative estimates of degree of risk and degree of benefit are very necessary. This may permit determination of the ranges of optimal intake of dietary macro- and microconstituents. Clearly, such determination has to include evaluation of adverse health effects of dietary constituents for conditions other than cancer.

E. Evaluate interventions to reduce the risk of cancer.

Intervention studies, carefully designed to assess the degree to which risk follows dietary modification, should be performed. A small trial (approximately 9000 women with mammary dysplasia on mammograms) of dietary fat reduction for breast cancer has been initiated in Canada. A major study in the United States that was designed to evaluate the effect of dietary fat reduction and other changes in reducing the risk of breast and other cancers has had funding problems. There is debate as to whether funds should be expended on large-scale trials or whether interventions should be advocated in the population, and their effectiveness assessed by careful monitoring of trends of cancer incidence and mortality. The latter option may be preferable, though if resources are available that permit large-scale trials, their conduct could substantially increase knowledge.

F. Evaluate the application of knowledge about diet and cancer in the development of programmes for public health policy.

Knowledge is required on the actions that should be performed in order to ensure that dietary recommendations achieve their full effect in the community. This will involve collaboration with experts in health promotion, and capitalising on the programmes that have already been mounted in some communities (e.g. Stockholm) on dietary modification [127]. Such programmes will almost certainly have to be carefully adapted to the cultural norms in the community.

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Invited Viewpoints

Petr Skrabanek

DIET AS the cause of cancer has exercised the minds of preventionists at least since the time of Hippocrates. A 1903 editorial on cancer noted that "there is hardly an article of food which has not at one time or another fallen under the ban of some more or less acute theoriser" [1]. Yet cancer mortality in afffluent countries, despite changes in dietary patterns, has remained unaffected.

Marked differences in the incidence of individual cancers in different countries have led risk factor epidemiologists to argue that most cancers are preventable. However, overall cancer mortality rates are very similar in countries with most unsimilar diets. Thus, even if diet were to be implicated, the same diet associated with a low rate of some cancer or disease could be linked to an increase in other causes of death, as if following the principle of communicating vessels. Therefore, before issuing recommendations for a change in the national diet, with all its cultural and economic consequences, the proponents of such a change should present convincing evidence for a beneficial effect on overall morbidity and mortality. It is not enough to assume such benefit, as witnessed by counter-intuitive results from cholesterol-lowering trials.

Miller and his colleagues provide no such evidence, and their recommendations do not follow from their literature review. While the bulk of their review deals with fat, the authors also state that sugars "may increase [cause?] the incidence of colon and other cancers". They do not mention protein, for which there is even more "evidence" for an association with cancer. If fat, sugar and protein are associated with cancer, a sceptic may be forgiven for drawing the conclusion that people who eat, die. However, it may be more true to say that cancer is as much "caused" by diet as tuberculosis was "caused" by diet before the real cause was found in the laboratory by Robert Koch.

Risk factor epidemiology is unlikely to advance our understanding of cancer, beyond the identification of "risk factors". It is a logical nonsequitur to assume that the removal of such markers of risk would remove the risk itself. Thus, for example, cutting off ears with the ear-lobe crease (a well-known risk factor for coronary heart disease) will do nothing for the risk of heart disease. Similarly, it does not follow that lowering (or increasing) the consumption of a particular dietary item will result in increased life expectancy.

The misuse of language betrays the authors' uncritical bias. Thus, when they describe dietary fat as a "determinant" of breast cancer, exerting a "significant effect", they imply causation. This is not science. An editorial in *Nature* [2] comments that "despite abundant evidence that dietary fat bears no relation to development of cancer of breast, the NIH intends (under the fashionable umbrella of "women's health") to initiate a study of 40 000 women. . . to try again to prove a link that is probably not there. Is it only because of the faddish infatuation with fat as the root of all dietary evil?"

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