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Dietary recommendations for coronary heart disease prevention: implications for non-cardiovascular diseases

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Summary

In order to reduce the lipoprotein-related risk of coronary heart disease, nutritional recommendations have been formulated for use by communities prone to atherosclerosis and its complications. As such recommendations are potentially of widespread application they require careful scrutiny to assess possible risks as well as benefits.

Epidemiological, clinical and experimental data concerning relationships between these nutrients and non-cardiovascular diseases are reviewed with emphasis on cancer mortality. Changes in intake of fats, including polyunsaturated fat, of cholesterol, carbohydrate, fibre, sodium and β-carotene are discussed, and evidence of a relationship between serum cholesterol concentration and cancer is examined. These considerations offer reasonable reassurance as to the safety of recent dietary recommendations for the reduction of coronary heart disease.

Zusammenfassung

Um das mit Lipoprotein verbundene Risiko von koronarer Herzerkrankung zu vermindern, sind Ernährungsempfehlungen für Populationen mit Empfänglichkeit für Atherosklerose und seine Komplikationen dargelegt worden. Da solche Empfehlungen möglicherweise weitverbreitet anzuwenden sind, müssen diese gründlich untersucht werden, um sowohl Risiken als auch Vorteile zu bestimmen.

Die vorliegende Arbeit bespricht epidemiologische, klinische und experimentelle Daten über Beziehungen zwischen diesen Nährstoffen und nichtkardiovaskulären Erkrankungen, mit Nachdruck auf Krebsmortalität. Veränderungen der Aufnahme von Fett (polyungesättigtes Fett mit eingeschlossen), Cholesterol, Kohlenhydraten, Natrium und β-Carotin werden diskutiert, und Beweise für eine Beziehung zwischen Serumcholesterol-Konzentration und Krebs werden geprüft. Es wird beschlossen, daß die jüngsten Ernährungsempfehlungen zur Verminderung von koronarer Herzerkrankung leidlich zuverlässig sind.

Key words: cholesterol, β-carotene, coronary heart disease, fibre, non-cardiovascular disease

Introduction

There is now broad consensus among informed scientists as to the major dietary guidelines for populations at high risk of coronary heart disease

(CHD) (1, 2). The 1982 WHO Expert Committee (1) recommends a reduced consumption of saturated fats and of cholesterol, and suggests that some of the saturated fat reduction may be made up by mono- and polyunsaturated fats. Obesity should be avoided. Other expert committees have made similar recommendations (3). In some communities where nutritional patterns are showing a trend towards these recommendations, a reduction in CHD mortality has commenced; it is probable that change in diet, among other factors, has contributed to this secular change, observed in Australia, the USA, Canada and, recently, the UK (4, 5). By contrast, contrary nutritional trends in Japan and the USSR have been associated with rising CHD death rates since the end of World War II (6, 7).

The purpose of the present review is to examine the possible effect of these dietary trends on diseases other than CHD. Three controlled trials, all of modest size, have been conducted in which the effect of a fat-modified diet on CHD incidence has been examined, and favourable results have been reported in each (8–10). There has been no consistent effect on non-cardiovascular mortality; in the diet group of one there was an excess of deaths from non-CHD causes, in one there were fewer deaths than in the controls and in the third there was no difference between the groups.

The possibility that dietary factors may play a role in the aetiology of certain cancers has been the subject of extensive epidemiological, experimental and clinical research in the past decade, and some of this body of information is relevant to a consideration of possible effects of the proposed dietary changes on the risk of malignant disease. These may be considered in turn.

1. *Reduction in intake of fat, with emphasis on saturated fat.* When age-adjusted cancer mortality is compared in countries with widely differing dietary patterns, some consistent correlations emerge (11, 12). Availability of dietary fat for consumption can be estimated and provides an index of average fat intake. A strong direct relationship exists between this measure of fat intake and mortality rates for cancers of the breast, colon, uterus, ovary and prostate.

There is also evidence from case-control comparisons that fat consumption may be higher in patients with colon cancer than in controls. Such evidence of association does not on its own establish an etiological role for dietary fat; it is, however, consistent with studies of the effects of diet on experimental models of colon and breast cancer, which reveal a dose-related effect of dietary fat as a promoter of neoplasms in rats pretreated with selective carcinogens.

These findings provide reassurance concerning the potential effects of reduction in intake of saturated fat on the risk of these common forms of cancer, and have been interpreted further as suggesting an aetiological role for high fat consumption in these diseases. Secular trends in age-standardized cancer mortality rates in Japan are compatible with this interpretation: in the period 1950–1970 dietary fat consumption has increased from 9% to 27% of energy. Age-standardized mortality rate from all cancers in man has risen by 25% and organ-specific rates from

colon (in men), breast, prostate and pancreatic cancer have increased by 43 %, 30 %, 700 % and 560 % (6).

2. *Reduction in dietary cholesterol.* While cholesterol is present in the diet of all non-vegetarian species, there is no evidence for a nutritional requirement for this sterol except in certain blood-sucking insects which are dependent on ingested cholesterol. The relationship between dietary cholesterol intake and plasma cholesterol in man shows a marked individual variation; the mean effect of increased dietary cholesterol is to raise plasma levels to a moderate extent (13, 14), though complete independence of plasma levels from dietary intake has been reported. Homeostatic regulation of endogenous cholesterol synthesis is a major factor in limiting the influence of change in dietary sterol intake on plasma levels and on exchangeable cholesterol pools (14–16). In man there is no ground for suspecting that reduction of dietary cholesterol has deleterious health effects, even during periods of rapid growth.

There is, on the other hand, some evidence suggesting that a high dietary cholesterol intake may be harmful. A minority of normal persons show a large rise in plasma cholesterol in response to a high intake (14), and others show an increase in tissue cholesterol without a rise in plasma levels (15). A direct relationship between availability of dietary cholesterol and mortality rates from colon cancer has been observed, the correlation being even closer than that between dietary fat and colon cancer (17).

3. *Polyunsaturated fatty acids.* An obligatory nutritional requirement for polyunsaturated fatty acids of the ω-6 series, e.g. linoleic acid, has been established in man and other mammals (18, 19). A physiological role is well defined for this group of nutrients as components of plasma membranes and intracellular membrane phospholipids in all tissues, but notably in the nervous system, and as the substrate for synthesis of the 2 series of prostaglandins. Polyunsaturated fatty acids of the ω-6 series reduce plasma cholesterol and reduce platelet aggregatability; those of the ω-3 series have potent effects in reducing elevated plasma triglyceride (20, 21) and reduce platelet aggregation, but are poor substrates for prostaglandin synthesis (22).

Despite these desirable or essential effects of specific polyunsaturated fatty acids, an optimal nutritional requirement for man has yet to be defined and remains an unresolved but important issue. A minimum intake to prevent the essential fatty acid (EFA) deficiency syndrome is of the order of 3 % dietary energy (23), an intake characteristic of the diet of Western man, e.g. in the UK. However, the minimum intake as so defined is modified considerably by intake of other nutrients; for example, it is increased by a high intake of saturated or monounsaturated fatty acids (24), for these compete with dietary linoleic acid for chain-elongation and desaturation mechanisms necessary to their roles in membrane structure and to prostaglandin production. Hence a diet rich in saturated fat increases the requirement for linoleic acid necessary to prevent EFA deficiency.

One criterion of the upper limit of polyunsaturated fat consumption is the highest habitual intake in communities with satisfactory health statis-

tics, up to an average of 7 % of dietary energy (25). The increased intake in the USA in recent years has not been associated with an increase in mortality from or incidence of common non-cardiovascular disease. Lung cancer rates have been rising but have levelled off. The rate of all cancers except lung cancer now shows a possibly significant downward trend (4). The pooled experience of dietary trials in which polyunsaturated fat intake has been increased to 10–15 % of energy intake have shown no significant effect on cancer mortality (26). Nor is a consistent trend of non-cardiovascular mortality evident in the three dietary coronary prevention trials referred to in the introduction.

Studies of the effects of polyunsaturated fat intake on experimental carcinogenesis in the rat must be referred to. The frequency of mammary tumours in animals pretreated with DMBA was greater when polyunsaturated fat provided about 1–3 % of dietary energy than when such fat was not present in the diet, or when a similar intake of a saturated fat was provided. The incidence was still greater when higher intakes of fat (providing about 40 % energy) were given. In this situation the frequency was greater in animals fed polyunsaturated or monounsaturated fat than in those receiving such saturated fats as tallow or coconut oil; however, if animals received a small intake of polyunsaturated fat, then *additional* saturated and unsaturated fats led to a similar incidence of tumours (27, 28).

These careful observations appear to reflect two distinct processes. The effects observed in the range of 0–3 % energy from fat is reasonably interpreted as indicating that tumour induction, like normal cell growth, is inhibited in the unphysiological state of EFA deficiency. The effects seen at 20–40 % dietary energy cannot be so interpreted, and suggest that in the DMBA-treated rat very high intakes of fatty acids are even more effective than lower intakes of fatty acids as promoters of mammary tumours; provided that EFA deficiency is prevented, the type of fat used does not influence tumour yield.

Such intakes of saturated and unsaturated fat are of course vastly in excess of those proposed as optimal for reduction of CHD risk, and exceed present levels of consumption.

Speculations concerning the risks of fatty acid peroxidation leading to free radical injury have appeared from time to time, but there is no evidence that such processes, if they occur, are dependent on the intake of particular fatty acids. They are, however, influenced by the amount of antioxidants in foods containing unsaturated fatty acids. Sources such as seed oils and fatty fish contain tocopherols in sufficient amount to inhibit peroxidation, and statutory requirements have long been in force specifying that seed oil products such as diet margarines should have a satisfactory α-tocopherol content. It is probably prudent to specify that seed oils used in frying should not be repeatedly heated to high temperatures.

Two sources of information have recently enhanced the view that a moderate increase in polyunsaturated fat intake is a justifiable part of an optimal diet for CHD prevention. One is the demonstration in case-control studies (29), cross-cultural observations (30) and prospective studies (31, 32) of an inverse relationship between CHD and intake of linoleic acid. The latter has been measured by blood and tissue analyses and by careful

assessment of a dietary "lipid score". Some (32, 33) but not all (34) studies have shown an inverse relationship between a diet score or P:S ratio and serum cholesterol. The second observation concerns the nutritional background accompanying the declining mortality from CHD in the USA. One of the associated secular trends in CHD risk factors has been a documented fall in plasma cholesterol varying from 3 % to 8 % in different population groups. Food availability data indicate only a minor decrease in saturated fat use during the past 15 years; the main nutritional trends likely to account for this fall in plasma cholesterol are the substantial increase in polyunsaturated fat intake and the considerable reduction in dietary cholesterol (4).

Summarizing this section, there appears to be a strong case justifying a moderate increase in dietary intake of linoleic acid, certainly for a two-fold increase in the current British intake of about 3.5 % dietary energy. This is an increase within the range observed in the free-living populations referred to. It is important to emphasize that a substantial fall in CHD risk would be expected only if this recommendation is part of a wider set of nutritional guidelines including a reduction of saturated fat intake to 9–10 % of energy intake. It should be recalled that the Oslo Heart Study (10) and other trials of diet in the primary prevention of CHD, including the European Multicentre Multiple Risk Factor Intervention Trial (35), were not and of course could not be studies of a change in intake of any single nutrient. The outcome of each of these studies reflected a nutritional "package" comprising a decrease in saturated fat and cholesterol and an increase in polyunsaturated fat and complex carbohydrate. When conclusions are drawn from these studies concerning optimal dietary patterns, it is quite improper to select any single change in nutrient intake as being justified by their results. The only tenable conclusion is that a favourable outcome was associated with the dietary intervention package as a whole.

4. *Increased carbohydrate.* An increase in complex carbohydrate, based on greater use of cereals, vegetables and fruit is an integral part of dietary goals for reduction of CHD risk; it is of course also a requirement for maintaining energy balance, except in obese persons needing a temporarily hypocaloric diet. Such foods are generally of low energy density, contain little or not saturated fat, no cholesterol and in general little sodium (unless added in processing), and are sources, to a varying extent, of fibre, ascorbic acid, β-carotene and other vitamins, and potassium. Such evidence as is available suggests that many of these nutrients may influence the risk of common diseases favourably. There are controlled trial data to support the view that symptoms of diverticular disease are lessened by a high fibre diet (36). The relationship between fibre intake and colon cancer remains a subject for debate. There is an inverse relationship between fibre intake and mortality from colon cancer in cross-cultural studies, though the correlation is weaker than that between colon cancer fat consumption (37). Fibre is partially protective against experimental colon carcinogens in the rat in some but not all studies (38). In man it has been speculated that, either by dilution into a larger faecal bulk or by adsorption of carcinogens (or promoters such as certain bile acids), fibre

may reduce mucosal exposure to mutagens or promoters in colon contents. The effect of fibre in reducing intestinal absorption of divalent cations (zinc, iron, calcium) is a potential adverse effect in persons receiving a marginally adequate intake of these nutrients (39). Slowing of glucose absorption by pectin-type fibre is a feature of modern diabetic diets (40).

Intake of β-carotene is inversely related to cancer mortality in cross-cultural studies; the inverse relationship with lung cancer rates is independent of cigarette use (41). Serum retinol is inversely related to total cancer incidence in longitudinal observations (42). Experimental evidence of protection against carcinogens has been obtained both for β-carotene and preformed retinol.

Attention has been drawn to the effects of nutrition on nitrosamine and nitrosamide formation, and by implication on gastric carcinogenesis. The reaction between nitrite and amines to form nitrosamines is inhibited by ascorbic acid (43) and is promoted by high sodium concentration (44). The geographical distribution of gastric cancer is directly related to sodium intake (45), and an inverse relationship to consumption of vegetables and fruit is suggested by case control studies on atrophic gastritis, a probable precursor of gastric cancer (46).

An extensive literature bears on the relationship between sodium intake (or excretion) and hypertension, based upon geographic epidemiology, nutritional experiments in rodents and man, and therapeutic trials (47). More recently, it has become clear that the ratio of sodium intake to potassium intake may be more strongly related to blood pressure in man than the absolute intake of sodium.

Discussion and conclusions

The considerations summarised in this review offer reasonable reassurance as to the safety of the dietary recommendations made for reducing coronary heart disease risk. They do not absolve the medical profession from the responsibility of maintaining careful surveillance of populations, experimental subjects and individual patients receiving modified diets over a long period.

In the past four years considerable attention has been given to the observation in several longitudinal studies of an inverse relationship between plasma cholesterol level and cancer mortality. We and others have reviewed this topic (49), which will not be discussed in the present article. The most extensive prospective study strongly suggests that the relationship, when present, reflects an effect of early unrecognized cancer in causing a low plasma cholesterol, rather than a role for hypolipidaemia as a cause of cancer (49). Though it has been hypothesized that reduction of plasma cholesterol may have adverse effects on the composition of cell membranes, direct studies in vivo and in vitro in this laboratory provide no evidence that such effects could result from levels of plasma cholesterol achievable by hypolipidaemic diets or drugs in present use (50).

We have referred to the evidence that low plasma retinol levels are predictive of increased cancer mortality; and the correlation between plasma retinol and both total cholesterol and LDL-cholesterol levels (50)

suggest that the inconsistent cholesterol-cancer relationship may therefore be an indirect one, i.e. that cholesterol is a confounding variable in the direct retinol-cancer association.

Results of the WHO European Collaborative Trial of multiple intervention against CHD risk factors suggest that the modest success in risk factor reduction was followed by a small reduction in CHD (51). The report of the British component of the study notes an early excess of CHD and non-CHD mortality in the intervention group. This was not sustained, nor did it occur in other participating centres. Nevertheless, the authors raise the question of "possible deleterious effects" from "abrupt changes in biological equilibrium", with particular reference to drug treatment (52). In the absence of supporting biological data or explanatory hypotheses, such a speculation has but a tenuous scientific basis; nor do the authors afford it great emphasis. However, the proponents of life-style change for risk factor reduction have repeatedly advocated the adoption of such changes early in life; the speculative "disequilibrium" following a period of hypothetical "adaptation to an adverse life-style" is particularly unlikely if this counsel is adopted.

The natural experiment of population life-style change in the USA has been referred to, and is likely to have been an important factor in the declining mortality from CHD. It is reassuring to note that other cardiovascular deaths have also been declining, and that cancer mortality (with the exceptions of lung cancer and pancreatic cancer) has been static or slowly decreasing (4). Thus life expectation from middle age is currently increasing in the USA. Further, it is clear from comparisons of countries with differing life-styles that those in which the habitual diet approximates to that advocated for CHD reduction, e.g. Japan and Italy, cancer mortality is lower, and life expectation higher than in the USA, Scotland or England and Wales.

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