Evidence-based nutrition

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What are the objectives of an ideal diet? Are they to prolong life or maximize quality adjusted life expectancy? Does this focus on individuals or on the population at large, taking equity and resources into account? What about externalities that should take into account cultural heritage, protection of the environment and macroeconomic considerations? Few people have the experience, expertise and knowledge to adequately address these questions. It is only feasible to argue that there are two approaches in order to establish the proper diet, with the limited objective of longevity. Contrary to the assertions of several influential groups, there is no such thing as a 'positive health', and longevity can only be defined as the inverse of mortality from all causes. The crucial questions are: do we need to study the proper diet to reduce incidence of and mortality from particular common diseases and then find the common elements in these various diets in order to construct *de novo* the ideal diet (bottom up approach)? Alternatively, is it better to harvest the experience of various cultures whose diets appear to protect against premature morbidity and mortality (top down approach)? The first approach would rely on associations between food groups, foods and nutrients on the one hand and the incidence of specific diseases on the other, whereas the second would evaluate and quantify the effects of 'natural' diets on longevity. The first approach has been largely followed by mainstream nutritional epidemiologists, whereas the second has been advocated by a few international experts.

Key words: nutrition, diet, cardiovascular disease, cancer.

Introduction

What is the best diet? As we enter a new millennium weighted with a lot of information, we need first to clarify what are the objectives of an ideal diet. Is the objective to prolong life as much as possible, or is it to maximize quality-adjusted life expectancy? And does this focus on individuals or on the population at large, taking equity and resources into account? And what about externalities that should take into account our cultural heritage, protection of the environment and macroeconomic considerations? Few people have the experience, the expertise and the knowledge to adequately address these questions, let alone to answer them satisfactorily. It is only feasible to argue that there are two approaches in order to establish the proper diet, with the limited objective of longevity.

Contrary to the assertions of several influential groups, there is no such thing as a 'positive health', and longevity can only be defined as the inverse of mortality from all causes. The crucial questions are, do we need to study the proper diet to reduce the incidence of and mortality from particular common diseases, and then find the common elements in these various diets in order to construct *de novo* the ideal diet (bottom up approach)? Or is it better to harvest the experience of various cultures whose diets appear to protect against premature morbidity and mortality (top down approach)? The first approach would rely on associations between food groups, foods and nutrients on the one hand, and incidence of specific diseases on the other, whereas the second would evaluate and quantify the effects of 'natural' diets on longevity. The first approach has been largely followed by mainstream nutritional epidemiologists,[1] whereas the second has been advocated by a few international experts.[2–4] This paper will concentrate on the first approach, with due acknowledgement of the insights and contributions of the second.

The bottom up approach

In the bottom up approach, nutritional factors may be identified as increasing or reducing the risk of a particular disease, through studies that are experimental, clinical or epidemiological in nature. Subsequently, considerations of risk, cost, benefit and freedom of choice determine whether no action, action at the individual level or action at the collective level is warranted.

The bottom up approach already has a place in the history of health sciences. The discovery of vitamin deficiency disorders and the identification of the essential nutrients have made a contribution to human health that could rank third after vaccines and water sanitation. These discoveries are not confined to the remote past. The relatively recent discovery of the role of folic acid in preventing neural tube defects and regulating homocysteine levels demonstrates that there is much to be learned from the study of metabolism and the role of various nutrients. Moreover, there are intriguing findings suggesting that micronutrients and non-nutrients, like certain antioxidant compounds, may reduce the risk for a number of chronic diseases at intake levels that are much higher than

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those usually associated with deficiency disorders.[5,6] Last, there are now reports that some micronutrients, particularly trace elements, may have adverse health effects.[7]

Other important contributions of the bottom up approach, which have their roots in physiology, experimental research or epidemiology, are those that have determined the role of nutrition-related conditions, like growth, obesity and physical activity, in health and disease. The issues surrounding these conditions also demonstrate that few nutritional initiatives are uniformly beneficial for all people. Thus, obesity has been shown to increase the risk for cardiovascular diseases and several forms of cancer, but also to reduce the extent of osteoporosis.[8] Growth and, ultimately, height are desirable attributes and are inversely related to risk of coronary heart disease, but they are also likely to increase the risk of several forms of cancer.[9] Physical activity and fitness, although central in the prevention strategies for coronary heart disease as well as osteoporosis and colorectal cancer, are also underlying a substantial fraction of home and leisure injuries.

The bottom up approach appears to be grounded in science, but scientists can make mistakes. For many years, hydrogenated fatty acids of plant origin were advocated as beneficial to the cardiovascular system, until recent evidence challenged that assumption,[10] and β-carotene has been taken in large supplementary quantities to increase defences against cancer on the basis of misinterpreted epidemiological evidence, until randomised trials failed to show an indication of a cancer preventing potential.[11] Another important drawback of the bottom up approach is the extreme difficulty for the scientific knowledge to be widely diffused and uniformly complied to. Citizens of northern European countries are as educated as those of any country and yet more than a third of them do not adhere to the best documented and best known nutritional advice: eat sufficient quantities of vegetables and fruits.[12]

A more serious objection to the bottom up approach may actually be identified in what is frequently thought of as the dream of molecular epidemiologists. The dream is that polymorphic genetic systems will be discovered and that nutritional and other environmental factors will be identified, which, in conjunction with various allelic forms, increase or reduce the risk of one or more diseases. Therefore, for every person, according to his/her genetic endowment, there will be a custom-made ideal diet and lifestyle to maximize life expectancy. However, this may be more a nightmare than a dream: people utilizing their genetic infrastructure, duly coded in a magnetic card, in order to make decisions about their food choices and ultimately their life.

In spite of these somewhat theoretical objections, most of our existing knowledge, which is translated in various guidelines or recommendations, relies on evidence accumulated through this approach, mainly with respect to the two most common categories of diseases; that is, cardiovascular disease and cancer. This knowledge will be summarized briefly.

Diet in relation to cardiovascular disease

With respect to cardiovascular disease (CVD), there is wide, although not universal, agreement that there is a monotonic positive association between obesity and the incidence of or mortality from coronary heart disease (CHD). This is largely mediated through the effects of obesity on hypertension, hyperlipidemia and manifestation of diabetes mellitus or, more generally, insulin resistance. It is also well established, although perhaps not generally recognized, that for a given body mass index, increased energy intake is inversely associated with CHD risk, as it implies a higher level of physical activity.[13]

Concerning the food groups, there is strong evidence that intake of vegetables, fruits and pulses reduces the risk of CVD, although there is no agreement to what extent the apparent protection is conveyed by fibre, homocysteine-reducing folic acid, antioxidant compounds in vegetables and fruits, the high quantities of olive oil that usually accompany high intake of vegetables and legumes, or the complementary reduced consumption of red meat and lipids of animal origin.[13,14]

Evaluating the effects of nutrients, rather than foods or food groups, on CVD risk illustrates how shifting from the empirical evidence to more abstract concepts increases uncertainty. The mainstream view is that dietary lipids that are high in saturated fatty acids and even more so trans-fatty acids increase the risk of CVD. On the contrary, polyunsaturated fatty acids have beneficial effects by reducing low-density lipoprotein (LDL) cholesterol, whereas some long chain *n*-3 fatty acids operate by modulating thrombotic processes and favourably affecting triglyceride levels. With respect to monounsaturated lipids, which are overwhelmingly present in olive oil, they do not only reduce LDL cholesterol, but they also increase the protective high-density lipoprotein (HDL) cholesterol.[14–16] Complex carbohydrates from foods rich in fibre do not adversely affect the risk for CVD, although their effect on HDL cholesterol is less favourable than that of monounsaturated lipids.[16] In contrast, refined carbohydrates substantially affect postprandial hyperglycemia and they appear to accentuate insulin resistance.

With respect to micronutrients and non-nutrients, there is converging, but not yet conclusive, evidence that vitamin E and folic acid are inversely associated with CHD risk.[17,18] It has also been established that moderate alcohol intake reduces the risk for CHD, probably by increasing serum levels of HDL cholesterol.[19] Salt intake, on the contrary, contributes to the elevation of blood pressure levels in susceptible individuals and thus to the increase of CVD risk.[20]

Diet in relation to cancer

The evidence on the role of diet in cancer aetiology has been critically summarized in recent reviews.[1,21] The effect of diet on cancer occurrence is not adequately understood, but appears to be complex (Table 1). With respect to food groups, vegetable consumption and, perhaps less definitely, fruit consumption have a beneficial effect on a broad spectrum of human cancer types. Red meat is closely linked to colorectal and, to a lesser extent, pancreatic cancer.

Among macronutrients, animal protein intake has been reported to increase the risk for colorectal cancer, while intake of saturated fat is positively associated with endometrial, prostate, colorectal, lung and kidney cancer. On the contrary, fibre intake appears to protect against cancer of the pancreas and the large bowel. There are also indications of a

Table 1. Risk implications for major forms of cancer by consumption of major food groups, macronutrient intake, exposure to selected non-nutrients and nutrition-related indicators

	Oral cavity	Nasopharynx	Oesophagus	Stomach	Large bowel	Liver	Pancreas	Larynx	Lung	Breast	Endometrium	Cervix uteri	Prostate	Urinary bladder	Kidney
Major food groups															
Vegetables	**Reduce**		**Reduce**	**Reduce**	**Reduce**	Reduce	Reduce	**Reduce**	**Reduce**	Reduce	Reduce	Reduce	Reduce	**Reduce**	Reduce
Fruits	**Reduce**		**Reduce**	**Reduce**	Reduce		Reduce	**Reduce**	Reduce	Reduce	Reduce	Reduce		Reduce	
Red meat					**Increase**		Increase								
Macronutrients															
Protein (animal)					Increase										
Fibre					Reduce		Reduce								
Saturated fat					Increase				Increase		Increase		Increase		Increase
Monounsaturated										Reduce					
Non-nutrients															
Alcohol	**Increase**		**Increase**		Increase	**Increase**		**Increase**		Increase					
Salt		Increase		**Increase**											
Nutritional covariates															
Height					Increase					**Increase**					
Obesity					Increase					Dual	**Increase**				Increase
Physical activity					**Reduce**					Reduce			Reduce		
Hot drinks			Increase												

Bold type indicates data are convincing.
Sources: Willett & Trichopoulos;[21] World Cancer Research Fund and American Institute for Cancer Prevention.[1]

protective role of monounsaturated lipids against breast cancer.[22]

Concerning micronutrients the evidence is largely insufficient. There have been recent studies indicating an inverse association of lycopene,[23] selenium[24] and vitamin E[25] with prostate cancer, while β-carotene supplements have been found to be ineffective against lung cancer risk.[11]

Consumption of large quantities of alcoholic beverages, particularly in conjunction with tobacco smoking, has been reported to increase the risk of cancer in the upper respiratory and digestive tract, whereas alcoholic cirrhosis frequently leads to liver cancer. There are also data suggesting that intake of smaller quantities of alcohol may be linked to the occurrence of breast and colorectal cancer. Among added substances, only salt appears to be an important contributor to stomach cancer. Moreover, intake of salty fish very early in life has been linked to the occurrence of nasopharyngeal cancer in southern Asia.

With respect to other nutritional covariates, excess energy intake in early life, which probably reflects reduced physical activity, appears to be responsible for the positive association between height and risk for breast cancer and possibly other cancers. Obesity in adult life, either due to excess energy intake or reduced expenditure, is an important cause of endometrial cancer, an established cause of postmenopausal breast cancer and a likely cause of cancers of the kidney and gall bladder. Evidence is also emerging that intrauterine growth is positively associated with some cancer types in the offspring, notably childhood leukaemia and breast cancer. Physical activity in adult life reduces the risk for colorectal cancer, possibly breast cancer and conceivably other cancers as well. Finally, the intake of very hot drinks has been found to increase the risk of esophageal cancer in central Asia and southern America.

The top down approach

In the top down approach, investigators look at populations that have been characterized by a particular traditional diet and a long adult life expectancy or low mortality from major groups of diseases. This approach, which has been championed by Mark Wahlqvist,[3,4] has similar philosophical foundations to the view expressed by several epidemiologists: that analytical epidemiological studies have compromised the larger public health objectives by concentrating on the trees rather than on the forest.[26,27] The latter view has been effectively criticized,[28] but its nutrition counterpart has more solid foundations. It can be argued that the traditional diet of a whole population has withstood the test of time, has accommodated social, economical and environmental factors, and has become an integral entity that is easily recognizable and adhered to. In other words, the top down approach is essentially ecological, with analytical elements focusing on the identification of the crucial beneficial components of the diet. This should be compared to the bottom up approach, in which the focus is as much on deleterious as on beneficial effects of particular foods or nutrients that need to be avoided or emphasized during the process of outlining a healthier diet. Keys and his colleagues are probably the first who used ecological evidence to illustrate the apparent advantages of the Mediterranean and the Japanese diets.[29] It is of interest that the three diets widely considered as healthy; that is, the

Mediterranean, the Japanese and the Chinese, have traditionally been high in plant foods.

The Mediterranean diet

The dietary patterns that prevail in the Mediterranean can legitimately be considered as variants of a single entity, the Mediterranean diet, as they have many common characteristics, most of which stem from the fact that olive oil occupies a central position in all of them. The Mediterranean diet can be defined as the dietary pattern found in the olive-growing areas of the Mediterranean region in the late 1950s and early '60s, when the consequences of World War II were overcome but the fast-food culture had not yet invaded the area. Other essential components of the Mediterranean diet are wheat, olives and grapes, and their derivatives. Total fat may be high, around or in excess of 40% of total energy intake as in Greece, or moderate, around 30% of total energy intake as in Italy. In all instances, however, the ratio of monounsaturated to saturated fats is much higher than in other places of the world, including northern Europe and North America.[30] Overall, the traditional Mediterranean diet may be thought of as having eight components: (i) a high monounsaturated to saturated fat ratio; (ii) moderate ethanol consumption; (iii) high consumption of legumes; (iv) high consumption of cereals (including bread); (v) high consumption of fruits; (vi) high consumption of vegetables; (vii) low consumption of meat and meat products; and (viii) moderate consumption of milk and dairy products.[31]

Mortality statistics from the World Health Organization covering the period 1960–90 indicate that death rates in the Mediterranean region were generally lower and adult life expectancy generally higher in comparison to the economically more developed countries of northern Europe and North America, particularly among men. Cause-specific mortality statistics, although less reliable than those for total mortality, indicate that the health advantage of the Mediterranean populations was mainly accounted for by lower mortality rates from coronary heart disease, as well as from cancers of the large bowel, breast, endometrium, ovary and prostate.

The international study launched by Keys in the 1950s was essentially ecological in design and focused on the role of diet in the occurrence of CHD.[29] The results of the Keys study were interpreted as indicating that saturated lipids could largely account for the variation of total cholesterol and, by inference, the incidence of coronary heart disease. Although it was clear that Mediterranean populations had a lower incidence not only of CHD, but also of other important causes of morbidity and mortality, the lasting conclusion was that Mediterraneans were privileged by having low rates of CHD simply because they consumed diets with low-saturated lipid content. Several authors, however, have pointed out that the Mediterranean diet is much more than a low-saturated lipid diet and has implications for diseases other than CHD.[32]

Three studies have recently been published evaluating the role of the Mediterranean diet as operationally defined through the eight components discussed previously. The first of these studies was conducted in Greece,[2] the second in Denmark[33] and the third in Australia.[34] All have shown that the Mediterranean diet has beneficial, substantial and statistically significant effects on longevity.

The Chinese diet

The Chinese diet is centred on rice. Large amounts of vegetables and fruits are also eaten, while foods of animal origin are eaten sparingly. Total protein intake amounts to about 10% of total energy intake and most of it comes from plant sources. Dietary lipid intake ranges from 6 to 24%, with an average of approximately 15% of total energy, and dietary fibre intake exceeds that recommended by Western guidelines (25–35 g per day).[35–38]

Cardiovascular disease mortality rates in China are generally low, particularly with respect to mortality from CHD, probably on account of the very low serum cholesterol levels, which are attributed to the limited dietary intake of fat and saturated fat.[39–42] Overall cancer mortality rates are also relatively low compared to the Western world, but the spectrum is very different with rates being high for cancers of the oesophagus, the stomach and the liver, but very low for cancers of the colon, the breast and the prostate.[43–45]

The Japanese diet

In the 1950s the diet in Japan was characterized by a high intake of carbohydrates, a moderate intake of protein and a very low intake of lipids. Rice and vegetables were consumed in high quantities, meat and dairy products in very low quantities, while potatoes, fruits, pulses and seafood were consumed in moderate quantities. Over the years, the Japanese have shifted towards a more Westernized pattern of diet, with increased intakes of meat, dairy products, eggs and lipids. In the 1970s, energy intake from carbohydrates, lipids and protein were estimated to be around 64%, 21% and 15% respectively.[46,47]

Mortality from coronary heart disease has been traditionally low in Japan compared to other industrialized countries, and is among the lowest in the world in spite of the high prevalence of smoking and hypertension.[46,48,49] The rate, however, has risen as has the intake of dietary lipids. A major concern remains the mortality from stroke, particularly haemorrhagic stroke, which is attributed to the high prevalence of hypertension. This is, in turn, attributed to the high salt intake and, possibly, to the extremely low serum cholesterol levels.[50,51] With respect to cancer, mortality rates for colon, breast and the prostate are very low.[48] The incidence of stomach cancer is high but decreasing, while that of lung and ovarian cancer are relatively low but increasing. Several foods in the Japanese diet have been implicated in the increase or decrease of risk for the various cancer sites,[52–56] but only the generally protective role of fruits and vegetables and the detrimental role of salt intake on the risk of stomach cancer are presently considered as established.

Combining the bottom up and top down approaches

Combining the two approaches has considerable advantages that can be best demonstrated by identifying errors that could have been avoided by such a combination. For many years, the guiding nutritional principle in the United States had been to reduce total fat intake, with little attention to the fact that Mediterranean populations who derive up to 40% of their energy from dietary lipids had traditionally very low incidence rates of coronary heart disease and several forms of cancer.[14,57] Moreover, the importance of excess energy intake in early life as a risk factor for a number of cancers had not

been recognized, in spite of the overwhelming animal evidence. This was until investigators contrasted Asian and Caucasian populations with sharp differences in the incidence of these cancers and energy intake in early life.[58] However, errors have also happened when evidence was derived exclusively from ecological associations, the most notable being the misidentification of total fat intake as a critical factor in the aetiology of breast cancer.[13,59] Although different patterns of disease occurrence may have different causes in different population groups, it is generally desirable to point to a factor as being responsible for both ecological associations and interindividual patterns within the same population. Thus, the hypothesis that consumption of olive oil may reduce the risk of breast cancer is strengthened by the fact that cohort and case-control studies in several countries have documented this association, but also by the fact that, among European countries, there is an inverse association between intake of olive oil and breast cancer rates.[22,48]

It should be obvious that the combination of the two approaches is far more promising. Even when technical problems make it difficult to combine the two approaches, investigators should use every opportunity to evaluate their analytical hypotheses through cross-cultural contrasts.

Choosing a diet: Longevity versus quality of life

As indicated in the beginning of this paper, there are no general criteria for assessing the best diet. Would people prefer a diet that increases longevity but also increases the risk of Alzheimer's disease, or would they opt for a diet that increases the risk of coronary heart disease and at the same time reduces the risk of cancer and senility? Would a population like to trade a diet which is compatible with their tradition for a diet that destroys this tradition but offers the hope for extended longevity? How should society confront the reality that a very healthy food (e.g. olive oil) may be in short supply or too expensive for the average consumer?

It is not the intention of these investigators to argue that nutrition should not be based on evidence — they strongly believe that it should. The evidence, however, must be broadly defined and not limited to biochemical, metabolic or simplistic epidemiological considerations. It should also weigh the symbolic and cultural value of food, the pleasure derived from it, as well as collective issues concerning equity, financial resources and preservation of the environment.

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