

## Chapter 2

# Public Health Benefits of Preventive Nutrition: Global Perspective

Walter C. Willett

### Key Points

- Staying lean and physically active throughout adult life has major health benefits.
- Diets low in the percentage of energy from fat have not been associated with lower risks of heart disease, cancer, or better long-term weight control.
- Avoiding industrially produced trans fat, keeping saturated fat low, and emphasizing unsaturated fats will minimize risks of heart disease and type 2 diabetes.
- Consuming grains in their original high fiber/whole grain form is likely to reduce risk of type 2 diabetes and heart disease. Consumption of sugary beverages increases risk of type 2 diabetes and probably heart disease.
- High intake of fruits and vegetables will help prevent risks of cardiovascular disease, but the benefits for cancer reduction appear modest.
- High consumption of alcohol and alcoholism have many adverse health and social consequences, and intakes as low as one drink per day or less are associated with greater risks of breast cancer. In contrast, moderate consumption of alcohol reduces risks of coronary heart disease and type 2 diabetes.

**Keywords** Diet • Nutrition • Health • Disease • Prevention

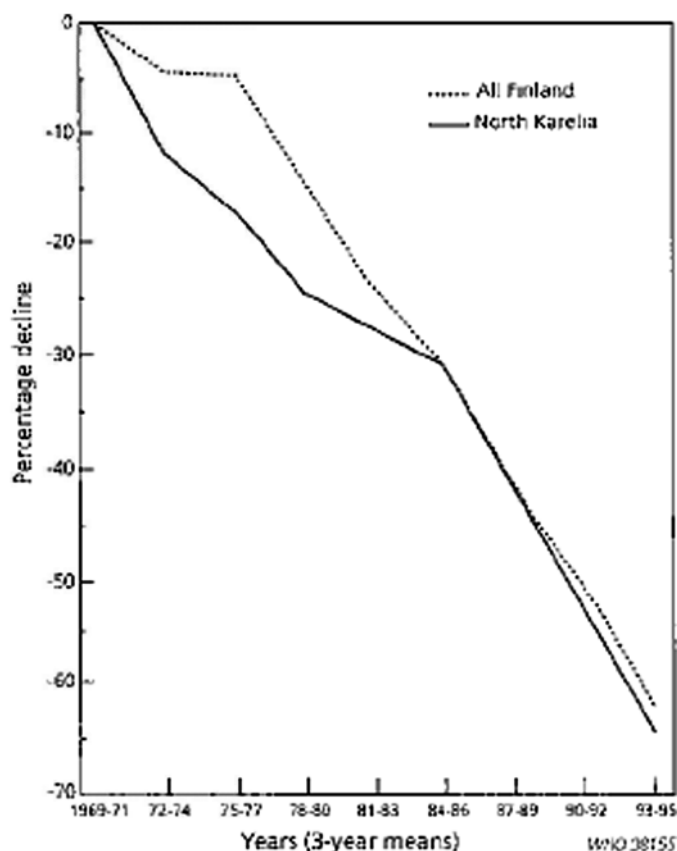
### Introduction

Until very recently, most populations had no choice but to consume foods that were produced locally, and availability was often extremely seasonal. This resulted in diets that were highly variable across the globe; for example, in some Arctic climates almost no carbohydrates, fruits, or vegetables were consumed and diets consisted mainly of fat and protein from animal sources. In other regions, populations subsisted on primarily vegetarian diets with the large majority of calories from carbohydrate sources. The fact that humans could survive and reproduce with such varied dietary patterns is a testimony to the adaptability of human biology. Yet, disease rates and overall mortality varied dramatically among these various population and formal studies of these relationships provided early clues about the importance of diet in human health and disease; these “ecological” studies are described in more detail below.

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**Fig. 2.1** Percentage decline in age-adjusted coronary mortality of 35–64-year-old males in Finland

In the last few decades, enormous changes have occurred in the diets of most populations. These changes were due to combination of increased wealth of some groups, new processing and preservation technologies, and greatly expanded transportation infrastructures. Collectively, these changes have allowed foods to be transported across and among continents and to be available virtually the whole year. At first, these changes globally were described as the “westernization” of diets because of increases in meat, dairy products, and processed foods. However, many of the more recent changes are not necessarily toward the diets of western countries, but instead emphasize refined starches, sugar and sugary beverages, and partially hydrogenated vegetable fats. These patterns, which have been described as “industrial diets” are usually the cheapest source of calories and they have permeated poor populations of both rural and urban countries around the world.

The recent changes in diets, along with changes in physical activity and tobacco use, have profoundly affected rates of disease, sometimes positively but often adversely. On the positive side, we have seen dramatic declines in rates of coronary heart disease (CHD) in many western populations, where this has been the leading cause of death. For example, in Finland, which at one time had the highest rates of CHD, mortality from this cause has declined by more than 80 % (see Fig. 2.1) [1]. On the other hand, in Japan, formerly a country with very low rates of colon cancer, rates of this malignancy have increased greatly and now have surpassed those of the USA [2]. Most importantly, at present an epidemic of obesity, cardiovascular disease, and diabetes has affected almost all the world’s populations, rich and poor [3]. This epidemic, which could reverse important gains in life expectancy [4] is likely to be the greatest challenge to public health in this century, unless an unforeseen problem emerges.

In this brief overview, I will address the components of diet and nutrition that have well-documented relationships to human health and disease. The focus is on the prevention of major illness in adults, and most of the evidence is based on studies of diet during midlife and later. A fundamental conclusion is that the vast majority of deaths due to coronary heart disease, stroke, diabetes, and some important cancers are preventable by healthy diets in combination with regular physical activity and avoidance of tobacco [5]. The relation of diet during pregnancy, infancy, and early childhood to childhood mortality, unfortunately still a major issue in many poor countries, has been extensively studied and is addressed in other chapters of this volume. This study builds on earlier reviews [6], emphasizing newer evidence and understanding.

## Sources of Evidence

Traditionally, animal experiments and small human metabolic studies formed the basis of dietary recommendations. Inevitably, the study of chronic disease in humans has required epidemiologic approaches. Initially, investigations compared dietary intakes and disease rates among populations in various countries, which were termed ecological studies. These analyses highlighted the large differences in disease rates worldwide and provided many hypotheses; however, such studies are limited because many other factors besides diet vary across cultures and the data are inherently aggregated. The next generation of studies was primarily case–control investigations, which mainly examined dietary factors retrospectively in relation to risk of cancer and other diseases. Not surprisingly, such studies have often been misleading due to biased recall of past diet and other artifacts. Now, large prospective studies of many thousands of persons are providing data based on both biochemical indicators of diet and dietary questionnaires that have been rigorously validated [7]. Prospective studies are less subject to biases resulting from the retrospective reporting of dietary intakes or the effects of disease on biochemical indicators. Micronutrient supplements can potentially be evaluated in randomized trials; however, trials of dietary interventions may often be unfeasible due to difficulties in maintaining compliance for the necessary long periods, which could be decades. Recent advances in molecular biology have yet to contribute substantially to dietary recommendations, but in the future these approaches may provide useful intermediary end points, allow the study of gene-diet interactions, and enhance our understanding of the mechanisms by which dietary factors influence disease. Ultimately, our knowledge is best based on a synthesis of epidemiologic, intervention, animal, and mechanistic studies.

## Specific Dietary Components

### *Dietary Fat*

Until recently, reviews and dietary guidelines have consistently emphasized reducing total fat intake, usually to 30 % of energy or less [8–10], to prevent coronary heart disease (CHD). The classical diet-heart hypothesis has rested heavily on the repeated observation that serum total cholesterol levels predict CHD risk; serum cholesterol has thus functioned as a surrogate marker of risk in hundreds of metabolic studies. These studies, summarized as equations by Keys [11] and Hegsted [12], indicated that, compared to carbohydrates, saturated fats and dietary cholesterol increase, and polyunsaturated fat decreases, serum cholesterol, whereas monounsaturated fat has no influence. These widely used equations, while valid for total cholesterol, have become less relevant as surrogate variables for CHD risk with the

recognition that the high-density lipoprotein cholesterol fraction (HDL) is strongly and inversely related to CHD risk, and that the ratio of total cholesterol to HDL is a better predictor [13, 14].

Substitution of carbohydrate for saturated fat (the basis of the American Heart Association diets during most of the last 30 years) tends to reduce HDL as well as total and low-density lipoprotein (LDL) cholesterol; thus, the ratio does not change appreciably [15]. In contrast, substituting poly- or monounsaturated fat for saturated fat reduces LDL without affecting HDL, thus providing an improved ratio [15]. In addition, monounsaturated fats, compared to carbohydrate, reduce blood sugar and triglycerides in adult onset diabetics [16]. Questions have been raised as to whether the reductions in HDL resulting from a high-carbohydrate diet have the same adverse effect as reductions caused by other factors [17], and some drugs that raise HDL have failed to reduce risk of CHD. Although the causal role of HDL is difficult to address directly, other factors that influence HDL levels, including alcohol, estrogens, obesity, smoking, exercise, and some medications, usually affect CHD risk in the predicted direction [18, 19].

The use of the usual cholesterol prediction equations has been further complicated by the recognition that different saturated fats vary in their influence on LDL levels: 18:0, stearic acid (the main fat in chocolate and a major saturated fat in beef fat), has little effect; 16:0, palmitic acid (the main fat in palm oil also found in beef fat), modestly increases LDL, and 14:0, myristic acid (the main saturated fat in butter and other dairy fats), most strongly increases LDL [20, 21]. However, this usually does not have practical importance in usual diets because intakes of the various saturated fats are strongly correlated with each other. However, stearic acid produced by the complete hydrogenation of vegetable oils is sometimes considered as a replacement for trans-fatty acids (see below). The assumption that stearic acid is “neutral” is not warranted as long-term studies are limited; the available evidence suggests that it may be more strongly related to risk of cardiovascular disease than other saturated fats [22, 23], and in a controlled feeding study high amounts of stearic acid (as in interesterified fat) had adverse effects on glucose regulation [24].

The optimal amount of polyunsaturated fat intake in the diet remains uncertain. The earlier metabolic studies predicting total serum cholesterol [11, 12] suggested that intakes should be maximized, and the American Heart Association has recommended intakes of 10 % of energy (compared to US averages of about 3 % in the 1950s and 6 % at present). Concerns have arisen from animal studies in which omega-6 polyunsaturated fat (typically as corn oil) has promoted tumor growth [25], and the possibility that high intakes of omega-6 relative to omega-3 fatty acids might promote coronary thrombosis [26, 27]. However, as described below, available evidence from human studies has not supported these concerns at levels of omega-6 fatty acid intake up to about 10 % of calories.

The relation to CHD incidence has been examined in many epidemiologic studies. In Keys’ pioneering ecological study of diets and CHD in seven countries [28, 29] total fat intake had little association with population rates of CHD; indeed, the lowest rate was in Crete, which had the highest fat intake due to the large consumption of olive oil. Saturated fat intake, however, was positively related to CHD in Keys’ study. In contrast to international comparisons, little relationship has been seen with saturated fat intake in many prospective studies of individuals [30–33] when compared to a similar intake of energy from carbohydrate or all other calories (which are primarily sugar and refined starch in most diets). Some studies, however, tend to support a modest association between dietary cholesterol and CHD risk [34], and inverse associations have been seen with polyunsaturated fat [30, 32, 35]. Similarly, dietary intervention trials have generally shown little effect on CHD incidence when carbohydrate replaces saturated fat, but replacing saturated fat with polyunsaturated fat has been associated with lower incidence of CHD [36–39]. In the Women’s Health Initiative (WHI), by far the largest trial to examine fat intake and incidence of CHD [40], 48,000 women were randomized to a low-fat diet or their normal diet. No effect was seen, which is consistent with epidemiologic studies because the type of fat was not modified, but any conclusion from this study must be tempered because the compliance with the low-fat diet was poor [41]. In contrast, to the WHI, a reduction in

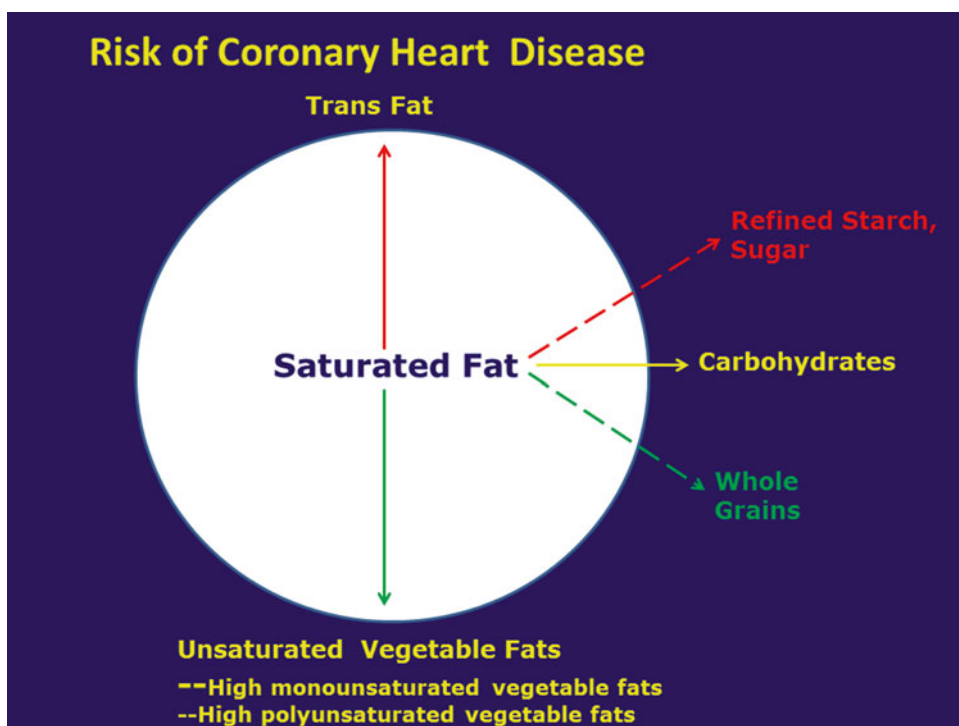
cardiovascular disease was observed in the Spanish PREDIMED study among those randomized to a Mediterranean diet with added nuts or olive oil when compared to those assigned to a low fat diet [42]. Although the study focused on increasing plant sources of monounsaturated fat, it is difficult to ascribe the benefits entirely to monounsaturated fats because this change was embedded in an overall Mediterranean diet.

Much confusion was generated by a recent meta-analysis of published papers concluding that saturated fat had no relation to risk of CHD, and that replacement of saturated fat with polyunsaturated fat is unsupported by evidence [43]. However, this meta-analysis was seriously flawed in many ways, including gross errors in data extraction, omission of important studies, and failure to cite previous analyses based on individual level data (see online comments regarding Chowdhury et al.). Most importantly, this analysis did not distinguish between substitution of carbohydrate for saturated fat versus substitution of polyunsaturated fat for saturated fat. As shown in a more complete and detailed analysis, the latter substitution is supported by prospective studies, randomized trials, and beneficial effects on CHD risk factors [35]. As shown in a more complete and detailed analysis, the latter substitution is supported by prospective studies, randomized trials, and beneficial effects on CHD risk factors [35]. Thus, the effect of saturated fat depends on the macronutrient to which it is compared (see Fig. 2.2).

Trans-fatty acids are formed by the partial hydrogenation of liquid vegetable oils in the production of margarine and vegetable shortening and can account for as much as 40 % of these products. Even higher levels of trans fats are found in “vegetable ghee,” which is widely used in the middle east and south Asia [44]. In the USA intake of trans-fatty acids from partially hydrogenated vegetable fats (which increased from nothing in 1900 to a peak of about 5.5 % of total fat by about the 1960s) has closely paralleled the epidemic of CHD during this century, in contrast to intake of animal fat, which has steadily declined over this period [45]. Trans-fatty acids increase LDL and decrease HDL [45–51], raise Lp(a), another lipid fraction implicated in CHD etiology [49, 52], and increase C-reactive protein and other inflammatory markers [53]. Positive associations between intake of trans-fatty acids and CHD have been seen among regions in the Seven Countries Study [54]. In the most detailed prospective study, trans-fatty acid intake was strongly associated with risk of CHD [32] and, as predicted by metabolic studies, this association was stronger than for saturated fat. The association between trans-fatty acid intake and risk of CHD has been confirmed in other prospective studies; in a meta-analysis, a 2 % energy increase in trans fat intake was associated with a 23 % increase in risk of CHD [51]. Higher intake of trans fat has also been associated with risk of type 2 diabetes [55], gall stones [56], dementia [57], weight gain [58], and an adverse effect on insulin resistance has been shown in a long-term study in monkeys [59].

Since 2005 the U.S. Food and Drug Administration has required that food labels include the trans fat content (see chapter by Mensink). Denmark has banned the sale of industrially produced trans fat, which was hardly noticed by consumers. In the USA the use of trans fats in restaurants has been banned by many cities, Puerto Rico, and the state of California. This has caused manufacturers to reformulate their products, and intake has decline by as much as 75 % [60], blood lipids have improved in national surveys [61], and cardiovascular disease is declining more rapidly in cities that first banned trans fats [62].

High intake of omega-3 fatty acids from fish reduces platelet aggregability and prolongs bleeding time [27], slightly reduces blood pressure [63], decreases serum triglycerides, but increases LDL cholesterol [64]. Fish consumption was associated with a greatly reduced risk of myocardial infarction (MI) in one prospective study [65] and in a randomized trial among postinfarction patients [66]. Subsequent data have been less supportive of a major effect of fish consumption on overall risk of CHD [67–69], but the benefits of omega-3 fatty acids appear to be primarily in prevention of fatal arrhythmias that can complicate CHD, rather than in prevention of infarction [70–72]. The amount of omega-3 fatty acids needed to prevent arrhythmia is remarkably modest—on the order of 1 g per day



**Fig. 2.2** Relation between saturated fat and risk of CHD depends on the macronutrient to which it is compared  
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or perhaps even less [72], and observational studies suggest that further increases are likely to have at most a small effect. Thus, adding supplements of omega-3 fatty acids to the diets of populations whose intakes are already high will likely have little effect. This is a likely explanation for some recent studies in which supplementation did not reduce serious cardiac arrhythmias [73]. Some plant oils, including soybean, rapeseed (canola), and flaxseed, also contain substantial amounts of the 18-carbon omega-3 fatty acid, alpha-linolenic acid (ALA). Because vast regions of the world consume little omega-3 fatty acids from any source, and the global supply of fish is limited, whether ALA can provide similar benefits as the longer-chain fish oils is a crucial public health issue. More data are needed, but available evidence suggests that higher intakes of ALA can prevent both fatal and nonfatal CHD [70, 74]; in eastern Europe, increases in rapeseed oil have been associated with rapid declines in CHD mortality [75].

### ***Dietary Fat and Cancer***

Another major justification for reduction of dietary fat has been anticipated decreases in the risk of cancers of the breast, colon and rectum, and prostate [76, 77]. The primary evidence has been that countries with low fat intake, also the less affluent areas, have had low rates of these cancers [77, 78]. These correlations have been primarily with animal fat and meat intake, rather than with vegetable fat consumption.

The hypothesis that fat intake increases breast cancer risk has been supported by most animal models [79, 80], although no association was seen in a large study that did not use an inducing agent [81].

Moreover, much of the effect of dietary fat in the animal studies appears to be owing to an increase in total energy intake, and energy restriction profoundly decreases incidence [25, 79, 81]. Many large prospective studies have been published [82–88], and little or no association has been seen in all. In a pooled analysis of prospective studies including 351,821 women and 7329 cases of breast cancer, the relative risk for a 5 % of energy increment in total fat was 1.00 (95 % CI 0.98–1.03) [86]. In the Nurses' Health Study, no decrease in risk was seen with less than 20 % of energy from fat [89], and with 20 years of follow-up and multiple measures of diet, there was no hint of any positive association with intake of total or specific types of fat [87]. In the AARP cohort a weaker positive association (RR = 1.11) was found for women with the highest compared to the lowest intake of fat that was statistically significant due to the large number of cases [88]. A similar weak association was seen in the large EPIC cohort, which appeared to be specifically related to intake of saturated fat [90]. In the WHI trial of dietary fat reduction, only a slight and not statistically significant reduction in risk was seen [91], and even this slight difference could be due to the transient loss of weight in the intervention group. Thus, over a wide range of intake, dietary fat consumed by middle-aged women appears to have little or no influence on breast cancer risk. However, higher intake of animal fat, but not vegetable fat, by young adult women has been associated with a greater risk of breast cancer before menopause, suggesting that some components of animal foods rather than fat per se may increase risk [92]. *The relation of fat intake during childhood to risk of breast cancer has been minimally studied.*

*As with breast cancer, prospective studies have not supported the hypothesized associations between dietary fat and risks of colorectal or prostate cancer [93]. However, positive association between consumption of red meat, and particularly processed meat, and risk of colorectal cancer has been seen in many prospective studies [93–96].* Also, consumption of red meat during adolescence or early adult life has been associated with a higher risk of breast cancer [35], although intake during midlife or later has not. These findings suggest that other components of red meat such as heat-induced carcinogens, the high content of heme iron, or nitroso compounds might be responsible for the elevated risk.

Although dietary fat does not appear to explain the high rates of breast, colon, and prostate cancer in Western countries, a massive body of evidence indicates that excessive body fat, the result of excessive energy intake in relation to physical activity, is an important risk factor for cancers of the endometrium, breast (after menopause), pancreas, colon, kidney, esophagus (adenocarcinoma), and some hematologic malignancies [93, 97, 98]. Excess body fat is now second only to smoking as a cause of cancer in the USA. This appears to be mediated through multiple mechanisms, including increases in circulating estrogen levels (breast and endometrial cancers), gastric reflux (esophageal cancer), insulin resistance (colon and pancreatic cancer), and possibly other pathways.

### ***Dietary Fat and Body Fatness***

In addition to being a major risk factor for cancer, overweight is an important cause of diabetes, cardiovascular disease, and other important diseases (see below), and short-term studies have suggested that reducing the fat content of the diet induces weight loss. However, population differences in weight do not appear to be due primarily to fat intake; in Europe, southern countries with relatively low fat intake have higher rates of obesity than Northern European countries [99]. Also, among 65 counties in China, no correlation was seen between body weight and fat intake, which varied from approx 6 to 30 % of energy [100]. Inconsistent associations have been observed in cross-sectional and prospective studies within countries, but such observations are particularly prone to distortion because subjects may alter their diets to modify their weight. In randomized trials of fat reduction, the optimal way to study this relationship, modest weight reductions are typically seen in the short term. However, in randomized



studies lasting a year or longer, reductions in fat from greater than 30 % of energy to 18–25 % of energy had minimal effects on overall long-term body weight [101]. Several recent randomized trials have compared very low fat, moderate fat, and low carbohydrate diets; weight loss over 1–2 years has been similar in all groups [102] or [103] on low fat/high carbohydrate diets. As predicted by shorter studies, cardiovascular risk factors have tended to be least desirable on low fat diets [103]. Very low fat intakes, less than 10 % of energy, in conjunction with a high volume of bulky food as consumed by some traditional societies, may induce weight loss [104], but long-term studies are needed. However, available evidence suggests that reductions in dietary fat over the ranges currently recommended will not have sustained benefits on body fatness, and that this is likely to have adverse metabolic effects.

What can we now say about dietary fat and health? In 1989, a major review concluded that dietary fat per se is not associated with risk of CHD [76]. This was generally ignored but subsequent studies have added further support for this conclusion and have also failed to support suggested major reductions in cancer and other risks. Both metabolic and epidemiological data strongly indicate that intake of partially hydrogenated vegetable fats should be minimized. Metabolic data and epidemiologic data suggest that saturated fat intake should be as low as reasonably feasible, but these data also suggest that the benefits will be minimal if carbohydrate rather than unsaturated fats replace the saturated fat. Definitive data are not available on the optimal intake of polyunsaturated fat, but intakes of up to at least 10 % of energy from linoleic acid (omega-6) have positive health benefits and no evidence of harm has been documented. Consumption of omega-3 fatty acids is essential and several servings of fish per week appear to provide adequate amounts for most healthy people. Whether ALA from plant sources can provide the same benefits as longer-chain fish oils is not fully resolved; this is a major global nutritional issue. Metabolic data as well as the experience of Southern European populations suggest that consuming a substantial proportion of energy as monounsaturated fat would be desirable. Although available evidence suggests that low total fat intakes have little benefit, consuming low amounts of red meat, especially processed meats, may decrease the incidence of colorectal cancer and possibly breast cancer.

## ***Vegetables and Fruits***

Recommendations to eat a generous amount of vegetables and fruits [76] are supported by epidemiologic studies of cardiovascular risk [105, 106]. Many early studies also suggested that high intake of these foods would greatly reduce the risk of a wide range of cancers [107, 108]. However, most of these studies were case-control investigations, and more recent cohort studies have tended to show much weaker—or no—relation between overall fruit and vegetable consumption and risks of common cancers, including those of the breast, lung, and large bowel [90, 93, 109, 110]. In a pooled analysis of large cohort studies, a modestly lower risk of estrogen receptor-negative (ER-negative) breast cancer was seen among women with greater intake of fruits and vegetables, although no relation was seen with overall risk of breast cancer [111]. This finding is supported by a pooled analysis in which prediagnostic plasma levels of beta-carotene and other carotenoids were inversely related to risk of breast cancer, again predominantly with ER-negative cases [112].

Plants contain numerous components that have potential anticancer activity [108]. Considerable evidence suggests that folic acid reduces risk of colorectal cancer [95, 113], but vitamin supplements and fortification are now greater sources in the USA than fruits and vegetables. Other chemical constituents of plants could reduce the formation of carcinogens, induce detoxifying enzymes, and block the effects of endogenous estrogens. Further details about the amounts of these substances in foods could permit more informative investigations as lumping fruits and vegetables all together has little biological rationale.

In contrast to the weakened evidence that high intake of fruits and vegetables reduces cancer incidence, evidence has been strengthened that greater consumption will reduce risk of cardiovascular



disease [105, 106]. High intake of fruits and vegetables reduces blood pressure [114], a major risk factor for cardiovascular disease, and potassium appears to be the primary explanation [115]. Evidence that elevated blood homocysteine is an independent risk factor for coronary heart and cerebrovascular disease [116–118], and that levels can be reduced by supplements of folic acid and vitamin B6 [119, 120] suggest one mechanism.

Some randomized trials of folate supplementation show a reduction in risk of stroke [121], although trials conducted in populations with high intakes of folate have not shown benefits of added supplement [122]. The evidence from randomized trials of folic acid in reduction of myocardial infarction has generally not supported the apparent benefit seen in epidemiologic studies [123]. However, this may be due to the existence of advanced coronary disease in most studies, the use of many drugs in these studies of ill patients, and the relatively short-term nature of these studies.

Suboptimal dietary folic acid, which is mainly obtained from fortified breakfast cereals, vegetables, and fruits, definitively increases risk of neural tube defects, the most common severe birth defect [124, 125] and may account for more than half of these cases. The effect of low folate intake may be particularly adverse among the approximately 10 % of the population who are genetically less efficient in utilizing the ingested form of this vitamin [126].

In both case–control [127] and prospective studies [128, 129], intake of dietary antioxidants, including the carotenoids lutein and zeaxanthin, and vitamin C has been inversely related to risk of cataracts. As cataract formation, which is increased by sunlight and cigarette smoking [130], involves the accumulation of oxidized and denatured proteins, this lesion may represent a convenient marker of long-term oxidative damage. High intake of lutein and zeaxanthin in the form of spinach has been associated with a decreased risk of advanced macular degeneration [131] and evidence for benefit in reducing progression of macular degeneration has been seen in a large randomized trial [132]. This is particularly notable because lutein and zeaxanthin are the carotenoids specifically concentrated in the macula, where they apparently play a protective role against photodamage [133].

## *Starches and Complex Carbohydrates*

As protein varies only modestly across a wide range of human diets, a higher carbohydrate consumption is, in practice, the reciprocal of a low-fat diet. For reasons discussed under the topic of fat, a high-carbohydrate diet may have adverse metabolic consequences. In particular, such diets are associated with an increase in triglycerides and a reduction in HDL cholesterol [20]. These adverse responses are aggravated in the context of insulin resistance [134, 135], which to some degree is highly prevalent in western populations. Although Asian populations had been thought to be at lower risk for insulin resistance and type 2 diabetes, much evidence now indicates that these populations, and also Hispanic and African populations have a higher risk of type 2 diabetes, probably due to genetic susceptibility, compared to European populations, given the same diet, activity level, and BMI [136]. This has enormous implications because many of these populations have traditionally consumed large amounts of carbohydrate, which was well tolerated as long they were lean and active, which may become deleterious in the background of lower activity and even modest amounts of weight gain.

Several reasons exist to emphasize whole grains and other less refined complex carbohydrates as opposed to the highly refined products and sugar generally consumed in the USA. Adverse consequences of highly refined grains appear to result both from the rapid digestion and absorption of these foods, as well as from the loss of fiber and micronutrients in the milling process. The glycemic response after carbohydrate intake, which has been characterized by the glycemic index, is greater with highly refined foods as compared to less-refined, whole grains [137]. The greater glycemic response owing to highly refined carbohydrates is accompanied by increased plasma insulin levels

and appears to augment the other adverse metabolic changes due to carbohydrate consumption noted above [137] to a greater degree than with less refined foods. Diets with a high-glycemic index or glycemic load (the product of dietary glycemic index and total carbohydrate intake) appear to increase the risk of noninsulin-dependent diabetes [138] and possibly risk of CHD, particularly among women with greater insulin resistance [139].

Fiber intake, particularly from grain sources, has consistently been inversely related to risk of coronary heart disease and type 2 diabetes [31, 140–142]. Risk of MI appears to be reduced by higher intake of dietary fiber from grains to a greater degree than can be explained by the effect of fiber on blood lipids alone [143]. Anticipated reductions in colon cancer risk by diets high in grain fiber have been difficult to document epidemiologically [144–146], although an inverse relation has been seen in Europe [147]. However, reduced constipation and risk of colonic diverticular disease [130] are clear benefits of such diets. The role of soluble fiber, found in oat bran and some other plant foods, in lowering blood lipids has been hotly debated; current evidence suggests that a small effect may exist with large intakes [148, 149].

The importance of micronutrients in the prevention of many chronic conditions, discussed below, has reemphasized the problem of “empty calories” associated with diets high in sugar and highly refined carbohydrates. In the standard milling of white flour, as much as 60–90 % of vitamins B6 and E, folate, and other nutrients are lost [150]; this may be nutritionally critical for persons with otherwise marginal intakes. In the USA, thiamin, riboflavin, folate, and niacin are presently replaced by fortification, but other nutrients remain substantially reduced. Fortification of grains with folic acid has not been implemented in many countries despite clear benefits for reduction of neural tube defects and probably stroke (see above). One reason expressed for not doing so is the potential promotion of existing neoplasias, especially those of the colon [151]. This concern was heightened by an apparent transient pause in the decline in incidence of colon cancer in the USA and Canada, but this may also have been due to increased diagnosis due to screening by colonoscopy. Importantly, in the USA there has been no suggestion of any increase in colon cancer mortality after folic acid fortification (<http://progressreport.cancer.gov/>); instead a sharp decline has occurred.

Sugar in the form of soda and other beverages is of special concern because of the large amounts consumed by many populations, and because this appears to result in excess energy intake due to failure to suppress satiety [152]. Not surprisingly, daily consumption of sugary beverages is associated with increased risks of type 2 diabetes [153, 154].

## ***Protein***

Average protein consumption in the USA and other affluent countries substantially exceeds conventional requirements [76] and adequate intake can be maintained on most reasonable diets, including those without animal products. High intake of animal protein can increase urinary calcium loss [155], contribute to homocysteinemia [156], and has been hypothesized to increase risk of various cancers [157]; however, there is little evidence for the latter effect. Substituting protein for carbohydrate improves blood lipids and blood pressure [158]. Also, because protein from foods is not consumed in isolation, the effects of these foods will depend mainly on the quality of fat and carbohydrate that they contain [159]. In a series of analyses of major protein sources, replacement of red meat with poultry, fish, nuts, and legumes has been associated with lower risks of coronary heart disease [160], diabetes [161], stroke [162], and breast cancer [35].

## ***Calcium, Vitamin D, and Dairy Products***

Recommendations to maintain adequate calcium intake [76, 163] and to consume dairy products on a daily basis [164] derive primarily from the role of calcium in maintaining bone health. Calcium supplements in conjunction with vitamin D have reduced fracture incidence in older adults [165, 166], but in such studies benefits of calcium cannot be distinguished from those of vitamin D. In a meta-analysis of randomized trials, no reduction in overall fracture risk was seen with supplemental calcium alone [167], and in a meta-analysis of prospective studies calcium intake over about 500 mg/day was not associated with lower risk of fractures. Uncertainty remains regarding the optimal intake. In the USA intakes as high as 1200 mg/day have been recommended for postmenopausal women at risk of fractures [163], which are difficult to achieve without supplements, but in the UK 700 mg/day is considered adequate for those over 19 years of age (<http://www.foodstandards.gov.uk/news/newsarchive/foodpromotionplans>). However, many populations have low-fracture rates despite minimal or no dairy product consumption and low overall calcium intake by adults [168], and for this reason the WHO considers 500 mg/day to be adequate intake [6].

Milk and other dairy products may not be directly equivalent to calcium from supplements, as these foods contain a substantial amount of protein, which can enhance renal calcium losses [155] and milk contains many other nutrients and hormones. Several prospective studies have directly addressed the relation of dairy product consumption to fracture incidence; with the exception of one small study [169]; higher consumption of calcium or dairy products as an adult has not been associated with lower fracture incidence [170–172]. At best, the benefits of high calcium intake are minor compared with those from regular physical activity [173–176]. Low-calcium intake has been associated with risk of colon cancer in large prospective studies [177]; evidence from a randomized trial that calcium supplementation modestly reduces colon adenoma recurrence adds important evidence of causality to the epidemiologic findings [178].

Although calcium intakes can be increased by a high consumption of greens and certain other vegetables, greatly increased intakes would be required for most women to achieve the high calcium recommended levels by diet without regular use of milk and other dairy products. Calcium supplements are an inexpensive form of calcium without accompanying calories or saturated fat. Thus, dairy product consumption can be considered an optional rather than a necessary dietary component. Enthusiasm regarding high dairy consumption should also be tempered by the suggestion in many studies that this is associated with increased risks of prostate cancer [93, 179, 180] and possibly ovarian cancer [181]. Whether an increased risk is due to the calcium, lactose, or endogenous hormones in milk remains uncertain.

Until recently, the consequences of low vitamin D status were thought to be limited to rickets, osteoporosis, and fractures. However, almost every organ has been found to have vitamin D receptors and inadequate vitamin D status has also been associated with greater risks of infections [182], some cancers [183, 184], multiple sclerosis [185, 186], muscle weakness [187], coronary heart disease [188], and other conditions. The optimal intake and blood level of vitamin D (25 OH vitamin D) have been topics of major debate; the IOM has set 50 nmol/mL as an adequate intake based on bone indicators [163], but if other outcomes are considered, optimal levels appear to be in the range of 70–100 nmol/mL [182]; even if the lower level is used, a majority of US residents have suboptimal vitamin D status, and among persons with dark skin this may be as high as 90 %. The alternatives for increasing blood levels are primarily to increase sun exposure, which if not done carefully will increase risks of skin cancer, or to take supplements; the levels of vitamin D naturally present in fish or fortified milk can prevent rickets, but for most people it is difficult to reach optimal levels from these sources.

## ***Salt and Processed Meats***

Reduction of salt (sodium chloride) intake will decrease blood pressure. Law et al. [189] have concluded that a 3-g/day decrease would reduce the incidence of stroke by 22 % and of CHD by 16 %. Although the decrease in risk of cardiovascular disease achieved by reducing salt consumption is small for most individuals, the overall number of deaths potentially avoided is large, supporting policies to reduce consumption, particularly in processed foods and by institutions. In several case-control studies, the consumption of salty and pickled foods has been associated with stomach cancer [93].

## **Body Weight**

Until recently, the issue of optimal body weight was controversial due to analyses that did not account for confounding influences of factors such as smoking (which is a strong cause of premature death and is also associated with low body weight) or the fact that many individuals, particularly at older ages, have low body weights because of chronic illness [190]. More detailed analyses indicate that middle-aged persons with a body mass index (BMI) even close to 25 kg/m<sup>2</sup> have a high prevalence of abnormal blood glucose, lipids, and blood pressure [191], and experience substantial increases in MI [192, 193], diabetes [194], hypertension [195], many cancers [97, 196], gallstones [197], and total mortality rates [98] compared to their leaner counterparts. Thus, the current guidelines based on a BMI range of 18–25 kg/m<sup>2</sup> are generally considered optimal, and the best health experience is achieved by avoiding increases in weight during adulthood [190]. As noted earlier, dietary fat composition over a wide range appears to have little relationship with weight maintenance; in contrast, low consumption of sugary beverages [152], trans fat [58], higher intake of dietary fiber [198], and overall diet quality such as a Mediterranean diet [103, 199] appear to be helpful for weight control. Regular physical activity and avoidance of extreme inactivity such as excessive television watching is crucial [200].

## **Alcohol**

Many adverse influences of heavy alcohol consumption are well recognized, but moderate consumption has both beneficial and harmful effects, greatly complicating decisions for individuals (see Chap. 29). Overwhelming epidemiologic data indicate that moderate consumption reduces risk of MI [201–203], one to two drinks a day decrease risk by approx 30–40 %. Although it has been suggested that this effect may be a result of antioxidants in red wine [204], similar protective effects for equivalent amounts of alcohol have been seen for all types of alcoholic beverages [205, 206]. On the other hand, modest positive associations with risk of breast cancer incidence have been observed in dozens of studies with even one alcoholic drink per day [207, 208], possibly because alcohol increases endogenous estrogen levels [209, 210] and interferes with folate metabolism [211]. The overall effect of alcohol, as represented by total mortality, appears beneficial up to about two drinks per day in men [212]. Overall, a similar relation with total mortality is seen among women, but no net benefit was observed among those at low risk of coronary heart disease because of age less than 50 years or lack of coronary risk factors [213]. Furthermore, the risk of transition from moderate alcohol consumption to addiction and uncontrolled drinking has not been well quantified.

## Vitamin Supplements

The most firmly established benefit of vitamin supplements, based on case-control, cohort, and randomized studies, is that folic acid supplements in the amounts contained in multiple vitamins can reduce the risks of neural tube defects by approximately 70 % [124, 214]. As noted above, correction of low folate levels can reduce the risk of stroke [121] and probably also the risks of coronary heart disease [123] and several cancers [215]. In a large randomized trial, a multiple vitamin/multimineral preparation modestly reduced total cancer incidence [216]; whether this was due to folate or other components is not known. The cardiovascular benefits of folate may be mediated in part through reductions of homocysteine, and in some populations correction of low levels of vitamin B-6 and B-12 as well as low folate may have similar benefits. Vitamin B-12 absorption declines with age, and supplements can prevent deficiency in older persons.

In prospective epidemiologic studies healthy men and women who consumed the highest amounts of vitamin E (mostly from supplements) had an approximately 40 % lower risk of MI compared to those having low vitamin E intakes [217, 218]. However, in randomized trials, mainly among patients with existing coronary heart disease, little benefit has been seen [219]. The apparent difference may relate to the study populations because persons with existing coronary disease were excluded from the epidemiologic studies, and they were typically on many drugs that could overlap in mechanisms with vitamin E. In a large trial among women without cardiovascular disease, a nonsignificant lower risk of coronary heart disease was seen with vitamin E supplementation, but vitamin E significantly reduced total cardiovascular mortality by 24 % [220]. The association between vitamin C and CHD risk has been inconsistent in prospective studies [218, 221]. Apart from a possible reduction in risk of cataracts [130], only limited evidence exists at present that high doses of vitamin C have substantial benefits.

Intake of preformed vitamin A (retinol) just above the RDA has been associated with excess risk of hip fracture in prospective studies [222, 223], possibly by competing with vitamin D at the receptor level, and elevated risks were seen for both use of multiple vitamins and specific supplements of vitamin A. In a more recent study, a modest positive association between vitamin A intake and risk of fractures was limited to those with low vitamin D intake, adding further evidence for an interaction with these vitamins [224]. The weaker association seen in this recent study may have resulted from reductions during the follow-up in the retinol content of breakfast cereals and multiple vitamins made in response to the evidence on fracture incidence. Serum levels of retinyl esters have not been associated with bone mineral density [225], but these findings are difficult to interpret because retinyl esters are highly variable and the degree to which a single measure represents long-term vitamin A intake is unclear.

In a randomized trial conducted in a region of China with low consumption of fruits and vegetables, a supplement containing beta-carotene, vitamin E, and selenium reduced incidence of stomach cancer [226].

Current evidence, although far from complete, suggests that supplements of folate and probably other vitamins, at the RDA level, contained in most nonprescription multivitamin preparations, have substantial benefits for at least an important, but unidentified, population subgroup, perhaps characterized by increased requirements or suboptimal diets. As intakes of many micronutrients appear marginal for many Americans [107, 227] the risks of using multivitamins low, and the cost of supplements is minimal (especially compared to that of fresh fruits and vegetables), the use of a daily or several-times-a-week multiple vitamin appears rational for the majority of Americans, given current knowledge. Multiple vitamins may have little benefit in someone consuming an optimal diet, but such persons are not common in the USA [228] and rare in low-income populations [229]. Further, inclusion of vitamin D, at doses of at least 1000 IU per day, will provide a critical nutrient that cannot be obtained in sufficient amounts by diet, although many people may require additional amounts as a separate supplement to reach adequate levels.

Vitamin E supplements do not benefit persons with established coronary heart disease, but for others at risk of CHD it can be rational to use these while waiting for further data. For other vitamins and minerals there is presently limited evidence of benefit of supplements over the RDA levels. Intake of vitamin A at levels above the RDA can potentially be harmful. In one study, intake of supplements containing more than 10,000 IU/d of preformed vitamin A was associated with risk of specific birth defects [230].

## Conclusions and Recommendations

Any set of dietary or nutritional recommendations must be made with the qualification that information is currently incomplete, and some conclusions may be modified with new data. Most importantly, the common major diseases in the USA develop over many decades, and large-scale nutritional epidemiologic studies have only begun in the last 30 years; a full picture of the relation between diet and disease will require additional decades of careful investigation. Nevertheless, combining metabolic, clinical, and epidemiologic evidence, several general recommendations that are unlikely to change substantially can be made to those who are interested in consuming a healthy diet.

1. Stay lean and active throughout life. For most individuals, body weight should not increase by more than 5–10 lb after age 21. Because most of us work at sedentary jobs, weight control will usually require conscious regular daily exercise as well as some effort to avoid overconsumption of energy, which can be facilitated by a high-quality diet.
2. Trans-fatty acids from partially hydrogenated vegetable oils should be avoided completely. These unhealthy fats can be replaced with a combination of vegetable oils that include a mix of monounsaturated and polyunsaturated fats.
3. Grains should be consumed primarily in a minimally refined, whole grain form and intake of simple sugars, especially as beverages, should be low.
4. Vegetables and fruits should be consumed in abundance (5 servings/day is minimal) and include green leafy and orange vegetables daily.
5. Red meat should be consumed only occasionally and in low amounts if at all; nuts and legumes as well as poultry and fish in moderation are healthy alternatives.
6. The optimal consumption of dairy products and calcium intake is not clear, and dairy products should be considered as optional. High consumption of milk (e.g., more than 2 servings per day) is not likely to be beneficial for middle-aged and older adults, and may increase risk of prostate and ovarian cancer. Adequate calcium intake may be particularly important for growing children, adolescents, and lactating women; supplements should be considered if dietary sources are low.
7. Unless one is extremely careful about a healthy food selection at every meal, consuming a daily RDA-level(DV) multiple vitamin containing folic acid and at least 1000 IU of vitamin D provides a sensible nutritional safety net. Because menstrual losses of iron are often not adequately replaced by iron intake on the low-energy diets of women in a sedentary society, it makes sense for most premenopausal women to use a multiple vitamin/multimineral that also contains iron. Pending further data, the use of a vitamin E supplement at 400–800 IU/day is reasonable for most middle-aged and older healthy persons as available evidence suggests that this may reduce risk of cardiovascular disease. Personal physicians should be made aware of any nutritional supplements that are being consumed in the event of possible interactions with medications or diagnostic tests. Further, use of supplements should not be considered as an alternative to eating a healthy diet because foods contain a wide variety of additional factors that are likely to contribute to good health.
8. Finally, be adventuresome in eating! Unfortunately, most of us in the USA are heirs to the rather monotonous Northern European dietary tradition centered on the consumption of meat, dairy products, and potatoes. Contemporary food processing has added to the deleterious effects of this diet



by the removal of dietary fiber and micronutrients through over-refining of foods, and has profoundly and adversely altered the biological effects of vegetable oils through the process of partial hydrogenation. To further aggravate matters, the worst aspects of diet tend to be the most heavily marketed and promoted. Fortunately, healthy diets do not have to be invented or discovered through new technological advances. Existing foods together with the lessons of various cultural models of eating based primarily around minimally processed foods from plant sources provide a means of achieving a diet that is healthy as well as interesting and enjoyable.

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