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Abstract

This review provides a scientific assessment of current knowledge of health effects of soybean oil (SBO) and sunflower oil (SFO). SBO and SFO both contain high levels of polyunsaturated fatty acids (PUFA) (60.8 and 69%, respectively), with a PUFA:saturated fat ratio of 4.0 for SBO and 6.4 for SFO. SFO contains 69% C18:2n-6 and less than 0.1% C18:3n-3, while SBO contains 54% C18:2n-6 and 7.2% C18:3n-3. Thus, SFO and SBO each provide adequate amounts of C18:2n-6, but of the two, SBO provides C18:3n-3 with a C18:2n-6:C18:3n-3 ratio of 7.1. Epidemiological evidence has suggested an inverse relationship between the consumption of diets high in vegetable fat and blood pressure, although clinical findings have been inconclusive. Recent dietary guidelines suggest the desirability of decreasing consumption of total and saturated fat and cholesterol, an objective that can be achieved by substituting such oils as SFO and SBO for animal fats. Such changes have consistently resulted in decreased total and low-density-lipoprotein cholesterol, which is thought to be favorable with respect to decreasing risk of cardiovascular disease. Also, decreases in high-density-lipoprotein cholesterol have raised some concern. Use of vegetable oils such as SFO and SBO increases C18:2n-6, decreases C20:4n-6, and slightly elevated C20:5n-3 and C22:6n-3 in platelets, changes that slightly inhibit platelet generation of thromboxane and ex vivo aggregation. Whether chronic use of these oils will effectively block thrombosis at sites of vascular injury, inhibit pathologic platelet vascular interactions associated with atherosclerosis, or reduce the incidence of acute vascular occlusion in the coronary or cerebral circulation is uncertain. Linoleic acid is needed for normal immune response, and essential fatty acid (EFA) deficiency impairs B and T cell-mediated responses. SBO and SFO can provide adequate linoleic acid for maintenance of the immune response. Excess linoleic acid has supported tumor growth in animals, an effect not verified by data from diverse human studies of risk, incidence, or progression of cancers of the breast and colon. Areas yet to be investigated include the differential effects of n-6- and n-3-containing oil on tumor development in humans and whether shorter-chain n-3 PUFA of plant origin such as found in SBO will modulate these actions of linoleic acid, as has been shown for the longer-chain n-3 PUFA of marine oils

Keywords

soybean oil, sunflower oil, linoleic acid, linolenic acid, polyunsaturated fatty acid, platelet, atherosclerosis, cholesterol, immune system, cancer, blood pressure

Disciplines

Food Biotechnology | Food Processing | Food Science | Human and Clinical Nutrition

Comments

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This review provides a scientific assessment of current knowledge of health effects of soybean oil (SBO) and sunflower oil (SFO). SBO and SFO both contain high levels of polyunsaturated fatty acids (PUFA) (60.8 and 69%, respectively), with a PUFA:saturated fat ratio of 4.0 for SBO and 6.4 for SFO. SFO contains 69% C18:2n-6 and < 0.1% C18:3n-3, while SBO contains 54% C18:2n-6 and 7.2% C18:3n-3. Thus, SFO and SBO each provide adequate amounts of C18:2n-6, but of the two, SBO provides C18:3n-3 with a C18:2n-6:C18:3n-3 ratio of 7.1. Epidemiological evidence has suggested an inverse relationship between the consumption of diets high in vegetable fat and blood pressure, although clinical findings have been inconclusive. Recent dietary guidelines suggest the desirability of decreasing consumption of total and saturated fat and cholesterol, an objective that can be achieved by substituting such oils as SFO and SBO for animal fats. Such changes have consistently resulted in decreased total and low-density-lipoprotein cholesterol, which is thought to be favorable with respect to decreasing risk of cardiovascular disease. Also, decreases in high-density-lipoprotein cholesterol have raised some concern. Use of vegetable oils such as SFO and SBO increases C18:2n-6, decreases C20:4n-6, and slightly elevated C20:5n-3 and C22:6n-3 in platelets, changes that slightly inhibit platelet generation of thromboxane and *ex vivo* aggregation. Whether chronic use of these oils will effectively block thrombosis at sites of vascular injury, inhibit pathologic platelet vascular interactions associated with atherosclerosis, or reduce the incidence of acute vascular occlusion in the coronary or cerebral circulation is uncertain. Linoleic acid is needed for normal immune response, and essential fatty acid (EFA) deficiency impairs B and T cell-mediated responses. SBO and SFO can provide adequate linoleic acid for maintenance of the immune response. Excess linoleic acid has supported tumor growth in animals, an effect not verified by data from diverse human studies of risk, incidence, or progression of cancers of the breast and colon. Areas yet to be investigated include the differential effects of n-6- and n-3-containing oil on tumor development in humans and whether shorter-chain n-3 PUFA of plant origin such as found in SBO will modulate these actions of linoleic acid, as has been shown for the longer-chain n-3 PUFA of marine oils. SBO and SFO are sources of linoleic acid and PUFA for prevention of gross EFA deficiency [recommended at 3% of energy (en) intake] and for prevention of heart disease (recommended at 8–10% en intake). In addition, SBO contains 7% linolenic acid with a linoleic to linolenic ratio of 7:1, which is within the recommended linoleic to linolenic ratio of 4:1 to 10:1.

Abbreviations: ADP = adenosine diphosphate, apo = apolipoprotein, BP = blood pressure, C18:2n-6 = linoleic acid, C18:3n-3 = α -linolenic acid, C20:4n-6 = arachidonic acid, C20:5n-3 = eicosapentaenoic acid, C22:6n-3 = docosahexaenoic acid, CHD = coronary heart disease, ConA = concanavalin A, DHA = docosahexaenoic acid, DMBA = 7,12-dimethylbenz[a]anthracene, EEC = European Economic Community, EFA = essential fatty acid, en = energy, EPA = eicosapentaenoic acid, ER = estrogen receptor, FA = fatty acid, FFA = free fatty acid, FFQ = food frequency questionnaire, HDL-C = high-density-lipoprotein cholesterol, IL = interleukin, LDL-C = low-density-lipoprotein cholesterol, LEAR = low erucic acid rapeseed, LPS = lipopolysaccharide, LT = leukotriene, MI = myocardial infarction, MUFA = monounsaturated fatty acid, NK = natural killer cell, PG = prostaglandin, PHA = phytohemagglutinin, P:S = polyunsaturated fat/saturated fat ratio, PUFA = polyunsaturated fatty acid, PV = peroxide value, PWM = pokeweed mitogen, RBD = refined, bleached, and deodorized, SBO = soybean oil, SFA = saturated fatty acid, SFO = sunflower oil, TBX = thromboxane, TC = total cholesterol, TV = total volatiles, VLDL-C = very-low-density-lipoprotein cholesterol

INTRODUCTION

Recent recommendations to decrease consumption of dietary fats and cholesterol while increasing the polyun-

saturated fatty acids (PUFA):saturated fatty acids (SFA) (P:S) ratio to reduce the risk of coronary heart disease have raised the public's interest in consumption of plant oils containing PUFA and no cholesterol. Many inves-

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Table 1. Typical Fatty Acid Composition (%) of Soybean, Sunflower, Corn, and Canola Oils [45]^a

	Soybean	Sunflower	Corn	Canola
16:0	10.9	6.2	11.4	4.1
18:0	4.0	4.7	1.9	2.1
18:1n-9	24.2	20.5	25.4	56.7
18:2n-6	54.1	69.0	60.9	26.8
18:3n-3	7.2	< 0.1	0.7	10.3
Total PUFA	60.8	69.0	61.6	37.1
Total MUFA	24.5	20.5	25.4	56.7
Total SFA	15.1	10.8	13.3	6.2

^a Values are normalized to total 100 ± 0.5%.

tigations indicate that, in addition to their effects on the cardiovascular system, PUFA can affect the immune system and platelet function, as well as the pathogenesis of chronic diseases such as cancer.

The physiological effects of plant oils are primarily due to their fatty acid (FA) composition, which varies depending on the specific oil. The health effects of canola and corn oil, and the need for inclusion in the diet of plant oils containing the essential fatty acids (EFA) linoleic and linolenic acid have been reviewed previously [1,2]. The present review evaluates the health effects of sunflower oil (SFO) and soybean oil (SBO) with respect to their composition, food uses, and cardiovascular effects, and their effect on platelet homeostasis, thrombosis, the immune system, and oncogenesis in animal and human models.

FOOD QUALITY AND SAFETY

Introduction

Soybeans (*soja max*) have an oil content of about 20% on a dry weight basis, which makes them a relatively good oil source. SBO, a minor edible oil in the 1940s, has become the dominant edible oil of the 1980s throughout the world, as well as in the United States [3]. The change in its economic position came about with improvements in industrial practices in handling SBO. SBO is now the major edible oil used in margarines (83%), salad and cooking oils (80%), solid shortenings (62%), and salad dressings (90%) [4]. In addition, SBO is used in many frozen foods and packaged dry mixes.

Sunflower oil is obtained from the seed of the plant *Helianthus annuus*, which is native to North America [5].

The plant is grown in large quantities in the Soviet Union, Argentina, China, the European Economic Community (EEC), and the United States [6]. Worldwide, the production of SFO is the largest among edible vegetable oils [5]. Generally, SFO is used as a cooking and salad oil and in the manufacture of shortenings and margarines [7]. High-oil seed sunflowers (40% oil) are generally grown for oil production, whereas low-oil seeds (about 30% oil) are grown for the confectionery, nut, and birdseed markets. SFO is used less frequently than SBO, probably because of its limited availability and higher cost.

Oil Composition

Crude SBO and SFO contain some (1.5–2.5%) of nonglyceride materials, consisting mainly of phosphatides which are removed during refining [7]. Refined SBO and SFO are composed mainly of triacylglycerols, about 99% for SBO and 99.2% for SFO [8]. Typical FA distributions for SBO and SFO are shown in Table 1. As listed, SBO has 60.8% PUFA, 24.5% monounsaturated fatty acid (MUFA), and 15.1% SFA. Northern grown SFO has 69.0% PUFA, 20.5% MUFA, and 10.8% SFA. The major difference between SBO and SFO is the amount of linolenic acid (C18:3n-3) synthesized by leaves and seeds. SBO contains almost 7%; SFO contains < 0.1%. [Note: The marine oil n-3 PUFA that has been investigated for antihypertensive and antithrombotic activity (see below) has a longer chain and is composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).] Northern grown SFO is most common and is referred to as SFO. The P:S ratio is about 4.0 for SBO and 6.4 for SFO. The PUFA levels of SBO and SFO compare favorably with other major vegetable oils

consumed in the United States [8]. Only safflower oil has a higher PUFA level than SBO and SFO.

The MUFA levels of SBO and SFO are intermediate among vegetable oils, with olive, canola, palm, peanut, and sesame oils and cocoa butter having higher levels. Canola oil has a MUFA level of 56.7%, corn oil and SBO have MUFA levels of 24 to 25%, and SFO and cottonseed oils are about 19%. Other oils such as coconut, palm kernel, safflower, and wheat germ oils have MUFA values that are less than 16%. Typical FA values are shown in Table 1.

Genetic Improvement

Recent research on genetic alterations of FA in SBO and SFO has resulted in the development of many specialty oils produced to improve the nutritional properties and/or stability of the oils. Some of these SBOs and SFOs are being processed and used by the food oil industry, so that, in the future, consumers will need to note not only the type of vegetable oil they are purchasing but also whether it is a specialty oil with an altered FA pattern.

In the case of SBO, the linolenic acid content has been reduced to 2% in some experimental oils [9-12]. Other experimental SBOs have been produced that provide one or more of the following FA alterations: high oleic, high palmitic, low palmitic, or high stearic [13,14]. In addition, experimental soybeans have been developed with reduced levels of lipoxxygenase, an enzyme thought to produce off-flavors in soybeans and soybean oils under certain conditions [15].

The FA composition of SFO and SBO is naturally variable, depending upon climate, temperature, genetic factors, and, in the case of SFO, the position of the seed in the flower head [5,16]. In fact, few vegetable oils reflect the influence of these factors as significantly as SFO. Average linoleic and oleic acid content of northern SFO (grown at about 39° latitude) compared with southern grown SFO ranged from 68 to 44% and 19 to 47%, respectively [5]. The warmer the climate, the lower the linoleic and the higher the oleic acid content become. Varieties of SFO have been developed that will produce a high oleic acid content when grown in cold climates [17]. It is difficult to know the exact FA content of SFO without actually measuring it. In general, most SFO produced in the United States is grown in northern climates, so the typical FA profile listed in Table 1 for northern grown SFO is fairly accurate for SFO used in the United States.

Most vegetable oils are refined, bleached, and deodorized (RBD), which removes most impurities before consumption. However, RBD oils retain small

amounts of trace components which are often measured as unsaponifiable materials, free fatty acid (FFA), and trace metals. In one report, the FFA concentration in fresh RBD oils was approximately 0.07% in both SBO and SFO, which is similar to most good quality edible vegetable oils [8]. Other research studies report FFA values of less than 0.07% in fresh SBO [18,19] and SFO [5].

Unsaponifiables that may be present in RBD oils include sterols, hydrocarbons, waxes, and tocopherols (vitamin E). Total unsaponifiables of RBD oils were measured at 1.0% in SBO and 0.8% in SFO [8]. Other researchers compared amounts of a group of materials (sterol esters and hydrocarbons) in SBO, SFO, and corn oil and found 0.3, 0.7, and 1.3% of the material, respectively [20].

Tocopherols are excellent natural antioxidants that protect oils against oxidative rancidity. The α form has the highest biological vitamin E activity, whereas the γ form has been reported to have the highest antioxidant activity [21]. SFO and SBO were reported to have 0.07% total tocopherols, the same level reported in corn and cottonseed oils [8]. The distribution of tocopherols was split between 0.01% α and 0.06% γ in SBO and 0.05% α and 0.01% γ in SFO. In another report, RBD SBO was reported to contain 0.11-0.18% total tocopherols [19]. Subsequent research reported α -tocopherol levels of 0.011% in SBO and 0.062% in SFO and total tocopherol levels of 0.11% for SBO and 0.07% for SFO [22]. The tocopherol levels in any RBD oil will vary depending upon the conditions during processing as well as natural variations in the original sources.

The sterols found in SBO are similar to those found in SFO and include β -sitosterol, stigmasterol, campesterol, δ -5-avenasterol, and δ -7-stigmasterol [20,23]. Total sterol content was reported to be 0.29% for SBO and 0.39% for SFO. These sterols are found in most major vegetable oils, although the amounts differ among species and samples. SBO, but not SFO, also contains a trace of cholesterol and brassicasterol, as do most other vegetable oils [23]. Plant sterols are only minimally absorbed by humans, and their ingestion appears to inhibit intestinal cholesterol and bile acid absorption [24]. When present in larger amounts than cholesterol, some sterols, including δ -5- and δ -7-avenasterol, have demonstrated antioxidant activities at frying temperatures [25,26].

SFO has a fairly high wax content, which differs with seed variety, geographical growing area, and seasonal growing conditions [27]. The waxes are generally removed from SFO by winterization (chilling and filtering), so that they do not cause cloudiness in RBD oil when refrigerated. This "dewaxed" SFO generally contains less than 80 ppm wax [27,28].

Most trace metals in RBD oil are removed during processing. It is particularly important that copper and iron be removed because they greatly reduce the oxidative stability of oil [29]. Evans et al [30] reported low iron levels of 0.06–0.20 ppm, and copper levels of undetectable to 0.01 ppm in RBD SBO. Jung et al [18] reported an iron level of 0.27 ppm in RBD SBO. Warner et al [31] measured iron in SFO at 0.52–0.62 ppm and in SBO at 0.52–0.83 ppm. DuPlessis et al [32] reported copper levels of 0.1 ppm in SFO.

Metals such as lead and cadmium are of particular concern due to their toxicity and their supposed link to coronary heart disease and hypertension [33]. Thomas [34] reported allowable low levels of lead in SBO (0.08 ppm) and SFO (0.10 ppm) and of cadmium in SBO (0.008 ppm) and SFO (0.007 ppm).

Both SBO and SFO are pale yellow in appearance and typically have a bland flavor when they are properly processed and fresh. The high content of PUFA in both oils, however, makes them susceptible to oxidative deterioration and thus reduced flavor stability. In particular, the 7% concentration of linolenic acid in SBO increases its oxidative instability [35]. Nonetheless, unhydrogenated SBO has been shown to be stable during storage and use at room temperature when handled properly, possibly because of naturally occurring tocopherols, which has led to the marketing of "natural" (unhydrogenated) soybean salad oils [36].

Snyder et al [37] compared the stabilities of eight vegetable oils. Samples of each oil were stored at 60°C for 8 and 16 days in clear glass bottles containing air in the headspace. The bottles were loosely capped with corks lined with cellophane paper. They measured the development of peroxide values (PV) and total volatiles (TV), both measures that increase with increasing oxidation of the oils. Peroxides are formed during one of the first steps of lipid oxidation, whereas volatiles are a breakdown product from the peroxides. After 8 days of storage, SBO and peanut oil had a PV of 7, and canola oil had a PV of 5. Cottonseed and corn oils had PVs of 9 and 10, respectively, whereas SFO had a PV of 11. Olive and safflower had higher PVs (> 7). By day 16, SBO still had a lower PV than did SFO, peanut, and safflower oils. After both 8 and 16 days of storage, the TVs of SBO were intermediate in value, with canola, corn, olive, and peanut oils having lower TVs, and SFO, cottonseed, and safflower oils having higher TVs. The PVs and TVs all were higher for safflower oil than for SFO and, for some values, SFO had lower (better) numbers than peanut and olive oils. In general, the PV and TV increases were related to the linoleate content. Minor constituents of the oils were not measured.

By measuring PV during storage at 98°C, SBO was just slightly less stable than canola and corn oils and more stable than SFO, which was more stable than butterfat [38]. The most stable fats and oils were olive oil, peanut oil, and lard. Warner et al [31] compared the flavor and oxidative stabilities of SBO, SFO, and low erucic acid rapeseed (LEAR) oil under a variety of storage conditions. In the dark, SBO was most stable; however, in the light, SFO was most stable. Light stability is largely affected by the presence of minor constituents such as metals and pigments (carotene and chlorophyll), which were not controlled in that study. TVs were significantly lower for SBO and LEAR oil than for SFO. In general, each oil type varied in flavor and oxidative stability depending on the conditions. SBO is now bottled in plastic, rather than glass containers, where it has been shown to be more stable to light-induced oxidation [39].

When fats and oils are heated to high temperatures, many chemical changes occur, including formation of volatile and nonvolatile degradation products. The higher the concentration of PUFA, the more susceptible it is to those changes. The temperature at which the volatiles begin to rise is called the smoke point and is an indicator of frying stability. Most major vegetable oils, including SBO and SFO, have smoke points around 230°C [40]. Also of importance are the nonvolatile components that are formed, including polymeric, dimeric, and monomeric acylglycerols and FA. Ingestion of these components has been linked to toxicity in some animal studies. In heating tests, SBO and SFO formed higher amounts of dimeric and oligomeric triacylglycerols than did corn oil and butterfat [41]. Corn oil, however, produced more monomeric compounds. Canola oil was similar to SBO and SFO in the amount and type of polymers formed.

In general, polyunsaturated oils such as SBO and SFO are partially hydrogenated to improve high-temperature stability [5,42]. This processing alters the FA composition, making the oils more saturated and more thermally stable. The exact FA makeup of the partially hydrogenated oils varies from product to product depending upon the intended use [43]. For example, margarines have the following ranges of FA [44]: all-vegetable stick margarines contain 14–35% PUFA, 45–66% MUFA, and 18–21% SFA; animal and vegetable blend stick margarines contain 9–19% PUFA, 46–52% MUFA, and 29–40% SFA; tub margarines generally contain 29–48% PUFA, 33–52% MUFA, and 17–19% SFA; spreads vary considerably, containing 27–50% PUFA, 32–54% MUFA, and 17–20% SFA.

CARDIOVASCULAR EFFECTS

Blood Pressure

Hypertension has been linked to increased incidence of cardiovascular and cerebrovascular disease [46]. Population-based studies have suggested an association between blood pressure (BP) and the type of dietary fat ingested [47-53]. Since dietary FA patterns recommended as therapy for elevated plasma lipids (see next section) are consistent with those patterns implicated in reducing BP, the area has received close scrutiny.

Early work suggested an inverse relationship between BP and dietary PUFA intake as summarized by Sacks et al [53] and Beilin et al [54]. This conclusion was based on an analysis of prospective studies and epidemiologic surveys. Early experimental short-term studies both supported and refuted the initial hypothesis, making interpretation of the data difficult. The determination of adipose tissue FA patterns has been used in an attempt to circumvent the problem associated with collecting accurate long-term dietary data on FA intake. The data suggested that BP is inversely correlated with linoleic acid [55-57], and, in one case, α -linolenic acid [58] content of adipose tissue. Since other studies failed to identify such relationships [59,60], some investigators focused on specific population groups. Groen et al [52] assessed the prevalence of hypertension in Trappist monks who consumed a vegetarian diet and Benedictine monks who consumed an omnivore diet. They reported that the incidence of diastolic BP > 95 mm Hg was 12% in Trappists and 30% in Benedictines. A slightly elevated systolic BP in Trappists was attributed to their higher mean age and frequency of obesity. Sacks et al [53] investigated the relationship between the intake of animal products and BP in members of communes adhering to a macrobiotic diet. They concluded that the consumption of animal protein was positively correlated with both systolic and diastolic BP. Rouse et al [50] reported that Seventh-Day Adventist vegetarians in Australia had lower BPs than nonvegetarian control subjects. Oster et al [47] reported that dietary intake of linoleic acid was negatively correlated with BP in a population of carefully studied males in Heidelberg, Germany. Work by Salonen et al [48] identified a positive association between BP and SFA intake in a cohort of males in eastern Finland. Subsequent work involving more detailed dietary assessments confirmed this finding and demonstrated a negative association between BP and linolenic acid intake in males with no history of hypertension [49]. After reanalyzing data from the Seven Countries Study [61], Sacks [62] recently concluded that mean systolic BP for populations was significantly correlated with

mean intake of saturated but not total fat. On the basis of data from the Health and Nutrition Examination Survey, Gruchow et al [63] found no relationship between BP and consumption of PUFA. Similar results were reported by Elliott et al [64] after analyzing data from the Caerphilly Heart Study. Joffres et al [65] reported no association between BP and PUFA intake in males of Japanese ancestry living in Hawaii. In summary, some epidemiological studies have suggested that diets containing higher proportions of food from vegetable origin (which have a higher PUFA content than omnivore diets) may be associated with lower BP, but the data are not conclusive.

Clinical trials investigating the effect of PUFA on BP have also yielded conflicting data. Iacono et al [66] reported that increasing the dietary P:S ratio in male and female subjects resulted in a significant decrease in systolic BP when subjects were fed diets containing either 25 or 35% of calories as fat. Significant decreases in diastolic BP were observed only on the lower-fat diet. Rouse et al [67] reported that switching healthy omnivore subjects to a lacto-ovo-vegetarian diet for 6 weeks resulted in significant decreases in both systolic and diastolic BP. After 6 weeks of a high-PUFA/low-fat diet, Iacono et al [68] and Pietinen et al [69] reported that systolic and diastolic BP declined. These changes were more pronounced in subjects with the highest initial BP. When subjects were switched back to their habitual diet, BP reverted to original levels. Puska and co-workers [70], in a larger group of subjects from the same geographic region, confirmed these findings and reported that alterations in salt intake had no effect on BP. In contrast, Sacks and co-workers [71,72] found that adding oils high in PUFA to the diet did not alter BP. Margetts et al [73] could not distinguish between the effects of PUFA and fiber on lowering BP during the consumption of a vegetarian diet. Current indications are that nutrients other than dietary fat or in combination with dietary fat that are relatively high in a vegetarian diet may be responsible for the hypotensive effects initially attributed to PUFA.

Much of the confusion over the effects of PUFA on BP arises from the frequent use of normotensive study subjects, the alteration of multiple variables simultaneously, the relatively short duration of studies, and the frequent lack of an appropriate control group. Additionally, virtually no information is available on the n-3 PUFA content of those diets associated with decreased BP. This point is important, because recent evidence confirms earlier reports that longer-chain n-3 PUFA derived from marine sources can result in decreased systolic and diastolic BP [74]. The relationship between PUFA consumption and BP observed in epidemiological

studies deserves further carefully controlled investigations.

Plasma Lipids

Epidemiological data have established a positive correlation between elevated levels of plasma cholesterol and the incidence of heart disease in populations [75–79]. From these studies a relationship between the consumption of SFA and coronary heart disease (CHD) was suggested. Subsequent primary and secondary prevention trials demonstrated that dietary modification can reduce plasma lipids [80–85] and in some cases the incidence of CHD [80–83]. These outcomes were primarily achieved by lowering dietary SFA intake and/or increasing PUFA. Equations have been derived which predict the change in plasma cholesterol expected from alterations in the SFA and PUFA content of the diet [79,86,87].

Current guidelines suggest that dietary modification can be used as the first approach to reducing plasma cholesterol in those persons identified as having elevated plasma lipids [88,89]. Evidence suggests that the most effective dietary modifications involve a decrease in the SFA and cholesterol content of the diet [70,71,86]. A recent report by the National Cholesterol Education Program Expert Panel [89] recommends that hypercholesterolemic patients consume a diet containing less than 30 en% fat and that, of this, less than 10 en% be derived from SFA, 10–15 en% from MUFA, and less than 10 en% from PUFA. Furthermore, it is recommended that cholesterol intake be limited to less than 300 mg/day. This diet has now been recommended for the general population by the US Surgeon General. Further restrictions in SFA intake to less than 7% of calories and cholesterol to less than 200 mg/day are recommended when an inadequate response in terms of low-density-lipoprotein cholesterol (LDL-C) lowering is achieved in hypercholesterolemic subjects. These recommendations are aimed at reducing the risk of CHD in the US population.

The literature is replete with clinical trials which demonstrate that decreasing SFA intake and/or increasing PUFA in the diet of humans results in a decrease in plasma cholesterol levels [86,90–99]. Even when expressed as a percent of total cholesterol (TC), reductions in plasma cholesterol concentration vary greatly among studies, due to differing genetic backgrounds, initial plasma lipid levels, age and sex of subjects, relative restrictiveness of the experimental diet, and variation in the baseline diet to which the modified diet is compared. Whether the diets are prepared and provided to the subjects in a controlled environment or dietary modification

is achieved by dietary counseling may also influence the magnitude of the change. Some of the intervention trials have been summarized previously [100–102].

SFO or SBO are frequently incorporated into study diets to increase the P:S ratio. Kohlmeier et al [103] have reported that altering the P:S ratio of the diet by incorporating SFO into diets of male subjects with mild hypercholesterolemia resulted in decreased TC and LDL-C, with no change in triglycerides or apolipoprotein (apo) A-I and A-II. In these studies there was no change in the clearance of triglyceride-rich lipoproteins as measured by fat tolerance test; however, there was increased excretion of endogenous sterols as assessed by fecal sterol balance. This change in sterol excretion correlated with the magnitude of change observed in plasma cholesterol. Despite the increased relative concentrations of bile acids and decreased relative concentrations of phospholipids and cholesterol in bile, the lithogenic indices of fasting gallbladder bile (risk of developing calculi) was not significantly changed [104].

Kromhout et al [96] found that subjects with stable angina pectoris who consumed a diet rich in linoleic acid for 2 years maintained reduced plasma cholesterol. Riemersma et al [105] reported an inverse relationship between adipose tissue linoleic acid and CHD, supporting the hypothesis that consumption of a high-PUFA diet has beneficial effects with respect to diet and adipose tissue FA. Similar changes have been reported by Shepherd et al [106].

Kuusi et al [107] investigated the relationship of diets with increased P:S ratios on plasma FA levels. A negative correlation was identified between the percent of linoleic acid in serum cholesteryl ester and the magnitude of the change in TC and LDL-C. Shepherd et al [106] reported that the percent of linoleic acid in very-low-density-lipoprotein cholesterol (VLDL-C), LDL-C, and high-density-lipoprotein cholesterol (HDL-C) increased when the PUFA content of the diet was increased at the expense of SFA.

Weisweiler et al [92] showed in one of the few studies on the effects of PUFA in females that increasing the SFO content of the diet and decreasing sources of saturated fat resulted in a decrease in TC, LDL-C, VLDL apo B, and LDL apo B. Similar results were observed at the same P:S ratio when the total fat content of the diet was decreased, with the additional effect of increasing the lipid:protein ratio of VLDL. Mensink and Katan [95] reported that diets enriched in SFO resulted in a decrease in TC in both males and females, a change that was less pronounced than that seen when olive oil was incorporated into the diet.

Somewhat controversial is the effect of diets with high P:S ratios on HDL-C. The majority of work indi-

cates that high PUFA diets result in a decrease in HDL-C [95,100,107,108], although the effect is not always consistent [92,94,96,106]. Gender effects may complicate this issue [95], as does the decrease in dietary SFA intake frequently accompanying a relatively high PUFA diet. The mechanism responsible for interindividual differences in HDL-C is distinct from that resulting in differences in HDL-C due to diet. Therefore, reduced HDL-C levels induced by high-PUFA diets may not predispose subjects to the same risk as those persons with inherently low baseline HDL-C levels [109]. This area clearly needs further investigation.

The reduction of plasma cholesterol by PUFA is multifactorial. Increased levels of dietary SFO vs palm oil resulted in an increased catabolic rate of VLDL [110]. Concomitant with the observed decrease in plasma triglyceride in subjects fed the high-PUFA diet was increased postheparin plasma lipoprotein lipase activity [58]. PUFA feeding has been shown to result in decreased apo B synthesis rates [99]. Shepherd et al [111] reported that increasing the PUFA content of the diet resulted in increased catabolism of LDL-C and reduced rates of apo A-I synthesis. Cortese et al [99] reported that feeding hyperlipidemic subjects a high-PUFA diet resulted in lower LDL concentrations induced by lower synthesis rates of VLDL and LDL apo B. No consistent effect on the fractional catabolic rates of LDL and VLDL apo B were observed.

A recent review of the effects of n-3 PUFA derived from marine oils concludes that increasing the consumption of EPA and DHA exerted little effect on TC, LDL-C, or HDL-C [112]. In a comparative study, lipid-lowering responses were reported from fish oil consumption, but not from linseed oil, which is relatively high in α -linolenic acid, the plant source of n-3 PUFA [113].

Increasing the PUFA and/or decreasing the SFA content of the diet consistently results in a lowering of plasma cholesterol and LDL-C, frequently accompanied by a decrease in HDL-C. Areas open for investigation with the intent of defining an optimal diet for decreasing plasma LDL-C levels include determining the most effective total fat content of the diet, as well as the amounts and types of various dietary FA. Baseline diets should be optimized so that changes observed on different low-fat/cholesterol diet regimes can be meaningfully evaluated. Similarly, more attention needs to be given to the time period necessary for stabilization of all parameters monitored in a dietary fat/cholesterol trial. Given the time course of development of CHD, it is unlikely that long-term studies actually documenting changes in the incidence of CHD with dietary modification will be available. Therefore, a consensus from the medical community needs to be reached as to whether

sustained changes in plasma lipids in response to dietary modification is adequate "proof" that the national effort currently underway to alter diet should be continued.

EFFECTS ON PLATELETS AND THROMBOSIS

It has been suggested that the ingestion of linoleic and α -linolenic acids might directly reduce the risk of thrombosis in patients with atherosclerosis, with additional benefit if they were to replace SFA in the diet [114]. Dietary PUFA could reduce thrombosis by blocking the formation of fibrin, enhancing fibrinolysis, or impairing platelet vascular interactions. To date, most investigators have focused their efforts on studies of platelets. When evaluating these studies, it is important to clearly identify the methods that were used to examine platelet function and platelet vascular interactions, since each of these approaches have substantially different biologic and clinical implications. Compare for example:

- acute ex vivo stimulation of platelets or blood vessels after the addition of agonists (e.g., platelet aggregation studies);
- measurements of chronic platelet vascular interactions in vivo (e.g., platelet survival time or quantitation of prostaglandin metabolites in the urine);
- models of acute thrombosis at sites of vascular injury (e.g., measurement of platelet deposition following carotid endarterectomy);
- prospective controlled dietary trials with arterial thrombosis as a primary endpoint [e.g., myocardial infarction (MI) or stroke].

This section critically examines the effects of dietary linoleic and α -linolenic acids on platelet function and platelet vascular interactions, emphasizing those studies that have been performed in humans.

Linoleic Acid (C18:2n-6)

The interpretation of the research on vegetable oils has long been clouded by controversy as to whether n-6 PUFA produced their effects because of their intrinsic antithrombotic properties or because they replaced thrombogenic SFA in the diet [114]. Moreover, researchers have often used large doses of oil in short-term experiments without proceeding to clinical trials where smaller amounts were given for much longer periods. Lastly, most of the studies have focused on ex vivo measurements of platelet function, which may have limited relevance to normal or pathologic events occurring within the vasculature.

A large number of studies [115] have shown that feeding linoleic acid to humans or animals increased C18:2n-6 in plasma, platelet, and vascular lipids. Importantly, however, the concentration of the prostaglandin (PG) precursor, arachidonic acid (C20:4n-6), concurrently decreased in platelets or vascular cells during vegetable oil ingestion, despite the fact that under ordinary circumstances most of the arachidonic acid in the body is derived from the elongation and desaturation of linoleic acid.

When platelets or portions of arteries are removed from humans or animals given large amounts of dietary linoleic acid and then stimulated with agonists such as collagen, adenosine diphosphate (ADP), or thrombin, the platelet production of thromboxane A₂ (TBXA₂) or vascular generation of prostacyclin was either unchanged or only modestly reduced, usually less in degree than that found after aspirin or fish oil administration [115,116]. In other studies, *ex vivo* platelet aggregation was only mildly inhibited, and cutaneous bleeding time was usually unchanged [115,117,118]. However, platelet production of TBXA₂, as measured in the blood issuing from bleeding time cuts, decreased following administration of SFO to healthy young men [118]. Bleeding time increased from a mean of 3.85 to 4.54 minutes.

Experiments in which thrombosis was produced in lower animals by implanting polyethylene tubing in the aorta, infusing ADP into the blood, or producing vascular injury showed that diets containing vegetable oils regularly inhibit thrombosis vs SFA-rich diets [119-121]. There are neither studies in nonhuman primates or humans on the effect of linoleic acid on experimental vascular injury or on *in vivo* platelet vascular interactions in patients with advanced atherosclerosis, nor rigorous prospective clinical trials on their effects on "hard" primary endpoints such as MI, stroke, or death. However, clinical and experimental data collected over the last several decades suggest that substitution of vegetable oils in the diet for SFA would be expected to produce mild inhibition of platelet function. Additional studies are needed to determine whether n-6 PUFA (perhaps as compared to n-3 PUFA) can inhibit platelet deposition at sites of acute vascular injury (e.g., following angioplasty), or prevent vascular occlusion in patients with atherosclerosis.

α -Linolenic Acid (C18:3n-3)

α -linolenic acid must be clearly distinguished from the longer-chain n-3 PUFA (EPA and DHA) found in marine oils, which have been shown to inhibit both TBX production and aggregation of platelets, prolong cutaneous bleeding time, increase platelet survival, and reduce excretion of PG metabolites in atherosclerotic

subjects, limit the deposition of platelets on injured vessels, and possibly lower the rate of vascular reocclusion following coronary angioplasty in humans [114,122-124].

The rationale for the use of vegetable oils containing α -linolenic acid in the diet would be strengthened if significant amounts of C18:3n-3 from SBO or other oils were desaturated and elongated to EPA and DHA in human platelets or blood vessels. Several studies have addressed this issue in humans. Renaud et al [125,126] showed that increasing C18:3n-3 from 1.2 to about 3.3 g/day increased plasma the EPA concentration from 0.56 to 0.71% ($p < 0.02$) and platelet EPA concentration from 0.36 to 0.52% ($p < 0.001$).

In another report, 6.5 g/day of C18:3n-3 as linseed oil was fed for 2 weeks, and plasma EPA concentration increased from 1.3 to 2.7%, while platelet EPA increased from 0.6 to 1.2% of FA. There was no change in DHA concentration. However, by comparison, feeding 5 g/day of n-3 PUFA derived from fish oil increased the concentration of platelet EPA to 4.1% [127]. In another study, large amounts of linseed oil (24 g C18:3n-3/day) produced only a slight increase in plasma EPA levels with no change in DHA levels, whereas cod liver oil in one-fifth the dose produced striking increases in both EPA and DHA levels [128].

When α -linolenic acid was given in increasing doses to six healthy women for 2 weeks, the small increases in C18:3n-3 concentration in plasma and platelet lipids were associated with decreases in oleic acid concentration, but no change was found in the concentration of arachidonic acid. The increase in platelet EPA was only barely detectable [129]. When large amounts of linoleic acid were ingested along with α -linolenic acid, conversion of linolenic acid to EPA and DHA was inhibited by the excess linoleic acid, perhaps due to competition for chain elongation or desaturating enzymes [127]. These studies indicate that short-term feeding of large doses of α -linolenic acid to humans produce slight increases of C20:5n-3 without detectable changes of C22:6n-3 in platelet phospholipids. Linolenic acid does not appear to inhibit conversion of linoleic acid to arachidonic acid in plasma or platelets, whereas fish oil feeding results in substantial increases in EPA and DHA in plasma and platelets with reductions in the concentration of arachidonic acid.

Few investigators have examined the effects of α -linolenic acid on platelet function or platelet vascular interactions in humans. In a study published several decades ago, platelet adhesiveness and bleeding time were unchanged in 10 patients taking 10-30 ml of linseed oil daily for 3 months as compared to a group given corn oil [130]. However, in a recent study, the admin-

istration of a vegetable oil containing 10% α -linolenic acid significantly prolonged bleeding time (3.85 vs 4.92 min, $p < 0.05$) and was associated with an increase in the production of 6-keto-PGF_{1 α} (stable metabolite of prostacyclin) [118]. In studies of French and British farmers, Renaud found that the dietary intake of linolenic acid correlated with a decrease in thrombin-induced platelet aggregation [131].

The addition of purified α -linolenic acid directly to human washed platelets *in vitro* has been reported to produce dose-dependent inhibition of platelet aggregation in response to collagen, ADP, and epinephrine with a reduction in synthesis of TBXB₂ [132,133]. In a recent study, a multivariate statistical analysis indicated that the increased platelet content of α -linolenic acid and EPA was strongly correlated with a lower risk of coronary artery disease in a group of subjects from Norway [134].

In rats, feeding linseed oil in high doses (in contrast to corn oil) inhibited collagen and thrombin-induced aggregation of platelet-rich plasma. In these experiments, platelet EPA and DHA significantly increased, along with a reduction in arachidonic acid [135]. Other studies have shown decreased synthesis of TBX and malondialdehyde (a measure of lipid peroxide generation) from platelets after α -linolenic acid feeding [136,137]. The production of prostacyclin-like activity from aortic vascular segments was also reduced [136]. Lastly, dietary linolenic acid inhibited thrombosis in several animal models, reminiscent of the findings with linoleic acid [119–121].

The applicability of the results of the animal studies to humans may be questioned because of the very large doses of oil used in these experiments, and because the rat and the rabbit have been shown to convert C18:3n-3 to EPA and DHA more efficiently than humans [136]. The reduction in arachidonic acid in platelets was also more marked than in the human studies, which could explain the decreased PG synthesis. Unfortunately, the effects of α -linolenic acid feeding on thrombosis in acute vascular injury models in higher animals or on *in vivo* platelet vascular interactions in humans have not been studied, and controlled clinical trials of α -linolenic acid for the prevention of thrombosis have not been performed.

This rather limited information suggests that dietary linolenic acid from soybean or other oils is converted to longer-chain n-3 PUFA in human platelets, and may have a mild inhibitory effect on platelet aggregation. However, most of the studies have been of short duration and used relatively high doses of linolenic acid. Long-term studies with more physiological doses of the oil need to be done before any conclusions can be drawn in humans.

In summary, the inclusion of vegetable oils such as SFO, SBO, and corn oil into the diet produce a modest increase of C18:2n-6 and C18:3n-3 in platelet and vascular phospholipids, along with a modest decrease in C20:4n-6. Slight elevations of EPA and DHA were also observed. These oils may produce a mild inhibitory effect on the propensity of platelets to generate thromboxane and to aggregate *ex vivo*. As yet, there are insufficient experimental data to predict whether their chronic use will effectively block thrombosis at sites of vascular injury, inhibit pathologic platelet vascular interactions associated with atherosclerosis, or reduce the incidence of acute vascular occlusion in the coronary or cerebral circulation. Nonetheless, inclusion of vegetable oils in the diet, especially as a substitute for SFA, would seem prudent and might produce a salutary effect on platelet-mediated thrombosis.

IMMUNE SYSTEM

The amount and degree of unsaturation of FA have a profound effect on development of normal immune response, as well as on pathogenesis of inflammatory and neoplastic diseases [138–143]. We recently reviewed the effect of n-6 PUFA of corn oil on immune response [1]. Briefly, we concluded that:

the majority of the studies reviewed indicate that n-6 essential fatty acids (EFA) are necessary for normal immune function. EFA deficiency impairs B and T cell-mediated responses. These impairments are normalized by inclusion of EFA in the diet. High-fat diets (about 45 en%), regardless of the degree of saturation, suppress *in vivo* and *in vitro* indices of the immune system. With few exceptions, in the absence of EFA deficiency and in naive animals, animals fed PUFA of plant origin (high percentage of n-6 fatty acids) had similar responses to those fed the same level of SFA from animal or plant origin. This is especially true at moderate levels of dietary fat (around 22 en%). At higher levels of dietary fat (about 45 en%) or when mice were challenged with infectious agents or chemical carcinogens, PUFA-fed mice tended to have lower responses to some, but not all, of the immunological tests used than those fed the same level of SFA.

The composition of SFO is comparable to that of corn oil (Table 1) and thus would be expected to have similar effects to corn oil on immune response. Soybean oil contents of SFA and MUFA are close to that of corn oil and SFO. However, it contains less n-6 PUFA (54%) and more n-3 PUFA (7%) than corn oil and SFO.

Because of its higher n-3 PUFA content, SBO would be expected to have a different effect on immunological and inflammatory processes than would corn oil. This is because C18:3n-3 can be converted to C20:5n-3, which can replace C20:4n-6 in membrane phospholipids and be preferentially used by cyclooxygenase. This results in reduced production of PG of the 2 series and leukotrienes (LTs) of the four series. These compounds have profound immunoregulatory and inflammatory properties [140,144,145].

In general, PGE₂ has been shown to have an immunosuppressive effect, inhibiting lymphokine production, lymphocyte proliferation, antibody production, and natural killer cell (NK) cytotoxicity. LTB₄ is a potent chemotactic and chemokinetic agent that stimulates NK cytotoxicity and production of interleukin-1 (IL-1) and IL-2, as well as proliferation of lymphocytes [144,145]. It should be noted that LTB₄ in some cases, has been shown to have either no effect or a suppressive effect on lymphokine production and lymphocyte proliferation (reviewed in [144,145]). LTC₄, D₄, and E₄ are bronchoconstrictors, increase vascular permeability, and are major components of anaphylactic shock. Lipoxins have been shown to inhibit NK activity [145].

Different studies have shown that n-3 PUFA of marine oils (C20:5n-3, C22:6n-3) can alter in vitro production of cytokines [146,147], lymphocyte proliferation [147,148], NK cytotoxicity [150,151], and in vivo delayed-hypersensitivity skin test [152]. Furthermore, these FA were shown to reduce pathological changes associated with autoimmune, antiinflammatory, and neoplastic diseases [153-156]. There are very few immunologic studies of plant oils containing n-3 PUFA. Plant oils containing n-3 PUFA include perilla seed oil, which has the highest content of n-3 PUFA (64%), followed by linseed oil (62%), canola oil (10%), and SBO (7%). In extrapolating the results obtained with n-3 PUFA of marine oil to SBO, two points should be kept in mind: (1) what is the conversion rate of C18:3n-3 to longer-chain n-3 PUFA (i.e., C20:5n-3 and C22:6n-3); and (2) what is the percentage of n-3 PUFA in SBO adequate to modify arachidonic acid metabolism and thereby immunological and inflammatory processes?

Increasing C18:3n-3 in the diet of French farmers for a year from about 1.2 g/day (0.37% of calories) to about 3.3 g/day (1.0% of calories) resulted in a significant increase in plasma (0.56-0.71%, $p < 0.02$) and platelet C20:5n-3 content (0.36-0.52%, $p < 0.001$) [125,126]. Sanders and Younger [127] showed that the intake of 20 ml linseed oil daily for 2 weeks increased EPA from 1.3 to 2.7% in plasma phosphatidylcholine and from 0.6 to 1.2% in platelet phospholipids.

Marshall and Johnston [157] compared the effect of feeding semipurified diets containing 20 en% by weight of corn oil (2.2% C18:3n-3), SBO (7.7% C18:3n-3), linseed oil (61.8% C18:3n-3), and a mixture of linseed oil and SBO (137.3% C18:3n-3) for 2 or 4 months on FA profile and PG synthesis of thymus, spleen, liver, and brain. No difference was observed in percent spleen phosphatidylethanolamine C20:5n-3 between rats fed corn oil and SBO, but percent C22:6n-3 was increased four times in rats fed SBO. No difference in spleen thymus PGE₂ synthesis was observed between corn oil and SBO fed rats, even when they were fed through the second generation. Liver PGE₂ synthesis, however, decreased after 4 months of feeding SBO compared to corn oil. Rats fed diets with fats containing more n-3 PUFA (i.e., linseed oil or the mixture of linseed oil and SBO) had decreased PGE₂ synthesis in thymus and spleen. Therefore, the amount of C18:3n-3 in SBO might not be adequate to cause immunological changes other than that observed with high n-6 containing oils such as corn oil and SFO. In fact, the few studies reported to date tend to support this notion.

Olson et al [158] fed weanling C3H/OUJ mice semipurified diets containing 5 or 20% by weight of SBO for 20 weeks and measured mitogenic response to T and B cell mitogens. Mitogenic response to the T cell mitogens concanavalin A (ConA) and phytohemagglutinin (PHA) but not to the B cell mitogens lipopolysaccharide (LPS) and pokeweed mitogen (PWM) was significantly lower in mice fed 20% SBO than those fed 5% SBO. This is similar to findings reported for high levels of other dietary fats [138]. Johnston and Marshall [138] did not observe a difference in the mitogenic response to T cell mitogens between rats fed 10% by weight of corn oil or linseed oil (containing 62% C18:3n-3).

In vitro addition of C18:3n-3 to human lymphocytes at high concentrations (5-100 µg/ml) inhibited mitogenic response to PHA. Similar effects were reported for C18:2n-6 [159]. Using a small number of mice ($n = 4$), Oarada et al [160] showed that oxidized SBO fed for 90 days inhibited mitogenic response of thymocytes to ConA but increased mitogenic response of spleen to ConA. The depressive effect on thymus was attributed to linoleate hydroperoxide and small aldehydes such as 4-hydroxynoneal. The augmentation in spleen was suggested to be a compensatory effect.

Inclusion of Intralipid (containing SBO) in total parenteral nutrition therapy of malnourished patients did not have an effect on total number of T cells, number of helper T cells, or mitogenic response to PHA and PWM [161].

In conclusion, very few studies have specifically looked at the effect of SFO or SBO on the immune

response. There is no reason to believe that SFO will affect the immune system differently from corn oil (which has a similar FA composition). Even though SBO contains 7% C18:3n-3, the available data indicate that the level of C18:3n-3 in SBO is not adequate to change PG production in the spleen or thymus and/or other biochemical events to induce immunological changes different from that observed with the same level of corn oil.

ONCOGENIC CONSIDERATIONS

Animal Models

There is compelling evidence that dietary fat (energy) intake influences both human risk for cancer and experimental carcinogenesis [162]. Increasing the total fat intake of experimental animals increases the incidence of chemically induced and spontaneous tumors at certain sites, predominantly the breast, pancreas, and colon, and the growth of transplanted tumors [163]. We recently reviewed papers addressing the role of linoleic acid and corn oil in experimental carcinogenesis published subsequent to the comprehensive 1982 review of the Committee on Diet, Nutrition, and Cancer [1]. Our review concluded that the impact of dietary linoleic acid on experimental carcinogenesis is confounded by variables including energy balance, and n-3 PUFA intake, as well as total fat calories. Nevertheless, data from carefully designed animal studies reveal that, when total fat intake is low but adequate in EFA, linoleic acid is more effective than SFA, MUFA, and n-3 PUFA in enhancing tumorigenesis during the promotion/progression and metastasis phases of experimental carcinogenesis [1]. One mechanism through which linoleic acid might affect these processes involves its conversion to arachidonic acid and hence to PG of the 2 series. Linoleic acid is readily converted to arachidonic acid in the rat, whereas in the human the conversion is limited [164]. It is possible that this difference in linoleic acid metabolism as well as the narrowly defined parameters of the experimental designs underlie the conflict between the results from animal studies and those from case-control and epidemiological studies which suggest that diets higher in linoleic acid tend to decrease the risk of human cancer [1]. Carroll and Hopkins [165] reconcile this difference with the observation that fats in the human diet supply PUFA at levels approaching those required to maximally promote carcinogenesis in animal models. They note that in countries where total fat available for human consumption is low, the fat is more likely derived from vegetable sources, whereas animal fats are predominant in the fat supplies of countries with high fat availability. For example, total fat intake [1] is reported

as 38 and 22 en%, respectively, in the United States and Japan. Intakes of SFA and MUFA in the United States are more than twice those of Japan, whereas the intake of PUFA is similar. As a result, fat en% rather than PUFA en% is more positively correlated with the difference in human breast cancer mortality between the two countries.

A crude approximation of the relationship between the levels of dietary fat (10–20 wt%) and linoleic acid (4–6 wt%) in promoting maximum chemically initiated mammary tumorigenesis drawn from studies reviewed by Dupont et al [1] translates to a diet providing 20–40 en% fat and 8–12 en% linoleic acid. It appears that a similar relationship holds for the metastasis phase of tumorigenesis. The impact of dietary fat during the initiation phase more likely rests only on total fat intake [166,167] or on the relationship between total fat intake and SFA content [168,169]. Total fat and PUFA provide, respectively, 37 and 8% of the energy consumed by 30–39-year-old women in the United States [170]. The animal data are compatible with the recommendation [89,171] that humans reduce their total fat intake. The animal data raise the concern that, by increasing the PUFA contribution in the United States diet to 10 en%, US women are placed at higher risk for breast cancer [165,172].

Soybean and Sunflower Seed Oils

Sundram et al [173] fed 40 en% fat diets to groups of 20 Sprague–Dawley rats during the promotion/progression phase of 7,12-dimethylbenz[a]anthracene (DMBA)-initiated mammary tumorigenesis. The composition of the dietary fats had no effect on tumor latency. At autopsy, 5 months post-DMBA, 70, 85, and 90%, respectively, of the rats fed palm oil, corn oil, and SBO had one or more tumors. The number of tumors/tumor-bearing rats in the respective groups were 2.0, 4.2, and 3.2. Rats fed fats high in linoleic acid developed significantly more tumors than did rats fed an EFA-adequate (4.5 en% PUFA) palm oil diet. According to their analysis, corn oil provided 19.9 and SBO 26.4 en% PUFA. Tumor-bearing animals in the latter group had 25% fewer tumors, possibly due to the difference in the ratio of n-6:n-3 PUFA in the two fats: 6.8 and 43.3, respectively, for SBO and corn oil. The enhancement of mammary tumorigenesis by dietary PUFA is suggested to be through increased synthesis of PG of the 2 series [174]. Linolenic acid has a higher affinity for δ -6-desaturase than does linoleic acid [175]. Hence, the linolenic acid constituent of SBO supports the production of the 3 series PG [174] and interferes with the synthesis of the series 2 precursor [176]. Studies addressing the prospective role of n-3 PUFA generally utilize the longer-chain

n-3 PUFA of fish oils [164] rather than α -linolenic acid. A preliminary communication points to the efficacy of this major constituent of linseed oil in suppressing the growth and metastasis of a transplanted mammary tumor [177].

Data from the report of Black et al [178] imply that the latency of ultraviolet light-induced skin tumors in a group of hairless mice fed a tocopherol-free and ascorbic acid-free semipurified diet providing 10 en% cold-pressed SBO was longer than that observed for a group whose diet provided 10 en% stripped corn oil. A similar increase in latency was recorded when the diets were supplemented with a mixture of antioxidants. These results may point to a protective effect of C18:3n-3.

Tinsley et al [179] assessed the influence of 11 different fats and oils and nine mixtures of the fats and oils on the incidence of spontaneous mammary tumors in C3H mice. Consistent with other reports, they found that increasing the level of linoleic acid at the expense of other FA in a diet providing 23 en% fat increased tumor incidence and decreased time to first tumor. Increasing the level of linolenic acid, however, had little influence on tumor incidence. Increasing the linolenic acid content of the diet at the expense of linoleic acid in a high-linoleic acid diet was not tested.

Olson et al [158] evaluated the impact of diets providing 12 and 40 en% SBO on the development of spontaneous mammary tumors in C3H/OUJ mice. They fed carefully constructed soybean protein-based diets with AIN-76A mineral and vitamin mixes adjusted to a constant nutrient-to-energy ratio to groups consisting of 34 female and 17 male mice. At 6 weeks of age, the females were mated with males from the same dietary group. They were bred at 8-week intervals thereafter for a maximum of three pregnancies. Beginning at 25 weeks and continuing for the duration of the study, the females were palpated twice weekly and tumors were measured. Female mice showing a 10% weight loss were necropsied; survivors were killed at 40 weeks of age. The diets had no impact on tumor latency; at 40 weeks, 89 and 65% of the surviving mice fed the 40 and 12 en% SBO diets, respectively, had tumors. The number of tumors per tumor-bearing mouse did not differ. However, tumors from the mice fed the high-fat diet were significantly heavier. The authors also noted that the high-fat diet was associated with increased metastatic spread of the tumors to the lungs. Although this effect of increasing dietary fat, independent of FA composition, on spontaneous mammary tumors is well established, enhancement of the metastatic spread of virally caused tumors has not been reported. The model used in this study differs markedly from the typical model utilized in studies of the impact of dietary fat level on spontaneous mammary

tumor development in that the mice were subjected to the stresses of pregnancy and lactation. During lactation and prior to the appearance of mammary tumors, 50% of the mice fed the 40 en% SBO diet died, while only 19% of those fed the 12 en% SBO diet died. The deaths were attributed to a strain-related dystrophic cardiac calcinosis [180], the incidence of which was influenced by pregnancy, dietary fat level, and, possibly, the purified diet [181]. At necropsy, greater myocardial involvement was noted in the females from the high-fat group. Dystrophic calcinosis was also present to a mild degree in lung and kidney sections. All male mice survived to 40 weeks. A larger number of males fed the high-fat diet had a mild calcinosis of the kidneys and lungs; all males and the single female from the low-fat group which did not become pregnant had a slight myocardial dystrophic calcinosis [158,180]. These findings led Everitt et al [181] to examine myocardial dystrophic calcinosis in C3H virgin and breeder mice that were fed either a natural ingredient or semipurified diet. The lesions were more prevalent and extensive in the breeder female mice fed the AIN-76A diet. Virgin female mice fed the NIH-07 diet and all male mice were free of lesions; breeder females fed NIH-07 diets and virgin females fed AIN-76A diets had lesions of similar incidence and severity. There is clear evidence that the purified diet, independent of protein and fat source, exacerbates this sex- and strain-specific cardiac degeneration. The diets used in these investigations were held under conditions to minimize lipid peroxide formation.

Boeryd and Hallgren [182] fed a commercial diet containing 4 en% animal fat to C3H mice prior to breeding. During gestation and lactation, the animal fat in the diet was replaced with an equal quantity of SBO with or without 0.1% methoxy-substituted glyceryl ester, an immunostimulant. The progeny derived from each group were divided into two groups which were fed the commercial diet with animal fat or SBO. The incidence of mammary tumor development in the force-bred female progeny was studied. Female offspring fed the SBO diet developed a nonsignificantly higher number of tumors compared to those fed the animal fat diet. These investigators [183] also report that the tumor-suppressive effect of Levamisol was counteracted by replacing the animal fat with SBO in the diet fed to C57BL/6J mice bearing transplanted Lewis lung tumors.

The immunosuppressive action of a high-PUFA diet was clearly shown in a study by Cameron et al [184]. Male and female SJL/J mice were fed tocopherol-supplemented diets providing 40 en% fat either as SBO (22 en% linoleic acid, 3 en% linolenic acid) or as a blend of SFO and beef tallow (2 en% linoleic acid). Between 12 and 14 months, a time when all mice fed the high-PUFA

diet had developed lymphomas, only 70% of the mice fed the low-PUFA diet had developed lymphomas. Historical controls fed a standard mouse diet showed an incidence of 91% lymphomas at 12–14 months; the low-PUFA diet may suppress lymphoma development.

Carroll, a pioneering investigator of the role of fat in the promotion of chemically induced rat mammary tumorigenesis, recognized the interplay between dietary fat level and composition in the early 1970s. For example, Carroll and Khor [172] studied the effect of level and type of fat on the incidence of tumors developing in DMBA-induced Sprague–Dawley rats. They first established the impact of level of fat, noting that tumor incidence increased as the en% of corn oil in a semi-purified diet was increased from 1.5 to 22 en%, but not from 22 to 39 en%. Their experiments with 10 fats and oils (39 en%) indicated that the oils relatively high in PUFA (corn, cottonseed, SBO, and SFO) enhanced the yield of adenocarcinomas by 40% when compared to fats and oils relatively high in SFA and MUFA (butter, coconut oil, lard, olive oil, rapeseed oil, and tallow). However, diets constructed with 39 en% fat blends consisting of 85% beef tallow or 85% coconut oil with 15% SFO were as effective as a diet providing 39 en% SFO in promoting DMBA-induced mammary tumorigenesis [165,185,186].

The aforementioned study demonstrated that diets providing 33 en% beef tallow or coconut oil and 6 en% SFO or 39 en% lard promoted DMBA-initiated mammary tumorigenesis as effectively as a diet providing 39 en% SFO [185]. Restated, 5 en% linoleic acid in diets providing 39 en% fat were as effective as a 38 en% fat diet providing 30 en% linoleic acid in promoting tumorigenesis. Studies previously reviewed suggested that diets ranging in fat content from 20 to 40 en% supported maximum tumorigenesis when linoleic acid contributed 12–8% of total energy intake [1].

Studies showing a promotional effect of high-PUFA fats reviewed above utilized an initiating dose of 5 mg DMBA. Jacobson et al [187] tested the promotional action of diets providing 3 and 20 wt% (7 and 39 en%) SFO in Sprague–Dawley female rats initiated with a low dose (1.5 mg) of DMBA. A typical study from this laboratory suggests a latency (50% incidence) of 10 weeks following an initiating dose of 5 mg DMBA for rats receiving a 20 wt% fat diet [172]. Latency was extended to 41 and 47 weeks ($p < 0.05$) for rats fed the 20 and 3 wt% SFO diets, respectively, following an initiating dose of 1.5 mg DMBA. At 55 weeks, all of the rats fed the high-fat diet had palpable nodules, 70% of which were confirmed as adenocarcinomas; 79% of the rats fed the low-fat diet had palpable nodules, 72% confirmed as adenocarcinomas, without a plateau incidence being

reached. The main effect of lowering the fat content of the diet was to delay the development of mammary tumors as the ultimate proportion of adenocarcinomas was the same.

Hopkins et al [188] examined the impacts of EFA-adequate diets containing either 17.5 wt% added SFO or beef tallow on the initiation and promotion/progression stages of DMBA-initiated carcinogenesis in male and female C3H mice. Results showed a significant promotional effect of the SFO diet in females and a nonsignificant effect in males when fed during that stage of tumorigenesis. A finding relevant to this review was that few spontaneous tumors developed in control (noninitiated) animals during the 80 weeks they were fed the high-fat diets. Moreover, spontaneous tumors developing in the mice fed the SFO diet did not differ in site or number from those appearing in the beef tallow group. Burns et al [189] compared L1210 murine leukemia growth and survival of hosts in male DBA/2J mice fed a diet containing 16 wt% SFO or coconut oil. The diets were fed for 4 weeks prior to and following tumor transplants. Tumor growth rate did not differ between the two groups. Nevertheless, mice in the group receiving coconut oil had a significantly longer survival. The weight of mice fed the EFA-deficient diet [190] for 4 weeks did not differ from that of mice fed the SFO diet.

In conclusion, these studies generally support the views documented in the report of the Committee on Diet, Nutrition, and Cancer [162] of the positive relationship between cancer incidence, dietary fat, and the role of diets high in linoleic acid content in the promotion of experimental tumorigenesis and the development of spontaneous tumors principally in female rats and mice. An interesting prospect, as yet undocumented, is that dietary α -linolenic acid will attenuate these actions of linoleic acid, as has been shown for the longer chain n-3 PUFA.

Human Studies

The literature addressing the relationship between cancer and PUFA contained in corn oil (n-6 PUFA) was recently reviewed [1]. In brief, data from diverse studies (international, cohort, and case-control) investigating risk, incidence, or mortality of breast and colon cancer indicate that PUFA does not increase risk and may be negatively associated with the incidence of cancers. Of the 35 studies reviewed, only 12 investigated the effects of dietary PUFA (PUFA, vegetable fat, or linoleic acid). One study reported a positive association of cancer incidence with PUFA intake [191] and one reported a negative association of cancer incidence with PUFA intake [192]. In total, four studies have now reported a negative association between PUFA intake and cancer

Table 2. Summary of Selected Human Studies Reporting Negative Association between PUFA and Cancer

Author	Type of study	Cancer	Results
McKeown-Eyssen [192] (1984)	International correlation	Colon (mortality)	Vegetable fat $r^a = -0.28$
Kaizer [193] (1989)	International correlation	Breast (mortality)	Fish consumption, $r^a = -0.47$ ($p = 0.0066$), assumed to be due to fatty acid composition of fish
Tuyns [194] (1988)	Case-control	Colorectal (incidence)	Oils of high P:S ratio (corn, soybean, sunflower), $RR^b = 0.48$ ($p < 0.0001$)
Verrault [195] (1988)	Cancer cases only	Breast number of positive nodes at diagnosis)	PUFA, $OR^c = 0.6$, χ^2 trend = -2.17 ($p = 0.03$)

^a r = correlation between dietary factor and mortality.

^bRR = relative risk; ratio of the number of persons with colon cancer in the third quartile of PUFA consumption compared to the number of colon cancer cases in the lowest quartile of PUFA consumption.

^cOR = odds ratio; ratio of the odds of having lymph node involvement at diagnosis in the highest quartile of PUFA intake to the same odds among those in the lowest intake of PUFA.

[192–195] (Table 2).

Few studies have adequately investigated the role of plant oils in the development of human tumors. Tuyns et al [194], in a case-control study in two provinces in Belgium, evaluated the role of dietary fat in development of colon and rectal cancers. Four hundred fifty-three subjects with colon cancer and 365 subjects with rectal cancer were compared to 2851 control subjects. Oils with a high P:S ratio of 4–6 (corn, soybean, and sunflower oil) were reported to be protective in both types of cancer across age, sex, and geographical location when compared to oils with a low P:S ratio of 0.6–2.0 (peanut and olive oil). A recent report by Kaizer et al [193] investigated the correlation of fish consumption and breast cancer incidence using international food consumption data. They found that, after adjusting for dietary fat intake, fish consumption (high in EPA and DHA) was the factor most strongly correlated with reduced breast cancer rates. This area is currently under increased investigation. Other epidemiological studies have reported reduced cancer risks in people with high intakes of fish [196–198].

A number of studies of cancer patients have investigated specific subcategories of risk and dietary intake [195,199–204]. Eid and Berry [199] used adipose tissue FA profiles from patients who underwent breast biopsies. Adipose tissue profiles have been reported to reflect

long-term dietary intake [205]. FA were reported for women with carcinoma ($n = 37$), fibroadenoma ($n = 27$), and others ($n = 21$; normal biopsies, fibrocystic disease, lipoma, and mastopathy). They concluded that there was no indication that adipose tissue FA, total PUFA, or increased P:S ratio increased risk of breast cancer, as suggested by some animal studies [165,172,173,179]. Analysis of the data for total n-3 vs total n-6 PUFA also showed no trends in relation to disease state. A similar study [203] was repeated in patients undergoing colonoscopy categorized patients with carcinoma of the colon, neoplastic polyps, or normal biopsy with respect to adipose tissue PUFA patterns. The data indicated that no individual FA or group of PUFA was associated with disease state. Hislop et al [200] investigated breast cancer patients and controls for a possible relationship between intake of specific food items and estrogen receptor (ER) status. Frequent consumption of meat fat was associated with both ER+ and ER– tumors. Frequent consumption of fish decreased the risk of ER– tumors ($p = 0.01$). Holm et al [206] studied dietary intake in relation to size of breast tumors and ER status. Intake of total fat and MUFA (en%) was associated with increased tumor size. Neither PUFA nor SFA showed an association with tumor size or ER status. Verrault [195] reported that SFA intake was associated with an increased number of positive nodes at diagnosis of breast cancer, whereas a

high intake of PUFA was associated with a decreased number of positive nodes at diagnosis.

The collection of accurate dietary intake data on individual FA is more difficult to obtain than total fat intake. In addition, daily variation in the intake of individual PUFA has been reported to be high [207,208]. The dietary instrument used in assessing type of fat becomes more critical in studies exploring type of fat. Misclassification can be expected with less rigorous methods of dietary assessment, leading to a greater likelihood of observing no effect of type of fat. Most of the published studies have used a food frequency questionnaire (FFQ) with 43–179 items [1]. This instrument was not designed to differentiate the different types of PUFA.

Interesting but conflicting data come from studies using cancer cell lines to explore the role of PUFA. These studies initially centered on all types of PUFA [209,210], and the data supported the finding that a decrease in cell growth was observed with increased concentrations of PUFA, especially those with a large number of double bonds [209,211,212]. Oleic acid was found to increase growth [210]. γ -linolenic acid (C18:3n-6) was found to be inhibitory to cancer cell growth [212–214], possibly via its cytotoxicity [215]. Supplementation of tumor cell lines with DHA [211] or EPA [212] resulted in accelerated differentiation of the neoplastic cells and a dose- and time-dependent decrease in their invasiveness, respectively. The mechanisms of their action are unknown, but both are FA with an n-3 configuration. In contrast to these possible protective effects of PUFA, Rose and Connolly [216] recently reported a stimulatory effect of C18:2n-6 on two breast cancer cell lines but no effect on three cell lines from other sites. In total, recent *in vitro* studies have reported significant and differential effects of n-3 vs n-6 PUFA on tumor cell lines [209–216]. This might be due to differences in the cytotoxicity of these FA or in their production of prostaglandins [217,218].

These findings, which present some conflicting results and no recognized mechanism, have increased interest in correlating the intake of individual PUFA in various human populations and the incidence of cancer [219,220]. It has been suggested that a low level of n-3 PUFA due to low dietary intake and the inability of the body to convert the n-6 series to n-3 may result in an imbalance of EFA and their eicosanoid metabolites [218,221]. The biological significance of different amounts and types of PUFA is largely unknown at levels above requirements, but their different antioxidant requirement, enzyme specificity, and production of different series of PG offer interesting potential areas of research with respect to carcinogenesis.

SUMMARY

SBO and SFO both contain high levels of PUFA (60.8 and 69.0%, respectively) with P:S ratios of about 4.0 for SBO and 6.4 for SFO. The PUFA composition of SBO, however, is different from SFO and corn oil in that it contains 54.1% linoleic acid and 7.2% linolenic acid, whereas SFO and corn oil contain 69 and 60.9%, respectively, of linoleic acid and < 0.1% of linolenic acid. Thus, SFO and SBO each provides adequate amounts of linoleic acid, but only SBO provides the other EFA, linolenic acid with a linoleic-to-linolenic ratio of 7:1. This ratio is within the recommended optimal dietary linoleic-to-linolenic ratio of 4:1 to 10:1 [222].

Some epidemiological studies have suggested that consumption of diets containing a high proportion of fat from vegetable origin is associated with lower BP than consumption of omnivore diets. The compensatory decrease in the consumption of foods of animal origin and frequency of increased fiber intake make it difficult to determine to which factors the antihypertensive effect can be attributed. Clinical trials which have increased the P:S ratio of the diets with vegetable oils have reported significant decreases in BP, although this change was not consistent. It has been suggested that nutrients other than dietary fat or in combination with dietary fat that are relatively high in a vegetarian diet may be responsible for the salutary effects on BP initially attributed to PUFA.

The substitution of vegetable (frequently in the form of SFO or SBO) for animal fat in the diet has consistently resulted in decreased plasma cholesterol and LDL-C levels. These changes are thought to be favorable with respect to decreasing risk of CHD. Plasma triglyceride concentrations are not generally affected. Of concern is the tendency of a high-PUFA diet to also decrease HDL-C. However, further work is needed to clarify the physiological significance of this change. Little effect on plasma cholesterol has been reported as a result of increased consumption of n-3 PUFA, primarily EPA and DHA. In general, recommendations established by the National Cholesterol Education Program Expert Panel [89] to decrease both total and saturated fat emphasizes the point that reduction of animal fat intake should not be compensated for by an increase in vegetable fat intake. The use of moderate amounts of SBO and SFO, while keeping within the guidelines, seems an appropriate yet prudent course to take.

The inclusion of vegetable oils such as SFO, corn oil, and SBO in the diet have been reported to produce an increase in the C18:2n-6 content of platelets along with a modest decrease in arachidonic acid and slight elevations of EPA and DHA. These oils may produce a mild

inhibitory effect on the propensity of platelets to generate thromboxane and to aggregate *ex vivo*. As yet, there are insufficient experimental data to predict whether their chronic use will effectively block thrombosis at sites of vascular injury, inhibit pathological platelet vascular interactions associated with atherosclerosis, or reduce the incidence of acute vascular occlusion in the coronary or cerebral circulation.

Linoleic acid is needed for normal immune function. EFA deficiency impairs B and T cell-mediated responses which are reversible following repletion with EFA. Very few studies have explored the effect of SFO or SBO on immune response. The effect of SFO on immune response should be similar to that of corn oil (which has a similar FA composition) (Table 1). Despite the relatively high content of C18:3n-3 in SBO (7%), the available data indicate that the level of n-3 PUFA in SBO is not adequate to alter PG production and/or other biochemical events sufficiently to induce immunological changes different from those observed with the same level of corn oil.

The studies on the carcinogenicity of PUFA in animal models generally support the view documented in the report of the Committee on Diet, Nutrition, and Cancer (1982) [162] on the positive relationship between cancer incidence, dietary fat, and the role of diets high in linoleic acid content, the promotion of experimental tumorigenesis, and the development of spontaneous tumors principally in female mice and rats. An interesting prospect, as yet not documented, is that shorter-chain n-3 PUFA of plant origin (i.e., C18:3n-3) will modulate these actions of linoleic acid, as has been shown for the longer-chain n-3 PUFA of marine oils.

Data from diverse human studies investigating risk, incidence, or progression of cancers of the breast and colon indicate that PUFA does not increase risk and may be negatively associated with these cancers. Of the 48 studies investigating dietary fat and breast or colon cancer (international, cohort case-control, special populations at risk, or disease progression), 19 reported on PUFA (PUFA, vegetable fat, or linoleic acid). In most of these studies, no association with PUFA intake was reported. Five studies out of this group reported an association between PUFA intake and cancer. Although the study designs were not comparable, it is useful to note that one study reported a positive association with PUFA [191] and four (Table 2) reported a negative association between PUFA and colon or breast cancer [192-195]. Areas yet to be investigated adequately include the differential effects of n-6 and n-3 PUFA and tumor development.

In conclusion, SBO or SFO can be used as a source of linoleic acid and PUFA to prevent EFA deficiency

(recommended at 3 en%) and for prevention of heart disease (recommended at 8-10 en%). In addition, SBO contains 7% linolenic acid with a linoleic/linolenic ratio of 7:1, which is within the recommended ratio of 4:1 to 10:1. The effect of higher than recommended levels of linoleic and linolenic acid on the immune response and host defense of humans needs to be determined.

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