FRI BRIEFINGS

Saturated Fat and Beef Fat as Related to Human Health

A Review of the Scientific Literature

Ellin Doyle, Ph.D.
Food Research Institute, University of Wisconsin
Madison, WI 53706
medoyle@wisc.edu

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Summary

Current health issues, including obesity, cancer, diabetes, and cardiovascular disease, have instigated a great deal of research aimed at discovering dietary constituents that may be related to these diseases. Saturated fat is one macronutrient considered by many people to be detrimental to health if consumed in large amounts. Meat, dairy products, and eggs are the primary dietary sources of saturated fats in the American diet. Most animal fats contain high levels of monounsaturated fats and small amounts of polyunsaturated fats in addition to saturated fat.

Fat molecules have a glycerol backbone that is usually attached to three fatty acids. Fatty acids vary in the number of carbon atoms and in the number of double bonds they contain; these structural features determine the solubility, absorption, and metabolism of the fatty acids. The position of different fatty acids in the fat molecule can also affect its digestion and absorption.

Saturated fatty acids are important as sources of energy and as components that make up cell membranes. They are not considered "essential" in the diet because the human body can synthesize its own saturated fatty acids.

This review concentrates on the scientific literature published during the past six years. Relevant scientific journal articles on saturated fat and beef fat as related to human health were identified using Current Contents and Medline databases. There is a large volume of research on health effects of dietary fats, including some comprehensive review articles that are used to summarize earlier literature.

Research Studies on Saturated Fat and Health

The significance and usefulness of the information from research on diet and health depends on experimental design and data analysis. Prospective, case–control, and clinical trial studies each have their strengths and weaknesses. A varied program of research with different study designs is probably needed to discern effects of diet on human health. Some issues that should be considered in evaluating research include:

- The extent to which other confounding factors, including total energy intake and other dietary components as well as lifestyle factors such as smoking and exercise, are considered in data analysis
- The reliability of methods for assessing dietary intake of fats
- Variations in individual susceptibility to different diseases according to the age, gender, genetics, and fitness/obesity of the subjects

Cancer

Numerous epidemiological studies have reported positive associations between total dietary fat or saturated fat and various types of cancer. However, some earlier studies may be less reliable because their analyses did not control for other factors that may affect cancer incidence.

Colorectal cancer. Nearly all of the recently published cohort studies failed to demonstrate a significant positive correlation between dietary total or saturated fat and colorectal cancer, but evidence from some studies indicated that meat or some other dietary component may be related to risk for this cancer. Total and saturated fat were also not identified as factors that increased risk for colorectal cancer in most recent case–control studies. Some evidence indicates that dietary fat or meat may be more important to development of cancer according to gender or to specific sites in the colon.

Pancreatic cancer. Smoking is an important risk factor for this cancer. In prospective studies, neither meat nor saturated fat was linked to incidence of this cancer in women but both have been linked to cancer in men. A collaborative case–control study of populations in four countries found no association with total or saturated fat in men or women.

Lung cancer. Smoking is also an important risk factor for this cancer. Prospective studies generally have not reported links between dietary fat and lung cancer among smokers or nonsmokers. However, saturated fat was linked to this cancer in male smokers in one study and dietary ham and sausage were linked to cancer in nonsmoking females in another study.

Breast, ovarian, and endometrial cancers. Large cohort studies generally have not provided evidence of a link between saturated fat intake and these cancers. One exception was a cohort study involving premenopausal women with breast cancer. Results from case–control studies have been inconsistent, but some indicated modestly elevated risks for these cancers associated with fat and/or meat intake.

Prostate cancer. One prospective and two case–control studies found no association of cancer with dietary fat. One study reported a weak inverse correlation between cancer and saturated fat intake while six other studies reported some degree of positive association with dietary saturated or total fat. These associations were stronger for more advanced cases of cancer in some studies.

Testicular cancer. One case–control study reported a nonsignificant increase in risk for seminoma and nonseminoma testicular cancers associated with higher total and saturated fat intake. Two other studies reported opposite results: an increased risk associated with saturated fat only for seminoma cancers in one study and only for nonseminoma cancers in the other study.

Cardiovascular Disease

Cardiovascular disease is a three-stage process involving injury to the inner endothelial cell layer of arteries, buildup of atherosclerotic plaque at the site of injury, and formation of a blood clot that occludes the narrowed arteries. Research indicates that dietary saturated fat may affect progression of plaque buildup and plaque formation. Nondietary factors that affect the atherosclerotic process include heredity, gender, and general level of aerobic fitness.

Saturated fat and heart disease. Numerous epidemiological studies indicate that a higher saturated fat intake is associated with increased incidence of or death from heart disease. In some studies results differ for males and females, and a high intake of dietary fiber weakens the association with saturated fat in some studies. Evidence from clinical studies is not as strong or consistent in suggesting that saturated fat causes cardiovascular disease, and some scientists question whether it really is a significant causative factor.

Saturated fat and stroke and hypertension. Dietary saturated fat has been linked to hypertension and to incidence of stroke in some studies. However, at least one large cohort study failed to find an association between stroke and saturated fat or total fat.

Saturated fat and serum cholesterol levels. Many studies have demonstrated that levels of serum LDL cholesterol are correlated with dietary total or saturated fat levels. However, it has also been demonstrated in numerous studies that some individuals do not respond to low saturated fat diets with decreased levels of LDL cholesterol. Populations with high rates of cardiovascular disease often have high LDL and low HDL levels, but this is not always the case.

Saturated fat and inflammatory mediators. Saturated fat intake has been associated with serum levels of C-reactive protein and some interleukins that are markers of inflammation. These relationships are not always significant and appear to be stronger in overweight people.

Saturated fat and endothelial function. Some research indicates that dietary saturated fats have a detrimental effect on endothelial function, a condition that is associated with early stages of atherosclerosis.

Saturated fat and clot formation. Both total and saturated fat levels in the diet appear to affect the coagulant activity of factor VII and therefore clot formation.

Obesity

Certainly excess calories from fats will cause weight gain if there is no compensatory increase in exercise to utilize this energy intake. Some data indicate that dietary fat may also affect food intake and fat deposition, but the physiological effects of a high fat diet are complex and depend on an individual's activity level and genetics. During the past two decades there has been a substantial decline in percentage of dietary energy from fat in U.S. diets but a massive increase in the prevalence of obesity. Although some studies report that obesity is associated with high-fat diets, some short-term trials indicate that persons lose weight on both low-fat high-carbohydrate diets and on low-carbohydrate high-fat diets. Excess calories (from fat or carbohydrate) contribute to weight gain but other lifestyle factors, in particular lack of exercise, are likely to be major factors responsible for the obesity epidemic.

Diabetes

A high fat diet generally has a negative effect on glucose metabolism and induces diabetic changes in laboratory animals. Epidemiological studies in humans also implicate high-fat diets in the development of diabetes. However, the significance of the association between dietary total or saturated fat and diabetes is often lost when data are adjusted for body mass index. Two large prospective studies in the U.S. found no significant correlation between saturated fat intake and type 2 diabetes after adjustment for BMI. However some smaller prospective studies in the U.S., Japan, and Europe did find such a correlation. Increased risks for insulin resistance and elevated serum insulin or glucose levels have been associated with diets containing more total or saturated fat in some, but not all, studies.

Introduction

Human health and its relation to diet have always been a topic of discussion and a subject for investigation. Current health concerns of obesity, cancer, diabetes, and cardiovascular disease have instigated numerous research projects on different types of foods and their constituents to determine whether there are some foods that should be increased, limited, or avoided in the diet to prevent such diseases. One such dietary component is "saturated fat," which is generally considered to be detrimental to health if consumed in large amounts. Data from NHANES III (National Health and Nutrition Survey) indicated that 34% of the total food energy intake in the U.S. in 1988–1991 was from total dietary fat and 12% was from saturated fat (*137*). According to the 2003 report from the Institute of Medicine, 20–35% of calories consumed daily should come from fat in order to meet the body's nutritional needs and minimize the risk of developing chronic diseases (*284*).

Animal products (meat, dairy products, and eggs) are the primary dietary sources of saturated fats for Americans. However, even vegetable oils that are high in unsaturated fats contain some saturated fat, and some plant products (cocoa butter, palm oil, and coconut oil) have saturated fat levels as high or higher than those in animal fats (see Tables 1 and 2). It is worth noting that animal fats also contain high levels of monounsaturated fats and small amounts of polyunsaturated fats.

This review concentrates on the scientific literature published during the past six years. Relevant journal articles on saturated fat and beef fat as related to human health were identified using Current Contents and Medline databases. There is a large volume of research on health effects of dietary fats, including some comprehensive review articles that are used to summarize earlier literature.

To provide some background, this review begins with a description of the structure of dietary fats and then presents information on the different fats present in lean beef, beef fat, tallow (rendered beef fat), and some other lean meats. Data on health effects of saturated fats will be summarized by considering: epidemiological studies in which the health of different groups of people, with different dietary habits, is compared; prospective or cohort studies in which a large group of apparently healthy people is examined at baseline and then followed for many years to identify incident cases of disease and baseline measurements can then be correlated with disease incidence; clinical studies in which groups of similar people are fed different diets and then some marker of health, such as serum cholesterol levels, is measured and compared between the dietary groups; and clinical studies with people or experimental studies with animals to determine the physiological effects of individual saturated fatty acids.

Fat Structure and Function

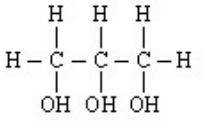
Fatty Acids and Triacylglycerol (Triglyceride) Structure

Fats are an important part of the human diet, providing a concentrated source of energy and important compounds for constructing cell membranes, hormones, prostaglandins, and other molecules. Saturated fats can be synthesized in the human body and therefore are not essential parts of the diet. Some unsaturated fats are considered "essential" because they are required for specific functions and the human body cannot synthesize them. These fatty acids must be ingested in food. Nevertheless, both saturated and unsaturated fats serve important functions and should be part of a healthy diet. Fats are the predominant group of lipids (i.e., compounds soluble in organic solvents) consumed in the diet. Other groups of dietary lipids, such as cholesterol and related compounds, are not covered in this review.

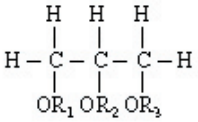
Fats are composed of fatty acids attached by ester bonds to a glycerol molecule (Figure 1). A glycerol molecule with three fatty acids is called a triacylglycerol or triglyceride. A fat molecule may contain three different fatty acids, three identical fatty acids or some other combination. The location of different fatty acids — at the exterior positions (#1 and 3) or at the middle position (#2) of the glycerol molecule — affects the digestibility and physiological fate of the fat molecule. In phospholipids, a phosphate group that is often attached to another organic molecule replaces the fatty acid in the #3 position.

Fatty acids differ in length (number of carbon atoms), the number of double bonds, and the spatial arrangement of hydrogen atoms attached to the carbon atoms that form a double bond (Figure 1). Fatty acids with no double bonds are called saturated; that is, they contain the maximum possible number of hydrogen atoms attached to the carbon atoms (e.g., palmitic acid).

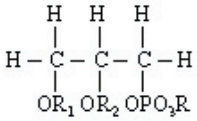
(*a*) Glycerol



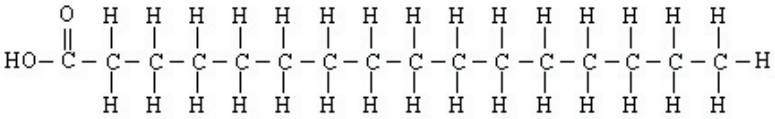
(*b*) Triacylglycerol



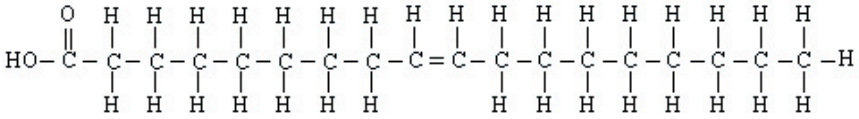
(*c*) Phospholipid



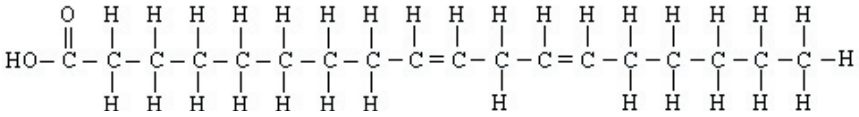
(*d*) Palmitic Acid:



(*e*) Oleic Acid:



(*f*) Linoleic Acid (*cis* isomer)



(*g*) *trans*-6, *cis*-9 isomer of linoleic acid

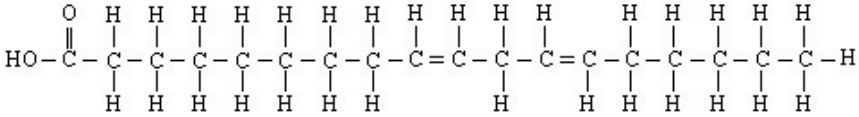


Figure 1. Components of fats and their structures. (*a*) glycerol; (*b*) triacylglycerol with three fatty acids (R_1, R_2, R_3) attached to glycerol; (*c*) phospholipid with a phosphate group and usually another molecule (R) attached at the #3 position; (*d*) saturated fatty acid; (*e*) monounsaturated fatty acid; (*f*) polyunsaturated fatty acid; (g) *trans* fatty acid.

Monounsaturated fatty acids (MUFA) have one double bond (e.g., oleic acid) while polyunsaturated fatty acids (PUFA) have two or more double bonds (e.g., linoleic acid). Most naturally occurring MUFA and PUFA have both hydrogen atoms adjacent to the double bond on the same side of the double bond in the *cis* configuration. Some unsaturated fats have the hydrogen atoms on opposite sides of the double bond in the *trans* position. *trans* fats are formed during hydrogenation of vegetable oils, and evidence indicates that they have more adverse health effects than their corresponding *cis* isomers (*41;115;160;239*).

Fatty acids have common names, such as palmitic and oleic, and are also designated by number of carbon atoms and number of double bonds. Palmitic acid is 16:0 (16 carbons long, no double bonds) while oleic acid is 18:1n9 (18 carbons long, 1 double bond at the 9th carbon from the methyl end of the chain). Most

of the fatty acids in meat contain an even number of carbon atoms, but small amounts of branched or odd-numbered-carbon fatty acids are present in some meats (*201*).

Beef Fat

Fat in cattle includes deposits between muscles, under the skin, and around internal organs (depot fat), and intramuscular fats, including marbling and cell membrane lipids. Depot fats consist primarily of triacylglycerols while intramuscular fats contain relatively larger amounts of phospholipids, many of which are associated with proteins. The most common saturated fatty acids in beef are myristic (14:0), palmitic (16:0), and stearic (18:0). Major MUFAs include palmitoleic (16:1) and oleic (18:1), and major PUFAs are linoleic (18:2), linolenic (18:3), and arachidonic (20:4) (*201*).

As may be observed in Tables 1 and 2, in most animal fats (except for tallow and butter), total MUFA content is approximately the same as, or exceeds, the saturated fat content. Saturated fatty acids in beef fat (uncooked), tallow, and roasted beef sirloin were 46.8%, 52.1%, and 40.3%, respectively, of the total fatty acids determined in 100-gram samples. Corresponding MUFA levels were 49.15%, 43.7%, and 56.1%. PUFAs comprise only about 3.6% of fatty acids in beef and slightly more in beef depot fat and tallow. Pork and chicken contain significantly less saturated and monunsaturated fatty acids and more PUFA.

It should be noted that the data cited in Tables 1 and 2 are only a small part of that available in the USDA National Nutrient Database (*252*). The concentrations of total fats and individual fatty acids vary with different grades and cuts of meats and methods of cooking. The data cited in the tables in this paper indicate relative amounts of different fats in lean portions of cooked beef as compared to other lean meats. Total fat and fatty acid content of beef also varies somewhat with breed of cattle, gender, and diet (*113;119;131;196;273*). Although cattle consume plant products that contain relatively high levels of unsaturated fats, bacteria in the rumen convert many of these unsaturated fats to saturated fats. Therefore, it has proven difficult to alter the relative amounts of saturated fats in cattle (and in other ruminants) by feeding different diets unless the dietary fats are protected from ruminal metabolism or cattle are fed for a long time (300–400 d) on a specific diet (*39;59;77;216;228;233*).

Data on the fatty acid composition of a fat do not specify in which position the fatty acids are attached to the glycerol molecule. These positions are important because the presence of a specific fatty acid in the #2 position, rather than in the #1 or 3 positions, affects the absorption of the fatty acids following digestion of the triacylglycerol molecule. A recent analysis of beef fat purchased in the UK demonstrated that the most abundant fatty acid in the 2-position is oleic acid, followed by stearic and palmitic acids (*171*). Similar patterns have been reported by other authors (*103*) although a comparison of fatty acid distribution in fat from Japanese and Australian steers revealed that fat from the Australian steers contained a higher proportion of saturated fatty acids in the #2 position (*273*).

Digestion and Absorption of Dietary Fats

Digestion of fats in humans is accomplished by two different lipase enzymes that hydrolyze the ester bonds, releasing the fatty acids from glycerol. In the stomach, the lingual lipase removes the #3 fatty acid from triacylglycerols. Liberated short-chain fatty acids (<12 C) are soluble and are absorbed through the stomach mucosa into the portal vein, which carries them to the liver where they are metabolized to release energy. Liberated long-chain fatty acids diffuse into fat droplets and pass into the small intestine along with the remaining diacylglycerol molecules that contain two fatty acids.

In the small intestine pancreatic lipase removes the #1 and any remaining #3 fatty acids, leaving a monoacylglycerol with only the #2 fatty acid. Short-chain fatty acids can be absorbed directly from the intestine and transported to the liver. Long-chain saturated fatty acids (>18 C) tend to form insoluble hydrated acid soaps in the less acidic environment of the small intestine, particularly when calcium and magnesium are present. These insoluble complexes are usually eliminated with the fecal matter. Medium-chain fatty acids may be absorbed or eliminated depending on acidity and availability of minerals that may form complexes. The monoacylglycerol attaches to two other free fatty acids and this triacylglycerol enters the lymphatic system and is transported to the liver and other parts of the body. A lipase in the liver may subsequently split off fatty acids from these molecules.

Absorption of fatty acids depends on their solubility (which is greater for unsaturated fatty acids and

Table 1. Fatty acid content of different dietary fats (g/100 g edible portion).*

	Saturated								PUFA	MUFA
Fat / Oil	Total	6:0	8:0	10:0	12:0	14:0	16:0	18:0	Total	Total
Beef fat	29.45			0.31	0.21	2.39	17.73	8.81	2.56	30.94
Tallow (beef)	49.8				0.9	3.7	24.9	18.0	4.0	41.8
Butter	51.37	2.01	1.19	2.53	2.59	7.44	21.7	10.0	3.04	21.02
Pork fat	17.1					0.61	10.19	6.03	7.186	18.81
Lard (pork)	39.2			0.1	0.2	1.3	23.8	13.5	11.2	45.1
Chicken fat	20.25				0.04	0.6	14.65	4.08	14.2	30.3
Turkey fat	29.4					0.9	20.6	6.2	23.1	42.9
Coconut oil	86.5	0.6	7.5	6.0	44.6	16.8	8.2	2.8	1.8	5.8
Cocoa butter	59.7					0.1	25.4	33.2	3.0	32.9
Palm oil	49.3				0.1	1.0	43.5	4.3	9.3	37.0
Canola oil	7.1						4.0	1.8	29.6	58.9
Soybean oil	14.4					0.1	10.3	3.8	57.9	23.3
Olive oil	13.45						10.93	1.98	10.0	73.9

*Data from USDA National Nutrient Database for Standard Reference (*252*).

Table 2. Fatty acid content of roasted meats and whole milk (g/100 g edible portion).*

	Saturated								PUFA	MUFA
Food	Total	6:0	8:0	10:0	12:0	14:0	16:0	18:0	Total	Total
Beef, sirloin (choice)	3.527				0.01	0.202	2.247	1.068	0.312	4.907
Pork, sirloin	2.97			0.01	0.01	0.100	1.840	0.950	0.730	3.620
Chicken (meat only)	2.040				0.020	0.060	1.410	0.490	1.690	2.660
Chicken (meat & skin)	3.790				0.020	0.110	2.780	0.770	2.970	5.340
Turkey (meat only)	1.640				0.020	0.030	0.820	0.490	1.430	1.030
Turkey (meat & skin)	2.840				0.010	0.070	1.730	0.700	2.480	3.190
Whole milk	1.865	0.075	0.075	0.075	0.077	0.297	0.829	0.365	0.195	0.812

*Data from USDA National Nutrient Database for Standard Reference (*252*).

shorter chain saturated fatty acids) and their position on the glycerol backbone. Some experiments with volunteers fed natural cocoa butter and randomized cocoa butter indicated that the natural cocoa butter was more readily absorbed. The randomized fat had higher levels of stearic acid (12% vs. 0.2%) in the #2 position of triacylglycerols as compared to the natural fat. The volunteers had 34% less stearic acid in their plasma after consuming the randomized fat (*210*).

To test the effects of calcium on the absorption of saturated fats, volunteers consumed chocolate (cocoa butter) with or without calcium supplements. Calcium increased fecal fat twofold and reduced absorption of cocoa butter by 13% (*221*). Another study with human volunteers indicated that increasing calcium intakes fivefold caused a decrease in fat absorption of only 5% (*148*). Effects of minerals have also been observed in experiments with rats fed calcium–magnesium-sufficient diets and synthetic triacylglycerols containing oleic and stearic acids. When stearic acid was in the #2 position (oleic–stearic–oleic), >97% of it was absorbed; when it was in the #1 and 3 positions (stearic–oleic–stearic), only 37% was absorbed. However, if the rats were deficient in calcium and magnesium, 70% of the stearic acid in the #1 and 3 positions was absorbed. In addition to the formation of insoluble soaps, it is likely that some of the stearic-acid-containing diacylglycerols, formed after the first lipase reaction, were also eliminated because they were less digestible (*18;148*).

For shorter saturated fatty acids, position on the fat molecule may not have as great an effect on absorption. When healthy adults were fed samples of two oils that had the same total palmitic acid (16:0) content but differed in the distribution of the palmitic acid in the molecule, there was no apparent difference in blood lipid levels after the meal. In one oil 6% of the palmitate

was in the #2 position while in the other, 73% was in this position (*277*).

To summarize, digestion and absorption of fats in the diet, including those in beef, depend to some extent on the size and degree of unsaturation of the fatty acids and on the structure of the fat molecules — the position of different fatty acids. Other items in the diet, including sources of calcium, magnesium, and dietary fiber, may also affect fat absorption.

Physiological Fate of Saturated Fatty Acids

Saturated fatty acids may be catabolized for energy, incorporated directly into membranes or other lipids such as circulating lipoproteins, or may be deposited as stored fat in various locations in the body. In addition, desaturation enzymes can create double bonds in saturated fatty acids, and the resulting unsaturated fatty acids may be used or stored in the body (*27*). To some extent, fatty acid composition of cell membranes and serum lipids reflects the dietary intake of these fatty acids. But the relationship is not exact because of the complex set of reactions occurring during lipid metabolism and the effects of other dietary components on the physiological fate of ingested lipids. Although reduction of dietary fat to approximately 26% of energy intake appears to have positive effects on serum lipids, more severe reductions in fat intake have been reported to increase plasma triglyceride levels and increase synthesis of palmitic acid in the body (*120*).

Research on Saturated Fat and Health — General Considerations

A very large number of studies have examined the importance of dietary fat to human health. The relevance and usefulness of such research depends on research design and data analysis. In a practical sense, it would be impossible to carry out a perfect research project to determine precisely the effects of dietary saturated fat on human health because it would involve decades of obtaining accurate and detailed daily dietary information for thousands of people. However, it is possible to obtain indications of the importance of different dietary constituents with the research designs currently used. Different types of human studies have their strengths and weaknesses. A varied program of research with different study designs is probably needed to discern effects of diet on health (*193*).

Some issues that should be considered in evaluating research results are listed below:

- Western diet" is a general term that may be defined differently by different people. Even among "Western" countries, diets vary: Consider the variations implied by the terms "Mediterranean diet" and "French Paradox."
- Variations in nutrient intake within one country may not be very great and this may mask correlations between dietary intake and cancer incidence. Therefore, multi-center studies assessing dietary intakes and cancer in several countries may have increased statistical power because of larger variations in nutrient intake (*109*).

Although North Americans and Western Europeans eat a very different diet from Asians, Africans, and South Americans, there are many other differences between more and less developed countries, including the amount of exercise people get, stress, prevalence of smoking, and pollutants that may be present in air or water. These other factors also affect human health.

Some older studies only estimated total fat intake and did not consider types of fats (saturated or unsaturated) or total energy or caloric intake. Different fatty acids are metabolized differently and therefore may have different physiological effects. Total energy intake is also an important factor affecting health, so fat intake should be corrected for total caloric intake (*129*). Some low-fat diets containing high levels of carbohydrates may provide the same number of calories as a high-fat diet.

"Saturated fat" in one diet may not be equivalent to "saturated fat" in another diet because of differences in proportions of individual fatty acids. The absorption and metabolic fate of saturated fatty acids depends on their chain length or size. Short-chain fatty acids are more readily absorbed and utilized for energy while long-chain fatty acids are not absorbed as well.

Diets that contain high levels of fat and meat usually contain fewer fruits and vegetables. If such a diet is unhealthy, it may be the excess of fat and meat or the deficit in vitamins, fiber, antioxidants, or other plant protective compounds, or both, that are to blame.

Risks attributed to "fat" or "saturated fat" may actually be correlations with intake of meat. Aside from saturated fat content, some meats may be sources of other compounds that may adversely affect health, e.g., nitrosamines in meats preserved with nitrites, PAHs

and heterocyclic amines in grilled meats, and excess iron which may act as an oxidant.

There is an issue of accuracy in assessing dietary intake of foods. This may be particularly true for case–control studies in which subjects are asked to try to remember their typical diet during the past (*23;192*). Analysis of dietary data obtained by two different assessments and its correlation with breast cancer incidence led to different conclusions. When saturated fat intake was assessed by a food frequency questionnaire, there was no significant association with cancer (odds ratio of 1.1); when saturated fat intake was assessed using a seven-day food diary there was a significant association (odds ratio 1.22). It may be that inaccurate measurements of dietary intakes of nutrients mask the health effects of those nutrients (*11*).

Some researchers analyze serum lipids or small samples of adipose tissue in an attempt to obtain a more objective measurement of fatty acid intake (*4;193*). However, it should be remembered that the body can synthesize many fatty acids. Not all the fatty acids found in serum phospholipids or body fat stores have come directly from dietary sources.

There is also the question of the significant stage of life for which diet should be assessed. Is diet during the previous 5 years, during adolescence, during childhood, or at some other time the most important for determining a particular health effect.

Genetic susceptibility to various diseases differs among individuals. Some people can consume a lot of salt or cholesterol and remain healthy while others develop high blood pressure or atherosclerosis. It is also true that people with different genetic backgrounds respond differently to high- and low-fat diets (*159;187*).

Cancer

Numerous epidemiological studies have reported significant positive associations between total dietary fat or saturated fat and various types of cancer. Results from a number of other studies indicate insignificant or even negative correlations between dietary fat and cancer incidence. It is not always possible to ascertain why different studies of the same disease yield different results. Some of the earlier studies may be less reliable because their analyses did not control for other factors that may affect cancer incidence. Other factors mentioned in the previous section (see General Considerations) may affect research results. In the discussions below, only more recent epidemiological studies, within approximately the last 10 years, will be described and reviews of earlier studies on the possible effects of dietary fat on cancer will be summarized. Table 3 briefly summarizes data from this research on different types of cancer for easier comparison.

Epidemiological research generally investigates factors affecting incidence of a particular kind of cancer. Some dietary nutrients may affect the initiation of tumors or promotion of their growth. These effects may be specific to cancer in one organ or they may promote growth of tumors at several sites within the body. Results from some studies have shown that serum concentrations of IGF-1, a regulator of growth and metabolism, are correlated with red meat, carbohydrate, and/or fat intake. Lifestyle factors can influence IGF-1 levels (*174;194*) and elevated levels of IGF-1 have been associated with several types of cancer (*111*). Dietary fats may alter hormone levels or cause other physiological effects that affect carcinogenesis (*72*).

Physiological responses to high-fat diets may be involved in cancer promotion and in insulin resistance and development of diabetes (*26*). Data from experimental studies with rats demonstrated that a high-fat diet promoted the development of colon cancer (after chemical initiation) and also increased serum insulin levels 180 minutes after an oral glucose load (*250*). Even though these diseases are often studied separately and are discussed in separate sections below, there may be some common physiological mechanisms that underlie them.

Colorectal Cancer

According to a 2002 overview on dietary fat and cancer, evidence from animal studies and international comparisons suggests that a high intake of dietary fat is a risk factor for colorectal cancer. However, data from prospective cohort studies and case–control studies generally do not support this hypothesis (*129*). Some case–control studies implicate high intakes of meat as a risk factor for colorectal cancer, but these studies do not always indicate that saturated fat is an important risk factor. It has been suggested that there may be some other component in meat or associated with meat that is important. One experimental study in rats provided evidence that the iron in meat, not the fat, causes proliferation of cells in the colon (*219*). The

Table 3. Summary of case–control and prospective studies of cancer.

Cancer / Study	Study details	Increased risk with total or saturated fat	Year	Ref.
Colorectal				
Prospective	46,632 men (HPFS) and 87,733 women (NHS); 14–20-yr follow-up; 1139 colon cases, 339 rectal cases; U.S.	None for rectal cancer; increased for beef, pork, lamb, processed meat for colon cancer	2004	(263)
	487 cases in cohort of 45,496 females; average 8.5-yr follow-up; U.S.	None for meat and fat intake	2003	(56)
	445 colon cases, 101 rectal cases in cohort of 76,399 females; 12-yr follow-up; U.S. (NHS)	None for rectal; increased risk for "Western" diet for colon	2003	(60)
	109 cases in cohort of 9959; ~30-yr follow-up; Finland	None for total and saturated fat for colon or rectal	2001	(108)
	460 cases in cohort of 61,463 females; average follow-up 9.6 yr; Sweden	None for "Western" diet	2001	(242)
	143 cases in cohort of 50,535 Norwegians; average follow-up 11.4 yr	None for total and saturated fat	1996	(61)
	205 colon cases in cohort of 47,949; 6-yr follow-up; U.S. (HPFS)	None for total and saturated fat; increased risk for red meat	1994	(71)
Case–Control	613 cases, 996 population controls; North Carolina	None for saturated fat; increased risk for total energy intake	2003	(212)
	402 cases, 668 population controls; Canada	None for C12-C18 saturated fatty acids; decreased risk for C12-C14 for females	2003	(178)
	286 cases, 550 hospital controls; Switzerland	Positive trend for saturated fat; borderline significance	2002	(138)
	208 cases with large adenomas, 427 polyp-free controls; France	Increased risk for total fat and fatty meat	2002	(217)
	1458 cases, 2410 population controls; U.S.	Inactivation of tumor suppressor gene related to "Western" diet	2002	(227)
	45 cases, 45 outpatient controls; China	Increased risk for saturated fat and meat	2000	(279)
	1953 cases, 4154 hospital controls; Italy	None for colon; nonsignificant increase for rectal	1998	(58)
	402 cases, 668 population controls; Canada	Slight decreased risk associated with total and saturated fat	1997	(67)
	1192 cases, 1192 population controls; Hawaii	None for total and saturated fat; increased risk for red or processed meat	1997	(134)
	Review of 13 earlier studies with total of 5287 cases, 10,470 controls in 10 countries	Little or no evidence of risk for energy-adjusted total or saturated fat	1997	(93)
Pancreatic				
Prospective	178 cases in cohort of 88,802 American women;18-yr follow-up	None for saturated fat or meat	2003	(167)
	163 cases in cohort of 27,111 male smokers; Finland; 12 yr follow-up	Increased risk for saturated fat and butter	2002	(235; 236)
	54 cases in 16,017 white men in U.S.; follow-up for 20 yr	Increased risk for red meat	1993	(280)
Case–Control	802 cases, 1669 population controls; Australia, Canada, Poland, The Netherlands	None for total or saturated fat	1992	(94)
Lung				
Prospective	Pooled analysis of 8 cohorts in U.S., Canada, Europe; 3188 cases, 430,281 cohort members	None regardless of smoking history	2002	(229)
	572 cases in cohort of 98,248 after 7–9 yr; Japan	Increased risk for ham, sausage, liver for females only	2001	(182)
	5941 deaths in cohort of 12,763 males in Europe, U.S., Japan after 25 yr	None for non-smokers; positive for saturated fat for smokers	2000	(173)
	153 cases in cohort of 51,452 Norwegians followed for 8–14 yr	None for saturated fat	1997	(255)
Case–Control	200 cases, 600 hospital controls; Uruguay	Increased risk for total fat; nonsignificant increase for saturated fat	2002	(42)
	360 cases, 574 population controls; female smokers and non-smokers; Iowa	Increased risk for total and saturated fat and red meat for both	2001	(1)
	506 cases, 1045 population and hospital controls; Europe	Slight increased risk for meat for some cancer types	2000	(22)
	593 female cases, 623 population controls; smokers and non-smokers; Missouri	Increased risk for red meat, especially fried or well done	1998	(226)
	429 cases, 1021 population controls; female, non-smokers; Missouri	Increased risk for saturated fat; association weakened by adjustment for total energy intake	1993, 1997	(2; 240)
	587 female cases, 687 population controls, mostly smokers; Missouri	None for fat or red meat	1997	(241)

Esophageal / Stomach				
Case–Control	124 esophageal, 124 stomach, 449 population controls; Proxies provided data for 76% of esophageal and 80% of stomach cases; Nebraska	Data from proxies – none; Data from patients, increased risk for saturated fat	2002	(32)
Breast				
Prospective	4107 pre- and postmenopausal cases in cohort of 88,647 U.S. women; 18-yr follow-up; (NHS)	None for red meat	2003	(88)
	714 premenopausal cases in cohort of 90,655 U.S. women; 8-yr follow-up	Increased risk for total, animal, and saturated	2003	(34)
	314 pre- and postmenopausal cases in cohort of 35,298 Singapore Chinese; after average of 5.3 yr	None for saturated fat	2003	(62)
	1071 postmenopausal cases in cohort of 44,697 U.S. women; 14-yr follow-up; (NHS)	None for saturated fat	2002	(29)
	711 pre- and postmenopausal cases in cohort of 111,526 U.S. women; 2-yr follow-up	None for total or saturated fat	2002	(91)
	941 postmenopausal cases from a cohort of 62,573 Dutch women followed for 6.3 yr; cases compared with 1598 subcohort members	None for total or saturated fat or palmitic or stearic acids	2002	(261)
	1328 pre- and postmenopausal cases in a cohort of 61,463 Swedish women; followed 9.6 yr	No association with "Western" dietary pattern	2001	(243)
	71 postmenopausal cases in a cohort of 4052 Italian women; followed 5.5 yr; analysis of erythrocyte membrane fatty acids	None for saturated fat	2001	(183)
	Pooled analysis of 8 studies from U.S., Canada, Sweden, Netherlands; 7,329 pre- and postmenopausal cases among 351,821 women; 5–10-yr follow-up	Slight increase in risk for saturated fat in pooled cases (RR=1.03); RR for individual studies ranged from 0.82 to 1.2	2001	(230)
	2956 pre- and postmenopausal cases in cohort of 88,795 U.S. women followed for 14 yr (NHS)	None for total or saturated fat	1999	(89)
	674 pre- and postmenopausal cases in cohort of 61,471 Swedish women followed an average of 4.2 yr	None for saturated fat	1998	(271)
	Review of data from 6 large cohort studies; total of 4218 pre- and postmenopausal cases in total cohort size of 385,044 women from U.S., The Netherlands, Canada, Finland; follow-up 3–20 yr	None for total or saturated fat	1994	(267)
Case–Control	414 pre- and postmenopausal cases, 429 population controls; Canada	None for saturated fat	2003	(177)
	441 postmenopausal cases, 370 population controls; Washington	Increased risk for red meat and high fat meat	2003	(222)
	127 pre- and postmenopausal cases, 242 population controls; Finland; analysis of serum lipids as measure of dietary intake	Higher level of saturated fat in cases but association weakened by adjustment for confounders	2003	(203)
	2385 pre- and postmenopausal cases, 19,013 hospital controls; Japan	None with meat or beef	2003	(86)
	168 pre- and postmenopausal cases, 672 controls; England	None with diet measured by questionnaire; positive for saturated fat when diet was measured by food diary	2003	(11)
	237 postmenopausal cases, 673 population controls; Sweden	None for saturated fat; positive trend for total fat	2002	(270)
	335 pre- and postmenopausal cases, 838 population controls; Germany	Slight increase for total and saturated fat; larger increase for beef and red meat	2002	(84)
	1459 pre- and postmenopausal cases, 1556 population controls in Shanghai	Increased risk for red meat especially well done or deep fried	2002	(40)
	197 pre- and postmenopausal cases, 197 population controls; U.S.; analysis of serum lipids as measure of dietary intake	Increased risk with higher percentage of saturated fatty acids	2002	(207)
	2569 pre- and postmenopausal cases, 2588 controls; Italy	None with saturated fat with standard multivariate model; increased risk for saturated fat (OR=1.22) with different adjustment for confounders	1996, 1997	(43; 57)
	220 postmenopausal cases, 825 population controls; England	Some increased risk for saturated fat but no significant trend	1998	(30)
	834 pre- and postmenopausal cases, 834 population controls; China	Modest non-significant increase with saturated fat	1995	(276)
	180 pre- and postmenopausal cases, 900 population controls; New York	Increased risk for meat; modest increase for saturated fat	1994	(249)
	820 pre- and postmenopausal cases, 1548 hospital and population controls; Greece	None for total or saturated fat	1994	(112)

Meta-analysis	23 studies (16 case–control, 7 prospective) published 1978–1992	Summary relative risk was 1.01 for cohort studies, 1.21 for case–control studies for total fat	1993	(16)
	45 studies (14 cohort, 31 case–control) on effects of dietary fat; 37 studies (12 cohort, 25 case–control) for foods	Summary relative risk for fat was 1.13; for saturated fat was 1.19; for meat was 1.17	2003	(17)
Ovarian				
Prospective	301 cases in cohort of 80,258 after 16 yr; U.S. (NHS)	None for total or saturated fat	2002	(9)
Meta-analysis	8 case–control studies (6689 subjects); 1984–1999	Increased risk for total, animal, and saturated fats	2001	(101)
Case–control	1031 cases, 2411 hospital controls; Italy	None for saturated fat	2002	(10)
Endometrial				
Prospective	221 cases in subcohort of 3918 Canadians; 8–13-yr follow-up	None; modest inverse relation between animal fat and cancer	2000	(107)
Case–Control	20 cases, 20 population controls; Sweden	Increased risk; abdominal fat of cases contained greater amounts of intermediate length saturated fatty acids	1993	(147)
Prostate				
Prospective	72 cases in cohort of 25,708 Norwegians followed 3–12 yr	None for total or saturated fat	1997	(256)
	279 cases (126 advanced) in cohort of 47,855 after 4 yr in U.S. (HPFS)	None for all cases; increased risk for total fat and red meat for advanced cases only	1993	(70)
	32 deaths among 384 cases after 5 yr; Quebec	Increased risk for saturated fat	1999	(165)
Case–Control	232 cases, 231 population controls; Canada	Weak inverse association with total, animal, and saturated fat	1996	(66)
	328 cases, 328 population controls; UK	None for total fat	1997	(114)
	133 cases, 265 neighborhood controls; China	Increased risk for total, saturated and unsaturated	1998	(136)
	217 cases, 434 hospital and community controls; Spain	Increased risk for animal fat and linolenic acid	2000	(197)
	605 cases, 592 controls; U.S.	Increased risk for total, saturated and monounsaturated only for cancers that had spread	2002	(126)
	101 cases, 202 hospital controls; Serbia	None when adjusted for total energy intake	1997	(259)
	1655 cases, 1645 population controls (Blacks, Whites, Asian-Americans/Canadians)	Increased risk for total fat in all groups; increased risk for saturated fat for Asians	1995	(265)
Testicular				
Case–Control	601 cases, 744 population controls; Canada	Nonsignificant increased risk for seminoma and nonseminoma for total and saturated fat	2003	(65)
	117 cases, 334 hospital controls; U.S.	None for nonseminoma; slight increased risk for seminoma for total/animal/saturated fat	2002	(15)
	160 cases, 136 population controls; U.S.	None for seminoma; increased risk for total and saturated fat for nonseminoma	1999	(224)

NHS = Nurses' Health Study
HPFS = Health Professionals Follow-up Study

risk associated with saturated fat and meat could also be due to the manner in which these foods are prepared. High-temperature cooking can produce heterocyclic amines that are known carcinogens. There is also evidence that certain people are genetically predisposed to developing colorectal cancer (*179*).

A recent review of the literature on the effects of different fatty acids on colon cancer risk concluded that long-chain saturated fatty acids have no significant effect on colorectal cancer risk. Risk appears to be increased by medium-chain saturated fatty acids and arachidonic acid (unsaturated) and to be decreased by short-chain saturated fatty acids and eicosapentaenoic acid (found in fish oil) (*179*).

Prospective cohort studies. Nearly all of the recently published cohort studies, including two large prospective studies published in 2003, failed to demonstrate a significant positive correlation between dietary total or saturated fat and colorectal cancer but evidence from some studies indicated that meat or some other dietary component may be related to risk for this cancer.

Prospective studies that found no significant effect of dietary total or saturated fat included the following: The Breast Cancer Detection Demonstration Project (BCDDP) with 487 colorectal cases in a cohort of 45,496 U.S. women (*56*); The U.S. Health Professionals Follow-Up Study (HPFS) with 205 colon cases in a cohort of 47,949 men (*71*); Combined analysis of HPFS

and the U.S. Nurses' Health Study (87,733 women) with 1139 cases of colon and 339 cases of rectal cancer (*263*); Finnish Mobile Clinic Health Examination Survey with 109 cases of colorectal cancer in a cohort of 9959 people (*108*); and Norwegian National Health Screening Service with 143 cases in a cohort of 50,535 persons (*61*).

Two other prospective studies found no association between colorectal cancer and dietary pattern: For 101 cases of rectal cancer detected in 76,402 women in the Nurses' Health Study (NHS), there was no association between cancer and consumption of a "prudent" or a "Western" diet (*60*). For 460 cases of colorectal cancer in a cohort of 61,463 women in Sweden, there was no significant correlation with a "Western," a "Healthy," or a "Drinker" dietary pattern (*242*).

Meat intake was associated with cancer risk in some prospective studies: In the combined analysis of NHS and HPFS, higher intakes of beef, pork, lamb, and processed meats were associated with colon cancer in 1139 cases (*263*). High intakes of meat, but not of animal fat, were associated with incidence of colon cancer in 205 cases in HPFS (*71*). Data on 455 cases of colon cancer in NHS indicated that the "Western" diet was associated with a relative risk of 1.46 (*60*). But data from BCDDP indicated that neither total meat nor red meat intake was associated with colorectal cancer that developed in 487 women during approximately ten years of follow-up (*56*).

Case–control studies. Total and saturated fat were not identified as factors that increased risk for colorectal cancer in most recent case–control studies (*58;67;134;178;212*). Total fat, animal fat, and fatty meat were associated with increased risk for large colorectal adenomas (which often become malignant) in a study in France (*217*). Saturated fat and meat were associated with colorectal cancer in a small study (45 cases, 45 controls) in China (*279*). A combined analysis was done for 13 case–control studies published from 1980 to 1992 on patients and controls in 10 countries [Argentina, Australia, Belgium, Canada, China, France, Greece, Singapore, Spain, U.S. (*93*)]. Eleven studies reported a positive association of colorectal cancer with total energy intake, but there was little evidence for a significant effect of dietary total or saturated fat on cancer incidence.

Some recent case–control studies on colorectal cancer suggest that there may be gender differences in the risk posed by dietary constituents. A Canadian study of 402 cases (202 females) and 668 controls found total saturated fatty acid intake was associated with a decreased cancer risk for women but not for men (*67*). Data on 427 controls and 208 cases (79 women) with large adenomas indicated that consumption of fatty meat was associated with an increased risk of adenomas. However, this increased risk was predominantly due to cancer in males. Men in the highest category of fatty meat intake had a relative cancer risk of 2.5 compared to men in the lowest category of intake. The relative risk for women in the highest meat intake category was 0.9 (*217*). Intakes of red meat and processed meats were associated with an increased risk for cancer in the right colon and rectum in males only in a case–control study in Hawaii (*134*).

Dietary factors may affect the incidence of cancers in different regions of the colon or rectum. According to a case–control study in Italy, saturated fat intake was not associated with tumors in the colon but was associated with rectal cancer. Both colon and rectal cancers were associated with total energy and starch intake (*58*). Another study of 286 cases (112 females) and 550 controls in Switzerland found that risk of colorectal cancer increased significantly with total energy intake while the increase noted for saturated fat intake was of borderline significance (*138*). Analysis of dietary intakes from a large number of cases in the U.S. indicated that mutations in the p53 tumor suppressor gene in colorectal cancer were correlated with diets high in red meat, fast foods, and *trans* fatty acids (*227*).

Experimental studies on colon cancer in animals have yielded varying results often associated with differences in protocol. Increased dietary fat has been reported to increase, decrease, or have no effect on colon carcinogenesis in rodents (*72*). Diets containing 3–30% lard (pork fat) as compared to control diets with no lard did not increase oxidative DNA damage, mutation frequency or DNA adducts in the colon of rats. This suggests that fat does not act as an initiator of colon carcinogenesis in rats (*260*). Some experiments demonstrated that diets high in saturated fat promoted tumor development in rats treated with chemical carcinogens (*198*) while others indicated that palmitic acid at low concentrations did not affect growth of rat colon cancer cells or increase metastasis (*106*). Hemoglobin or hemin in meat promoted colon cancer development in rats, suggesting that it may be

the myoglobin in meat rather than (or in addition to) saturated fat that is responsible for promoting colon carcinogenesis (*188;219*).

Pancreatic Cancer

A recent review of the epidemiology of pancreatic cancer reports that links have been observed between consumption of animal fats, cholesterol and total energy and risk of pancreatic cancer. Methods of cooking and preservation of foods may also affect cancer risk. Smoking showed the strongest positive association with risk of pancreatic cancer (*68*).

Data from a large prospective study of dietary factors associated with pancreatic cancer in women in the U.S. revealed no significant associations between total fat or saturated fat intake and this disease. Participants in the Nurses' Health Study originally included over 121,000 women who were predominantly former or never smokers. Dietary habits were assessed four times during 18 years of follow-up and a median saturated fat intake of 28 g/day was noted at baseline. There were 178 confirmed cases of pancreatic cancer during this time. Neither specific foods nor estimates of intakes of total fat, different fatty acids or cholesterol were significantly associated with risk of developing pancreatic cancer (*167*).

Data from another large prospective study involving 27,111 male smokers in Finland (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) indicated that intakes of saturated fat and beef (adjusted for total energy intake) were associated with an increased risk of pancreatic cancer. During 12 years of follow-up, 163 cases of pancreatic cancer were identified. Baseline median intake of saturated fat was 61.8 g/day for cases and 58.5 g/day for non-cases. Median intakes of dairy products and red meat were much higher for the male smokers in this study than for the nurses in the previous study (*236*).

A third cohort study of 17,633 white men in the U.S. identified 57 cases of pancreatic cancer after 20 years of follow-up. Smoking was confirmed as an important risk factor and dietary analyses revealed that higher meat consumption was associated with an increased risk for pancreatic cancer mortality but risk was not calculated for fat intake (*280*).

A collaborative case–control study investigated the relationship between nutrient intake and pancreatic cancer in five populations from Australia, Canada, The Netherlands, and Poland. Positive associations were observed between cancer and intakes of carbohydrate and cholesterol but not for fat or saturated fat; inverse associations were noted for intakes of dietary fiber and vitamin C (*94*).

Data from rodent studies indicate that dietary fat, by itself, does not cause pancreatic cancer but it can promote tumor development. Saturated fats do not appear to affect tumorigenesis, while dietary n-6 polyunsaturated fats promote the growth of pancreatic tumors and n-3 polyunsaturated fats inhibit them (*206*).

Lung Cancer

Smoking is widely recognized as a cause of lung cancer. However, there are some non-smokers who get this disease and some smokers who remain free of cancer. It has been suggested that various dietary ingredients may either promote or prevent carcinogenesis.

Several prospective studies following large cohorts of smokers and non-smokers have failed to find a link between dietary saturated fat and lung cancer development. One study found an increased risk for lung cancer in women consuming fatty meat and another study reported an increased risk associated with consumption of saturated fat for smokers but not for nonsmokers. A pooled analysis of eight prospective studies starting from 1976 to 1986 and following subjects for 6–16 years did not demonstrate any positive association between intakes of total or specific kinds of fats and lung cancer risk among never, past, or current smokers (*229*). There were 3188 lung cancer cases identified among 430,281 members of these cohorts. Neither was there a significant association between dietary saturated fat and lung cancer in an analysis of data on 153 lung cancer cases in a cohort of 51,452 Norwegian men and women that included both smokers and nonsmokers (*255*). In a cohort of 98,248 Japanese men and women, 572 lung cancer cases were identified during the 7–9-year follow-up. Ham and sausage were significantly negatively associated with lung cancer in men but significantly positively associated with lung cancer in women (*182*). Of 12,763 men participating in the Seven Countries Study (including U.S., Japan, and Europe), there were 5941 lung cancer deaths identified during the 25-year follow-up. Lung cancer mortality was positively associated with total and saturated fat intake in smokers. No significant associations were observed between diet and cancer in non-smokers (*173*).

Some case–control studies investigated lung cancer specifically in non-smokers as related to dietary factors.

One analysis, published in 1993, of 429 female cases and 1021 population controls in Missouri concluded that there was a clear positive association between lung cancer incidence in non-smokers and saturated fat intake (*2*). A reanalysis of the data from this study using a different statistical method for adjusting dietary intakes for total energy intake found that the correlation between saturated fat was still positive but weakened by this adjustment (*240*). A multicenter study of lung cancer in male and female non-smokers in several European countries (506 cases, 1041 population and hospital controls) found that meat consumption was positively associated with some types of lung cancer but not with others (*22*).

Case–control studies of lung cancer in groups including both smokers and non-smokers have yielded inconsistent results although several noted an association with red meat. Intakes of total and saturated fat were positively correlated with lung cancer in women in Iowa [360 cases, 574 controls (*1*)] and total fat but not saturated fat was correlated with lung cancer in Uruguay [200 cases, 600 controls (*42*)]. However, a study of female smokers with lung cancer in Missouri found no association between intakes of fat or red meat and cancer after adjusting for confounding factors (*241*). Further analysis of the data on these Missouri women indicated that there was a positive correlation with red meat intake, particularly if it was fried or well done (*226*).

Breast Cancer

Incidence rates of breast cancer vary geographically and migrant studies suggest that some lifestyle and environmental factors may influence the development of this cancer. For example, breast cancer incidence in women in Asia, in Asian-Americans in the U.S., and in Caucasian women in the U.S. is 20–30, 50–60, and 90–120 cases/100,000, respectively. One theory is that migrants (after the first generation) consume higher fat diets and this may be related to an increasing incidence of breast cancer as migrants become assimilated. Both individual reports of studies and review articles provide conflicting evidence on the possible effects of dietary fat.

According to one review, evidence for a link between dietary fat and breast cancer does not appear strong. Among 21 case–control studies published in the 1990s, nine showed a significant positive association between intakes of total fat or saturated fat and breast cancer. Only one of 11 cohort studies published during this time reported a significantly increased risk associated with total fat intake. Two meta-analyses of cohort studies published during this period showed no association between dietary fat or saturated fat and breast cancer (*135*). In another review of previous studies, only two of 31 studies reported a significant association between saturated fat intake and breast cancer (*202*).

A recent meta-analysis of 45 studies (14 cohort and 31 case–control) published from 1978 to 2003 calculated a summary relative risk for total fat of 1.13. Data from studies assessing the risk for high intakes of saturated fat and meat indicated summary relative risks of 1.19 and 1.17, respectively. Analyses of studies to determine characteristics that might explain variations in results showed that studies judged to be of higher quality gave slightly higher risk estimates (1.17 for total fat) and that studies from Asia and Europe gave higher estimates of relative risk for total fat (1.42 and 1.17, respectively) than studies from North America (1.04) (*17*).

Prospective studies. Eight prospective studies of breast cancer that included at least 200 cases each from the U.S., Canada, Sweden, and The Netherlands were analyzed using a standardized approach. There were 7329 incident cases in the pooled database among 351,821 total women. When dietary data were analyzed by quartiles of intake there was no association between saturated fat intake and breast cancer. When saturated fat data were analyzed as replacing an equivalent amount of energy from carbohydrates or monounsaturated fat, there was a marginally significant increase in relative cancer risk of 9–18% (*230*).

Another analysis of data from six large cohort studies, published from 1987 to 1992, reported that saturated fat was not significantly associated with risk of breast cancer in any of the studies. These studies were carried out in the U.S., Canada, The Netherlands and Finland (*267*).

The Nurses' Health Study cohort was started in 1976 with over 121,000 registered nurses in the U.S. Dietary intake of various foods has been assessed several times since then and information on morbidity and mortality has been collected. Data from this cohort have been used to investigate possible dietary correlates with a number of diseases. A recent examination of data from the Nurses' Health Study indicated that intake of meat during midlife and later was not associated with

development of breast cancer in 4107 women who developed invasive breast cancer during 18 years of follow-up (*88*). An earlier study of 2956 breast cancer cases, after 14 years' follow-up, did not find any evidence that a lower intake of animal fat or saturated fat was associated with a lower risk of breast cancer (*89*). To determine whether dietary fat may have affected postmenopausal cancer patients differently, data were analyzed separately for 1071 postmenopausal cancer cases after 14 years' follow-up. Neither total nor saturated fat intake was associated with an increased rate of breast cancer (*29*). Recently published data from five other cohort studies in Sweden (*243;271*), California (*91*), The Netherlands (*261*), Singapore (*62*) and Italy (*183*) also do not support the hypothesis that saturated fat or a "Western" diet is related to breast cancer incidence.

Data from the Nurses Health Study II, in which 90,655 premenopausal women followed for eight years included 714 incident cases of breast cancer, did indicate that higher intakes of total fat and animal fat were associated with a modestly increased risk of invasive breast cancer for premenopausal women (*34*).

Case–Control studies. Nine case–control studies on diet and breast cancer have been published within the past two years. Of these, three found no association between breast cancer and intakes of meat, saturated fat or total fat. Three studies reported a positive association with higher intakes of meat, and four studies reported some increase in risk associated with increased saturated fat intake. No significant difference in relative risk was observed between dietary intake of specific fatty acids, total fat, or saturated fat for 414 cases in Canada (*177*), 355 cases in Germany (*84*), and 237 cases in Sweden (*270*) and their controls. A Japanese study of 2385 breast cancer cases and 19,013 hospital controls did not find a significant relation between breast cancer and a greater consumption of meat (*86*). But, higher intakes of red meat [in China (*84*)] and particularly if it was deep fried or cooked until well done [in Germany (*40*)] were associated with an increased risk of breast cancer. A significantly increased risk for breast cancer was also associated with consumption of fatty meat in 441 cases in the U.S. as compared to controls. A non-significant decrease in risk was observed for consumption of low-fat meat (*222*).

Some earlier case–control studies also indicated that dietary fat was not significantly related to breast cancer, including data for 820 cases in Greece (*112*), 834 cases in China (*276*), 220 cases in England (*30*), and a meta-analysis of 23 studies published between 1978 and 1992 (*16*). Higher intakes of meat, particularly red meat, were associated with breast cancer risk in the U.S. (*249*).

Comparison of data from different studies can be difficult because of differences in methodology and analysis of data. One study, involving 168 cases and 672 controls, suggests that errors in dietary measurement may obscure a relation between dietary fat and cancer. When diet was assessed by use of a food frequency questionnaire, there was no correlation between saturated fat intake and breast cancer; when diet was measured using a food diary, there was an increased risk of cancer at higher levels of dietary saturated fat (*11*). Analyses of data from an Italian case–control study involving 2569 cases of breast cancer revealed that the statistical method used for adjusting fat intake for other possible confounding factors could alter the significance of dietary fat (*43;57*).

As an alternative to direct dietary assessment, two studies examined the fatty acid composition of serum lipids, which are believed to reflect medium-term (weeks to months) consumption of dietary fat. Analyses of serum lipids from 127 breast cancer cases in Finland (*203*) and 197 cases in the U.S. (*207*) and their controls revealed that the percentage of saturated fatty acids was significantly higher in cases. In the Finnish study, this was found to be primarily due to greater levels of palmitic acid.

Clinical studies. Some clinical trials investigated the possible association between diet and breast cancer by feeding women carefully controlled diets and observing any changes in biomarkers associated with breast cancer. A randomized trial was conducted to determine the effects of a low-fat, high-carbohydrate diet on women with extensive areas of radiologically dense breast tissue, a known risk factor for cancer. After two years, there was a significant reduction in the area of density in women consuming the experimental diet as compared to the normal diet. Analysis of the foods in the two diets revealed that the women on the low-fat diet consumed significantly more cholesterol. Saturated fat intake was of borderline significance (*118*).

In another trial, 14 women consumed, in a randomized crossover fashion, both a high saturated fat "Western" diet and a diet with a similar amount of total fat but most of the saturated fat was replaced by polyunsaturated fat (*24*). There was no significant dif-

ference between serum estrogen levels or urinary estrogen metabolites during the two months on the different diets. The authors concluded that if saturated fat does affect cancer incidence, it apparently does not do so by affecting hormone levels. A year-long randomized trial of a low-fat, high-fiber diet also failed to demonstrate a significant effect on female hormone levels (*63*). Other dietary intervention trials are underway and may provide more useful information in the future.

Animal studies. A meta-analysis of data from 97 reports of experiments with a total of 12,803 rodents examined the relationship between different dietary fatty acids and tumor incidence. Some polyunsaturated fatty acids (n-6 compounds) had a strong tumor enhancing effect while saturated fatty acids had a weaker enhancing effect (*53*).

In a recent experiment, human breast cancer cells were inoculated into mice that were maintained on different diets. Tumor growth rates were highest and metastasis occurred in mice fed a diet high in linoleic acid (n-6 polyunsaturated fatty acid), whereas tumor growth was significantly slower in mice fed a diet high in palmitic acid and the cancer did not spread in these mice (*218*).

Ovarian Cancer

Ovarian cancer is a major cause of cancer mortality in the U.S. because of the difficulty in early diagnosis and the invasiveness of the disease. As with many other cancers there are international differences in incidence, which suggest that dietary or lifestyle variations may affect development of this cancer. A meta-analysis of eight case–control studies of a total of 6689 subjects (2529 cases), published between 1984 and 1999, indicated that risk for ovarian cancer was associated with an odds ratio of 1.2 for saturated fat, 1.24 for total fat, and 1.7 for animal fat (*101*). Results from four of the eight studies controlled for total caloric intake; the others did not. A more recent Italian study of 1031 cases of ovarian cancer and 2411 controls reported no increased cancer risk associated with higher intakes of total fat, saturated fat, or animal fat (*10*). No association was observed between intake of any type of fat and ovarian cancer in a prospective cohort (Nurses' Health Study) with 80,258 cohort members and 301 incident cases of ovarian cancer (*9*).

Endometrial Cancer

Endometrial cancer has been associated with obesity and with use of hormone replacement therapy and reproductive factors that affect hormone levels. It has been suggested that dietary factors may also play a role in development of this cancer. As with some other cancers, case–control studies indicate that total, saturated or animal fat intake may be important whereas data from prospective cohort studies have failed to support this relationship. A case–control study of 20 cases and 20 population controls in Sweden attempted to circumvent the recall bias that may be associated with dietary questionnaires and analyzed the fatty acid content of abdominal fat samples as a biomarker for dietary fat. Cases had higher concentrations of intermediate chain length fatty acids (C12-C16), a lower ratio of polyunsaturated to saturated fatty acids, and lower levels of C18 saturated and polyunsaturated fatty acids (*147*). They also reported consuming more butter, bacon and whole milk. On the other hand, 221 Canadian women who developed endometrial cancer after 8–13-years' follow-up had not reported, at baseline, diets significantly higher in total, saturated, or animal fat than 3697 cancer-free cohort members (*107*). In fact, a modest decrease in risk was noted for higher intakes of saturated and animal fats.

Prostate Cancer

Despite much research, causes for prostate cancer remain elusive. Incidence increases exponentially with age and varies by geography, family history, and race/ethnicity. Early epidemiological studies implicated dietary fat as a possible causal factor for this cancer. More recent studies have yielded inconsistent results although several studies have implicated some factor associated with meat or animal fat. If there is a causal relationship between dietary fat and prostate cancer, it has been suggested that it is mediated through effects on prostaglandin synthesis or sex hormone metabolism which, in turn, promote tumor growth (*121;172;184;266;282*). It has also been suggested that diet may not be an important factor in younger men who develop this cancer as compared to older men (*256*).

One prospective study of 25,708 men in Norway followed for 3–12 years after an initial assessment identified 72 cases of prostate cancer. Examination of dietary history revealed no association between cancer and energy adjusted intakes of total, saturated, monounsaturated, or polyunsaturated fats (*256*). Another prospective study (*70*), the Health Professionals Follow-Up Study, identified 279 new cases of prostate

cancer, including 126 advanced cases, among 47,855 participants after four years of follow-up. Dietary intakes of total fat, red meat, and saturated fat were not significantly associated with incidence of prostate cancer in the whole group but consumption of total fat, red meat and butter (but not other dairy products) was related to an increased risk of advanced prostate cancer. A third prospective study of 384 men diagnosed with prostate cancer in Quebec elicited information on usual dietary intake within a few months of diagnosis. In the next five years, 32 patients died. After controlling for stage of cancer, age, and total energy intake, saturated fat was found to be associated with disease-specific mortality (*165*).

Recent case–control studies have yielded inconsistent results. For 232 cases and 231 controls in Canada, there was some evidence of an inverse association between prostate cancer and intakes of total, animal, and saturated fats — i.e., higher fat intake was weakly correlated with lower cancer risk (*66*). No evidence for an association between prostate cancer risk and total or saturated fat was observed in a study of 328 cases and 328 controls in the UK although average fat intake of both groups was high (*114*). For 133 cases and 265 neighborhood controls in China (where prostate cancer is relatively rare), daily fat intake was significantly higher in cases. The calculated odds ratios for the association between prostate cancer and saturated fat intake was 2.9 while odds ratios for total and unsaturated fat intakes were 3.6 and 3.3, respectively (*136*). Animal fat and linolenic acid (an unsaturated fatty acid) were positively associated with prostate cancer among 217 cases and 434 controls in Spain (*197*). Total energy intake was positively associated with both localized prostate cancer and cancers that had spread in 605 cases of prostate cancer in the U.S. as compared to 592 controls. Total, monounsaturated, and saturated fats were positively associated only with prostate cancers that had spread (*126*). When total fat, animal fat and saturated fat intakes of 101 prostate cancer patients in Serbia were adjusted for total energy intake and compared to that of 202 controls, there was no significant association between cancer incidence and fat intake. Adjustment of the data for 17 other nutrients yielded a positive correlation for the third compared to the first tertile of saturated fat intake but the linear correlation was not significant (*259*).

Ethnicity is correlated with prostate cancer risk but it is not known whether this is related to heredity, diet, or other cultural lifestyle differences. To investigate possibly relevant factors, 1655 black (high risk), white (moderate risk), and Asian-American/Canadian (low risk) patients in Canada and the U.S. were compared with 1645 matched controls (*265*). Total fat intake was significantly associated with prostate cancer risk in all groups. Saturated fat intake was associated with a higher risk for patients with an Asian background than for the other two groups. In all groups, risk was higher when cases with advanced cancer (as compared to total cancer cases) were compared to controls. The authors concluded that saturated fat may be related to prostate cancer risk but that other factors are largely responsible for ethnic differences in risk.

Lack of an animal model for prostate cancer has hampered laboratory experiments to investigate the possible role of dietary fat in cancer development. Some in vitro studies with cultures of prostate cancer cells demonstrated that n-6 polyunsaturated fatty acids (such as linoleic acid) promote growth of cancer cells while n-3 polyunsaturated fatty acids (such as linolenic acid) inhibit tumor growth (*184*). Experiments with branched chain fatty acids suggest that they may be involved in prostate cancer development. An enzyme required for the metabolism of these fatty acids is overexpressed in most prostate cancers. Branched chain fatty acids are present in meat and dairy products (*169*).

Testicular Cancer

Testicular cancer is relatively rare and its incidence varies internationally, suggesting that environmental or lifestyle differences may contribute to the etiology of this disease. Several risk factors have been suggested for testicular cancer but there have been few studies on the role of diet. Results of a case–control study of testicular cancer (160 cases, 136 controls) in the U.S. indicated that higher dietary intakes of total fat, saturated fat, and cholesterol (adjusted for total energy intake) were each associated with an increased risk of nonseminoma testicular cancer but did not appear to be associated with increased risks for seminoma or mixed germ cell tumors (*224*). Another U.S. case–control study (117 cases, 334 hospital controls) indicated that intakes of dietary fat and saturated fat (adjusted for total energy intake) were not associated with an increased risk of nonseminoma and mixed germ cell types of cancer but were suggestive of an increased risk of seminomas (*15*). Both research groups caution that the sample sizes were small (because this disease

is relatively rare) and that diet during adolescence may be more relevant to development of testicular cancer than more recent dietary history. They also point out that diet and other environmental factors may play a greater role in the etiology of some types of testicular cancer than for others.

A Canadian case–control study of testicular cancer, involving 601 cases and 744 population controls, reported data that suggested that a high intake of dairy products, particularly of cheese, is associated with an elevated risk of testicular cancer. Associations between testicular cancer and intakes of saturated fat and total fat (adjusted for energy intake), luncheon meats, and other meats were inconsistent (*65*).

Other Cancers

A recent case–control study of adenoma of the esophagus (124 cases) and of the distal stomach (124 cases) from Nebraska suggested that fat intake may be associated with development of these cancers (*32*). Because of the rapid course of this disease, a majority of cases had died before the researchers could interview them. Dietary information on 76% of the esophageal cancer cases and 80% of the stomach cancer cases was provided by close relatives (proxies). Data from proxy interviews revealed no correlation between total or saturated fat intake and risk of either cancer. Data from interviews with 31 esophageal case patients indicated an odds ratio risk of 4.6 for the highest compared to the lowest tertile of saturated fat intake; for 23 stomach cancer cases, the corresponding odds ratio was 3.6.

Cardiovascular Disease

Cardiovascular disease (CVD) involves a progressive buildup of plaque on the inside of artery walls that gradually narrows the internal diameter of the artery and may culminate in a heart attack or stroke if the narrowed arteries are blocked by a blood clot. This process of atherosclerosis may be initiated by injury to the epithelial lining of the artery by: (1) lipid oxidation products — produced internally by oxidation of polyunsaturated fatty acids or consumed in the diet in deep fried foods; (2) smoking — from carbon monoxide and other toxins; (3) hypertension that produces shear stress; (4) bacterial or viral agents — *Chlamydia pneumoniae* and cytomegalovirus have been detected in diseased arteries; or (5) other compounds. Plaque formation begins at the site of injury and progresses over many years as cholesterol esters are deposited, macrophages consume lipid oxides and form foam cells, and smooth muscle proliferates in the area. A third phase of this process involves thrombosis or production of an internal blood clot by aggregation of blood platelets and coagulation initiated by factor VII. If the clot is not dissolved normally, it may occlude the plaque-filled artery causing a heart attack or stroke.

Numerous factors contribute to or are associated with this process. Serum cholesterol levels appear to affect plaque buildup, with LDL (low density lipoprotein) enhancing atherosclerotic plaque buildup while HDL (high density lipoprotein) transports cholesterol away from the arteries to the liver for elimination from the body. Inflammatory mediators may also be involved in plaque formation and several factors affect clot formation. Dietary saturated fat does not appear to be linked to the epithelial injury that initiates the process of atherosclerosis but it may be involved in the progression of plaque formation and the formation of the thrombus (*27;127;164;214*).

Nondietary Factors Affecting Results of Studies of Dietary Fat and Cardiovascular Disease

Despite the epidemiological and clinical data described in the following sections that support a role for dietary fat in the atherosclerotic process, there are many unanswered questions as to how dietary fat is involved in the development of cardiovascular disease. Although dietary fat intake and serum cholesterol levels in men aged 55–64 in Ireland and France were similar in 1985–1987, mortality from heart disease was 761/100,000 in Belfast and 175/100,000 in Toulouse. Some other countries with relatively high fat intakes also have a relatively low incidence of cardiovascular disease (*127*). Low-fat diets have been shown to reduce average serum cholesterol levels during clinical trials, but individuals respond differently to these dietary interventions. Hereditary effects on enzymes related to lipid metabolism and effects of gender (perhaps involving hormonal effects) may explain some of these differences.

Genetic effects. Some of the international discrepancies among epidemiological studies and the inconsistent results of some clinical trials may be the result of hereditary susceptibility to development of cardiovascular disease. A significant interindividual variation in the

response of serum cholesterol levels to diets low in total or saturated fats is well recognized, and several recent reviews have discussed evidence that genetic differences in genes coding for apolipoproteins, lipoprotein lipase, cholesteryl ester transfer protein, LDL receptor, and a number of other proteins affect whether an individual's serum cholesterol levels respond favorably to diets restricted in fat (*123;159;258;274*). Other recent studies have implicated variations in hepatic lipase (*181*) and scavenger receptor class B (*187*), both of which affect HDL metabolism, as related to dietary effects on serum cholesterol levels.

Gender effects. Some epidemiological research has documented differences between males and females in the association between dietary fat and cardiovascular disease. Results from a cohort of 1225 men and 1451 women in Great Britain with a total of 155 cardiovascular deaths indicated a strong relationship between dietary fat and mortality from heart disease in women but not in men (*14*). There may be physiological reasons for these differences but the authors also suggest that differences between the sexes in rates of smoking and exercise (even though these factors were considered in statistical calculations) and in socioeconomic status as well as in the methods for gathering dietary information may have contributed to the differences observed.

In a crossover clinical study, moderately hypercholesterolemic men and postmenopausal women consumed a diet containing 25% of energy as fat, 4% as saturated fat and a diet with 35% of energy as fat, 14% as saturated fat for 6 weeks each. The lower fat diet resulted in greater reductions in total cholesterol and LDL cholesterol in men than in women, and postprandial triglycerides were reduced in men but not in women. The lower fat diet also decreased levels of beneficial HDL cholesterol in both sexes but the reduction was less in men (*140*). Other studies of normolipidemic or hypercholesterolemic men and women on high- and low-fat diets also reported that women experienced a larger drop in HDL levels when consuming a lower fat diet (*37;120*).

Aerobic fitness. Despite having similar dietary intakes of fat, overweight, middle-aged men who were more aerobically fit were found to have lower levels of plasma saturated fatty acids than less fit men. This may be caused by differences in fat metabolism in the liver and muscles related to general aerobic fitness (*122*).

General Epidemiological and Clinical Studies on Dietary Fat and Cardiovascular Disease

Heart disease. Coronary heart disease remains the major cause of premature death in affluent countries despite declining rates in recent years (*157*). Dietary fat and saturated fat are frequently linked to the incidence of cardiovascular disease and to risk factors or physiological conditions correlated with heart disease. This general section will include studies that relate dietary fat to the incidence of or death from cardiovascular disease. Later sections will include papers related to diet and serum cholesterol levels, oxidative stress, and other conditions related to development of cardiovascular disease.

A prospective study of 80,082 women in the Nurses' Health Study identified 939 cases of cardiovascular mortality or non-fatal heart attack during 14 years of follow-up. After adjustment for confounding variables (but not for intake of dietary fiber), saturated fat and *trans* unsaturated fat intakes were positively and significantly related to cardiovascular events, but total fat intake was not associated with increased risk. Of the individual saturated fatty acids, those with less than 12 carbons were not associated with risk while C12-C18 fatty acids were each associated with increased risk (*97;98*).

Data on 734 men with fatal and non-fatal coronary events from a cohort of 43,757 in the Health Professionals Follow-Up indicated a significant positive association between coronary events and dietary saturated fat. This relationship remained significant after controlling for several known risk factors. But after adjustment for intake of dietary fiber, saturated fat intake was no longer significantly associated with non-fatal cardiac events (*5*). Higher intakes of saturated fat were related to a higher prevalence of cardiovascular disease among type 1 diabetics in Europe, but this relationship was also attenuated by adjustment for dietary fiber intake (*248*).

Other epidemiological studies reported statistically significant associations between saturated fat intake and coronary heart disease mortality among ethnic Chinese in Singapore as compared to Hong Kong and mainland China (*47;278*) and nonfatal heart attacks in Costa Rica (*110*). Lower dietary P/S ratios (polyunsaturated to saturated fatty acid ratios) were correlated

with fatal heart attacks in males (but not females) with type 2 diabetes in Finland (*231*) and lower extremity arterial disease in males (but not in females) in the U.S. (*281*). Still other epidemiological studies that indicate an association between dietary total or saturated fat and cardiovascular disease were summarized in recent review articles (*96;100;124;128;214*).

In addition to epidemiological studies, numerous intervention studies or clinical trials have tested hypotheses concerning the role of dietary fat in development of cardiovascular disease. A systematic review and meta-analysis of 27 randomized controlled trials involving modification of dietary fat and cardiovascular disease (CVD) provided weak evidence that reducing serum cholesterol levels reduced CVD. The authors concluded that there was only limited and inconclusive evidence of the effects of total and saturated fat on cardiovascular mortality and morbidity (*90*). Other reviews reported that cardiovascular disease could be reduced by several dietary strategies: (1) replacing saturated fat with polyunsaturated fat (same total fat); (2) a Mediterranean diet with more monounsaturated fats replacing some saturated fats and more fruits and vegetables; (3) an Indian vegetarian diet; and (4) fish oil supplements (or consumption of fatty fish twice a week) (*78;96;100;124;128;208;283*). Some of these dietary changes reduced cardiovascular events but did not significantly lower serum cholesterol levels. Most of these reviews concluded that reduction of dietary saturated fat was beneficial to cardiovascular health, but one reviewer concluded that evidence from clinical trials suggested it was more important to increase dietary unsaturated fats than to decrease saturated fats (*180*).

Some scientists who have reviewed the literature on cardiovascular disease contend that some of the risk factors associated with cardiovascular disease are not causative factors and that fat or saturated fat intake may not be a major determinant of cardiovascular disease. One such proponent has written two recent reviews. In the first, Ravnskov points out that not all epidemiological studies support an association between dietary fat and CVD. In the majority of the cross-sectional studies, cohort studies, and case–control studies reviewed, data were not supportive of a specific harmful effect of dietary saturated fat (*199*). In comments on this paper, it was pointed out that some of the studies classified as negative were partially supportive and that some of the epidemiological studies described did not adequately assess other factors that might contribute to CVD. However, some randomized clinical trials (which are considered a better indicator of causality) fail to offer proof that reducing saturated fat intake reduces CVD risk (*73*).

A later review by Ravnskov (*200*) contends that most studies that contradict the hypothesis that dietary saturated fat causes cardiovascular disease are ignored. Dietary saturated fats do appear to increase serum cholesterol levels, but a reduction in serum cholesterol levels (in the absence of statin drugs) does not appear to translate into lower risk for cardiovascular disease. Dissenting comments on this review point out that there are many studies in which serum cholesterol levels and dietary fat are correlated with atherosclerosis and cardiovascular disease (*264*).

Stroke. A broad epidemiological survey of average alcohol and saturated fat intake in 17 countries was compared to stroke mortality in those countries. Dietary saturated fats and urinary sodium excretion were positively associated with stroke mortality (*211*). Serum fatty acids were measured in stored serum samples from 197 Japanese cases of stroke and compared to those in samples from 591 controls. Percentage composition of myristic and palmitic acids (but not of stearic acid) were significantly higher and of linoleic acid were significantly lower in cases than in controls. These associations remained significant after adjustment for smoking and other cardiovascular risk factors (*105*). On the other hand, a study of serum fatty acids in 96 cases of incident stroke and 96 age-matched controls from a U.S. cohort (Multiple Risk Factor Intervention Trial) demonstrated a positive association between stearic acid (but not myristic or palmitic acids) and a negative association between linolenic acid in serum phospholipids and incidence of stroke. When data were adjusted for smoking, blood pressure and serum cholesterol levels, these associations were not significant (*225*). Data from the large Health Professionals Follow-Up Study also failed to provide significant evidence that dietary total or saturated fat was related to the incidence of ischemic or hemorrhagic stroke. During 14 years of follow-up of this group, there were 725 incident cases of stroke, but neither fat intake nor consumption of red meat or dairy products was associated with incidence of stroke (*83*).

Hypertension. Several dietary factors have been linked to development of hypertension. Epidemiological studies in the U.S. (*232*) and in India (*8*) have

identified multiple dietary factors, including saturated fat intake, associated with hypertension.

Saturated Fat and Serum Cholesterol Levels

Data from the U.S. National Health and Nutrition Surveys (NHANES I, II, III) documented an average decrease in the age-adjusted mean percentage of energy consumed as fat from 36.4% (in 1978) to 34.1% (1990) and dietary saturated fat levels decreased from 13.2% to 11.7%. Total and LDL cholesterol levels also declined during this time by 8 mg/dL each (*50*). These data suggest a correlation between serum LDL levels and dietary fat. Effects of a variety of dietary factors on serum cholesterol and lipoprotein levels were discussed in a comprehensive review in 2002 (*214*). A meta-analysis of 224 published studies on diet and serum cholesterol levels indicated that consumption of a diet containing less fat and less saturated fat decreased total and LDL cholesterol levels. A diet containing 30% of energy from fat with <10% from saturated fat as compared to the "average" American diet was predicted to lower total and LDL cholesterol by about 5% (*95*). Other population studies have demonstrated that lower intakes of total or saturated dietary fat correlate with lower serum cholesterol levels in: 870 10–11-year-old children in Taiwan (*33*); 858 individuals with type 2 diabetes in the U.S. (*161*); and 423 adults in Taiwan compared to 420 adults in the U.S. (*152*).

However, in clinical trials, there is inter-individual variation in response to dietary changes, and replacement of dietary fat with carbohydrates may decrease the "good" HDL cholesterol levels. Lower intakes of saturated fats have been shown to reduce serum LDL cholesterol in: other trials with 1182 adolescents in the U.S. (*176*); 139 healthy Australian men (*139*); 42 healthy young adults in New Zealand (*87*); 55 overweight or obese postmenopausal women in the U.S. (*28*); hypercholesterolemic Canadian men (*7*); 14 hypercholesterolemic subjects in the U.S., aged 46–78 years (*142*); 36 hypercholesterolemic subjects in the U.S., aged 52–73 years (*143*); 162 healthy subjects in Australia and Europe (*205*); and 2868 European diabetic subjects (*248*).

Studies of the effects of individual saturated fatty acids indicate that myristic acid (C14) is the most hypercholesterolemic while stearic acid has no effect, either positive or negative, on serum cholesterol levels (*75;125*). Myristic acid is reported to increase serum LDL levels by repressing receptor-dependent LDL transport into the liver (*272*). Myristic acid also increases serum levels of beneficial HDL cholesterol (*245*).

Oxidation of serum lipoproteins is also related to development of atherosclerosis. Consumption of a high-fat diet was found to increase the susceptibility of lipoproteins to oxidation in healthy men and women (*275*).

Serum cholesterol levels are very likely related to heart disease and some populations with the highest rates of coronary heart disease mortality have high total and LDL cholesterol levels. One such population is located in northern Norway where approximately 25% of 13–14-year-old students had total cholesterol levels >200mg/dl. Dietary fat intake of these students was estimated at 30–34% of energy (*25*). However, there are other populations with very low rates of CVD in spite of having "unfavorable" LDL and HDL cholesterol levels. An example is a group of people living on Trobriand Islands in the Pacific. The diet of these people includes about 69% of energy from carbohydrate and 21% from fat, including 17% from saturated fat. LDL levels are higher and HDL levels are lower than what is considered healthy for Western populations. Nevertheless, CVD appears to be absent among Trobriand Islanders (*145*). Certainly there are other dietary and lifestyle and probably genetic differences between these populations that also affect development of CVD.

Saturated Fat and Inflammatory Mediators

C-reactive protein (CRP) is a marker of inflammation that has been associated with development of cardiovascular disease. Analysis of data from 4900 participants in the NHANES survey from 1999–2000 indicated that saturated fat consumption was modestly associated with CRP levels (*116*). However, a clinical trial utilizing diets with six different fat components found that the saturated fat (butter)-containing diet did not increase CRP levels as compared to the other diets with unsaturated fats. This discrepancy may be explained by another epidemiological study in which dietary intake was compared to inflammatory mediators in overweight and lean subjects. An association of CRP levels and interleukin–6 levels with saturated fat was only observed in the overweight subjects (*54*). In subjects with moderately elevated serum cholesterol levels, a clinical trial with a diet containing butter as compared to soybean oil was associated with higher levels of interleukin-6 and interleukin-1β but the differ-

ences were not statistically significant (*79*). A high-fat meal was also associated with interleukin-18 levels in type 2 diabetics (*51*).

Saturated Fat and Arterial Endothelial Function

Impaired endothelial function in arteries is an early stage in atherosclerosis, and this reduced function has been correlated inversely with the proportion of total serum saturated fatty acids, particularly of myristic acid in men (but not in women) (*234*). High saturated fat meals decreased endothelial function in healthy males compared to a low-fat meal (*175*). Effects of unsaturated and saturated fatty acids on endothelial function were discussed in a recent review (*36*).

Saturated Fat and Thrombus (Clot) Formation

Several sets of reactions, involving a number of factors, occur as blood coagulates and clots form. Coagulant activity of factor VII (VIIc) is predictive of fatal heart disease, and it appears that factor VII concentration determines the severity of thrombosis. Total dietary fat has a long-term effect on this process by increasing plasma factor VII antigen concentration. When the usual diet is rich in saturated fatty acids, there is also an acute effect whereby some of the factor VII is converted to active form for several hours after a meal. Fibrinogen is also involved in clotting reactions; concentrations are higher in men at high risk for heart attacks and appear to be predictive of both fatal and nonfatal cardiac events. However, fibrinogen concentrations do not appear to be influenced by dietary fat content or composition (*168*).

Factor VII coagulant activity decreased by 11% in premenopausal women after they consumed a lower fat (30% of calories) diet for 20 weeks as compared to a diet with 38% of calories as fat (*19*). In another test of the effects of dietary fat on VIIc, 25 healthy women consumed diets containing high or low levels of saturated fats or high levels of unsaturated fats for three weeks each. After the high saturated fat diet, VIIc, fasting activated factor VII, and factor VII antigen levels were all higher than following the other two diets. However, both high fat diets caused an increase in activation of factor VII after a meal as compared to the low-fat diet (*146*). It appears that both quantity and composition of dietary fat are important.

In a clinical trial with healthy young men, no difference in VIIc or other blood coagulation factors was noted after two weeks of consuming diets containing 38% of calories as fat, primarily as stearic, oleic or linoleic acids (*104*). Following consumption of a diet enriched with stearic acid for 40 days, blood platelets and some other hemostatic factors were less activated than following a diet enriched in palmitic acid (*215*).

Obesity

Obesity is increasing worldwide and has become a major health concern because it is associated with numerous chronic diseases. Many scientific articles on this topic have analyzed the relationship between obesity and diabetes, cardiovascular disease, and cancer. In this review, the question of primary importance is: Is a diet high in saturated fats associated with the development of obesity? Certainly excess calories from fats and carbohydrates will cause weight gain if there is no compensatory increase in exercise to utilize this energy intake. Beyond the imbalance between energy intake and expenditure, do saturated fats have specific physiological effects, for example on hormone levels, that promote fat cell formation or fat deposition, more than other fats or carbohydrates? Some data reviewed in 2002 indicate that dietary fat may affect food intake, by its effects on metabolic signals and hormones, and may affect fat deposition, by decreasing fatty acid oxidation and increasing fat synthesis. The physiological effects of a high-fat diet are complex and also depend on the activity level and genetics of an individual (*81*).

Some research indicates that some fatty acids are oxidized more rapidly than others. If saturated fatty acids are more likely to be stored than to be oxidized to produce energy, then a diet high in saturated fats might be more conducive to obesity. Six male subjects consumed two diets differing in the ratio of polyunsaturated to saturated fats (P/S ratio) for two weeks each to determine different effects on energy metabolism. When fed a diet with a P/S ratio of 1.67, resting metabolic rate and diet-induced thermogenesis were both higher than with a diet with a P/S ratio of 0.19 (*141*). To investigate the *in vivo* oxidation of different fatty acids, four volunteers consumed heated meals containing labeled saturated fatty acids [C12 (lauric), C16 (palmitic), or C18 (stearic)] or a C18 unsaturated fatty acid. Lauric acid was the most highly oxidized, followed by the unsaturated fatty acids; stearic acid was oxidized the least (*44*). These results indicate that

saturated fats are oxidized more slowly than unsaturated fats. In a comparison of fat oxidation rates after a meal, 14 volunteers consumed meals rich in monounsaturated fat (olive oil) or saturated fat (cream). Fat oxidation rate was significantly greater and carbohydrate oxidation was lower after the meal containing olive oil (*189*).

Epidemiological data comparing fat intake in various countries with incidence of obesity and migrant studies, comparing migrants to the U.S. with others who did not migrate from their home country, support a positive association between dietary fat and obesity. However, recent reviews presenting evidence from medium- and long-term trials, weight loss studies, and intervention trials conclude that dietary fat is not the major determinant of body fat. During the past two decades there has been a substantial decline in percentage of dietary energy from fat in U.S. diets but a massive increase in the prevalence of obesity. Other lifestyle factors, in particular lack of exercise, are likely to be major factors responsible for the obesity epidemic. Other dietary factors such as the glycemic index (related to content of refined, rapidly absorbed carbohydrates) and genetic factors may also contribute to development of obesity (*151;195;268*).

Some recent epidemiological studies report no significant association between dietary fat, as assessed by questionnaires, and body mass index (BMI) or other measures of adiposity. Fat intake, including saturated fat intake, was only weakly correlated with amount of adipose tissue or BMI in 349 white adults in the U.S. (*132*); 2868 persons with type 1 diabetes in Europe (*247*); 27,862 adults in Greece (*251*); and 181 children in Canada (*69*). Overall, evidence linking dietary saturated fats to body fatness appears to be weak according to a review of earlier work (*6*).

Results from other studies indicate that dietary fat may contribute to an increase in adiposity. Higher levels of dietary fat were correlated with increased body fatness in 128 male Canadians (*46*); 85 obese Spaniards (*64*); and 15,266 males in the U.S. (*213*). Percentage of dietary energy from total fat (but not saturated fat) was significantly associated with indices of adiposity in 221 non-obese French girls but was not significant for 280 French boys (*155*).

Another approach to assessing the importance of dietary fat to obesity involves examining the effects of low-fat diets as compared to low-carbohydrate diets on weight loss. Overall, in the short-term trials to date, the data indicate that persons lose weight on both types of diets and may, in fact, lose weight faster on the low-carbohydrate diets. However, neither diet appears to be better than the other at producing a weight loss that is maintained in the long term (*195;268*). A randomized crossover trial of 8 obese men in Australia involved consumption of diets high in saturated fat or in monounsaturated fat for four weeks each. A slightly greater average weight loss (2.6 vs. 2.1 kg) occurred on the high saturated fat diet compared to the high monounsaturated fat diet (*190*). Another dietary intervention in the U.S. with 23 obese patients with atherosclerosis found that body weight and percent fat decreased during 6 weeks on a high saturated fat (up to 50% of energy consumed) diet that contained no starch (*82*).

Results of two six-month comparisons of low-carbohydrate and low-fat diets both indicated that weight loss was greater on the very low carbohydrate diet (*21;209*). Subjects on the low carbohydrate diets increased total fat intake to 41% of calories in one study and 50% of calories (with 20% as saturated fat) in the other study. Both studies reported some issues with dietary compliance which may affect the effectiveness of these diets in long term weight loss programs. But both studies demonstrated that diets containing high levels of fat and saturated fat can result in weight loss rather than weight gain.

One recent review suggests that certain fatty acids may affect weight gain and loss by interacting with receptors that determine insulin responsiveness and satiety (*20*). However, a trial with food enriched in either saturated or monounsaturated fats fed to lean volunteers demonstrated no difference in satiety (*3*).

Genetic factors are believed to be responsible for a high percentage of the population variance in obesity. Therefore, it could be that persons with some genetic traits are more susceptible to high levels of dietary fat than others. In a study of 334 female twins in the UK, no gene–environment interactions involving total or saturated fat intakes were observed (*74*). However, an analysis of PPARγ (peroxisome proliferator-activated receptor γ) genes in 2141 subjects from the Nurses' Health Study indicated that there was an interaction between genotype and dietary fat in relation to BMI (*163*). Among women with two wild-type alleles, those with the highest intake of dietary total or saturated fat had the greatest BMI. This relationship was not observed in women with one or two variant alleles. Thus PPARγ genotype may be a factor in determining physiological responses to dietary fat.

Approximately a decade ago, the compound leptin was hailed as the "obesity hormone" because it is produced primarily by fat cells and acts to reduce food intake and increase energy expenditure in laboratory animals. Numerous animal experiments have demonstrated that dietary fat and saturated fat can affect leptin production and leptin receptors. Leptin levels increase as dietary fat and saturated fat increase but obese humans and animals appear to develop leptin resistance such that this compound is no longer as effective in regulating appetite and fat metabolism. This may be a result of impaired leptin-receptor signaling or reduced transport of leptin into the brain (*85;92*). Such experiments indicate that dietary fat and saturated fat may have effects beyond their caloric value. They may alter leptin-mediated reactions and may also affect formation of new fat cells (*223*).

Diabetes

A rapid increase in non-insulin-dependent diabetes mellitus (NIDDM, also known as type 2 diabetes) has accompanied the dramatic increase in obesity among middle-aged and older people, and the two are thought to be causally related (*38;102*). (Type 1 diabetes, insulin-dependent diabetes, usually occurs in childhood when pancreatic cells fail to produce insulin.) NIDDM patients produce insulin but their tissues have become resistant or insensitive to this hormone. Therefore, cells such as those in skeletal muscles do not readily take up glucose from the blood and serum glucose levels rise. At high blood concentrations, glucose reacts with amino groups of proteins, including those in hemoglobin. Glycated hemoglobin (HbA_{1C}) levels are considered a measure of blood glucose levels during the previous 6–8 weeks. Hyperinsulinemia also occurs in NIDDM as the body attempts to compensate for insulin resistance by producing more insulin. Long-term elevated induction of insulin activity can damage the pancreatic β-cells that produce insulin, causing a subsequent decline in insulin levels. Elevated serum glucose and insulin concentrations and insulin sensitivity are often used as measures of a pre-diabetic or diabetic condition.

Reviews. Several recent articles have reviewed previous animal experiments and epidemiological studies and discussed the possible effects of dietary components on the development of diabetes (*38;99;102;144;204;257*). A high-fat diet generally has a negative effect on glucose metabolism and induces diabetic changes in laboratory animals. Epidemiological studies in humans also implicate high-fat diets in the development of diabetes. However, the significance of the association between dietary total or saturated fat and diabetes is often lost when data are adjusted for body mass index (a measure of obesity). Obesity and lack of exercise appear to be major determinants of type 2 diabetes. There are some studies indicating that high intakes of saturated fat are associated with insulin resistance. Higher proportions of saturated fatty acids in serum cholesterol esters and cell membranes were directly correlated with insulin resistance. The presence of more saturated fatty acids in membranes could affect transport of materials in and out of cells and the binding of insulin to cells. Results of clinical trials of feeding diets varying in total or saturated fat content have been inconsistent.

Recent general epidemiological studies. Epidemiological studies published during the past 3 years also produced variable results. Data from the Iowa Womens' Health Study [cohort of 35,988 women followed for 11 yr, 1890 incident cases of type 2 diabetes (*166*)] and the Health Professionals Follow-Up [cohort of 42,504 men, followed for 12 yr, 1321 incident cases of type 2 diabetes (*254*)] demonstrated that total and saturated fat intakes were not associated with development of diabetes after adjustment for body mass index and other confounding factors. No dietary differences in saturated fat intake were noted between 90 men who developed diabetes or impaired fasting glycemia and 805 other cohort members followed for four years in Finland (*130*). However, at baseline, there was a higher proportion of saturated fatty acids in serum fatty acids of the men who later developed diabetes. A higher baseline proportion of saturated fatty acids was also present in phospholipids and serum cholesterol esters of 252 people who developed diabetes compared to 2657 other U.S. cohort members after nine years of follow-up (*262*). The multinational Mediterranean Group for the Study of Diabetes reported an association between intakes of total and animal fat and development of diabetic or pre-diabetic conditions. Lack of exercise and a family history of diabetes were also strongly correlated with development of type 2 diabetes (*244*). The prospective Japanese Hisayama study of 1075 subjects found 24 cases of diabetes and 119 cases of glucose intolerance after 5–6 years of follow-up. Females with glucose intolerance had a decreased dietary P/S ratio (ratio of polyunsaturated to saturated fatty acids) after follow-up as compared to the diet of

those who remained healthy, but the P/S ratio was not associated with glucose intolerance in males (*117*). Two case–control studies of diabetes occurring during pregnancy (gestational diabetes) reported that intakes of total and saturated fat were significantly higher among cases than controls (*12;170*).

Serum insulin levels. Hyperinsulinemia is a marker for insulin resistance. Higher serum insulin concentrations were associated with higher levels of dietary saturated fats in several epidemiological and clinical studies: 652 U.S. males (*185*), 389 elderly Dutch males (*55*), 16 obese, Danish, type 2 diabetics (*35*), 1069 persons in the U.S. (*158*). Higher dietary saturated fat was also associated with greater insulin secretion in rats (*246*). Other research studies reported that saturated fat intake did not increase insulin secretion: 173 men in England (*220*), 8 Austrian men (*52*), and 74 Swedish women (*133*).

β-cell function. As type 2 diabetes progresses, there is a progressive deterioration in the insulin secretory function of the β-cells of the pancreas. One proposed mechanism for the deleterious effects of saturated fatty acids on glucose metabolism is a toxic effect on β-cells. Several *in vitro* studies with β-cells from rats, hamsters, and humans demonstrated that saturated fatty acids caused death of β-cells; monounsaturated fatty acids could exert a protective effect (*48;49;153;154;191*). High-fat diets significantly decreased insulin secretion and elevated triglyceride levels in mice (*269*). However, recent experiments in rats do not support the theory that exposure to excess saturated fatty acids impairs glucose-stimulated insulin secretion (*45*).

Serum glucose levels. Some epidemiological evidence supports a positive correlation between dietary fat and diabetes. In studies using glycated hemoglobin as a marker of elevated blood glucose levels, HbA_{1C} levels were positively correlated with dietary saturated fat in 150 diabetics in New Zealand (*76*); total dietary fat and negatively correlated with P/S ratio in 6223 nondiabetics in England (*80*); and higher total energy and energy-adjusted saturated fat intakes in 1773 healthy people in Europe (*13*). Randomized crossover trials utilizing different diets for three-week periods found that glucose tolerance was less with a saturated fat as compared to a monounsaturated fat diet for 10 healthy females in Finland (*253*) but was similar for 15 NIDDM patients in Denmark whether they consumed low fat/high carbohydrate or high palmitic acid or high stearic acid diets (*237*). Saturated fat intake was not related to impaired glucose tolerance or to serum glucose levels after a glucose tolerance test in 74 postmenopausal women in Sweden (*133*).

Insulin sensitivity/resistance. Correlations of dietary variables demonstrate an inverse relation between insulin sensitivity and total energy or fat intake but this relation often becomes nonsignificant when data are adjusted for body fat or BMI. In recent studies this was true for 74 postmenopausalwomen in Sweden (*133*) and 1173 male and female subjects in the U.S. (*162*). Different fatty acids in plasma phospholipids (as a measure of dietary intake) were not correlated with insulin sensitivity in elderly diabetic subjects (*156*). Higher intakes of total and saturated fat were associated with fasting insulin levels in 38 subjects, nine of whom were diabetic or had impaired glucose tolerance (*149*).

Several clinical trials have tested the short-term effects of different diets on insulin sensitivity. Two studies [a four-week, randomized, double-blind crossover trial with diets high in saturated, monounsaturated, or *trans* fats (*150*) and a one-week crossover diet with diets high in saturated, polyunsaturated, or monounsaturated fats (*52*)] reported that there was no variation in insulin sensitivity with the different types of dietary fat. Two other trials [a four-week, randomized, crossover trial with diets high in saturated, monounsaturated, or a high carbohydrate diet (*186*) and five-week, randomized, crossover trial with diets high in saturated or polyunsaturated fats (*238*)] reported that insulin sensitivity was lowest on the saturated fat diet.

Parkinson's Disease

Since data from previous epidemiological studies on the effects of dietary fat on development of Parkinson's Disease (PD) have been inconclusive, dietary information from 359 incident cases of PD in two large prospective cohorts (Nurses' Health Study and Health Professionals Follow-Up Study) was analyzed and compared to others in these cohorts who did not develop this disease. Intakes of total fat and saturated fat were not significantly related to disease incidence in either males or females. Higher intakes of animal fat were associated with an increased (but not statistically significant) risk for PD in men and a decreased risk for PD in women (*31*).

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References

1. Alavanja MC, Field RW, Sinha R, Brus CP, Shavers VL, Fisher EL, Curtain J, and Lynch CF. 2001. Lung cancer risk and red meat consumption among Iowa women. Lung Cancer 34:37–46.

2. Alavanja MCR, Brown CC, Swanson C, and Brownson RC. 1993. Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. J Natl Cancer Inst 85:1906–1916.

3. Alfenas RCG and Mattes RD. 2003. Effect of fat sources on satiety. Obesity Res 11:183–187.

4. Arab L. 2003. Biomarkers of fat and fatty acid intake. J Nutr 133:925S–932S.

5. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, and Willett WC. 1996. Dietary fat and risk of coronary heart disease in men — cohort follow up study in the United States. Brit Med J 313:84–90.

6. Astrup A, Buemann B, Flint A, and Raben A. 2002. Low-fat diets and energy balance: how does the evidence stand in 2002? Proc Nutr Soc 61:299–309.

7. Beauchesne-Rondeau E, Gascon A, Bergeron J, and Jacques H. 2003. Plasma lipids and lipoproteins in hypercholesterolemic men fed a lipid-lowering diet containing lean beef, lean fish, or poultry. Am J Clin Nutr 77:587–593.

8. Beegom R and Singh RB. 1997. Association of higher saturated fat intake with higher risk of hypertension in an urban population of Trivandrum in South India. Int J Cardiol 58:63–70.

9. Bertone ER, Rosner BA, Hunter DJ, Stampfer MJ, Speizer FE, Colditz GA, Willett WC, and Hankinson SE. 2002. Dietary fat intake and ovarian cancer in a cohort of US women. Am J Epidemiol 156:22–31.

10. Bidoli E, La Vecchia C, Montella M, Dal Maso L, Conti E, Negri E, Scarabelli C, Carbone A, Decarli A, and Franceschi S. 2002. Nutrient intake and ovarian cancer: an Italian case–control study. Cancer Causes Control 13:255–261.

11. Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, and Day N. 2003. Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 362:212–214.

12. Bo S, Menato G, Lezo A, Signorile A, Bardelli C, De Michieli F, Massobrio N, and Pagano G. 2001. Dietary fat and gestational hyperglycaemia. Diabetologia 44:972–978.

13. Boeing H, Weisgerber UM, Jeckel A, Rose HJ, and Kroke A. 2000. Association between glycated hemoglobin and diet and other lifestyle factors in a nondiabetic population: cross-sectional evaluation of data from the Potsdam cohort of the European Prospective Investigation into Cancer and Nutrition Study. Am J Clin Nutr 71:1115–1122.

14. Boniface DR and Tefft ME. 2002. Dietary fats and 16-year coronary heart disease mortality in a cohort of men and women in Great Britain. Eur J Clin Nutr 56:786–792.

15. Bonner MR, McCann SE, and Moysich KB. 2002. Dietary factors and the risk of testicular cancer. Nutr Cancer 44:35–43.

16. Boyd NF, Martin LJ, Noffel M, Lockwood GA, and Tritchler DL. 1993. A meta-analysis of studies of dietary fat and breast cancer risk. Brit J Cancer 68:627–636.

17. Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, and Minkin S. 2003. Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. Brit J Cancer 89:1672–1685.

18. Bracco U. 1994. Effect of triglyceride structure on fat absorption. Am J Clin Nutr 60:S1002–S1009.

19. Brace LD, Gittler-Buffa C, Miller GJ, Cole TG, Schmeisser D, Prewitt TE, and Bowen PE. 1994. Factor VII coagulant activity and cholesterol changes in premenopausal women consuming a long-term cholesterol-lowering diet. Arteriosclerosis Thrombosis 14:1284–1289.

20. Bray GA, Lovejoy JC, Smith SR, DeLany JP, Lefevre M, Hwang D, Ryan DH, and York DA. 2002. The influence of different fats and fatty acids on obesity, insulin resistance and inflammation. J Nutr 132:2488–2491.

21. Brehm BJ, Seeley RJ, Daniels SR, and D'Alessio DA. 2003. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 88:1617–1623.

22. Brennan P, Fortes C, Butler J, Agudo A, Benhamou S, Darby S, Gerken M, Jöckel KH, Kreuzer M, Mallone S, Nyberg F, Pohlabeln H, Ferro G, and Boffetta P. 2000. A multicenter case–control study of diet and lung cancer among non-smokers. Cancer Causes Control 11:49–58.

23. Broadfield E, McKeever T, Fogarty A, and Britton J. 2003. Measuring dietary fatty acid intake: validation of a food-frequency questionnaire against 7 d weighed records. Br J Nutr 90:215–220.

24. Brown BD, Thomas W, Hutchins A, Martini MC, and Slavin JL. 2002. Types of dietary fat and soy minimally affect hormones and biomarkers associated with breast cancer risk in premenopausal women. Nutr Cancer 43:22–30.

25. Brox J, Bjørnstad E, Olaussen K, Østerud B, Almdahl S, and Løchen ML. 2002. Blood lipids, fatty acids, diet and lifestyle parameters in adolescents from a region in northern Norway with a high mortality from coronary heart

disease. Eur J Clin Nutr 56:694–700.

26. Bruce WR, Wolever TMS, and Giacca A. 2000. Mechanisms linking diet and colorectal cancer: The possible role of insulin resistance. Nutr Cancer 37:19–26.

27. Bruckner G. 2000. Fatty acids and cardiovascular disease, pp. 843–863. In: Chow CK (ed.), *Fatty Acids in Foods and Their Health Implications*. Marcel Dekker, Inc., New York.

28. Bunyard LB, Dennis KE, and Nicklas BJ. 2002. Dietary intake and changes in lipoprotein lipids in obese, postmenopausal women placed on an American Heart Association Step 1 diet. J Am Diet Assoc 102:52–57.

29. Byrne C, Rockett H, and Holmes MD. 2002. Dietary fat, fat subtypes, and breast cancer risk: Lack of an association among postmenopausal women with no history of benign breast disease. Cancer Epidemiol Biomark Prevent 11:261–265.

30. Cade J, Thomas E, and Vail A. 1998. Case–control study of breast cancer in south east England — nutritional factors. J Epidemiol Comm Health 52:105–110.

31. Chen H, Zhang SMM, Hernán MA, Willett WC, and Ascherio A. 2003. Dietary intakes of fat and risk of Parkinson's disease. Am J Epidemiol 157:1007–1014.

32. Chen HL, Tucker KL, Graubard BI, Heineman EF, Markin RS, Potischman NA, Russell RM, Weisenburger DD, and Ward MH. 2002. Nutrient intakes and adenocarcinoma of the esophagus and distal stomach. Nutr Cancer 42:33–40.

33. Cheng HH, Wen YY, and Chen C. 2003. Serum fatty acid composition in primary school children is associated with serum cholesterol levels and dietary fat intake. Eur J Clin Nutr 57:1613–1620.

34. Cho EY, Spiegelinan D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, and WillettWC. 2003. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 95:1079–1085.

35. Christiansen E, Schnider S, Palmvig B, Tauberlassen E, and Pedersen O. 1997. Intake of a diet high in trans monounsaturated fatty acids or saturated fatty acids — effects on postprandial insulinemia and glycemia in obese patients with NIDDM. Diabetes Care 20:881–887.

36. Christon RA. 2003. Mechanisms of action of dietary fatty acids in regulating the activation of vascular endothelial cells during atherogenesis. Nutr Rev 61:272–279.

37. Cobb M, Greenspan J, Timmons M, and Teitelbaum H. 1993. Gender differences in lipoprotein responses to diet. Ann Nutr Metab 37:225–236.

38. Costacou T and Mayer-Davis EJ. 2003. Nutrition and prevention of type 2 diabetes. Ann Rev Nutr 23:147–170.

39. da Silva RG, do Prado IN, Matsushita M, and de Souza NE. 2002. Dietary effects on muscle fatty acid composition of finished heifers. Pesquisa Agropecuaria Brasileira 37:95–101.

40. Dai Q, Shu XO, Jin F, Gao YT, Ruan ZX, and Zheng W. 2002. Consumption of animal foods, cooking methods, and risk of breast cancer. Cancer Epidemiol Biomark Prevent 11:801–808.

41. de Roos NM, Schouten EG, and Katan MB. 2003. Trans fatty acids, HDL-cholesterol, and cardiovascular disease. Effects of dietary changes on vascular reactivity. Eur J Med Res 8:355–357.

42. De Stefani E, Brennan P, Boffetta P, Mendilaharsu M, Deneo-Pellegrini H, Ronco A, Olivera L, and Kasdorf H. 2002. Diet and adenocarcinoma of the lung: a case–control study in Uruguay. Lung Cancer 35:43–51.

43. Decarli A, Favero A, La Vecchia C, Russo A, Ferraroni M, Negri E, and Franceschi S. 1997. Macronutrients, energy intake, and breast cancer risk: implications from different models. Epidemiology. 8:425–428.

44. DeLany JP, Windhauser MM, Champagne CM, and Bray GA. 2000. Differential oxidation of individual dietary fatty acids in humans. Am J Clin Nutr 72:905– 911.

45. Dobbins RL, Szczepaniak LS, Myhill J, Tamura Y, Uchino H, Giacca A, and McGarry JD. 2002. The composition of dietary fat directly influences glucose-stimulated insulin secretion in rats. Diabetes 51:1825–1833.

46. Doucet E, Alméras N, White MD, Després JP, Bouchard C, and Tremblay A. 1998. Dietary fat composition and human adiposity. Eur J Clin Nutr 52:2–6.

47. Dwyer T, Emmanuel SC, Janus ED, Wu ZS, Hynes KL, and Zhang CM. 2003. The emergence of coronary heart disease in populations of Chinese descent. Atherosclerosis 167:303–310.

48. Eitel K, Staiger H, Brendel MD, Brandhorst D, Bretzel RG, Häring HU, and Kellerer M. 2002. Different role of saturated and unsaturated fatty acids in beta-cell apoptosis. Biochem Biophys Res Comm 299:853–856.

49. El-Assaad W, Buteau J, Peyot ML, Nolan C, Roduit R, Hardy S, Joly E, Dbaibo G, Rosenberg L, and Prentki M. 2003. Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. Endocrinology 144:4154–4163.

50. Ernst ND, Sempos CT, Briefel RR, and Clark MB. 1997. Consistency between US dietary fat intake and serum total cholesterol concentrations — the National Health and Nutrition Examination surveys. Am J Clin Nutr 66:S 965–S 972.

51. Esposito K, Nappo F, Giugliano F, Di Palo C, Ciotola M, Barbieri M, Paolisso G, and Giugliano D. 2003. Meal modulation of circulating interleukin 18 and adiponectin concentrations in healthy subjects and in patients with type 2 diabetes mellitus. Am J Clin Nutr 78:1135–1140.

52. Fasching P, Ratheiser K, Schneeweiss B, Rohac M, Nowotny P, and Waldhäusl W. 1996. No effect of short-term

dietary supplementation of saturated and poly- and monounsaturated fatty acids on insulin secretion and sensitivity in healthy men. Ann Nutr Metab 40:116–122.

53. Fay MP, Freedman LS, Clifford CK, and Midthune DN. 1997. Effect of different types and amounts of fat on the development of mammary tumors in rodents — a review. Cancer Res 57:3979–3988.

54. Fernandez-Real JM, Broch M, Vendrell J, and Ricart W. 2003. Insulin resistance, inflammation, and serum fatty acid composition. Diabetes Care 26:1362–1368.

55. Feskens EJM, Loeber JG, and Kromhout D. 1994. Diet and physical activity as determinants of hyperinsulinemia — the Zutphen Elderly Study. Am J Epidemiol 140:350–360.

56. Flood A, Velie EM, Sinha R, Chaterjee N, Lacey JV, Schairer C, and Schatzkin A. 2003. Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. Am J Epidemiol 158:59–68.

57. Franceschi S, Favero A, Decarli A, Negri E, Lavecchia C, Ferraroni M, Russo A, Salvini S, Amadori D, Conti E, Montella M, and Giacosa A. 1996. Intake of macronutrients and risk of breast cancer. Lancet 347:1351–1356.

58. Franceschi S, Lavecchia C, Russo A, Favero A, Negri E, Conti E, Montella M, Filiberti R, Amadori D, and Decarli A. 1998. Macronutrient intake and risk of colorectal cancer in Italy. Int J Cancer 76:321–324.

59. French R, O'Riordan EG, Monahan FJ, Caffrey PJ, and Moloney AP. 2003. Fatty acid composition of intramuscular triacylglycerols of steers fed autumn grass and concentrates. Livestock Prod Sci 81:307–317.

60. Fung T, Hu FB, Fuchs C, Giovannucci E, Hunter DJ, Stampfer MJ, Colditz GA, and Willett WC. 2003. Major dietary patterns and the risk of colorectal cancer in women. Arch Int Med 163:309–314.

61. Gaard M, Tretli S, and Løken EB. 1996. Dietary factors and risk of colon cancer — a prospective study of 50,535 young Norwegian men and women. Eur J Cancer Prevent 5:445–454.

62. Gago-Dominguez M, Yuan JM, Sun CL, Lee HP, and Yu MC. 2003. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. Brit J Cancer 89:1686–1692.

63. Gann PH, Chatterton RT, Gapstur SM, Liu K, Garside D, Giovanazzi S, Thedford V, and Van Horn L. 2003. The effects of a low-fat/high-fiber diet on sex hormone levels and menstrual cycling in premenopausal women — A 12-month randomized trial (the diet and hormone study). Cancer 98:1870–1879.

64. Garaulet M, Pérez-Llamas F, Canteras M, Tebar FJ, and Zamora S. 2001. Endocrine, metabolic and nutritional factors in obesity and their relative significance as studied by factor analysis. Int J Obesity 25:243–251.

65. Garner MJ, Birkett NJ, Johnson KC, Shatenstein B, Ghadirian P, and Krewski D. 2003. Dietary risk factors for testicular carcinoma. Int J Cancer 106:934–941.

66. Ghadirian P, Lacroix A, Maisonneuve P, Perret C, Drouin G, Perrault JP, Béland G, Rohan TE, and Howe GR. 1996. Nutritional factors and prostate cancer — a case–control study of French-Canadians in Montreal, Canada. Cancer Causes Control 7:428–436.

67. Ghadirian P, Lacroix A, Maisonneuve P, Perret C, Potvin C, Gravel D, Bernard D, and Boyle P. 1997. Nutritional factors and colon carcinoma — a case–control study involving French Canadians in Montreal, Quebec, Canada. Cancer 80:858–864.

68. Ghadirian P, Lynch HT, and Krewski D. 2003. Epidemiology of pancreatic cancer: an overview. Cancer Detect Prev 27:87–93.

69. Gillis LJ, Kennedy LC, Gillis AM, and Bar-Or O. 2002. Relationship between juvenile obesity, dietary energy and fat intake and physical activity. Int J Obesity 26:458–463.

70. Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, and Willett WC. 1993. A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst 85:1571–1579.

71. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, and Willett WC. 1994. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 54:2390–2397.

72. Glauert HP. 2000. Dietary fatty acids and cancer, pp. 865–882. In: Chow CK (ed.), *Fatty Acids in Foods and their Health Implications*. Marcel Dekker, Inc., New York.

73. Golomb BA. 1998. Dietary fats and heart disease — dogma challenged? J Clin Epidemiol 51:461–464.

74. Greenfield JR, Samaras K, Jenkins AB, Kelly PJ, Spector TD, and Campbell LV. 2003. Moderate alcohol consumption, dietary fat composition, and abdominal obesity in women: Evidence for gene–environment interaction. J Clin Endocrinol Metab 88:5381–5386.

75. Grundy SM. 1994. Influence of stearic acid on cholesterol metabolism relative to other long chain fatty acids. Am J Clin Nutr 60:S 986–S 990.

76. Grylls WK, McKenzie JE, Horwath CC, and Mann JI. 2003. Lifestyle factors associated with glycaemic control and body mass index in older adults with diabetes. Eur J Clin Nutr 57:1386–1393.

77. Gulati SK, Ashes JR, Ryde I, Scott TW, Brown GH, Rich AC, and Rich JC. 1996. Fatty acid profile of adipose tissue and performance of feedlot steers supplemented with dehulled cottonseed and sunflower seed meal protected from ruminal metabolism. Aust J Agric Res 47:953–960.

78. Gylling H and Miettinen TA. 2001. A review of

clinical trials in dietary interventions to decrease the incidence of coronary artery disease. Curr Controlled Trials Cardiovas Med 2:123–128.

79. Han SN, Leka LS, Lichtenstein AH, Ausman LM, Schaefer EJ, and Meydani SN. 2002. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. J Lipid Res 43:445–452.

80. Harding AH, Sargeant LA, Welch A, Oakes S, Luben RN, Bingham S, Day NE, Khaw KT, and Wareham NJ. 2001. Fat consumption and HbA(1c) levels — The EPIC-Norfolk Study. Diabetes Care 24:1911–1916.

81. Hausman DB, Higbee DR, and Grossman BM. 2002. Dietary fats and obesity, pp. 663–694. In: Akoh CC and Min DB (eds.), *Food Lipids*. Marcel Dekker, Inc., New York.

82. Hays JH, DiSabatino A, Gorman RT, Vincent S, and Stillabower ME. 2003. Effect of a high saturated fat and no-starch diet on serum lipid subfractions in patients with documented atherosclerotic cardiovascular disease. Mayo Clin Proc 78:1331–1336.

83. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, and Ascherio A. 2003. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. Brit Med J 327:777–782.

84. Hermann S, Linseisen J, and Chang-Claude J. 2002. Nutrition and breast cancer risk by age 50: A population-based case–control study in Germany. Nutr Cancer 44:23–34.

85. Heshka JT and Jones PJH. 2001. A role for dietary fat in leptin receptor, OB-Rb, function. Life Sciences 69:987–1003.

86. Hirose K, Takezaki T, Hamajima N, Miura S, and Tajima K. 2003. Dietary factors protective against breast cancer in Japanese premenopausal and postmenopausal women. Int J Cancer 107:276–282.

87. Hodson L, Skeaff CM, and Chisholm WAH. 2001. The effect of replacing dietary saturated fat with polyunsaturated or monounsaturated fat on plasma lipids in free-living young adults. Eur J Clin Nutr 55:908–915.

88. Holmes MD, Colditz GA, Hunter DJ, Hankinson SE, Rosner B, Speizer FE, and Willett WC. 2003. Meat, fish and egg intake and risk of breast cancer. Int J Cancer 104:221–227.

89. Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, and Hankinson SE. 1999. Association of dietary intake of fat and fatty acids with risk of breast cancer. J Am Med Assoc 281:914–920.

90. Hooper L, Summerbell CD, Higgins JP, Thompson RL, Capps NE, Smith GD, Riemersma RA, and Ebrahim S. 2001. Dietary fat intake and prevention of cardiovascular disease: systematic review. Brit Med J 322:757–763.

91. Horn-Ross PL, Hoggatt KJ, West DW, Krone MR, Stewart SL, Anton-Culver H, Bernstein L, Deapen D, Peel D, Pinder R, Reynolds P, Ross RK, Wright W, and Ziogas A. 2002. Recent diet and breast cancer risk: the California Teachers Study (USA). Cancer Causes Control 13:407–415.

92. Houseknecht KL and Spurlock ME. 2003. Leptin regulation of lipid homeostasis: dietary and metabolic implications. Nutr Res Rev 16:83–96.

93. Howe GR, Aronson KJ, Benito E, Castelleto R, Cornée J, Duffy S, Gallagher RP, Iscovich JM, Dengao J, Kaaks R, Kune GA, Kune S, Lee HP, Lee M, Miller AB, Peters RK, Potter JD, Riboli E, Slattery ML, Trichopoulos D, Tuyns A, Tzonou A, Watson LE, Whittemore AS, Wu-Williams AH and others. 1997. The relationship between dietary fat intake and risk of colorectal cancer — evidence from the combined analysis of 13 case–control studies. Cancer Causes Control 8:215–228.

94. Howe GR, Ghadirian P, Bueno de Mesquita HB, Zatonski WA, Baghurst PA, Miller AB, Simard A, Baillargeon J, de Waard F, and Przewozniak K. 1992. A collaborative case–control study of nutrient intake and pancreatic cancer within the search programme. Int J Cancer 51:365–372.

95. Howell WH, Mcnamara DJ, Tosca MA, Smith BT, and Gaines JA. 1997. Plasma lipid and lipoprotein responses to dietary fat and cholesterol — a meta-analysis. Am J Clin Nutr 65:1747–1764.

96. Hu FB, Manson JE, and Willett WC. 2001. Types of dietary fat and risk of coronary heart disease: A critical review. J Am Coll Nutr 20:5–19.

97. Hu FB, Stampfer MJ, Manson JE, Ascherio A, Colditz GA, Speizer FE, Hennekens CH, and Willett WC. 1999. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. Am J Clin Nutr 70:1001–1008.

98. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, and Willett WC. 1997. Dietary fat and the risk of coronary heart disease in women. N Engl J Med 337:1491–1499.

99. Hu FB, van Dam RM, and Liu S. 2001. Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. Diabetologia 44:805–817.

100. Hu FB and Willett WC. 2002. Optimal diets for prevention of coronary heart disease. J Am Med Assoc 288:2569–2578.

101. Huncharek M and Kupelnick B. 2001. Dietary fat intake and risk of epithelial ovarian cancer: A meta-analysis of 6,689 subjects from 8 observational studies. Nutr Cancer 40:87–91.

102. Hung T, Sievenpiper JL, Marchie A, Kendall CWC, and Jenkins DJA. 2003. Fat versus carbohydrate in insulin

resistance, obesity, diabetes and cardiovascular disease. Curr Opin Clin Nutr Metabol Care 6:165–176.

103. Hunter JE. 2001. Studies on effects of dietary fatty acids as related to their position on triglycerides. Lipids 36:655–668.

104. Hunter KA, Crosbie LC, Weir A, Miller GJ, and Dutta-Roy AK. 2000. A residential study comparing the effects of diets rich in stearic acid, oleic acid, and linoleic acid on fasting blood lipids, hemostatic variables and platelets in young healthy men. J Nutr Biochem 11:408–416.

105. Iso H, Sato S, Umemura U, Kudo M, Koike K, Kitamura A, Imano H, Okamura T, Naito Y, and Shimamoto T. 2002. Linoleic acid, other fatty acids, and the risk of stroke. Stroke 33:2086–2093.

106. Iwamoto S, Senzaki H, Kiyozuka Y, Ogura E, Takada H, Hioki K, and Tsubura A. 1998. Effects of fatty acids on liver metastasis of ACL-15 rat colon cancer cells. Nutr Cancer 31:143–150.

107. Jain MG, Rohan TE, Howe GR, and Miller AB. 2000. A cohort study of nutritional factors and endometrial cancer. Eur J Epidemiol 16:899–905.

108. Järvinen R, Knekt P, Hakulinen T, Rissanen H, and Heliövaara M. 2001. Dietary fat, cholesterol and colorectal cancer in a prospective study. Brit J Cancer 85:357–361.

109. Kaaks, R. and E. Riboli. 1997. The role of multicentre cohort studies in studying the relation between diet and cancer. Cancer Lett 114:263–270.

110. Kabagambe EK, Baylin A, Siles X, and Campos H. 2003. Individual saturated fatty acids and nonfatal acute myocardial infarction in Costa Rica. Eur J Clin Nutr 57:1447–1457.

111. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, and Mantzoros CS. 1999. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. J Clin Oncol 17:3291–3298.

112. Katsouyanni K, Trichopoulou A, Stuver S, Garas Y, Kritselis A, Kyriakou G, Stoikidou M, Boyle P, and Trichopoulos D. 1994. The association of fat and other macronutrients with breast cancer — a case–control study from Greece. Brit J Cancer 70:537–541.

113. Kazala EC, Lozeman FJ, Mir PS, Laroche A, Bailey DRC, and Weselake RJ. 1999. Relationship of fatty acid composition to intramuscular fat content in beef from crossbred Wagyu cattle. J Anim Sci 77:1717–1725.

114. Key TJA, Silcocks PB, Davey GK, Appleby PN, and Bishop DT. 1997. A case–control study of diet and prostate cancer. Brit J Cancer 76:678–687.

115. Khosla P and Hayes KC. 1996. Dietary trans-monounsaturated fatty acids negatively impact plasma lipids in humans: critical review of the evidence. J Am Coll Nutr 15:325–339.

116. King DE, Egan BM, and Geesey ME. 2003. Relation of dietary fat and fiber to elevation of C-reactive protein. Am J Cardiol 92:1335–1339.

117. Kiyohara Y, Shinohara A, Kato I, Shirota T, Kubo M, Tanizaki Y, Fujishima M, and Iida M. 2003. Dietary factors and development of impaired glucose tolerance and diabetes in a general Japanese population: The Hisayama study. J Epidemiol 13:251–258.

118. Knight JA, Martin LJ, Greenberg CV, Lockwood GA, Byng JW, Yaffe MJ, Tritchler DL, and Boyd NF. 1999. Macronutrient intake and change in mammographic density at menopause: results from a randomized trial. Cancer Epidemiol Biomark Prevent 8:123–128.

119. Knight TW, Knowles S, Death AF, West J, Agnew M, Morris CA, and Purchas RW. 2003. Factors affecting the variation in fatty acid concentrations in lean beef from grass-fed cattle in New Zealand and the implications for human health. N Z J Agr Res 46:83–95.

120. Knopp RH, Retzlaff B, Walden C, Fish B, Buck B, and McCann B. 2000. One-year effects of increasingly fat-restricted, carbohydrate-enriched diets on lipoprotein levels in free-living subjects. Proc Soc Exp Biol Med 225:191–199.

121. Kolonel LN. 2001. Fat, meat, and prostate cancer. Epidemiol Rev 23:72–81.

122. König D, Väisänen SB, Bouchard C, Halle M, Lakka TA, Baumstark MW, Alen M, Berg A, and Rauramaa R. 2003. Cardiorespiratory fitness modifies the association between dietary fat intake and plasma fatty acids. Eur J Clin Nutr 57:810–815.

123. Krauss RM. 2001. Dietary and genetic effects on low-density lipoprotein heterogeneity. Ann Rev Nutr 21:283–295.

124. Kris-Etherton PM, Binkoski AE, Zhao G, Coval SM, Clemmer KF, Hecker KD, Jacques H, and Etherton TD. 2002. Dietary fat: assessing the evidence in support of a moderate-fat diet; the benchmark based on lipoprotein metabolism. Proc Nutr Soc 61:287–298.

125. Kris-Etherton PM and Yu SM. 1997. Individual fatty acid effects on plasma lipids and lipoproteins — human studies. Am J Clin Nutr 65:S1628–S1644.

126. Kristal AR, Cohen JH, Qu PP, and Stanford JL. 2002. Associations of energy, fat, calcium, and vitamin D with prostate cancer risk. Cancer Epidemiol Biomark Prevent 11:719–725.

127. Kritchevsky D. 2002. Fats and oils in human health, pp. 543–558. In: Akok CC and Min DB (eds.), *Food Lipids*. Marcel Dekker Inc., New York.

128. Kromhout D, Menotti A, Kesteloot H, and Sans S. 2002. Prevention of coronary heart disease by diet and lifestyle — Evidence from prospective cross-cultural, cohort,

and intervention studies. Circulation 105:893–898.

129. Kushi L and Giovannucci E. 2002. Dietary fat and cancer. Am J Med 113:63–70.

130. Laaksonen DE, Lakka TA, Lakka HM, Nyyssönen K, Rissanen T, Niskanen LK, and Salonen JT. 2002. Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. Diabetic Med 19:456–464.

131. Laborde FL, Mandell IB, Tosh JJ, Wilton JW, and Buchanan-Smith JG. 2001. Breed effects on growth performance, carcass characteristics, fatty acid composition, and palatability attributes in finishing steers. J Anim Sci 79:355–365.

132. Larson DE, Hunter GR, Williams MJ, Kekesszabo T, Nyikos I, and Goran MI. 1996. Dietary fat in relation to body fat and intraabdominal adipose tissue: a cross-sectional analysis. Am J Clinical Nutr 64:677–684.

133. Larsson H, Elmståhl S, Berglund G, and Ahrén B. 1999. Habitual dietary intake versus glucose tolerance, insulin sensitivity and insulin secretion in postmenopausal women. J Int Med 245:581–591.

134. Le Marchand L, Wilkens LR, Hankin JH, Kolonel LN, and Lyu LC. 1997. A case–control study of diet and colorectal cancer in a multiethnic population in Hawaii (United States)— lipids and foods of animal origin. Cancer Causes Control 8:637–648.

135. Lee MM and Lin SS. 2000. Dietary fat and breast cancer. Ann Rev Nutr 20:221–248.

136. Lee MM, Wang RT, Hsing AW, Gu FL, Wang T, and Spitz M. 1998. Case–control study of diet and prostate cancer in China. Cancer Causes Control 9:545–552.

137. Lenfant C and Ernst N. 1994. Daily dietary fat and total food-energy intakes — NHANES III, phase 1, 1988–91. Morbid Mortal Weekly Rep 43:116–117; 123–125.

138. Levi F, Pasche C, Lucchini F, and La Vecchia C. 2002. Macronutrients and colorectal cancer: a Swiss case–control study. Ann Oncol 13:369–373.

139. Li D. 2001. Relationship between the concentrations of plasma phospholipid stearic acid and plasma lipoprotein lipids in healthy men. Clin Sci 100:25–32.

140. Li ZL, Otvos JD, Lamon-Fava S, Carrasco WV, Lichtenstein AH, McNamara JR, Ordovas JM, and Schaefer EJ. 2003. Men and women differ in lipoprotein response to dietary saturated fat and cholesterol restriction. J Nutr 133:3428–3433.

141. Lichtenbelt WDV, Mensink RP, and Westerterp KR. 1997. The effect of fat compositionm of the diet on energy metabolism. Zeitschr Ernahrungswiss 36:303–305.

142. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, and Schaefer EJ. 1994. Hypercholesterolemic effect of dietary cholesterol in diets enriched in polyunsaturated and saturated fat — dietary cholesterol, fat saturation, and plasma lipids. Arteriosclerosis Thrombosis 14:168–175.

143. Lichtenstein AH, Erkkilä AT, Lamarche B, Schwab US, Jalbert SM, and Ausman LM. 2003. Influence of hydrogenated fat and butter on CVD risk factors: remnant-like particles, glucose and insulin, blood pressure and C-reactive protein. Atherosclerosis 171:97–107.

144. Lichtenstein AH and Schwab US. 2000. Relationship of dietary fat to glucose metabolism. Atherosclerosis 150:227–243.

145. Lindeberg S, Ahrén B, Nilsson A, Cordain L, Nilsson-Ehle P, and Vessby B. 2003. Determinants of serum triglycerides and high-density lipoprotein cholesterol in traditional Trobriand Islanders: the Kitava Study. Scan J Clin Lab Invest 63:175–180.

146. Lindman AS, Müller H, Seljeflot I, Prydz H, Veierød M, and Pedersen JI. 2003. Effects of dietary fat quantity and composition on fasting and postprandial levels of coagulation factor VII and serum choline-containing phospholipids. Br J Nutr 90:329–336.

147. Lissner L, Kroon UB, Björntorp P, Blosk S, Wilhelmsen L, and Silverstolpe G. 1993. Adipose tissue fatty acids and dietary fat sources in relation to endometrial cancer — a retrospective study of cases in remission, and population-based controls. Acta Obstet Gynecol Scan 72:481–487.

148. Livesey G. 2000. The absorption of stearic acid from triacylglycerols: an inquiry and analysis. Nutr Res Rev 13:185–214.

149. Lovejoy JC, Champagne CM, Smith SR, DeLany JP, Bray GA, Lefevre M, Denkins YM, and Rood JC. 2001. Relationship of dietary fat and serum cholesterol ester and phospholipid fatty acids to markers of insulin resistance in men and women with a range of glucose tolerance. Metab Clin Exp 50:86–92.

150. Lovejoy JC, Smith SR, Champagne CM, Most MM, Lefevre M, DeLany JP, Denkins YM, Rood JC, Veldhuis J, and Bray GA. 2002. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. Diabetes Care 25:1283–1288.

151. Ludwig DS. 2003. Dietary glycemic index and the regulation of body weight. Lipids 38:117–121.

152. Lyu LC, Shieh MJ, Posner BM, Ordovas JM, Dwyer JT, Lichtenstein AH, Cupples LA, Dallal GE, Wilson PWF, and Schaefer EJ. 1994. Relationship between dietary intake, lipoproteins, and apolipoproteins in Taipei and Framingham. Am J Clin Nutr 60:765–774.

153. Maedler K, Oberholzer J, Bucher P, Spinas GA, and Donath MY. 2003. Monounsaturated fatty acids prevent the deleterious effects of palmitate and high glucose on human pancreatic beta-cell turnover and function. Diabetes

52:726–733.

154. Maedler K, Spinas GA, Dyntar D, Moritz W, Kaiser N, and Donath MY. 2001. Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function.Diabetes 50:69–76.

155. Maillard G, Charles MA, Lafay L, Thibult N, Vray M, Borys JM, Basdevant A, Eschwège E, and Romon M. 2000. Macronutrient energy intake and adiposity in non obese prepubertal children aged 5-11y (the Fleurbaix Laventie Ville Santé Study). Int J Obesity 24:1608–1617.

156. Manzato E, della Rovere GR, Avogaro A, Zambon S, Romanato G, Corti MC, Sartori L, Baggio G, and Crepaldi G. 2002. The fatty acid composition of plasma phospholipids and the insulin sensitivity in elderly diabetic patients. The Pro.VA study. Aging Clin Experimental Res 14:474–478.

157. Marshall JA and Bessen DH. 2002. Dietary fat and the development of type 2 diabetes. Diabetes Care 25:620–622.

158. Marshall JA, Bessesen DH, and Hamman RF. 1997. High saturated fat and low starch and fibre are associated with hyperinsulinemia in a non-diabetic population: the San Luis Valley Diabetes Study. Diabetologia 40:430–438.

159. Masson LF, McNeill G, and Avenell A. 2003. Genetic variation and the lipid response to dietary intervention: a systematic review. Am J Clin Nutr 77:1098–1111.

160. Mauger JF, Lichtenstein AH, Ausman LM, Jalbert SM, Jauhiainen M, Ehnholm C, and Lamarche B. 2003. Effect of different forms of dietary hydrogenated fats on LDL particle size. Am J Clin Nutr 78:370–375.

161. Mayer-Davis EJ, Levin S, and Marshall JA. 1999. Heterogeneity in associations between macronutrient intake and lipoprotein profile in individuals with type 2 diabetes. Diabetes Care 22:1632–1639.

162. Mayer-Davis EJ, Monaco JH, Hoen HM, Carmichael S, Vitolins MZ, Rewers MJ, Haffner SM, Ayad MF, Bergman RN, and Karter AJ. 1997. Dietary fat and insulin sensitivity in a triethnic population: the role of obesity. The Insulin Resistance Atherosclerosis Study (IRAS). Am J Clinical Nutr 65:79–87.

163. Memisoglu A, Hu FB, Hankinson SE, Manson JE, De Vivo I, Willett WC, and Hunter DJ. 2003. Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. Human Mol Gen 12:2923–2929.

164. Mensink RP, Plat J, and Temme EHM. 2002. Dietary fats and coronary heart disease, pp. 603–636. In: Akoh CC and Min DB (eds.), *Food Lipids*. Marcel Dekker, Inc., New York.

165. Meyer F, Bairati I, Shadmani R, Fradet Y, and Moore L. 1999. Dietary fat and prostate cancer survival. Cancer Causes & Control 10:245–251.

166. Meyer KA, Kushi LH, Jacobs DR, and Folsom AR. 2001. Dietary fat and incidence of type 2 diabetes in older Iowa women. Diabetes Care 24:1528–1535.

167. Michaud DS, Giovannucci E, Willett WC, Colditz GA, and Fuchs CS. 2003. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. Am J Epidemiol 157:1115–1125.

168. Miller GJ. 1998. Effects of diet composition on coagulation pathways. Am J Clin Nutr 67:S 542–S 545.

169. Mobley JA, Leav I, Zielie P, Wotkowitz C, Evans J, Lam YW, L'Esperance BS, Jiang Z, and Ho S. 2003. Branched fatty acids in dairy and beef products markedly enhance alpha-methylacyl-CoA racemase expression in prostate cancer cells in vitro. Cancer Epidemiol Biomark Prevent 12:775–783.

170. Moses RG, Shand JL, and Tapsell LC. 1997. The recurrence of gestational diabetes — could dietary differences in fat intake be an explanation? Diabetes Care 20:1647–1650.

171. Mottram HR, Crossman ZM, and Evershed RP. 2001. Regiospecific characterisation of the triacylglycerols in animal fats using high performance liquid chromatography–atmospheric pressure chemical ionisation mass spectrometry. Analyst 126:1018–1024.

172. Moyad MA. 2002. Dietary fat reduction to reduce prostate cancer risk: Controlled enthusiasm, learning a lesson from breast or other cancers, and the big picture. Urology 59(4A Suppl S):51–62.

173. Mulder I, Jansen MCJF, Smit HA, Jacobs DR, Menotti A, Nissinen A, Fidanza F, and Kromhout D. 2000. Role of smoking and diet in the cross-cultural variation in lung-cancer mortality: The Seven Countries Study. Int J Cancer 88(4):665–671.

174. Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, and Yasuda K. 2003. Dietary soy and fats in relation to serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels in premenopausal Japanese women. Nutr Cancer 45:185–189.

175. Ng CK, Chan AP, and Cheng A. 2001. Impairment of endothelial function — a possible mechanism for atherosclerosis of a high-fat meal intake. Ann Acad Med Singapore 30:499–502. [erratum appears in Ann Acad Med Singapore 2001;30:679]

176. Nicklas TA, Dwyer J, Feldman HA, Luepker RV, Kelder SH, and Nader PR. 2002. Serum cholesterol levels in children are associated with dietary fat and fatty acid intake. J Am Diet Assoc 102:511–517.

177. Nkondjock A, Shatenstein B, and Ghadirian P. 2003. A case–control study of breast cancer and dietary intake of individual fatty acids and antioxidants in Montreal, Canada. Breast 12:128–135.

178. Nkondjock A, Shatenstein B, Maisonneuve P, and Ghadirian P. 2003. Assessment of risk associated with

specific fatty acids and colorectal cancer among French-Canadians in Montreal: a case–control study. Int J Epidemiol 32:200–209.

179. Nkondjock A, Shatenstein B, Maisonneuve P, and Ghadirian P. 2003. Specific fatty acids and human colorectal cancer: an overview. Cancer Detect Prevent 27:55–66.

180. Oliver MF. 1997. It is more important to increase the intake of unsaturated fats than to decrease the intake of saturated fats: evidence from clinical trials relating to ischemic heart disease. Am J Clin Nutr 66:980S–986S.

181. Ordovas JM, Corella D, Demissie S, Cupples LA, Couture P, Coltell O, Wilson PWF, Schaefer EJ, and Tucker KL. 2002. Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism — Evidence of a strong dose effect in this gene–nutrient interaction in the Framingham Study. Circulation 106:2315–2321.

182. Ozasa K, Watanabe Y, Ito Y, Suzuki K, Tamakoshi A, Seki N, Nishino Y, Kondo T, Wakai K, Ando M, and Ohno Y. 2001. Dietary habits and risk of lung cancer death in a large-scale cohort study (JACC study) in Japan by sex and smoking habit. Jap J Cancer Res 92:1259–1269.

183. Pala V, Krogh V, Muti P, Chajès V, Riboli E, Micheli A, Saadatian M, Sieri S, and Berrino F. 2001. Erythrocyte membrane fatty acids and subsequent breast cancer: A prospective Italian study. J Natl Cancer Inst 93:1088–1095.

184. Pandian SS, Eremin OE, McClinton S, Wahle KWJ, and Heys SD. 1999. Fatty acids and prostate cancer: current status and future challenges. J Roy Coll Surg Edinburgh 44:352–361.

185. Parker DR, Weiss ST, Troisi R, Cassano PA, Vokonas PS, and Landsberg L. 1993. Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations — the normative aging study. Am J Clin Nutr 58:129–136.

186. Pérez-Jiménez F, López-Miranda J, Pinillos MD, Gómez P, Paz-Rojas E, Montilla P, Marín C, Velasco MJ, Blanco-Molina A, Perepérez JAJ, and Ordovás JM. 2001. A Mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. Diabetologia 44:2038–2043.

187. Perez-Martinez P, Ordovás JM, López-Miranda J, Gómez P, Marin C, Moreno J, Fuentes F, de la Puebla RAF, and Pérez-Jiménez F. 2003. Polymorphism exon 1 variant at the locus of the scavenger receptor class B type I gene: influence on plasma LDL cholesterol in healthy subjects during the consumption of diets with different fat contents. Am J Clin Nutr 77:809–813.

188. Pierre F, Taché S, Petit CR, Van der Meer R, and Corpet DE. 2003. Meat and cancer: haemoglobin and haemin in a low-calcium diet promote colorectal carcinogenesis at the aberrant crypt stage in rats. Carcinogenesis 24:1683–1690.

189. Piers LS, Walker KZ, Stoney RM, Soares MJ, and O'Dea K. 2002. The influence of the type of dietary fat on postprandial fat oxidation rates: monounsaturated (olive oil) vs saturated fat (cream). Int J Obesity 26:814–821.

190. Piers LS, Walker KZ, Stoney RM, Soares MJ, and O'Dea K. 2003. Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweightand obese men. Brit J Nutr 90:717–727.

191. Popov D, Simionescu M, and Shepherd PR. 2003. Saturated-fat diet induces moderate diabetes and severe glomerulosclerosis in hamsters. Diabetologia 46:1408–1418.

192. Prentice RL. 2003. Dietary assessment and the reliability of nutritional epidemiology reports. Lancet 362:182–183.

193. Prentice RL, Sugar E, Wang C, Neuhouser M, and Patterson R. 2002. Research strategies and the use of nutrient biomarkers in studies of diet and chronic disease. Public Health Nutr 5:977–984.

194. Probst-Hensch NM, Wang H, Goh VHH, Seow A, Lee HP, and Yu MC. 2003. Determinants of circulating insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations in a cohort of Singapore men and women. Cancer Epidemiol Biomark Prevent 12:739–746.

195. Racette SB, Deusinger SS, and Deusinger RH. 2003. Obesity: Overview of prevalence, etiology, and treatment. Physical Therapy 83:276–288.

196. Raes K, Balcaen A, Dirinck P, De Winne A, Claeys E, Demeyer D, and De Smet S. 2003. Meat quality, fatty acid composition and flavour analysis in Belgian retail beef. Meat Sci 65:1237–1246.

197. Ramon JM, Bou R, Romea S, Alkiza ME, Jacas M, Ribes J, and Oromi J. 2000. Dietary fat intake and prostate cancer risk: a case–control study in Spain. Cancer Causes Control 11:679–685.

198. Rao CV, Hirose Y, Indranie C, and Reddy BS. 2001. Modulation of experimental colon tumorigenesis by types and amounts of dietary fatty acids. Cancer Res 61:1927–1933.

199. Ravnskov U. 1998. The questionable role of saturated and polyunsaturated fatty acids in cardiovascular disease. J Clin Epidemiol 51:443–460.

200. Ravnskov U. 2002. A hypothesis out-of-date: The diet–heart idea. J Clin Epidemiol 55:1057–1063.

201. Rhee KS. 2000. Fatty acids in meat and meat products, pp. 83–108. In: Chow CK (ed.), *Fatty Acids in Foods and Their Health Implications*. Marcel Dekker, Inc., New York.

202. Richter WO. 2003. Fatty acids and breast cancer

— Is there a relationship? Eur J Med Res 8:373–380.

203. Rissanen H, Knekt P, Järvinen R, Salminen I, and Hakulinen T. 2003. Serum fatty acids and breast cancer incidence. Nutr Cancer 45:168–175.

204. Rivellese AA and Lilli S. 2003. Quality of dietary fatty acids, insulin sensitivity and type 2 diabetes. Biomed Pharmacotherap 57:84–87.

205. Rivellese AA, Maffettone A, Vessby B, Uusitupa M, Hermansen K, Berglund L, Louheranta A, Meyer BJ, and Riccardi G. 2003. Effects of dietary saturated, monounsaturated and n-3 fatty acids on fasting lipoproteins, LDL size and post-prandial lipid metabolism in healthy subjects. Atherosclerosis 167:149–158.

206. Roebuck BD. 1992. Dietary fat and the development of pancreatic cancer. Lipids. 27:804–806.

207. Saadatian-Elahi M, Toniolo P, Ferrari P, Goudable J, Akhmedkhanov A, Zeleniuch-Jacquotte A, and Riboli E. 2002. Serum fatty acids and risk of breast cancer in a nested case–control study of the New York University Women's Health Study. Cancer Epidemiol Biomark Prevent 11:1353–1360.

208. Sacks FM and Katan M. 2002. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. Am J Med 113:13–24.

209. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams T, Williams M, Gracely EJ, and Stern L. 2003. A low-carbohydrate as compared with a low-fat diet in severe obesity. N E J Med 348:2074–2081.

210. Sanders TAB, Berry SEE, and Miller GJ. 2003. Influence of triacylglycerol structure on the postprandial response of factor VII to stearic acid-rich fats. Am J Clin Nutr 77:777–782.

211. Sasaki S, Zhang XH, and Kesteloot H. 1995. Dietary sodium, potassium, saturated fat, alcohol, and stroke mortality. Stroke 26:783–789.

212. Satia-Abouta J, Galanko JA, Potter JD, Ammerman A, Martin CF, and Sandler RS. 2003. Associations of total energy and macronutrients with colon cancer risk in African Americans and Whites: Results from the North Carolina Colon Cancer Study. Am J Epidemiol 158:951–962.

213. Satia-Abouta J, Patterson RE, Schiller RN, and Kristal AR. 2002. Energy from fat is associated with obesity in US men: Results from the prostate cancer prevention trial. Prev Med 34:493–501.

214. Schaefer EJ. 2002. Lipoproteins, nutrition, and heart disease. Am J Clin Nutr 75:191–212.

215. Schoene NW, Allman MA, Doughtery RM, and Iacono JM. 1994. Dissimilar responses of platelets to dietary stearic and palmitic acids. Am J Clin Nutr 60:S1059.

216. Scollan ND, Enser M, Gulati SK, Richardson I, and Wood JD. 2003. Effects of including a ruminally protected lipid supplement in the diet on the fatty acid composition of beef muscle. Brit J Nutr 90:709–716.

217. Senesse P, Boutron-Ruault MC, Faivre J, Chatelain N, Belghiti C, and Méance S. 2002. Foods as risk factors for colorectal adenomas: A case–control study in Burgundy (France). Nutr Cancer 44:7–15.

218. Senzaki H, Iwamoto S, Ogura E, Kiyozuka Y, Arita S, Kurebayashi J, Takada H, Hioki K, and Tsubura A. 1998. Dietary effects of fatty acids on growth and metastasis of KPL-1 human breast cancer cells in vivo and in vitro. Anticancer Res 18:1621–1627.

219. Sesink ALA, Termont DSML, Kleibeuker JH, and Van der Meer R. 2000. Red meat and colon cancer: dietary haem, but not fat, has cytotoxic and hyperproliferative effects on rat colonic epithelium. Carcinogenesis 21:1909–1915.

220. Sevak L, McKeigue PM, and Marmot MG. 1994. Relationship of hyperinsulinemia to dietary intake in South Asian and European men. Am J Clin Nutr 59:1069–1074.

221. Shahkhalili Y, Murset C, Meirim I, Duruz E, Guinchard S, Cavadini C, and Acheson K. 2001. Calcium supplementation of chocolate: effect on cocoa butter digestibility and blood lipids in humans. Am J Clin Nutr 73:246–252.

222. Shannon J, Cook LS, and Stanford JL. 2003. Dietary intake and risk of postmenopausal breast cancer (United States). Cancer Causes Control 14:19–27.

223. Shillabeer G and Lau DCW. 1994. Regulation of new fat cell formation in rats — the role of dietary fats. J Lipid Res 35:592–600.

224. Sigurdson AJ, Chang S, Annegers JF, Duphorne CM, Pillow PC, Amato RJ, Hutchinson LP, Sweeney AM, and Strom SS. 1999. A case–control study of diet and testicular carcinoma. Nutr Cancer 34:20–26.

225. Simon JA, Fong J, Bernert JT, and Browner WS. 1995. Serum fatty acids and the risk of stroke. Stroke 26:778–782.

226. Sinha R, Kulldorff M, Curtin J, Brown CC, Alavanja MC, and Swanson CA. 1998. Fried, well-done red meat and risk of lung cancer in women (United States). Cancer Causes Control 9:621–630.

227. Slattery ML, Curtin K, Ma K, Edwards S, Schaffer D, Anderson K, and Samowitz W. 2002. Diet, activity, and lifestyle associations with p53 mutations in colon tumors. Cancer Epidemiol Biomark Prevent 11:541–548.

228. Smith SB, Yang AJ, Larsen TW, and Tume RK. 1998. Positional analysis of triacylglycerols from bovine adipose tissue lipids varying in degree of unsaturation. Lipids 33:197–207.

229. Smith-Warner SA, Ritz J, Hunter DJ, Albanes D, Beeson WL, van den Brandt PA, Colditz G, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Kushi LH, Miller AB, Rohan TE, Speizer

FE, Virtamo J, and Willett WC. 2002. Dietary fat and risk of lung cancer in a pooled analysis of prospective studies. Cancer Epidemiol Biomark Prevent 11:987–992.

230. Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, and Hunter DJ. 2001. Types of dietary fat and breast cancer: A pooled analysis of cohort studies. Int J Cancer 92:767–774.

231. Soinio M, Laakso M, Lehto S, Hakala P, and Rönnemaa T. 2003. Dietary fat predictscoronary heart disease events in subjects with type 2 diabetes. Diabetes Care 26:619–624.

232. Stamler J, Caggiula A, Grandits GA, Kjelsberg M, and Cutler JA. 1996. Relationship to blood pressure of combinations of dietary macronutrients — findings of the Multiple Risk Factor Intervention Trial (MRFIT). Circulation 94:2417–2423.

233. Steen RWJ, Lavery NP, and Kilpatrick DJ. 2003. Effects of pasture and high-concentrate diets on the performance of beef cattle, carcass composition at equal growth rates, and the fatty acid composition of beef. N Z J Agr Res 46:69–81.

234. Steer P, Vessby B, and Lind L. 2003. Endothelial vasodilatory function is related to the proportions of saturated fatty acids and alpha-linolenic acid in young men, but not in women. Eur J Clin Invest 33:390–396.

235. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, and Albanes D. 2002. Prospective study of diet and pancreatic cancer in male smokers. Am J Epidemiol 155:783–792.

236. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, and Albanes D. 2002. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). Cancer Causes Control 13:417–426.

237. Storm H, Thomsen C, Pedersen E, Rasmussen O, Christiansen C, and Hermansen K. 1997. Comparison of a carbohydrate-rich diet and diets rich in stearic or palmitic acid in NIDDM patients. Diabetes Care 20:1807–1813.

238. Summers LKM, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, Moore NR, and Frayn KN. 2002. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. Diabetologia 45:369–377.

239. Sundram K, French MA, and Clandinin MT. 2003. Exchanging partially hydrogenated fat for palmitic acid in the diet increases LDL-cholesterol and endogenous cholesterol synthesis in normocholesterolemic women. Eur J Nutr 42:188–194.

240. Swanson CA, Brown CC, Brownson RC, and Alavanja MCR. 1997. Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. J Natl Cancer Inst 89(22):1724–1725.

241. Swanson CA, Brown CC, Sinha R, Kulldorff M, Brownson RC, and Alavanja MCR. 1997. Dietary fats and lung cancer risk among women — the Missouri Womens Health Study (United States). Cancer Causes Control 8(6):883–893.

242. Terry P, Hu FB, Hansen H, and Wolk A. 2001. Prospective study of major dietary patterns and colorectal cancer risk in women. Am J Epidemiol 154:1143–1149.

243. Terry P, Suzuki R, Hu FB, and Wolk A. 2001. A prospective study of major dietary patterns and the risk of breast cancer. Cancer Epidemiol Biomark Prevent 10:1281–1285.

244. Thanopoulou AC, Karamanos BG, Angelico FV, Assaad-Khalil SH, Barbato AF, Del Ben MP, Djordjevic PB, Dimitrijevic-Sreckovic VS, Gallotti CA, Katsilambros NL, Migdalis IN, Mrabet MM, Petkova MK, Roussi DP, and Tenconi MTP. 2003. Dietary fat intake as risk factor for the development of diabetes — Multinational, multicenter study of the Mediterranean Group for the Study of Diabetes (MGSD). Diabetes Care 26:302–307.

245. Tholstrup T, Vessby B, and Sandstrom B. 2003. Difference in effect of myristic and stearic acid on plasma HDL cholesterol within 24h in young men. Eur J Clin Nutr 57:735–742.

246. Tinahones FJ, Pareja A, Soriguer FJ, Gómez-Zumaquero JM, Cardona F, and Rojo-Martínez G. 2002. Dietary fatty acids modify insulin secretion of rat pancreatic islet cells in vitro. J Endocrinol Invest 25:436–441.

247. Toeller M, Buyken AE, Heitkamp G, Cathelineau G, Ferriss B, and Michel G. 2001. Nutrient intakes as predictors of body weight in European people with type 1 diabetes. Int J Obesity 25:1815–1822.

248. Toeller M, Buyken AE, Heitkamp G, Scherbaum WA, Krans HMJ, and Fuller JH. 1999. Associations of fat and cholesterol intake with serum lipid levels and cardiovascular disease: The EURODIAB IDDM Complications Study. Exp Clin Endocrinol Diabetes 107:512–521.

249. Toniolo P, Riboli E, Shore RE, and Pasternack BS. 1994. Consumption of meat, animal products, protein, and fat and risk of breast cancer — a prospective cohort study in New York. Epidemiology 5:391–397.

250. Tran TT, Gupta N, Goh T, Naigamwalla D, Chia MC, Koohestani N, Mehrotra S, McKeown-Eyssen G, Giacca A, and Bruce WR. 2003. Direct measure of insulin sensitivity with the hyperinsulinemic-euglycemic clamp and surrogate measures of insulin sensitivity with the oral glucose tolerance test: correlations with aberrant crypt foci promotion in rats. Cancer Epidemiol, Biomark Prevent 12:47–56.

251. Trichopoulou A, Gnardellis C, Benetou V, Lagiou P, Bamia C, and Trichopoulos D. 2002. Lipid, protein and carbohydrate intake in relation to body mass index. Eur J Clin Nutr 56:37–43.

252. U.S. Department of Agriculture, Agricultural Research Service. 2003. USDA National Nutrient Database for Standard Reference, Release 16. Nutrient Data Laboratory Home Page. July 2003. http://www.nal.usda.gov/fnic/foodcomp

253. Uusitupa M, Schwab U, Mäkimattila S, Karhapää P, Sarkkinen E, Maliranta H, Ågren J, and Penttilä I. 1994. Effects of two high-fat diets with different fatty acid compositions on glucose and lipid metabolism in healthy young women. Am J Clin Nutr 59:1310–1316.

254. van Dam RM, Stampfer M, Willett WC, Hu FB, and Rimm EB. 2002. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. Diabetes Care 25:417–424.

255. Veierød MB, Laake P, and Thelle DS. 1997. Dietary fat intake and risk of lung cancer — a prospective study of 51,452 Norwegian men and women. Eur J Cancer Prevent 6:540–549.

256. Veierød MB, Laake P, and Thelle DS. 1997. Dietary fat intake and risk of prostate cancer — a prospective study of 25,708 Norwegian men. Int J Can 73:634–638.

257. Vessby B. 2000. Dietary fat and insulin action in humans. Br J Nutr 83:S91–S96.

258. Vincent S, Planells R, Defoort C, Bernard MC, Gerber M, Prudhomme J, Vague P, and Lairon D. 2002. Genetic polymorphisms and lipoprotein responses to diets. Proc Nutr Soc 61:427–434.

259. Vlajinac HD, Marinkovic JM, Ilic MD, and Kocev NI. 1997. Diet and prostate cancer — a case–control study. Eur J Cancer 33:101–107.

260. Vogel U, Danesvar B, Autrup H, Risom L, Weimann A, Poulsen HE, Møller P, Loft S, Wallin H, and Dragsted LO. 2003. Effect of increased intake of dietary animal fat and fat energy on oxidative damage, mutation frequency, DNA adduct level and DNA repair in rat colon and liver. Free Rad Res 37:947–956.

261. Voorrips LE, Brants HAM, Kardinaal AFM, Hiddink GJ, van den Brandt PA, and Goldbohm RA. 2002. Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: the Netherlands Cohort Study on Diet and Cancer. Am J Clin Nutr 76:873–882.

262. Wang L, Folsom AR, Zheng ZJ, Pankow JS, and Eckfeldt JH. 2003. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 78:91–98.

263. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, and Colditz GA. 2004. Comparison of risk factors for colon and rectal cancer. Int J Cancer 108:433–442.

264. Weintraub WS. 2002. Is atherosclerotic vascular disease related to a high-fat diet? J Clin Epidemiol 55:1064–1072.

265. Whittemore AS, Kolonel LN, Wu AH, John EM, Gallagher RP, Howe GR, Burch JD, Hankin J, Dreon DM, West DW, Teh CZ, and Paffenbarger RS. 1995. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. J Natl Cancer Inst 87:652–661.

266. Willett WC. 1997. Specific fatty acids and risks of breast and prostate cancer — dietary intake. Am J Clin Nutr 66:S1557–S1563.

267. Willett WC and Hunter DJ. 1994. Prospective studies of diet and breast cancer. Cancer 74:1085–1089.

268. Willett WC and Leibel RL. 2002. Dietary fat is not a major determinant of body fat. Am J Med 113:47–59.

269. Winzell MS, Holm C, and Ahrén B. 2003. Downregulation of islet hormone-sensitive lipase during long-term high-fat feeding. Biochem Biophys Res Comm 304:273–278.

270. Wirfalt E, Mattisson I, Gullberg B, Johansson U, Olsson H, and Berglund G. 2002. Postmenopausal breast cancer is associated with high intakes of omega 6 fatty acids (Sweden). Cancer Causes Control 13:883–893.

271. Wolk A, Bergström R, Hunter D, Willett W, Ljung H, Holmberg L, Bergkvist L, Bruce A, and Adami HO. 1998. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. Arch Intern Med 158:41–45.

272. Woollett LA and Dietschy JM. 1994. Effect of long-chain fatty acids on low-density-lipoprotein-cholesterol metabolism. Am J Clin Nutr 60:S 991–S 996.

273. Yang A, Larsen TW, Powell VH, and Tume RK. 1999. A comparison of fat composition of Japanese and long-term grain-fed Australian steers. Meat Sci 51:1–9.

274. Ye SQ and Kwiterovich PO. 2000. Influence of genetic polymorphisms on responsiveness to dietary fat and cholesterol. Am J Clin Nutr 72:1275S–1284S.

275. Yu-Poth S, Etherton TD, Reddy CC, Pearson TA, Reed R, Zhao GX, Jonnalagadda S, Wan Y, and Kris-Etherton PM. 2000. Lowering dietary saturated fat and total fat reduces the oxidative susceptibility of LDL in healthy men and women. J Nutr 130:2228–2237.

276. Yuan JM, Wang QS, Ross RK, Henderson BE, and Yu MC. 1995. Diet and breast cancer in Shanghai and Tianjin, China. Brit J Cancer 71:1353–1358.

277. Zampelas A, Williams CM, Morgan LM, and Wright J. 1994. The effect of triacylglycerol fatty acid positional distribution on postprandial plasma metabolite and hormone responses in normal adult men. Br J Nutr 71:401–410.

278. Zhang JJ and Kesteloot H. 2001. Differences in all-cause, cardiovascular and cancer mortality between Hong Kong and Singapore: Role of nutrition. Eur J Epidemiol 17:469–477.

279. Zhang X, Zhang B, Li X, Wang X, and Nakama H. 2000. Relative risk of dietary components and colorectal cancer. Eur J Med Res 5:451–4.

280. Zheng W , McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, Wacholder S, Co-Chien HT, Blot WJ, and Fraumeni JF Jr. 1993. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control 4:477–82.

281. Zheng ZJ, Folsom AR, Shahar E, McGovern PG, and Eckfeldt JH. 1997. Association of plasma fatty acid composition with lower extremity arterial disease — the Atherosclerosis Risk in Communities (ARIC) study. Nutr Metab Cardiovascular Dis 7:360–370.

282. Zhou JR and Blackburn GL. 1997. Bridging animal and human studies — what are the missing segments in dietary fat and prostate cancer. Am J Clin Nutr 66: S1572–S1580.

283. Zyriax BC and Windler E. 2000. Dietary fat in the prevention of cardiovascular disease — a review. Eur J Lipid Sci Technol 102:355–365.

284. Institute of Medicine. 2003. Informing the Future. Critical Issues in Health. 2nd ed. National Academy of Sciences, Washington, D.C. http://books.nap.edu/html/informing_the_future/report.pdf