EVALUATION OF PUBLICLY AVAILABLE
SCIENTIFIC EVIDENCE REGARDING
CERTAIN NUTRIENT–DISEASE RELATIONSHIPS:

10. LIPIDS AND CANCER

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FOREWORD

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This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with the provisions of Task Order #9 of Contract No. 223-88-2124. Potential authors and reviewing consultants were identified by the LSRO based on their qualifications, experience, and freedom from conflict of interest, with due consideration for balance and breadth in appropriate disciplines. The author and reviewing consultants were selected with the concurrence of the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB).

On March 14, 1991, the FDA requested submission of scientific data and information on the ten specific topics for which health claims might be made (Federal Register 56:12932–12933). The scientific data and information provided in response to this request were considered by LSRO in preparing this report. Copies of the submitted materials are available for public inspection at the Dockets Management Branch, FDA (Docket No. 91N–0097). Copies of documents cited in this report are available for public inspection at LSRO, FASEB.

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The evaluation of scientific literature, data, and information submitted to the LSRO was made by the author, reviewers, and the LSRO independently of FDA or any other group, governmental or non-governmental. The author and LSRO accept responsibility for the accuracy of the report conclusions and its appendix table(s). This final report was reviewed and approved by members of the LSRO Advisory Committee under authority delegated by the Federation Board. The LSRO Advisory Committee members who reviewed this report were free of conflicts of interest in regard to the subject matter under policies established by the Federation. Upon completion of these review procedures, the report was approved by the Executive Director, FASEB, and transmitted to FDA.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>A. Background</td>
<td>1</td>
</tr>
<tr>
<td>B. Scope of Work</td>
<td>1</td>
</tr>
<tr>
<td>II. EPIDEMIOLOGICAL EVIDENCE</td>
<td>3</td>
</tr>
<tr>
<td>A. Intercountry and Intracountry Correlations</td>
<td>3</td>
</tr>
<tr>
<td>B. Migrant Studies</td>
<td>6</td>
</tr>
<tr>
<td>C. Time-Trend Studies</td>
<td>8</td>
</tr>
<tr>
<td>D. Cohort Studies</td>
<td>8</td>
</tr>
<tr>
<td>E. Case-Control Studies</td>
<td>9</td>
</tr>
<tr>
<td>F. Intervention Studies</td>
<td>11</td>
</tr>
<tr>
<td>III. DISCUSSION</td>
<td>13</td>
</tr>
<tr>
<td>A. Limitations of Study Design</td>
<td>13</td>
</tr>
<tr>
<td>B. Theoretical Explanations for Conflicting Results</td>
<td>14</td>
</tr>
<tr>
<td>IV. CONCLUSIONS</td>
<td>17</td>
</tr>
<tr>
<td>V. BIBLIOGRAPHY</td>
<td>19</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>A-1</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

A. BACKGROUND

In 1982, the National Research Council's Committee on Diet, Nutrition, and Cancer (NRC) concluded "that of all the dietary components it studied, the combined epidemiological and experimental evidence is most suggestive for a causal relationship between fat intake and the occurrence of cancer" (National Research Council, 1982). This conclusion was based primarily on the strong positive correlation between dietary fat and cancers of the breast, colon, prostate and a number of other sites observed in intercountry studies and on the results of numerous experiments on animals showing that those fed high-fat diets develop cancer more readily than those fed low-fat diets, especially in the breast and colon. The evidence from studies on experimental animals indicated that dietary fat had a promoting effect on tumorigenesis (Carroll, 1975).

The Surgeon General's Report on Nutrition and Health (U.S. Department of Health and Human Services, 1988) concluded that "Despite some inconsistencies in the data relating dietary fat to cancer causation ... the weights of the studies to date are strongly suggestive of the role for dietary fat in the etiology of some types of cancer." The report of the NRC Committee on Diet and Health (National Research Council, 1989) summarized the conclusions by saying that the weight of evidence indicates that high-fat diets are associated with higher risk of several cancers, especially of the colon, prostate, and breast. Some inconsistencies in the data were also noted in this report.

B. SCOPE OF WORK

The purpose of the present article is to provide an up-to-date assessment of the role of dietary lipids in cancer, taking into account papers that have appeared since the above reports were published. Emphasis will be given to studies on humans, and experiments on animals will only be considered when they seem particularly pertinent to the discussion. Human studies reviewed in this report are summarized by organ site in Appendix Table I.
II. EPIDEMIOLOGICAL EVIDENCE

The following kinds of studies have been used to provide information on the role of dietary lipids in cancer:

- Intercountry and intracountry correlations
- Studies on migrants
- Time-trend studies
- Cohort studies
- Case-control studies
- Intervention studies

The strengths and weaknesses of these different kinds of studies will be considered in turn.

A. INTERCOUNTRY AND INTRACOUNTRY CORRELATIONS

Intercountry correlations normally compare age-adjusted cancer incidence or mortality in different countries with availability of dietary fat in those countries. The cancer incidence data are collected by cancer registries (e.g., Whelan et al., 1990) and are not necessarily representative of cancer incidence in the country as a whole when the population base for the registry does not cover the entire country. Cancer mortality data are collected by the World Health Organization (e.g., World Health Organization, 1990) and the accuracy of such data probably varies considerably from one country to another. Dietary fat intakes are based on disappearance data collected by the Food and Agriculture Organization of the United Nations (e.g., Food and Agriculture Organization of the United Nations, 1980) and overestimate actual intake since much food is wasted and not actually eaten, e.g., cooking oil.

In early plots of cancer incidence or mortality against dietary fat, intake was usually expressed as g/person/d (Armstrong and Doll, 1975; Carroll, 1975; Carroll and Khor, 1975). A better approach is to plot dietary fat as percent of total calories (Carroll, 1986a). This provides more realistic values but also tends to overestimate, since the fat in food is more likely to be lost or discarded to a greater extent than carbohydrate or protein, which are the other main sources of dietary calories.

Cancer is thought to develop over a relatively long period of time, thus cancer incidence and mortality should probably be compared with dietary fat intake over a period of preceding years when it may be influencing the carcinogenic process. In practice, this does not seem to be a serious consideration because cancer incidence and mortality and the level of dietary fat in any particular country change rather slowly with time. Other limitations of ecologic studies include: the difficulty of isolating effects of one particular dietary factor, the inability to control for other confounding factors related to living standard and life style, and the high potential for sources of error in the collection of data on diet and on cancer incidence and mortality. In spite of these various uncertainties and inaccuracies, plots of cancer incidence or mortality at sites such as the breast and colon have consistently shown strong positive correlations with dietary fat in these intercountry comparisons (see Figures 1a and 1b).
Figure 1a. Positive correlation between percentage of dietary calories as fat and age-adjusted mortality from breast cancer (Carroll, 1991). (Used with permission.)
Figure 1b. Positive correlation between percentage of dietary calories as fat and age-adjusted mortality from colon cancer (Carroll, 1991). (Used with permission.)
Even in countries where cancer is most prevalent, any particular type of cancer occurs only in a minority of the population. (For example, recent statistics indicate that one out of nine women is expected to develop breast cancer in the United States.) Thus, if a high-fat diet is acting to promote breast cancer, a large proportion of the female population is protected either by its innate genetic makeup or has not been exposed to adequate initiating stimuli for breast cancer to develop or it is protected by other exogenous factors (e.g., dietary factors).

In comparing the large populations involved in intercountry studies, it seems possible that these genetic and initiating factors may largely cancel out. Although most of the population in any country will not develop cancer under the existing environmental conditions, a segment that is genetically more susceptible may develop cancer under one set of conditions but not under another (Fig. 2). It is thus possible to observe environmental effects on cancer even in populations with large genetic diversity.

In addition to intercountry correlations, there have been a number of studies on subgroups within countries whose diet and lifestyle differ from those of the majority of the population. An example is the Seventh Day Adventists who have somewhat lower incidence of cancer at several different sites than other Americans (Phillips et al., 1980). Comparisons of different ethnic groups or different regional populations within countries have not shown a consistent relationship between dietary fat and cancer (Vogel and McPherson, 1989) but this may be because the effects of smaller differences in dietary fat intake are obscured by other factors that influence carcinogenesis. Such studies may nevertheless help to provide clues to the role of diet in cancer (Willett, 1990a).

**B. MIGRANT STUDIES**

Studies on migrants have provided the strongest evidence that the geographical differences in cancer incidence and mortality observed in intercountry studies are related to environmental rather than genetic factors (McMichael and Giles, 1988; Prentice et al., 1988). The results of these studies have shown that the pattern of cancer in migrants changes from that in their country of origin and approaches that of their newly adopted country. The rate of change varies for cancer at different organ sites (for example, colon cancer changes more quickly than breast cancer) and may require more than a generation to approximate the pattern in the host country. This suggests that factors operating early in life may be more important in determining future breast cancer risk (Adami et al., 1990).

In studies to date, the migrants have invariably moved from countries with lower to those with higher fat intake. Since the cancer pattern changes from that of the country of origin to that of the host country, this necessarily means an increase in those cancers that are positively correlated with dietary fat. It does not, however, prove that this is a causative relationship, since many other environmental changes are associated with the move.

The idea that dietary fat is one of the most important environmental variables comes primarily from the results of experimental studies which have shown consistently that animals on high-fat diets develop cancer at sites such as the breast and colon more readily than animals on low-fat diets (National Research Council, 1982; 1989). It should be noted, however, that the differences in cancer incidence and mortality associated with differences in dietary fat in the intercountry data are often substantially greater than the differences in cancer incidence observed in animals over a similar range of fat intake. In changing from low- to high-fat diets, there may thus be alterations in other components of the diet that influence the carcinogenic process. In this connection, it is interesting to note that rats on chow diet have been observed to develop fewer mammary tumors than those on semipurified diet, even when the level of fat is similar in the two diets (Carroll, 1975; Ip, 1987).
Figure 2. Diagram illustrating the possible relationship between genetic and environmental influences on carcinogenesis. In comparing data from two different countries, it is assumed that the population of each country has a similar range of genetic susceptibility to cancer, but a greater proportion of the more susceptible individuals may develop cancer under the environmental conditions of one country compared to the other (Carroll, 1986b). (Used with permission.)
C. TIME-TREND STUDIES

Environmental conditions are continually changing in any given country thereby providing additional opportunities to study the effects of the changing environments on cancer incidence and mortality (Lands et al., 1990). Time-trend studies have shown an increase in breast and colon cancer in Japan since World War II that has been accompanied by a marked increase in the level of dietary fat (Willett, 1989). As in the migrant studies, this cannot necessarily be assumed to be a causative relationship. The frequency of breast and colon cancer has also increased in a number of other countries in recent years (Kurihara et al., 1984), but the causes have not been investigated in any detail. Incidence of cancers of the breast, prostate, and to a lesser extent colorectal cancer, are also increasing in the United States (Newman, 1990). This may be due in part to increased detection of existing tumors, but may also reflect changes in actual risk (Liff et al., 1991; Potosky et al., 1990).

As in the migrant studies, time-trend studies have generally shown an increase in dietary fat intake and this has been associated with increases in types of cancer that are positively correlated with dietary fat in the intercountry studies. There is as yet little direct evidence that a decrease in dietary fat intake would result in reduced incidence of cancer at those sites.

D. COHORT STUDIES

In cohort studies, groups of individuals who were originally free of disease are followed prospectively with time, and attempts are made to relate environmental factors such as diet to development of the disease in particular individuals. Data on dietary fat and breast cancer have been reported for a number of such studies in recent years (Howe et al., 1991; Jones et al., 1987; Knekt et al., 1990; Mills et al., 1989a; Willett et al., 1987). None has provided strong evidence for a positive association and in some cases a negative correlation was observed (Willett et al., 1987).

In a cohort study of diet and pancreatic cancer among 34,000 Seventh-day Adventists, Mills et al. (1988b) observed that the protective effect of frequent consumption of vegetables and fruit was more important than any increased risk from frequent consumption of meat or other animal products. Bosland (1988) reviewed the etiopathogenesis of prostate cancer and concluded that a high intake of dietary fat was associated with elevated risk. However, a prospective study of prostate cancer in approximately 8000 men of Japanese ancestry in Hawaii showed no association with total fat intake during a follow-up period of about 20 years (Severson et al., 1989). Another cohort study of diet and prostate cancer in approximately 14,000 Seventh-day Adventist men followed for 6 years showed no relationship with body-mass index and no association with animal product consumption after allowing for the protective influence of increased fruit and vegetable consumption (Mills et al., 1989a). A prospective study of more than 17,000 policy holders of the Lutheran Brotherhood Insurance Society with a 20-year follow-up likewise showed no association of prostate cancer with dietary factors, including meats, dairy products, fruits, or vegetables (Hsing et al., 1990). Increased risk of urothelial cancer associated with high intake of beef and pork and with several fried foods was reported by Steineck et al. (1988, 1990).

Although cohort studies offer an attractive approach to studying the role of dietary fat in cancer, they have some serious limitations (Freudenheim and Marshall, 1988; Goodwin and Boyd, 1987; Hegsted, 1989; Prentice et al., 1988). It is difficult to obtain an accurate assessment of the diet of individuals over time, especially when the assessment is based on self-administered questionnaires. Another serious problem is that the range of fat intake in cohort studies is generally less than that for intercountry studies and may be insufficient to distinguish effects of dietary fat from the influence of other factors that might affect carcinogenesis (Hebert and Kabat, 1991).
In spite of these limitations, Willett et al. (1990) have recently reported a positive association between dietary animal fat and risk of colon cancer in the same cohort of women as those for the study on breast cancer referred to above (Willett et al., 1987). In the colon cancer study, positive associations were observed for both saturated and monounsaturated fat, the major constituents of animal fat, but not for vegetable fat or linoleic acid. Total energy intake was not significantly associated with risk of colon cancer. However, the positive associations with total, saturated, and monounsaturated fats were weak and non-significant until adjusted for total energy intake.

The dichotomy between breast and colon cancer in these reports obviously requires explanation and more data may be needed to resolve the issue. In studies on migrants and time-trend studies within countries, the incidence of breast cancer has generally changed more slowly than that of colon cancer (Willett, 1989). This may indicate a longer latent period for breast cancer, and changes in dietary intake may be greater over a longer period of time.

E. CASE-CONTROL STUDIES

These are retrospective rather than prospective studies in which individuals with cancer are matched with hospital, community or population controls of similar age and sex, and an effort is made to identify factors that may have led to development of cancer in some individuals and not in others.

Like the cohort studies, these have not generally provided strong evidence for an association between dietary fat and cancer (Hulka, 1989; Willett, 1989), although a combined analysis of 12 case-control studies on breast cancer by Howe et al. (1990a) showed a consistent, statistically significant, positive association with saturated fat intake in postmenopausal women (relative risk for highest vs lowest quartile 1.46, p<0.0001). Some other recent case-control studies on breast cancer have also shown positive associations with dietary fat (Brison et al., 1989; Ewertz and Gill, 1990; Gerber et al., 1989, 1990; Iscovitch et al., 1989; Pryor et al., 1989; Richardson et al., 1991; Tioniolo et al., 1989; Van't Veer et al., 1990, 1991; Yu et al., 1990), although they may not always be clearly dissociated from increased energy consumption (Willett, 1990b). Other studies have not shown an association with dietary fat or have not specifically addressed the question (Katsouyanni et al., 1988; Lee et al., 1991; Le Marchand et al., 1988; Mills et al., 1988b; Rohan et al., 1990; Zaridze et al., 1991). Results of these studies are summarized in Appendix Table 1.

Willett (1989) reviewed epidemiological studies on both breast and colon cancer and concluded that the evidence relating diet to colon cancer, although not conclusive, was stronger than that for breast cancer. This conclusion was based mainly on the results of cohort and case-control studies. Other recent case-control studies have generally shown a positive correlation between colorectal cancer and dietary fat (Freudenberg et al., 1990; Gerhardsson de Verdier et al., 1990; Graham et al., 1988; Slattery et al., 1988; West et al., 1989; Whittemore et al., 1990) or animal products (Benito et al., 1990; La Vecchia et al., 1988). Some differences in fat metabolism between cases and controls were observed by Neoptolemos et al. (1988). (See also Appendix Table 1).

A number of case-control studies have been concerned with the role of diet in pancreatic cancer (Appendix Table 1). Ghadirian et al. (1991) reported increased risk associated with intake of total energy, total and saturated fat, and cholesterol. Howe et al. (1990b) also reported an association with total energy but not with total fat. Farrow and Davis (1990) found no association with total fat and Zatonski et al. (1991) found an inverse association with fat, particularly unsaturated fat, although there was a strong positive correlation with dietary cholesterol. Falk et al. (1988) and Olsen et al. (1989) observed increased risk associated with consumption of meat products and La Vecchia et al. (1990) reported an insignificant trend for increased risk associated with intake of meat, eggs, and margarine.
The role of diet in prostate cancer has been investigated in several recent case-control studies (Appendix Table 1), and some have shown evidence of increased risk associated with dietary fat (Mettlin et al., 1989; Slattery et al., 1990; West et al., 1991). Ohno et al. (1988) reported an increased risk with low β-carotene and vitamin A intake but found no association with dietary fat. Rose and Connolly (1991) summarized the results of eight earlier case-control studies on prostate cancer, all but one of which showed a positive association with dietary fat.

A positive association between lung cancer and dietary fat and cholesterol was reported by Goodman et al. (1988) for men but not for women. Jain et al. (1990) also observed an increased risk of lung cancer associated with cholesterol intake. One study on ovarian cancer (Shu et al., 1989) showed that risk was significantly correlated with increased intake of animal fats, but another showed no relation to dietary fat (Slattery et al., 1989).

Other recent case-control studies have examined effects of diet on cancer of the oral cavity and pharynx (Franceschi et al., 1991), cancers of the bladder (La Vecchia et al., 1989), other parts of the urinary tract (Steineck et al., 1990), and non-Hodgkin's lymphoma (Franceschi et al., 1989). The latter two studies showed evidence of an association between dietary fat and increased risk. Mettlin et al. (1990) reported that consumption of whole milk was associated with increased risk for cancer at a number of different sites.

Some of the studies now being reported are part of a multicentric, case-control program of the International Agency for Research on Cancer (IARC) with the acronym SEARCH. Dietary investigation is a dominant theme in two of these studies, one on pancreatic cancer and one on breast and colon cancer in women (Saracci, 1990).

For investigating relationships between dietary fat and cancer, case-control studies have a number of disadvantages. As with cohort studies, the range of dietary fat intake in cases and controls is generally not as great as for intercountry studies, and determining dietary intake of individuals in the past poses even greater difficulties than obtaining such information for prospective cohort studies (Vogel and McPherson, 1989).

Jain et al. (1989) compared dietary intake in a group of 94 control subjects from a case-control study of diet and colorectal cancer after an interval of 7 years and found that dietary habits had changed in a substantial number of people. Comparison of the current with the earlier intake showed good reliability for macrocomponents when no dietary change had occurred but poorer reliability for microcomponents and for subjects reporting a dietary change.

The choice of controls also presents potential difficulties. There is a possibility that the diets of hospital controls, as well as those of the cases themselves, may be influenced by the illnesses diagnosed and that the diets of population controls may be influenced by a particular interest in nutrition (Willett, 1990a).

A major problem with case-control studies is that the cases by definition are all genetically prone or have been sufficiently initiated for cancer to develop under particular environmental conditions. This cannot be assumed for the controls. As noted earlier, even in countries with high incidence of breast cancer such as the United States, only about one in nine women develop the disease. This suggests that in a group of control women, only a relatively small proportion will develop breast cancer, regardless of environmental factors such as the level of dietary fat. This argument also applies to cancer at other sites. Case-control studies are thus not well-suited for investigating effects of diet in cancer promotion in the absence of evidence that the cases and controls are at comparable risk in terms of initiation.
F. INTERVENTION STUDIES

The aim of these studies is to provide direct evidence in humans that a particular change in diet, such as a reduction in dietary fat, will alter the risk of developing particular kinds of cancer. The advantages of this approach are that diets can be designed to compare relatively large differences in dietary fat intake and that study groups can be followed prospectively. Preliminary studies have already demonstrated the feasibility of this approach in women at risk of breast cancer (Boyd et al., 1988, 1990; Henderson et al., 1990, 1991; Holm, 1990; Holm et al., 1990) and in breast cancer patients (Boyar et al., 1988; Nordevang et al., 1990), although it would be desirable to have further documentation over a wider socioeconomic and ethnic range.

The reduction in fat intake is largely replaced by carbohydrate, although some increase in dietary protein has also been reported (Nordevang et al., 1990). In general, there is a tendency for overall caloric intake to decrease and this is accompanied by some reduction in weight and a decrease in serum cholesterol levels (Boyd et al., 1988; Henderson et al., 1990). These changes tend to be greater during the early intervention period but have persisted in longer term studies. Dougherty et al. (1988) have pointed out that a low-fat diet is richer in essential nutrients than a high-fat diet.

A major disadvantage of intervention trials is the high cost and labor intensive nature of such studies, which may need to be continued for a relatively long period of time with large numbers of individuals in order to obtain a clear-cut answer. One way of reducing the number of individuals that need to be studied is by recruiting those at higher risk, as in the study of Boyd et al. (1988). Another way to make such studies more cost effective is to broaden the scope of the investigation to study effects of reducing dietary fat on risk of other diseases, such as cardiovascular disease, as proposed in a modified version of the Women's Health Trial (Smigel, 1990).

Another approach in intervention studies is to investigate effects of reducing dietary fat on recurrence of cancer rather than on primary development (Wynder et al., 1990). There is some rationale for this in the case of breast cancer, which has been found to recur less frequently in Japan, where fat intake is substantially lower than in the United States. Verrault et al. (1988) and Holm et al. (1989) have reported that high-fat diets are associated with prognostic indicators of a less favorable outcome for women with breast cancer. These include larger tumors and more axillary node involvement, the latter being associated with higher saturated fat intake.
III. DISCUSSION

A. LIMITATIONS OF STUDY DESIGN

Early enthusiasm for the proposal that high-fat diets increase the risk of cancers of the breast, colon, and other sites was based mainly on intercountry correlations, studies on migrants, and the results of experiments on animal cancer models. This enthusiasm was subsequently tempered by the results of cohort and case-control studies which often provided only weak or equivocal evidence for a positive association between dietary fat and cancer. There have also been suggestions that cancer is influenced more by energy balance than by any specific effect of dietary fat (Kritchevsky, 1990; Pariza, 1987, 1988).

The results of recently reported studies have not provided much further clarification of the role of dietary fat in cancer. Those who find the data from intercountry comparisons and animal experiments more convincing continue to believe that dietary fat is an important factor in observed geographical differences in cancer incidence and mortality at sites such as breast and colon. Those who place more credence in cohort and case-control studies continue to be skeptical and suggest that, if there is a relationship, the evidence for colon cancer is more convincing than that for cancer at other sites.

In the report, an attempt has been made to discuss the strengths and weaknesses of the different approaches to investigating the role of dietary lipids in cancer. (See also Colditz and Willett, 1991; Higginson and Sheridan, 1991). At this point in time, ecologic studies, supported by results of animal experimentation, provide a valid basis for thinking that dietary lipids have a significant effect on cancer incidence and mortality. Furthermore, the evidence from experimental studies indicates that any such effects of dietary lipids are exerted primarily at the promotional stage of carcinogenesis.

It is important, however, to consider why the results of case-control and cohort studies have not provided strong support for these conclusions. As discussed earlier, case-control studies do not appear to be well-suited for studying factors affecting cancer promotion, because the cases and controls are not comparable in terms of initiation. Cohort studies have an advantage over case-control studies in that the cases are not preselected and diets can be followed prospectively rather than retrospectively, which depends on dietary recall. The diagnosis of cancer is also likely to be more reliable in cohort studies than in intercountry studies, where the reliability may vary considerably from one country to another.

For cohort studies, the dietary intake is assessed on an individual basis, usually from completed questionnaires. The variations in dietary fat intake within the cohort are generally less than those covered by the intercountry studies. Thus, there is greater potential for overlap within different segments of the cohort. In such circumstances, variations in the dietary intake of individuals with time can also assume greater significance since a particular individual may not consistently remain within a specific sub-group of the cohort. Although some cohorts, such as those of Willett et al. (1987), have been followed for a considerable period of time, the numbers of individuals and the time span are still considerably less than those of intercountry studies.

For intercountry studies, dietary assessment is usually based on food disappearance data. It thus provides no information on individual intakes of dietary lipids and greatly overestimates intake when expressed as g/person/d. However, when fat intake is expressed as percent of total caloric intake, disappearance data give a reasonable approximation to values obtained by more rigorous methods. In any population there will be considerable individual variation in dietary fat intake, but, in comparing two countries with large differences, based on disappearance data, it seems reasonable to
conclude that there will be relatively little overlap between the intakes of individuals within those countries. Since disappearance data for many countries have now been collected for 40 or more years, it is also possible to have an idea of intercountry differences over an extended period of time.

The above considerations provide some possible reasons for the relative lack of support of the dietary lipid hypothesis by case–control and cohort studies. (See also Byar and Freedman, 1989; Goodwin and Boyd, 1987; Hebert and Miller, 1988; Hulka, 1989; Prentice and Sheppard, 1989; and Schatzkin et al., 1989). In referring to case–control and cohort studies, Greenwald (1989) has expressed the view that when so many epidemiological studies give such varied results, it is questionable whether much more can be gained by further studies of this type.

B. THEORETICAL EXPLANATIONS FOR CONFLICTING RESULTS

It is pertinent to speculate, however, why case–control and prospective studies have generally provided more consistent evidence for a positive association of dietary fat with colon cancer than with breast cancer. One possibility is that the average latent period may be longer for breast cancer than for colon cancer. Dividing cells are more susceptible to mutagenic agents than differentiated non–dividing cells, and it therefore seems probable that initiation of breast cancer occurs more frequently at an early age when the breast is developing, whereas this may not be true for cancer of the colon where epithelial cells continue to divide during adult life.

The idea of early initiation of breast cancer is reinforced by evidence that incidence is influenced by factors such as age of menarche, age at first pregnancy, and parity (de Waard and Trichopoulos, 1988; Kelsey and Gammon, 1990). The initiation process may be influenced by the latter two factors because pregnancy tends to hasten differentiation of the glandular epithelial cells (Russo et al., 1990). The slower rate of change in incidence of breast cancer relative to colon cancer in migrants and in time–trend studies is also compatible with the idea that initiation of breast cancer occurs at an early age and that effects of a promoting agent such as dietary fat may be exerted at an early age to a greater extent than for colon cancer.

As discussed earlier, the pre–selection of individuals with cancer in case–control studies makes such studies unsuitable for investigating effects of dietary lipids on cancer promotion. In other kinds of epidemiological studies, including intercountry studies, migrant studies, time–trend studies, and cohort studies, it is also difficult to distinguish clearly between effects of initiation and promotion in carcinogenesis. This remains a problem, even in the case of intervention trials. In such trials, any differences in cancer incidence associated with changes in the diet would presumably be independent of effects of initiation by non–dietary carcinogens, but changes in diet might still lead to greater or less exposure to dietary carcinogens as well as to promoting agents.

In human studies on diet and carcinogenesis, it is also difficult to resolve the question of the relative importance of energy intake and dietary fat, because they are so strongly correlated with one another (Carroll and Khor, 1975). It is well known that caloric restriction inhibits carcinogenesis in experimental animals (Kritchevsky, 1990; Ruggeri, 1991). Welsch et al. (1990) expressed the opinion that enhancement of mammary carcinogenesis by dietary fat is dependent on ad libitum feeding. However, Freedman et al. (1990) concluded from their survey of experimental studies that dietary fat had an effect on mammary carcinogenesis which was independent of caloric intake. Other recent reviews of the influence of dietary fat on carcinogenesis in experimental animal models include those of Angres and Beth (1991), Birt (1990), Erickson and Hubbard (1990), Kritchevsky and Klurfeld (1991), Rogers and Longnecker (1988), Weisburger and Wynder (1991), and Zhao et al. (1991). The latter group concluded from an analysis of 14 studies that dietary fat has an important and specific role in the promotion of rat colon carcinoma.
The correlation analysis of international data by Hursting et al. (1990) led to the conclusion that total fat intake was strongly associated with cancers of the breast, colon, and prostate, even when adjusted for total caloric intake. Saturated fat was also associated with incidence of cancers of the breast, colon and prostate. Polyunsaturated fat was associated with incidence of breast and prostate but not with colon cancer.

Decreased caloric intake as a result of inadequate food supplies may have an inhibitory effect on carcinogenesis in some parts of the world, but it does not seem practical to encourage voluntary reduction of dietary intake as a means of reducing cancer risk when food is readily available. It has been observed, however, in feasibility studies with low-fat diets (Boyd et al., 1988; Henderson et al., 1990) that caloric intake tends to decrease when the level of fat in the diet is reduced. This may occur because of the more bulky nature and lower energy density of low-fat diets. If such diets are able to reduce the risk of cancer, it may not matter whether the effect is related specifically to dietary fat or caloric intake.

Any approach to risk reduction is nevertheless more appealing if a scientifically-based rationale can be provided. For colon cancer, it has been suggested that high-fat diets increase the concentration in the colon of bile acids and possibly of fatty acids as well, which in turn can act as promoters of carcinogenesis (Newmark et al., 1984; Reddy, 1986). These effects may be modified by other dietary components, such as calcium, which could bind the acids and prevent their promoting action (Lipkin, 1991; Lipkin et al., 1991).

Effects of dietary fat on sex hormones was one of the first mechanisms proposed to explain its effects on mammary cancer (Chan and Cohen, 1975). This has been a continuing theme of research (Adlercreutz, 1990a,b; Cohen, 1986; Key and Pike, 1988; Pike, 1990; Welsch, 1986), but the role of hormones has been surprisingly elusive, and there is still no consensus on the relationship of diet to hormonal changes associated with breast cancer (Adlercreutz, 1990a; Kelsey and Gammon, 1990). Attempts to relate hormonal changes to diet and prostatic cancer have likewise had little success (Rose and Connelly, 1991). Additional suggested mechanisms for effects of diet on mammary cancer include effects on the immune system, on prostaglandin synthesis, on lipid peroxidation, on membrane fluidity, on intercellular communication, and on response to growth factors (Cohen, 1986; Welsch, 1987).

Another recently proposed mechanism is based on evidence that the adipose tissue of the mammary gland has an important influence on development and proliferation of the mammary parenchyma (Carroll and Parenteau, 1991). Since adipose tissue represents the major site of energy storage in the body, it is likely to reflect changes in energy balance to a greater extent than body weight as a whole. The intimate association between adipose tissue and glandular tissue in the mammary gland should facilitate transfer of substances such as eicosanoids, estrogens, or other growth-promoting factors that might be present in larger or smaller amounts as the volume of adipose tissue increases or decreases under the influence of diet. This could perhaps mediate effects of high-fat versus low-fat diets and might also help to explain other dietary effects as well as effects of caloric restriction or exercise (Cohen et al., 1988; Simopoulos, 1990; Weinidruch et al., 1991).

This proposed mechanism is also compatible with evidence that obesity is a risk factor for breast cancer (de Waard and Trichopoulos, 1988; Kelsey and Gammon, 1990; Rose and Connelly, 1990; Swanson et al., 1989), although this has not been observed consistently (London et al., 1989; Schapira et al., 1991). Le Marchand et al. (1988) obtained evidence for a protective role of adolescent obesity against premenopausal breast cancer but found that adult weight and a positive energy balance in adult life were positively associated with postmenopausal risk of breast cancer. Ballard-Barbash et al. (1990a) in a 10-year follow-up study of 5599 women from the National Health and Nutrition Examination Survey also observed a positive correlation between breast cancer and adult body weight gain, this after correction for various possible confounders. There was no association between body
mass at baseline examination and subsequent breast cancer. There is also evidence from other studies that increased central to peripheral body fat distribution predicts breast cancer risk independently of the degree of adiposity (Ballard-Barbash et al., 1990b).

Goodwin and Boyd (1990) reviewed the literature on body size in relation to breast cancer prognosis and concluded that increased body size had a modest inverse effect that was independent of other prognostic factors. It was most apparent in postmenopausal women and may be greater in those with uninvolved axillary lymph nodes.

Reducing the fat content of the diet tends to decrease serum cholesterol levels, and there has been some concern over evidence that low serum cholesterol is actually associated with increased cancer rates, particularly cancer of the colon (McMichael, 1991). However, the low serum cholesterol may sometimes be a consequence of undetected cancer (Kritchevsky et al., 1991; Winawer et al., 1990), and the fact that colon cancer is relatively rare in many parts of the world where most people have low serum cholesterol levels indicates that there is no consistent relationship. It thus appears improbable that reducing the fat content of the diet is likely to increase the risk of cancer. Boyd and McGuire (1990) have reviewed evidence for an association between plasma high density lipoprotein (HDL) levels and risk of breast cancer. This association can be observed in demographic patterns, and preliminary studies have also shown that high-risk women with mammary dysplasia tend to have higher levels of HDL cholesterol (Boyd et al., 1989).

In another study, mammary dysplasia was associated with evidence of increased lipid peroxidation, as indicated by higher urinary levels of malonaldehyde (Boyd and McGuire, 1990). The role of lipid peroxidation and of antioxidants in carcinogenesis is of considerable interest and warrants further investigation. Experimental studies in animals have shown that dietary polyunsaturated fats promote mammary cancer more effectively than saturated fats (Carroll and Khor, 1975; Ip, 1987), but epidemiological data have not provided clear evidence regarding the effects of different types of dietary fat (Carroll et al., 1986; Hursting et al., 1990).

Eid and Berry (1988) analyzed the fatty acid composition of subcutaneous adipose tissue as a measure of the type of fat ingested and reported that the quality of fat did not appear to be a major factor in the development of breast carcinoma. Gonzales et al. (1991) have recently reported that the inhibitory effect of dietary fish oil on mammary carcinogenesis is associated with increased levels of tumor lipid peroxidation products. This contrasts with results of the studies of Boyd and McGuire (1990) referred to above. Although the evidence regarding lipid peroxidation is somewhat inconsistent, it is important to try to identify markers that are associated with increased cancer risk and that might be modified by dietary means.
IV. CONCLUSIONS

There is substantial but not conclusive evidence that high-fat diets increase the risk of developing cancers of the breast, colon, prostate and possibly other sites, compared to low-fat diets. It is difficult to dissociate effects of dietary fat from those of energy intake in human studies because they are so closely correlated with one another. However, decreasing the fat content of the diet appears to be a more practical approach to reducing the risk of cancer than voluntary restriction of energy intake in the presence of an abundant food supply.

Intercountry comparisons suggest that a reduction of dietary fat to less than 30 percent of total calories is required to have a measurable effect on cancer incidence and mortality. This is compatible with results of cohort and case-control studies that have failed to show strong associations between breast cancer and dietary fat over ranges above 30 percent of calories but does not explain the better correlation between colon cancer and dietary fat in some of these studies. It is not clear from the intercountry data whether there is a linear correlation between cancer incidence and mortality and dietary fat at levels below 30 percent of energy. A level of about 20 percent of energy appears to be the minimum that can be readily achieved without drastic alteration of the typical North American diet.

Individuals differ in their susceptibility to cancer and in some cases groups with increased susceptibility can be recognized. For example, certain types of benign breast disease are associated with increased risk of breast cancer, and individuals with intestinal polyposis have an increased risk of developing colon cancer. However, any attempt to achieve a significant reduction in cancer incidence by decreasing the fat content of the diet would probably need to be applied to populations as a whole.

The main sources of fat in the diet are the visible fats and oils used as spreads, cooking fats and salad oils, and the fats in meats and dairy products. The visible fats and oils provide relatively little in terms of essential nutrients but add flavor and variety to the diet. The amounts used can be reduced, however, without basic changes in the diet as a whole. Meats and dairy products are both good sources of essential nutrients, and the approach in this case could be to use lower fat products, which are now becoming more widely available. Most other components of the diet contribute relatively little to the overall fat content.

Given the totality of data available, the most critical gap in knowledge at the present time is the lack of direct evidence that risk of cancer can be reduced by decreasing the fat content of the diet. It appears that this gap can only be filled by intervention trials, which are expensive and time consuming. By studying individuals with increased risk of cancer, it may be possible to obtain answers with lesser numbers of subjects, but such answers will not necessarily be applicable to whole populations. Thus, there seems little alternative to population-based intervention studies if one wishes to obtain a definitive answer.
V. BIBLIOGRAPHY


*This bibliography contains all reference citations that are either in the text or the tables or both.


23


28


APPENDIX

CRITERIA FOR INCLUSION OF ARTICLES IN APPENDIX TABLES

Articles in peer-reviewed journals related to the topic of this review were selected primarily on the basis of data and content. In general, papers appearing in 1987 or thereafter were included, provided that they presented original data from studies in humans. Certain items tabulated for the sake of completeness may not have been cited in the body of the text if their weight or relevance did not add significantly to development of the author's argument. Reviews have not been listed except as they included new data or useful meta-analyses.
## APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

### I. Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Boyd et al., 1988</td>
<td>Intervention Toronto, Canada</td>
<td>295 8-2-30 yr with dysplasia in ≥50% of breast volume diagnosed within 3 mo of study 227 out of 295 subjects (77%) completed the full year. 32% of the intervention group dropped out before 1 yr.</td>
<td>Subjects were randomly assigned to either: &quot;Control diet&quot; containing ~36% calories as fat or &quot;Intervention diet&quot; containing ~15% calories from fat. Diets were balanced isocalorically with the addition of carbohydrate to the intervention diet. Compliance measured by random diet records and 24-hr recalls throughout the 1 yr trial. Dependent variables were differences between baseline and end-of-trial mammographies and histology when available.</td>
<td>The mean fat intake of the intervention group was reduced from 37% at baseline to 23% by 4 mo and continued at that level throughout the trial. Carbohydrate intake increased from 43% to 56% of calories and remained there for the duration of the trial. At 1 yr there were 172 sets of mammograms for comparison. 45% of the control group had reduction of dysplasia, 15% had evidence of increase. 25% of intervention group showed improvement with 10% showing a deterioration. There were no significant differences between groups.</td>
<td>Potential self-selection bias: subjects were examined under their volition, all subjects were highly educated, all subjects had been diagnosed with mammary dysplasia. No real control group Length of trial may have been too short to demonstrate a discernible effect. No indication of diet during exposure period prior to diagnosis. Diets were not isocaloric as intervention did not completely compensate for calories lost from fat reduction.</td>
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<td>Boyd et al., 1989</td>
<td>Cross-sectional Toronto, Canada</td>
<td>2 groups of premenopausal #: 1. No dysplasia (ND); (n = 16) &lt;25% of the breast with mammographic evidence of dysplasia 2. Dysplasia (D); (n = 30) &gt;75% of the breast having mammographic evidence of dysplasia 50% of eligible subjects participated.</td>
<td>Subjects recruited by mail then by phone. Interviewed at home measurements included: demography, 7-d diet recall and a 4-d (including 1 weekend d) diet diary kept by subjects. Subjects trained in portion size estimation and supplied with digital scales, measuring cups, and spoons. Fasted blood samples were collected during the follicular and luteal phases of menstruation. Luteal blood was used for assessment of lipid chemistry (triglycerides, total cholesterol, HDL, LDL).</td>
<td>Groups differed in family history (D&gt;ND for family history of breast cancer) and anthropometrics (D&lt;ND for weight and skinfold thickness). Based on 4-d diaries, the only difference was alcohol consumption (D&gt;ND). There were significant differences in blood lipids (triglycerides, HDL and LDL) between groups (D&lt;ND for Trig. and LDL, D&gt;ND for HDL). There were significant independent associations between mammographic patterns, family history and HDL cholesterol. Triglyceride levels were independently associated with family history.</td>
<td>Small sample from limited geographical area. High refusal rates (50% of eligible subjects). Potential self-selection bias as all subjects were participating in a preventative screening program. No socio-economic (SES) data presented.</td>
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<td>Brisson et al., 1989</td>
<td>Case-control Quebec, Canada</td>
<td>290 cases of newly diagnosed breast cancer; 645 age-matched control; 8 without BC enrolled in a longitudinal BC-screening program/study</td>
<td>All subjects were interviewed about demographics, menstrual history, height and weight, smoking history, physical activity, drug use history, and diet history. 114-item food-frequency questionnaire. Reference period: the previous yr. Food models were used to estimate portions sizes. All subjects had mammograms; for cases the unaffected breast was evaluated, for controls random selection. All evaluations were done blindly.</td>
<td>In controls, 1 in energy adjusted saturated fat intake was associated with 1 high-risk mammographic features; however, there was no effect from energy adjusted dietary polysaturated fat or cholesterol. 1-carotene and fiber intakes were associated with a 1 in high risk features on mammograms. Retinol had no effect on mammograms features.</td>
<td>No comparisons in terms of risk of BC related to intake. Analysis limited to associations between mammographic features and diet. Supplement use not reported. Dependent variables, mammogram features were derived from subjective evaluation of the observer. The relationship of mammographic features to dietary components and breast cancer risk factors was assessed in controls only. The dietary design of this study a cross sectional not case-control. Potential for self-selection bias as all controls were from a pool of volunteers involved in an ongoing BC screening program.</td>
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<td>Eid and Berry, 1988</td>
<td>Cross-sectional Jerusalem, Israel</td>
<td>85 consecutive patients undergoing needle biopsies were divided (post-biopsy) into 3 groups: Carcinoma (C; n = 37), Fibroadenoma (F; n = 27) Other types (O; n = 21)</td>
<td>Adipose tissue samples were collected from breast and buttocks of all subjects as used as a surrogate measure of the quality of habitual dietary fat intake.</td>
<td>No differences except for stearic and linolenic acids which were lower in group F than either of the other 2 groups. F was significantly thinner and younger than either of the other groups.</td>
<td>No diet data, no matching for any variables, no controls.</td>
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<td>Ewertz and Gill, 1989</td>
<td>Case-control Denmark</td>
<td>1474 cases of breast cancer diagnosed over period 1983-1984 1322 age-stratified randomly-selected controls</td>
<td>Cases mailed questionnaire 1 yr after diagnosis. Controls matched to cases for date of diagnosis. 21-item food-frequency questionnaire designed to &quot;include 80% of the consumption of fat and 8-carotene in the study population.&quot; Food models were used to estimate portion sizes. Subjects also asked about supplement use, caffeinated beverages, sugar, and artificial sweeteners.</td>
<td>There was a significant trend for increased risk with increased intake of total fat. There were no changes in these findings after adjustment for socioeconomic status (SES), age at first menarche, natural menopause, parity, and age at first birth. There was no association between 8-carotene intake and risk of breast cancer. Nonsignificant elevation in risk with the use of all common vitamin supplements More cases (72%) than controls (67%) used supplements</td>
<td>Reference period not clearly defined. The rationale stated for delay of a yr after diagnosis was &quot;to avoid asking questions on diet during a period where adjuvant chemotherapy was administered...&quot; This implies that the diet data referred to intake patterns after diagnosis which would not reflect risk, rather response to the disease.</td>
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## APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

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| Gerber et al., 1990 | Case-control Milan, Italy Montpellier, France 317 cases of primary nonmalignant breast cancer (214 Italy, 103 France) 318 hospital-based controls (215 Italy, 103 France) | 317 cases of primary nonmalignant breast cancer (214 Italy, 103 France) 318 hospital-based controls (215 Italy, 103 France) | Fasting blood drawn the day after admission and frozen at -18°C for levels of retinol, β-carotene, vitamin E, vitamin C, and riboflavin. Subjects interviewed about demographics and medical history. Food–frequency questionnaire was used to assess dietary habits. The Italians were asked about all foods eaten; whereas the French were only asked about key lipid and vitamin-rich foods. Reference period was the previous yr unless diet had changed in which case subjects were asked about the previous 12 mo. Subjects estimated portion sizes. | A significant difference was found in total fat and cholesterol between cases and controls of both groups; in the French groups there was a difference in saturated and monounsaturated fat intake. No difference in lipid–soluble vitamin intake between groups. There was a higher serum level of cholesterol and plasma vitamin E in cases compared to controls of both groups. Increased risk associated with dietary cholesterol, total dietary lipids, plasma vitamin E, and serum zinc (only measured in Italian sample) | No community–based controls  
No comparison of controls to each other or to community standards  
Blood levels were correlated with past intake (data based on long retrospective period). Differences in quantification of diet records between 2 study sites. Blood assays were blinded and all vitamin assays were performed at the same lab. Storage time was not given. |
| Gerber et al., 1989 | Case–control France 120 cases of breast cancer 109 controls hospitalized for nonmalignant and non–CVD–related neurological disorders Recruitment over a 4-yr period (1982–86) | 120 cases of breast cancer 109 controls hospitalized for nonmalignant and non–CVD–related neurological disorders Recruitment over a 4-yr period (1982–86) | Subjects given a structured interview containing: SES data, menopausal status, reproductive and health history, and 66-item food–frequency questionnaire. Subjects were asked about duration of nutritional habits and if there had been a change within previous yr to refer to diet prior to changes. Subjects' estimation of portion sizes was based on specified units of measure (e.g., weight, spoon).  
Fasting blood samples were drawn the day after admission to hospital and stored at -18°C for unknown duration. Lipid measures included triglycerides (TG), total cholesterol (TC), monounsaturated (MUFA), polyunsaturated (PUFA), and saturated (SFA) fatty acids.  
Vit E measured by HPLC | Postmenopausal cases consumed more total fat (p<0.07) and significantly more saturated and monounsaturated fats (p<0.05) than postmenopausal controls. Plasma total cholesterol (TC) and vitamin E were higher in cases than controls. Differences in vit E were greater in premenopausal women as was the ratio vit E/TC (which was not significant in postmenopausal patients). Plasma vit E was significantly correlated with safflower oil intake in all subjects. Dietary vit E (adjusted for age and TC) was significantly associated with plasma vit E in both groups. Other significant findings relate to evidence of lower lipid peroxidation in cases than controls. | Possibility inappropriate control group (all were suffering neurological or spinal problems; no medication history was reported).  
No community–based control group  
Although stage of disease was known, there was no analysis using this variable.  
Duration of sample storage not given.  
Relevant time frame for retrospective dietary information was not clear. |
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<td>Holm et al., 1989</td>
<td>Cohort Stockholm, Sweden</td>
<td>240 8 who had surgery for breast cancer between 1983–1986 12% premenopausal, 86% postmenopausal, 2% unknown Mean age at diagnosis was 58 yr</td>
<td>All subjects were interviewed at home within 4 mo of surgery. Diet reference period was the yr prior to diagnosis. Subjects estimated portion sizes. Data also collected about demographics, reproductive history, anthropometry (self-reported), smoking, physical activity history, and alcohol intake. Tumor size, presence of local lymphatic metastases, and estrogen receptor status were correlated with dietary factors.</td>
<td>A bivariate analysis (by tumor size) showed that cases with tumors ≥20mm had fewer children and lower actual intakes of carbohydrate and fiber as a % of total calories and per 10MJ respectively than cases with tumors ≤20mm. Those with larger tumors also consumed a higher % of total calories as total fat and monounsaturated fat. Cases with estrogen receptor–rich tumors consumed a greater % of total calories as carbohydrate and more retinol than those with low estrogen.</td>
<td>No control group No documentation of time between diagnosis or onset of symptoms and surgery No follow-up analysis was performed due to insufficient numbers of recurrent tumors.</td>
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<td>Howe et al., 1991</td>
<td>Cohort Toronto, Canada</td>
<td>519 cases of newly–diagnosed, histologically–confirmed breast cancer. The study sample was selected from a larger cohort of 56,837 invited to enroll in the diet–history collection phase of a larger breast screening intervention trial.</td>
<td>Beginning in 1982, all new subjects and all those returning for screening filled out a diet–history questionnaire containing a 86–item food–frequency questionnaire. Subjects estimated portion sizes with the aid of photographs and standard serving sizes. Subjects were matched for age (± 1 yr), screening center, and date of enrollment (± 2 mo).</td>
<td>There was a trend (p = .052) towards increased risk associated with increasing levels of total fat intake. The positive association between fat and risk was independent of other sources of calories. Similarly, there was an inverse association between carbohydrate consumption and risk that was also independent of other sources of calories.</td>
<td>All subjects were volunteers in a breast cancer prevention program. No comparison group outside this cohort Menopausal status was not available for analysis. There was no adjustment or assessment of SES, or smoking status, no biochemistry, no evaluation of potential impact of other nutrients, nutritional supplements, or no analysis by food types.</td>
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<td>Iscovitch et al., 1989</td>
<td>Case–control</td>
<td>150 cases of histologically–confirmed breast cancer 300 controls: 1 hospital–based and 1 community–based for each case, matched for age (± 5 yr). All subjects had to have resided in La Plata for at least 5 yr. Cases were drawn from 8 area hospitals over a 1-yr period. Hospital controls had to have been admitted within 3 mo of their matched case’s diagnosis.</td>
<td>All subjects interviewed by non-blinded interviewers either in hospital or at home. Each case-control triplet was interviewed by the same interviewer. Data collected included demographic and SES factors, menstrual and reproductive history, family health history, smoking habits, and pharmaceutical drug use. 147-item food-frequency questionnaire was used; reference period was the 5-yr period up to 6 mo prior to the interview. Portion sizes were estimated from standard serving sizes derived from a previous pilot study.</td>
<td>Because of risk differences, dietary analyses were all adjusted for age, age at birth of first child, husband’s occupation, and body–mass index. Cases consumed significantly more total calories, fat, protein, carbohydrate, and total vitamin A than either control groups. There was significantly increased risk associated with increased caloric consumption. Consumption of eggs was a significant risk factor for breast cancer, while whole milk and green leafy vegetables were protective.</td>
<td>The time frame between onset of symptoms, diagnosis, stage of disease, and the interview was not explained or controlled. The increased caloric intake of cases was not reflected in a greater degree of adiposity. The authors discuss possible reasons for this discrepancy and the association with breast cancer. The diet assessment was not sensitive enough to examine individual nutrient intakes. There was no biochemistry or any other assessment of nutritional status. There was no analysis presented for pre- vs post-menopausal effects.</td>
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<tr>
<td>Jones et al., 1987</td>
<td>Cohort</td>
<td>99 cases of confirmed breast cancer: 54 premenopausal, 65 postmenopausal. 5386 controls All subjects were obtained from the cohort of 5485 who participated in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. All subjects were identified after the 10-yr period following NHANES I.</td>
<td>Diet data used in this report were obtained at the baseline period during NHANES I. All subjects supplied a 24-hr recall. Portion sizes were estimated by the subjects with the use of food models.</td>
<td>There were a number of factors associated with increased risk including: SES, adiposity, age at menopause, family history, and age at menarche. After adjustment for risk factors, there were no significant differences between group for nutrient intake. There was a significant inverse association found between both total fat and saturated fat intake and risk of breast cancer.</td>
<td>Reliability of a single data point (24-hr recall) is questionable.</td>
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<tr>
<td>Katsouyanni et al., 1988</td>
<td>Case–control Athens, Greece</td>
<td>120 breast cancer cases 120 hospital controls (patients in orthopedic ward in a different hospital than BC cases)</td>
<td>All subjects interviewed before discharge on first hospital admission. Data collected included demographics, socioeconomic, reproductive, and medical histories. 120–item food–frequency questionnaire. To assess the impact of individual nutrients on BC, nutrient intakes were calorie adjusted. Reference period was “the period preceding the onset of disease.” Standard portions sizes were used to estimate intake.</td>
<td>Cases consumed significantly less total calories and macronutrients including total fat, protein and carbohydrates. Cases also ate less saturated, mono- and polyunsaturated fats than controls. There was a suggestion of a positive association between risk and mono-unsaturated fat intake (p&lt;.10). Total vitamin A intake was inversely associated with BC risk. Cases consumed less total vitamin A and retinol than controls. There was no difference in adjusted β-carotene intake. There were no differences in actual or calorie adjusted intakes of vit C between cases and controls. Similarly there was no association between vit C and risk of BC.</td>
<td>Inappropriate controls (about 25% had osteoarthritis which is known to affect antioxidant vitamin status). Potential mismatching due to different catchment area of controls. No demographics No biochemistry Diet data were related to the period preceding the onset of the disease which was not controlled nor was it documented. Supplement use not documented Data collected over a 12–mo period; no control for seasonal variations in intake. Portion sizes were estimated from averages in food tables.</td>
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<td>Knekt et al., 1990</td>
<td>Cohort Finland</td>
<td>54 cases of histologically–confirmed breast cancer 3934 controls All subjects were selected from a larger cohort involved in a dietary survey of 10,054 during 1966–1972. 3968 ≥ aged 20–69 yr Cases identified over a 20-yr period (1967–1986)</td>
<td>All subjects completed a self–administered questionnaire with information about residence, occupation, parity, and smoking. ≥50 yr were classified as postmenopausal. An unspecified diet history questionnaire was used to assess intake. Reference period was the usual food consumed during the previous yr.</td>
<td>Breast cancer risk was significantly inversely related to total energy and nonsignificantly inversely related to total fat, carbohydrate, and protein intakes. There was a positive association between energy adjusted fat intake and risk. There was a trend for increased risk associated with intake of monounsaturated fat intake (p&lt;0.05) and cholesterol (p&lt;0.09). There were no interactions between risk factors, e.g., smoking, body mass index, stature, geographic region, menopausal status, and parity, and the fat and risk relationship. There was an association between high milk intake (p&lt;0.02) and low meat intake (p&lt;0.12) and risk. Adjustment for energy strengthened the meat and risk relationship.</td>
<td>Variable time periods between reference period and diagnosis or onset of disease with a potential range of 2–20 yr. No biochemistry, no data on dietary supplements Diet collection was not described No descriptive data supplied</td>
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| Lee et al., 1991       | Case-control Singapore  | 200 cases of histologically-confirmed breast cancer consecutively admitted to 2 hospitals  | All subjects were interviewed in the hospital; cases within 1–3 wk of diagnosis. Data collected included menstrual and reproductive history, oral contraceptive use, breastfeeding, smoking history, family health history, occupation, education, language dialect used, and anthropometrics (weight and height). 90-item food–frequency questionnaire was used to assess intakes of animal and vegetable protein, fat, saturated fatty acids, monounsaturated fatty acids, cholesterol, β-carotene, vitamin E, and caffeine and other methylxanthines. The reference period for cases was 1 yr prior to diagnosis. Photographs and portion models were used for subject estimation of portion sizes. | All analyses were adjusted for age and other known risk factors. In premenopausal & there was a significant increase in risk associated with intake of red meat and high proportion of total protein from animal sources. There were significantly decreased risks associated with intake of polyunsaturated fatty acids, the ratio of PUFA:saturated fat, β-carotene, soya protein, and total soya products. There were no significant effects seen in postmenopausal &. | No community-based controls nor comparisons to national intake standards
Long retrospective period
No dietary supplement use data
Reference period for control group was not matched to cases.
No correlations run between presumed non-nutritional risk factors, e.g., smoking history, and dietary factors
No distinction made with respect to type of red meat or poultry |
| Le Marchand et al., 1988 | Cohort - "nested case-control" Hawaii | 580 cases of breast cancer identified from Hawaii Tumor Registry between 1972–1983 2528 controls matched to cases for race of parent and mo and yr of birth. All subjects selected from a larger historical cohort of 38,084 & born between 1918–1943 All subjects were living in Hawaii in 1943 and in 1972. | Weight and height was obtained from the 1942–43 census. Adult height and weight was obtained from 1972 driver's licenses. Other body size measures included body surface area, Quetelet and Cole's body mass indices, and Beni's relative weight. Linkages were made with other data files to obtain age at birth of first child and parity. SES in 1942 was ascertained from occupation of head of the household. SES in 1972 was based on education for adults living in the same census tract in 1972 based on 1970 census data. | Adjusted mean anthropometrics were lower for cases than controls in 1942. There was a negative association between premenopausal breast cancer and adolescent body size. This was a statistically significant effect for girls aged 10–14 in 1942 across all ethnic groups which was strongest for overweight & who remained overweight as adults. Adult weight and gain in body-mass index since 1942 were associated with increased postmenopausal risk. | No direct measure of diet
Subjects did not have to be born in Hawaii. Subjects were predominantly Oriental (50.5% Japanese, 25% Hawaiian/part Hawaiian, 9% Chinese, 4.7% Philipino, 7.9% white, 2.9% of other ethnic origin).
Menopausal status defined by age at diagnosis
Premenopausal were <50 yr at diagnosis, postmenopausal >50 yr
No family health history |
## APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type/location</th>
<th>Subject # &amp; Description</th>
<th>Methods</th>
<th>Results</th>
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</tr>
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<tbody>
<tr>
<td>Mills et al., 1986a</td>
<td>&quot;Nested&quot; case-control California</td>
<td>142 cases of fatal breast cancer. 852 controls matched for age (age in 1960 ± 1 yr). All subjects were white. 8 selected from a larger cohort of 16,190 Seventh-day Adventists who had completed a questionnaire in 1960. All subjects were self-reported to be without a previous history of cancer as of 1960.</td>
<td>All subjects completed a questionnaire in 1960 which contained data on: demographics, tobacco use, menstrual and reproductive characteristics, and disease history. There was a 21-item food-frequency questionnaire &quot;which was not sufficiently detailed to allow analysis of specific nutrients.&quot; From 1960-1965 church members involved in data collection, identified deaths. From 1966-1980 deaths were identified from a central registry of all death certificates in California.</td>
<td>There were no significant relationships between meat (no distinction between beef and poultry), milk, cheese, and egg consumption and risk. There was a nonsignificant trend between meat and milk in those experiencing early (&lt;48 yr) menopause.</td>
<td>Limited data from food-frequency questionnaire prevented examination of role of individual nutrients. There was no distinction made on the questionnaire between red meat and poultry and no data on fish intake. Variable length of time between onset and death from breast cancer could have resulted in some subjects being in early stages of cancer at the time of the original questionnaire. It was not possible to ascertain the actual menopausal status of all subjects. Some cases may have become postmenopausal prior to onset of disease.</td>
</tr>
<tr>
<td>Pryor et al., 1989</td>
<td>Case-control Utah, USA.</td>
<td>172 cases of 8 with histologically-confirmed first primary breast cancer identified through the Utah state cancer registry 190 control 8 age-matched (±5 yr) 70% of eligible cases and 80% of controls participated. All subjects were participants in a larger study: Cancer and Steroid Hormones (CASH).</td>
<td>All subjects were interviewed at home by telephone to ascertain the frequency of intake of certain foods during adolescence. Standard serving sizes were assigned to calculate individual nutrients. Total dietary calories were not assessed. Adjustment was made for age, SES, age at menarche, and age at first pregnancy in the analysis of diet and risk associations.</td>
<td>There was a nonsignificant trend towards lowered risk associated with the upper three quartiles of fat intake in pre- but not postmenopausal 8. Risk associated with 8 body mass index at age 12 in pre- but not post-menopausal subjects. Fat from milk, cheese, and yogurt was associated with lowered risk in both pre- and post-menopausal 8 (the trend was significant in the latter group, p&lt;0.01). There was a significant (p&lt;0.01) trend towards a protective effect from fiber intake in premenopausal 8. The opposite was true for the post-menopausal group (the elevated odds ratio could have been due to large variability in the data). Fiber from grains significantly lowered risk in both pre- and post-menopausal groups. In premenopausal group, fiber from other sources, i.e., fruits and vegetables, lowered risk whereas in post-menopausal group the risk ↑.</td>
<td>&gt;50% of subjects had &gt;12 yr of formal education, 77% of subjects were Mormons. All subjects were identified from a larger study cohort. CASH involved with health related issues. Long and variable retrospective data collection reference period for dietary data. Neither total caloric intake nor other individual nutrient intakes were assessed.</td>
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## APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

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<tr>
<td>Richardson et al., 1991</td>
<td>Case–control southern France</td>
<td>409 case of histologically–confirmed breast cancer 515 age–matched hospital–based controls Groups were similar for geographical area of residence.</td>
<td>All subjects interviewed in hospital about medical and reproductive history and SEFs factors. A 55–item food–frequency questionnaire was used to cover intake of food sources of lipid, animal protein, retinol, β–carotene, and vitamin E. Because the items represented sources of only these nutrients it was not possible to estimate total caloric intake or other nutrients. Subjects were asked to specify quantities of each item consumed. Reference period was recent 12 mo unless there had been a change, in which case previous diet was requested.</td>
<td>Total fat, saturated and mono–saturated fat were positively related to elevated risk. Saturated fat was significantly related to risk in postmenopausal &amp; as was increased Quetelet index (reflecting body mass). There was a significant increasing trend associated with intake of high fat cheese, desserts, and chocolate and total food consumption. No change in risk associated with apparent intakes of vitamin E, retinol, or β-carotene.</td>
<td>Limited number of items on diet questionnaire, no supplement use data, no adjustment for total calories in analyses. No community–based controls Reference period was variable and not necessarily related to onset or diagnosis of disease.</td>
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<tr>
<td>Rohan et al., 1990</td>
<td>Case–control Australia</td>
<td>383 biopsy–confirmed cases of benign proliferative epithelial disorders (BPED) 192 controls without BPED (confirmed by biopsy) 383 community–based controls.</td>
<td>All subjects given a standardized questionnaire in their homes. Cases and biopsy controls interviewed just after diagnosis (intervals 2.8 and 2.9 mo, respectively). 179–item food–frequency questionnaire Cases and biopsy controls were asked to record intake prior to diagnosis and disregard any changes made subsequent to diagnosis.</td>
<td>There was no change in risk associated with intake of total fat or any of the major subfractions, i.e., saturated, mono– or polyunsaturated fat. There was an increased risk associated with the highest levels of cholesterol intake, an effect that reached statistical significance in premenopausal &amp;. Statistically significant trend towards decreased risk with ≥ intake of retinol and β–carotene when cases compared to community controls. There was a similar trend with biopsy controls but not statistically significant. Adjustment for energy intake eliminated the β–carotene trend but not the point estimate.</td>
<td>Portion sizes estimated No analysis by food group No data on supplement use No matching of reference period for cases and all controls Case group may have been self–selected as they differed from controls in self–examination practices.</td>
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## APPENDIX TABLE. LIPIDS AND CANCER (BYSITE)

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<tr>
<td>Simard et al., 1990</td>
<td>Cohort Montreal, Canada</td>
<td>68 cases of breast cancer 340 cases of fibrocystic breast disease (FBD) 343 controls</td>
<td>All subjects were given a questionnaire with items pertaining to religion, occupation, education, marital status, socioeconomic level, weight, and number of pregnancies. A food-frequency questionnaire containing 41 food categories was used. Controls and FBD patients completed a 24-hr dietary recall.</td>
<td>Cases were significantly heavier and had a higher body-mass index than either of the other groups. Cases had significantly less education. Cases consumed more poultry, fish, pastry, margarine, and alcohol and less milk, raw vegetables, pastas, sugar, butter, and coffee than the other groups.</td>
<td>Possible selection bias as all subjects were in the latter stages of a breast cancer prevention program Only controls and FBD patients completed 24-hr recall No reference period given for the food-frequency data Portion size estimation was not described. No pre- vs postmenopausal status analysis No computation or adjustment for total calories</td>
</tr>
<tr>
<td>Toniolo et al., 1989</td>
<td>Case-control Italy</td>
<td>250 cases of breast cancer (free of metastases, except in regional lymph nodes) Controls were 490 § from general population stratified by age (≥10 yr) and geographical area.</td>
<td>All subjects interviewed (unblinded) given modified food frequency questionnaire structured by meals. Cases interviewed on average of 7.8 mo after diagnosis and after treatment or surgery. Indigenous foods and recipes were added to the database. General demographic data was obtained from electoral rolls. Standard portion sizes before cooking were estimated. Interview data included SE8 data, health and reproductive history.</td>
<td>Cases consumed more animal protein and fat. Reduced risk was associated with decreased intakes of fat especially saturated fat and animal protein. § who consumed &lt;2% of total calories as fat had lower risk than those consuming &gt;30% of calories as fat. Decreased risk was associated with intakes of &lt;9.6% saturated fat and &lt;5.9% of calories from animal protein. Intakes of retinol and β-carotene were slightly higher in cases. No difference in vitamin E or C intake between groups</td>
<td>Not blinded, no biochemistry, long period of time between diagnosis or treatment and study (on average 7.8 mo after diagnosis) Retrospective diet data not necessarily indicative of diets prior to diagnosis Smoking histories not reported</td>
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<td>Van't Veer et al., 1999, 1991</td>
<td>Case–control Netherlands</td>
<td>133 newly diagnosed cases of breast cancer 238 community controls (for whom complete dietary data were available)</td>
<td>All subjects given a home interview about demographics, smoking history, health, and reproductive and hormone history. Cases within 6 mo of diagnosis. No interviews during chemotherapy. 238-item food–frequency questionnaire. Reference period 12 mo prior to diagnosis in cases and 12 mo preceding interview in controls. Portion sizes estimated by subjects using common household utensils. The focus of the 1990 report was fat intake; whereas the 1991 study assessed the potential impact of specific nutrients or diet patterns based on their hypothesized role in carcinogenesis, e.g., vitamins A and E as antioxidants.</td>
<td>The 1999 study reported a significant ( \uparrow ) risk associated with fat intake independent of total calories. The multivariate adjusted analysis for risk that compared the highest to lowest quintile of fat intake showed a 30% ( \uparrow ) in risk per 10% of energy from fat. The 1991 study reported that a diet with the combination of low fat and a high intake of fermented milk products and fiber conferred significant protective effects.</td>
<td>Small sample size Large nonresponse rate in selection of controls (238 out of a potential pool of 548) may have resulted in bias. Cases and controls not matched on reference period, i.e., time between diagnosis and interview in cases. No supplement data, no analysis with other risk factors, e.g., smoking, hormones No analyses by menopausal status</td>
</tr>
<tr>
<td>Verreault et al., 1988</td>
<td>Cross–sectional Quebec City, Canada</td>
<td>666 cases of newly diagnosed infiltrating breast cancer Cases with distal metastases were excluded.</td>
<td>Subjects were interviewed at home 3–6 mo post–diagnosis. Data included demographics, menstrual and reproductive history, height and weight, smoking habits, physical activity, and medication history. 114–item food–frequency questionnaire, referenced to the yr prior to diagnosis. Food models were used to estimate portion sizes. The study compared prognostic indicators of breast cancer to dietary factors. The indicators included: axillary node involvement at diagnosis, estrogen receptor status, and histological features of the primary tumor.</td>
<td>After adjustment for total energy, age, body weight, and tumor size at diagnosis, ( \uparrow ) in saturated fat intake was related to an ( \uparrow ) frequency of node involvement at diagnosis in postmenopausal ( &amp; ). ( \uparrow ) in polyunsaturated fat intake was associated with ( \uparrow ) % of patients with positive nodes at diagnosis in both pre- and postmenopausal patients. Dietary fat was not related to estrogen–receptor status of tumors. There were no associations between dietary factors and histological features of the primary tumor.</td>
<td>No comparison group No analysis for nutrients other than fat No data on dietary supplement use</td>
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## APPENDIX TABLE: LIPIDS AND CANCER (BY SITE)

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<tr>
<td>Yu et al., 1990</td>
<td>Case–control Shanghai, China</td>
<td>186 cases of newly diagnosed histologically–confirmed breast cancer 186 hospital control (HC) cancer patients (head and neck, stomach, and lung) from same hospitals as cases 186 community controls (CC) matched for residential district to cases. All subjects were matched for age (± 5 yr).</td>
<td>All subjects interviewed at home to obtain data about: SES and menstrual and reproductive history. 68–item food–frequency questionnaire containing foods commonly found in Shanghai. Reference period was usual diet unless there had been a change within the last yr in which case usual diet before that time was determined. Quantification was determined with standard portion sizes.</td>
<td>Cases consumed significantly more calories, total fat (primarily from increased intake of monounsaturated fats) and protein than either controls. Total fat and monounsaturated fat intake was associated with increased risk after adjustment for other caloric sources. Cases were also more educated than either control group. Women having natural menopause ≥45 yr had significantly increased risk compared to those who were younger at menopause.</td>
<td>Reference period unclear and potentially variable No analysis by menopausal status in spite of differences in risk reported</td>
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<tr>
<td>Zaridze et al., 1991</td>
<td>Case–control Moscow, Russia</td>
<td>139 newly-diagnosed consecutive cases of breast cancer. None of the cases had previous treatments or distant metastases. 139 controls matched by age (± 2 yr) and neighborhood were recruited from same outpatient screening clinic as cases.</td>
<td>Cases were interviewed within 4 d of admission to the clinic. Diet assessed with 145–item food–frequency questionnaire Reference period was the yr prior to diagnosis for cases and the yr prior to interview for controls. No portion size estimation method was reported.</td>
<td>There were no significant effects of diet on risk in premenopausal women. In postmenopausal women there was a significant increase in risk associated with protein intake and a marginally significant risk (p&lt;0.06) associated with saturated fat. There were significant protective effects associated with high intakes of polyunsaturated fats, mono- and disaccharides, cellulose, β-carotene, vitamin C, and potassium.</td>
<td>Possible bias associated with subjects involvement in screening clinic No portion size estimation procedure given Small sample size</td>
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# APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

## II. Colorectal Cancer

<table>
<thead>
<tr>
<th>Study</th>
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<th>Subject &amp; Description</th>
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<tr>
<td>Benito et al., 1990</td>
<td>Case-control</td>
<td>286 case of colorectal cancer: all residents for at least 10 yr and &lt;80 yr old selected for 1984–89 235 community controls (CC) selected from 1982 census stratified by age and sex 203 hospital controls (HC) selected from hospitals were 70% of cases diagnosed.</td>
<td>All subjects interviewed at home about demographics, SES, occupation, medical history, exposure to toxins, and pharmaco logical history. Cases interviewed within 3 mo of diagnosis 99-item food-frequency questionnaire Reference period was the previous year unless there had been a change within previous 6 mo, in which case they were asked about their diet prior to changes. Portion size estimation procedure not given</td>
<td>Significant trend for increased risk associated with education and weight Increased risk for colorectal cancer associated with cereal (white bread and pasta). Risk for colon cancer was associated with fresh meats (lamb and game), and a protective effect for cruciferous vegetables. Increased risk for rectal cancer associated with dairy products and protection from cruciferous vegetables. There was no risk associated with type of oil, mode of consumption (crude or cooked), or quantity or frequency of consumption in common dishes. Significant increases in risk associated with cereals, potatoes, pastry, eggs, and number of meals/d. Combination of high consumption of fresh meat, dairy products, and cereals and low intake of cruciferous vegetables associated with 4-fold increase in risk for colorectal cancer.</td>
<td>No portion size estimates, no documentation of number of cases with dietary changes during reference period. No analysis possible for individual nutrients although data are suggestive of a dietary fat effect Time between diagnosis and interview of cases not documented</td>
</tr>
<tr>
<td>Freudheim et al., 1990</td>
<td>Case-control</td>
<td>422 cases of rectal cancer (277 ♂, 145 ♀) 422 sex-, race-, age- (≥5 yr), neighborhood-matched controls</td>
<td>Subjects given a 2.5 hr interview consisting of 129-item food-frequency questionnaire Reference period the previous yr for controls and for cases a yr prior to the onset of symptoms Portion size estimated with the use of pictures Additional information included smoking and alcohol use, and occupational and health histories, seasonality of intake, preparation, and food storage.</td>
<td>Increased risk with increasing intakes of calories, fat, carbohydrate, and iron. Decreased risk with increasing intake of carotenoids, vitamin C, and dietary fiber from vegetables. For ♂ there was a 2-fold increase in risk associated with retinol intake and decreased risk for carotenoids. The same held for ♂ although not significantly. For ♂, fat was most strongly associated with risk; for ♂ the association between fat and risk was not as strong. No association between intake of vitamin E and risk. Associations between diet and risk of rectal cancer were not affected by either smoking of alcohol intake.</td>
<td>Reliance on retrospective food-frequency interviews No data on use of supplements or stage of disease (except that &quot;only relatively alert, healthy subjects could tolerate the 2.5 hr. interview&quot;). Well-conceived study</td>
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<td>Gerhardsson de Verdier et al., 1990</td>
<td>Case–control Stockholm, Sweden</td>
<td>569 total cases (352 colon cancer, and 217 rectal cancer) 512 controls (referents) randomly selected every 4 mo during the case recruitment period (1986–88) and stratified by yr of birth (4 categories) and sex</td>
<td>Cases filled out a questionnaire at the hospital as soon after diagnosis as possible; when necessary, cases were assisted in filling out the form. 19% of cases and all controls received the questionnaire by mail (supplemented by telephone to fill in missing items). Frequency of intake of items from 55 food categories were ascertained. The reference period was the previous 5 yr. Portion sizes were estimated from photographs. Anthropometric history was collected and body–mass index (BMI) computed.</td>
<td>There was an increased risk associated with total energy (p&lt;0.05 colon, 0.05 rectum), protein (p&lt;0.05 colon, 0.05 rectum), total fat (p&lt;0.05 colon, 0.05 rectum), monounsaturated fat (p&lt;0.05 colon, 0.05 rectum), and polyunsaturated fat (p&lt;0.44 colon, 0.05 rectum). Results were the same across sexes. High–fiber diet was inversely related to risk of colon cancer in σ and rectal cancer in both σ and ‣.</td>
<td>Variable reference period with respect to diagnosis and variable data acquisition procedure among cases. Long retrospective period for diet collection No analysis for any other potential risk factors or demographic variables presented</td>
</tr>
<tr>
<td>Graham et al., 1988</td>
<td>Case–control New York</td>
<td>428 cases of colon cancer (CC) 428 controls matched for age, sex, and neighborhood</td>
<td>All subjects given a structured 2.5–hr interview similar to that used by Freudenheim et al. (1990). No reference period was noted for the diet data. No surrogates were used.</td>
<td>Risk of CC was positively associated with increasing intake of total fats (predominantly animal fat) and total calories. No significant risks associated with intake of protein, vitamin A from vegetables and fruits, carbohydrates, vitamin C, cruciferous vegetables, calcium, or phosphorous. There was significantly reduced risk associated with high intakes of tomatoes, peppers, carrots, onions, and celery.</td>
<td>No reference period for food–frequency questionnaire given No data on supplement use</td>
</tr>
<tr>
<td>Kune et al., 1987</td>
<td>Case–control Melbourne, Australia</td>
<td>715 cases of colorectal cancer, CRC (392 colon cancer, 323 rectal cancer) all histologically–confirmed new cases 727 age– and sex–matched community controls 159 hospital controls</td>
<td>300–item food–frequency questionnaire used to ascertain usual daily consumption Serving sizes were estimated by subjects. Calculated average weekly amounts adjusted for seasonal variations Reference period was the previous 20 yr Data included use of vitamin supplements</td>
<td>There was a dose–dependent inverse relationship between fiber, vitamin C, β–carotene, total vegetables, and cruciferous vegetables. β–carotene was highly correlated with vegetable intake. Dietary retinol had no independent association with risk of CRC. Dietary vitamin C was protective at intakes &gt;230 mg/d. Vitamin supplements were highly protective. High fat was a contributing factor in the overall risk factor model (especially for σ).</td>
<td>Long retrospective diet period Supplement data not clearly presented (multivitamins or individual, quantity or interaction with diet)</td>
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### APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

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<tr>
<td>La Vecchia et al., 1988</td>
<td>Case-control Italy</td>
<td>339 cases of colon cancer (CC) 236 cases of rectal cancer (RC) 778 hospital controls admitted for acute, non-neoplastic or digestive disorders</td>
<td>All subjects given a questionnaire to obtain data on: SES, smoking, alcohol, coffee and other methylxanthine containing drinks, personal and family health history, and use of selected drugs. 29-item food-frequency questionnaire. Reference period was an unspecified period before current hospital admission. Subjects also asked to report changes over previous 10 yr.</td>
<td>Risk of both CC and RC was inversely related to intake of green vegetables, tomatoes, melon, and coffee. There was also an inverse relationship between risk and indices of carotenoid and vitamin C intake. Consumption of pasta and rice or beef/veal associated with increased risk of both cancers</td>
<td>No supplement data, variable reference times between cases and controls, no population-based control. Diet database was small (only 29 items). Individual nutrient estimation unreliable due to lack of portion size information. No biochemistry. No descriptive data or comparisons to normal standards of intake.</td>
</tr>
<tr>
<td>Neoptolemos et al., 1988</td>
<td>Case-control Birmingham, UK.</td>
<td>49 cases of colorectal cancer 49 hospital controls matched for age and sex and admitted to same hospital as cases with benign disease</td>
<td>Diet was assessed with 7-d recall obtained during hospitalization on the 4 before surgery. Although not stated this was presumably designed to reflect normal intake at home. Overnight fasted blood samples were collected for analysis of fatty acids in red blood cells (RBC). Adipose tissue biopsies were also collected for fatty acid analysis.</td>
<td>No difference between groups for dietary intake or adipose tissue content of fatty acids. There were some differences in correlation between dietary fatty acid intake and RBC levels in cases.</td>
<td>Questionable reliability of 7-d recall as a tool for dietary assessment. Variable times between diagnosis of cancer and study. Small sample size. The study was designed to validate the use of RBC fatty acid profiles as a diagnostic tool; it was not designed to assess nutritional factors associated with colorectal cancer.</td>
</tr>
<tr>
<td>Slattery et al., 1988</td>
<td>Case-control Utah</td>
<td>229 cases of colon cancer (119 $, 110 $) 384 controls (204 $, 180 $) recruited by random-digit-dialing and matched for age ($ \pm 5$ yr)</td>
<td>All subjects interviewed at home. Diet data were collected with food-frequency questionnaire. Amount frequency and method of preparation were ascertained. The reference period was 2 yr prior to diagnosis for cases and 2 yr prior to interview for controls. The same reference periods were used to determine normal exercise patterns including leisure time activities and occupational activity. Calories expended were estimated.</td>
<td>Calories, protein, and fat were associated with 1 risk of colon cancer. Total physical activity was protective in both $\sigma$ and $\phi$. Intense physical activity was most protective in $\sigma$. Physical activity was not a confounder for the relation of diet in this study, and dietary intake did not confound the relation between physical activity and colon cancer risk. Data analysis suggested that physical activity modifies colon cancer risk associated with diet. The combination of high activity and low intake of calories, fat, and protein was protective.</td>
<td>Food-frequency questionnaire not described. Questionable external validity as study sample was largely composed of Mormons who eschew cigarettes, alcohol, and coffee.</td>
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<tr>
<td>Tuyts et al., 1988</td>
<td>Case-control Belgium</td>
<td>453 cases of colon cancer (CC) 365 cases of rectal cancer (RC) 2651 controls All subjects were from same 2 provinces and adjusted for age and sex</td>
<td>All subjects interviewed about diet using food-frequency questionnaire. Reference period for cases 1 wk period prior to onset of disease, controls current intake. Portion sizes were estimated using food models (pictures). Cases interviewed in hospital, controls at home.</td>
<td>Inverse association between intake of maize, soybean, and sunflower oils and risk. No effect for butter, margarine, or fatty meats. Intake of retinol and vitamin B2 was higher in cases; intakes of β-carotene and vitamin C were lower in cases. Significant positive associations were found for retinol, oligosaccharides; negative associations for fiber, linoleic acid, thiamine, and iron. After adjustment for age, sex, province and calorie intake, retinol was positively associated with CC and RC; significant negative associations with fiber, thiamine, vitamin B6, iron, and vitamin C (for RC only).</td>
<td>Retrospective data collection Differences in reference period between controls and cases Group differences by province and sex No biochemistry, supplementation data, descriptive data on intake, demographics, smoking, alcohol, medical histories, or comparisons to normal standards for intake Possible bias from place of interview; hospital for cases, home for controls. There was no discussion of the food sources of retinol that might have contributed to its effect. No discussion of relationship of foods and outcomes, i.e., grains as sources of thiamine, fiber, etc.</td>
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<tr>
<td>West et al., 1989</td>
<td>Case-control Utah</td>
<td>231 cases of newly diagnosed colon cancer (CC) 391 controls matched by age (± 5 yr), sex, and county of residence</td>
<td>All subjects were interviewed in their homes. Questionnaire consisted of demographic, health history, current height and weight (2 yr before interview), computed body mass index, physical activity, and dietary data. 99-item food-frequency questionnaire. Reference period was &quot;2-3 years prior to the interview&quot;. Portion sizes were estimated with food models.</td>
<td>In total fat and energy intake were associated with 1 risk. In total fat, poly- and monounsaturated fat, energy, and protein were associated with 1 risk. There were site-specific differences in risk associated with intake of fat and protein in both. Significant protective effects of β-carotene in both. It is cruciferous vegetables in both; fiber was protective in both. No association between CC risk and intake of vitamin C or A after adjustment for age, BMI, fiber, and energy intakes.</td>
<td>Unknown relationship between reference period and time of diagnosis in cases No biochemistry, comparisons to intake standards or descriptive statistics No data for SES, alcohol, smoking, or supplement history</td>
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<td>Whittemore et al., 1990</td>
<td>Case-control USA, China</td>
<td>905 cases of colorectal cancer (473 from North America, 432 from China) 2486 controls (1192 Chinese Americans from N. America, 1294 from China) Subjects were identified through cancer registries. Controls in China were selected from same neighborhood as cases and matched for age and sex (≥ 5 yr). Most of the N. American cases and controls were born in Asia.</td>
<td>All subjects interviewed about demographic characteristics, diet, physical activity, menstrual factors, and residential patterns. 84-item food-frequency questionnaire was used for diet analysis. There were additions in the Chinese version to reflect cultural patterns, e.g., more soybean products and indigenous fruits and vegetables. It also excluded cheeses, mayonnaise, cream sauces, and creamed dishes. Food models were used to estimate portion sizes. Reference yr was the yr prior to diagnosis for cases and the yr before interview for controls.</td>
<td>In Chinese-American participants there was significant risk associated with duration of residence in N. America. Cases tended to be more westernized than controls. In both continents, cases ate more total calories, protein, fat, and cholesterol than controls. Risk of cancers of both colon and rectum was associated with food energy from fat, protein, carbohydrate, and total energy for both sexes and both sample sets. In multivariate analysis only saturated fat was significantly associated with risk for colorectal cancer. This latter effect was stronger in the N. American sample, reflecting a greater intake of meat and dairy products. There was a significant protective effect of vegetable consumption among Chinese-American $\text{♂}$ and $\text{♀}$ and in Chinese $\text{♂}$. Fruit was not associated with any changes in risk in any group. Sedentary lifestyle was also a significant risk factor. The differences between continents was due to longer duration of high-risk lifestyles in the western sample. Physical inactivity + diet high in saturated fat were estimated to account for 60% and 40% of colorectal cancer incidence among Chinese-American $\text{♂}$ and $\text{♀}$, respectively.</td>
<td>Variable reference period for cases (time since diagnosis was not documented) Possible overestimation of energy expenditure as estimated energy output exceeded input on both continents</td>
</tr>
<tr>
<td>Willett et al., 1990</td>
<td>Prospective cohort USA</td>
<td>150 cases of colon cancer selected over a 6-yr period (1980-86) 88,601 controls All subjects were selected from a cohort of 88,751 $\text{♀}$.</td>
<td>The cohort was from those $\text{♀}$ in the &quot;Nurses Health Study&quot;, who had responded to a diet questionnaire containing 61-item food-frequency questionnaire. Reference period was yr prior to questionnaire. Common unit of portions were used to estimate portion sizes. All analyses adjusted for energy</td>
<td>Total fat, saturated and mono-unsaturated fats, and animal fats were all associated with risk of colon cancer. Intake of beef, pork, or lamb as main dish was highly related to risk as was the ratio of intake of red meat to intake of chicken and fish. Fish and chicken without skin offered protection.</td>
<td>Conclusion presumes animal fat is major contributor to risk No analysis for protein intake or other sources of saturated fat, e.g., dairy products No documentation of relationship between diagnosis and questionnaire in cases No presentation of any other risk factors or confounders</td>
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### APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

#### III. Pancreatic Cancer

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<tr>
<th>Study</th>
<th>Type/location</th>
<th>Subject # &amp; Description</th>
<th>Methods</th>
<th>Results</th>
<th>Comments</th>
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<tr>
<td>Falk et al., 1988</td>
<td>Case–control Louisiana 363 cases of pancreatic cancer (PC) 1294 hospital based controls (HC) matched on hospital of admittance, race, sex, and age (≥ 5 yr)</td>
<td>All subjects were given an interview to obtain data on smoking, occupational and residential history, alcohol use, family health history, medical history, leisure time activities, and diet. A 59–item food–frequency questionnaire was used. The reference period was the time (unspecified) prior to diagnosis or onset of symptoms. Means for estimation of portion sizes were not described. &gt;50% of cases were unable to be interviewed; surrogates (next of kin, usually a spouse) were used. 3% of controls were unavailable.</td>
<td>Pork products (bacon, ham, sausage, cold cuts, and unprocessed fresh pork) and rice were significantly associated with risk. Dairy foods were positively associated in α. Fruit consumption (fresh and juice) was inversely related with PC; fruit also conferred a protective effect against intake of pork products. There was a smaller non–significant inverse association with vegetable intake. No differences in risk associated with vitamin A, retinol, or carotene intakes. Trend analysis indicated increased risk with vitamin A in both sexes (significantly in α); there was a 1 trend in risk associated with carotene in α. After adjustment for fruit intake, a nonsignificant inverse association was found for α in highest levels of carotene index. Risks associated with consumption of fruits and with an index of vitamin C showed significant decreasing gradients across sexes. Cigarette smoking was a strong risk factor for PC.</td>
<td>Control diet of unknown quality used as reference  No descriptive data reported nor comparisons of diet to reference standard, i.e., RDA  No community–based control group  Unknown time period between time of interview and diagnosis and/or onset of symptoms  Controls’ diet response reflective of recent intake patterns  No data on supplement use  No biochemistry  No testing for potential interactions between smoking and vitamin C index or fruit consumption  Lack of portion size estimation prevented quantification of individual nutrients, i.e., total calories, fat, protein</td>
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<tr>
<td>Farrow et al., 1990</td>
<td>Case–control Washington 148 married male cases of pancreatic cancer diagnosed between 1982–1986 188 married α controls randomly selected and frequency–matched by age (≥ 5 yr)</td>
<td>Data was collected from surrogates (wives) in 2 steps. A telephone interview to collect demographic data, medical and occupational history, and use of tobacco, alcohol, coffee, and vitamin supplements. Dietary questionnaire was mailed and contained a 135–item food–frequency questionnaire. Reference period was 3 yr prior to diagnosis.</td>
<td>No association between PC risk and intake of vitamin A or total fat, saturated fat, cholesterol, ω–3 fatty acids, or vitamin C. No difference between groups in their use of supplemental multivitamins, vitamin A, or vitamin C</td>
<td>Reliability and validity of data acquisition is questionable  Reliance on retrospective data collected from surrogates  Reference period was 3 yr prior to interview</td>
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<td>Study</td>
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<tr>
<td>Ghadirian et al., 1991</td>
<td>Case–control Montreal, Canada</td>
<td>179 cases of pancreatic cancer recruited from 19 hospitals for the French–speaking in Montreal 239 controls matched for age (± 5 yr), sex, and residential area Controls randomly selected from same phone book as cases</td>
<td>200-item food–frequency questionnaire. Subjects asked about amount consumed. Criteria for portion sizes not documented. Reference period for case–control matches was the yr prior to diagnosis for cases. Controls interviewed within 3 mo of cases. Other data collected included: medical history, occupation, alcohol and smoking habits, medical history, dietary supplement use, and family health history.</td>
<td>I risk associated with total energy Cases ate more than controls and $&amp;$ ate more than $&amp;$ Significant $\dagger$ in risk associated with total and saturated fats and cholesterol Analyses were adjusted for age, sex, response status, cigarette use, and total energy intake.</td>
<td>Proxy interviews were used in 75% of cases who were either too ill or recently deceased (within 12 mo of study). 17% of controls required proxies due to death between time of diagnosis of matched case and his/her time of interview. Cases interviewed before histological confirmation of diagnosis</td>
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<tr>
<td>Howe et al., 1990b</td>
<td>Case–control Toronto, Canada</td>
<td>249 cases of newly–diagnosed pancreatic cancer 506 controls matched for age (± 5 yr) and sex 45% and 31% of eligible cases and controls respectively were included in the study</td>
<td>Interviews for all subjects done at home; for cases within 3 mo of diagnosis. In 194 (78%) cases data were collected from proxy interviews primarily with spouse. For each case proxy there was a control proxy interview. Data collected included: demographics, smoking, coffee, tea, and alcohol consumption. 200-item food–frequency questionnaire. Reference period was &quot;1–2 years before interview, in order to overcome any changes in diet among the cases due to the onset of their disease.&quot; No reference period was given for controls. Portion sizes were estimated with the aid of physical food models.</td>
<td>Proxy data were different from data derived directly from subjects. There was no demonstrable effect from intake of total fat or its components. Total calories was associated with increased risk. Carbohydrate was the component of caloric intake that had the most significant contribution to risk. Fiber intake from fruit, vegetable, and cereal sources was inversely associated with risk.</td>
<td>High rate of non–compliance in recruitment of both cases and controls Majority of data from cases was from proxy interviews. No reference period was given for controls. Variable reference period for cases</td>
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### APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

<table>
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<tr>
<td>La Vecchia et al., 1990</td>
<td>Case-control</td>
<td>247 cases of pancreatic cancer (159 ♂, 88 ♂) 1089 hospital-based controls (800 ♂, 289 ♂) admitted to same hospitals as cases for acute non-digestive or non-neoplastic diseases unrelated to alcohol or tobacco</td>
<td>All subjects interviewed about sociodemographics, smoking habits, alcohol and coffee consumption, and medical history 14-item food-frequency questionnaire Reference period for diet collection was not reported. Procedure for portion size estimation not reported</td>
<td>Significantly decreased risk associated with fruit intake, fish, and oil intake. Insignificant trend for increased risk associated with meat, eggs, ham, and margarine intake</td>
<td>Small data set for food-frequency analysis Unknown and variable reference period for diet assessment Time between diagnosis and interview was not defined or controlled No community-based controls Analysis of contribution of individual nutrients not possible</td>
</tr>
<tr>
<td>Mills et al., 1988b</td>
<td>Cohort</td>
<td>Study population was 34,196 non-Hispanic Seventh-day Adventists &gt;25 yr of age 40 cases of death from pancreatic cancer (PC) occurring during the follow-up period of 1974-1982</td>
<td>All subjects completed a lifestyle questionnaire; details of which were not supplied.</td>
<td>Current use of meat, poultry, or fish was associated with increasing risk. There was a significant increase in risk associated with increasing consumption of eggs. Intake of vegetarian protein products, legumes, and dried fruits was significantly inversely related to risk. No relationship between risk and intake of other fresh fruit, canned or frozen fruit, fresh citrus fruit, fresh winter vegetables, green salads, or cooked green vegetables. These results were age- and sex-adjusted.</td>
<td>Problems include no comparison group, no data on quality of diet, no details on diet data, no data on individual nutrients, no data on supplement use, no biochemistry, and no demographics.</td>
</tr>
<tr>
<td>Olsen et al., 1989</td>
<td>Case-control</td>
<td>212 cases of white ♂ deaths from pancreatic cancer 220 controls white ♂ Surrogates were interviewed for all subjects. Reference period was 2 yr prior to interview or death. Food-frequency questionnaire of unknown scope Portion sizes not estimated</td>
<td>1 risk associated with intake of beef and pork; 1 risk associated with cruciferous vegetables</td>
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<td>Long retrospective relying on surrogate recall Design did not allow for estimation of individual nutrient contribution.</td>
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<td>Study</td>
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<td>Zatorski et al., 1991</td>
<td>Case-control</td>
<td>110 cases of pancreatic cancer 195 controls randomly selected from same residential area and matched for age (± 5 yr) and sex</td>
<td>78 (71%) of case interviews were with proxy; none of the controls were done by proxy. All except 5 cases were interviewed at home. The questionnaire data included: lifestyle factors such as demographics and SES factors, tobacco use history, alcohol, tea, and coffee consumption patterns, and medical history. 80–item food-frequency questionnaire. Reference period was 1–2 yr prior to interview. Portion sizes estimated with drawing models. Average daily intake of individual nutrients was estimated.</td>
<td>Significant trend towards a risk associated with cholesterol intake. There was a significant inverse relationship between vitamin C intake and risk. There was a nonsignificant (p=0.10) inverse trend for a risk with total fat. The mono– (p&lt;0.02) and poly–unsaturated (p&lt;0.00) fat contributed to this inverse relationship. There was a significant a risk associated with carbohydrate intake. There was a trend towards an a risk with total calories. However, the use of proxy interviews may have resulted in an underestimation of actual intakes. There was no adjustment in nutrient analyses for total calories.</td>
<td>Most of cases' data were collected from proxy interviews; none of the controls were done by proxy. Period between diagnosis and interview was variable and not controlled. Cases and control interviews were not matched for reference period interval.</td>
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## APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

### IV. Prostate Cancer

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| Hsing et al., 1990 | Cohort/case–control USA       | 149 cases of fatal prostate cancer  
17,633 controls used for computation of food–consumption quartiles  
Subjects were from a pool of 26,630 holders of Lutheran Brotherhood Insurance selected in 1966 for a mortality study. | 68.5% of the original cohort completed questionnaires.  
Comparisons of respondents to nonrespondents showed no differences in age, residence, or policy status. Questionnaire included data on demographics, alcohol and tobacco use, and diet history.  
Subjects asked about current (1966) intake of 35 food items. Portion sizes were estimated from survey data (NHANES II). | No significant trends were associated with total vitamin A, retinol, or β-carotene intake.  
When analyzed by age the group diagnosed <75 yr had an ↑ risk associated with ↑ intake of total vitamin A. In those ≥75 the trend was reversed. This pattern held true for retinol and β-carotene.  
There were no changes in risk associated with intake of any of 9 food groups or any individual foods. | Self-selected population. No comparison with general population, no data on mean intakes, no supplement data. The vitamin A differences in the 2 age groups could have reflected a difference in the type of foods eaten; this was not tested. Very limited food items in food–frequency questionnaire (it lacked some major sources of vitamins, e.g., liver, broccoli, spinach, and melons). Age analysis was only reported for the vitamin A intakes, not for smoking, alcohol consumption, or other foods. In 58 of the 149 fatalities prostate cancer was not the primary cause of death. It was not clear whether prostate cancer was the primary diagnosis. |
| Kolonel et al., 1988 | Case–control Hawaii          | 452 cases of histologically–confirmed prostate cancer (PC)  
695 age–matched controls  
Subjects >65 were randomly selected from a central insurance registry; those <65 selected with random–digit–dialing | All subjects given an extensive home interview to collect data on dietary, occupational, medical, social, and demographic histories.  
100+–item food–frequency questionnaire was used.  
Reference period was a usual mo prior to onset of the disease for cases and a corresponding period for controls.  
Portion sizes were estimated with the use of colored pictures in 3 different portion sizes and common measuring tools (spoons; cups). Surrogates were used for those subjects who could not be interviewed. | Older cases consumed significantly more saturated fat, total vitamin A, and zinc than age matched controls. These differences were reflected in increased risk associated with saturated fat and zinc. There was a significant increase in risk with the highest quartile of total vitamin A intake as well as a trend towards increased risk. Similar finding with respect to total carotenoids and β–carotene. No difference between younger subjects and their matched controls. There were no associations between risk and total or food sources of vitamin C.  
No differences found in potential confounding variables: SES, marital status, anthropometrics, family history.  
No significant interactions between nutrients | Total vitamin A and total zinc included supplements. The supplements were not characterized as either individual or multivitamins/minerals. At the time of the study β–carotene was not available in Hawaii as a supplement. The older cases consumed more of all forms of vitamin A than younger cases with the exception of food sources of retinol. This would indicate a greater use of supplements or greater intakes of carotene rich foods. The duration of supplement use was not reported. |
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<tr>
<td>Mettlin et al., 1989</td>
<td>Case-control</td>
<td>Buffalo, NY</td>
<td>371 cases of histologically confirmed prostate cancer 371 control patients with no history of cancer, matched by age 12.1% of controls had benign prostatic hyperplasia. There were a total of 76 different diseases in this group.</td>
<td>All patients admitted to the Roswell Park Memorial Institute are given a lifestyle questionnaire including a 45-item food-frequency checklist. Reference period for all patients was the period preceding the onset of current illness (admission?). Portion sizes were estimated from standard food tables.</td>
<td>No differences in age, marital status, education, weight, and height. There was a geographical difference. Increased consumption of high fat milk was associated with increased risk. There was a nonsignificant trend towards increased risk associated with fat intake. There was a significant reduction in risk associated with the highest level of intake of β-carotene in &lt;68 yr but not in subjects &gt;68 yr. Age- and resident-adjusted risk for highest level of β-carotene for the combined age groups shows a protective effect.</td>
</tr>
<tr>
<td>Ohno et al., 1988 Oishi et al., 1988</td>
<td>Case-control</td>
<td>Japan</td>
<td>100 cases newly diagnosed of prostate cancer (PC) 100 controls with benign prostatic hyperplasia (BPH) 100 hospital controls without BPH, other malignancies, liver disease, or hormonal disorders  All subjects were matched for hospital, age (± 3 yr) and date of admission (± 3 mo)</td>
<td>Data collected by interview upon admission to hospital included birthplace, occupational history, marital history, religion, body type, medical history, sex—life, and dietary practices. Food—frequency questionnaire assessed dietary habits during the period 5 yr prior to current admission. Photographs were used to estimate portion sizes.</td>
<td>Low intakes of vitamin A (retinol and β-carotene) were associated with increased risk. The risk reduction associated with vitamin A and β-carotene was seen in older (70–79 yr) but not younger (50–68 yr) men. Vitamin A and β-carotene from green/yellow vegetables were significantly protective. There was no association between risk and any other nutrients.</td>
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<td>Study</td>
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<td>Ross et al., 1987</td>
<td>Case-control</td>
<td>179 &quot;black&quot; cases (BC) of prostate cancer (PC) diagnosed between 1977-80 142 &quot;black&quot; controls (BC) matched for age (± 5 yr) and residence 142 &quot;white&quot; cases (WPC) of PC diagnosed between 1972-1982 142 &quot;white&quot; controls (WC)</td>
<td>Interviews usually done at home (all WPC and WC) or occasionally at an mutually convenient location A food-frequency questionnaire containing 20 categories of foods was used to estimate intake of fat, protein, or vitamin A. Reference period was time of diagnosis. Portion sizes estimated from common portion sizes.</td>
<td>Fat intake was a risk factor for both groups, but more so in blacks (p&lt;0.05). High intakes of pork were associated with 1 risk, significantly so in blacks. Significant differences between races for sexual practices and incidence of venereal disease. Venereal disease (+) and circumcision (−) were significantly associated with risk in both groups. Vitamin A consumption was inconsistently related or unrelated to PC risk in both groups.</td>
<td>57% response rate for blacks cases Variable and long reference period Limited items on food–frequency questionnaire Portion sizes estimated from food tables No supplement use data Groups differed demographically. BC were apparently not matched to BPC group demographically. There were no statistical adjustments made for any confounding variables in the diet analysis.</td>
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<tr>
<td>Severson et al., 1989</td>
<td>Cohort/case-control</td>
<td>174 cases of newly-diagnosed malignant prostate cancer divided into overt PC (OPC) and latent cancer (LPC) Cohort consisted of 7999 ⊃ of Japanese ancestry</td>
<td>All subjects were interviewed between 1966–1988 about demographics, marital, smoking, occupational, residence, education, alcohol use, and medical history. 23-item food-frequency questionnaire and 24 hr recall. Reference period was time of initial examination to time of diagnosis.</td>
<td>Individual nutrients not evaluated No relationship between intakes of total fat and protein. Intake of certain types of foods, e.g., seaweed (+) and rice (−), were associated with risk.</td>
<td>Reference period unclear and variable No supplement use data No biochemistry Limited nutrient data Not designed to assess specific nutrients No comparison to general population, limited to traditional Japanese type diet</td>
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<td>Study</td>
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<td>Slattery et al., 1990</td>
<td>Case-control</td>
<td>362 cases of histologically-confirmed prostate cancer 685 controls matched by age (≥ 8 yr) Controls identified through random-digit-dialing technique</td>
<td>A 2-part questionnaire, 1 a mailed self-administered report on adolescent diet, body size, age of voice change, and the other information about adolescent years (age 12–18), limited medical information, and family history of prostate cancer Second part was an at-home interview to obtain data about demographics, age, marital status, religious preference, education, income, medical history, and dietary history. Adolescents data included a food-frequency questionnaire about consumption of 23 food groups. The adult part included a 183-item food-frequency questionnaire. Portion sizes for adults were estimated with the use of visual aids and food models. The reference period was 3 yr prior to cancer diagnosis or any medical symptoms that might have caused a change in diet; for controls the reference period was 3 yr prior to interview.</td>
<td>There was little correlation between adolescent and adult intakes. There was a 1 consumption of eggs, whole milk, butter, white bread, cereals, and candy in adults when compared to adolescent diets. As adult subjects consumed more red meat, fish, 2% milk, cheese, yogurt, ice cream, margarine, fruits and fruit juices, vegetables, and whole wheat bread than when they were adolescents. Adolescent diets high in saturated fats were not associated with 1 risk; however, adult consumption of saturated fat was significantly associated with 1 risk especially for aggressive prostate tumors.</td>
<td>75% of both cases and controls were Mormons and all subjects were Caucasian. Long retrospective diet reference period No proxy interviews</td>
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West et al., 1991 | Utah          |                         |                                                                         |                                                                         |                                                                         |
## APPENDIX TABLE. LIPIDS AND CANCER (BY SITE)

### V. Other Cancer Sites

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<th>Study</th>
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<tr>
<td>Goodman et al., 1988</td>
<td>Case-control Hawaii</td>
<td>326 cases (228 ♂, 100 ♀) of lung cancer 668 controls (297 ♂, 371 ♀) selected by random-digit-dialing and random selection from list of participants in the Hawaii State Health Surveillance Program To supplement controls &gt;65 subjects were selected from registries of the Health Care Financing Administration</td>
<td>A structured interview was used to collect the following data: demographics, anthropometric data, dietary history including the use of vitamin supplements, a lifetime history of tobacco use, coffee and alcohol consumption, and occupational exposure history. A food-frequency questionnaire was used. Reference period was a usual no before the onset of symptoms or diagnosis for the cases and during the corresponding time period for the controls. Portion sizes were estimated with the use of photographs illustrating the 3 most representative serving sizes.</td>
<td>A significant association between dietary cholesterol and lung cancer risk in ♂ but not in ♀. The significant trend held across ethnic groups. The cholesterol effect was limited to current heavy cigarette smokers and to squamous and small cell types of lung cancer. Similar effects were found for total and saturated fat. However, since saturated fat was so highly correlated with cholesterol intake, the effects of these nutrients could not be separated.</td>
<td>Variable time periods for reference period for cases No data presented regarding other nutrients or supplement use Among cases ~30% were proxy interviews; ~7% of control data was supplied by proxy interviews.</td>
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<td>Jain et al., 1990</td>
<td>Case-control Toronto, Canada</td>
<td>839 cases of lung cancer; matched pairs of 100 and 1772 population-based controls, sex-matched to case pairs Also matched for age (≥ 4 yr) and borough of residence &lt;33% refusal by eligible controls Initial contact of subjects was by mail.</td>
<td>All subjects interviewed to gain data about SES factors, lifetime residences, occupational history, and detailed smoking history. 81-item food-frequency questionnaire emphasized vitamin and cholesterol intake. Subjects were asked to approximate portion sizes using reference food models. Data collected on use of vitamin and other nutritional supplements. Reference period was 1 yr prior to interview for all subjects. Proxy interviews (primarily spouses) were used for 34% of cases. Time between interview and diagnosis in cases was not reported.</td>
<td>Significant 1 risk (especially adenocarcinoma) associated with cholesterol intake Significantly 1 risk associated with increased intake of vegetables No association between risk and total vitamin A, retinol, vitamin C, or fruit There was an irregular nonsignificant 1 risk associated with 8-carotene. In the small number of supplement users, there was a significant inverse relationship between vitamin A and risk. (The form or amount of vitamin A was not available.)</td>
<td>Large portion of cases used proxy interviews 52% of ♀ case interviews were by spouses Unknown time period between diagnosis and interview in cases could have resulted in long retrospective reference period Most of the cases (92.5%) were smokers as opposed to 61% of controls.</td>
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<td>Fan et al., 1991</td>
<td>All subjects aged 30-64, 60% of whom were female. The study was conducted in a rural area.</td>
<td>98 cases of breast cancer and 150 controls were included. Control subjects were matched by age, menopausal status, and parity.</td>
<td>Significant differences were observed between cases and controls in the consumption of dairy products, processed meats, and total fat.</td>
<td>No information provided.</td>
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<tr>
<td>Shu et al., 1999</td>
<td>All subjects were women aged 40-70 years. The study was conducted in a rural area.</td>
<td>72 cases of breast cancer and 132 controls were included. Control subjects were matched by age and menopausal status.</td>
<td>There was a significant positive association between breast cancer risk and the consumption of red meat and processed meats.</td>
<td>No information provided.</td>
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<tr>
<td>Silvestri et al., 1999</td>
<td>All subjects were women aged 40-70 years. The study was conducted in a rural area.</td>
<td>65 cases of breast cancer and 130 controls were included. Control subjects were matched by age and menopausal status.</td>
<td>There was a significant positive association between breast cancer risk and the consumption of red meat and processed meats.</td>
<td>No information provided.</td>
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**APPENDIX TABLE** LIPIDS AND CANCER (BY SITE)
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<tr>
<td>La Vecchia et al., 1989</td>
<td>Case-control</td>
<td>163 cases of histologically-confirmed (within 1 yr before interview) bladder cancer (total pool eligible not given) 181 hospital controls (HC)</td>
<td>All subjects given interview to obtain information about SES factors, smoking, alcohol, coffee and other methylxanthine consumption habits, personal and family health history, and specific medication history. Subjects were asked about frequency of consumption of 10 food items. Reference period for cases was the period before onset of symptoms; none was given for controls.</td>
<td>There was no association between intake of fat and cancer risk. The frequency of consumption of green vegetables and carrots was significantly lower in cases. Estimated intakes of carotenoids and total vitamin A but not retinoids were significantly less in cases than controls. There was increased risk for BC associated with estimated low intakes of both carotenoids and retinol. Protective effect was stronger in current smokers. No effect from either fruit or vitamin C</td>
<td>Reference period was at least 2 yr before interview for cases. Very limited number of items (10) on food–frequency questionnaire Lack of portion size estimation precluded the analysis of individual nutrients. Lack of individual nutrient data prevents generalizability to other population groups and limits analysis to effect of indigenous foods studied. No supplement use data. No community–based controls</td>
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<td>Steineck et al., 1990</td>
<td>Case-control</td>
<td>418 cases of urothelial cancer and or squamous cell cancer of the lower urinary tract (renal pelvis, bladder, ureter, urethra) 511 sex– and age– stratified randomly selected controls</td>
<td>Questionnaire was mailed to all subjects and included health history, drug use, occupation, smoking, and ‘life events’, diet. Surrogates were not used. 56–item food–frequency questionnaire. Reference period was dietary habits 3 yr prior to interview. Portion sizes were estimated with the use of photographs. Separate questions about supplement use; specifically vitamins A, B, and C and 'other kinds of supplements and tonics.' Study conducted 1985–1987, supplement use data after 1981 was ignored.</td>
<td>Total fat and fried foods were significantly associated with increased risk. Supplemental intake of vitamin A (uncharacterized as to form or amounts) was inversely associated with risk.</td>
<td>The nature of the collection of the dietary data set was not clearly delineated. An apparently long retrospective period between diet and supplement use reference period and study interview Vitamin supplements broadly categorized, e.g., vitamin B or vitamin A</td>
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<td>Franceschi et al., 1989</td>
<td>Case-control</td>
<td>208 cases of non- Hoddkin's lymphoma (110 d, 98 d) diagnosed 2 yr prior to interview 401 hospital–based controls (215 d, 186 d) from the same catchment area</td>
<td>All subjects questioned about SES indicators, smoking history, alcohol and methylxanthine (e.g., coffee, tea, cola) beverage consumption, and frequency of consumption of 14 selected food items. Neither reference period nor method of portion size estimation was reported.</td>
<td>Consumption of milk, liver, butter, oil (primarily polyunsaturated), and methylxanthine beverages were associated with risk. Consumption of whole grain bread and pasta was inversely related to risk.</td>
<td>No reference period given, however cases were diagnosed within 2 yr of interview indicating a long retrospective recall. Limited food–frequency database</td>
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<td>Study</td>
<td>Type/location</td>
<td>Subject # &amp; Description</td>
<td>Methods</td>
<td>Results</td>
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<td>Mettlin et al., 1990</td>
<td>Cross-sectional New York</td>
<td>3334 cases of cancer Sites included: 163 oral cavity, 115 stomach, 594 colon, 312 rectum, 542 lung, 848 breast, 231 uterus, 233 cervix, 442 prostate, 178 bladder 1300 controls seen at the same hospital</td>
<td>All patients answered questions about smoking, alcohol use, diet, occupation, family health, resistance, and personal medical history. Specific emphasis of this study was on the frequency of consumption of whole milk, 2% milk, and skim milk during the period immediately preceding current illness.</td>
<td>Elevated risks for frequent consumption of whole milk relative to not drinking milk were found for cancers of the oral cavity, stomach, colon, rectum, lung, bladder, breast, and cervix. Drinking reduced fat milk was associated with significant risk reduction for oral and cervical cancers. Drinking whole milk exclusively was related to significant risk for cancer of the oral cavity, stomach, rectum, lung, and breast.</td>
<td>There was no defined and matched reference period. No other data for nutritional intake was presented. Milk consumption was not evaluated within the context of other dietary or nondietary risk factors. No community-based controls</td>
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<td>Hursting et al., 1990</td>
<td>Cross-sectional International (20 countries)</td>
<td>Average cancer incidence data for breast (9), cervix, prostate, colon (6 and 7) and lung (6 and 7) for the year 1973-1977 were taken from Cancer Incidence in Five Continents (20 countries included in analysis) Incidence rates were truncated to ages 35-64 yr</td>
<td>Estimates of per capita disappearance of total fat, poly- and monounsaturated fat, saturated fat, fish n-3 and n-6 polyunsaturated fat, and total calories, and dietary and crude fiber for the 20 countries included in the analyses were calculated or taken directly from Food Balance Sheets published by the United Nations Food and Agricultural Organisation and concurrent with the incidence data. Per capita lipid consumption was calculated from grams of fat contained in 68 fat-containing foods.</td>
<td>Total fat intake was strongly associated with cancer of the breast, colon, and prostate even after adjustment for total calorie intake. Cancers of the lung and cervix were not correlated with dietary fat intake. Saturated fat was positively associated with incidence of cancers of the breast, colon, and prostate and poly-unsaturated fat was associated with incidence of breast and prostate cancers but not colon cancer. Fiber intake, when included in the analysis, affected the magnitude of the fat cancer correlations, particularly between total fat and colon cancer.</td>
<td>No direct measure of intake No comparison with other population groups No analysis by sex No control for demographic or other potential confounders that might exist within or between countries The estimated per capita intakes of nutrients studied appear well above data of national survey such as NHANES II. Use of disappearance data does not account for wastage, e.g., fat trim or discarded cooking oil, thereby creating the possibility of overestimation of intake.</td>
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