The Association Between Different Kinds of Fat Intake and Breast Cancer Risk in Women

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Review Article

ABSTRACT

So far several animal and case-control studies have confirmed this hypothesis that dietary fat increases the risk of breast cancer. However, cohort studies have not shown this relationship. The aim of this study was to review the studies on the relationship between dietary fat intake and breast cancer risk among women. Electronic database PubMed and Google Scholar were searched using the key words: Breast cancer, dietary fat, serum estrogen, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). The evidence of the studies regarding to the association of total and subtypes of fat intake with breast cancer risk are inconsistent. Several studies have shown that, among several types of fat, SFAs and w-3 PUFA intake are associated with an increased and reduced risk of breast cancer, respectively. The relationship between MUFAs intake and breast cancer risk is conflicting. Narrow ranges of fat intake among populations, measurement errors, high correlation between specific types of dietary fat, the confounding variables like body fatness and high-energy intake and other dietary components such as fiber and antioxidants might be probable explanations for these inconsistent results. Although we are not at a stage where we can justifiably advise women to reduce their fat intake to decrease the risk of developing breast cancer, it seems the current guidelines to lower total fat consumption and recommendation to consumption of unsaturated fats such as MUFAs and w-3 fatty acids and also reduction of SFAs (meat and dairy products) intake to avoid heart disease is also useful for breast cancer risk.

Keywords: Breast cancer, dietary fat, monounsaturated fatty acid, polyunsaturated fatty acid, saturated fatty acid, serum estrogen

INTRODUCTION

Breast cancer is the most common type of cancer in women world-wide. This kind of cancer was accounted for 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths in 2008.[1,2] The breast cancer is considered as a prevalent disease in the developed world; however, half of the breast cancer cases and 60% of deaths due to this cancer

happen in developing countries.[1-6] In Iran, the prevalence of breast cancer was increased during the last four decades and it is one of the prevalent cancer among Iranian women (24/100,000).[7]

The role of diet is implicated in incidence of breast cancer.[8] There are some evidence that the dietary intake of subjects in developing countries needs improvement[9] and the kind of fat intake should be changed.[10,11] There is obvious evidence that lifestyle changes may increase the treatment results of breast cancer.[11,12] The hypothesis that dietary fat can increase breast cancer risk has been supported by animal experiments,[13] epidemiologic and some case-control studies.[14] However, this association has not been supported by cohort studies.[3,15,16] Several combined analyses have been performed on the basis of published results or pooled data to estimate the possible association between fat intake and breast cancer risk.[17] For example, a pooled analysis of subsequent cohort studies found no relationship of fat intake and breast cancer risk.[18] However, a meta-analysis of 14 cohort studies showed that women who were in the highest levels of total fat intake had 13% higher risk of breast cancer.[19] Narrow ranges of fat intake may be probable explanation for this lack of association in some prospective studies.[15,20,21] The evidence is more complicated for different fat subtypes.[20] Among types of fat, saturated fat intake is shown to be positively related with breast cancer risk.[18,20] Problems in obtaining exact estimates of various types of fat intake due to high correlation between specific types of dietary fat, which existed in the same food sources and also differences in dietary patterns among populations are probably causes of contradictory results of epidemiologic studies.[20,22,23] There is a strong evidence that estrogen level is a main determinant for breast cancer risk.[24] Observational studies have shown that dietary fat by increasing production of endogenous estrogen may lead to breast cancer.[8,20,24] Concentration of free estradiol may be increased due to replacement of transporter albumin estradiol with free fatty acids in the blood.[23] Collected evidences showed that western dietary habits, which contain higher dietary fat are related to this high-risk hormonal profile.[25] However, the real association between fat intake and breast cancer risk is not still consistent. Thus, the aim of this review article is to investigate the association between dietary fat and breast cancer risk among women.

METHODS

In this study, electronic database, PubMed and Google Scholar were searched using the key words: Breast cancer, dietary fat, serum estrogen, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFAs). Cross-sectional, clinical trial, prospective cohort, pooled analysis and meta-analysis studies that published from 1986 to 2011 were selected. We also reviewed the reference lists of the related publications to recognize additional studies.

Selection of studies

After limiting the words to titles, about 44 articles were found. First, we read the title and abstract of all gathered articles and selected those that were related to the subject. Twenty eight studies were found by searching in the reference list of selected articles. We excluded four articles due to irrelevant to subject as well as lack of access to their full text. Overall, 68 studies were selected and analyzed. A summary of articles with titles and various designs is shown in the Table 1.

RESULT

Total fat intake and breast cancer risk

The results of observational epidemiologic studies about the relationship between total fat intake and breast cancer risk are complicated. Evidence from case-control studies have indicated that increasing total fat and specific type of fat intake is associated with elevated breast cancer risk among adult women.[26-28] However, this result is not supported by some prospective cohort studies.[18,29] Animal studies,[30] international comparisons[31] have shown that high intake of total dietary fat increase risk of breast cancer. So far, several combined analyses have been performed on the basis of published results or pooled data to estimate the possible association between fat intake and breast cancer risk.[17] For example pooled analysis of subsequent cohort studies found no relationship of fat intake and breast cancer risk.[18] However, a meta-analysis of 14 cohort studies showed that women who were in the highest levels of total fat

Table 1: Some of the investigated studies in present article

Author	Publish year	Study design	Country	Number of subjects	Age of subjects	Main results
Thiébaut *et al*.[26]	2007	Prospective cohort	US	188 736 postmenopausal women 3501 breast cancer event	50-71	Dietary fat intake was directly associated with the risk of invasive breast cancer
Sieri *et al*.[21]	2008	Prospective cohort	10 European countries	319 826 women, 7119 breast cancer event	20-70	A weak positive association showed between saturated fat intake and breast cancer risk. This association was more pronounced for postmenopausal women who never used hormone therapy
Cho *et al*.[27]	2003	Prospective cohort	United States	90655 premenopausal women 714 breast cancer event	26-46	Intake of animal fat, mainly from red meat and high fat dairy foods, during premenopausal years is associated with an increased risk of breast cancer
Smith-Warner *et al*.[18]	2001	Pooled analysis of cohort studies	US	351 821 women, 7329 incident invasive breast cancer	28-93	A weak positive association showed with substitution of saturated fat for carbohydrate consumption
Nagata *et al*.[4]	2005	Cross-sectional	Japan	324 healthy postmenopausal women	57.5	High intake of fat is associated with higher serum levels of estrone and DHEAS in postmenopausal women

DHEAS=Dehydroepiandrosterone

intake had 13% higher risk of breast cancer.[19] In general, prospective studies do not support from the fat-breast cancer relation or only have reported a small positive relation.[32] The investigators have suggested that measurement errors may be as one of the reasons for the null results that reported in some studies.[33] Bingham *et al.*[33] and Freedman *et al.*[34] proposed that food diaries and records compared to food frequency questionnaires (FFQs), which used in most cohort studies for assessment of dietary intake, might estimate stronger relationship between dietary fat and breast cancer risk. The Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition reported statistically significant positive associations between the risk of breast cancer and both total and saturated fat, but when intakes were analyzed by FFQ this relation were non-significant.[33] As well as, a Swedish cohort which used FFQs found no association between total or saturated fat intakes with breast cancer risk.[15] The studies have reported that, non-dietary breast cancer risk factors such as menopausal status[3,18,35] and history of benign breast disease[26] may be effective on the associations of total or saturated fat with breast cancer risk. Interaction between dietary fat intake and menopausal hormone therapy may lead to the null results reported in some cohort studies.[18,36] The fat-breast cancer risk relation may be confounded by factors such as energy intake and weigh change.[26,37] Because, obesity is identified as risk-factor for breast cancer among postmenopausal women, it seems that high energy intake and body fatness might be confound the observed positive association of fat intake with breast cancer risk in postmenopausal.[26,34,37] However, the effect of obesity in premenopausal is not consistent.[37] In this regard, an inverse association of breast cancer incidence with low fat diet has been suggested in Women's Health Initiation randomized control

dietary modification trial.[38] However, reduced fat intake alone cannot decrease breast cancer risk since the reduction of fat intake accompanied by changing in dietary components such as total calories, fiber, carbohydrates, fruits and vegetables and micronutrients.[39] Thus, the effects of confounding variables on breast cancer risk might be obscure a true relationship between dietary fat and cancer risk and even explain inconsistent results of studies.[40] Evidence has been shown that estrogen develops breast tumorigenesis.[41] For example, in one study among 324 healthy postmenopausal Japanese women, high fat intake after controlling for age and other potential breast cancer risk factors was related to higher serum levels of estrone and dehydroepiandrosterone.[4] Higher serum levels of androgens have been suggested to be associated with greater breast cancer risk.[4] A meta-analysis of 13 studies showed that reduction of fat intake lead to a 7.4% reduction in serum estradiol levels among premenopausal women and 23% among postmenopausal women.[24] However, results of prior studies provide this suggestion that the fat-estrogen hypothesis necessitate greater studies.[4]

SFAs and breast cancer risk

The association of specific types of fat with breast cancer risk is more complex. In similar to total fat intake, the positive association of SFA intake with breast cancer risk has been suggested in several case-control studies.[19,42,43] Some cohort studies have also supported the results of case control studies on SFA.[18,21,33,35,44] As well as, a meta-analysis of 14 cohort studies reported a statistically significant higher risk of breast cancer among women who consumed the highest levels of SFA compared to the lowest levels of SFA.[19] In contrast, summary analyses of cohort studies found no association between intakes of total, SFA, MUFA or PUFA and breast cancer risk.[45] In addition, a recent meta-analysis of 11 cohort studies also found no association between the animal fat intake (source of SFA) and the breast cancer.[46] Since the composition of fatty acids differs between animal sources, thus may be lead to different effects of animal fat on breast cancer risk.[27,46] Different finding obtained in case-control and cohort studies may be attributable to recall bias and measurement errors by a single FFQ.[47] As well as, differences in dietary patterns among populations, high correlation between specific types of dietary fat, which existed in the same food sources[3] and also the confounding role of obesity, reproductive factors and history of benign breast may be reasons for obscuring true relationship between fat subtypes and breast cancer risk.[20] However, Smith-Warner *et al.* in a pooled analysis of 8 cohort studies has shown a weak elevation (relative risk [RR]: 1.09, 95% confidence interval [CI]: 1.00,1.19) in breast cancer risk by replacement of SFA intake for carbohydrate consumption in an isocaloric diet.[18] It seems that prevention of coronary heart disease in addition to breast cancer is good reason for choosing low intake of animal fat (red meat and high fat dairy), which is the source of SFA.[48]

MUFAs and breast cancer risk

The relationship between MUFA intake and breast cancer risk seems to depend on the contributing food source such as olive oil and margarines, food processing and varies confounding variables including energy intake and other subtypes of fat intake. Some animal studies,[49] a combined analysis of 12 case-control studies[28] and also a meta-analysis of 10 case-control studies[45] have shown a positive role of MUFA in the pathogenesis of breast cancer. A meta-analysis of prospective studies has reported a significant increase of 2-fold risk for the highest versus the lowest level of MUFAs (RR = 2.15, 95% CI: 1.68-2.74).[50] In contrast, several cohort studies have shown an inverse association of MUFA intake and breast cancer risk.[51,52] As well as, some other studies have shown no association MUFAs intake and breast cancer risk.[36,38] Epidemiological evidence has shown that olive oil, which contains MUFAs, might reduce the risk of breast cancer risk.[53-55] Beneficial effects of olive oil on breast cancer may be attributable to improvement of insulin resistance.[56] Hyperinsulinemia through reducing the production of sex hormone-binding globulin and also by inhibiting apoptosis may increase breast cancer.[57] However, the protective effects of olive oil have not been supported by some of cohort studies.[58] Since olive oil is an indicator of a healthy Mediterranean diet, its association with breast cancer may be confounded by other favorable life-style behaviors and polyphenolic compounds.[59] Certain foods that contribute to supply of MUFA maybe the possible explanation for different effects of this kind of fat

subtypes on breast cancer risk.[3] For example, olive oil is source of oleic acid intake in Mediterranean diet.[60] Whereas, in U.S diet margarines that contain hydrogenated form of oleic acid are the primary source, that may increase breast cancer risk.[61]

PUFAs and breast cancer risk

Animal studies have indicated that PUFAs based on double-bond position may have varies effects on breast cancer risk.[49,62] Animal studies have confirmed promoting effect of polyunsaturated fats particularly linoleic acid and arachidonic acid and also inhibitory effect of marine derived w-3 fatty acids on mammary tumorigenesis.[62,63] Some of the case-control studies have reported positive[64,65] relation of w-6 fatty acids intake with breast cancer risk. W-6 fatty acids by competition with w-3 fatty acids to produce eicosanoids increase the risk of breast cancer and also because of having many double bonds are easily oxidized and enhance cellular damage.[64] Other case-control studies showed that serum w-6 fatty acids are inversely related to breast cancer risk.[66] The evidence from other cohort studies have reported a protective effect of n-3 PUFAs from fish/shellfish (marine n-3 fatty acids) on breast cancer.[67,68] Gago-Dominguez *et al.*[68] in a cohort study by 7 years follow up suggested that an intake level of approximately 40 g of fish/shellfish/day can 25% decrease the risk of breast cancer. Moreover, a meta-analysis of cohort studies[50] and also a systematic review[69] showed an inverse association of w-3 fatty acids with breast cancer risk. In this mentioned meta-analysis very long chain n-3 PUFAs intake, which was estimated by using the composition of fatty acids in biological samples such as adipose tissue, erythrocyte membranes, serum and plasma showed a protective effect on breast cancer.[50] The estimation of fatty acid intake from biological samples in compared with dietary questionnaires is more accurate measurement because, it eliminate inadequacies and limitation of dietary questionnaires like a variation of fatty acid composition of the same food. Thus, the results of studies on biological markers of fat intake and breast cancer risk are more reliable. However, the effects of omega-3 fatty acids on breast cancer were not shown in two other case-control studies that had investigated constituent fatty acids in the adipose tissue.[70,71] Eventual chemical contaminants might confound true beneficial effects of long chain n-3 PUFAs that existed in marine sources.[71] For explaining this conflicted result, the investigators have suggested that rather than single fatty acid the ratio of n-6 PUFAs to n-3 may be effective on breast cancer risk.[39] The European community multi-center study on antioxidants, myocardial infarction and breast cancer reported that omega-3 to omega-6 ratio is related to breast cancer inversely.[72] The mechanisms that have been proposed for the protective effect of n-3 PUFAs include suppression of arachidonic acid – derived eicosanoid biosynthesis, alteration of estrogen metabolism and they also reduce production of free radicals and modify the insulin sensitivity.[73] The investigators suggest that high intake of w-3 fatty acids as the supplements might indicate an association.[69] For example Patterson *et al.* in a cohort study after 7.3 years following up[74] has showed that higher intakes (>73 mg/d) of eicosapentaenoic acid and docosahexaenoic acid from foods (marine sources) reduce the risk of additional breast cancer events approximately in 25%. This was associated with reduced risk of all-cause mortality but fish oil supplements because of low use of them in this cohort were not related to improved outcomes. Omega-3 PUFAs-breast cancer relation may be confounded by other protective factors such as vitamin E and C, which exist in their source (fish oils and marine oils).[73] It seems other dietary factors, life-style components and even overall dietary pattern may contribute in the protective role of marine foods.

DISCUSSION

The results of epidemiological studies, which have investigated the association between total fat intake and breast cancer risk, are inconsistent. Some animal studies have shown that the incidence of mammary tumors plateau when about 20% of total calorie intake from fat.[75,76] If existence of threshold effect of fat generalized to breast cancer in human, it may be a reason for lack of relationship between fat intake and breast cancer that have been reported in some western studies because the most of western populations consume more than 20% of calories from fat.[24] Thus, the narrow ranges of fat intakes in the studies maybe one possible explanation for this lack of relationship between total fat intake and breast cancer risk in some prospective studies.[36] In addition, different biases in dietary measurements

could interfere with a true relationship.[35] For example, a pooled analyses of cohort studies that was performed by Bingham *et al*. reported a non-significant increase in the risk of breast cancer when fat intake was measured by FFQ but a significant stronger increase when was measured by food records. Age, family history and various menstrual and reproductive factors[77] and also obesity are important factors that may contribute in developing breast cancer and so confound the association of fat intake with breast cancer risk. Thus, the effects of dietary fat on breast cancer risk may be different regarding to menopausal status. Some of studies have suggested that, diet like fat intake in early adult years[78] may be effective on breast cancer. For example, the cohort study that was done on the premenopausal women that enrolled in the Nurse's Health Study II reported a direct relationship of animal fat intake with breast cancer was associated with a higher risk of breast cancer.[27] However, reported a positive association between total fat intake and breast cancer risk among postmenopausal in some studies[35] may be due to confounding effect of potent variables like weight loss. Moreover, intake of specific fatty acids rather than total fat intake may be related to breast cancer risk and lead to inconsistent results of prospective and retrospective studies.[20]

In addition to total fat intake, the association between intake of subtypes of fat and breast cancer risk is also conflicting. Different dietary pattern of populations and consequently, the strong correlation between types of fat may be resulted in different association between each types of fat and breast cancer risk. This correlation reduces the statistical power to disentangle the true association between each type of fat and breast cancer risk.[18] Differences in population of studies, duration of study follow-up, food source of specific types of fat and amount of total and specific types of fat intake may be an effective factor for different report in studies.[15] For example, the inverse association of oleic acid have indicated in some studies,[60] which olive oil is the source of oleic acid, whereas, in other studies, which margarines are the primary source (contain hydrogenated form of oleic acid)[61] a direct association of them have been seen. Moreover, other carcinogen compound that found in the food source of specific fatty acid may confound the real relationship of the subtypes of fat with breast cancer. Soluble hormones or growth factor, which exists in high fat dairy, may be the result of increased risk of breast cancer.[79] Carcinogens such as heterocyclic amines, N-nitroso compound and polycyclic aromatic hydrocarbons, which are found an abundance in cooked red meat could cause to mammary tumor in animal.[80] Dietary fat could result in to initiation and development of breast tumor by several mechanisms. These mechanisms include the stimulation of production of estrogen and other endogenous hormone, regulation of immune function and modulation of gene expression.[35] Pooled-analysis of six prospective studies reported that mean concentration of serum estradiol was 15% higher in women who had developed breast cancer than those who did not have.[81] There is an evidence regarding the relationship between a low fat intake and the reduction of the concentrations of bio-available serum sex hormones.[35] Thus, high levels of serum sex hormones are the main risk factors for breast cancer. High fat intake through increasing intestinal reabsorption and elevating levels of blood free fatty acids may increase the serum concentration of free estrogens.[8,23] Studies suggest that SFA intake may increase breast cancer risk by increasing insulin resistance.[82] The association between plasma concentration of insulin, c-peptide and insulin growth factor-1 and breast cancer risk have been shown in several studies.[83] However, biological mechanisms of the effects of animal fat (SFA or MUFA) on breast cancer risk are not clearly stated yet.[2] Health-conscious behaviors may also interfere in the real association between breast cancer and fat intake. For example, the subjects who participate in mammographic screening may choose a low fat diet and so lead to earlier detection of cases among women that consume low fat diet.[20] Moreover, consumption of diet with high grain and vegetable, other rich source food of lignans and other phytostrogen, which may inhabit the cell-proliferating effects of endogenous estrogens, are health-conscious behaviors that may effect on artificial reduction of breast cancer incidence.[84] Large-scale studies with different dietary patterns and also well-designed trials may help to appear true relationship between total and specific types of fat and breast cancer. Thus, because diets high

in fat contribute to obesity the current guidelines to lower total fat consumption to avoid heart disease are appropriate also for breast cancer.

CONCLUSIONS

The results of epidemiological studies which have investigated the association between total and subtypes of fat intake and breast cancer risk are inconsistent. Narrow ranges of fat intake among populations, measurement errors and high correlation between specific types of dietary fat are probable explanations for these inconsistent results. As well as, the confounding variables such as body fatness and high-energy intake and other dietary components like fiber and antioxidants might modify the real association of total and certain subtypes of fat intake with breast cancer risk. Although, we are not at a stage where we can justifiably advise women to reduce their fat intake to reduce the chances of them developing breast cancer, but it seems recommendation of unsaturated fats such as MUFAs and w-3 fatty acids may be useful with regard to cardiovascular disease and also little evidence support the adverse effects of them on cancer risk. As well as, regarding to the direct relationship of SFAs, which found in animal fat (meat and dairy), with coronary heart disease, reduction of meat and dairy products intake may be beneficial. As well as, because diets high in fat contribute to obesity the current guidelines to lower total fat consumption to avoid heart disease are appropriate also for cancer. Thus, irrespective of specific types of fat, it does not seem that efforts for severe reduction of total dietary fat intake relation to breast cancer useful now.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Davari M, Yazdanpanah F, Aslani A, Hosseini M, Nazari AR, Mokarian F. The Direct Medical Costs of Breast Cancer in Iran: Analyzing the Patient's Level Data from a Cancer Specific Hospital in Isfahan. International Journal of Preventive Medicine 2013;4:748-54.
3. Velie E, Kulldorff M, Schairer C, Block G, Albanes D, Schatzkin A. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: A prospective cohort study. J Natl Cancer Inst 2000;92:833-9.
4. Nagata C, Nagao Y, Shibuya C, Kashiki Y, Shimizu H. Fat intake is associated with serum estrogen and androgen concentrations in postmenopausal Japanese women. J Nutr 2005;135:2862-5.
5. Mokarian F, Ramezani MA, Heydari K, Tabatabaeian M, Tavazohi H. Epidemiology and trend of cancer in Isfahan 2005-2010. Journal of Research in Medical Science 2011;16:1228-33.
6. Tazhibi M, Fayaz M, Mokarian F. Detection of prognostic factors in metastatic breast cancer. Journal of Research in Medical Science. 2013;18:283-90.
7. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Ann Oncol 2009;20:556-63.
8. Parry BM, Milne JM, Yadegarfar G, Rainsbury RM. Dramatic dietary fat reduction is feasible for breast cancer patients: Results of the randomised study, WINS (UK)-stage 1. Eur J Surg Oncol 2011;37:848-55.
9. Azadbakht L, Mirmiran P, Hosseini F, Azizi F. Diet quality status of most Tehranian adults needs improvement. Asia Pac J Clin Nutr 2005;14:163-8.
10. Shafaeizadeh S, Jamalian J, Owji AA, Azadbakht L, Ramezani R, Karbalaei N, *et al*. The effect of consuming oxidized oil supplemented with fiber on lipid profiles in rat model. J Res Med Sci 2011;16:1541-9.
11. Esmaillzadeh A, Azadbakht L. Consumption of hydrogenated versus nonhydrogenated vegetable oils and risk of insulin resistance and the metabolic syndrome among Iranian adult women. Diabetes Care 2008;31:223-6.
12. Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, *et al*. Dietary fat reduction and breast cancer outcome: Interim efficacy results from the Women's Intervention Nutrition Study. J Natl Cancer Inst 2006;98:1767-76.
13. Connolly JM, Gilhooly EM, Rose DP. Effects of reduced dietary linoleic acid intake, alone or combined with an algal source of docosahexaenoic acid, on MDA-MB-231 breast cancer cell growth and apoptosis in nude mice. Nutr Cancer 1999;35:44-9.
14. Marshall JR, Qu Y, Chen J, Parpia B, Campbell TC. Additional ecological evidence: Lipids and breast cancer mortality among women aged 55 and over in China. Eur J Cancer 1992;28:1720-7.
15. Löf M, Sandin S, Lagiou P, Hilakivi-Clarke L, Trichopoulos D, Adami HO, *et al*. Dietary fat and breast cancer risk in the Swedish women's lifestyle and health cohort. Br J Cancer 2007;97:1570-6.
16. Kim EH, Willett WC, Colditz GA, Hankinson SE, Stampfer MJ, Hunter DJ, *et al*. Dietary fat and risk of postmenopausal breast cancer in a 20-year follow-up. Am J Epidemiol 2006;164:990-7.

17. Psaltopoulou T, Kosti RI, Haidopoulos D, Dimopoulos M, Panagiotakos DB. Olive oil intake is inversely related to cancer prevalence: A systematic review and a meta-analysis of 13,800 patients and 23,340 controls in 19 observational studies. Lipids Health Dis 2011;10:127.
18. Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, *et al*. Types of dietary fat and breast cancer: A pooled analysis of cohort studies. Int J Cancer 2001;92:767-74.
19. Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S. Dietary fat and breast cancer risk revisited: A meta-analysis of the published literature. Br J Cancer 2003;89:1672-85.
20. Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, Hankinson SE, Speizer FE, *et al*. Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999;281:914-20.
21. Sieri S, Krogh V, Ferrari P, Berrino F, Pala V, Thiébaut AC, *et al*. Dietary fat and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 2008;88:1304-12.
22. Schatzkin A, Greenwald P, Byar DP, Clifford CK. The dietary fat – Breast cancer hypothesis is alive. JAMA 1989;261:3284-7.
23. Rock CL, Flatt SW, Thomson CA, Stefanick ML, Newman VA, Jones LA, *et al*. Effects of a high-fiber, low-fat diet intervention on serum concentrations of reproductive steroid hormones in women with a history of breast cancer. J Clin Oncol 2004;22:2379-87.
24. Wu AH, Stram DO, Pike MC. RESPONSE: Re: Meta-analysis: Dietary Fat Intake, Serum Estrogen Levels, and the Risk of Breast Cancer. J Natl Cancer Inst 1999;91:1512.
25. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, *et al*. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: The Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 2007;298:289-98.
26. Thiébaut AC, Kipnis V, Chang SC, Subar AF, Thompson FE, Rosenberg PS, *et al*. Dietary fat and postmenopausal invasive breast cancer in the National Institutes of Health-AARP Diet and Health Study cohort. J Natl Cancer Inst 2007;99:451-62.
27. Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, *et al*. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079-85.
28. Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, *et al*. Dietary factors and risk of breast cancer: Combined analysis of 12 case-control studies. J Natl Cancer Inst 1990;82:561-9.
29. Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, *et al*. Dietary fat and postmenopausal breast cancer. J Natl Cancer Inst 1992;84:1092-9.
30. Birt DF. Dietary fat and experimental carcinogenesis: A summary of recent *in vivo* studies. Adv Exp Med Biol 1986;206:69-83.
31. Patterson RE, Haines PS, Popkin BM. Diet quality index: Capturing a multidimensional behavior. J Am Diet Assoc 1994;94:57-64.
32. Key TJ, Appleby PN, Cairns BJ, Luben R, Dahm CC, Akbaraly T, *et al*. Dietary fat and breast cancer: Comparison of results from food diaries and food-frequency questionnaires in the UK Dietary Cohort Consortium. Am J Clin Nutr 2011;94:1043-52.
33. Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N. Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 2003;362:212-4.
34. Freedman LS, Potischman N, Kipnis V, Midthune D, Schatzkin A, Thompson FE, *et al*. A comparison of two dietary instruments for evaluating the fat-breast cancer relationship. Int J Epidemiol 2006;35:1011-21.
35. Toniolo P, Riboli E, Protta F, Charrel M, Cappa AP. Calorie-providing nutrients and risk of breast cancer. J Natl Cancer Inst 1989;81:278-86.
36. Hunter DJ, Spiegelman D, Adami HO, Beeson L, van den Brandt PA, Folsom AR, *et al*. Cohort studies of fat intake and the risk of breast cancer: A pooled analysis. N Engl J Med 1996;334:356-61.
37. Cummings JH, Bingham SA. Diet and the prevention of cancer. BMJ 1998;317:1636-40.
38. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, *et al*. Low-fat dietary pattern and risk of invasive breast cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:629-42.
39. Rose DP. Diet, hormones, and cancer. Annu Rev Public Health 1993;14:1-17.
40. Smith-Warner SA, Stampfer MJ. Fat intake and breast cancer revisited. J Natl Cancer Inst 2007;99:418-9.
41. Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001;344:276-85.
42. Ronco A, De Stefani E, Mendilaharsu M, Deneo-Pellegrini H. Meat, fat and risk of breast cancer: A case-control study from Uruguay. Int J Cancer 1996;65:328-31.
43. Wakai K, Dillon DS, Ohno Y, Prihartono J, Budiningsih S, Ramli M, *et al*. Fat intake and breast cancer risk in an area where fat intake is low: A case-control study in Indonesia. Int J Epidemiol 2000;29:20-8.
44. Toniolo P, Riboli E, Shore RE, Pasternack BS. Consumption of meat, animal products, protein, and fat and risk of breast cancer: A prospective cohort study in New York. Epidemiology 1994;5:391-7.

45. Boyd NF, Martin LJ, Noffel M, Lockwood GA, Trichler DL. A meta-analysis of studies of dietary fat and breast cancer risk. Br J Cancer 1993;68:627-36.
46. Alexander DD, Morimoto LM, Mink PJ, Lowe KA. Summary and meta-analysis of prospective studies of animal fat intake and breast cancer. Nutr Res Rev 2010;23:169-79.
47. Gaard M, Tretli S, Løken EB. Dietary fat and the risk of breast cancer: A prospective study of 25,892 Norwegian women. Int J Cancer 1995;63:13-7.
48. Willett WC. Fat, energy and breast cancer. J Nutr 1997;127:921S-3.
49. Welsch CW. Relationship between dietary fat and experimental mammary tumorigenesis: A review and critique. Cancer Res 1992;52:2040s-8.
50. Saadatian-Elahi M, Norat T, Goudable J, Riboli E. Biomarkers of dietary fatty acid intake and the risk of breast cancer: A meta-analysis. Int J Cancer 2004;111:584-91.
51. Voorrips LE, Brants HA, Kardinaal AF, Hiddink GJ, van den Brandt PA, Goldbohm RA. Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: The Netherlands Cohort Study on Diet and Cancer. Am J Clin Nutr 2002;76:873-82.
52. Wolk A, Bergström R, Hunter D, Willett W, Ljung H, Holmberg L, *et al*. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. Arch Intern Med 1998;158:41-5.
53. Pelucchi C, Bosetti C, Negri E, Lipworth L, La Vecchia C. Olive oil and cancer risk: An update of epidemiological findings through 2010. Curr Pharm Des 2011;17:805-12.
54. Trichopoulou A, Katsouyanni K, Stuver S, Tzala L, Gnardellis C, Rimm E, *et al*. Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. J Natl Cancer Inst 1995;87:110-6.
55. la Vecchia C, Negri E, Franceschi S, Decarli A, Giacosa A, Lipworth L. Olive oil, other dietary fats, and the risk of breast cancer (Italy). Cancer Causes Control 1995;6:545-50.
56. Farnetti S, Malandrino N, Luciani D, Gasbarrini G, Capristo E. Food fried in extra-virgin olive oil improves postprandial insulin response in obese, insulin-resistant women. J Med Food 2011;14:316-21.
57. Gupta K, Krishnaswamy G, Karnad A, Peiris AN. Insulin: A novel factor in carcinogenesis. Am J Med Sci 2002;323:140-5.
58. Buckland G, Travier N, Agudo A, Fonseca-Nunes A, Navarro C, Lagiou P, *et al*. Olive oil intake and breast cancer risk in the Mediterranean countries of the European Prospective Investigation into Cancer and Nutrition study. Int J Cancer 2012;131:2465-9.
59. Newcomb PA, Klein R, Klein BE, Haffner S, Mares-Perlman J, Cruickshanks KJ, *et al*. Association of dietary and life-style factors with sex hormones in postmenopausal women. Epidemiology 1995;6:318-21.
60. Greenwald P. Role of dietary fat in the causation of breast cancer: Point. Cancer Epidemiol Biomarkers Prev 1999;8:3-7.
61. Kohlmeier L. Biomarkers of fatty acid exposure and breast cancer risk. Am J Clin Nutr 1997;66:1548-56.
62. Fay MP, Freedman LS, Clifford CK, Midthune DN. Effect of different types and amounts of fat on the development of mammary tumors in rodents: A review. Cancer Res 1997;57:3979-88.
63. Calder PC. Dietary modification of inflammation with lipids. Proc Nutr Soc 2002;61:345-58.
64. Wirfält E, Mattisson I, Gullberg B, Johansson U, Olsson H, Berglund G. Postmenopausal breast cancer is associated with high intakes of omega6 fatty acids (Sweden). Cancer Causes Control 2002;13:883-93.
65. De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco A. Essential fatty acids and breast cancer: A case-control study in Uruguay. Int J Cancer 1998;76:491-4.
66. Rissanen H, Knekt P, Järvinen R, Salminen I, Hakulinen T. Serum fatty acids and breast cancer incidence. Nutr Cancer 2003;45:168-75.
67. Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, *et al*. Dietary intakes of fat and fatty acids and risk of breast cancer: A prospective study in Japan. Cancer Sci 2005;96:590-9.
68. Gago-Dominguez M, Yuan JM, Sun CL, Lee HP, Yu MC. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. Br J Cancer 2003;89:1686-92.
69. Gerber M. Omega-3 fatty acids and cancers: A systematic update review of epidemiological studies. Br J Nutr 2012;107 Suppl 2:S228-39.
70. Petrek JA, Hudgins LC, Levine B, Ho M, Hirsch J. Breast cancer risk and fatty acids in the breast and abdominal adipose tissues. J Natl Cancer Inst 1994;86:53-6.
71. London SJ, Sacks FM, Stampfer MJ, Henderson IC, Maclure M, Tomita A, *et al*. Fatty acid composition of the subcutaneous adipose tissue and risk of proliferative benign breast disease and breast cancer. J Natl Cancer Inst 1993;85:785-93.
72. Simonsen N, van't Veer P, Strain JJ, Martin-Moreno JM, Huttunen JK, Navajas JF, *et al*. Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC study. European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer. Am J Epidemiol 1998;147:342-52.
73. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A.

Dietary long-chain n-3 fatty acids for the prevention of cancer: A review of potential mechanisms. Am J Clin Nutr 2004;79:935-45.
74. Patterson RE, Flatt SW, Newman VA, Natarajan L, Rock CL, Thomson CA, *et al*. Marine fatty acid intake is associated with breast cancer prognosis. J Nutr 2011;141:201-6.
75. Zevenbergen JL, Verschuren PM, Zaalberg J, van Stratum P, Vles RO. Effect of the amount of dietary fat on the development of mammary tumors in BALB/c-MTV mice. Nutr Cancer 1992;17:9-18.
76. Cohen LA, Choi K, Weisburger JH, Rose DP. Effect of varying proportions of dietary fat on the development of N-nitrosomethylurea-induced rat mammary tumors. Anticancer Res 1986;6:215-8.
77. Mazhar D, Waxman J. Dietary fat and breast cancer. QJM 2006;99:469-73.
78. Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: Prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev 1995;4:567-71.
79. Outwater JL, Nicholson A, Barnard N. Dairy products and breast cancer: The IGF-I, estrogen, and bGH hypothesis. Med Hypotheses 1997;48:453-61.
80. World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: A Global Perspective. Breast. Ch. 4.11. Washington (DC): American Institute for Cancer Research; 1997. p. 252-87.
81. Thomas HV, Reeves GK, Key TJ. Endogenous estrogen and postmenopausal breast cancer: A quantitative review. Cancer Causes Control 1997;8:922-8.
82. Riccardi G, Giacco R, Rivellese AA. Dietary fat, insulin sensitivity and the metabolic syndrome. Clin Nutr 2004;23:447-56.
83. Kaaks R. Nutrition, insulin, IGF-1 metabolism and cancer risk: A summary of epidemiological evidence. Novartis Found Symp 2004;262:247-60;260.
84. Kushi LH, Potter JD, Bostick RM, Drinkard CR, Sellers TA, Gapstur SM, *et al*. Dietary fat and risk of breast cancer according to hormone receptor status. Cancer Epidemiol Biomarkers Prev 1995;4:11-9.

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