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Dietary fat and breast cancer survival.

## **Dietary fat and breast cancer mortality: A systematic review and meta-analysis.**

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### **Abstract**

**Background:** The influence of dietary fat upon breast cancer mortality remains largely understudied despite extensive investigation into its influence upon breast cancer risk **Objective:** To conduct meta-analyses of studies to clarify the association between dietary fat and breast cancer mortality **Design:** MEDLINE and EMBASE were searched for relevant articles published up to March 2012. Risk of all-cause or breast cancer specific death was evaluated by combining

multivariable adjusted estimates comparing highest versus lowest categories of intake; and per 20 gram increase in intake of total and/or saturated fat (g/day) using random-effects meta-analyses. **Results:** Fifteen prospective cohort studies investigating total fat and/or saturated fat intake (g/day) and breast cancer mortality were included. There was no difference in risk of breast cancer specific death (n=6; HR=1.14; 95% CI: 0.86, 1.52; P=0.34) or all cause death (n=4; HR=1.73; 95% CI: 0.82, 3.66; P=0.15) for women in the highest versus lowest category of total fat intake. Breast cancer specific death (n=4; HR=1.51; 95% CI: 1.09, 2.09; P<0.01) was higher for women in the highest versus lowest category of saturated fat intake. **Conclusions:** These meta-analyses have shown that saturated fat intake negatively impacts upon breast cancer survival.

## **Keywords**

dietary fat; saturated fat; breast cancer survival

## Introduction

As the number of breast cancer survivors increases worldwide (Cancer Research UK, 2011), there is growing interest in the potential effect of dietary and lifestyle behaviours on overall prognosis. This is especially important as a cancer diagnosis is often referred to as a ‘teachable moment’ when patients are motivated to make changes to their lifestyle and so provision of evidence-based guidelines is essential (Demark-Wahnefried et al., 2005).

The widely postulated association between dietary fat and breast cancer risk was initially based upon ecologic and animal studies (Willett, 1998; Greenwald, 1999; Hunter, 1999). Subsequently, a randomised controlled trial (Rohan et al., 2008) and multiple observational studies investigating the association have been conducted and several meta-analyses have reported increased breast cancer risk with increased dietary fat intake (Boyd et al., 1993; Boyd et al., 2003). In a combined analysis of 12 case-control studies, saturated fat intake was also associated with an increased risk of breast cancer, especially in postmenopausal women (Howe et al., 1990). Yet in a pooled analysis of cohort studies, no evidence of any association was observed (Hunter et al., 1996). The inconsistencies observed may be due to the studies included in the different meta-analyses, which span 13 years, or the methodologies used in these studies (Howe, 1994). Consequently, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report on ‘Food, Nutrition, Physical Activity, and the Prevention of Cancer’ (2007) concluded that there was limited suggestive evidence that total fat increases risk of postmenopausal breast cancer, but that for premenopausal breast cancer there was limited evidence and no conclusions could be drawn (WCRF/AICR, 2007).

The influence of dietary fat on breast cancer mortality also remains unclear as the results of several randomised controlled trials are conflicting. In the Women's Intervention Nutrition Study (WINS), a reduction in breast cancer recurrence was seen in those who had adopted a low-fat dietary pattern (15% of energy intake from fat) with decreased intakes of oils and sweets and increased fruit consumption, in comparison with those in the control group. Yet there was significant weight loss in the intervention group and a higher frequency of mastectomy which may have confounded results (Chlebowski et al., 2006). In contrast, in the Women's Healthy Eating and Living (WHEL) randomised controlled trial, women in the intervention arm who consumed 15-20% of energy, 5 vegetable servings, 16 oz vegetable juice, 3 fruit servings and 30g fibre per day did not have a significantly reduced risk of recurrence (Pierce et al., 2007). Although the results obtained are of interest, it is impossible from these studies to firmly establish the effect of dietary fat intake on breast cancer mortality as they were designed to achieve an overall dietary intervention change which only included a reduction in dietary fat intake.

In the absence of randomised controlled trials of fat and breast cancer recurrence, it is important to review other sources of evidence. A substantial number of cohort studies have examined the relationship between habitual dietary fat intake and breast cancer survival, yet, to date, the evidence provided by these has not been systematically reviewed. Our aim is to conduct a systematic review to establish whether an association exists between dietary fat intake and breast cancer mortality and, where possible, to quantify the relationship using meta-analysis of individual studies to produce a pooled estimate.

## **Methods**

### **Study selection**

An electronic literature search was conducted in the databases Ovid MEDLINE (US National Library of Medicine, Bethesda, MD) and EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands) to identify human studies published in the English language up to March 2012 that included the following keywords or phrases: (dietary fat(s) or dietary cholesterol or saturated dietary fat(s)) and (survivorship or disease-free survival or survival rate or survival) and (breast neoplasm(s) or breast tumo(u)r or breast cancer survival or breast cancer or cancer of the breast). Four independent reviewers (SFB, PML, JVW, MMC) considered the abstracts of the articles retrieved in the initial search to identify potentially relevant studies which examined dietary fat and breast cancer mortality. All reviewers agreed on the potential articles and full-texts of these were obtained. Reference lists of the considered articles were searched for any further papers which may not have been identified in the database searches. Only studies which reported risk estimates (hazard ratios, odds ratios and relative risks), and measures of variability (standard errors [SEs] or 95% confidence intervals [CIs] from which these could be derived), for all-cause and/or breast cancer mortality according to total fat intake and/or saturated fat intake were included.

### **Data extraction**

Information extracted from each study included geographic region, study design, year of publication, sample size, number of cancer cases, dietary assessment method, timing of dietary

assessment (relative to diagnosis), duration of follow-up, risk estimates with 95% CIs and confounding variables adjusted for in the analysis.

## **Statistical analyses**

The original studies reported hazard ratios (HR) for all-cause or breast cancer specific death by categories (in fifths, fourths or thirds) of total fat/saturated fat intake. Where possible, results were converted to g/day by calculation or by requesting the results in this format from the article author. Meta-analyses were conducted to evaluate the risk of all-cause or breast cancer specific death in women in the highest compared with the lowest reported categories of total fat intake (g/day) and women in the highest compared with the lowest categories of saturated fat (g/day). Additionally, the linear increase in risk of breast cancer and all-cause death per percentile increase in total fat and saturated fat intake (g/day) was estimated by conducting a regression of the HRs in the categories of total and saturated fat intake against the average percentile in each category where possible using the methods by Greenland and Longnecker and otherwise using variance-weighted least-squares linear regression (Greenland & Longnecker, 1992). This linear increase was converted to an estimate for a 20<sup>th</sup> percentile increase in total fat and/or saturated fat intake. Multivariable adjusted hazards ratios, odds ratios and relative risks with 95% CIs from individual studies were weighted and combined using an inverse-variance weighted random-effects model to produce a pooled estimate (DerSimonian & Laird, 1986). Heterogeneity was tested with a chi-squared test and measured using the  $I^2$  statistic (Higgins et al., 2003). Each study's estimate and 95% CI and SE were presented in a forest plot along with the pooled

estimate. Publication bias was assessed from inspection of the funnel plot and by statistical analysis using Begg's and Egger's tests (Sterne & Egger, 2001).

Subgroup analyses were conducted for: studies which had adjusted for energy intake and for those which had not; studies which used FFQs for dietary assessment and those which used diet histories/recalls; and finally studies which assessed diet pre-diagnosis and those which assessed diet post-diagnosis

Statistical analyses were conducted with Intercooled STATA version 9.2 (2005; StataCorp, College Station, TX).

## **Results**

### **Inclusion**

The electronic literature search identified 82 potentially relevant publications. Of these, 33 papers were initially excluded as they did not examine dietary fat and breast cancer mortality. Of the 49 articles which remained, the following papers were excluded: 5 randomised controlled trials (Chlebowski et al., 2006; Pierce et al., 2007; Winters et al., 2004; Stolley et al., 2009; Hoy et al., 2009), 1 ecological study (Kesteloot et al., 1994), 18 reviews (Wynder et al., 1986; Chlebowski et al., 1992; Wynder et al., 1992; Colditz, 1993; Cohen et al., 1993; Ganz & Schag, 1993; Nixon, 1996; Stoll, 1996; Wynder et al., 1997; Jatoi & Loprinzi, 1999; Newman et al., 1999; Rock & Demark-Wahnefried, 2001; Blackburn et al., 2003; Holmes & Kroenke, 2004; Blackburn & Wang, 2007; Kellen et al., 2009), 7 editorials/letters/supplements/communications (Hebert & Wynder, 1987; Lipmann, 1987; Thiébaud et al., 2006; Kurt & Altundag, 2007; Pierce



et al., 2007; Gapstur & Khan, 2007; Nelson, 2008) one study which examined marine fatty acid intake (Patterson et al., 2011), one study which presented results as foods and not nutrients (Hebert et al., 1998) and one study which did not provide usable estimates for dietary fat and breast cancer survival (Holm et al., 1993).

Fifteen articles examined dietary fat intake (total fat and/or saturated fat (g)) and all-cause and breast cancer mortality and were included in the analyses (Gregorio et al., 1985; Newman et al., 1986; Nomura et al., 1991; Ewertz, 1993; Rohan et al., 1993; Jain et al., 1994; Zhang et al., 1995; Staessen et al., 1997; Holmes et al., 1999; Saxe et al., 1999; Goodwin et al., 2003; Borugian et al., 2004; McEligot et al., 2006; Holmes et al., 2009; Beasley et al., 2011).

Information extracted from each study included geographical region, sample size, age range, length of follow-up, dietary assessment method, timing of dietary assessment (relative to diagnosis), number of deaths, factors that were adjusted for in the analysis and risk estimates (HR, OR, RR) and factors that were adjusted for in the analysis (Table 1; Figure 1).

### **Total fat intake**

The association between highest compared with lowest categories of intake of total fat (g/day) and breast cancer specific and all-cause death are shown in **Figure 2** (A & B respectively). There was no evidence of an association between total fat intake and risk of breast cancer specific death (n=6; HR=1.14; 95% CI: 0.86, 1.52; P=0.34) or all cause death (n=4; HR=1.73; 95% CI: 0.82, 3.66; P=0.15) for women in the highest compared with the lowest categories of total fat intake. There was evidence of study heterogeneity in studies that examined the association between all-cause death and total fat intake (P<0.01; I<sup>2</sup>=84%). There was less evidence of heterogeneity

between studies that examined breast cancer specific death and total fat intake ( $P=0.115$ ;  $I^2=44\%$ ).

Similarly, no significant difference in risk of all cause ( $n= 3$ ;  $HR=1.06$ ; 95% CI: 0.88, 1.28;  $P=0.52$ ) or breast cancer specific death ( $n=4$ ;  $HR= 1.03$ ; 95% CI; 0.97, 1.10;  $P=0.26$ ) was observed per linear (20 gram) increase in total fat intake. Once again, heterogeneity was most apparent in the analysis with studies providing estimates for all-cause death ( $P=0.03$ ;  $I^2=70\%$ ); no heterogeneity was evident for the studies providing estimates for breast cancer specific death ( $P=0.44$ ;  $I^2=0\%$ ).

### **Saturated fat intake**

The association between highest compared with lowest categories of intake of saturated fat (g/day) and breast cancer specific death is shown in **Figure 3**. There was evidence of an increased risk of breast cancer death ( $n=4$ ;  $HR=1.51$ ; 95% CI: 1.09, 2.09) for the highest compared with the lowest category of intake of saturated fat (g/day) and these studies showed no evidence of heterogeneity ( $P=0.317$ ,  $I^2=15\%$ ). Only one study provided an estimate of risk for women in the highest compared to the lowest category of saturated fat intake and all-cause death ( $HR=2.4$ ; 95% CI: 1.1, 4.9) (Zhang et al., 1995).

No significant difference in risk of breast cancer specific death ( $n=4$ ;  $HR=1.03$ ; 95% CI: 0.77, 1.38;  $P=0.80$ ) was observed per linear (20 gram) increase in saturated fat intake (results not shown). Heterogeneity was apparent in the analysis ( $P<0.01$ ;  $I^2=75\%$ ). Only one study provided an estimate of risk of all-cause death per linear (20 gram) increase in saturated fat intake ( $HR=1.01$ ; 95% CI: 1.08, 1.88) (Zhang et al., 1995).

## **Publication Bias**

Funnel plots revealed little evidence of asymmetry (not shown) and therefore little evidence of publication bias for studies examining the relationship between categories of total fat intake (g/day) and all cause death (Begg's test:  $P=0.355$ ), and saturated fat intake (g/day) and breast cancer specific death (Begg's test:  $P=0.156$ ). There was some evidence of publication bias the studies that reported an association between categories of total fat intake and breast cancer death (Begg's test:  $P=0.05$ ).

## **Sensitivity Analyses**

Sensitivity analyses were performed by removing studies which did not adjust for energy intake and by removing studies which used a dietary history/recall as opposed to a food frequency questionnaire, but no difference in the risk of all-cause or breast cancer death was observed for highest compared to the lowest intake of total fat (g/day) or saturated fat (g/day). Although not significant, slightly stronger associations were seen in studies investigating highest versus lowest intakes of total fat and breast cancer specific death which had adjusted for energy ( $n=3$ ; HR: 1.26; 95% CI: 0.84, 1.89) compared to those which did not ( $n=3$ ; HR: 1.10; 95% CI: 0.72, 1.68) and in studies which did not use FFQs ( $n=2$ ; HR: 1.59; 95% CI: 0.52, 4.91) compared to those which used FFQs to assess dietary intake ( $n=4$ ; HR: 1.08; 95% CI: 0.78, 1.48) . Further sensitivity analyses involved examining the effect of the timing of dietary intake assessment. Again, the main results did not change markedly, but in studies which examined diet pre-diagnosis, highest versus lowest intakes of total fat intake were associated with an increased risk of all-cause death ( $n=3$ ; HR: 2.65; 95% CI: 1.73, 4.05).

## Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis of observational studies examining dietary fat intake and breast cancer mortality. Results indicate that overall, a higher intake of saturated fat may increase the risk of breast cancer death. It has also shown that a higher total fat intake pre-diagnosis may increase the risk of all-cause death. In the absence of randomised controlled trials, which specifically test the efficacy of a low fat or low saturated fat diet in breast cancer survivors, this meta-analysis suggests that lower intakes of both total and saturated fat could be beneficial in terms of survival after a breast cancer diagnosis.

Although two randomised controlled trials (RCTs), the WINS and the WHEL studies (Chlebowski et al., 2006; Pierce et al., 2007) have been conducted to examine the role of dietary fat on breast cancer prognosis to date, it is difficult to compare their results with the results of our meta-analysis. The investigators of these RCTs aimed to reduce the total fat intake of women in the intervention arm of the studies to 15-20% of energy intake. Women in the intervention arm of the WINS trial had a 24% reduction in risk of breast cancer death compared with the control group (Chlebowski et al., 2006). However, women in the intervention arm also had significant weight loss, which could account for their lower risk of death, rather than the reduction in fat intake *per se*. Women in the intervention arm were also more likely to have had a mastectomy than in the control arm, which could also explain the difference in breast cancer survival between the study groups. Although the investigators of the WHEL trial reported no effect of their low fat intervention on breast cancer survival (Pierce et al., 2007), it should be noted that women in the

intervention arm also changed several other aspects of their diet to include 5 vegetable servings, 16 oz vegetable juice, 3 fruit servings and 30g fibre per day. Moreover, 75% of WHEL participants had healthy lifestyles and consumed at least 5 servings of fruit and vegetables per day at baseline and prior to randomisation. The prevalence of healthy eating in the WHEL study is higher than other breast cancer survivor populations (Caan et al., 2005; Wayne et al., 2004) and it is possible that this intervention would have resulted in different outcomes in a population with less healthy lifestyles prior to the intervention.

There are a number of biologically plausible mechanisms whereby total or saturated fat intake may increase risk of breast cancer death. It has been hypothesised that fat intake promotes malignant mammary cell growth by increasing circulating oestrogens (Wu et al., 1999; Löf et al., 2007). It has also been proposed that saturated fat intake may promote breast tumour growth by increasing low-density lipoprotein and cholesterol levels (Le Guevel, R & Pakdel, 2001), by promoting an inflammatory response and by reducing apoptosis as a result of altered gene expression (Lee et al., 2001, Willett, 1998). As publications on dietary fat and breast cancer mortality and survival are few, our analyses were somewhat limited by the information available, and we were only able to examine total and saturated fat, but not monounsaturated, polyunsaturated, or trans-unsaturated fat intake and breast cancer survival, as these were not provided by the individual studies. It is likely however that these factors could also influence breast cancer survival for example through formation of reactive oxygen species (Kang, 2002).

Overall, total fat intake was not associated with breast cancer specific or all cause death in the present study. However, women in the highest versus lowest category of total fat intake had an

increased risk of all-cause death in studies which assessed diet pre-diagnosis. Although our results are limited by the information provided by the individual studies, they suggest the potential significance of the timing of dietary assessment around breast cancer diagnosis. As it has been widely reported that a cancer diagnosis motivates many cancer patients to adopt a lifestyle change (Demark-Wahnefried et al., 2005), it would be of interest to further clarify the nature of this association. Furthermore, it is also possible that dietary intake during childhood and adolescence, which may influence a woman's future breast cancer risk, may also impact upon her prognosis (Moisan, 1990). Therefore, it would also be of interest to further examine the association between dietary fat and mortality after breast cancer using more considered dietary assessment methods.

In the present study, a higher versus lower intake of saturated fat was associated with an increased risk of breast cancer death, yet no linear relationships were observed. Similar results have been previously reported in a study by Goodwin et al. (2003), where extremes of intake of polyunsaturated-saturated fat ratio, cholesterol and percentage intake from fat, amongst other dietary components, were associated with breast cancer survival but linear associations were not observed. It is therefore possible, that a mid-range intake of dietary fat, perhaps through consumption of a balanced diet, is most beneficial in terms of survival after a breast cancer diagnosis.

Of the 15 studies included in our analyses, 11 used a FFQ to assess dietary intake. The limitations of FFQs are well documented and include measurement error due to overestimation of the range of nutrient intakes and attenuation of risk estimates. Five studies included in our

review used diet histories/records, which are often considered more robust dietary assessment methods, to assess dietary fat intake. In our sensitivity analyses, we observed stronger associations when we removed studies which used FFQs (analysing only those which used diet histories), although these results were not significantly different from the overall results. However, the results of the individual studies, regardless of whether they used an FFQ or a diet history, are limited by their use of one single measurement of diet, which cannot capture changes in dietary intake during the follow-up period and may not be representative of a woman's habitual diet. It has also been suggested that FFQs more accurately measure food intake rather than nutrient intake (Hebert et al., 1998). Hebert et al (1998) reported a positive association between intakes of butter, margarine, lard, red meat and bacon and breast cancer recurrence (Hebert et al., 1998). This finding supports the association shown between saturated fat and breast cancer death in our meta-analysis.

There are inherent difficulties associated with combining results from individual studies, and the results of our meta-analysis are subject to the strengths and limitations of each study's design. The studies differed by geographical region, age range of participants and time from diagnosis when the dietary assessment was made. Adjustment for confounders was also inconsistent between studies resulting in the potential for residual confounding; for example some studies did not adjust their analyses for total energy intake. However, we conducted sensitivity analyses excluding studies that did not report adjustment for energy intake and although the differences were not significant, we observed slightly stronger associations. Body Mass Index (BMI) or a change in weight after a breast cancer diagnosis, which has previously been shown to be associated with breast cancer prognosis (Conroy et al., 2011; Protani et al., 2010) could not be

controlled for in our analyses since adjustment across the individual studies was inconsistent.

Additionally, it has been suggested that the influence of dietary fat on breast cancer risk and outcome may be dependent upon the hormone receptor status of the breast cancer (Chlebowski et al., 2006, Prentice et al., 2007), but it was not possible to examine this as estimates were not provided by the original articles

In conclusion, our results suggest that highest versus lowest intakes of saturated fat are associated with breast cancer specific death, whilst highest versus lowest intakes of total fat pre-diagnosis are associated with all-cause death. Modification of dietary intake, both prior to and at the time of diagnosis, to reduce total and saturated fat intake may therefore be warranted.

Additional studies that assess dietary fat intake at the time of or after breast cancer diagnosis, rather than using pre-diagnostic measures as surrogates of post-diagnostic intake are required to develop specific dietary recommendations for breast cancer survivors.

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**Table 1. Descriptions of the studies included in the systematic review and meta-analysis of dietary fat and breast cancer survival.**

<b>Study</b>	<b>Location</b>	<b>Sample size; age range (follow-up)</b>	<b>Diet assessment method</b>	<b>Time of dietary assessment relative to diagnosis</b>	<b>Factors adjusted for in analysis</b>	<b>No. of events (deaths)/total number of cases</b>	<b>Risk estimate (95% CI)</b>
Gregorio et al, 1985 <sup>3</sup>	USA	854; 46-55 (18-26 yrs)	FFQ (33 item)	PRE; Asked to recall diet prior to symptom onset	Stage of disease, age at diagnosis, treatment delay, relative obesity	Information not available	1.14 (0.13, 0.08) <sup>3</sup>
Newman et al, 1986 <sup>1</sup>	Canada	300; 35-74 (Max 7 years)	Diet history (150 item); 24-hr diet recall; 4-day diet record  All converted to estimates of daily intake	POST; Diet history (previous 2 months)  24-hr diet recall (previous 24 hrs)  4-day diet record (previous 4 days)	Weight	87/300	0.99 (0.74, 1.23) <sup>1</sup>
Nomura et al, 1991 <sup>1</sup>	Hawaii	343; 45-74 (7-12 years)	Diet history (43 item) consumption during usual week	POST; Usual consumption	Stage of disease, menopausal status, obesity index, oestrogen use, age	Information not available	3.17 (1.17, 8.55) <sup>1</sup>

Ewertz 1993 <sup>2</sup>	Denmark	2445; <75 years (6-7 years)	FFQ (21 item)	POST	Tumour size, skin invasion, no of positive lymph nodes, grade, age, residence	805/2445	0.96 (0.77, 1.23) <sup>2</sup>
Rohan et al, 1993 <sup>1,3,5,6</sup>	Australia	412; 20-74 years (Median 5.5 years)	FFQ (179 item)	POST	Age at menarche, Quetelet index, total energy intake	123/451	1.40 (0.66, 2.96) <sup>1</sup> 1.00 (0.00, 0.00) <sup>3</sup> 1.65 (0.73, 3.75) <sup>5</sup> 1.65 (0.73, 3.75) <sup>6</sup>
Jain et al, 1994 <sup>5,6</sup>	Canada	678; 40-59 years (Mean 7.7 years)	Diet history questionnaire (previous month)	POST (previous month)	Total energy, age at diagnosis, smoking, body weight.	83/678	1.91 (0.73, 5.02) <sup>5</sup> 1.00 (0.92, 1.4) <sup>6</sup>
Zhang et al, 1995 <sup>2,4</sup>	USA	893; 55-69 years (Max 6 years)	FFQ	PRE; asked about habitual consumption before diagnosis occurred	Age, extent of disease, oestrogen receptor status, progesterone receptor status, tumour size, smoking status, education, family history, total energy	56/698	2.50 (1.20, 5.30) <sup>2</sup> 1.00 (0.00, 0.00) <sup>4</sup>
Staessen et al,	Belgium	Total cohort: 11,302;	24 hour food record	POST	Age, sex, region, energy intake,	Information not available	0.92 (-0.08,

1997 <sup>6</sup>		25-74 years (3-10 years)			smoking, education		0.00) <sup>6</sup>
Holmes et al, 1999 <sup>5</sup>	USA	1982; Mean 54 years (4-18 years)	FFQ completed most closely to BC diagnosis	POST	Age, diet interval, year of diagnosis, BMI, OC use, menopausal status, postmenopausal hormone use, smoking, age at first birth, parity, no of metastatic lymph nodes, tumour size, caloric intake	378/1982	1.23 (0.89, 1.69) <sup>5</sup>
Holmes et al, 2009 <sup>1,3</sup>	USA	3846; 30-55 years (83 months)	FFQ	POST (previous year)	Dietary factors, physical activity, BMI, weight change, reproductive factors, treatment, smoking	446/3846	0.88 (0.63, 1.25) <sup>1</sup>
Saxe et al, 1999 <sup>4,6</sup>	USA	149; Mean 57.8 years (at least 5 years)	FFQ	PRE (asked about consumption during year prior to diagnosis)	Energy intake, menstrual status, BMI, disease stage	Information not available	1.51 (0.41, 0.51) <sup>4</sup> 1.72 (0.54, 0.27) <sup>6</sup>
Goodwin et al, 2003 <sup>2,4</sup>	Canada	477; <75 years (Median	FFQ	PRE (completed approx. 9 weeks post-	BMI, age, tumour stage, nodal stage, adjuvant	52/477	1.08 (0.25, 4.73) <sup>2</sup>

		6.1 years)		diagnosis, reported preceding 12 month consumption)	hormone therapy, adjuvant chemotherapy, total energy		0.99 (-0.00, 0.00) <sup>4</sup>
Borugian et al, 2004 <sup>1,3,5</sup>	Canada	603; 19-75 years (9-10 years)	FFQ	POST	Age, total caloric intake, stage at diagnosis.	112/603	1.80 (0.90, 4.80) <sup>1</sup> 1.00 (0.00, 0.00) <sup>3</sup> 2.5 (1.2, 5.3) <sup>5</sup>
McEligot et al, 2006 <sup>2</sup>	USA	516; Mean 64.78 years (Mean 6.6 years)	FFQ (100 item)	PRE (asked about diet during year prior to diagnosis)	Stage of disease, age at diagnosis, BMI, parity, HRT use, alcohol use, multivitamin use, energy intake	96/516	3.12 (1.79, 5.44) <sup>2</sup>
Beasley et al, 2011 <sup>1</sup>	USA	4441; 20-79 years (Mean 5.5 years)	FFQ (126 item)	POST (previous year)	Factors at diagnosis: age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, history of hormone replacement therapy; interval between	137/4441	0.92 (0.52, 1.60) <sup>1</sup>

					diagnosis and diet assessment; Factors at follow up: energy intake, breast cancer treatment, BMI, physical activity		
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<sup>1</sup>Studies included in analysis for highest vs lowest categories of total fat intake and breast cancer specific death

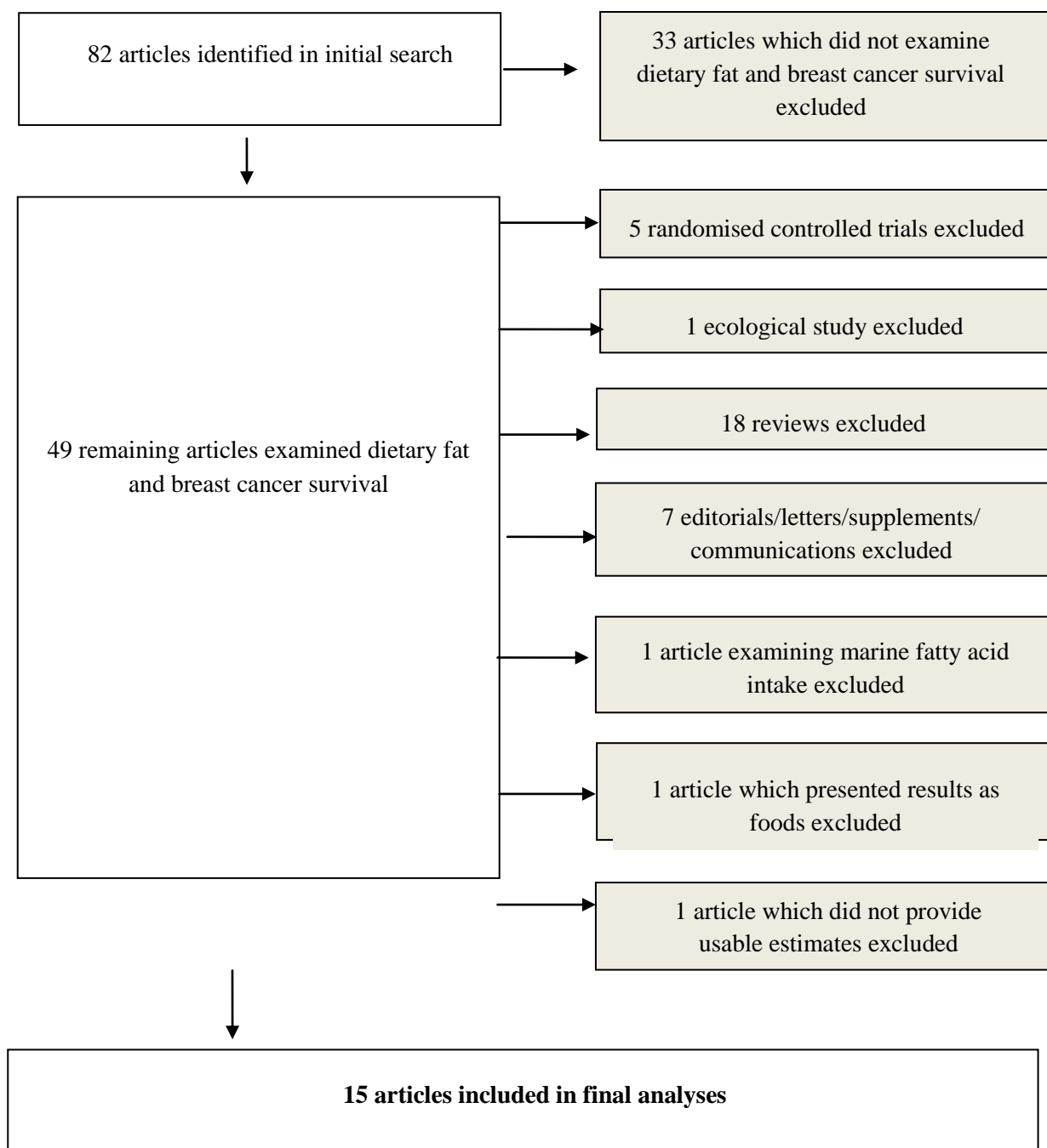
<sup>2</sup>Studies included in analysis for highest vs lowest categories of total fat intake and all cause death

<sup>3</sup>Studies included in analysis of per 20g increase in intake of total fat and breast cancer specific death

<sup>4</sup>Studies included in analysis of per 20g increase in intake of total fat and all-cause death

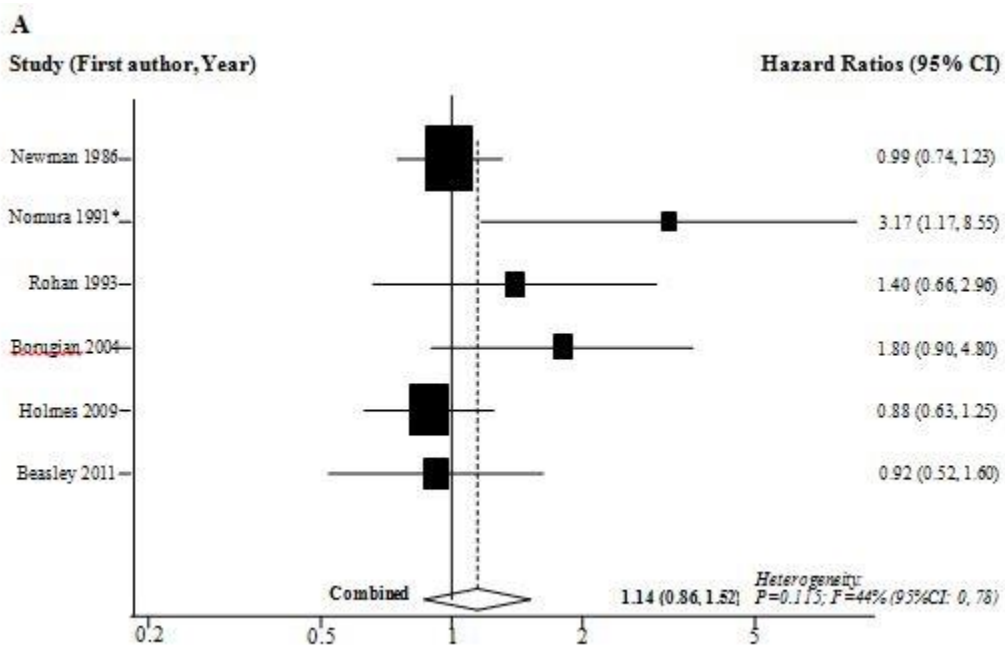
<sup>5</sup>Studies included in analysis for highest vs lowest categories of saturated fat intake and breast cancer specific death

<sup>6</sup>Studies included in analysis of per 20g increase in intake of saturated fat and breast cancer specific death

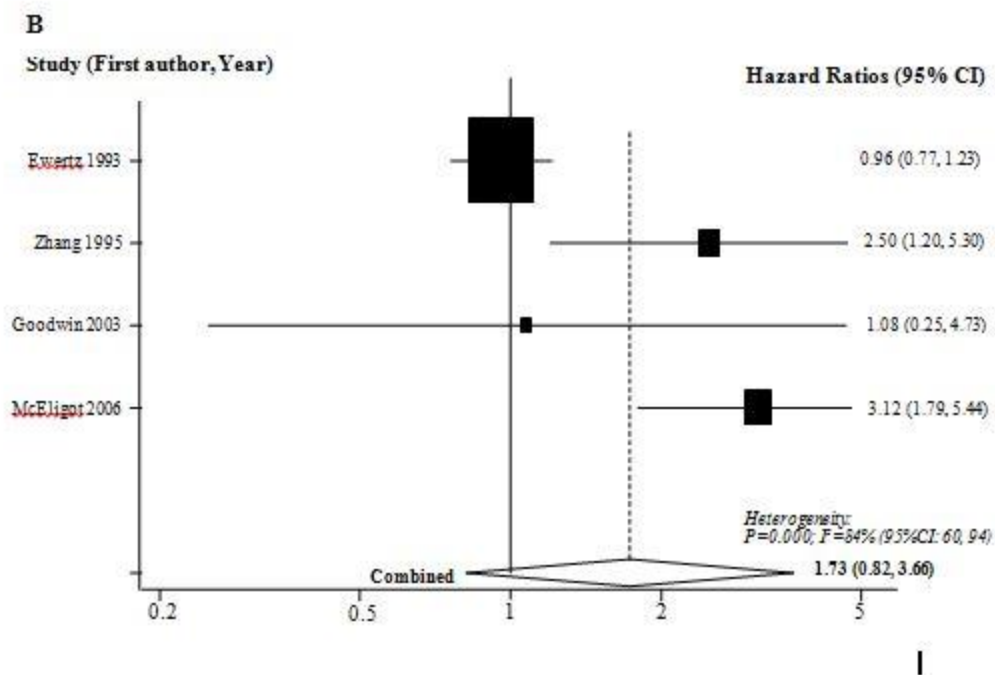


**Figure 1** Flow diagram of study selection

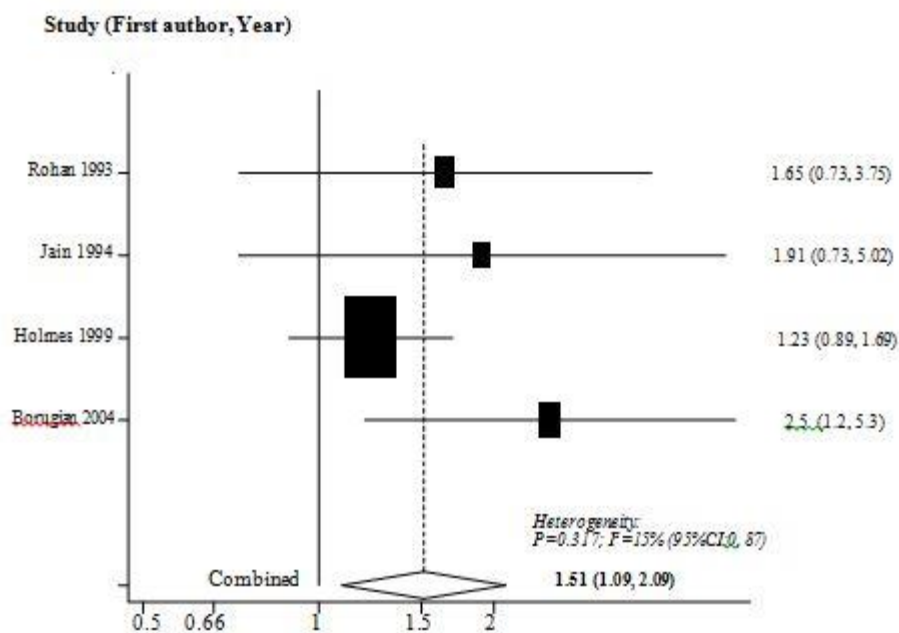




**Figure 2 A:** Forest plot of the highest compared with the lowest categories of total fat intake (g/day) and breast cancer specific death.\* Nomura: Caucasians only.



**Figure 2 B:** Forest plot of the highest compared with the lowest categories of total fat intake (g/day) and all-cause death



**Figure 3.** : Forest plot of the highest compared with the lowest categories of saturated fat intake (g/day) and breast cancer specific death.