RESEARCH ARTICLE

Effect of Low-fat Diet on Breast Cancer Survival: a Meta-analysis

Mei-Yuan Xing[1], Su-Zhen Xu[2], Peng Shen[2]*

Abstract

Background: Even though many studies have examined the possible effect of low-fat diet on breast cancer survival, the relationship remains unclear. Objectives: To summarize the current evidence about the effect of post-diagnostic low-fat diet on recurrence and all-cause mortality of breast cancer. Methods: We conducted a search of Pubmed, Embase, Web of Science, and Cochrane Library and as a result two randomized controlled trials (RCT) and one large multi-center prospective cohort study with 9,966 breast cancer patients were included in this report. Results: Post-diagnostic low-fat diet reduced risk of recurrence of breast cancer by 23% (HR=0.77, 95%CI 0.63 to 0.94, *P*=0.009) and all cause mortality of breast cancer by 17% (HR=0.83, 95%CI 0.69 to 1.00, *P*=0.05). Conclusions: This meta-analysis suggested the post-diagnostic low-fat diet can improve breast cancer survival by reducing risk of recurrence. However, more trials of the relationship between low-fat diet and all-cause mortality of breast cancer are still needed.

Keywords: Post-diagnosis - low-fat diet - breast cancer - survival - meta-analysis

Asian Pac J Cancer Prev, **15 (3)**, 1141-1144

Introduction

Breast cancer is the most common cancer diagnosed among women in the world. During the 2012, more than 225, 000 new cases of invasive breast cancer occurred in US (American Cancer Society, 2012). Thanks to earlier detection and improved treatment, the five-year relative survival rate of early stage breast cancer is more than 93%. However, to reduce the recurrence and mortality of breast cancer, not only effective treatment but also intervention of lifestyle plays an important role. With the change of medical model, the function of the patient's self-intervention on disease attracts much more eyes of doctors, especially the diet and physical activity.

In 2012, the American Cancer Society (ACS) released nutrition and physical activity guidelines for cancer survivors (Kushi et al., 2012). It indicated low-fat diet was associated with improving breast cancer survival. Since the 1900s, a number of studies have investigated the associations between dietary fat and breast cancer survival (Newman et al., 1986; Nomura et al., 1991; Ewertz et al., 1991; Jain et al., 1994; Zhang et al., 1995; Saxe et al., 1999; Holmes et al., 1999; Goodwin et al., 2003; Borugian et al., 2004; McEligot et al., 2006; Dal Maso et al., 2008). But the results were not consistent. The conclusion of The Women's Intervention Nutrition Study (Chlebowski et al., 2006) suggested that low-fat diet can reduce the recurrence risk of breast cancer. However, the Women's Health Eating and Lifestyle Study (Pierce et al., 2007) reported that no significant interactions were observed between low-fat diet and breast cancer survival. So we need a meta-analysis addressed that pertinent issue to evaluate whether low-fat diet can reduce recurrence and all-cause mortality of breast cancer. In this report, we focused on post-diagnosis, because breast cancer patients still have a chance to change their post-diagnostic diet other than pre-diagnostic diet.

Materials and Methods

Search criteria

We did a comprehensive search of Pubmed, Embase, Web of Science, and Cochrane Library, databasing from the earliest record in the databases to August, 2013. The search strategy consisted of three parts. Firstly, we searched the articles about breast cancer, using the medical subject heading (MeSH) terms ''breast neoplasms'' and other terms as "breast", "mammary", "cancer", "carcinoma", "neoplasm", "tumor". The second part was about low-fat diet, the key words of which included "Diet, Fat-Restricted (Mesh)", "low fat", "less fat", "diet", "dietary", "nutrition". The survival of breast cancer was the third part. "recurrence", "survival", "mortality", "death", "relapse", "prognosis", "rehabilitation", "prevention", "outcome" were used. Then we combined the three parts and got the initial list of relevant studies. Hand searches of reference lists from relevant primary studies and review articles were also marked to review.

Inclusion and exclusion criteria

We selected the studies about the effect of post-diagnostic low-fat diet on survival of breast cancer if

[1]*Library of the First Affiliated Hospital,* [2]*The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China*
**For correspondence: peggyxsz@gmail.com*

Table 1. Characteristics of the Studies Included in This Meta-analysis

Study	Location	design	Participations(n)	Indicator	Outcome	Follow-up
WINS Chlebowski R et al. (2006)	United States	RCT	2,437 women	low-fat diet (% energy)	relapse-free survival; overall survival; disease-free survival; recurrence-free survival	median 60 months
WHEL Pierce JP et al. (2007)	United States	RCT	3,088 women	low-fat diet (% energy)	breast cancer events and deaths due to any cause	mean 7.3 years
CWLS Beasley JM et al. (2011)	United States	Large multi-center prospective cohort	4,441 women	low-fat diet (% energy)	all-cause and breast cancer survival	mean 5.5 years

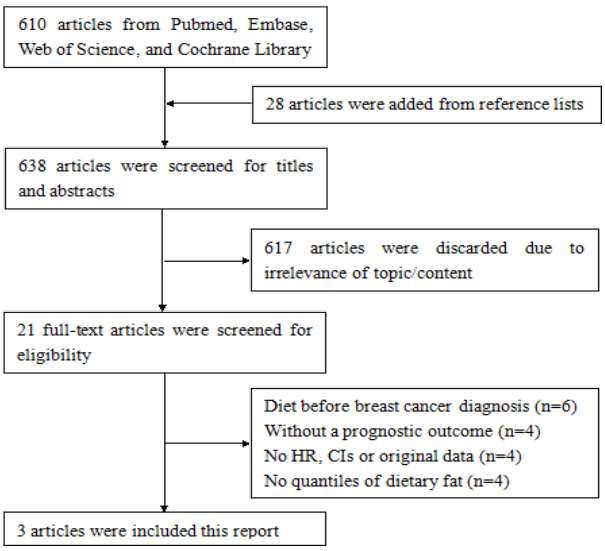

Figure 1. Flow Diagram for the Selection of Studies

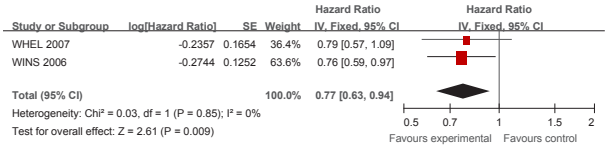

Figure 2. Forest Plot for Effect of Post-diagnostic Low-fat Diet on the hazard ratio of Breast Cancer Recurrence

they contained the following information: (i) reported the recurrence, breast cancer -specific mortality or all-cause mortality among breast cancer women; (ii) presented multivariate analysis (not univariate analysis); (iii) provided an estimate of the hazard ratio (HR) and 95% confidence intervals (CI) comparing the high-fat with the low-fat. Studies without a comparator, editorials, reviews, animal studies, and in vitro studies were excluded.

Data extraction

Two authors independently extracted data using standardized data collection form. The extracted data from each study included: first author, published year, location, study design, number of participation, follow-up time, measurement indicators, outcome. When the two authors had disagreements, one or more author joined to discussion until consensus achieved.

Statistical Analysis

We used the RevMan 5.1 analysis software (The Cochrane Collaboration, Copenhagen, Denmark) to extract and combine data for meta-analysis. In this report, we used generic inverse variance method (DerSimonian et al., 1986) to statistics hazard ratio (HR). The method reported by Parmar et al. could be used to extract estimates of log hazard ratio (HR) and its variance, if they were not provided clearly (Parmar et al., 1998). X2 statistics (Cochran, 1954) and I^2 statistics (Higgins et al., 2003) were used to estimate statistical heterogeneity. According to the result of statistical heterogeneity, we chose fixed or random effect models. *P*-values <0.05 was considered statistically significant.

Results

The process of selecting studies was shown in Figure 1. After titles and abstracts were reviewed, 21 articles met the criteria for inclusion in the report. The two authors independently reviewed the full-text and discarded 18 articles for the following reasons: studies that did not investigate the diet after breast cancer diagnosis; studies that did not evaluate a prognostic outcome (recurrence or all-cause mortality of breast cancer); studies which did not report HR, CI or original data; studies which did not show quantiles of dietary fat.

Characteristics of included studies

In the end, three studies (Chlebowski et al., 2006; Pierce et al., 2007; Beasley et al., 2011) reached the inclusion criteria and were included in this meta-analysis. The characteristics of this studies were shown in table 1. There were two RCTs (Chlebowski et al., 2006; Pierce et al., 2007) with a total of 5, 525 breast cancer women and one large multi-center prospective cohort study (Beasley et al., 2011) with 4, 441 breast cancer women. They were all conducted in United States. One study (Chlebowski et al., 2006) reported the effect of post-diagnostic low-fat diet on relapse-free survival, overall survival, disease-free survival and recurrence-free survival. The endpoints of the WHEL study (Pierce et al., 2007) were breast cancer events (the combined outcome of invasive breast cancer recurrence or new primary breast cancer) and deaths due to any cause. The last study's (Beasley et al., 2011) outcomes were all-cause and breast cancer survival. All of the studies presented the HRs and CIs calculating from Cox proportional hazard model. The covariates contained the stage, age, body mass index (BMI), breast cancer treatment, smoking and so on.

Meta-analysis

Two RCTs (Chlebowski et al., 2006; Pierce et al., 2007) reported the effect of the post-diagnostic low-fat diet on breast cancer recurrence. We combined the result of the two studies with the RevMan 5.1 analysis software, the result showed in Figure 2. According to the little heterogeneity (I^2=0%, *P*=0.85), we chose the fixed effect model. The total effect suggested that post-diagnostic low-fat diet could reduce 23% (HR=0.77, 95%CI 0.63 to 0.94)

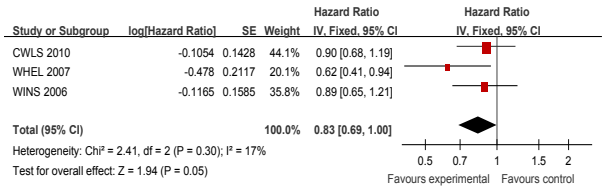

Figure 3. Forest Plot for Effect of Post-diagnostic Low-fat Diet on the Hazard Ratio of All-cause Mortality

recurrence risk of breast cancer, comparing with high-fat diet. The benefit was highly significant (*P*=0.009).

All the three studies (Chlebowski et al., 2006; Pierce et al., 2007; Beasley et al., 2011) were included in the meta-analysis of the relationship between post-diagnostic low-fat diet and all-cause mortality among breast cancer women. The heterogeneity was tested among the studies (I^2 =17%, *P*=0.30), and the fixed effect model was used. The Figure 3 presented a nonsignificant 17% (HR=0.83, 95%CI 0.69 to 1.00, *P*=0.05) reduction in all-cause mortality, when comparing the low-fat diet to the high-fat diet.

Discussion

There were so many studies (Kruk J et al., 2013; Sangrajrang S et al., 2013; Mirzayi B R et al., 2013) that had proved the associations between the lifestyle and the risk of breast cancer, such as diet and physical activity. In another way, we can assume that changes in behavior can improve the prognosis of breast cancer. In this report, we focused on the associations between diet and breast cancer survival.

In the past several decades, there were a number of studies that suggested low-fat diet played an important role in improving the prognosis of breast cancer patients. Some studies focused on prediagnostic low-fat diet. For example, the Iowa Women's Health Study (Zhang et al., 1995) showed a relative risk of death after breast cancer was greater than 2.0 for the highest tertiles of total fat compared to the lowest tertiles. McEligot et al. (2006) observed pre-diagnostic high-fat diet made the all-cause mortality of breast cancer increase by threefold than the low-fat diet. Meanwhile, some studies evaluated the relationship between post-diagnostic low-fat diet and breast cancer survival. Nomura et al. (Nomura et al., 1991) showed a 3.17 times significant higher risk of breast cancer mortality (RR=3.17, 95%CI 1.17 to 8.55) for high-fat diet versus low-fat diet. Similarly, in the Nurses' Health Study (Holmes et al., 1999), high-fat diet could increase the breast cancer-specific mortality by 44% (RR=1.44, 95%CI 1.01 to 2.04) and all-cause mortality by 51% (RR=1.51, 95%CI 1.02 to 2.24) in comparison with low-fat diet. Moreover, an Australian cohort study (Rohan et al., 1993) suggested high risk of breast cancer mortality with high-fat diet. They all supported the hypothesis that the pre-diagnostic or post-diagnostic low-fat diet is associated with improved prognosis of breast cancer.

If patients don't kown they has breast cancer, they will not try to change their diet. However, they must be willing to change their diet after the diagnosis of breast cancer. So the intervention of post-diagnostic diet has a greater clinical significance. Because of this, we concentrated on the post-diagnostic low-fat diet in this meta-analysis. We summarized the current evidences about the effect of post-diagnostic low-fat diet on recurrence and all-cause mortality among breast cancer survivors. After integrating the results of two studies (Chlebowski et al., 2006; Pierce et al., 2007) with 5, 525 breast cancer patients, it indicated that women in post-diagnostic low-fat diet group had a 23% (HR=0.77, 95%CI 0.63 to 0.94, *P*=0.009) statistically significant lower risk of recurrence than women in high-fat diet group. All the three studies (Chlebowski et al., 2006; Pierce et al., 2007; Beasley et al., 2011) evaluated the association between prost-diagnostic low-fat diet and all-cause mortality of breast cancer, and 9, 966 breast cancer patients were included in this report. Though the effect of post-diagnostic low-fat diet on all-cause mortality of breast cancer has no statistical significance (*P*=0.05), the result still suggested a trend that post-diagnostic low-fat diet could reduce 17% risk of all-cause deaths compared to high-fat diet, and which need more studies to confirm.

The current meta-analysis has much strength. Firstly, it is the only attempt to try to conduct a meta-analysis about the the effect of post-diagnostic low-fat diet on breast cancer survival. Then, it combined the results of existing studies and made the results more practical. In this way, it reduced the effect of publication bias. Moreover, the meta-analysis included so many samples that made the result more trustable. Additionally, the results are encouraging and it can be a new direction for doctors to manage breast cancer survivors. The diet management is so convenient that every breast cancer patient could have a try and it may change their breast cancer outcome.

On the other hand, some limitations may occur in this meta-analysis. First of all, the measurement of dietary fat intake used different methods. The WINS (Chlebowski et al., 2006) used diet records (Winters et al., 2004), the WHELS (Pierce et al., 2007) used 24-hour dietary recalls and the CWLS (Beasley et al., 2011) used food frequency questionnaire (FFQ) (Willett et al., 1985). As a result, it may lead to various degrees of measurement bias of dietary fat intake and make results difficult to compare across studies.

What's more, the three studies fit a Cox proportional hazards model to adjusted the factors that can influence the effect of post-diagnostic low-fat diet on breast cancer survival. The covariates of the WINS (Chlebowski et al., 2006) were ER status, tumor size, surgery type. The WHELS (Pierce et al., 2007) contained stage of disease, age, hormone receptor characteristics of initial tumor and body mass index. The CWLS (Beasley et al., 2011) included age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, history of hormone replacement therapy, energy intake, breast cancer treatment, body mass index, and physical activity metabolic equivalents. Then the bias occurred inevitably when we combined the all data.

In conclusion, this meta-analysis provides supporting evidence for a beneficial effect of post-diagnostic low-fat diet on breast cancer survival. Now, more and more diet intervention studies are ongoing in breast cancer survivors, such as ENERGY (Rock et al., 2012), SUCCESS-C (Rack

et al., 2010) and DIANA-5 (Villarini et al., 2012). We are looking forward to the results of this studies and then we will update our meta-analysis to direct the diet intervention of breast cancer survivors.

References

Am. Cancer Soc (2012). Cancer Facts & Figures 2012. Atlanta, GA: Am. Cancer Soc. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf.

Am. Cancer Soc (2013). Survival Rates for Breast Cancer. Atlanta, GA: Am. Cancer Soc. http://www.cancer.org/Cancer/BreastCancer/OverviewGuide/breast-cancer-overview-survival-rates.

Beasley JM, Newcomb PA, Trentham-Dietz A, et al (2011). Post-diagnosis dietary factors and survival after invasive breast cancer. *Breast Cancer Res Treat*, **128**, 229-36.

Borugian MJ, Sheps SB, Kim-Sing C, et al (2004). Insulin, macronutrient intake, and physical activity: Are potential indicators of insulin resistance associated with mortality from breast cancer? *Cancer Epidemiol. Biomarkers Prev*, **13**, 1163-72.

Chlebowski R, Blackburn GL, Thomson CA, et al (2006). Dietary fat reduction and breast cancer outcome: interim efficacy results for the Women's Intervention Nutrition Study (WINS). *J Natl Cancer Inst*, **98**, 1767-76.

Cochran WG (1954). The combination of estimates from different experiments. *Biometrics*, **10**, 101-29.

Dal Maso L, Zucchetto A, Talamini R, et al (2008). Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer*, **123**, 2188-94.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.

Ewertz M, Gillanders S, Meyer L, Zedeler K (1991). Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. *Int. J. Cancer*, 49, 526-30.

Goodwin PJ, EnnisM, Pritchard KI, et al (2003). Diet and breast cancer: evidence that extremes in diet are associated with poor survival. *J Clin Oncol*, **21**, 2500-7.

Higgins JP et al (2003). Measuring inconsistency in meta-analyses. *BMJ*, **327**, 557-60.

Holmes MD, Stampfer MJ, Colditz GA, et al (1999). Dietary factors and the survival of women with breast carcinoma. *Cancer*, **86**, 826-35.

Jain M, Miller AB, To T (1994). Premorbid diet and the prognosis of women with breast cancer. *J Natl Cancer Inst*, **86**, 1390-7.

Kruk J, Marchlewicz M (2013). Dietary fat and physical activity in relation to breast cancer among Polish women. *Asian Pac J Cancer Prev*, **14**, 2495-502.

Kushi LH, Doyle C, McCullough M, et al (2012). American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*, **62**, 30-67.

McEligot AJ, Largent J, Ziogas A, et al (2006). Dietary fat, fiber, vegetable, and micronutrients are associated with overall survival in postmenopausal women diagnosed with breast cancer. *Nutr Cancer*, **55**, 132-40.

Mirzayi BR (2013). Dietary phytochemical index and the risk of breast cancer: a case control study in a population of Iranian women. *Asian Pac J Cancer Prev*, **14**, 2747-51.

Newman SC, Miller A, Howe GR (1986). A study of the effect of weight and dietary fat on breast cancer survival time. *Am J Epidemiol*, **123**, 767-74.

Nomura A, Le Marchand L, Kolonel LN, Hankin JH (1991). The effect of dietary fat on breast cancer survival among Caucasian and Japanese women in Hawaii. *Breast Cancer Res*, **18**, 135-41.

Parmar MK, Torri V, Stewart L (1998). Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*, **17**, 2815-34.

Pierce JP, Natarajan L, Caan BJ, et al (2007). 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*, **298**, 289-98.

Rack B, Andergassen U, Neugebauer J, et al (2010). The German SUCCESS C Study–the first European lifestyle study on breast cancer. *Breast Care*, **5**, 395-400.

Rock CL, Byers TE, Colditz GA, et al (2012). Reducing breast cancer recurrence with weight loss, a vanguard trial: The Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Trial. *Contemp Clin Trials,* **34**, 282-95.

Rohan TE, Hiller JE, McMichael AJ (1993). Dietary factors and survival from breast cancer. *Nutr Cancer*, **20**, 167-77.

Saxe GA, Rock CL, Wicha MS, et al (1999). Diet and risk for breast cancer recurrence and survival. *Breast Cancer Res Treat*, **53**, 241-53.

Sangrajrang S, Chaiwerawattana A, Ploysawang P, et al (2013). Obesity, diet and physical inactivity and risk of breast cancer in Thai women. *Asian Pac J Cancer Prev*, **14**, 7023-27.

Villarini A, Pasanisi P, Traina A, et al (2012). Lifestyle and breast cancer recurrences: the DIANA-5 trial. *Tumori*, **98**, 1.

Willett WC, Sampson L, Stampfer MJ, et al (1985). Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*, **122**, 51-65.

Winters BL, Mitchell DC, Smiciklas-Wright H, et al (2004). Dietary patterns in women treated for breast cancer who successfully reduce fat intake: the Women's Intervention Nutrition Study (WINS). *J Am Diet Assoc*, **104**, 551-9.

Zhang S, Folsom AR, Sellers TA, et al (1995). Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. *Cancer*, **76**, 275-83.