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Effect of dietary patterns on the prognosis of breast cancer patients

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Abstract. Breast cancer (BC) is a serious threat to women's health. Higher BC risk is allegedly related to personal lifestyle like diet. However, it is still unclear how dietary quality affect BC survivors. This meta-analyse aimed to figure out it. The highest and lowest categories of healthy and unhealthy dietary patterns were compared by using the random-effects meta-analyses, which combined relative risks (RRs) and 95% confidence intervals (CIs) that were multivariable-adjusted. 11 eligible articles, including two RCTs, three case-control studies, and six cohort studies, were found and included in this paper after they met the inclusion criteria. According to the pooled analyses, when compared to the lowest group, women with the highest quality healthy diet (highest quintile/quartile/tertile) had 24% lower risk of overall death(random effects (RR = 0.76; 95%CI = 0.67-0.86), 16% lower risk of BC specific death (random effects (RR = 0.84; 95%CI = 0.75-0.94), 28% lower risk of No-BC death (random effects (RR = 0.72; 95%CI = 0.63-0.83),and 4% higher risk of recurrence (random effects (RR = 1.04; 95%CI = 0.97-1.12). According to our meta-analysis, consuming a high-quality healthy diet was linked to a lower risk of all-cause death. The results could have significant effects on encouraging the use of daily dietary treatment regimen to benefit breast cancer patients. To achieve better long-term survival and better quality of life for BC patients, definitively establishing effective interventions will necessarily require further researches.

Keywords: breast cancer, dietary pattern, food, survival, recurrence.

1. Introduction

Breast cancer (BC), which will account for 11.7% of all cases in 2020, will be the most prevalent type of cancer diagnosed in women. Additionally, it is the main reason for cancer deaths globally [1]. In the United States, it is anticipated that in 2022 there will be around 51,400 new cases of ductal carcinoma in situ (DCIS) , about 287,850 new reported incidents of invasive BC and around 43,250 women die from BC [2].

The extensive screening, advances in early detection, and efficient treatment of BC have all contributed, at least partially, to a significant decline in the disease's mortality rate over the past 40 years [3]. Over the past few decades, parallel to the increasing number of new BC patients, the proportion of BC survivors has also grown.

In developed countries, 90% of BC patients can survive for at least 5 years, and long-term survival is common [4,5]. Around 6.9 million female BC survivors lived in the world in 2018, comprising nearly

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one-sixth of all-cancer sufferers [6]. As the number of BC survivors increases and medical treatment is optimized, more attention is being paid to self-intervention and the desire to improve the quality of BC survivors' lives. Many studies have shown links between lifestyle behaviors, including diet and exercise, and the risk of BC [7-9]. A different point of view suggests that a higher-quality diet may improve the prognosis of BC patients. The 2007 WCRF report came up with the conclusion that there wasn't sufficient data to make any decision regarding the connection between eating habits and the risk of BC [10]. However, a few studies showed that high-quality dietary habits can improve BC prognosis in the past few years. Chlebowski et al, suggested that lowering dietary fat consumption might increase the likelihood that BC patients receiving conventional cancer treatment will survive without relapsing [10]. According to the research by Jang, anti-inflammatory diet pattern may reduce the risk of BC recurrence and all-cause death [11].

Nowadays, in order to improve the prognosis of BC survivors, a number of dietary guidelines have been developed. The American Cancer Society recommends eating more vegetables and fruits (5-9 servings daily) and low fat (less than 30% of total energy) is a healthy balanced eating pattern.The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) suggests a higher intake of foods containing fiber and soy to lower the risk of all-cause death of BC patients by reviewing a continuous update project [12-24]. In addition to these, anti-inflammatory diets, Mediterranean diets, etc. are also demonstrated to offer a better prognosis [25-27].

However, due to the difficulty of measuring adherence to dietary guidelines, some studies only have a small sample size, making it hard to obtain a more statistically significant result. Additionally, many research has just concentrated on the impact of one dietary pattern on BC patients. As a result, it is still unclear how crucial a high-quality diet is to long-term survival in BC. Moreover, with a limited sample size and following-up period, survival outcomes other than overall survival, such as BC-specific mortality or recurrence, were rarely studied, which may cause some limitations in determining the overall prognostic impact.

Therefore, we aim to categorize a variety of diets as both healthy and unhealthy and use a meta-analysis to relatively more comprehensively investigate the relationship between dietary patterns and long-term BC survival, including BC-specific death, recurrence, all-cause death and Non-BC death.

2. Methods

2.1. Search strategy

The relevant literature search was performed using the electronic database PubMed up to February 2022, with the following key words: Cancer of Breast, Breast Tumor, and Dietary Pattern.

2.2. Study selection

Studies were eligible to be included if:

(i)The study population consisted of women diagnosed with breast cancer,

(ii)The study design is cohort or case-control or RCT design,

(iii)The exposure of interest was the commonly used dietary patterns, including both priori indices (e.g., diet quality scores) and patterns derived from posteriori methods, (e.g., principal component analysis (PCA))

(iv)The primary outcomes of interest were BC-specific death, recurrence, all-cause death and/or Non-BC death,

(v)All BC cases, including those with in situ or invasive cancer, were identified and confirmed to be cases of BC by using pathologic biopsy or other accepted techniques, and

(vi) Relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) with corresponding 95% CI. Following the literature search, studies were screened, and the non-relevant ones were excluded: 1) cross-sectional studies 2) Studies with weight loss or behavioral changes as endpoints, and 3). studies about supplements, individual nutrients or foods.

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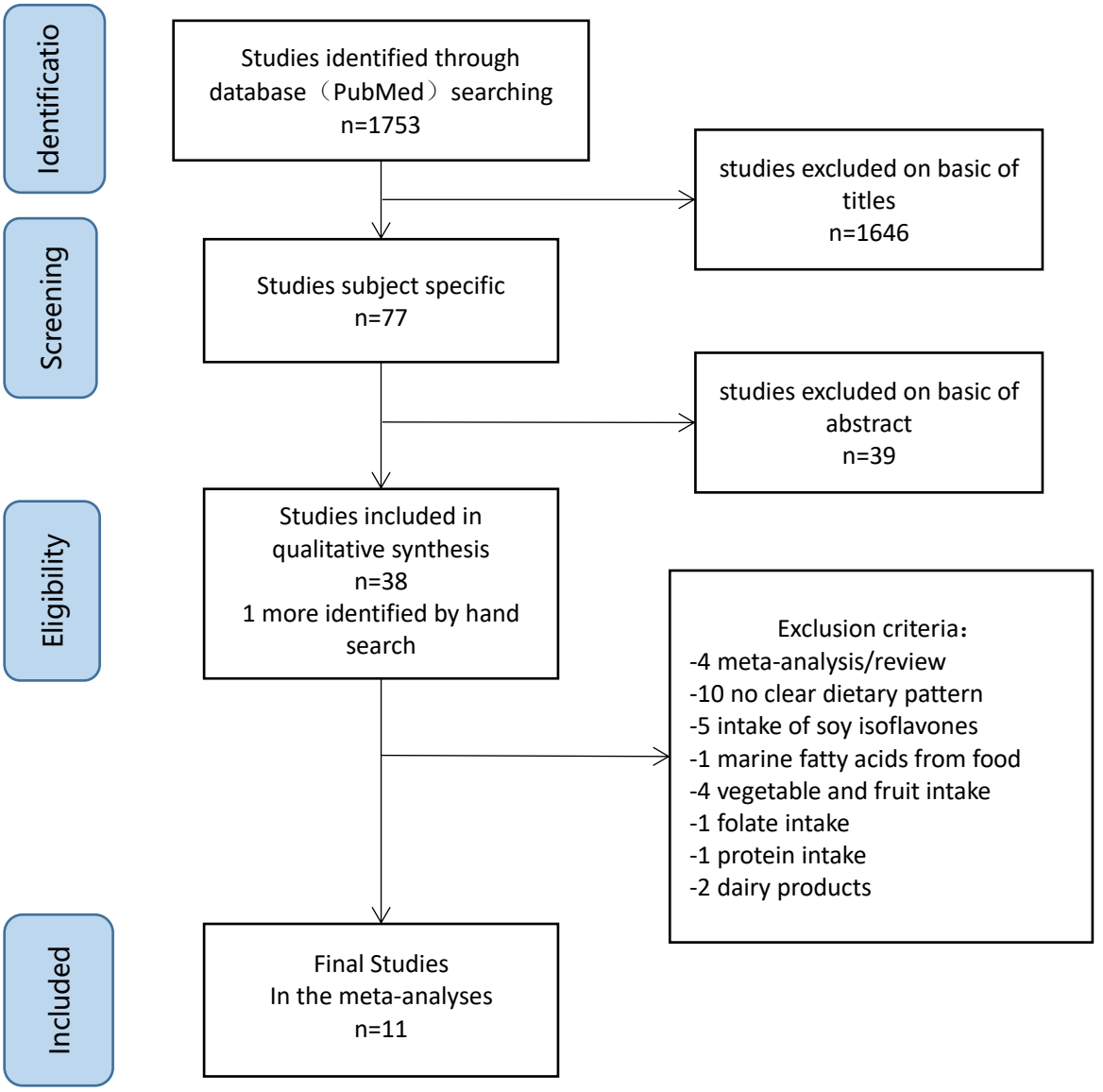

Figure 1. Literature screening process and results.

2.3. Data extraction

Data include data of the author, published year and area, study design, number of study subjects, age, follow-up duration, outcome, dietary pattern studied and recall method used, adjustment factors, and the reported measure hazard ratio (HR) with the 95% confidence intervals (CIs) for the association of dietary pattern with the outcomes of interest. We considered the assumptions for the highest vs the lowest level of the categories of a dietary pattern that was utilized in each study (tertile/quartile/quintile).

2.4. Quality assessment

We also conducted systematic assessments of each study's quality. With regards to particular nutrition-relevant requirements, such as dietary assessment approaches and their verification, food recall collection method, or the evaluation of diet-related biological markers, NutriGradewas is used to evaluate the quality of the collected studies. The planning phase, the design and development phase, and the validation phase made up the three stages of the development of NutriGrade. Nine items were ultimately selected for the NutriGrade scoring system. The NutriGrade scoring system has 8 items for

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meta-analyses of cohort studies and 7 items for meta-analyses of RCTs. The modified classification for RCT and cohort study meta-analyses is NutriGrade's most significant benefit. NutriGrade is based on clear instructions and a checklist-like assessment. The evaluation results are presented in Table 2.

2.5. Statistical analysis

We used the RevMan 5.4.1 analysis software (The Cochrane Collaboration, Copenhagen, Denmark) to extract and combine data for meta-analysis. X2 statistics and I^2 statistics were used to estimate statistical heterogeneity [28]. In this meta-analysis, we chose random effect models rather than fixed effect models due to the statistical heterogeneity. The random effects model was used to take into account both within-study and between study variations. Utilizing Q and I2 statistics, the heterogeneity among the studies was evaluated. I^2 values over 50% or P-values of < 0.05 indicated significant heterogeneity.

we divided all dietary patterns into two categories:

a) healthy dietary pattern (DP), including low-fat DP, prudent DP, healthy DP, Mediterranean DP, healthy plant-based dietary index (hPDI), American Cancer Society nutrition guidelines (ACS) DP, alternate Mediterranean (aMED) DP, Dietary Approach to Stop Hypertension (DASH) DP, 2015 Healthy Eating Indexn (2015HEI) DP and diabetes risk reduction diet (DRRD),

b) unhealthy dietary pattern, which refers to an unhealthy DP, western DP, unhealthy plant-based (uPDI) DPand pro-inflammatory DP.

3. Results

3.1. Study characteristics

Figure 1 shows the flow diagram of the study selection process. In the end, eleven studies reached the inclusion criteria and were included in this meta-analysis (Table 1)， including two RCTs with a total of 5, 525 BC female patients, three case-control studies with 5428 BC female patients, and six cohort studies with 19,426 BC female patients. The articles were published between 2006 and 2021, and most studies were carried out in U.S, Italy, Chin, and Korea. The number of studies' sample sizes ranged from 511 to 8,482. Dietary intake was estimated by using FFQ in 8 studies and diet recall questionnaire in 3 studies. A wide variety of potential confounding factors were adjusted, including the age when they are interviewed, the age when they got cancer, age of their first birth, body mass index (BMI), smoking and alcohol consumption, physical activity, energy intake, family history of BC, whether they use hormone, and BC status. The methodological quality of the included studies were shown in Table 2. All the studies except two RCTs all got a nice and similar score. Therefore, the weights of the data in the study were calculated in terms of the number of people. BC events of recurrence or new primary BC and all-cause death were the study's endpoints.

Table 1. General characteristics of prospective studies included in meta-analysis.

Autho, year, location	Definition of breast cancer cases, stage	study design	Outcome	Numbers, age range, follow-up duration	exposure	DP assessment tools	Summary of results

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Table 1. (continued).

Kwan et al, 2009, Northern California	invasive breast cancer	cohort	all-cause death, BC-specific death, Non-BC death	1901, 18-79 years,, follow-up=8 years	Prudent DP, Western DP	questionnaires	for prudent DP, recurrence :HR Q4 vs Q1=0.95; 95% CI, 0.63-1.43; P trend = 0.94 BC-specific death:HR Q4 vs Q1=0.79; 95% CI, 0.43-1.43; P trend = 0.57 for western DP，recurrence:HR Q4 vs Q1=0.98; 95% CI, 0.62-1.54; P trend = 0.94 BC-specific death :HR Q4 vs Q1=1.20; 95% CI, 0.62-2.32; P trend =0.60
Vrieling et al, 2013, U.S. sites and Shanghai, China	primary invasive (stage I to IV)	case–control	all-cause death, BC-specific death, Non-BC death	2522, 50-74 years, follow-up=5-8 years	Healthy DP Unhealthy DP	questionnaires	Healthy DP recurrence :HR Q4 vs Q1=0.84; 95% CI, 0.59-1.21; P trend = 0.11 BC-specific death :HR Q4 vs Q1=0.73; 95% CI, 0.51-1.05; P trend = 0.04 Unhealthy DP recurrence :HR Q4 vs Q1=1.20; 95% CI, 0.85-1.70; P trend = 0.32 BC-specific death :HR Q4 vs Q1=1.06; 95% CI, 0.74-1.50; P trend = 0.44
Chlebowski R et al. 2006 , US	resected, unilateral invasive breast cancer	RCT	recurrence	2437, 48-79 years, follow-up=median 60 months	Low-fat DP	Visits, calls, questionnaires	Recurrence HR = 0.76; 95% CI = 0.60-0.98, P = 0.34
Pierce JP et al. 2007, US	a primary operable invasive breast cancer	RCT	recurrence,all-cause death	3088, 18-70 years, follow-up=7.3 years	Low-fat DP	calls	BC Event-Free Survival HR =0.96 (95% CI, 0.80-1.14; P=.63) overall death HR =0.91 (95% confidence interval, 0.72-1.15; P=.43)

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Table 1. (continued).

Jang et al, 2018, Korean	(stage0-3)breast cancer	cohort	recurrence,all-cause death	511, 51.9± 10.7 years follow-up=213 months	Pro-flammatory DP	questionnaires	Recurrence: HR T3 vs T1=2.371; 95% CI, 1.17-4.71; P = 0.019 overall death: HR T3 vs T1=3.049; 95% CI, 1.08-8.83; P= 0.041
Zucchetto, A. et al. 2017, Italy	breast cancer	case–control	all-cause death, BC-specific death,	1453,23-74 years , follow-up=12.6 years	Prudent DP, Western DP	questionnaires	All-cause death: HR T3 vs T1=1.00; 95% CI,0.78-1.28; P = 0.95 BC-specific death:HR T3 vs T1=0.97; 95% CI, 0.73-1.27; P= 0.86
Ergas et al, 2021, Kaiser Permanente Northern California (KPNC)	invasive breast cancer	cohort	recurrence,all-cause death, BC-specific death, Non-BC death	3660, more than 21years, follow-up=14 years	ACS aMED DASH 2015 HEI	questionnaires	BC-specific death ACS: HR Q5 vs Q1=0.75; 95% CI, 0.52-1.09; P = 0.29 aMED:HR Q5 vs Q1=0.79; 95% CI, 0.54-1.16; P = 0.25 DASH:HR Q5 vs Q1=0.93; 95% CI, 0.63-1.39; P= 0.68 2015HEI:HR Q5 vs Q1=0.84; 95% CI, 0.56-1.27; P= 0.44
Lei et al, 2021, Hong Kong	early-stage invasive breast cancer	cohort	all-cause death, BC-specific death,	1226, more than 21years, follow-up=15.4 months	Western DP Healthy DP	questionnaires	For Western DP recurrence :HR T3 vs T1=0.88; 95% CI, 0.58-1.33; P= 0.52 BC-specific death: HR T3 vs T1=0.79; 95% CI, 0.46-1.35; P = 0.38 For Healthy DP recurrence: HR T3 vs T1=0.88; 95% CI, 0.59-1.30; P= 0.50 BC-specific death: HR T3 vs T1=1.23; 95% CI, 0.67-1.88; P = 0.67
Wang et al, 2021, U.S.	stage I-III breast cancer	cohort	all-cause death, BC-specific death,	8482, 25-55 years follow-up= 25 years	diabetes risk reduction diet (DRRD)	questionnaires	BC-specific mortality (Q5 VS Q1 HR = 0.80; 95% CI = 0.65-0.97; P (trend) = 0.02)

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Table 1. (continued).

Anyene et al, 2021, KPNC	invasive breast cancer	cohort	recurrence,all-cause death,	3646, 25-79 years,, follow-up=14 years	Plant-based DP	questionnaires	PDI recurrence: HR :1.13; 95% CI: 0.97-1.33; BC-specific mortality:HR :1.03; 95% CI: 0.85-1.24;
Di et al, 2020, Italy	breast cancer	case–control	all-cause death, BC-specific death,	1453, 23-78 years follow-up=12.6 years	Mediterranean diet;	questionnaires	BC-specific mortality HR :0.83; 95% CI: 0.62-1.11;

Table 2. The result of using NutriGradewas to assess the study quality.

Author，Year,	Risk of bias assessment of cohort studies (0–2 points)	Assessing precision in NutriGrade (0–1points)	Assessment of directness (0–1 points)	Assessment of publication bias (0–1 points)	Assessing funding bias in meta-analyses (0–1 points)	Scoring for effect size based on risk estimates (0–2points)	Scoring dose-response analysis (0–1 points)	Final score
Kwan et al, 2009,	1.25	1	1	1	1	2	0	7.25
Vrieling et al, 2013,	1.5	1	1	1	1	2	0	7.5
Chlebowski R et al, 2006	1.5	1	0	1	1	/	/	4.5
Pierce JP et al. 2007	1.5	1	0	1	1	/	/	4.5
Jang et al, 2018,	2	1	1	1	1	2	0	8
Zucchetto, A. et al. 2017,	2	1	1	1	1	0	0	6

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Table 2. (continued).

Ergas et al, 2021,	2	1	1	1	1	1	0	7
Lei et al, 2021,	1.5	1	1	1	1	1	0	6.5
Wang et al, 2021,	2	1	1	1	1	2	0	8
Anyene et al, 2021,	2	1	1	1	1	1	0	7
Di et al, 2020,	2	1	1	1	1	2	0	8

3.2. healthy dietary pattern and BC prognosis

The results of this meta-analysis for all types of healthy dietary patterns with recurrence, overall death, BC specific death and No-BC death among breast cancer survivors(As shown in 2-6). Comparing with the lowest group, female patients with the highest quality healthy diet (highest quintile/quartile/tertile) had 24% lower risk of overall death(random effects (RR = 0.76; 95%CI = 0.67-0.86; I^2=76%), 16% lower risk of BC specific death (random effects (RR = 0.84; 95%CI = 0.75-0.94; I^2=44%), 28% lower risk of No-BC death (random effects (RR = 0.72; 95%CI = 0.63-0.83; I^2=44%),and 4% higher risk of recurrence (random effects (RR = 1.04; 95%CI = 0.97-1.12; I^2=0%). There was no evidence of asymmetry in the funnel plots, but evidence of significant heterogeneity(I^2=76% ; P(het) ＜0.0001) was observed.

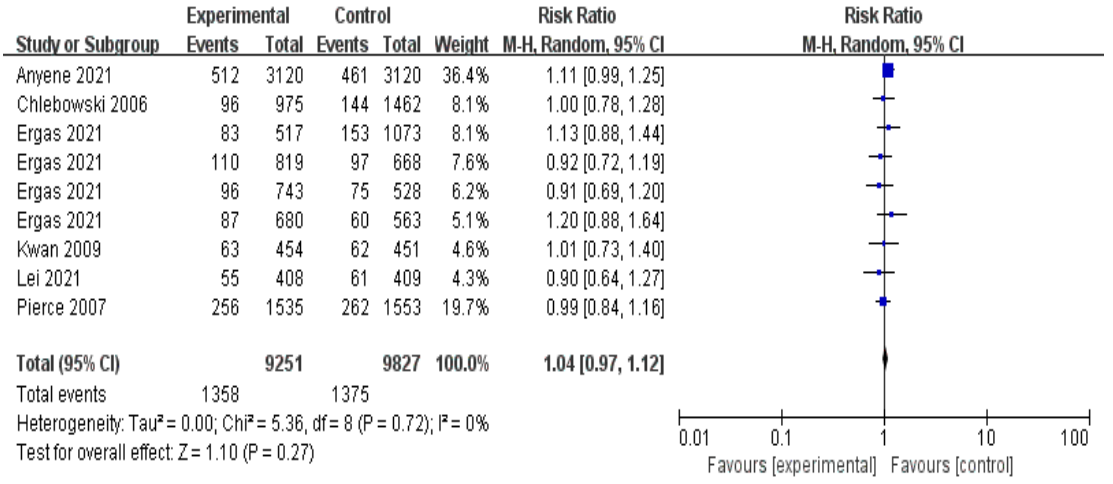

Figure 2. Relationship between healthy dietary patterns and risk of breast cancer. Recurrence.

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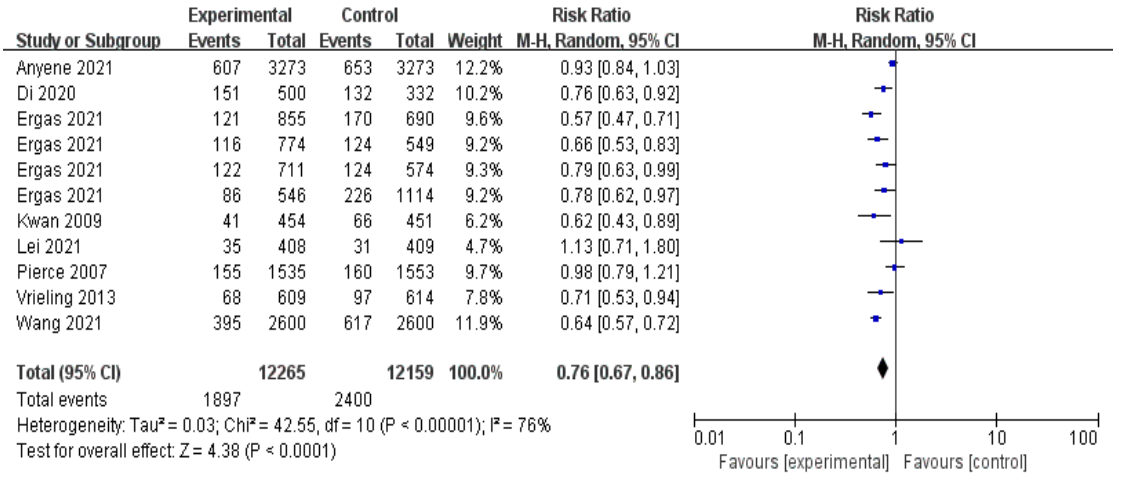

Figure 3. Relationship between healthy dietary patterns and risk of overall death.

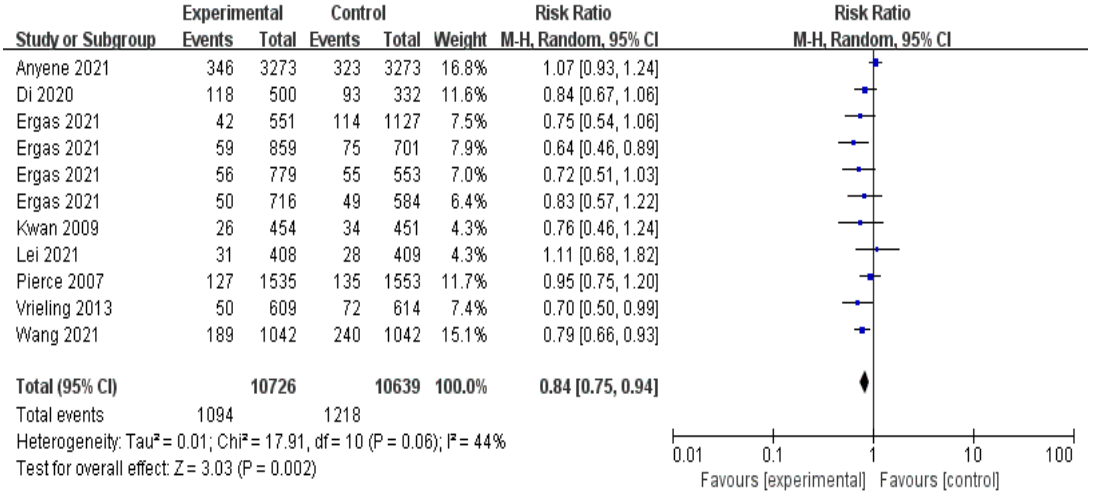

Figure 4. Relationship between healthy dietary patterns and risk of BC-specific death.

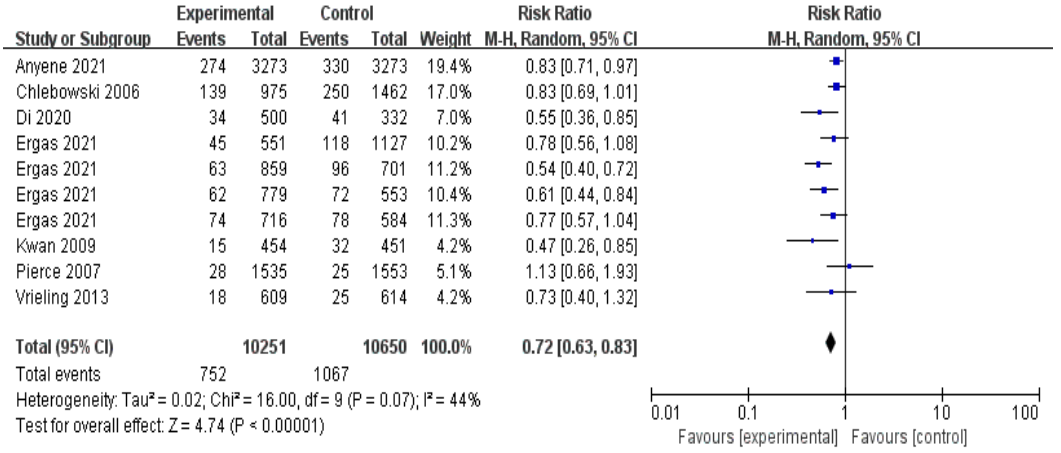

Figure 5. Relationship between healthy dietary patterns and the risk of Non-BC death.

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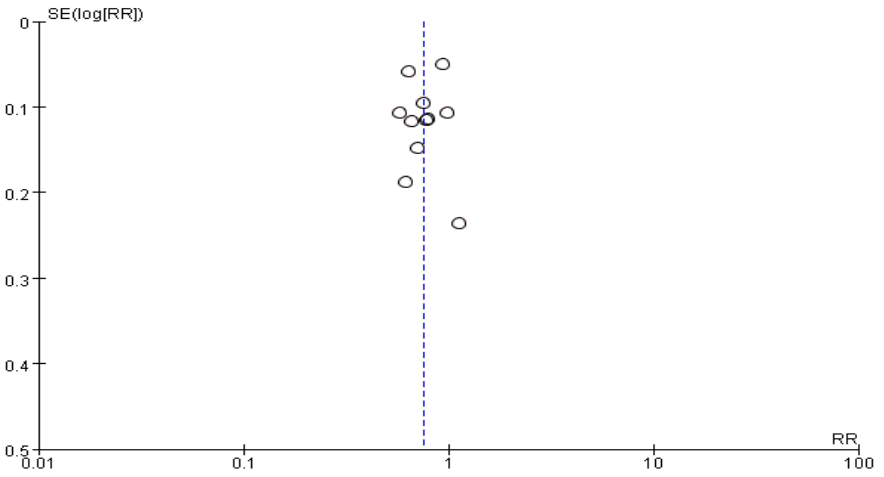

Figure 6. The publication bias of healthy dietary patterns.

3.3. Unhealthy dietary pattern and BC prognosis

Less data available on unhealthy dietary patterns. Fig 6-10.shows the results of the meta-analysis for these unhealthy dietary patterns. Women with poor quality healthy diet (highest quintile/quartile/tertile) had 13% higher risk of recurrence (random effects (RR = 1.13; 95%CI = 0.83-1.53; I^2=76%), 10% higher risk of overall death (random effects (RR =1.10; 95%CI = 0.94-1.29; I^2=55%) , 63% higher risk of No-BC death(random effects (RR =1.63; 95%CI = 0.96-2.75; I^2=55%) and 6% lower risk of BC specific death (random effects (RR = 0.94; 95%CI = 0.85-1.05; I^2=72%),which was nonsignificant. In the funnel plots, no evidence of asymmetry has been found, but evidence of significant heterogeneity(I^2=76% P(het) ＜0.0001) was observed.

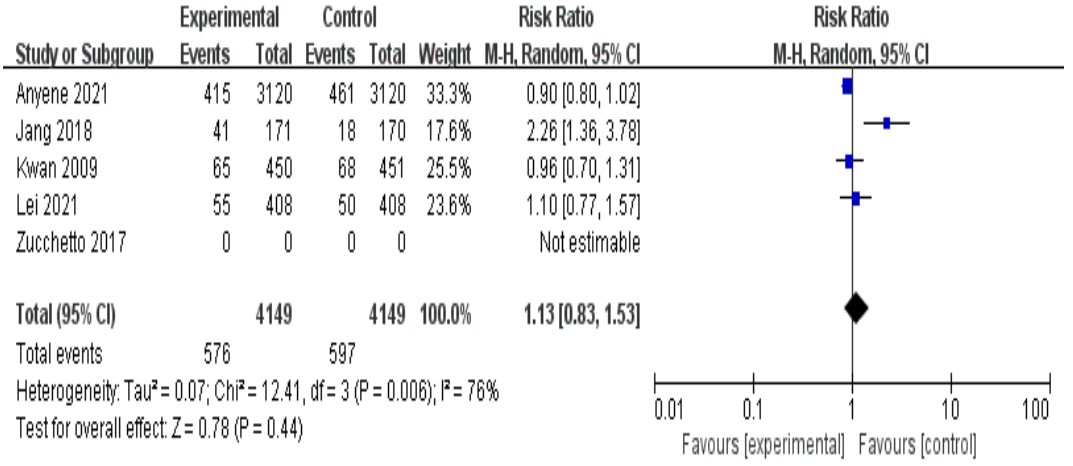

Figure 7. The relationship between unhealthy dietary patterns and the risk of breast cancer recurrence.

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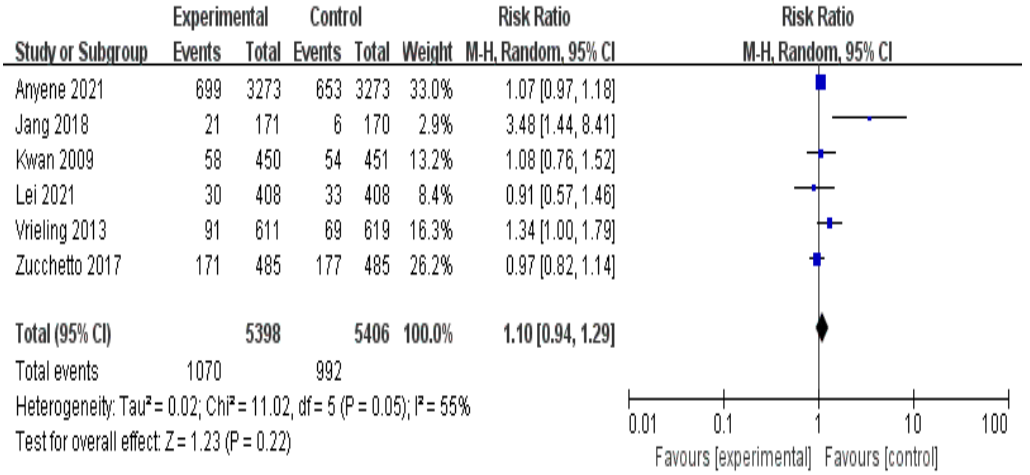

Figure 8. The relationship between unhealthy dietary patterns and the risk of overall death.

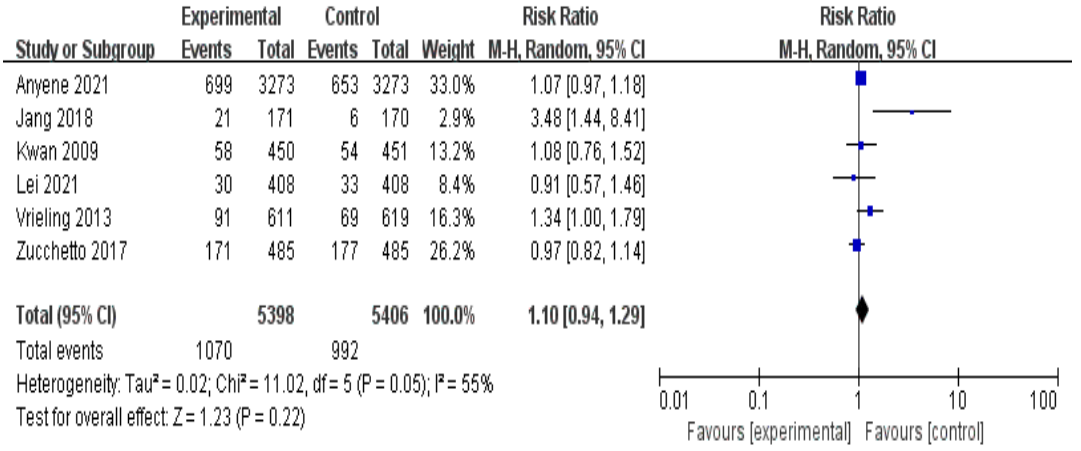

Figure 9. The relationship between unhealthy dietary patterns and the risk of BC-specific death.

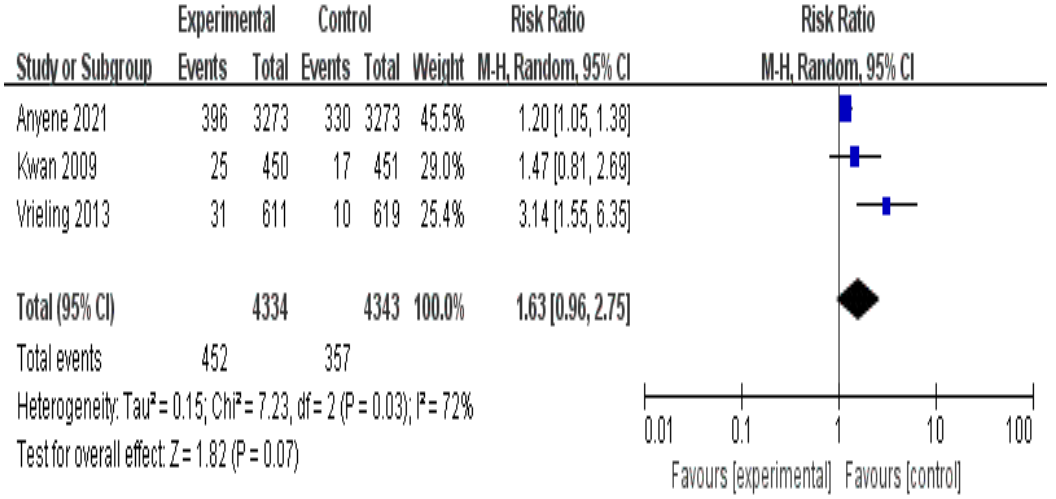

Figure 10. The relationship between unhealthy dietary patterns and the risk of No-BC death.

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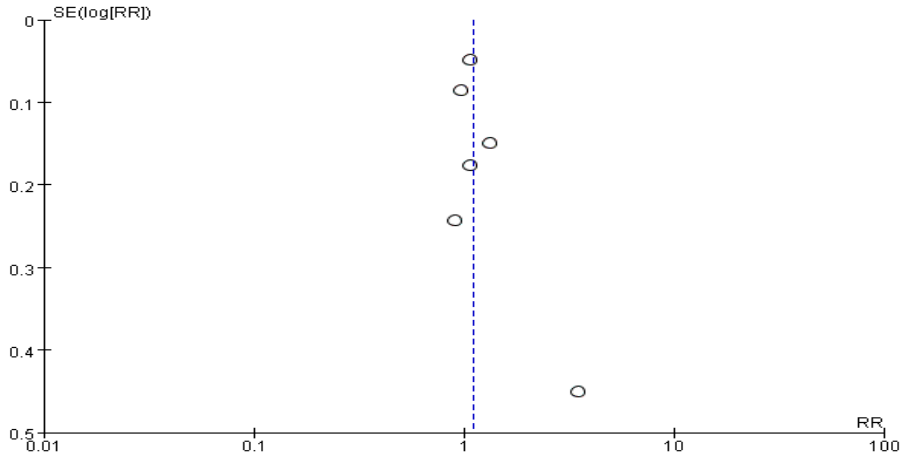

Figure 11. Funnel plot shows the publication bias of unhealthy dietary patterns.

4. Discussion

Through screening, a total of 11 studies, two RCTs, three case-control studies, and six cohort studies, met the inclusion criteria and were included in this meta-analysis. The result indicated that women with the highest quality healthy diet had a 24% statistically significant lower risk of overall death than those with poor quality healthy diet. Even though the effect of other outcomes did not have any statistical significance, the result still suggested a trend that high-quality healthy dietary pattern could reduce the BC risk compared to low-quality healthy diet. However, more research is needed to verify this. In addition to this, the result shown that women with unhealthy dietary pattern had a 10% statistically significant higher risk of overall death than women with better quality healthy diet. The unhealthy dietary pattern also caused higher risk of recurrence and Non-BC death, which was nonsignificant. Although there is a high degree of heterogeneity in this study, I believe it is still relevant.

First and foremost, there is abundant evidence that environmental factors will influence the incidence of BC [29]. The nature of environmental influences can be partially explained by the differences in reproductive practices, such as the timing of the birth of the first child and how many children she have. [30]. An additional or alternative explanation is differences in nutrition. Dietary fat and calories have been shown in animal experiments to promote BC, both naturally and experimentally [31]. Numerous studies also demonstrate that certain nutrients and diets, such as fatty acids, carbohydrates, vitamins B and D, carotenoids and fiber, have an effect on BC risk, and evidence supports a mechanistic explanation for how certain nutrients affect it. Data from the published studies suggested a healthy dietary pattern, consisting of a high consumption of unrefined cereals, fruits, vegetables, nuts, and olive oil and a moderate or low intake of red meat and saturated fatty acids, might increase BC patients' overall survival [32]. However, these studies have resulted in some contradictory findings, and it is still unsure how diet quality affects BC recurrence and mortality [33].

To find out if a healthy dietary pattern (DP) really leads to a better prognosis for breast cancer patients, we conducted this analysis. We summarized the current evidence about the effect of different dietary patterns on recurrence, all-cause death, BC-specific death and Non-BC death among BC survivors. According to a previous study, we category dietary patterns as healthy or unhealthy in this report. Healthy dietary pattern, including low-fat DP, prudent DP, healthy DP, Mediterranean DP, healthy plant-based dietary index (hPDI), American Cancer Society nutrition guidelines (ACS) DP, alternate Mediterranean (aMED) DP, Dietary Approach to Stop Hypertension(DASH) DP, 2015 Healthy Eating Index(2015HEI) DP and diabetes risk reduction diet(DRRD). And unhealthy DP, which refers to an unhealthy DP, western DP, unhealthy plant-based(uPDI) DP and pro-inflammatory DP. This meta-analysis, including 11 observational studies, which totally included 30,379 cases of BC, supports a positive association between unhealthy DP and the risk of developing BC and an inverse association

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between a healthy DP and the risk.

The current meta-analysis has several strengths. Then, the results were combined with earlier studies to make them more applicable. Our meta-analysis also had more statistical power to identify a strong connection between the unhealthy DP and BC risk and to determine a more accurate estimate for the healthy DP and BC association because it included more studies and BC cases than the previous meta-analysis. Additionally, the findings are positive, and they may represent a novel approach for medical professionals managing and researching BC survivors. Every BC patient can easily try diet management in their daily lives to get a better breast cancer prognosis because it is so convenient.

On the other hand, this meta-analysis still have some limitations. First, the current meta-analysis included two RCTs, three case-control studies and six cohort studie. Therefore, the possibility of recall bias cannot be completely ruled out, which may be related to the different intake recall methods between cases and controls. At the same time, the tendency of control group selection bias in case-control studies also cannot be completely precluded. And there are too few data and information on how unhealthy dietary pattern affect the BC patients. All of these could lead to biased results. Second, even though all of these studies used a Cox proportional hazards model to adjust the lifestyle and other factors that may potentially confound the effect of healthy diet on BC survival, unmeasured and uncontrolled confounding is always a problem in epidemiological studies. And, it will also contribute to the inevitable bias that resulted from combining all the data. Third, we broadly classified dietary patterns into healthy and unhealthy categories, but in fact we cannot conclude whether what we consider to be a healthy diet is necessarily beneficial to the prognosis of breast cancer patients, so there may have been a bias in combining all the data. Fourth, diet records, 24-hour dietary recalls and FFQ were used to evaluate intake and dietary patterns in the studies. Therefore, the findings from various studies may it hard to compare and measurement bias of dietary fat intake may occur to varying degrees. Additionally, even though the reproducibility and validity of these methods were reported, the factor analysis and/or principal component analysis may still exhibit some level of variability. As a final point, the data are highly heterogeneous. In fact, in the funnel plot, we can see that the data we obtained already has a certain publication bias, and the exposure of the population itself is different in different cohorts so that it also brings different effects. All these make it difficult to eliminate this high heterogeneity. The heterogeneity of the unhealthy eating pattern is more pronounced, I think it is because there are relatively fewer data and the population of cohort included in the data varies a lot, so the heterogeneity is more pronounced. This is one of the most obvious problems with this meta-analysis.

So, we need more future researches to get a more accurate and conclusive result. First, the existing outcome data are more about the overall mortality, but there are many causes of death in BC patients, which does not accurately determine the influence of dietary pattern on the prognosis of BC patients so that more recurrence and BC-specific death data should be collected. Secondly, studies on unhealthy dietary patterns are generally scarce, which is not conducive to analysis and makes it difficult to came to a conclusion clearly.

In summary, our meta-analysis found that high-quality healthy dietary guidelines was associated with lower risk of both overall deaths, BC-specific death and no-BC death. As diet is potentially modifiable, the findings may have significant implications for promoting the use of dietary patterns to help BC survivors.

5. Conclusion

By dividing dietary patterns into healthy and unhealthy categories and using meta-analysis to analyze them, we found that high-quality healthy dietary pattern was significantly associated with improved overall survival of breast cancer. This analysis included a larger sample and four endpoints than previous studies that were limited to one or two dietary patterns with a smaller population so that it showed the huge impact of diet quality on the prognosis of breast cancer patients more clearly. This can help promote the use of high-quality diets to improve the survival of BC patients. Considering the limitations, further studies with larger sample size, more similar dietary recall methods, well-controlled confounding factors are warranted.

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