National Institute for Health and Care Excellence

Final

Early and locally advanced breast cancer: diagnosis and management

[K] Evidence reviews for lifestyle

NICE guideline NG101

Evidence reviews

July 2018

Final

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Lifestyle

This evidence report contains information on 1 review relating to lifestyle.

- Review question 11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?

Review question 11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?

Introduction

Survival rates in breast cancer are steadily improving thanks to earlier detection, better diagnostics and treatments. However, data is now emerging regarding the impact of lifestyle choices on outcomes following treatment for breast cancer.

Disease recurrence, survival and emotional well-being are all potentially affected by the lifestyle choices and changes people make following treatment for breast cancer. It is important that people can be advised and informed of the evidence-based benefits of lifestyle changes. This information will support and empower people in making informed decisions to support breast cancer survivorship, potentially improving disease specific outcome.

The aim of this review is to determine which lifestyle changes improve breast cancer-specific outcomes and develop recommendations to guide discussion and advice.

PICO table

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (18 or over) treated for invasive breast cancer (M0) and/or DCIS
Intervention	• Lifestyle changes: • Dietary • Physical exercise • Weight management • Stress management • Reduction in smoking • Level of alcohol consumption
Comparison	• No lifestyle changes • Each other • Combinations of lifestyle changes
Outcome	• **Critical** • Overall survival • Disease-free survival • **Important** • Intervention related morbidity • Health related quality of life (HRQoL)

DCIS, ductal carcinoma in-situ; HRQoL, Health related quality of life; M0, no distant metastases

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Seven studies (number of participants, N=11,361) identified by literature search were included in the review. These included 3 randomized controlled trials (RCTs; Anderson 2008; Chlebowski 2006; Courneya 2014) and 4 cohort studies (Bertram 2011; Chen 2011; Fentiman 2005 & Kwan2010). All 7 studies reported on disease free survival and 6 reported on overall survival rate. None of the studies reported on intervention-related morbidities or health related quality of life. Evidence from these studies are summarised in the clinical GRADE evidence profiles below (Table 3 to Table 8).

See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies

Table 2: Summary of included studies

Study	Additional inclusion/exclusion criteria	Intervention/ Comparison
Andersen 2008	Age 20-85 years	Intervention arm: Stress management intervention: 26 sessions (39 therapy hours) over 12 months Control arm: Assessments only
Bertram 2011	Breast carcinoma within the past 4 years	Exposure arm: Adherence to physical activity guidelines Control arm: Assessments only
Chen 2011	Age 20-75 years	Exposure arm: 2.5 hours physical exercise per week and 8.3 MET-hours per week Control arm: Assessments only
Chlebowski 2006	Baseline caloric intake from fat of ≥20%	Intervention arm: Counselling from registered dietitians to reduce fat intake, delivered over 8 biweekly individual sessions, followed by individual sessions every 3 months Control arm: Contact with dietician every three months
Courneya 2014	No additional criteria	Intervention arm: Thrice a week exercise beginning 1–2 wk after starting chemotherapy and ending 3 wk after completing chemotherapy Control arm: Assessments only
Fentiman 2005	No additional criteria	Exposure arm: Current smokers Control arm: Non-smokers
Kwan 2010	Enrolment between 11 and 39 months post diagnosis	Exposure arm: Alcohol consumption >6g/day Control arm: No alcohol consumption

MET, Metabolic equivalent of task; wk, week

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (lifestyle changes to improve breast cancer-specific outcomes) is presented in Table 3 through to Table 8. The included evidence was of moderate to very low quality. Main reasons for downgrading evidence was inconsistency due to heterogeneity in outcomes, imprecision around the estimates due to a small number of events and indirectness due to use of recurrence data instead of disease free survival.

Table 3: Summary clinical evidence profile: Comparison 1. Stress management intervention versus standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard Care	Stress management Intervention			
Disease free survival Follow-up: median 11 years	292 per 1000	173 per 1000 (108 to 267)	HR 0.55 (0.33 to 0.9)	227 (1 study[1])	Low[2,3]
Overall Survival Follow-up: median 11 years	265 per 1000	146 per 1000 (88 to 235)	HR 0.51 (0.3 to 0.87)	227 (1 study[1])	Moderate[2]

CI: Confidence interval; HR: Hazard ratio
[1] Anderson 2008
[2] downgraded by 1 level for serious indirectness due to use of recurrence free survival events instead of disease free survival events
[3] downgraded by 1 level for serious imprecision: number of events < 300

Table 4: Summary clinical evidence profile: Comparison 2. Physical activity intervention versus standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard Care	Physical activity Intervention			
Disease free survival Follow-up: median 8 years	220 per 1000	153 per 1000 (85 to 268)	HR 0.67 (0.36 to 1.26)	242 (1 study[1])	Very low[2,3]
Overall Survival Follow-up: median 8 years	134 per 1000	80 per 1000 (62 to 87)	HR 0.58 (0.25 to 1.36)	242 (1 study[1])	Very low[2,3]

CI: Confidence interval; HR: Hazard ratio;
[1] Courneya 2014
[2] downgraded by 1 level for serious indirectness due to intervention arm having two subgroups with different types of exercises

3 downgraded by 2 levels for very serious imprecision due to number of events < 300, confidence interval includes no effect and MID

Table 5: Summary clinical evidence profile: Comparison 3. Physical activity versus standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard Care	Physical activity Intervention			
Disease free survival Follow-up: 4-7 years	115 per 1000	91 per 1000 (77 to 106)	HR 0.78 (0.66 to 0.92)	6872 (2 studies[1,2])	Very low[3,4]
Overall Survival Follow-up: 4-7 years	93 per 1000	74 per 1000 (62 to 87)	HR 0.79 (0.66 to 0.94)	6872 (2 studies[1,2])	Very low[3,4]

CI: Confidence interval; HR: Hazard ratio
[1] Bertram 2011
[2] Chen 2011
[3] downgraded by 2 levels for very serious inconsistency, i square =89%
[4] downgraded by 1 level for serious indirectness due to inclusion of some subjects with 3b stage

Table 6: Summary clinical evidence profile: Comparison 4. Dietary intervention aimed at reducing fat intake versus standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard Care	Dietary Intervention			
Disease free survival Follow-up: median 5 years	171 per 1000	141 per 1000 (116 to 171)	HR 0.81 (0.66 to 1)	2437 (1 study[1])	Moderate[2]
Overall Survival Follow-up: median 5 years	13 per 1000	12 per 1000 (8 to 16)	HR 0.89 (0.65 to 1.21)	2437 (1 study[1)]	Low[2,3]

CI: Confidence interval; HR: Hazard ratio
[1] Chlebowski 2006
[2] downgraded by 1 level for risk of bias due to self-reporting of diet
[3] downgraded by 1 level for serious imprecision: number of events < 300

Table 7: Summary clinical evidence profile: Comparison 5. Smokers versus non-smokers

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE) Comments
	Assumed risk	Corresponding risk			
	Non Smokers	Smokers			
Disease free survival Follow-up: median 11 years	Not estimable	Not estimable	HR 1.39 (0.72, 2.68)	166 (1 study[1])	Very low[2,3]
Overall Survival Follow-up: median 11 years	Not estimable	Not estimable	HR 1.18 (0.68,2.05)	166 (1 study[1])	Very low[3]

CI: Confidence interval; HR: Hazard ratio
[1] Fentiman 2005
[2] downgraded by 1 level for serious indirectness due to inclusion of distant relapse free survival events instead of disease free survival events
[3] downgraded by 1 level for serious imprecision due to number of events < 300

Table 8: Summary clinical evidence profile: Comparison 6. Alcohol versus no alcohol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Alcohol consumption			
Disease free survival Follow-up: median 7.4 years	146 per 1000	192 per 1000 (146 to 251)	HR 1.35 (1 to 1.83)	1417 (1 study[1])	Very low[2]

CI: Confidence interval; HR: Hazard ratio
[1] Kwan 2010
[2] downgraded by 1 level for serious indirectness due to inclusion of recurrence free survival events instead of disease free survival events

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Stress management intervention versus standard care

Critical outcomes

Overall survival

- There is moderate quality evidence from 1 RCT (N=227) that stress management intervention brings a clinically meaningful increase in overall survival at 11 years follow up compared with no intervention for people with invasive breast cancer.

Disease free survival

- There is low quality evidence from 1 RCT (N=227) that stress management intervention brings a clinically meaningful increase in disease free survival at 11 years follow up compared with no intervention for people with invasive breast cancer.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 2. Physical activity intervention versus standard care

Critical outcomes

Overall survival

- There is very low quality evidence from 1 RCT(N=242) that physical activity intervention does not bring a clinically meaningful change in overall survival at 7.4 years follow up compared with no intervention for people with invasive breast cancer.

Disease free survival

- There is very low quality evidence from 1 RCT(N=242) that physical activity intervention does not bring a clinically meaningful change in disease free survival at 7.4 years follow up compared with no intervention for people with invasive breast cancer.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 3. Physical activity versus standard care

Critical outcomes

Overall survival

- There is very low quality evidence from 2 cohort studies (N=6872) that physical activity brings a clinically meaningful increase in overall survival (4 to 7 years follow up) compared with no physical activity for people with invasive breast cancer.

Disease free survival

- There is very low quality evidence from 2 cohort studies (N=6872) that physical activity brings a clinically meaningful increase in disease free survival (4 to 7 years follow up) compared with no physical activity for people with invasive breast cancer.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 4. Dietary intervention aimed at reducing fat intake versus standard care

Critical outcomes

Overall survival

- There is low quality evidence from 1 RCT (N=2437) that dietary intervention does not bring a clinically meaningful change in overall survival at 5 years follow up compared with no intervention for people with invasive breast cancer.

Disease free survival

- There is moderate quality evidence from 1 RCT (N=2437) that dietary intervention brings a clinically meaningful increase in disease free survival at 5 years follow up compared with no intervention for people with invasive breast cancer.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 5. Smokers versus non-smokers

Critical outcomes

Overall survival

- There is very low quality evidence from 1 cohort study (N=166) that smoking status does not bring a clinically meaningful change in overall survival at 11 years follow up compared with no intervention for people with invasive breast cancer.

Disease free survival

- There is very low quality evidence from 1 cohort study (N=166) that smoking status does not bring a clinically meaningful change in disease free survival at 11 years follow up compared with no intervention for people with invasive breast cancer**.**

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 6. Alcohol versus no alcohol

Critical outcomes

Overall survival

- No evidence was found for this outcome.

Disease free survival

- There is very low quality evidence from 1 cohort study (N=1417) that consuming ≥6 gm/day of alcohol brings clinically meaningful decrease in disease free survival at 7.4 years follow up compared with no drinking for people with invasive breast cancer.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Since this review question was about lifestyle interventions to improve breast cancer specific outcomes, disease free survival and overall survival were considered as most important and were included as critical outcomes. Health-related quality of life (HRQoL) and intervention-related morbidities were considered important outcomes. There was no evidence for health related quality of life or intervention related morbidities.

The quality of the evidence

The quality of evidence for this review was assessed using GRADE. For the comparison stress management intervention versus no intervention, the evidence was moderate to low quality due to imprecision because of small number of events and indirectness due to inclusion of relapse free survival events instead of disease free survival events.

For the comparison of physical activity intervention versus standard care, the evidence from one randomized controlled trial was very low quality due to imprecision because of small

number of wide confidence intervals and indirectness due to two different types of physical activity groups in intervention group. For this comparison, evidence from two cohort studies was of very low quality. The evidence was downgraded due observational study design, inconsistency due to I^2 of 89% and indirectness due to inclusion of some stage 3b cases in one study.

The evidence for comparison dietary intervention aimed at reducing fat intake versus standard care was moderate to low quality. The main reasons for downgrading evidence was risk of bias and imprecision due to wide confidence interval.

The evidence for comparisons smoking versus no smoking and alcohol consumption compared to no alcohol drinking was very low quality. The reason for downgrading for the comparison smoking versus no smoking was observational study design, imprecision due to small number of events, wide confidence intervals and indirectness due to inclusion of distant relapse free survival data for disease free survival. The main reason for downgrading evidence for the comparison of alcohol versus no alcohol was indirectness, as recurrence was reported instead of disease free survival, and also as this was an observational study.

Benefits and harms

The committee discussed that there is evidence that engaging in physical activity and maintaining a healthy weight are associated with improved disease-free survival in people with invasive breast cancer. The evidence for a dietary intervention was a reduced fat diet that led to weight loss, and the committee agreed that the benefit was likely to be due to weight loss, and not the low fat diet *per se.*

Evidence from one cohort study showed higher recurrence events for those adults with invasive breast cancer consuming greater than 3-4 alcohol drinks per week or 6g of alcohol per day. The committee discussed that this translates to approximately 5 units of alcohol per week and agreed that people with breast cancer should be advised that alcohol intake less than this limit is associated with a lower risk of recurrence.

The committee also discussed that there can also be general physical and mental health benefits with healthier lifestyle with potential of improvement in health related quality of life and reduced rates of depression in those who undertake regular exercise.

Although there was no evidence regarding clinically meaningful change in breast cancer outcomes from smoking, the committee agreed that doctors will raise smoking cessation with smokers as usual practice.

The committee discussed that potential harms from the recommendations could be people feeling guilty or stigmatised if recurrence is seen as their fault for not being healthier. Another potential harm discussed by the committee was the potential decrease in health-related quality of life (HRQoL) if people have to adjust their lifestyles (drinking less alcohol, taking more exercise) to fit with the advice.

There was evidence that the stress management intervention improves disease free survival and overall survival in people with invasive breast cancer. However, no separate recommendation was made for this intervention as stress management was already included in the recommendations on the provision of information and psychological support.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed that there could be potential increase in uptake of weight reduction and alcohol reduction services and possibly exercise classes, but these may also be accessed by many people on a ‘self-help’ basis and so may not increase costs to the NHS.

The committee also discussed that there may be a reduction in the cost to the NHS as a result of reduced breast cancer recurrence and associated management. There could be further cost savings as a result of people being generally healthier with a healthy weight which should result in a reduction in the rate of other comorbidities such as cardiovascular disease and diabetes.

Other factors the committee took into account

The committee were aware of a NICE alcohol and breast cancer fact sheet which provided similar advice. However, the fact sheet was aimed at preventing breast cancer, and the committee therefore did not feel it was relevant to a population who already had a diagnosis of breast cancer and therefore did not cross-refer to it in their recommendations. However, they were also aware of a NICE guideline on obesity, which defined healthy weight ranges, and so cross-referred to this instead of defining a healthy weight in their recommendations, and also referred to the NICE guideline on physical activity.

References

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Appendices

Appendix A – Review protocols

Review protocol for 11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?

Field (based on PRISMA-P)	Content
Review question	What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?
Type of review question	Intervention review
Objective of the review	The aim of this review is to determine which lifestyle changes improve breast cancer-specific outcomes and develop recommendations for patient discussion and advice.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) treated for invasive breast cancer (M0) and/or DCIS
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Lifestyle changes: • Dietary • Physical exercise • Weight management • Stress management • Reduction in smoking • Level of alcohol consumption
Eligibility criteria – comparator(s)/control or reference (gold) standard	• No lifestyle changes • Each other • Combinations of lifestyle changes
Outcomes and prioritisation	Critical (up to 3 outcomes) • Overall survival (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference)

Field (based on PRISMA-P)	Content
	Important but not critical • Intervention related morbidity (MID: any statistically significant difference) • HRQOL (MID: values from the literature where available; GRADE default value for FACT-B endocrine scale) 5 year follow-up periods will be prioritised when multiple follow-up periods are reported MID values from the literature: HRQOL: • FACT-G total: 3-7 points • FACT-B total: 7-8 points • TOI (trial outcome index) of FACT-B: 5-6 points • BCS of FACT-B: 2-3 points • WHOQOL-100: 1 point
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs • Prospective observational non-randomised trials
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included. Studies to be excluded if they don't report DFS.
Proposed sensitivity/sub-group analysis, or meta-regression	• Invasive breast cancer • DCIS
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records as study design is not limited to RCTs and studies will be excluded if they do not include DFS, which may be difficult to determine from the abstract; 90% agreement is required and any discussions will be resolved through discussion and consultation with senior staff where necessary.

Field (based on PRISMA-P)	Content
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Data extraction will be undertaken in Microsoft Excel. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	In anticipation of the large number of studies in this area, a date limit of 2000 (which will include all the modern trials) will be imposed if the size of the search results is unmanageable within the available time frame. The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate.
Identify if an update	N/A
Author contacts	For authors please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.

Field (based on PRISMA-P)	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; DCIS, Ductal carcinoma in-situ; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; M0, no distant metastases; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 September 12**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 13 September 2017.

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.

#	Searches
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	exp Smoking Cessation/ use prmz
34	exp "Tobacco Use Cessation"/ use prmz
35	exp "Tobacco Use Cessation Products"/ use prmz
36	exp "Tobacco Use Disorder"/ use prmz
37	Smoking/pc, th use prmz
38	exp smoking cessation/ use oemezd
39	exp nicotine gum/ use oemezd
40	exp smoking/pc, th use oemezd
41	(smoking adj3 (cessation or ceas$ or intervention or withdrawal or quit$ or stop$ or reduc$)).tw.
42	Weight Loss/ use prmz
43	weight reduction/ use oemezd
44	Weight Reduction Programs/ use prmz
45	weight loss program/ use oemezd
46	((caloric or hypocaloric) adj2 (restrict* or diet*)).tw.
47	(weight adj3 (los$ or reduc$ or manag$ or intervention)).tw.
48	exp Diet Therapy/ use prmz
49	exp diet therapy/ use oemezd
50	Energy Intake/ use prmz
51	dietary intake/ use oemezd
52	(diet$ adj3 (manag$ or intervention or modif$)).tw.
53	((health$ adj eat$) or (eat$ adj health$)).tw.
54	(balanced adj diet$).tw.
55	Alcohol Drinking/ use prmz
56	exp Drinking Behavior/ use prmz
57	drinking behavior/ use oemezd
58	((alcohol$ or drink$) adj3 (cessation or ceas$ or intervention or withdrawal or quit$ or stop$)).tw.
59	((alcohol$ or drink$) adj (level$ or consumption)).tw.
60	exp Life Style/ use prmz
61	exp lifestyle/ use oemezd
62	lifestyle modification/ use oemezd
63	((lifestyle$ or life-style$) adj3 (advice$ or intervention$ or modif$ or change$ or recommend$)).tw.
64	Health Behavior/ use prmz
65	health behavior/ use oemezd
66	exp Cognitive Therapy/ use prmz
67	*Behavior Therapy/ use prmz
68	exp cognitive behavioral therapy/ use oemezd
69	*behavior therapy/ use oemezd
70	((behaviour$ or behavior$ or psycholog$) adj3 (advice$ or intervention$ or modif$ or change$ or recommend$)).tw.
71	Stress, Psychological/ use prmz

#	Searches
72	exp Adaptation, Psychological/ use prmz
73	exp Mind-Body Therapies/ use prmz
74	stress management/ use oemezd
75	adaptive behavior/ use oemezd
76	alternative medicine/ use oemezd
77	(stress adj3 (manag$ or intervention$ or recommend$)).tw.
78	exp Exercise/ use prmz
79	exp Exercise Movement Techniques/ use prmz
80	exp Exercise Therapy/ use prmz
81	exp exercise/ use oemezd
82	exp kinesiotherapy/ use oemezd
83	exp physical activity/ use oemezd
84	((exercis$ or activit$) adj3 (advice$ or intervention$ or modif$ or change$ or recommend$ or manag$)).tw.
85	or/33-84
86	32 and 85
87	quality-adjusted life years/ use prmz
88	quality adjusted life year/ use oemezd
89	"quality of life index"/ use oemezd
90	short form 12/ or short form 20/ or short form 36/ or short form 8/ use oemezd
91	sickness impact profile/ use prmz
92	sickness impact profile/ use oemezd
93	(quality adj2 (wellbeing or well being)).ti,ab.
94	sickness impact profile.ti,ab.
95	disability adjusted life.ti,ab.
96	(qal* or qtime* or qwb* or daly*).ti,ab.
97	(euroqol* or eq5d* or eq 5*).ti,ab.
98	(qol* or hql* or hqol* or h qol* or HRQoL* or hr qol*).ti,ab.
99	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
100	(hui or hui1 or hui2 or hui3).ti,ab.
101	(health* year* equivalent* or hye or hyes).ti,ab.
102	discrete choice*.ti,ab.
103	rosser.ti,ab.
104	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
105	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
106	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
107	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
108	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
109	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
110	87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
111	disease-free survival/ use prmz
112	disease free survival/ use oemezd
113	recurrence free survival/ use oemezd
114	(disease$ adj free$ adj surviv$).tw.

#	Searches
115	(relaps$ adj free$ adj surviv$).tw.
116	(recurren$ adj free$ adj surviv$).tw.
117	(DFS or DFSR).tw.
118	(RFS or RFSR).tw.
119	((disease$ adj free$) or (relaps$ adj free$) or (recurren$ adj free$)).tw.
120	*cancer survival/ use oemezd
121	cancer specific survival/ use oemezd
122	(breast$ adj cancer$ adj survival).tw.
123	(breast$ adj cancer$ adj specific$).tw.
124	111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123
125	meta-analysis/
126	meta-analysis as topic/
127	systematic review/
128	meta-analysis/
129	(meta analy* or metanaly* or metaanaly*).ti,ab.
130	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
131	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
132	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
133	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
134	(search* adj4 literature).ab.
135	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
136	cochrane.jw.
137	((pool* or combined) adj2 (data or trials or studies or results)).ab.
138	or/125-126,129,131-136 use prmz
139	or/127-130,132-137 use oemezd
140	138 or 139
141	86 and 110
142	86 and 124
143	86 and 140
144	survival.tw.
145	143 and 144
146	141 or 142 or 145
147	remove duplicates from 146 [and general exclusions filter applied]

Database: Cochrane Library via Wiley Online

Date of last search: 13 September 2017

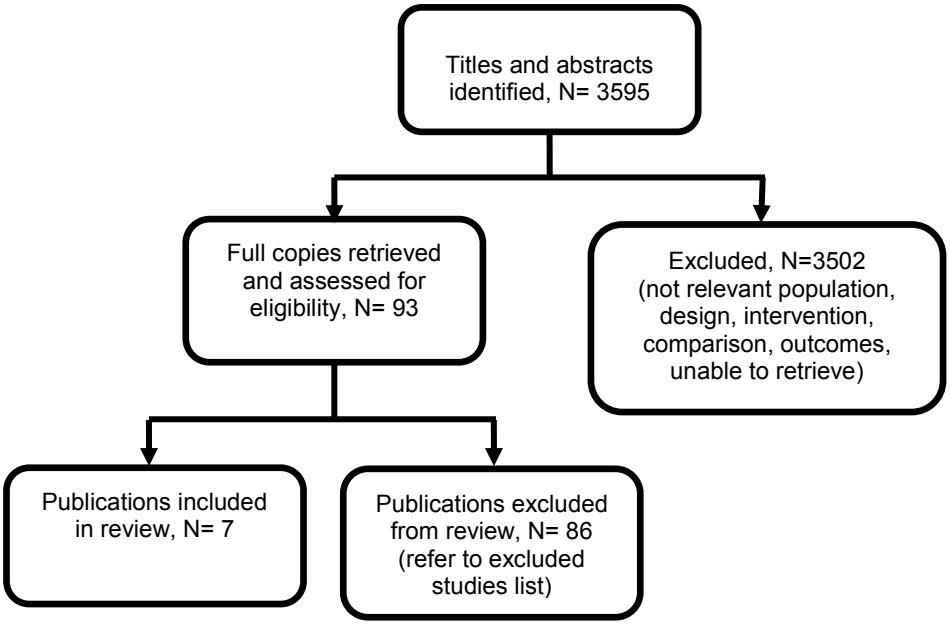
#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only

#	Searches
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Smoking Cessation] explode all trees
#23	MeSH descriptor: [Tobacco Use Cessation] explode all trees
#24	MeSH descriptor: [Tobacco Use Cessation Products] explode all trees
#25	MeSH descriptor: [Tobacco Use Disorder] explode all trees
#26	(smoking near/3 (cessation or ceas* or intervention or withdrawal or quit* or stop* or reduc*)):ti,ab,kw (Word variations have been searched)
#27	MeSH descriptor: [Weight Loss] this term only
#28	MeSH descriptor: [Weight Reduction Programs] this term only
#29	(weight near/3 (los* or reduc* or manag* or intervention)):ti,ab,kw (Word variations have been searched)
#30	((caloric or hypocaloric) near/2 (restrict* or diet*)):ti,ab,kw (Word variations have been searched)
#31	MeSH descriptor: [Diet Therapy] explode all trees
#32	MeSH descriptor: [Energy Intake] this term only
#33	(diet* near/3 (manag* or intervention or modif*)):ti,ab,kw (Word variations have been searched)
#34	((health* next eat*) or (eat* next health*)):ti,ab,kw (Word variations have been searched)
#35	(balanced next diet*):ti,ab,kw (Word variations have been searched)
#36	MeSH descriptor: [Alcohol Drinking] this term only
#37	MeSH descriptor: [Drinking Behavior] explode all trees
#38	((alcohol* or drink*) near/3 (cessation or ceas* or intervention or withdrawal or quit* or stop*)):ti,ab,kw (Word variations have been searched)
#39	((alcohol* or drink*) next (level* or consumption)):ti,ab,kw (Word variations have been searched)
#40	MeSH descriptor: [Life Style] explode all trees

#	Searches
#41	((lifestyle* or life-style*) near/3 (advice* or intervention* or modif* or change* or recommend*)):ti,ab,kw (Word variations have been searched)
#42	MeSH descriptor: [Health Behavior] this term only
#43	MeSH descriptor: [Cognitive Therapy] explode all trees
#44	MeSH descriptor: [Behavior Therapy] this term only
#45	((behaviour* or behavior* or psycholog*) near/3 (advice* or intervention* or modif* or change* or recommend*)):ti,ab,kw (Word variations have been searched)
#46	MeSH descriptor: [Stress, Psychological] this term only
#47	MeSH descriptor: [Adaptation, Psychological] explode all trees
#48	MeSH descriptor: [Mind-Body Therapies] explode all trees
#49	(stress near/3 (manag* or intervention* or recommend*)):ti,ab,kw (Word variations have been searched)
#50	MeSH descriptor: [Exercise] explode all trees
#51	MeSH descriptor: [Exercise Movement Techniques] explode all trees
#52	MeSH descriptor: [Exercise Therapy] explode all trees
#53	((exercis* or activit*) near/3 (advice* or intervention* or modif* or change* or recommend* or manag*)):ti,ab,kw (Word variations have been searched)
#54	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53
#55	#21 and #54

Appendix C – Clinical evidence study selection

Figure 1: Flow diagram of clinical article selection for lifestyle changes to improve breast cancer specific outcomes review



Appendix D – Clinical evidence tables

Table 9: Summary clinical evidence

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Andersen, Bl, Yang, Hc, Farrar, Wb, Golden-Kreutz, Dm, Emery, Cf, Thornton, Lm, Young, Dc, Carson, We, Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial, Cancer, 113, 3450-3458, 2008 **Ref Id** 677741 **Country/ies where the study was carried out** United States **Study type** Randomized controlled trial **Aim of the study** To assess if the cancer patients coping with their recent diagnosis but receiving a psychologic intervention would have improved survival compared	**Sample size** N=227 **Characteristics** Age 20-85 yrs. Mean age not mentioned. Stages IIA to IIIB **Inclusion criteria** 1) Women diagnosed with breast carcinoma stage IIA, IIB, IIIA, or IIIB 2) Surgically treated and awaiting adjuvant therapy **Exclusion criteria** Exclusion criteria included prior cancer diagnosis; refusal of cancer treatment; age <20 years or >85 years; residence >90 miles from the research site; and diagnoses of mental retardation, severe or untreated psychopathology (e.g.,	**Interventions** Stress management intervention was provided in small cohorts (n= 13) ranging from 8 to 12 participants and led by 2 psychologists. The format was 4 months of weekly sessions (Intensive phase) followed by 8 monthly sessions (Maintenance phase). In combination, a total of 26 sessions (39 therapy hours) over 12 months were delivered. Strategies included: progressive relaxation for stress reduction, problem solving, identifying supportive family members or friends, using assertive communication, strategies to increase daily activity, improving dietary habits and maintain adherence to treatment.	**Details** Median follow up 11 years (7-13 years)	**Results** Disease recurrence was reported to occur in 62 of 212 (29%) women and death was reported for 54 of 227 (24%) women. Participants in the Intervention arm were found to have a reduced risk of breast cancer recurrence (hazards ratio [HR] of 0.55; P=.034) and death from breast cancer (HR of 0.44; P=.016) compared with patients in the Assessment only arm. Follow-up analyses also demonstrated that Intervention patients had a reduced risk of death from all causes (HR of 0.51; P=.028).	**Limitations** Risk of Bias: 1) Selection Bias: a) Random sequence generation: Low risk b) Allocation concealment: unclear risk 2) Performance bias: Low risk 3) Detection bias: Low risk 4) Attrition bias: Low risk 5) Reporting bias: Low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
with patients who were only assessed **Study dates** Not described **Source of funding** Supported by the National Institute of Mental Health (RO1MH51487) and the National Cancer Institute (R01CA92704, K05 CA098133, KA24 CA93670, and P01 CA95426), with additional support from the American Cancer Society (PBR-89), the Longaberger Company-American Cancer Society (PBR-89A), the US Army Medical Research Acquisition Activity (DAMD17-94-J-4165, DAMD17-96-1-6294, and DAMD17-97-1-7062), the Ohio State University Comprehensive Cancer Center (P30 CA16058), and the Walther Cancer Institute.	schizophrenia), neurologic disorders, dementia, or any immunologic condition/disease				
Full citation Bertram, L. A. C., Stefanick, M. L., Saquib, N., Natarajan, L., Patterson, R. E., Bardwell, W., Flatt, S. W.,	**Sample size** N=2361 **Characteristics**	**Interventions** Adherence to physical activity guidelines	**Details** Median follow up was 7.1 years	**Results** Those who were most active at baseline had a 53% lower mortality risk compared to the least active women (HR =	**Limitations** Risk of Bias: 1) Selection: Exposed and non exposed

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Newman, V. A., Rock, C. L., Thomson, C. A., Pierce, J. P., Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: Findings from the WHEL Study, Cancer Causes and Control, 22, 427-435, 2011 **Ref Id** 677907 **Country/ies where the study was carried out** United States **Study type** Follow Up of Randomized Controlled trial **Aim of the study** To determine whether baseline activity and 1-year change in activity are associated with breast cancer events or mortality **Study dates** 1995 to 2000 **Source of funding** Initiated with the support of the Walton Family	Mean age: 54.3 (9.1) ;Stages I to III Breast cancer **Inclusion criteria** 1) Diagnosis of primary operable invasive stage I , II, or III and 2) Breast carcinoma within the past 4 years 3) Age 18–70 years at the time of diagnosis **Exclusion criteria** 1) Current or planned chemotherapy 2) Evidence of recurrent disease or new breast cancer since completion of initial treatment 3) Any other cancer in the past 10 years.			0.47; 95% CI: 0.26, 0.84; p = .01). Adherence to activity guidelines was associated with a 35% lower mortality risk (HR = 0.65, 95% CI: 0.47, 0.91). Neither baseline nor 1-year change in activity was associated with additional breast cancer events.	were from the same population. 2) Comparison: The ones doing exercise might be more physically fit than those not exercising. 3) Outcome: Outcome measurement & follow up adequate **Other information** The Women's Healthy Eating and Living (WHEL) Study

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Foundation and continued with funding from National Cancer Institute Grant CA 69375. Some of the data were collected from General Clinical Research Centers, National Institute of Health grants M01- RR00070, M01-RR00079, and M01-RR00827.					
Full citation Chen, X., Lu, W., Zheng, W., Gu, K., Matthews, C. E., Chen, Z., Zheng, Y., Shu, X. O., Exercise after diagnosis of breast cancer in association with survival, Cancer Prevention Research, 4, 1409-1418, 2011 **Ref Id** 678155 **Country/ies where the study was carried out** China **Study type** Cohort study **Aim of the study**	**Sample size** N=4826 **Characteristics** Age : 53.5(10) **Inclusion criteria** 1) Age between 20 and 75 years 2) Stage I to III disease **Exclusion criteria** Not described	**Interventions** Exposure: Regular exercisers were categorized by 2.5 hours per week and 8.3 MET-hours per week, the medians for exercise duration and exercise-MET score at 6 months post diagnosis, levels similar to recent recommendations for physical activity for Americans and for cancer patients.Walking was the most common type of regular exercise carried out in this study population (52%), followed by gymnastics (14%), body building (7%), and traditional Chinese exercises(5%,	**Details** Study participants were followed through in-person interviews administered approximately 18, 36, and 60 months after cancer diagnosis.	**Results** After adjustment for QOL, clinical prognostic factors, and other covariates, exercise during the first 36 months post diagnosis was inversely associated with total mortality and recurrence/disease-specific mortality with HRs of 0.70 (95% CI: 0.56–0.88) and 0.60 (95% CI: 0.47–0.76), respectively.Significant dose–response relationships between total and recurrence/disease specific mortality rates and exercise duration and MET scores were observed (all values for Ptrend < 0.05). The exercise–mortality associations were not modified by menopausal status, comorbidity, QOL, or body size assessed at	**Limitations** Risk of Bias: 1) Selection: Exposed and non exposed were from the same population. 2) Comparison: The ones doing exercise might be more physically fit than those not exercising. 3) Outcome: Outcome measurement & follow up adequate **Other information** Shanghai Breast Cancer Survival Study (SBCSS)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To evaluate associations of exercise after breast cancer diagnosis with total mortality and recurrence/disease-specific mortality, accounting for conditions that restrict exercise participation **Study dates** Recruitment between 2002 and 2006 **Source of funding** This study was supported by the Department of Defense Breast Cancer Research Program(DAMD 17-02-1-0607) and by U.S. Public Health Service grant number R01 CA118229 from the National Cancer Institute.		including Qigong and Tai Chi).		approximately 6 months post diagnosis.	
Full citation Chlebowski, R. T., Blackburn, G. L., Thomson, C. A., Nixon, D. W., Shapiro, A., Hoy, M. K., Goodman, M. T., Giuliano, A. E., Karanja, N., McAndrew, P., Hudis, C., Butler, J., Merkel, D., Kristal, A., Caan, B., Michaelson, R., Vinciguerra, V., Del Prete,	**Sample size** N=2347 (Intervention= 975, Control= 1462) **Characteristics** Women between 48 and 79 years with Stage I or II disease **Inclusion criteria**	**Interventions** Intervention Group: Counseling from registered dietitians to reduce fat intake, delivered over 8 biweekly individual sessions, followed by individual sessions every 3 months.	**Details** At baseline, there were no significant differences between the groups in age, tumor size, nodal status, histologic tumor type, systemic treatment	**Results** Disease Free Survival For disease- free survival, the HR was 0.81 (95% CI = 0.65 to 0.99; stratified log rank P = .078). Overall Survival	**Limitations** Risk of Bias: 1) Selection Bias: a) Random sequence generation: Low risk b) Allocation concealment: Not practical to achieve

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
S., Winkler, M., Hall, R., Simon, M., Winters, B. L., Elashoff, R. M., Dietary fat reduction and breast cancer outcome: Interim efficacy results from the women's intervention nutrition study, Journal of the National Cancer Institute, 98, 1767-1776, 2006 **Ref Id** 670338 **Country/ies where the study was carried out** United States **Study type** Randomized controlled trial **Aim of the study** To determine the influence of low-fat dietary interventions on body weight and breast cancer recurrence **Study dates** 1994-2001 **Source of funding** This study was primarily funded by the National Cancer Institute, National	1) Completely resected unilateral invasive breast carcinoma 2) Baseline caloric intake from fat of ≥20% 3) Receiving adjuvant systemic therapy appropriate to their condition 4) life expectancy of at least 10 years excluding the cancer diagnosis 5) Medically able to accept either randomization assignment; and trial entry within 365 days of surgery. **Exclusion criteria** 1) inflammatory carcinoma 2) chest wall or skin involved 3) tumor size less than 1 cm with negative nodes 4) tumor size greater than 5 cm with positive nodes	Additional monthly group sessions were instituted to reinforce behavior changes. Control Group: women in the control group had contact with dietitians only every 3 months.	chemotherapy regimen, estrogen receptor status, or progesterone receptor status	There was no difference in overall survival comparing women receiving the dietary intervention with control group women (HR = 0.89; 95% CI = 0.65 to 1.21; stratified log rank P = .56).	2) Performance bias: Low risk 3) Detection bias: High risk. Self reporting 4) Attrition bias: Low risk 5) Reporting bias:Low risk **Other information** Women's Intervention Nutrition Study(WINS) trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Institutes of Health, Department of Health and Human Services. Funding for supplemental projects was provided by the Breast Cancer Research Foundation and the American Institute for Cancer Research. This study was supported by an investigator-initiated RO1 grant.	5) 10 or more nodes positive 6) preoperative chemotherapy or any previous neoplasm other than carcinoma in situ of the cervix or basal cell skin carcinoma				
Full citation Courneya, K. S., Segal, R. J., McKenzie, D. C., Dong, H., Gelmon, K., Friedenreich, C. M., Yasui, Y., Reid, R. D., Crawford, J. J., Mackey, J. R., Effects of exercise during adjuvant chemotherapy on breast cancer outcomes, Medicine & Science in Sports & ExerciseMed Sci Sports Exerc, 46, 1744-51, 2014 **Ref Id** 567184 **Country/ies where the study was carried out** Canada	**Sample size** 242 **Characteristics** Supervised aerobic exercise intervention (n=78) Resistence training exercise intervention (n= 82) Usual care (n=82) Disease stage 1 to 3A **Inclusion criteria** 1) English- or French-speaking nonpregnant women 2) >18 yr old	**Interventions** Aerobic exercise training and resistance exercise training participants were asked to exercise for the duration of their chemotherapy, including delays, beginning 1–2 wk after starting chemotherapy and ending 3 wk after completing chemotherapy. All exercise sessions (thrice per week) were supervised by qualified exercise trainers. Warm-up and cool-down periods were 5 min of light aerobic activity and stretching	**Details** Median follow up 89 months (8 year disease free survival)	**Results** After a median follow-up of 89 months, there were 25/160 (15.6%) DFS events in the exercise groups and 18/82 (22.0%) in the control group. Eight-year DFS was 82.7% for the exercise groups compared with 75.6% for the control group (HR, 0.68; 95% confidence interval (CI), 0.37–1.24; log-rank, P = 0.21). Slightly stronger effects were observed for overall survival (HR, 0.60; 95% CI, 0.27–1.33; log-rank, P = 0.21), distant DFS (HR, 0.62; 95% CI, 0.32–1.19; log-rank, P = 0.15), and recurrence-free interval (HR, 0.58; 95% CI, 0.30–1.11; Gray test, P = 0.095)	**Limitations** Selection Bias: Low risk Random sequence generation: Low risk Allocation concealment: Low risk Performance Bias: Blinding not possible. Low risk Detection Bias: Outcome not subjective. Low risk Attrition Bias:Low risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type Multicenter randomized controlled trial **Aim of the study** To examine the effects of aerobic and resistance exercise on patient survival outcomes **Study dates** February 2003 to July 2005 **Source of funding** This study was funded by the Canadian Breast Cancer Research Alliance. Authors were also supported by the Canada Research Chairs Program, Alberta Innovates—Health Solutions, Health Senior Scholar Award from Alberta Innovates—Health Solutions and through the Alberta Cancer Foundation's Weekend to End Women's Cancers Breast Cancer Chair.	3) Stage I–IIIA breast cancer starting adjuvant chemotherapy **Exclusion criteria** 1) Incomplete axillary surgery 2) Transabdominal rectus abdominus muscle reconstructive surgery 3) Uncontrolled hypertension, cardiac illness, and psychiatric illness or were otherwise not cleared by their oncologist				**Other information** ClinicalTrials.gov Identifier NCT00115713

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Fentiman, I. S., Allen, D. S., Hamed, H., Smoking and prognosis in women with breast cancer, International journal of clinical practice, 59, 1051-1054, 2005 **Ref Id** 678522 **Country/ies where the study was carried out** United Kingdom **Study type** Cohort study **Aim of the study** To study the effect of smoking on prognosis of patients with invasive breast cancer **Study dates** 1984-2004 **Source of funding** Not described	**Sample size** N=166 **Characteristics** Mean age= 54 years, Women with Invasive breast carcinoma (Stage I/II) **Inclusion criteria** 1) Women with invasive breast cancer 2) Treated by means of either modified radical mastectomy or breast conservation therapy **Exclusion criteria** Not described	**Interventions** Current smoking was the exposure	**Details** Mean follow up : 132 months	**Results** The hazard ratio for distant relapse free survival at median follow up of 132 months for current smokers was : 1.39 [0.72, 2.68] The hazard ratio for overall survival at median follow up of 132 months for current smokers was 1.18 [0.68, 2.05]	**Limitations** Risk of Bias: 1) Selection: Exposed and non exposed were from the same population. 2) Comparison: Groups are comparable 3) Outcome: Outcome measurement & follow up adequate. Indirectness in outcome as relapse free survival instead of disease free survival **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Kwan, M. L., Kushi, L. H., Weltzien, E., Tam, E. K., Castillo, A., Sweeney, C., & Caan, B. J. , Alcohol Consumption and Breast Cancer Recurrence and Survival Among Women With Early-Stage Breast Cancer: The Life After Cancer Epidemiology Study. Journal of Clinical Oncology, 28(29), 4410–4416, 2010 **Ref Id** 678708 **Country/ies where the study was carried out** United States **Study type** Cohort study **Aim of the study** To examine the association of alcohol consumption after breast cancer diagnosis with recurrence and mortality among early-stage breast cancer survivors **Study dates**	N=1897 **Characteristics** Mean age: 58 (10.7) years for alcohol consumers and 59.1(10.9) for non consumers. Stage I -IIIA **Inclusion criteria** 1) Age between 18 and 70 years at enrollment 2) Diagnosis of early-stage primary breast cancer (stage I1 cm, II, or IIIA) 3) Enrollment between 11 and 39 months postdiagnosis 4) Completion of breast cancer treatment (except for adjuvant hormone therapy) **Exclusion criteria** 1) Recurrence 2) History of other cancers in last 5 years	Drinking of alcohol (≥ 6g/day) was the main exposure	Follow up : 7.4 years	Drinking ≥ 6 g/d of alcohol compared with no drinking was associated with an increased risk of breast cancer recurrence (HR, 1.35; 95% CI, 1.00 to 1.83) and death due to breast cancer (HR, 1.51; 95% CI, 1.00 to 2.29).	Risk of Bias: 1) Selection: Exposed and non exposed were from the same population. 2) Comparison: Groups are comparable 3) Outcome: Outcome measurement & follow up adequate. Indirectness in outcome as recurrence measured instead of disease free survival **Other information** Life After Cancer Epidemiology (LACE) Cohort Study

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
1997-2002 **Source of funding** Supported by Grant No. R01 CA129059 from the National Cancer Institute.					

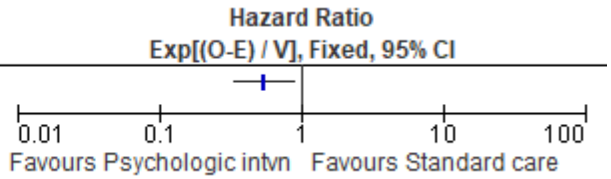
CI, Confidence interval; DFS, Disease free survival; HR, Hazards ratio; LACE, Life after cancer epidemiology; MET, metabolic equivalent of task; QOL, Quality of life; SBCSS, Shanghai breast cancer survival study; WHEL, Women's healthy eating and living; WINS, Women's intervention nutrition study

Appendix E – Forest plots

Comparison 1. Stress management intervention versus standard care

Figure 2: Disease free survival at 11 year follow up

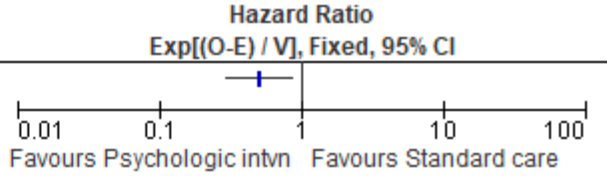
Study or Subgroup	Psychologic intervention Events	Total	Standard care Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Anderson 2009	29	114	33	113	-9.27	15.5	0.55 [0.33, 0.90]



CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance

Figure 3: Overall survival at 11 year follow up

Study or Subgroup	Psychologic intervention Events	Total	Standard care Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Anderson 2009	24	114	30	113	-8.98	13.33	0.51 [0.30, 0.87]

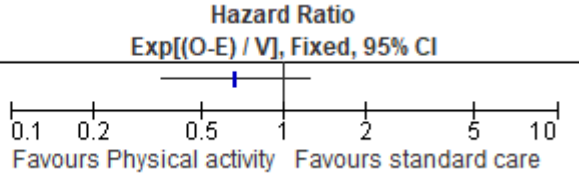


CI: Confidence Interval: HR: Hazard Ratio; IV: Inverse Variance

Comparison 2. Physical activity intervention versus standard care

Figure 4: Disease free survival at 8 year follow up

Study or Subgroup	Physical activity Events	Total	Standard care Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Courneya 2014	25	160	18	82	-3.89	9.63	0.67 [0.36, 1.26]



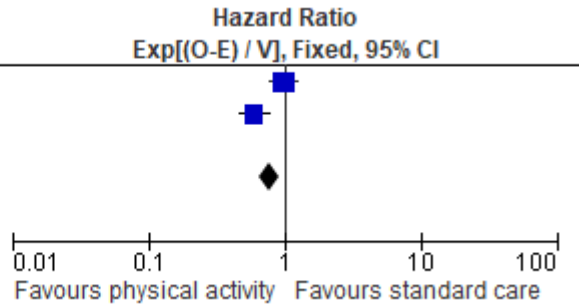
CI: Confidence Interval: HR: Hazard Ratio; IV: Inverse Variance

Figure 5: Disease free survival 4-7 year follow up

Study or Subgroup	Physical activity Events	Total	Standard care Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Bertram 2011	152	1175	143	1186	-0.74	73.68	52.5%	0.99 [0.79, 1.24]
Chen 2011	276	2931	174	1580	-33.98	66.53	47.5%	0.60 [0.47, 0.76]
Total (95% CI)		**4106**		**2766**			**100.0%**	**0.78 [0.66, 0.92]**
Total events	428		317					

Heterogeneity: Chi² = 8.76, df = 1 (P = 0.003); I² = 89%

Test for overall effect: Z = 2.93 (P = 0.003)

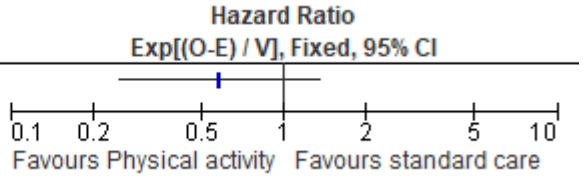


CI: Confidence Interval: HR: Hazard Ratio; IV: Inverse Variance

Comparison 3. Physical activity versus standard care

Figure 6: Overall survival at 8 year follow up

Study or Subgroup	Physical activity Events	Total	Standard care Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Courneya 2014	13	160	11	82	-2.91	5.38	0.58 [0.25, 1.36]

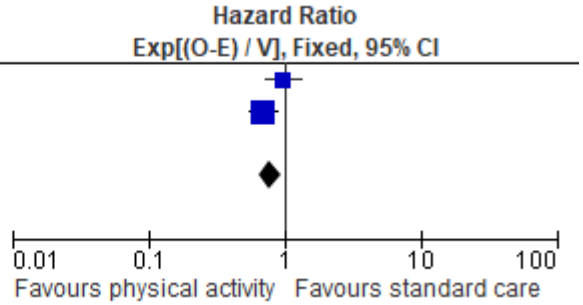


CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance

Figure 7: Overall survival at 4-7 year follow up

Study or Subgroup	Physical activity Events	Total	Standard care Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Bertram 2011	92	1175	71	1186	-0.81	40.07	34.8%	0.98 [0.72, 1.34]
Chen 2011	251	2931	185	1580	-26.83	75.22	65.2%	0.70 [0.56, 0.88]
Total (95% CI)		**4106**		**2766**			**100.0%**	**0.79 [0.66, 0.94]**
Total events	343		256					

Heterogeneity: Chi² = 2.96, df = 1 (P = 0.09); I² = 66%
Test for overall effect: Z = 2.57 (P = 0.01)

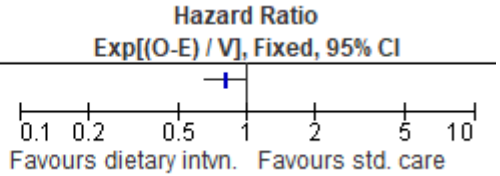


CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance

Comparison 4. Dietary intervention aimed at reducing fat intake versus standard care

Figure 8: Disease free survival at 5 year follow up

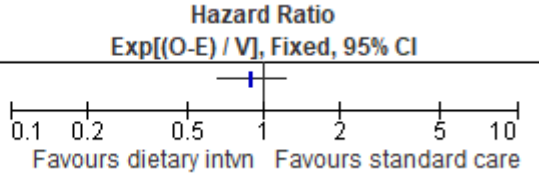
Study or Subgroup	Dietary intervention Events	Total	Standard Care Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Chlebowski 2006	139	975	250	1462	-18.29	86.8	0.81 [0.66, 1.00]



CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance; intvn.:intervention; std.:standard

Figure 9: Overall survival at 5 year follow up

Study or Subgroup	Dietary intervention Events	Total	Standard care Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Chlebowski 2006	15	975	19	1462	-4.64	39.79	0.89 [0.65, 1.21]

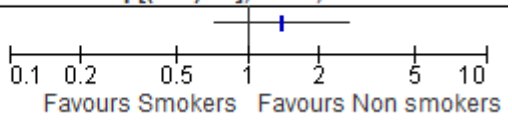


CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance; intvn.:intervention; std.:standard

Comparison 5. Smokers versus non-smokers

Figure 10: Disease free survival at 11 year follow up

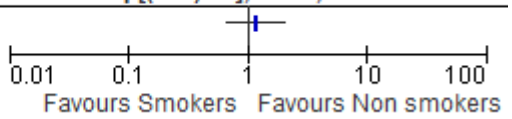
	Smokers		Non Smokers				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
Fentiman 2005	0	40	0	126	2.93	8.9	1.39 [0.72, 2.68]	



CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance

Figure 11: Overall survival at 11 year follow up

	Smokers		Non Smokers				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
Fentiman 2005	0	40	0	126	2.07	12.51	1.18 [0.68, 2.05]	

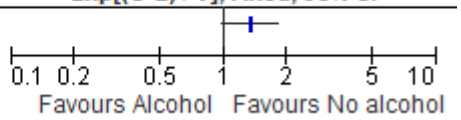


CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance

Comparison 6. Alcohol versus no alcohol

Figure 12: Disease free survival at 7.4 year follow up

	Alcohol		Control				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
Kwan 2010	78	478	137	939	12.63	42.08	1.35 [1.00, 1.83]	



CI: Confidence Interval; HR: Hazard Ratio; IV: Inverse Variance

Appendix F – GRADE tables

Table 9: Clinical evidence profile: Comparison 1. Stress management intervention versus standard care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stress management Intervention	Standard Care	Relative (95% CI)	Absolute		
Recurrence free survival (follow-up median 11 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	29/114 (25.4%)	33/113 (29.2%)	HR 0.55 (0.33 to 0.9)	119 fewer per 1000 (from 25 fewer to 184 fewer)	LOW	CRITICAL
Overall Survival (follow-up median 11 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	24/114 (21.1%)	30/113 (26.5%)	HR 0.51 (0.3 to 0.87)	120 fewer per 1000 (from 30 fewer to 177 fewer)	MODERATE	CRITICAL

CI: Confidence interval; HR: Hazard ratio
[1] Anderson 2008
[2] Downgraded by 1 level for serious indirectness due to use of recurrence free survival events instead of disease free survival events
[3] Downgraded by 1 level for serious imprecision: number of events < 300

Table 10: Clinical evidence profile: Comparison 2. Physical activity intervention versus standard care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical activity Intervention	Standard Care	Relative (95% CI)	Absolute		
Disease free survival (follow-up median 8 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	25/160 (15.6%)	18/82 (22%)	HR 0.67 (0.36 to 1.26)	67 fewer per 1000 (from 134 fewer to 49 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical activity Intervention	Standard Care	Relative (95% CI)	Absolute	Quality	Importance
Overall Survival (follow-up median 8 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	13/160 (8.1%)	11/82 (13.4%)	HR 0.58 (0.25 to 1.36)	54 fewer per 1000 (from 99 fewer to 44 more)	VERY LOW	CRITICAL

CI: Confidence interval; HR: Hazard ratio
[1] Courneya 2014
[2] Downgraded by 1 level for serious indirectness due to intervention arm having two subgroups with different types of exercises
[3] Downgraded by 2 levels for very serious imprecision due to number of events < 300, confidence interval includes no effect and MID

Table 11: Clinical evidence profile: Comparison 3.Physical activity versus standard care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical activity Intervention	Standard Care	Relative (95% CI)	Absolute	Quality	Importance
Disease free survival(follow-up median 4-7 years)												
2[1,2]	Observational studies	No serious risk of bias	Very serious[3]	Serious[4]	No serious imprecision	None	453/4266 (10.6%)	335/2848 (11.8%)	HR 0.77 (0.66 to 0.91)	26 fewer per 1000 (from 10 fewer to 38 fewer)	VERY LOW	CRITICAL
Overall Survival (follow-up median 4-7 years)												
2[1,2]	Observational studies	No serious risk of bias	No serious inconsistency	Serious[4]	No serious imprecision	None	356/4266 (8.3%)	267/2848 (9.4%)	HR 0.78 (0.65 to 0.93)	20 fewer per 1000 (from 6 fewer to 32 fewer)	VERY LOW	CRITICAL

CI: Confidence interval; HR: Hazard ratio
[1] Bertram 2011
[2] Chen 2011
[3] Downgraded by 2 levels for very serious inconsistency, I square =89%
[4] Downgraded by 1 level for serious indirectness due to inclusion of some subjects with 3b stage

Table 12: Clinical evidence profile: Comparison 4. Dietary intervention aimed at reducing fat intake versus standard care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dietary Intervention	Standard Care	Relative (95% CI)	Absolute	Quality	Importance
Disease free survival (follow-up median 5 years)												
1[1]	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	139/975 (14.3%)	250/1462 (17.1%)	HR 0.81 (0.66 to 1)	30 fewer per 1000 (from 55 fewer to 0 more)	MODERATE	CRITICAL
Overall Survival (follow-up median 5 years)												
1[1]	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	15/975 (1.5%)	19/1462 (1.3%)	HR 0.89 (0.65 to 1.21)	1 fewer per 1000 (from 5 fewer to 3 more)	LOW	CRITICAL

CI: Confidence interval; HR: Hazard ratio
[1] Chlebowski 2006
[2] Downgraded by 1 level for risk of bias due to self-reporting of diet
[3] Downgraded by 2 levels for serious imprecision due to confidence interval including no difference and 1 MID; < 300 events

Table 13: Clinical evidence profile: Comparison 5. Smokers versus non-smokers

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smokers	Non Smokers	Relative (95% CI)	Absolute	Quality	Importance
Disease free survival (follow-up median 11 years)												
1[1]	Observational studies	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	Not known	Not known	HR 1.39 (0.72 to 2.68)	Not estimable	VERY LOW	CRITICAL
Overall Survival (follow-up median 11 years)												
1[1]	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	Not known	Not known	HR 1.18(0.68 to 2.05)	Not estimable	VERY LOW	CRITICAL

CI: Confidence interval; HR: Hazard ratio
[1] Fentiman 2005
[2] Downgraded by 1 level for serious indirectness due to inclusion of distant relapse free survival events instead of disease free survival events

[3] Downgraded by 2 levels for very serious imprecision due to small number of events, wide confidence intervals including no difference

Table 14: Clinical evidence profile: Comparison 6. Alcohol versus no alcohol

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alcohol consumption	Control	Relative (95% CI)	Absolute	Quality	Importance
Disease free survival (follow-up median 7.4 years)												
1[1]	Observational studies	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	78/478 (16.3%)	137/939 (14.6%)	HR 1.35 (1 to 1.83)	46 more per 1000 (from 0 more to 105 more)	VERY LOW	CRITICAL

CI: Confidence interval; HR: Hazard ratio
[1] Kwan 2010
[2] Downgraded by 1 level for serious indirectness due to inclusion of recurrence free survival events instead of disease free survival events
[3] < 300 events

Appendix G – Economic evidence study selection

See Supplement 1: Health economics literature review for details of economic study selection.

Appendix H – Economic evidence tables

No health economic evidence was identified for this review.

Appendix I – Health economic evidence profiles

No health economic evidence was identified for this review.

Appendix J – Health economic analysis

A health economic analysis was not conducted for this review question.

1 Appendix K – Excluded studies

2 Clinical studies

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Ammitzboll, G., Sogaard, K., Karlsen, R. V., Tjonneland, A., Johansen, C., Frederiksen, K., Bidstrup, P., Physical activity and survival in breast cancer, European Journal of Cancer, 66, 67-74, 2016	No data on disease free survival
Arun, B., Austin, T., Babiera, G. V., Basen-Engquist, K., Carmack, C. L., Chaoul, A., Cohen, L., Connelly, L., Haddad, R., Harrison, C., Li, Y., Mallaiah, S., Nagarathna, R., Parker, P. A., Perkins, G. H., Reuben, J. M., Shih, Y. C. T., Spelman, A., Sood, A., Yang, P., Yeung, S. C. J., A Comprehensive Lifestyle Randomized Clinical Trial: Design and Initial Patient Experience, Integrative Cancer Therapies, 16, 3-20, 2017	Survival outcomes not reported so far.
Augustin, L. S., Libra, M., Crispo, A., Grimaldi, M., De Laurentiis, M., Rinaldo, M., D'Aiuto, M., Catalano, F., Banna, G., Ferrau, F., Rossello, R., Serraino, D., Bidoli, E., Massarut, S., Thomas, G., Gatti, D., Cavalcanti, E., Pinto, M., Riccardi, G., Vidgen, E., Kendall, C. W., Jenkins, D. J., Ciliberto, G., Montella, M., Low glycemic index diet, exercise and vitamin D to reduce breast cancer recurrence (DEDiCa): design of a clinical trial, BMC Cancer, 17, 69, 2017	Article deals with only study design
Ballard-Barbash, R., Friedenreich, C. M., Courneya, K. S., Siddiqi, S. M., McTiernan, A., Alfano, C. M., Physical activity, biomarkers, and disease outcomes in cancer survivors: A systematic review, Journal of the National Cancer Institute, 104, 815-840, 2012	Systematic review of observational studies
Bao, P. P., Zhao, G. M., Shu, X. O., Peng, P., Cai, H., Lu, W., Zheng, Y., Modifiable lifestyle factors and triple-negative breast cancer survival: A population-based prospective study, Epidemiology, 26, 909-916, 2015	Same study as Chen (Shanghai Breast Cancer Study)
Beasley,J.M., Newcomb,P.A., Trentham-Dietz,A., Hampton,J.M., Bersch,A.J., Passarelli,M.N., Holick,C.N., Titus-Ernstoff,L., Egan,K.M., Holmes,M.D., Willett,W.C., Post-diagnosis dietary factors and survival after invasive breast cancer, Breast Cancer Research and Treatment, 128, 229-236, 2011	No data on disease free survival
Belle, F. N., Kampman, E., McTiernan, A., Bernstein, L., Baumgartner, K., Baumgartner, R., Ambs, A., Ballard-Barbash, R., Neuhouser, M. L., Dietary fiber, carbohydrates, glycemic index, and glycemic load in relation to breast cancer prognosis in the HEAL cohort, Cancer Epidemiology Biomarkers and Prevention, 20, 890-899, 2011	No data on disease free survival
Berube, S., Lemieux, J., Moore, L., Maunsell, E., Brisson, J., Smoking at time of diagnosis and breast cancer-specific survival: New findings and systematic review with meta-analysis, Breast Cancer Research, 16 (2) (no pagination), 2014	No data on disease free survival

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Bicego, D., Brown, K., Ruddick, M., Storey, D., Wong, C., Harris, S. R., Effects of exercise on quality of life in women living with breast cancer: A systematic review, Breast Journal, 15, 45-51, 2009	No data on survival outcomes
Blackburn, G. L., Wang, K. A., Dietary fat reduction and breast cancer outcome: results from the Women's Intervention Nutrition Study (WINS), The American journal of clinical nutrition, 86, s878-881, 2007	Same study as Chlebowski
Boone, S. D., Baumgartner, K. B., Baumgartner, R. N., Connor, A. E., John, E. M., Giuliano, A. R., Hines, L. M., Rai, S. N., Riley, E. C., Pinkston, C. M., Wolff, R. K., Slattery, M. L., Active and passive cigarette smoking and mortality among Hispanic and non-Hispanic white women diagnosed with invasive breast cancer, Annals of Epidemiology, 25, 824-831, 2015	No data on disease free survival
Borch, K. B., Braaten, T., Lund, E., Weiderpass, E., Physical activity before and after breast cancer diagnosis and survival - the Norwegian women and cancer cohort study, BMC Cancer, 15, 967, 2015	No data on disease free survival
Borugian, M. J., Sheps, S. B., Kim-Sing, C., Van Patten, C., Potter, J. D., Dunn, B., Gallagher, R. P., Hislop, T. G., Insulin, macronutrient intake, and physical activity: Are potential indicators of insulin resistance associated with mortality from breast cancer?, Cancer Epidemiology Biomarkers and Prevention, 13, 1163-1172, 2004	Data on disease free survival not reported
Bradshaw, P. T., Ibrahim, J. G., Khankari, N., Cleveland, R. J., Abrahamson, P. E., Stevens, J., Satia, J. A., Teitelbaum, S. L., Neugut, A. I., Gammon, M. D., Post-diagnosis physical activity and survival after breast cancer diagnosis: The Long Island Breast Cancer Study, Breast Cancer Research and Treatment, 145, 735-742, 2014	No data on disease free survival
Brennan, S. F., Woodside, J. V., Lunny, P. M., Cardwell, C. R., Cantwell, M. M., Dietary fat and breast cancer mortality: A systematic review and meta-analysis, Critical reviews in food science and nutrition, 57, 1999-2008, 2017	No data on disease free survival
Brenner, D. R., Brockton, N. T., Kotsopoulos, J., Cotterchio, M., Boucher, B. A., Courneya, K. S., Knight, J. A., Olivotto, I. A., Quan, M. L., Friedenreich, C. M., Breast cancer survival among young women: a review of the role of modifiable lifestyle factors, Cancer Causes and Control, 27, 459-472, 2016	Review article
Brenner, D. R., Neilson, H. K., Courneya, K. S., Friedenreich, C. M., Physical activity after breast cancer: Effect on survival and patient-reported outcomes, Current Breast Cancer Reports, 6, 193-204, 2014	Does not include disease free survival
Buffart, L. M., Kalter, J., Sweegers, M. G., Courneya, K. S., Newton, R. U., Aaronson, N. K., Jacobsen, P. B., May, A. M., Galvao, D. A., Chinapaw, M. J., Steindorf, K., Irwin, M. L., Stuiver, M. M., Hayes, S., Griffith, K. A., Lucia, A., Mesters, I., van Weert, E., Knoop, H., Goedendorp, M. M., Mutrie, N., Daley, A. J., McConnachie, A., Bohus, M., Thorsen, L., Schulz, K. H., Short, C. E., James, E. L., Plotnikoff, R. C., Arbane, G., Schmidt, M. E., Potthoff, K., van Beurden, M., Oldenburg, H. S., Sonke, G. S., van Harten, W. H., Garrod, R., Schmitz, K. H., Winters-Stone, K. M., Velthuis, M. J., Taaffe, D. R., van Mechelen, W.,	No data on survival

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Kersten, M. J., Nollet, F., Wenzel, J., Wiskemann, J., Verdonck-de Leeuw, I. M., Brug, J., Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs, Cancer Treatment Reviews, 52, 91-104, 2017	
Buffart, Lm, Uffelen, Jgz, Riphagen,, Ii, Brug, J, Mechelen, W, Brown, Wj, Chinapaw, Mjm, Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials (Provisional abstract), BMC Cancer, 12, 559, 2012	No survival outcomes
Caan, Bj, Natarajan, L, Parker, B, Gold, Eb, Thomson, C, Newman, V, Rock, Cl, Pu, M, Al-Delaimy, W, Pierce, Jp, Soy food consumption and breast cancer prognosis, Cancer Epidemiology Biomarkers and Prevention, 20, 854-8, 2011	No data on disease free survival
Cadmus, Bertram La, Pierce, Jp, Patterson, Re, Ojeda-Fournier, H, Newman, Va, Parker, Ba, Training overweight/obese older women at high risk for breast cancer to use web-based weight loss tools: The HELP pilot study, Journal of Clinical Oncology, 29, 2011	Not related to survival after breast cancer
Campbell, A, Mutrie, N, Tovey, S, Barry, S, McLoed, J, Five year follow up of an exercise intervention during breast cancer treatment, Journal of Science and Medicine in Sport, 15, S334, 2012	No data on disease free survival
Casellas-Grau, A, Font, A, Vives, J, Positive psychology interventions in breast cancer: a systematic review (Provisional abstract), Psycho-Oncology, 23, 9-19, 2014	No survival outcomes
Cheema, B, Gaul, C A, Lane, K, Fiatarone, Singh M A, Progressive resistance training in breast cancer: a systematic review of clinical trials (Provisional abstract), Breast Cancer Research and Treatment, 109, 9-26, 2008	No survival outcomes reported
Chi, F., Wu, R., Zeng, Y. C., Xing, R., Liu, Y., Xu, Z. G., Post-diagnosis soy food intake and breast cancer survival: A meta-analysis of cohort studies, Asian Pacific Journal of Cancer Prevention, 14, 2407-2412, 2013	No data on disease free survival
Chida, Y., Hamer, M., Wardle, J., Steptoe, A., Do stress-related psychosocial factors contribute to cancer incidence and survival?, Nature Clinical Practice OncologyNat Clin Pract Oncol, 5, 2008	No data on disease free survival
Chlebowski, R. T., Blackburn, G. L., Elashoff, R. E., Thomson, C., Goodman, M. T., Shapiro, A., Giuliano, A. E., Karanja, N., Hoy, M. K., Nixon, D. W., Wins Investigators, Dietary fat reduction in postmenopausal women with primary breast cancer: Phase III Women's Intervention Nutrition Study (WINS), Journal of Clinical Oncology, 23, 10, 2005	Same as Chlebowski 2005
Chlebowski, R. T., Reeves, M. M., Weight loss randomized intervention trials in female cancer survivors, Journal of Clinical Oncology, 34, 4238-4248, 2016	No survival outcomes
Chlebowski, Rt, Blackburn, Gl, Buzzard, Im, Rose, Dp, Martino, S, Khandekar, Jd, York, Rm, Jeffery, Rw, Elashoff, Rm, Wynder, El, Adherence to a dietary fat intake reduction program in postmenopausal women	No survival outcomes

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
receiving therapy for early breast cancer. The Women's Intervention Nutrition Study, Journal of Clinical Oncology, 11, 2072-2080, 1993	
Choi, J., Kuo, C. W. J., Sikorskii, A., You, M., Ren, D., Sherwood, P. R., Given, C. W., Given, B. A., Cognitive behavioral symptom management intervention in patients with cancer: Survival analysis, Supportive Care in Cancer, 20, 1243-1250, 2012	Not specific to breast cancer
Cleveland, R. J., Eng, S. M., Stevens, J., Bradshaw, P. T., Teitelbaum, S. L., Neugut, A. I., Gammon, M. D., Influence of prediagnostic recreational physical activity on survival from breast cancer, European Journal of Cancer Prevention, 21, 46-54, 2012	No data on disease free survival
Cormie, P., Zopf, E. M., Zhang, X., Schmitz, K. H., The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects, Epidemiologic Reviews, 39, 71-92, 2017	No data on disease free survival
Cramer, Holger, Lauche, Romy, Klose, Petra, Lange, Silke, Langhorst, Jost, Dobos, Gustav J, Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer, Cochrane Database of Systematic Reviews, 2017	No survival related outcomes
Dal Maso, L., Zucchetto, A., Talamini, R., Serraino, D., Stocco, C. F., Vercelli, M., Falcini, F., Franceschi, S., Effect of obesity and other lifestyle factors on mortality in women with breast cancer, International Journal of Cancer, 123, 2188-2194, 2008	No data on disease free survival
Davies, A. A., Davey Smith, G., Harbord, R., Bekkering, G. E., Sterne, J. A. C., Beynon, R., Thomas, S., Nutritional interventions and outcome in patients with cancer or preinvasive lesions: Systematic review, Journal of the National Cancer Institute, 98, 961-973, 2006	Systematic review with studies including cancer at different sites. Breast cancer studies do not specify disease stage
De Glas, N. A., Fontein, D. B. Y., Bastiaannet, E., Pijpe, A., De Craen, A. J. M., Liefers, G. J., Nortier, H. J. R., De Haes, H. J. C. J. M., Van De Velde, C. J. H., Van Leeuwen, F. E., Physical activity and survival of postmenopausal, hormone receptor-positive breast cancer patients: Results of the Tamoxifen Exemestane Adjuvant Multicenter Lifestyle study, Cancer, 120, 2847-2854, 2014	No data on disease free survival
Dean, C., Surtees, P. G., Do psychological factors predict survival in breast cancer?, Journal of Psychosomatic Research, 33, 561-9, 1989	No intervention.
Din, N., Allen, I. E., Satariano, W. A., Demb, J., Braithwaite, D., Alcohol consumption and mortality after breast cancer diagnosis: The health and functioning in women study, Breast Disease, 36, 77-89, 2016	No data on disease free survival
Enger, S. M., Bernstein, L., Exercise activity, body size and premenopausal breast cancer survival, British Journal of Cancer, 90, 2138-2141, 2004	No data on disease free survival
Fong, Dy, Ho, Jw, Hui, Bp, Lee, Am, Macfarlane, Dj, Leung, Ss, Cerin, E, Chan, Wy, Leung, Ip, Lam, Sh, Taylor, Aj, Cheng, Kk, Physical activity for cancer survivors: meta-analysis of randomised controlled trials (Structured abstract), BMJBmj, 344, e70, 2012	No survival outcomes

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Fontein, D. B. Y., de Glas, N. A., Duijm, M., Bastiaannet, E., Portielje, J. E. A., Van de Velde, C. J. H., Liefers, G. J., Age and the effect of physical activity on breast cancer survival: A systematic review, Cancer Treatment Reviews, 39, 958-965, 2013	Does not include disease free survival
Friedenreich, C. M., Gregory, J., Kopciuk, K. A., Mackey, J. R., Courneya, K. S., Prospective cohort study of lifetime physical activity and breast cancer survival, International Journal of Cancer, 124, 1954-1962, 2009	No intervention. Prediagnostic data
Gold, Eb, Pierce, Jp, Natarajan, L, Stefanick, Ml, Laughlin, Ga, Caan, Bj, Flatt, Sw, Emond, Ja, Saquib, N, Madlensky, L, Kealey, S, Wasserman, L, Thomson, Ca, Rock, Cl, Parker, Ba, Karanja, N, Jones, V, Hajek, Ra, Pu, M, Mortimer, Je, Dietary pattern influences breast cancer prognosis in women without hot flashes: the women's healthy eating and living trial, Journal of Clinical Oncology, 27, 352-359, 2009	Data not available for disease free survival
Gou, Y. J., Xie, D. X., Yang, K. H., Liu, Y. L., Zhang, J. H., Li, B., He, X. D., Alcohol consumption and breast cancer survival: A meta-analysis of cohort studies, Asian Pacific Journal of Cancer Prevention, 14, 4785-4790, 2013	Individual eligible study included
Groenvold, M., Petersen, M. A., Idler, E., Bjorner, J. B., Fayers, P. M., Mouridsen, H. T., Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 105, 209-19, 2007	No intervention
Harris, H. R., Bergkvist, L., Wolk, A., Alcohol intake and mortality among women with invasive breast cancer, British Journal of Cancer, 106, 592-595, 2012	No information on disease free survival
Harris, H. R., Orsini, N., Wolk, A., Vitamin C and survival among women with breast cancer: A Meta-analysis, European Journal of Cancer, 50, 1223-1231, 2014	No data on disease free survival
Ibrahim, E. M., Al-Homaidh, A., Physical activity and survival after breast cancer diagnosis: Meta-analysis of published studies, Medical Oncology, 28, 753-765, 2011	No data on disease free survival
Irwin, M. L., McTiernan, A., Manson, J. E., Thomson, C. A., Sternfeld, B., Stefanick, M. L., Wactawski-Wende, J., Craft, L., Lane, D., Martin, L. W., Chlebowski, R., Physical activity and survival in postmenopausal women with breast cancer: Results from the women's health initiative, Cancer Prevention Research, 4, 522-529, 2011	No data on disease free survival
Izano, M., Satariano, W. A., Hiatt, R. A., Braithwaite, D., Smoking and mortality after breast cancer diagnosis: The health and functioning in women study, Cancer Medicine, 4, 315-324, 2015	No data on disease free survival
Jackson, S. E., Heinrich, M., Beeken, R. J., Wardle, J., Weight Loss and Mortality in Overweight and Obese Cancer Survivors: A Systematic Review, 12, e0169173, 2017	No data on disease free survival
Kakugawa, Y., Kawai, M., Nishino, Y., Fukamachi, K., Ishida, T., Ohuchi, N., Minami, Y., Smoking and survival after breast cancer diagnosis in Japanese women: A prospective cohort study, Cancer Science, 106, 1066-1074, 2015	No data on disease free survival

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Kroenke, C. H., Fung, T. T., Hu, F. B., Holmes, M. D., Dietary patterns and survival after breast cancer diagnosis, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 23, 9295-9303, 2005	No data on disease free survival
Lahart, I. M., Metsios, G. S., Nevill, A. M., Carmichael, A. R., Physical activity, risk of death and recurrence in breast cancer survivors: A systematic review and meta-analysis of epidemiological studies, Acta Oncologica, 54, 635-654, 2015	No data on disease free survival
Lew, J. Q., Freedman, N. D., Leitzmann, M. F., Brinton, L. A., Hoover, R. N., Hollenbeck, A. R., Schatzkin, A., Park, Y., Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: the NIH-AARP Diet and Health Study, American Journal of Epidemiology, 170, 308-17, 2009	Related to occurrence of breast cancer
Lowry, S. J., Kapphahn, K., Chlebowski, R., Li, C. I., Alcohol use and breast cancer survival among participants in the Women's Health Initiative, Cancer Epidemiology Biomarkers and Prevention, 25, 1268-1273, 2016	Does not include data on disease free survival
Magne, N., Melis, A., Chargari, C., Castadot, P., Guichard, J. B., Barani, D., Nourissat, A., Largillier, R., Jacquin, J. P., Chauvin, F., Merrouche, Y., Recommendations for a lifestyle which could prevent breast cancer and its relapse: Physical activity and dietetic aspects, Critical Reviews in Oncology/Hematology, 80, 450-459, 2011	Review article
Makarem,N., Chandran,U., Bandera,E.V., Parekh,N., Dietary fat in breast cancer survival, Annual Review of Nutrition, 33, 319-348, 2013	Only one study from review reports disease free survival, which is already included in review.
Maliniak, M. L., Patel, A. V., McCullough, M. L., Campbell, P. T., Leach, C. R., Gapstur, S. M., Gaudet, M. M., Obesity, physical activity, and breast cancer survival among older breast cancer survivors in the Cancer Prevention Study-II Nutrition Cohort, Breast Cancer Research and Treatment, 1-13, 2017	No data on disease free survival
Marinac, C. R., Nelson, S. H., Flatt, S. W., Natarajan, L., Pierce, J. P., Patterson, R. E., Sleep duration and breast cancer prognosis: perspectives from the Women's Healthy Eating and Living Study, Breast Cancer Research and Treatment, 162, 581-589, 2017	Exclusion by intervention
Marinac, C., Patterson, R. E., Villasenor, A., Flatt, S. W., Pierce, J. P., Mechanisms of association between physical functioning and breast cancer mortality: evidence from the Women's Healthy Eating and Living Study, Journal of cancer survivorship : research and practice, 8, 402-409, 2014	No data on disease free survival
Marinho, L. A. B., Rettori, O., Vieira-Matos, A. N., Body weight loss as an indicator of breast cancer recurrence, Acta Oncologica, 40, 832-837, 2001	No intervention
Pierce, J. P., Stefanick, M. L., Flatt, S. W., Natarajan, L., Sternfeld, B., Madlensky, L., Al-Delaimy, W. K., Thomson, C. A., Kealey, S., Hajek, R., Parker, B. A., Newman, V. A., Caan, B., Rock, C. L., Greater	Does not include data on disease free survival

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity, Journal of Clinical Oncology, 25, 2345-2351, 2007	
Pierce, Jp, Natarajan, L, Caan, Bj, Parker, Ba, Greenberg, Er, Flatt, Sw, Rock, Cl, Kealey, S, Al-Delaimy, Wk, Bardwell, Wa, Carlson, Rw, Emond, Ja, Faerber, S, Gold, Eb, Hajek, Ra, Hollenbach, K, Jones, La, Karanja, N, Madlensky, L, Marshall, J, Newman, Va, Ritenbaugh, C, Thomson, Ca, Wasserman, L, Stefanick, Ml, 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, JAMAJama, 298, 289-298, 2007	No data on disease free survival
Pourmasoumi, M., Karimbeiki, R., Vosoughi, N., Feizi, A., Ghiasvand, R., Barak, F., Miraghajani, M., Healthy Eating Index/Alternative Healthy Eating Index and Breast Cancer Mortality and Survival: A Systematic Review and Meta-analysis, Asiapacific Journal of Oncology NursingAsia-Pac, 3, 297-305, 2016	Disease free survival not included as outcome
Reding, K. W., Daling, J. R., Doody, D. R., O'Brien, C. A., Porter, P. L., Malone, K. E., Effect of prediagnostic alcohol consumption on survival after breast cancer in young women, Cancer Epidemiology Biomarkers and Prevention, 17, 1988-1996, 2008	No data on disease free survival
Rohan, T. E., Hiller, J. E., McMichael, A. J., Dietary factors and survival from breast cancer, Nutrition and Cancer, 20, 167-177, 1993	No data on disease free survival
Rohan, Te, Jain, M, Howe, Gr, Miller, Ab, Alcohol consumption and risk of breast cancer: a cohort study, Cancer Causes & ControlCancer Causes Control, 11, 239-247, 2000	Related to risk of breast cancer
Romy, L, Holger, C, Anna, P, Gustav, D, Effectiveness of mindfulness-based stress reduction (MBSR) for breast cancer-a systematic review and meta-analysis, European Journal of Integrative Medicine, 4, 126-7, 2012	No survival outcomes
Saquib, An, Natarajan, L, Flatt, S, Bardwell, Wa, Pierce, Jp, Physical health and cancer-free survival in women diagnosed with breast cancer, 2008	No data on disease free survival
Saquib, N., Stefanick, M. L., Natarajan, L., Pierce, J. P., Mortality risk in former smokers with breast cancer: Pack-years versus. smoking status, International Journal of Cancer, 133, 2493-2497, 2013	No data on disease free survival
Saxe, G. A., Rock, C. L., Wicha, M. S., Schottenfeld, D., Diet and risk for breast cancer recurrence and survival, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 53, 241-53, 1999	No data on disease free survival. No intervention.
Seibold, P., Vrieling, A., Heinz, J., Obi, N., Sinn, H. P., Flesch-Janys, D., Chang-Claude, J., Pre-diagnostic smoking behaviour and poorer prognosis in a german breast cancer patient cohort - differential effects by tumour subtype, NAT2 status, BMI and alcohol intake, Cancer Epidemiology, 38, 419-426, 2014	Pre diagnostic data. No lifestyle change intervention

Excluded studies -11.1 What lifestyle changes improve breast cancer-specific outcomes in people treated for early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Stagl, J. M., Lechner, S. C., Carver, C. S., Bouchard, L. C., Gudenkauf, L. M., Jutagir, D. R., Diaz, A., Yu, Q., Blomberg, B. B., Ironson, G., Gluck, S., Antoni, M. H., A randomized controlled trial of cognitive-behavioral stress management in breast cancer: survival and recurrence at 11-year follow-up, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 154, 319-28, 2015	No data for disease free survival
Villarini, A, Pasanisi, P, Traina, A, Mano, Mp, Bonanni, B, Panico, S, Scipioni, C, Galasso, R, Paduos, A, Simeoni, M, Bellotti, E, Barbero, M, Macellari, G, Venturelli, E, Raimondi, M, Bruno, E, Gargano, G, Fornaciari, G, Morelli, D, Seregni, E, Krogh, V, Berrino, F, Lifestyle and breast cancer recurrences: the DIANA-5 trial, Tumori, 98, 1-18, 2012	Study Protocol
Vrieling, A., Buck, K., Seibold, P., Heinz, J., Obi, N., Flesch-Janys, D., Chang-Claude, J., Dietary patterns and survival in German postmenopausal breast cancer survivors, British Journal of Cancer, 108, 188-192, 2013	No lifestyle change intervention. Prediagnostic patterns
Vrieling,A., Buck,K., Heinz,J., Obi,N., Benner,A., Flesch-Janys,D., Chang-Claude,J., Pre-diagnostic alcohol consumption and postmenopausal breast cancer survival: A prospective patient cohort study, Breast Cancer Research and Treatment, 136, 195-207, 2012	No lifestyle intervention. prediagnosis
Wang, K., Li, F., Zhang, X., Li, Z., Li, H., Smoking increases risks of all-cause and breast cancer specific mortality in breast cancer individuals: A dose-response metaanalysis of prospective cohort studies involving 39725 breast cancer cases, Oncotarget, 7, 83134-83147, 2016	No data on disease free survival
Weaver, A. M., McCann, S. E., Nie, J., Edge, S. B., Nochajski, T. H., Russell, M., Trevisan, M., Freudenheim, J. L., Alcohol intake over the life course and breast cancer survival in Western New York exposures and breast cancer (WEB) study: Quantity and intensity of intake, Breast Cancer Research and Treatment, 139, 245-253, 2013	No data on disease free survival
Xing, M. Y., Xu, S. Z., Shen, P., Effect of low-fat diet on breast cancer survival: A meta-analysis, Asian Pacific Journal of Cancer Prevention, 15, 1141-1144, 2014	No data on disease free survival
Zhong, S., Jiang, T., Ma, T., Zhang, X., Tang, J., Chen, W., Lv, M., Zhao, J., Association between physical activity and mortality in breast cancer: A meta-analysis of cohort studies, European Journal of Epidemiology, 29, 391-404, 2014	No data on disease free survival

Economic studies

See Supplement 1: Health economics literature review for the list of excluded economic studies.

Appendix L – Research recommendations

No research recommendations were made for this review question.