The relationship between healthy lifestyle behaviours and outcomes for people living with and beyond cancer: an overview of Systematic Reviews

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Background

There are an extensive number of published evidence reviews examining the influence of lifestyle behaviours on cancer outcomes. Healthy lifestyles are a significant topic of debate in oncology and in policy and practice organisations that support people living with and beyond cancer. Such reviews vary in quality, address different relationships, outcomes and cancers, and there is often more than one review on important topics. This makes it difficult for policy and practice professionals to make decisions about the prescription and promotion of lifestyle behaviours for cancer populations. An overview of systematic reviews provides a single, overarching summary of evidence from published systematic reviews and compares and contrasts the findings of systematic reviews, providing healthcare professionals with the evidence needed for more effective decision making (Smith et al. 2011). This overview of systematic reviews synthesises evidence from systematic reviews on smoking, physical activity, dietary behaviours and alcohol consumption to present a summary of evidence about the relationships between these lifestyle behaviours and outcomes for people living with and beyond cancer.

Protocol registration

The protocol for this review was registered on the PROSPERO International Prospective Register of Systematic Reviews (Registration number CRD42016032857).

Methodology

Aim

To synthesise the findings of an overview of systematic reviews that investigated the relationship between healthy lifestyle behaviours on outcomes for people living with and beyond cancer.

Criteria for considering reviews for inclusion

Types of studies

We included systematic reviews that assessed the relationship between healthy lifestyle behaviours and outcomes in people living with and beyond cancer. This included reviews of non-randomised observational studies including cross-sectional, prospective cohort and case-control studies. To be included any review must have achieved a judgement of "Yes" on the third criterion on the AMSTAR tool for assessing the quality of systematic reviews (Shea 2007): "Was a comprehensive literature search performed?" as we considered this a minimum requirement for a review to be deemed systematic. Our additional criteria for considering a search to be systematic were that authors must

have searched at least 2 electronic databases using a clear search strategy, and screened the reference lists of identified studies. We excluded reviews published prior to 2010. We only included reviews published in the English language.

Types of participants

Adults, 18 years or older living with or beyond cancer. This included any group who had received a cancer diagnosis for any cancer type, at any stage in the treatment or recovery pathway. We did not consider evidence relating to the risk of incident primary cancer diagnoses. That is, we were interested in the influence of healthy lifestyle behaviours on outcomes for people living with and beyond cancer, not as risk factors for primary cancer.

Types of behaviour

Any behaviour commonly associated with a healthy or unhealthy lifestyle. This included participation in exercise and exertional physical activity, dietary choices, tobacco use and consumption of alcohol. Obesity and BMI were also included as variables of interest related to dietary behaviours. While we recognise that obesity and BMI are not lifestyle choices per se they were considered as variables partially related to lifestyle behaviours.

Types of outcome measure

We included reviews that measured the following core cancer outcomes:

- Mortality
- Recurrence
- Remission/ recovery
- Disease progression
- Late effects and Consequences of Treatment (incidence or severity of any known consequence of cancer treatment)

and/ or measures of physical health or wellness which could include physical function, quality of life, wellbeing, fatigue, anxiety and depression.

Search methods for identification of reviews

Electronic searches

Electronic databases were searched using a combination of controlled vocabulary (MeSH) and free text terms from 2010 to Jan 2016. Search terms were incorporated to target cancer and systematic reviews. We incorporated the BMJ Clinical Evidence search filter for systematic reviews. The OVID MEDLINE search strategy can be found in Appendix A. All database searches were based on this strategy but appropriately revised to suit each database. The following databases were searched:

- Cochrane Database of Systematic reviews
- Centre for Reviews and Dissemination

- OVID MEDLINE
- EMBASE
- CINAHL plus

Searching other sources

The reference lists of all eligible reviews were hand-searched to attempt to identify additional relevant reviews.

Identification of reviews

Search results were independently checked by two overview authors and eligible reviews were included. Initially the titles and abstracts of identified studies were reviewed. Where it was clear from the title that the study did not meet the inclusion criteria it was excluded. Where it was not clear from the title and abstract whether a study was relevant the full review was checked to confirm eligibility. The selection criteria were then independently applied to the full papers of identified reviews by two overview authors. Where two independent reviewers did not agree in their primary judgements they discussed the conflict and attempted to reach a consensus. If this was not successful a third member of the review team considered the title and a majority decision was made.

Data collection and analysis

Data extraction and management

Data were extracted independently by two overview authors using a standardised form. Discrepancies were resolved by consensus. Where agreement could not be reached a third overview author considered the paper and a majority decision was reached. The data extraction included the following details:

- the assessment of methodological quality of the included review
- the objectives of the review
- details of the included participants
- the exposures (healthy lifestyle behaviours) studied, including detail where available on the measurements used and the severity or amount of exposure
- the outcomes and time-points assessed (primary and secondary) and estimates of association (effect size) with measures of imprecision at all time-points available
- The assessment of the methodological quality/ risk of bias of the included studies and judgements of the quality of the body of evidence (for example using GRADE)
- The presence of possible conflicts of interest for authors of the included trials within a review, and for the authors of the review themselves

We did not seek information from the included clinical trials that is not presented in the identified reviews.

Assessment of methodological quality of included reviews

We used the AMSTAR tool to assess the methodological quality of the included reviews (Shea 2007) (see Appendix B for an example of the tool)

Assessment of the quality of the evidence in included reviews

We expected that included reviews are likely to have assessed the methodological quality/risk of bias of included studies in a variety of ways. We used the judgements made by the authors of original reviews regarding the quality of evidence/risk of bias but have reported it within the context of our assessment of the quality of the review itself.

Data synthesis

We tabulated summaries of the characteristics of the included reviews. The precise comparisons presented were primarily determined by the content of the included reviews. We have presented effect sizes using appropriate metrics including estimates of precision where available. Data were grouped where possible according to diagnosis (cancer type), stage in the cancer journey (during treatment, after treatment, advanced cancer), the type of exposure (exercise/ physical fitness, smoking behaviour, drinking behaviour, healthy eating/ dietary behaviours, general healthy lifestyle behaviours) and outcome. Important limitations within the evidence base are presented and discussed. We considered the possible influence of publication/small study biases on review findings. Where included reviews did not rate the quality of the body of evidence we applied, where possible, the GRADE approach for all key comparisons (Guyatt et al. 2008). In the GRADE approach evidence from non-randomised studies is rated as low. Ratings can be further downgraded where there is concern over the limitations of the included studies, imprecision in observed effects, inconsistency, and indirectness of the evidence to the population of interest or evidence of publication bias. Ratings can be upgraded where there is consistent evidence of large effects, or other indicators that increase confidence in an estimate such as evidence of a dose-response relationship. Ratings can be high, moderate, low or very low quality. In terms of confidence in the findings the ratings can be defined as follows:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

FINDINGS

Results of the searches

After removal of duplicates the electronic searches returned 6404 records for screening. Of these 120 were retained after abstract and title screening and the full texts were assessed. 93 records were excluded at this stage and 3 further relevant reviews were identified through hand-searching of the reference lists of included reviews, resulting in 30 reviews in total included in this overview. The search screening process is illustrated in **Figure 1**. See Appendix 2 for a list of excluded studies with reasons for exclusion.

Characteristics of Included Reviews

The included reviews investigated the relationships of a range of lifestyle behaviours for a broad range of different cancer types and stages if disease. For a summary of the characteristics of the included reviews see **Table 1.**

Nine reviews (Cao et al. 2011, Chi et al. 2013, Davies et al. 2011, Lee et al. 2015, Koutoukidis et al. 2015, Ogunleye et al. 2010, Smits et al. 2015, Xing et al. 2014, Zhang et al. 2013) investigated the influence of dietary behaviours and/ or obesity on outcomes of interest. Nine reviews (Barbaric et al. 2010, Davies et al. 2011, Fontein et al. 2013, Henneghan et al. 2016, Ibrahim et al. 2011, Kim et al. 2013, Koutoukidis et al. 2015, Lahart et al. 2015, Zhong et al. 2014) investigated the relationship between physical activity and exercise behaviours on relevant outcomes. Nine reviews investigated smoking behaviours (Braithewaite et al. 2012, Crivelli et al. 2014,Florou et al. 2014, Pang et al. 2015, Parsons et al. 2014, Rowland et al. 2012, Walter et al. 2014, Xu et al. 2014, Zhang et al. 2013) and two reviews investigated alcohol consumption (Druesne-Pecollo et al.2014, Gou et al. 2013). Outcomes measured, relevant to this overview, included survival and mortality (all-cause or cancer specific), recurrence, disease progression, quality of life, cancer treatment related complications and cognitive dysfunction. All of the included evidence included in this overview related to people following diagnosis of cancer but few reviews specifically focused on people at a specific stage of their cancer journey.

Quality of Included Reviews

The AMSTAR quality assessment scores for the included reviews ranged from 2 to 7 out of a maximum of 11 (median 4). It was not clear for any of the reviews whether an a priori protocol was used in the conduct of the review and none of the reviews appeared to have been pre-registered on PROSPERO. Only 2 reviews searched for grey literature and included studies regardless of language, and only 3 reviews presented a full list of excluded studies. Notable, of 30 reviews 19 did not report a formal assessment of the quality of included studies, something we consider a major flaw. The possibility of publication bias was commonly not considered in the included reviews. The full results for the AMSTAR quality assessment are presented in table 2.

RESULTS OF THE SEARCHES

Figure 1: PRISMA flow diagram of the search screening process

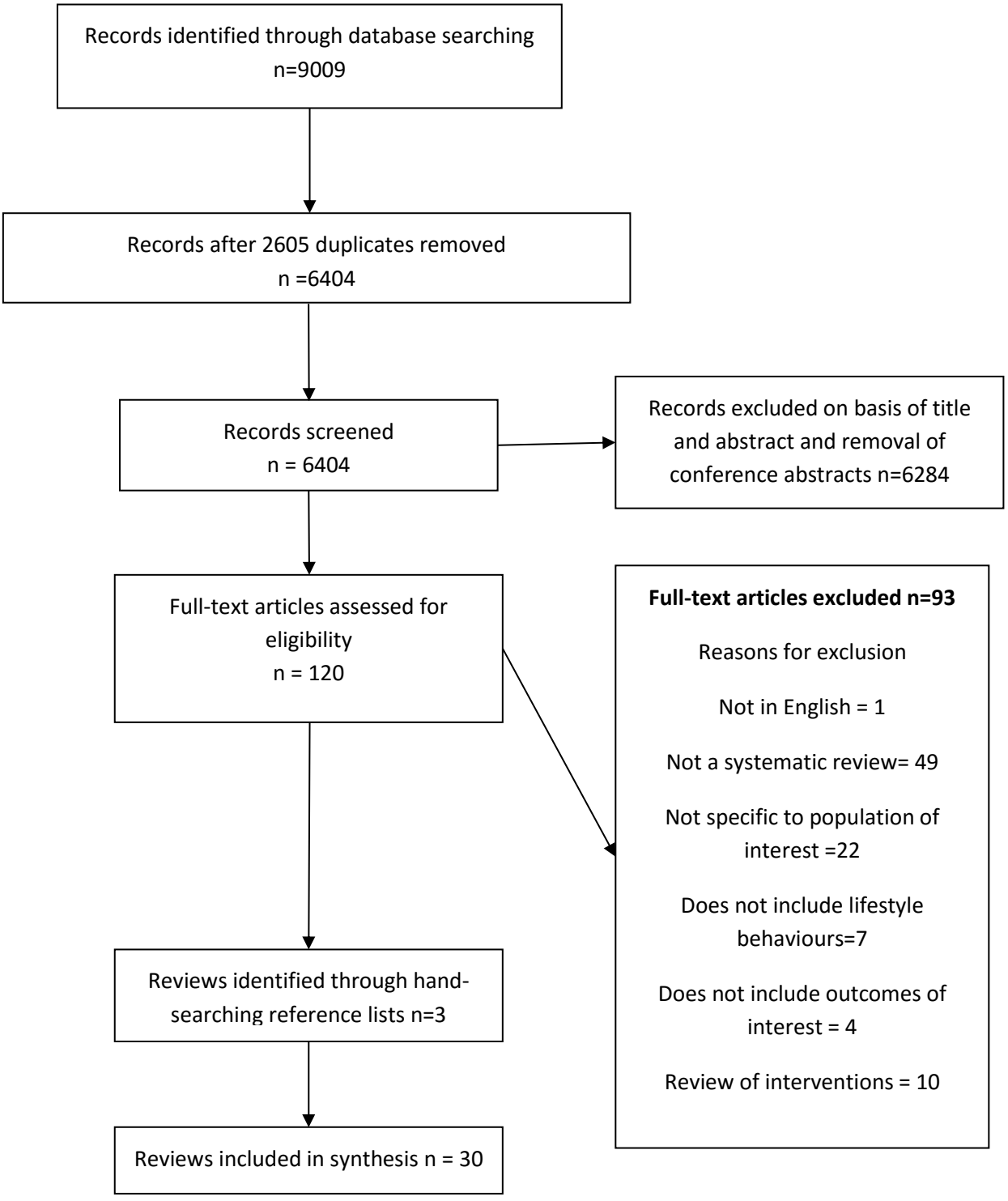

Table 1. Characteristics of included reviews

Review	Search dates (to)	Participants or cancer type*	Behaviour related factors*	Outcomes*	N of studies/participants* Design of included studies	Study quality tool used.
Barbaric 2010	1950-2008	Patients with breast, colorectal or colon cancer	PA	Primary outcome = survival; secondary outcomes = cancer-specific and overall mortality	10 prospective cohort studies, N= 13824	PEDro scale for RCTs Newcastle-Ottawa Scale (NOS)
Braithewaite 2012	July 2012	Adult Women with invasive breast cancer	Smoking	Mortality	7 cohort studies, N=>14,000	No formal assessment of study quality
Cao 2011	Jan 2010	Men diagnosed with prostate cancer.	BMI	Prostate Ca specific mortality Biochemical recurrence	22 studies, Prospective, and retrospective Mortality N=18203 Recurrence N=26479	No formal assessment of study quality
Chi 2013	Jan 2013	People with abreast cancer diagnosis	Soy intake	Mortality (? All-cause or Ca-specific) Recurrence	5 studies All prospective N= 11224	No formal assessment of study quality
Crivelli 2014	July 2012	Patients with urothelial cancer of the bladder or upper tract urothelial cancer treated with surgery	Smoking	Recurrence, progression, cancer-specific mortality, all-cause mortality	29 studies, designs unclear. N=15,116	No formal assessment of study quality
Davies 2011	Aug 2011	Breast, prostrate, colorectal survivors	PA and diet	Recurrence and progression	14 studies on diet (1 colorectal, 5 prostate, 8 breast) – RCTs, longitudinal studies, prospective cohort, cohort, retrospective, review of epidemiology literature, interview study 14 studies on PA (9 breast, , 3 colorectal, , 2 prostate) N = 121, 845	No formal assessment of study quality

Druesne-Pecollo 2014	July 2012	Adults with upper aerodigestive tract (UADT) as first primary cancer site	Alcohol consumption	Second primary cancer risk	19 studies 8 cohort studies; 11 case-control studies N= not reported	No formal assessment of study quality
Florou 2014	July 2013	Adults with any cancer type	Smoking	Overall survival, Progression-free survival, Recurrence-free survival, Mortality, Recurrence, Progression, Quality of life Performance status response to therapy, risk for second cancer, risk for second primary tumour,	20 studies, 4 retrospective, 15 prospective observational, 3 RCTs N=12,725	No formal assessment of study quality
Fontein 2013	November 2012.	Breast cancer patients	PA	Survival outcomes All-cause mortality Breast cancer specific mortality	N = 35,026	No formal assessment of study quality
Gou 2013	February 2013	Breast cancer patients	Alcohol consumption	Survival	25 prospective cohort studies. N=719555	No formal assessment of study quality
Henneghan 2016	June 2015	Breast cancer survivors	PA	Cancer related cognitive impairment	2 cross sectional studies N=55	9 point quality scale, results not reported.
Ibrahim 2011	Not stated	Breast cancer patients	PA	Breast cancer outcomes Breast cancer mortality All cause mortality	6 studies 4 observational (2 prospective), 1 interview study 1 population-based case control study N =12,108	No formal assessment of study quality

Jansen 2010	January 2010	Colorectal cancer survivors	BMI	Quality of Life	One study, design not reported 259 participants	Mols 14-item standardised checklist
Kayani 2012	January 2012	Esophageal cancer post-oesophagectomy	BMI	Successful tumour resection Complications Reoperation rate Mortality and long-term survival	5 retrospective cohort studies N=1682	No formal assessment of study quality
Kim 2013	May2013	Breast cancer over 18 years	PA	Breast cancer mortality risk	breast cancer mortality risk total N= 35, 504 physiological functions N = 1027	No formal assessment of study quality
Koutoukidis 2015	January 2014	Endometrial cancer survivors stages I-IV	Obesity Diet Physical activity	HRQoL Adherence to physical activity guidelines	8 studies, 6 relevant to review 4 cross-sectional 1 retrospective 1 prospective n of participants for all studies not reported	SIGN checklists 0 high quality studies 2 acceptable quality 2 unacceptable quality
Lahart 2015	October 2014,	Breast cancer survivors	PA	breast cancer outcomes (i.e. breast cancer-related deaths or recurrences). average follow-up periods ranging from 4.3 to 12.7 years	Twenty-two prospective cohort studies 123 574 participants	The Newcastle-Ottawa scale was used to critically appraise the risk of bias across studies.
Lee 2015	September 2014	Patients with colorectal cancer	BMI	colorectal cancer-specific mortality all-cause mortality	16 studies 14 prospective 2 case-control n= 58,917	The Newcastle-Ottawa Scale (NOS) Results not reported
Ogunleye 2010	December 2008	Breast cancer	Green tea consumption	Breast cancer recurrence	2 studies, both prospective cohort. n=1588	No formal assessment of study quality
Pang 2015	September 2014	People with liver cancer	Smoking	Mortality, Recurrence	4 Cohort studies n= 1031	Newcastle-Ottawa scale. Studies scored between 6-8/9

Parsons 2010	December 2008	Lung cancer, any type or stage.	Smoking cessation	All-cause mortality, Second primary cancer Recurrence	10 observational studies, 4 prospective, 5 retrospective, 1 unclear. N=1929	Altman criteria for prognostic studies
Rowland 2012	June 2010	Adults with a lung cancer diagnosis	Smoking	HRQoL	8 studies 5 cross-sectional 3 longitudinal N=2100	CASP appraisal tool
Smits 2015	October 2014	Endometrial cancer survivors	BMI	Quality of life Anxiety and depression Sexual function	7 studies Cross sectional, retrospective, prospective n=1774	Cochrane Non-Randomised Studies Methods Group tool. All studies at high risk of bias on more than one criteria
So 2012	December 2011	Head and neck cancer survivors	Smoking	Quality of Life	One prospective longitudinal study. N=316	Mols 14-item standardised checklist
Walter 2014	August 2013	People with colorectal cancer	Smoking	Recurrence-free survival, Disease-free survival, All-cause mortality Colorectal cancer mortality	16 studies Designs not reported N=62,278	4 point tool based on MOOSE checklist
Xing 2014	August 2013	Women with breast cancer	Low fat diet	Breast cancer specific mortality All-cause mortality	1 cohort study N=4441 (USA) 2 RCTs Pooled n= 9966	No formal assessment of study quality
Xu 2014	November 2013	People with renal cell carcinoma	Smoking	Overall mortality, Disease specific mortality, Overall survival, Cancer specific survival progression free survival	14 studies, designs not reported. N=343,993	Newcastle Ottawa.
Zhang 2013	December 2012	People who underwent surgery for oesophageal cancer	BMI	Postoperative complications Survival	14 studies Designs not clear n=2031	No formal assessment of study quality

Zhang 2015	Not reported	NSCLC patients with EGFR mutations after EGFR-TKI treat-ment that were not used as combined therapy or maintenance therapy	Smoking	Progression free survival	9 studies 2 prospective, 7 retrospective. N=1029	Quorum and the Cochrane Collaboration guidelines. Results not reported.
Zhong 2014		People with breast cancer	PA	All-cause mortality and breast cancer specific mortality	16 cohort studies involving N = 42,602	No formal assessment of study quality

*Relevant to this overview **Conclusions of authors of the included review

Abbreviations

a/w associated with

CASP Critical Skills Appraisal Programme

EGFR Epidermal growth factor receptor

HR-QoL Health Related Quality of Life

MOOSE Meta-analysis Of Observational Studies in Epidemiology

NSCLC Non-small cell lung carcinoma

SIGN Scottish Intercollegiate Guidelines Network

TKI Tyrosine-kinase inhibitors

Table 2. AMSTAR scoring results for all included reviews

REVIEW	*1. a priori design ?*	*2. duplicate selection & extraction ?*	*3. comprehen-sive search?*	*4. Incl. grey lit and language ?*	*5. List of studies incl/excl*	*6. characteris-tics of studies presented?*	*7. quality assessed and reported?*	*8. Quality used appro-priately*	*9. pooling appro-priate?*	*10. publicatio n bias assessed?*	*11. CoI stated?*	*Overall SCORE /11*
Barbaric 2010	CA	Y	N	N	Y	Y	Y	Y	CA	N	N	5
Braithewaite 2012	CA	N	Y	N	N	Y	N	CA	NA	N	N	3
Cao 2011	CA	Y	Y	N	N	Y	N	N	Y	Y	N	5
Chi 2013	CA	Y	Y	N	N	Y	N	N	Y	Y	N	5
Crivelli 2014	CA	Y	Y	N	N	Y	CA	CA	NA	N	N	4
Davies 2011	CA	Y	N	N	N	Y	N	N	N	N	N	2
Druesne-Pecollo 2014	CA	Y	Y	Y	N	Y	N	N	Y	Y	N	6
Florou 2014	CA	N	Y	N	N	Y	N	CA	NA	N	N	3
Fontein 2013	CA	Y	N	N	N	Y	N	N	NA	N	N	3
Gou 2013	CA	Y	Y	N	N	Y	N	N	Y	Y	N	5
Henneghan 2016	CA	N	Y	N	N	Y	Y	CA	NA	N	N	4
Ibrahim 2011	CA	CA	Y	N	N	Y	CA	CA	Y	Y	N	4
Jansen 2010	CA	N	Y	N	N	Y	Y	N	NA	N	N	4
Kayani 2012	CA	N	Y	N	N	Y	N	N	Y	Y	N	4
Kim 2013	CA	Y	N	N	N	Y	N	N	NA	N	N	3
Koutoukidis 2015	CA	Y	Y	Y	N	Y	Y	N	NA	N	N	6
Lahart 2015	CA	Y	Y	N	N	Y	Y	Y	Y	Y	N	7
Lee 2015	CA	Y	Y	N	N	Y	Y	N	Y	Y	N	6

Ogunleye 2010	CA	N	Y	N	N	Y	N	N	NA	Y	N	4
Pang 2015	CA	Y	Y	N	Y	Y	Y	N	Y	Y	N	7
Parsons 2010	CA	Y	Y	Y	N	Y	Y	CA	Y	N	N	6
Rowland 2012	CA	Y	Y	N	N	Y	Y	CA	NA	N	N	5
Smits 2015	CA	N	Y	CA	N	Y	Y	Y	CA	N	N	4
So 2012	CA	N	Y	N	N	Y	Y	N	NA	N	N	4
Walter 2014	CA	Y	Y	N	Y	Y	Y	CA	Y	CA	N	6
Xing 2014	CA	CA	Y	N	N	Y	N	N	Y	N	N	3
Xu 2014	CA	Y	Y	N	N	Y	Y	CA	Y	N	N	5
Zhang 2013	CA	N	N	N	N	Y	N	N	Y	Y	N	3
Zhang 2015	CA	Y	Y	Y	N	N	N	CA	Y	CA	N	4
Zhong 2014	CA	Y	Y	N	N	Y	Y	Y	Y	Y	N	7

Findings of included reviews

DIETARY BEHAVIOURS AND OBESITY

Breast cancer

Green tea consumption

Outcome: Recurrence

One review (Ogunleye et al. 2010) investigated the association between green tea consumption and breast cancer risk. Relevant to this overview it included the outcome of recurrence of breast cancer. For this outcome the review identified two prospective cohort studies conducted in Japan, including 1,588 participants in total. The review presented no formal quality assessment for the included studies. Pooling of these studies resulted in a marginally statistically significant 27% reduction in the relative risk (RR) of breast cancer recurrence (RR 0.73 95%CI 0.56-0.956) among "heavy" green tea drinkers compared to non-drinkers with no heterogeneity. The duration of follow up and degree of attrition of both studies was not reported in this review. The authors of the review concluded that the data provide preliminary evidence for a benefit of green tea consumption in preventing recurrence. The AMSTAR quality score for this review was 4/11.

Given the lack of information regarding study quality, length of follow up and the fact that both studies were conducted in Japan (raising issues of generalisability and directness given likely differences in environment and average diet compared with the UK)the GRADE level of evidence for this association was rated as very low (downgraded for limitations and indirectness).

Soy intake

Outcome: mortality and recurrence

One review (Chi et al 2013) investigated whether soy intake was associated with breast cancer survival or recurrence after diagnosis. This review included five cohort studies, three from China and two from the USA which included a combined 11,224 participants. The studies all recruited participants following breast cancer diagnosis and follow-up duration was between 3.9 to 7.3 years. Soy intake was measured in grams per day. The review presented no formal quality assessment for the included studies. The AMSTAR score for this review was 5/11.

For mortality the review found a statistically significant 15% reduction either when all doses of soy were compared to the lowest dose (5 studies, n for comparison not reported, Hazard Ratio HR 0.85, 05%CI 0.77 to 0.93), or when the highest dose was compared with the lowest dose (5 studies, n for comparison not reported, HR 0.84, 95%CI 0.71 to 0.99) with no significant heterogeneity.

For recurrence similar reductions were observed (4 studies, n for comparison not reported, all doses vs highest dose HR 0.79, 95%CI 0.72 to 0.87; highest vs lowest dose HR 0.74, 95%CI 0.64 TO 0.85). On a secondary analysis this review found that these associations were not statistically significant in patients taking tamoxifen. Subgroup analyses found that association between soy intake and mortality was unchanged by menopausal status or the estrogen receptor (ER) status of the cancer but that soy food intake was associated with lower recurrence in ER negative, ER+/progesterone receptor (PR)+, and postmenopausal patients.

The review authors conclude that soy intake might be associated with lower mortality and recurrence. Given the lack of information regarding study quality, the GRADE level of evidence for this association was rated as very low (downgraded for limitations).

Low fat diet

Outcome mortality

One review (Xing et al. 2014) aimed to investigate the effect of a low fat diet post breast cancer diagnosis on recurrence and all-cause mortality. Relevant to this overview they included one multi-centre cohort study of 4441 participants, conducted in the USA with an average 5.5 year follow up period. No formal quality assessment of included studies was presented in this review and the cohort study investigated survival but not recurrence. The AMSTAR score for this review was 3/11.

The cohort study found no statistically significant effect of low fat diet on all-cause mortality in people following breast cancer diagnosis (HR 0.89 (95%CI 0.65-1.21). When data from that study was pooled with the results of 2 RCTs, also conducted in the USA of low fat diet interventions post diagnosis (not strictly relevant to this review) the effect remained statistically non-significant (HR 0.83, 95%CI 0.69-1.0, P=0.05, pooled n= 9966) with no significant heterogeneity. The authors of the review concluded that more evidence was needed to evaluate the effect of a low fat diet on all-cause mortality following breast cancer. Given the lack of clarity on study quality, the low AMSTAR score of the review, and the fact that the estimate of the pooled effect came close to the threshold for statistical significance the GRADE level of evidence was rated as of very low quality(downgraded for limitations and imprecision) for no association between low fat diet and all-cause mortality in people following breast cancer diagnosis.

Endometrial cancer

BMI and diet

Outcome: QoL (Quality of Life)

Two reviews (Koutoukidis et al. 2015; Smits et al 2015) aimed to explore the relationships between obesity and/ or diet with HRQoL in survivors of endometrial cancer.

Koutoukidis et al. (2015) identified 8 studies of which 2 were RCTs and not relevant to this review. The review included studies of survivors of stage I-IV endometrial cancers. Survivorship was defined as

those surviving at the end of primary or adjuvant therapy, with or without disease. The review only reported the characteristics of 4 of the 6 relevant studies, 3 of which were cross-sectional and one a retrospective study. Study quality was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) checklists. 2 studies were rated as of acceptable quality, 2 as of unacceptable quality. No studies were rated as high quality. The AMSTAR score for this review was 6/11.

No meta-analysis was conducted in this review. Of three studies (combined n =1212) that assessed the relationship between BMI and HRQoL all showed improved HRQoL with BMI, with standardised effect sizes (Cohen's d)ranging between small (≥0.2) and large (≥0.8) effects.

One study (n= 729) showed an improved general HRQoL with lower BMI and increased physical activity after adjusting for major confounders.

The authors conclude that a healthy lifestyle is positively associated with HRQoL in this population, but the number and quality of studies is limited.

Smits et al. (2015) included HRQoL but also anxiety, depression and sexual function as outcomes. They included seven studies of 1,744 adult women who had completed treatment for endometrial cancer. Studies had a mix of cross-sectional, retrospective and prospective designs of which four studies (3 cross-sectional and 1 retrospective, n=1362) were included in meta-analyses. 3 of these studies were included in the review of Koutoukidis. Risk of bias of the included studies was assessed using the Cochrane non-Randomised Studies Methods Group tool. All studies were judged as at high risk of bias on more than one criteria. The AMSTAR score for this review was 4/11.

The analyses suggested that obese survivors had significantly poorer physical functioning (4 studies, pooled n=1235, mean difference (MD) −11.61, 95% CI −18.66 to −4.55, p=0.001), social functioning (2 studies, pooled n= 797, MD −4.37, 95% CI: −7.75 to −1.00, p=0.01) and role functioning (3 studies, pooled n=693, MD −5.44 95% CI: −8.90 to −1.98, p=0.002) when compared to non-obese women. Emotional functioning and cognitive functioning did not show significant differences.

For sexual function one study of 666 patients showed an inverse relationship with a higher BMI associated with less sexual/vaginal problems and this persisted after adjustment for patient characteristics. Sexual interest and enjoyment were not associated with BMI.

The review found no studies that investigated the relationship between anxiety and depression and BMI in this population.

The GRADE level of evidence for the association between obesity and the various QoL domains is very low (downgrade for limitations of studies). The level of evidence for sexual function relationships is very low (downgrade for limitations of studies and imprecision (single study only).

Prostate Cancer

BMI

Outcome: mortality and recurrence

One review (Cao et al. 2011) investigated the associations between BMI and risk of dying from prostate cancer. Relevant to this Overview they conducted an analysis of this relationship in people post-diagnosis and an analysis of the association between BMI and biochemical recurrence of cancer. The review reported no formal quality assessment of the included studies and was rated at 5/10 on the AMSTAR scale.

This review included six studies including 18,203 participants that evaluated the association between BMI and prostate cancer-specific mortality. Follow-up ranged from 4 to >7 years. In a meta-analysis of these studies there was a 20% higher relative risk for every 5kg/m^2 increase in BMI (Risk Ratio (RR) 1.20, 95%ci 0.99-1.46), though this did not meet statistical significance (p=0.06). There was high heterogeneity between the studies. No publication bias was observed.

This review included 16 studies including 26,479 participants that assessed the relationship between BMI and biochemical recurrence. Follow-up ranged from 2 to 10 years. Meta-analysis of these studies found an 21% increase in the relative risk of recurrence (RR 1.21, 95%ci 1.11-1.31). Heterogeneity was again high and asymmetric funnel plots suggested the presence of possible publication bias.

The authors conclude that higher BMI is associated with higher mortality in people post-diagnosis of prostate cancer and higher risk of recurrence following primary treatment. The GRADE level of evidence for the association between BMI and mortality is very low (downgraded for limitations due to the lack of quality assessment, imprecision due to non-significance and inconsistency due to the high heterogeneity). For the association between BMI and recurrence the level of evidence is also very low (downgraded for limitations, inconsistency and possible publication bias).

Oesophageal cancer

BMI

Outcomes: post-operative complications and mortality

2 reviews (Kayani et al. 2012, Zhang et al. 2013) reviewed studies of the association between BMI, post-operative complications and survival in people who had undergone surgery for oesophageal cancer.

Zhang included 14 studies in total with 2031 participants. The design on the included studies was not clearly reported. The review reported no formal assessment of study quality. The AMSTAR score for this review was 4/11.

Meta-analysis found very small increases in the relative riskof post-operative complications in the highest compared to the lowest BMI group for anastomotic leakage (RR 1.04, 95%CI 1.02 to 1.0, p = 0.001), wound infection (RR = 1.03, 95%CI 1.00 to 1.05, p = 0.031), CVD (RR = 1.02, 95%CI 1.00 to 1.05,

p = 0.039), decreased incidence of Chylor's leakage (RR = 0.98, 95%CI 0.96-0.99, p < 0.001), but no difference for the incidence of respiratory diseases or in-hospital mortality. The number of participants for each comparison were not reported.

Higher BMI was associated with a 22% decrease in the relative risk of mortality (Highest vs lowest BMI RR 0.78, 95%CI 0.71 to 0.85, p<0.001) with no heterogeneity or publication bias detected. The pooled number of participants for each analysis was not reported.

The authors concluded that high BMI was positively associated with the incidence of some post-operative complications but that higher BMI was an independent prognostic factor for survival.

Kayani et al. 2012 included 5 retrospective cohort studies of 1682 people, 3 of which were not included by Zhang et al. The AMSTAR score for this review was 4/11. This review also reported no formal assessment of study quality. This included 446 obese (BMI ≥30kg/m^2) and 1236 non-obese patients with a mix of adenocarcinoma and squamous cell carcinoma who had undergone oesophagectomy.

Meta-analysis found no effect of obesity on the completeness of surgical resection (2 studies n=640),post-operative mortality (5 studies n=1682), respiratory failure (4 studies n=1478) or rates or reoperation (3 studies, n=1250) all with no heterogeneity. There were non-significant trends towards a relationship between obesity and rate of pulmonary embolism (4 studies, n=1478, OR 2.03, 95%CI 0.94 to 4.39), p=0.07, I^2=0%) and anastomotic leakage (5 studies, n=1682, OR 1.56, 95%CI 0.95 to 2.55, p=0.08 I^2 42% not significant) with obese patients demonstrating higher rates of these events.

Similar to the analysis of Zhang et al. (2013), there was a statistically significant relationship between obesity and long-term survival indicating better long term survival (22% decrease in the relative risk of mortality) in the obese group (3 studies, n=1196, HR 0.78 95%CI 0.64 to 0.96, p=0.02, I^2=0%).

Kayani et al. (2012) concluded that obesity alone does not increase risk of post-operative complications or mortality and that obesity may improve long term survival, though higher quality evidence is needed.

The evidence for the relationship between obesity and post-operative complications following oesophagectomy is somewhat inconsistent between these reviews. However both suggest a possible positive effect of obesity on survival rates. The GRADE level of evidence for this comparison is very low (downgraded for unknown limitations of studies, since not formal quality assessment was reported in either review).

Colorectal cancer

Outcome: mortality

One review (Lee et al. 2015) investigated the association between pre- and post-diagnostic BMI with colorectal cancer-specific mortality and all-cause mortality in patients with colorectal cancer.

They included 16 studies including a total of 58,917 people with colorectal cancer. The follow up period for these studies ranged from 4.9 to 20 years. The quality of included studies was assessed

using the Newcastle-Ottawa scale but the reports of this assessment are not reported in the review. The AMSTAR score for this review was 6/11.

Pre-diagnosis, underweight was not associated with colorectal cancer-specific mortality but was associated with a 63% increase in the relative risk of all-cause mortality (six studies, n for comparison not reported, RR 1.63, 95%CI 1.18 to 2.23, p<0.01). Pre-diagnosis overweight was not associated with cancer-specific or all-cause mortality.

Pre-diagnosis obesity was associated with a 22% increased colorectal cancer-specific mortality (six studies, n for comparison not reported, RR 1.22, 95%CI 1.003 to 1.35, p<0.01) and all-cause mortality; number of studies and participants for comparison not reported, (RR 1.25, 95%CI 1.14 to 1.36, p<0.01).

Post-diagnosis, underweight was associated with significantly increased all-cause mortality (10 studies, n for comparison not reported, RR: 1.33, 95% CI: 1.20–1.47,p<0.01). Post-diagnosis overweight was associated with significantly improved colorectal cancer-specific mortality (4 studies, n for comparison not reported RR: 0.84, 95% CI: 0.73–0.97,p<0.05) and all-cause mortality (number of studies and participants for comparison not reported, RR: 0.93, 95% CI: 0.86–0.997,p<0.05).

Post-diagnosis obesity was significantly associated with an 8% relative increase in all-cause mortality (number of studies and participants for comparison not reported, RR: 1.08, 95%CI: 1.03–1.13, p<0.01) while no association was found between post-diagnosis obesity and colorectal cancer-specific mortality. There was no suggestion of publication bias for any analyses.

The review authors concluded that pre-diagnosis obesity and post-diagnosis underweight and are associated with increased risk of mortality whereas post-diagnosis overweight is associated with decreased all-cause mortality. The grade level of evidence for these associations is very low (downgrade for limitations as the quality of studies was not reported).

Outcome QoL

One review (Jansen et al. 2010) investigated quality of life among long term survivors of colorectal cancer (≥ 5 years from diagnosis). This review included 10 studies and explored a range of possible determinants of quality of life. The quality of included studies was assessed using the Mol 14 item checklist. The AMSTAR score for this review was 4/11. The review found that higher BMI was associated with lower scores in physical functioning,, bodily pain, general health and vitality subscales of the SF-36, though psychological QoL was not associated with BMI. These findings arose from 2 reports of one study of 259 female CRC survivors. The study was given a quality score of 12/14. No effect sizes were reported in this review.

Using GRADE there is very low quality evidence (downgraded for imprecision due to inadequate reporting and results derived from a single study) that higher BMI is associated with lower quality of life scores on some subscales of the SF-36 tool.

PHYSICAL ACTIVITY/ EXERCISE BEHAVIOURS

Breast cancer

Outcome: Mortality

Seven systematic reviews (Barbaric et al 2010, Davies et al. 2011, Fontein et al. 2013, Ibrahim et al. 2011, Kim et al. 2013, Lahart et al. 2015, Zhong et al. 2014) investigated the relationship between physical activity behaviours and mortality in people with breast cancer.

The most recent of these (Lahart et al. 2015) included 22 prospective cohort studies with 123,574 participants in total with a median follow up of eight years. The AMSTAR score for this review was 7/11, the highest of the six reviews to investigate this topic.

The quality of included studies was assessed using the Newcastle-Ottawa scale. Out of a maximum 9 'starts' the mean quality score of included studies was 6 (range 4 to 8). 64% of studies were judged to not have controlled for known confounders adequately and only 41% of studies controlled for the influence of cancer stage and nodal status. 45% of studies were considered at risk of bias due to the degree of loss to follow-up or the completeness of statistical data.

Meta-analysis was used to examine the relationship between PA and mortality comparing thhighest versus the lowest physical activity categories. The following comparisons were made (number of participants for each comparison were not reported in the review), with physical activity associated with a relative decrease in the risk of mortality for all comparisons:

Lifetime pre-diagnosis PA and mortality

All-cause mortality Hazard Ratio (HR) 0.82, 95%CI 0.70 to 0.96, I^2 49%, 6 studies, n for comparison not reported

Breast cancer related mortality: HR 0.73 95%CI 0.54 to 0.82, I^2 67%, 5 studies, n for comparison not reported

Recent pre-diagnosis physical activity and mortality

All-cause mortality Hazard Ratio (HR) 0.73, 95%CI 0.65 to 0.82, I^2 0%, 9 studies, n for comparison not reported

Breast cancer related mortality: HR 0.84 95%CI 0.73 to 0.97, I^2 0%, 11 studies, n for comparison not reported

Post-diagnosis physical activity and mortality

All-cause mortality: HR 0.52 95%CI 0.43 to 0.64 I^2 54%, 8 studies, n for comparison not reported

Breast cancer related mortality: HR 0.59 95%CI 0.45 to 0.78, I^2 57%, 7 studies, n for comparison not reported

An analysis of the effect of meeting recommended physical activity guidelines post-diagnosis found the following effects:

All-cause mortality: HR 0.54, 95%CI 0.38 to 0.76, I^2 87%, 6 studies, n for comparison not reported

Breast cancer related mortality: HR 0.67 95%CI 0.50 to 0.90, I^2 73%, 7 studies, n for comparison not reported

Physical activity post-diagnosis was associated with a greater risk reduction in all cause death in post-menopausal survivors. However no clear pattern was found relating to the effect of ER and PR status. There was evidence suggestive of publication bias across all comparisons except lifetime recreational physical activity and both all-cause and breast cancer-related death.

The review authors concluded that there are associations between pre and post-diagnosis physical activity levels and both all-cause and breast cancer specific mortality, but that effect estimates for these associations should be treated with caution due to evidence of heterogeneity. Of the remaining, less recent reviews (Barbaric et al. 2010, Davies et al. 2011, Fontein et al. 2013, Ibrahim et al. 2011, Kim et al. 2013, Zhong et al. 2014) all concluded in agreement with the key findings of Lahart et al. (2015), of a relationship between higher levels of PA and reduced all-cause and breast cancer specific mortality with the exception of Ibrahim et al. (2011) who found no statistically significant difference between pre-diagnosis PA and breast cancer specific mortality except in a subgroup of those with a BMI> 25kg/m^2. However this analysis included only 2 studies compared to the inclusion of 11 studies in the more up to date review by Lahart et al.

The GRADE level of evidence for these associations was rated as very low (downgraded variously for limitations, inconsistency (heterogeneity) and evidence of publication bias.

Outcome: Recurrence and progression

One review (Lahart et al. 2015) investigated the relationship between PA and breast cancer recurrence. This review found three studies and combined in their analysis studies which measured recurrence as an outcome with those which combined recurrence, progression and new primary breast cancers as one outcome. The included studies scored 6 or 7 out of a possible 9 on the quality assessment scale.

i. Pre-diagnosis physical activity and progression/ recurrence

HR 0.72 95%CI 0.56 to 0.91, I^2 0% (2 studies, n for comparison not reported)

ii. Post-diagnosis physical activity and progression/ recurrence

HR 0.79 95%CI 0.63 to 0.98, I^2 0% (2 studies, n for comparison not reported)

Lahart et al. (2015) concluded that recreational physical activity is significantly associated with a lower risk of breast cancer events. The GRADE rating for these associations is rated as very low (downgraded for limitations of studies and risk of publication bias).

Outcome: cancer-related cognitive impairment

One review (Henneghan et al 2016) investigated the effect of modifiable factors and cancer-related cognitive impairment in breast cancer survivors. The AMSTAR score for this review was 4/11. Of the factors investigated, physical activity/exercise was the only one relevant to this overview. Risk of bias was assessed using a 0-9 scale though the specific criteria are not reported. The review identified two small cross-sectional studies (combined n=55). The quality score of these studies was not reported. The results are described narratively. One study reported that exercise moderated the negative effects of higher BMI on perceived cognitive impairments and one reported a statistically significant positive relationship (r=0.47, p=0.004) between self-reported exercise levels and cognitive impairment. The GRADE rating for these findings is very low, downgraded for (limitations due to unknown study quality).

Prostate cancer

Outcome: Mortality

One review investigated the relationship between PA and survivorship in prostate cancer. The AMSTAR score for this review was 2/11. This review applied no formal quality assessment to included studies and described the findings of included studies narratively, with no meta-analysis performed.

They identified one prospective study of 2686 men with a 4 year follow-up which found that those who engaged with >3 hours of Metabolically Equivalent Tasks (MET-h) of weekly activity following diagnosis reduced their risk of death (HR 0.65; 95% CI 0.52 to 0.82) from any cause and a nonsignificant reduction in risk of prostate cancer death (H 0.88, 95% CI 0.52 to 1.49) when compared with those who did less than 3MET-h of weekly activity.

More vigorous activity, and longer duration of activity, were associated with further reductions in risk for all-cause mortality. The review authors concluded that the findings are indicative of a benefit of physical activity in terms of prostate cancer/and overall mortality and that there appears to be a dose gradient for this relationship. The GRADE rating for this association is very low (downgraded for unknown limitations of studies).

Colorectal cancer

Outcome: Mortality

The same review Davies et al. (2011) investigated the relationship between PA and survivorship in colorectal cancer and identified two prospective observational studies of 1342 participants with a diagnosis of colorectal cancer.

One study (n=526) with a 5.5 year follow up found that self- reported leisure time physical activity at least, once per week was associated with reduced disease specific mortality (HR 0.73, 95% CI 0.54 to 1.00, p value not reported). This benefit was greater in a subgroup of participants with stage II – III tumours (HR 0.49; 95% CI 0.30 to 0.79).

One study (n= 816) followed stage III colon cancer participants up for 6 months following post-operative adjuvant chemotherapy. They report that physical activity was associated with improved disease-free survival but the overall effect size was not reported in this review. In a subgroup analysis of females, the effect size was HR 0.33, 95%CI 0.11 to 0.99, p=0.046. In males it was HR 0.89, 95% CI 0.44 to 1.78, p= 0.3. Barbaric et al (2010), also included studies investigating this relationship and included the same studies. They also concluded that there was evidence of an association between physical activity and survival but that these results should be interpreted with caution.

The GRADE rating for these associations is very low (downgraded for unknown limitations of studies, imprecision due to uncertain statistical significance and focus on subgroup analyses).

Endometrial cancer

Outcome: Quality of Life

One review (Koutoukidis et al. 2015) explored the associations between physical activity and health related quality of life in survivors of endometrial cancer. The AMSTAR score for this review was 6/11. Study quality was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) checklists. This review included three relevant cross-sectional studies (combined n 706) though details of the characteristics of these studies was only provided for two of them and the quality assessment results for only one of them.

No meta-analysis was reported. Across HRQoL domains there was inconsistency in the statistical significance of effects, though the authors report that the direction of observed effect was consistently towards a benefit of meeting physical activity guidelines. Effect sizes, expressed as standardised mean difference (Cohen's d) ranged from small to moderate.

The authors conclude that being physically active correlates with an improved quality of life in this group of cancer patients. However the inconsistency of statistically significant effects, combined with the incomplete reporting of study details and study quality on this review lead to a GRADE rating of very low for this comparison (downgraded for limitations, imprecision and inconsistency).

SMOKING BEHAVIOURS

Lung cancer

Three reviews (Parsons et al. 2010, Rowland et al. 2012, Zhang et al. 2015) examined the relationship between smoking behaviours and outcomes in people with lung carcinomas.

Outcome: Survival and recurrence

One review (Parsons et al. 2010) reviewed the evidence that smoking cessation after diagnosis of a primary lung tumour affects prognosis. They included studies of people with a diagnosis of lung cancer at any stage with the outcomes of all-cause mortality and recurrence. The definition of smoking cessation was not clearly defined.

This review identified 10 observational cohort studies (4 prospective, 5 retrospective and one unclear) with 1929 participants. Study quality was assessed with the Altman criteria and scores ranged from 5 to 9 out of 11 points. In all but one study patients presented with early stage lung cancer and so the results largely reflect the possible impact of cessation in that group. 5 studies were in non-small cell lung cancer and 5 in small cell lung cancers and these groups were analysed separately.

Four studies with 460 participants with non-small cell carcinoma were meta-analysed with unadjusted estimates and demonstrated a non-statistically significant 19% increase in the risk with continued smoking with no heterogeneity (HR= 1.19 (95%CI 0.91-1.54) I^2 = 0%).

Two studies with 278 people with small cell carcinoma were pooled. Unadjusted estimates demonstrated a non-statistically significant 18% increase in the risk with continued smoking with no heterogeneity (HR = 1.18 (95%CI 1.03-1.36), I^2 = 0%).

Estimates with adjustment for key prognostic variables, derived from single studies, were presented and demonstrated larger effect sizes (non-small cell, one study n=204, HR 2.94 (95%CI 1.15 to 7.54); small cell, one study n=186, HR = 1.86 (95%CI 1.33-2.59).

In in non-small cell cancer adjusted and unadjusted estimates from a single small study (n= 35) did not show an increase in second primary tumours associated with continued smoking. However one study showed an 86% increase in recurrence with continued smoking (HR 1.86, 95%CI 1.01to 3.41, n=204).

In small cell cancers continued smoking was associated with an increase in second primary cancers with both unadjusted (3 studies, n= 518, HR 1.86, 95%CI 0.96 to 3.60, $I^2$0%) and adjusted estimates (1 study, n=64 HR 4.31, 95%CI 1.09 to 16.98).

One study (N=186) showed an increase in recurrence in small cell carcinoma with continued smoking (HR 1.26, 95%CI 1.06 to 1.50).

The review authors concluded that there is preliminary evidence that smoking cessation after diagnosis improves prognosis and that offering smoking cessation to this group may be beneficial.

The GRADE rating for these associations is there is low quality evidence that continued smoking is associated with increased all-cause mortality in lung cancer and very low quality evidence (downgraded for imprecision as non-statistically significant or based on single studies) that continued smoking post diagnosis is associated with increased cancer recurrence.

Zhang et al. (2015) investigated the relationship between smoking and response to treatment with epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitors in advanced non-small cell lung cancer EGFR-mutant patients and reported progression free survival as an outcome. They identified 9 studies (2 prospective and 7 retrospective) of 1029 participants. Study quality was assessed using the Quorum and Cochrane collaboration guidelines but the results of this assessment were not reported. This review had an AMSTAR score of 4/11.

Comparing those who had ever smoked with those who had never smoked, meta-analysis of 9 studies n= 1029 reported a 27% reduction in progression free survival in ever smokers (HR 0.73, 95%CI 0.60 to 0.88), I^2=0%). There is very low quality evidence (downgraded for unknown quality of studies) that having ever smoked is associated with a decrease in progression-free survival in advanced non-small cell lung cancer EGFR-mutant patients treated with epidermal growth factor receptor (EGFR) –tyrosine kinase inhibitors.

Outcome: Quality of Life

One review (Rowland et al. 2012) investigated the differences in HRQoL between patients with lung cancer who smoke and those who have quit smoking or never smoked. This review had an AMSTAR score of 5/11. They identified 8 studies including 2,100 participants, 5 of which were cross-sectional and 3 longitudinal in design. Study quality was assessed using the CASP appraisal tool. The authors judged all studies to be "methodologically sound" with scores ranging from 7 to 10 out of a maximum 12.

No meta-analysis was conducted and results were summarised narratively. Four studied found no difference in overall HRQoL dependant on smoking status. Two studies demonstrated lower HRQoL in smokers compared to never smokers, with one study (n=1019) showing that the scores of those who quit smoking and did not resume were closer to those of never smokers than current smokers. 2 studies found lower scores on subscales of HRQoL in current smokers. In one longitudinal study (n=438) current smokers reported worse HRQoL than former smokers who reported worse HRQoL than never smokers at less than 3 years and more than 5 years following diagnosis. Effect sizes were not presented for any of these comparisons.

The authors of the review concluded that smoking is associated with lower HRQoL in lung cancer patients. The GRADE quality of evidence for this association is very low (downgraded for inconsistency).

Breast cancer

Outcome: Survival

One review (Braithewaite et al. 2012) investigated the association between smoking and breast cancer mortality. This review included 7 cohort studies, including their own study, of adult women with

invasive breast cancer. Sample sizes ranged from 528 to 604,412 participants. No assessment of study quality was reported. This review had an AMSTAR score of 3/11.

No meta-analysis was conducted. Four of seven studies found a significant increase in breast cancer related death in current versus never smokers. There was little evidence of an increase in breast cancer mortality in former smokers compared with never smokers. For those studies that found an association effect sizes ranged from a 43% increase in the relative risk of breast cancer related death (RR 1.43, 95%CI 1.24 to 1.65) to a twofold increase in relative risk (HR 2.01, 95%CI 1.27 to 3.18). Three studies showed no significant association.

The authors conclude that there is a positive association between current smoking and breast cancer mortality, but that the evidence for an effect of former smoking is very weak. The GRADE quality of evidence for these associations is very low (downgraded for inconsistency and the unknown quality of the included studies).

Liver cancer

One review (Pang et al. 2015) investigated the effect of smoking liver cancer mortality. Within this review they included 4 studies (one prospective, 3 retrospective) relevant to this overview which evaluated the effect of smoking on people with a diagnosis of hepatocellular carcinoma (HCC). Study quality was assessed using the Newcastle-Ottawa scale and scores for the relevant studies ranged from 6 to 8 out of 9. This review has an AMSTAR score of 7/11.

Outcome: Survival

Pooling of studies did not demonstrate a statistically significant relationship between smoking status and overall survival (3 studies, pooled n= 729) HR 1.90, 95%CI 0.84 to 4.30, I^2 87%) or recurrence free survival (2 studies, pooled n=286, HR 1.75, 95%CI 0.87 to 3.53, I^2 54.4though there was substantial heterogeneity for both analyses. Sensitivity analyses using a fixed effect statistical model showed a significant association for both outcomes.

Outcome: Recurrence

One study (n=304) found that smoking was associated with an increased recurrence (HR 1.40, 95%CI 1.12 to 1.74).

Then authors of the review concluded that smoking was associated with post-operative recurrence in liver cancer but was not a useful predictor of overall or recurrence-free survival. Using GRADE, there is very low quality evidence that smoking is associated with a higher rate of recurrence in people with HCC (downgraded for imprecision as single study).

Colorectal cancer

One review (Walter et al. 2014) investigated the effect of smoking on survival in colorectal cancer (CRC) patients. This review had an AMSTAR score of 6/11. The review included 16 studies with 62,278 participants. Study designs were not reported.

Study quality was assessed using a 4 point tool based on the Meta-analysis of observational studies in epidemiology (MOOSE) checklist. Scores ranged from 1 to 4. Meta-analysis only included studies with a score range 2-4.

This review found no effect of former smokers (compared to never smokers) on all-cause mortality in a random effects model meta-analysis (4 studies, n= not reported for this analysis) , though a fixed effect model suggested a 15% increase in mortality in former smokers (HR 1.15, 95%ci 1.01 to 1.31) with low heterogeneity.

Current smoking (compared with never smoking) was associated with a relative increased in all-cause mortality of 26% (6 studies, n not reported for this analysis. HR 1.26,95%CI 1.15 to 1.37, I^2 35.2%) in a random effects meta-analysis. Across individual studies around half demonstrated no statistically significant association.

Of three studies that analysed the group 'ever smokers' all showed effects or trends towards a significant effect of smoking on mortality and survival, favouring never smokers. Of five studies that assessed the relationship between smoking intensity (measured in pack-years or cigarettes per day) and mortality or recurrence free survival a positive dose-response relationship could be seen though a number of the effect estimates this was based on were not statistically significant.

The authors conclude that the results support the existence of detrimental effects of smoking after CRC diagnosis. Using GRADE there is very low quality evidence of an association with current smoking and all-cause mortality (downgraded for unclear limitations of studies, inconsistency and imprecision).

Renal cancer

One review (Xu et al 2014) investigated the impact of smoking and survival in patients with renal cell carcinoma (RCC). This review had an AMSTAR score of 5/11.The review included 14 studies including 343,993 patients with RCC, but did not report the study designs. Methodological quality was assessed using the Newcastle-Ottawa scale and scores ranged from 5 to 9 out of 9.

Outcome: SurvivalMeta-analysis included subgroup analyses separating current from former smokers. These demonstrated a 57% relative increase overall mortality in current vs never smokers (3 studies, n for analysis not reported, HR 1.57, 95%CI 1.20 to 2.06, I^2 31.6%), but no significant increase in former smokers vs never smokers (2 studies, n for analysis not reported HR 1.14, 95%CI 0.79 to 1.53).

Similarly or disease specific mortality current smokers had a 50% increase in overall mortality compared with never smokers (HR 1.50, 95%CI 1.10 to 2.05, 4 studies, n for analysis not reported) but no significant effect was observed for former smokers (HR 0.98, 95%CI 0.72 to 1.34, 3 studies, n for analysis not reported).

In terms of survival current but not former smoking was associated with poorer overall survival (HR 2.70, 95%CI1.70 to 4.29, one study, n for analysis not reported) and progression free survival (HR 2.94, 95%CI 1.89 to 4.58, one study, n for analysis not reported). Finally a history of smoking (current and

former smokers) was associated with a 1% relative difference in overall survival with no heterogeneity (HR 1.01, 95%CI 1.00 to 1.02, I^2 0%).

The authors concluded that current smoking is associated with poorer survival in patients with RCC. Using grade the quality of the evidence for this association is very low (downgraded for limitations of studies as the designs are unclear).

Urothelial cancer

One review (Crivelli et al. 2014) reviewed the evidence regarding the impact of smoking status or exposure on recurrence, cancer specific and any-cause mortality in patients with urothelial carcinoma (UC) treated surgically. They included no assessment of study quality. This review had an AMSTAR score of 4/11.

The review included 29 studies but did not clearly report the study designs. No meta-analysis was conducted and results were synthesised narratively. Synthesis largely took a "vote counting" approach quantifying the number of studies that found significant relationships for key comparisons.

Findings of significant associations between smoking status or exposure and key outcomes were inconsistent across studies regardless of the surgical management approach. The majority of studies demonstrated an association of smoking status and exposure with recurrence following transurethral resection of the bladder (TURB).

The authors concluded that smoking may lead to less favourable outcomes for patients with UC of the balder and upper tract. Using GRADE the quality of evidence is very low (downgraded for limitations of studied due to unknown study design and quality and inconsistency).

Head and neck cancer

Outcome HRQoL

One review (So et el. 2012) investigated the determinants of quality of life among head and neck cancer survivors at one year after treatment. The review explored a broad range of possible determinants. This review had an AMSTAR score of 4/11. Methodological quality was assessed using a 14 item checklist.

This review included one prospective longitudinal study of 316 participants that demonstrated that smoking in the previous 2 months was predictive or poor QoL scores on all items of the SF-36 scale except the role-emotional functioning subscale. This study scored 11/14 and was rated by the review authors as of high quality. No effect size was reported. Using GRADE there is very low quality evidence (downgraded for imprecision due to inadequate reporting and results derived from a single study) that smoking is associated with lower quality of life in head and neck cancer survivors.

All cancers

One review (Florou et al. 2014) reviewed the evidence of association between smoking and survival, treatment effectiveness, second primary tumours and quality of life in people with any form of cancer. This review scored 3/11 on the AMSTAR scale. The review included 20 studies (4 retrospective observational, 15 prospective observational and 3 randomised trials) but presented no formal assessment of study quality. No meta-analysis was conducted and results were synthesised narratively.

The majority of studies identified were in smoking-related cancers such a lung, bladder and head and neck cancer. Following a descriptive review of the included studies the authors conclude that continued smoking after cancer diagnosis is related to reduced treatment efficacy, survival and increased risk for second primary malignancies and deterioration of quality of life. The descriptive nature of the reporting of this review precludes GRADE assessment for specific comparisons.

ALCOHOL–RELATED BEHAVIOURS

Breast cancer

One review (Gou et al. 2013) investigated the relationship between alcohol consumption and breast cancer survival and recurrence. This review had an AMSTAR score of 5/11 and included 25 cohort studies including 719,555 breast cancer survivors. No formal assessment of study quality was reported.

Meta-analysis comparing highest versus lowest consumption demonstrated no significant association between alcohol intake and breast cancer mortality (25 studies, pooled n not reported, HR 1.06, 95%CI 0.97 to 1.17, I^2 31%) or recurrence (5 studies, pooled n not reported HR 1.21, 95%CI 0.895 to 1.53, I^2 0%). Similarly no association was seen in an analysis of post-diagnosis consumption. Subgroup analysis by oestrogen receptor status or menopausal status demonstrated no difference in mortality.

In a subgroup of premenopausal participants an association was seen between alcohol consumption and recurrence (2 studies, n for analysis not reported, HR 1.52, 95%CI 1.21 to 1.90, $I^2$0%). The authors report that subgroup analysis of levels of alcohol consumption showed an apparent dose-response

relationship for mortality and recurrence though the evidence for this is questionable with only one dose subgroup (>20g/day) showing a statistically significant effect and only on mortality.

The review authors conclude that alcohol drinking was not associated with increased breast cancer recurrence or mortality but based on the purported dose response relationship breast cancer patients should avoid drinking >20g/day. Using GRADE there is low quality evidence that alcohol consumption is not associated with mortality or recurrence in breast cancer.

Head and neck cancer

Outcome HRQoL

One review (So et el. 2012) investigated the determinants of quality of life among head and neck cancer survivors at one year after treatment. The review explored a broad range of possible determinants. This review had an AMSTAR score of 4/11. Methodological quality of the included studieswas assessed using a 14-item checklist.

This review included one prospective longitudinal study of 316 participants that found no influence of alcohol consumption on QoL . This study scored 11/14 and was rated by the review authors as of high quality. Using GRADE there is very low quality evidence (downgraded for imprecision due to inadequate reporting and results derived from a single study) that alcohol consumption is not associated with QoL in head and neck cancer survivors.

Upper aerodigestive tract cancer

One review (Druesne-Pecollo et al. 2013) investigated the association between alcohol drinking with second primary cancer risk in patients with upper aerodigestive tract (UADT) cancers, including those of the oral cavity, pharynx, larynx and oesophagus.

This review had an AMSTAR score of 6/11. It included 19 studies of which 8 were cohort studies and 11 case-control studies. No formal assessment of study quality was reported.

Outcome: UADT second primary cancer

Comparing highest to lowest alcohol intake, alcohol intake was associated with an almost 2-foldincrease in the risk of a second primary UADT cancer (10 studies, 6385 participants, RR 2.97 95%CI 1.96 to 4.50, p-0.001, $I^2$31.3%) with no evidence of small study bias. In a dose response relationship analysis (2 studies, 3614 participants) the relative risk increased by 9% with every 10 gram/ day increase in alcohol consumption (RR 1,09, 95%CI 1.04 TO 1.14, p=0.001).

Outcome: UADT and lung second primary cancer

Comparing highest to lowest alcohol intake, alcohol intake was associated with a 91% relative increase in the risk of second primary UADT or lung cancer (7 studies, 3720 participants, RR 1.91, 95%CI 1.17 TO 3.13, p=0.01, I^2 58%) with heterogeneity, but no evidence of small study bias. Subgroup analyses showed that studied adjusted for age, gender and smoking tended to report weaker associations and

that the association was significant for studies conducted in the USA, studies assessing consumption by interview, studies comparing drinkers to non-drinkers, studies not exclusively examining metachronous second primary cancers and case-control but not cohort studies.

A positive association was also found comparing highest to lowest alcohol intake on all-site second primary cancers with no heterogeneity or evidence of small study bias (6 studies, 4267 participants, RR 1.60, 95%CI 1.22 to 2.10, I^2 4.4%).

The authors conclude that alcohol drinking is associated with an increased risk of second primary cancers. The GRADE rating for this association is low (downgraded once for limitations due to unknown quality of included studies, upgraded once for consistency and dose-response relationship).

Discussion

SUMMARY OF KEY FINDINGS

Dietary behaviours and obesity

There is **very low** quality evidence that:

- Higher soy consumption may be associated with lower mortality and recurrence in people following breast cancer diagnosis
- Green tea consumption may be associated with lower recurrence in people following breast cancer diagnosis
- Low fat diet is not associated with all-cause mortality in people following breast cancer diagnosis.
- Obesity is associated with lower quality of life in people following endometrial cancer diagnosis.
- Obesity is associated with higher mortality and risk of recurrence in people following prostate cancer diagnosis.
- Higher BMI is associated with an increase in specific post-operative complications in people undergoing surgical treatment of oesophageal cancer but is associated with better survival rates.
- Pre-diagnosis obesity and post-diagnosis underweight are associated with increased risk of mortality, while post diagnosis overweight is associated with decreased mortality in people with colorectal cancer.
- Higher BMI is associated with lower quality of life on some quality of life subscales in colorectal cancer.

Physical activity and exercise behaviour

There is **very low** quality evidence that:

- Pre and post-diagnosis physical activity levels are associated with lower all-cause and cancer specific mortality, recurrence and disease progression in people with breast cancer.
- More vigorous physical activity is associated with reduced all-cause and cancer specific mortality in men with a diagnosis of prostate cancer.
- Higher levels of physical activity are associated with lower cancer specific mortality/ disease free survival in people with colorectal cancer.
- Being physically active is associated with higher quality of life in people with endometrial cancer.

Smoking related behaviours

There is **very low** quality evidence that:

- Smoking cessation after diagnosis is associated with improved prognosis in people with lung cancer.
- Continued smoking is associated with increased all-cause mortality and increase risk of disease recurrence in people following lung cancer diagnosis.
- Smoking is associated with lower HRQoL in people with lung cancer and head and neck cancer.
- Current smoking is associated with higher breast cancer related mortality.
- Smoking is associated with a higher risk of recurrence in people with a history of liver cancer but is not a useful predictor of survival.
- Current smoking is associated with higher all-cause mortality in people with colorectal cancer and renal cancer, and less favourable outcomes in urothelial cancer.

Alcohol related behaviours

There is **very low** quality evidence that:

- Alcohol drinking is not associated with increased breast cancer recurrence or mortality.
- Alcohol consumption is not associated with quality of life in head and neck cancer survivors.

There is **low** quality evidence that:

- Alcohol consumption is associated with an increased risk of second primary cancers in people diagnosed with upper aerodigestive tract cancer.

Completeness of the included evidence

In terms of volume of systematic reviews more reviews have been published relating to breast cancer than for other forms of cancer, particularly in relation to dietary and physical activity related behaviours. In terms of behaviours across a number of cancer types, there were numerous reviews for dietary, physical activity and smoking behaviours but the review evidence for other behaviours was either piecemeal or absent. Predictably most reviews of smoking behaviours specifically for people with a diagnosis of lung cancer. Other cancers were more poorly represented. The lack of review evidence identified for other cancers and behaviours is not a direct measure of the amount of available evidence on those topics, although the lack of review conducted may in part reflect a tacit knowledge in the research community of the paucity of primary literature. Additionally it may also reflect the relative rarity of those cancers with low coverage in this overview.

Due to the way most reviews were conducted and reported it was not possible to clearly stratify the results by the stage in the cancer journey of various populations. The majority of reviews took a broad approach, including people post-diagnosis or post-cancer treatment.

Quality of the included evidence

The evidence for all findings was rated as low or more commonly very low using the GRADE approach (Guyatt et al. 2008). In the GRADE approach evidence from non-randomised studies starts with a rating of “low quality” and may then be up or downgraded on a number of different criteria. For most comparisons evidence was downgraded from “low” to "very low” on the basis of imprecision, inconsistency or limitations in the included studies. Where an included review did not conduct or report a formal assessment of the quality of the included evidence we downgraded that evidence for limitations in the included studies. Common reasons for upgrading observational data are where effect sizes or associations are large and consistent or where a clear dose-response relationship was observed, but those features were not commonly present in the reviewed evidence.

It is arguable that GRADE lacks some discriminatory value for evaluating the quality these types of data. However it is well accepted that observational data carry a high risk of potential confounding. While 'very low' is the lowest judgement that can be made in the GRADE system, where some evidence exists, such a judgement indicates that there are numerous sources of potential bias that might explain the observed effects. It is notable that the majority of the included reviews recommended caution in interpreting the observed associations.

The majority of associations were presented as odds ratio, risk ratios or hazard ratios. These effect sizes represent the relative rather than absolute difference in risk and as such can give estimates of the difference in risk that appear more dramatic than they are in reality. So in instances where the baseline risk for an event is low, a large relative increase or decrease in the risk may still represent a small difference in real terms.

At the review level, the quality of reviews measured using the AMSTAR tool was generally low with a median score of 4/11. Many of the included reviews omitted fundamental aspects of good practice in systematic review methods such as assessing the quality of the included studies and few searched for grey literature, raising the risk that important evidence may have been missed. The universal lack of pre-registration of review protocols on PROSPERO also raises the risk of post-hoc alterations in the approach taken to data synthesis, which also introduces a potential bias. It should be noted that the AMSTAR assessment effectively assesses the quality of reporting rather than directly measuring the quality of review conduct. In some cases reviews may be disadvantaged by the limitations on full and thorough reporting imposed by a journal's publishing requirements.

It is important to note that obesity and BMI are not lifestyle behaviours. We included them in this overview as we felt they were factors that are partially associated with lifestyle behaviours of diet and physical activity. However we recognise that they arenot always easily modifiable. It is also recognised that BMI has important limitations. In tends to overestimate adiposity in those with a more lean body mass and does not adequately account for variations in physical build (Nuttall 2015).

It is also important to recognise that many lifestyle behaviours are measured using self-report indexes and as such as prone to inaccuracy through recall bias and misreporting, particularly when behaviours are associated with cultural beliefs relating to virtue and good health (Short et al. 2009).

Strengths and Limitations of the overview process

The comprehensive search strategy ensures that this overview represents a comprehensive summary of all existing eligible systematic reviews in the English language published prior to the search dates and the pre-publication of our protocol on PROSPERO ensures methodological transparency and militates against potential post-hoc decision making which can introduce bias to the process. Dual screening of searches and data extraction and independent quality assessment of included reviews ensured a rigorous process.

Taking published systematic reviews as the sole evidence increases the potential risk of publication lag, wherein possible important new evidence that has not yet been included in published systematic reviews is not identified and included. The included reviews used a range of different methodological quality and risk of bias assessment tools, or none. Given that we relied primarily on the quality and bias judgements of the included reviews, and did not systematically apply a standard risk of bias tool to each original study, it is possible that important sources of potential bias may have been missed. The restriction to only included English language reviews led to the exclusion of one review of diet and physical activity in colorectal cancer (Perez-Cueto et al. 2011) which is a topic area covered by our included reviews.

The use of the GRADE criteria introduces an element of subjective judgement. It was also found to be more difficult when we were primarily assessing the included reviews rather than the original studies, all of which assessed and reported study quality in different ways. A consistent approach to judgements across the different interventions has been applied but it should be recognised that these judgements are open to interpretation.

Changes between the review protocol and the final review.

Our initial protocol included the use of recreational drugs as an included lifestyle behaviour. We removed the use of recreational drugs from the list of included, lifestyle choices. This arose from a decision taken between the research team and the funding body prior to the conduct of any searches for this review as it was considered that the practical difficulties of sensitively searching for this evidence in an already broad review or reviews, and the likely quality of the available data suggest that this topic might be better answered by a separate, focused systematic review of original studies. This amendment was made to the PROSPERO record prior to the searches.

Implications for practice

While the evidence is low to very low the majority of findings in this review seem well aligned with accepted public health messages relating to the benefits of physical exercise, weight control and smoking cessation. The evidence related to alcohol consumption is more limited. It is interesting that current smoking appears more consistently associated with undesirable outcomes than former

smoking or ever smoking, perhaps suggesting that encouragement to quit smoking remains a positive message at any stage in the cancer journey.

While obesity appears to be related to post-operative complications in cancers of the gastro-intestinal tract, it should also be borne in mind that higher BMI appears to be associated with higher survival rates in this group and that underweight may be a risk for higher mortality, suggesting that a more nuanced message is possible in this group regarding weight control and diet and that it is important to discriminate between healthy and unhealthy levels of low weight.

Implications for research

The available evidence demonstrates that some behaviours may be associated with important outcomes in people living with and beyond cancer. However it does not inform us of whether specifically delivering interventions aimed at modifying those behaviours are effective. For that to be the case interventions must be first successful at altering the desired behaviour to the necessary extent and in a reliable fashion, and then change in that behaviour must be effective in altering the outcomes of interest. It should not be assumed that either of these requirements are inevitable. The effectiveness of interventions aimed at altering lifestyle behaviours for improving outcomes for people living with and beyond cancer is beyond the scope of this overview but is the core aim of an overview being conducted alongside this one (currently in process).

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SUPPLEMENTARY MATERIAL

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APPENDIX A Ovid Medline Search Strategy

1. MeSH descriptor: [neoplasms] explode all trees)

2. Lifestyle OR healthy OR exercis* OR fit* OR active*OR diet* OR eating* OR smok* OR sedentar* OR tobacco OR drink* OR alcohol* OR nutrit*.ab.ti

3. meta-analysis.pt.

4. meta-analysis.sh.

5. (meta-analys* or meta analys* or metaanalys*).tw,sh.

6. (systematic* adj5 review*).tw,sh.

7. (systematic* adj5 overview*).tw,sh.

8. (quantitativ* adj5 review*).tw,sh.

9. (quantitativ* adj5 overview*).tw,sh.

10. (quantitativ* adj5 synthesis*).tw,sh.

11. (methodologic* adj5 review*).tw,sh.

12. (methodologic* adj5 overview*).tw,sh.

13. (integrative research review* or research integration).tw.

14. OR/ 3-13

15. 1 AND 2 AND 14

SUPPLEMENTARY MATERIAL

APPENDIX B Reasons for study exclusions

Review	Reason for exclusion
Albrecht et al. 2012	Review of interventions
Albuquerque et al. 2014	Not specific to the population of interest
Ali et al. 2014	Not a systematic review
Arden-Close et al. 2010	Not a systematic review
Arem et al. 2013	Not a systematic review
Asemi et al. 2015	Not specific to the population of interest
Azim et al. 2011	Not a systematic review
Ballard-Barbash et al. 2011	Not a systematic review
Barber et al. 2012	Does not include relevant lifestyle behaviours
Bellury et al. 2011	Not a systematic review
Biswas et al. 2015	Not specific to the population of interest
Boje et al. 2014	Does not include relevant lifestyle behaviours
Buffart et al. 2014	Not a systematic review
Burris et al. 2015	Does not include outcomes of interest
Butow et al. 2012	Does not include relevant lifestyle behaviours
Cai et al. 2014	Not specific to the population of interest
Cannioto et al. 2013	Not a systematic review
Cemal et al. 2013	Does not include relevant lifestyle behaviours
Charlette et al. 2013	Not a systematic review
Chlebowski et al. 2013	Not a systematic review
Craft et al. 2010	A review of interventions
Duijts et al. 2014	Does not include relevant lifestyle behaviours
Eakin et al. 2015	Not a systematic review
Ernst et al. 2012	Does not include relevant lifestyle behaviours (supplements)
Golabek et al. 2014	Not specific to population of interest
Goodwin et al. 2010	Not a systematic review
Hamaker et al. 2014	Does not include relevant lifestyle behaviours
Hasegawa et al. 2015	Not a systematic review
Hasenoehrl et al. 2015	A review of interventions
Hauner et al. 2011	Not a systematic review
Hori et al. 2011	Not a systematic review
Islami et al. 2014	Not specific to the population of interest
Je et al. 2013	Not a systematic review
Jiang et al. 2015	Not specific to population of interest
Jones et al. 2013	Not a systematic review
Jones et al. 2011	Does not include the outcomes of interest.
Jun et al. 2012	A review of interventions
Kampman et al. 2012	Not a systematic review
Keogh et al. 2012	A review of interventions
Knobf et al. 2011	Not a systematic review
Kwan et al. 2011	Not a systematic review
Kwan et al. 2011	A review of interventions
Lassig et al. 2012	Not a systematic review
Lee et al. 2012	Not a systematic review
Leone et al. 2013	An interventions review.

Li et al. 2013	Not specific to the population of interest
Li et al. 2014	Not specific to the population of interest
Lis et al. 2012	Not a systematic review
Liu et al. 2015	Not specific to the population of interest
Lof et al. 2012	Not a systematic review
Lonbro et al. 2014	Does not include outcomes of interest
Loprinzi 2012	Not a systematic review
Loprinzi et al. 2014	Not a systematic review
Ma et al. 2015	Not specific to the population of interest
Makarem et al. 2013	Not a systematic review
Malerba et al. 2013	Not specific to the population of interest
Mandair et al. 2014	Not specific to the population of interest
Masko et al. 2013	Does not include outcomes of interest
Mazzarino et al. 2015	A review of interventions
Millar et al. 2012	Not a systematic review
Mishra et al. 2015	A review of interventions
Nelson et al. 2013	Not specific to the population of interest
Noguchi et al. 2015	Not a systematic review
Okamoto et al. 2012	Not a systematic review
O'Rorke et al. 2010	Not specific to the population of interest
Paramanandam et al. 2015	A review of interventions
Perez-Cueto et al. 2011	Not in English language
Pierce et al. 2014	Not a systematic review
Proper et al. 2011	Not specific to the population of interest
Qin et al. 2014	Not a systematic review
Rafie et al. 2015	Not specific to the population of interest
Rehm et al. 2010	Not specific to the population of interest
Reynolds et al. 2011	Not a systematic review
Rossi et al. 2014	Not a systematic review
Schmid et al. 2014	Not a systematic review
Secord et al. 2016	Not a systematic review
Shi et al. 2015	Not a systematic review
Stolley et al. 2010	Not a systematic review
Storic et al. 2013	A review of interventions
Szymlek-Gay et al. 2011	Not a systematic review
Tarraga Lopez et al. 2014	Not a systematic review
Van Blarigan et al. 2015	Not a systematic review
Van Meer et al. 2013	Not a systematic review
Vance et al. 2011	Not a systematic review
Vijayvergia et al. 2015	Not a systematic review
Wang et al. 2012a	Not specific to the population of interest
Wang et al. 2012b	Not specific to the population of interest
Wang et al. 2011	Not a systematic review
Wang et al. 2014	Not specific to the population of interest
Weikert et al. 2010	Not a systematic review
Wooding et al. 2014	Not a systematic review
Xue et al. 2012	Not a systematic review
Zaman et al. 2012	Not specific to the population of interest

SUPPLEMENTARY MATERIAL