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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of dietary interventions for adult cancer survivors on morbidity and mortality, changes in dietary behaviour, body composition, health-related quality of life and clinical measurements.

BACKGROUND

There are reported to be more than 24 million cancer survivors worldwide, based on data derived from population-based cancer registers (Parkin 2006). This includes 10 million survivors of cancer in the United States (Ganz 2005) and 2 million in the United Kingdom, along with an estimated 3% increase annually (Maddams 2009). The proportion of people who survive cancer is increasing, which may be attributed to an increase in the aging population and advancements in anti-cancer therapies (chemotherapy and radiotherapy), which have improved the outcomes of treatments (Aziz 2003; Lancet 2004). Over 60% of those living beyond a cancer diagnosis are over 65 years of age (Ravasco 2003), approximately 60% are female, and the majority are diagnosed initially with either breast, prostate or colorectal malignancy (Maddams 2009). However, negative factors influencing cancer survival have been highlighted and include people who have a lower socioeconomic status combined with higher levels of co-existing conditions and unhealthy lifestyle choices (Louwman 2010). It is now recognised that as survival increases, associated long-term health issues of cancer will emerge as a significant public health concern (Mosher 2009) and this is reflected in healthcare strategies (Department 2010; Lippman 2004).

Health promotion initiatives aimed at improving the well-being of people who have survived cancer are now essential in order to decrease co-morbidities and improve quality of life (QoL). Focus groups have reported that people who have survived cancer are often confused regarding future strategies to improve their health and well-being (Armes 2009; Marbach 2011).

Description of the condition

For the purpose of this review, cancer survivors are defined as people living beyond a diagnosis of cancer after all treatment interventions have been discontinued, where treatment interventions may include surgery, chemotherapy, radiotherapy and active hormone replacement therapy. Those receiving adjuvant maintenance hormone treatments will be included. This review does not include the patients with cancer who are currently undergoing active or palliative treatment.
**Description of the intervention**

International recommendations on how to maintain healthy lifestyles are currently available for the prevention of cancer and also for those who are living beyond a cancer diagnosis from the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR 2007; Kushi 2012). Healthy lifestyle changes recommended by the WCRF/AICR 2007 have been linked to longevity. From a large European study, those who followed a higher proportion of healthy lifestyle recommendations had a 34% lower hazard ratio (HR) of death compared to those who adhered to fewer recommendations (Vergnau 2013). Low compliance with the WCRF/AICR recommendations was significantly associated with increased HRs of dying from cancer, circulatory and respiratory disease (Vergnau 2013). The healthy lifestyle recommendations for those living beyond cancer include: maintaining a healthy weight throughout life; adopting an active lifestyle; consuming a healthy diet with an emphasis on plant foods; and limiting alcoholic beverages (WCRF/AICR 2007). Dietary interventions include any method of delivering an intervention that is aimed at altering an individual’s food or drink intake.

**How the intervention might work**

Lifestyle factors predispose people to the development of chronic diseases and cancer. These include being overweight or obese, lack of physical activity and high saturated fat intake combined with a low intake of fruit and vegetables (Daar 2007). There is a plethora of data linking chronic diseases, including diabetes, cardiovascular, and respiratory diseases, to lifestyle factors, so it would seem reasonable that these co-morbidities, in people who have survived cancer, could be reduced by modifying lifestyle factors (Kushi 2012). Those who live beyond cancer also have an elevated incidence of recurrent disease and other cancers, so would potentially benefit from modifying their behaviour to adhere to the recommendations for cancer prevention. Furthermore, patients have been found to have a higher level of motivation to change lifestyle behaviours after a cancer diagnosis than prior to their diagnosis (Demark-Wahnefried 2005; Ganz 2005; Satia 2004). A survey of modifications in health-related behaviours demonstrated that two thirds of people surviving breast, colorectal and prostate cancer made positive health-related changes to their diet and changed supplement usage up to two years after their cancer diagnosis (Patterson 2003). Others have concurred that patients are willing to change their behaviour after a diagnosis of cancer and have already made changes (Demark-Wahnefried 2000).

**Why it is important to do this review**

Those who have survived cancer not only have an increased risk of secondary malignancies, but also a higher incidence of co-morbidities, compared to the general population (Nord 2005). An increased incidence of cardiovascular disease, diabetes and osteoporosis have been reported in survivors of cancer (Demark-Wahnefried 2009; Hawkes 2011; Janssen-Heijnen 2009). Genotype and lifestyle are also considered significant contributory factors that lead to increased morbidity and cancer recurrence in people who have survived cancer (Daar 2007; Demark-Wahnefried 2009). Furthermore, survivors of cancer use healthcare services and receive social welfare benefits more frequently than controls (Nord 2005). In addition, it has been shown that those who have survived cancer visit their general practitioners more frequently than their non-cancer counterparts (Khan 2011). Research has demonstrated that the poorer health status identified in survivors of cancer detrimentally influences QoL (Baker 2003). In older people who have survived cancer, improved diet and enhanced physical activity has been shown to relate to better vitality and functioning (Hewitt 2003).

This systematic review is important to determine which dietary interventions are effective in those who have survived cancer. There is now evidence to support exercise initiatives in cancer survivors, in relation to health-related QoL (Misra 2012). In the promotion of lifestyle behaviours it is difficult to unravel the contribution of individual components on overall health and well-being. However, it would be useful to determine the most appropriate dietary interventions that are effective in people who have survived cancer, to inform clinical practitioners, and also to assist in improving the long-term health of people who have survived cancer. Evidence on dietary interventions in survivors of cancer is now developing, so it is timely to review the literature to summarise the research, in order to inform clinical practice and policy development, and identify gaps in the literature for further research.

**OBJECTIVES**

To assess the effects of dietary interventions for adult cancer survivors on morbidity and mortality, changes in dietary behaviour, body composition, health-related quality of life and clinical measurements.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised controlled trials (RCTs) and cluster RCTs published in peer reviewed journals. We will also contact investigators of eligible unpublished studies identified from the
abstracts of conference proceedings for relevant unpublished data and search trial registries for additional studies.

Types of participants
All adult cancer survivors, defined as those who have lived beyond a cancer diagnosis which occurred after the age of 18 years, and have completed all active anti-cancer interventions, such as surgery, radiotherapy, chemotherapy or active hormone replacement (patients receiving adjuvant maintenance hormone replacement will be included). Patients with pre-cancerous lesions will not be included.

Types of interventions
All dietary interventions for healthy eating and weight loss or weight maintenance. Specific nutritional interventions, including only those based on food, will be included. Dietary interventions need to include multiple nutrients, fat, carbohydrate, protein, vitamins and minerals. Oral supplements, including those with single or multiple nutrients, are to be excluded. Probiotic supplements will be excluded, along with all intravenous nutrient solutions containing single or multiple nutrient administrations. All enteral feeding will also be excluded.

Types of outcome measures

Primary outcomes
- Overall survival
- Incidence of secondary malignancy or other cancer
- Incidence of co-morbidities

Secondary outcomes
- Dietary changes measured by dietary analysis using food frequency questionnaires, dietary recall, food diaries or assessed by dietary assessment methodology
- Changes in body weight or anthropometric measurements including hip and waist ratios, skin fold thickness, or functional capacity measurements
- Patient - outcomes, including quality of life (QoL) questionnaires
- Biochemical measurements, which may include lipid profiles or serum glucose as surrogate markers
- Number of healthy eating changes made to habitual eating patterns

Search methods for identification of studies

Electronic searches
We will search the following electronic databases:
- the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, latest issue)
- the Cochrane Gynaecological Cancer Review Group's Trial Register
- MEDLINE (Ovid) (1946 to latest issue)
- EMBASE (Ovid) (1980 to latest issue)
- AMED
- CINAHL
- DARE

We present the MEDLINE search strategy in Appendix 1. For databases other than MEDLINE, the search strategy will be adapted accordingly. All relevant articles will be identified on PubMed and using the 'related articles' feature, and a further search will be carried out for newly published articles. Reports in all languages will be sought and translations carried out if necessary.

Searching other resources
We will review the reference list of all retrieved articles and other reviews on the topic. We will also search World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en).

We will search MetaRegister (www.controlled-trials.com), Physicians Data query (nci.nih.gov), www.clinicaltrials.gov and www.cancer.gov/clinicaltrials for ongoing trials. If ongoing trials that have not been published are identified through these searches, the principal investigators will be approached to ask for relevant data. Conference proceedings and abstracts will be searched through ZETOC (zetoc.mimas.ac.uk) and WorldCat Dissertations.

We will handsearch the abstracts from meetings held by the American Institute for Cancer Research.

Data collection and analysis

Selection of studies
Two review authors (DG and EG) will independently assess the titles and abstracts retrieved from the searches to determine relevance and eligibility. All papers failing to meet the eligibility criteria will be excluded. Full text articles of potentially relevant studies will be retrieved and reviewed by two review authors independently, to assess whether they meet the inclusion criteria. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of included or excluded
studies tables. A third review author will be called upon to resolve any conflicts that arise during study selection. Multiple reports of the same study will be linked. We will translate any non-English articles before assessment, as required.

Data extraction and management
A standardised data collection form will be devised to facilitate data collection from the included studies. The data extraction form will be piloted and modified as required. Two review authors (DG and EG) will independently extract data and any discrepancies will be discussed with a third author. The following information will be recorded for each trial:
- Year of publication, country of origin, source of funding and number of participants.
- Study population
  - Age, gender, location of tumour, previous therapy, cancer staging or classification.
  - Other baseline characteristics, including proportion of overweight or obese survivors (defined by body mass index greater than 25 kg/m$^2$ or nutrition status assessment derived from a validated tool), alcohol intake, smoking status, current physical activity and socioeconomic group.
- Overall survival
- Incidence of secondary malignancy or other cancer
- Incidence of co-morbidities
- Dietary changes measured by dietary analysis using food frequency questionnaires, dietary recall, food diaries or assessed by dietary assessment methodology
- Changes in body weight or anthropometric measurements including hip and waist ratios, skin fold thickness, or functional capacity measurements
- Patient outcomes, including quality of life (QoL) questionnaires
- Biochemical measurements, which may include lipid profiles or serum glucose as surrogate markers.
- Number of healthy eating changes made to habitual eating patterns
- Details of type of intervention, including nutritional education, change behaviour techniques employed and delivery method of intervention (written, telephone, face to face or Internet based).

Assessment of risk of bias in included studies
The risk of bias in included studies will be assessed using the Cochrane Collaboration’s tool (Higgins 2011). This will include assessment of the following:
- Selection bias
  - random sequence generation
  - allocation concealment
- Performance bias
- Detection bias
- blinding of outcome assessment
- Attrition bias
- incomplete outcome data: We will record the proportion of participants whose outcomes were not reported at the end of the study and categorise as follows;
  - low risk of bias, if fewer than 20% of patients were lost to follow up and reasons for loss to follow up were similar in both treatment arms
  - high risk of bias, if more than 20% of patients lost to follow up or reasons for loss to follow up differed between treatment arms
  - unclear risk of bias if loss to follow up was not reported
- Reporting bias
  - selective reporting of outcomes
- Other possible sources of bias

Two review authors will independently apply the ’Risk of bias’ tool and differences will be resolved by discussion or by appeal to a third review author. Results will be summarised in both a ’Risk of bias’ graph and a ’Risk of bias’ summary. Results of meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect
The measurement of treatment effect will be expressed as follows. For dichotomous variables, risk ratios (RR) will be calculated and expressed with 95% confidence intervals (CI). For continuous data expressed as means with standard deviations, we will use mean difference to show effect size. For data presented as time-to-event, if they are dichotomous, odds ratios will be used and for a log rank approach we will calculate hazard ratios (HR).

Unit of analysis issues
We will include cluster randomised trials. In these trials individuals are randomised as a block, from one centre or one clinic, so this will be dealt with on a trial by trial basis, depending on the study design.

Dealing with missing data
An intention-to-treat analysis is planned and we will contact authors for any missing ’Risk of bias’ information or outcome data required, if appropriate. We will report on the levels of loss to follow-up and assess this as a source of potential bias. We will investigate, through sensitivity analyses, the effects of any imputed data on pooled effect estimates.
Assessment of heterogeneity
We will assess the heterogeneity of any combined studies in the meta-analysis using $I^2$. If $I^2$ is greater than 30% we will examine possible reasons for heterogeneity in relation to clinical setting, study participants and similarity of clinical parameters in studies.

Assessment of reporting biases
We will search multiple sources including trial registries as detailed above. We will consider whether trials were undertaken and reported according to their trial protocol. If there is a sufficient number of included studies, we will attempt to assess publication bias using a funnel plot as detailed in section 10.4 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Data synthesis
Review Manager 2014 will be used for any data synthesis. Meta-analyses will only be conducted if there are studies reporting similar comparisons for the same outcomes. Meta-analyses will be performed using the Mantel-Haenszel random-effects method for the synthesis of the dichotomous data, due to the anticipated level of heterogeneity in the studies. For continuous variables, inverse variance will be used in a random-effects method if there are suitable data to perform a meta-analysis. If there are enough studies reporting time-to-event data then Peto method will be used in a fixed-effect model if a meta-analysis is appropriate (random-effects model is not available for Peto method in Review Manager 2014). If we establish that there is significant heterogeneity ($I^2$ more than 30%) between the studies, we will not undertake a meta-analysis but will investigate possible causes of heterogeneity. If a meta-analysis cannot be undertaken we will undertake a descriptive review of the studies.

Subgroup analysis and investigation of heterogeneity
If the data allow, planned subgroup analysis will be undertaken on different cancer types and also on different dietary intervention methods delivered for specific interventions. This could include subgroup analysis of interventions for weight management, or analysis which looks at interventions delivered by telephone interviewing.

Sensitivity analysis
Sensitivity analysis will be undertaken to evaluate the effects of bias on the results by investigating the impact of trials that have a high level of bias or an unclear level of bias. Each of the items assessed to indicate bias will bias evaluated separately.

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References

Additional references

Armes 2009

Aziz 2003

Baker 2003

Daar 2007
Reducing the risk of cancer with healthy food choices and physical activity.


Review Manager 2014


**WCRF/AICR 2007**


* Indicates the major publication for the study

**APPENDICES**

**Appendix 1. MEDLINE Ovid search strategy**

1 exp neoplasms/
2 (cancer* or tumor* or tumour* or neoplasm* or malignant* or carcinoma* or adenocarcinoma* or choriocarcinoma* or leukemia* or leukaemia* or metastasis* or sarcoma* or teratoma*).ti,ab.
3 1 or 2
4 Diet/
5 exp nutrition assessment/
6 exp Nutrition Therapy/
7 exp Nutrition Disorders/
8 Food Habits/
9 Food Preferences/
10 exp Food/
11 (diet* or nutrition* or nutrient* or food* or feed* or eat* or drink*).ti,ab.
12 (fat* or carbohydrate* or protein* or fruit* or vegetable* or fibre* or fiber* or fish* or meat* or poultry or dairy or salt* or sugar* or cereal* or nut* or seed* or alcohol* or caffeine).ti,ab.
13 (macrobiotic or ketogenic or vegetarian or (low adj (glycemic* or glycaemic*))).ti,ab.
14 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 survivors/
16 (survivors or survival*).ti,ab.
17 15 or 16
18 3 and 14 and 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 randomized.ab.
22 placebo.ab.
23 clinical trials as topic.sh.
24 randomly.ab.
25 trial.ti.
26 19 or 20 or 21 or 22 or 23 or 24 or 25
27 18 and 26
28 exp animals/ not humans.sh.
29 27 not 28

key:

[mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
CONTRIBUTIONS OF AUTHORS

SB wrote the proposal and SL, EG and DG have commented on the nutritional and clinical components of the protocol. The methodological aspects of the systematic review protocol have been commented on by CT and MP has reviewed the plan for data analysis.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service or Department of Health.

DECLARATIONS OF INTEREST

None known

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