Review question(s)
To assess the risks and protective effects of altering omega 3, omega 6 and total polyunsaturated fat (PUFA) intake on cancer in adults.

Searches
Electronic searches
We will identify trials through systematic searches of the following bibliographic databases:
1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
2. MEDLINE (Ovid)
3. Embase (Ovid)
We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication or time.

Types of study to be included
We will include randomized controlled trials (RCTs) that compare higher with lower polyunsaturated fat intakes and assess effects over at least 12 months. We will include studies reported as full-text, those published as abstracts only, and unpublished data. We will not include cross-over studies as this design is inappropriate for cancer outcomes but will include cluster-randomised studies, as long as there are at least six clusters.

Condition or domain being studied
Cancer (any)

Participants/ population
We will include studies of adults (18 years of age and above). Included participants can have current chronic disease such as cardiovascular disease, nephritis in systemic lupus erythematosus, diabetes mellitus, rheumatoid arthritis, depression, cognitive impairment, multiple sclerosis. The study will also include those with a previous cancer diagnosis or defined as at increased risk of cancer.
We will exclude participants who are current undergoing cancer treatment, undergoing heart or renal transplantation, with HIV or AIDS, on haemodialysis, with immunoglobulin A (IgA) glomerulonephritis, or any other renal problem (except in diabetes). We will also exclude pregnant women.

Intervention(s), exposure(s)
Eligible trials will compare higher with lower omega 3, omega 6 and total polyunsaturated fat (PUFA) intakes. The intervention must be either dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements must aim to increase or decrease total PUFA intake, or, if no clear aim is stated (but implied, such as aiming to provide a ‘heart health’ or ‘Mediterranean’ diet) then the intervention must achieve an increase or decrease of at least 10% of the baseline total PUFA level. Supplementation may be in oil or capsule form, or as food-stuffs provided, to be consumed by mouth (we will exclude enteral and parenteral feeds, and enemas).
Studies will not be included if they include a multiple risk factor intervention on lifestyle factors other than diet and supplementation (unless the effect of diet or supplementation could be separated out from the other interventions). Where the alteration of PUFA intake is only part of a dietary intervention (such as a combined intervention to increase PUFA and fruit and vegetable intake) the study will be included. Studies will be included if they compared the effect of this intervention with usual diet, no advice, no supplementation or placebo (as appropriate) or with the opposite intervention (raised versus lowered PUFA intake).

Comparator(s)/ control
Eligible trials will compare higher with lower omega 3, omega 6 and total polyunsaturated fat (PUFA) intakes.

Outcome(s)
Primary outcomes
1. Cancer diagnosis (including recurrence of a previous diagnosis)
2. Cancer mortality
3. Breast cancer (incidence and mortality)
4. Biochemical markers of risk, for example PSA levels for prostate cancer and breast density for breast cancer

Secondary outcomes
1. Body weight and measures of adiposity
2. Quality of life measures
3. Drop-outs

Data extraction, (selection and coding)
Review authors will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as ‘retrieve’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. If there are any disagreements, a third author will be asked to arbitrate. We will retrieve the full text study reports/publication and two review authors will independently screen the full-text, identify studies for inclusion, and identify and record reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion.

Risk of bias (quality) assessment
Two reviews will independently assess risk of bias for each study, alongside data extraction, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We will resolve any disagreements by discussion or by involving another reviewer.

Additional review specific criteria will include similarity or not of type and intensity of intervention in both arms (attention) and compliance. A study will be considered at low risk of attention bias when participants were given the same amount of time and attention from study staff and health professionals whether they were in the intervention or control arms, and at low risk of compliance bias when compliance was assessed, results of that assessment clearly reported for both intervention and control arms, and where most participants appeared to have taken at least 75% of the intended PUFA dose. A trial will be considered to be at low risk of bias if allocation concealment was adequate, and participant, provider and outcome assessor blinding were all coded at low risk of bias. All other trials were considered at moderate or high risk of bias.

**Strategy for data synthesis**

Primary measures of interest will be effects of dietary advice or supplementation of omega 3 fats, omega 6 fats, and total PUFA, on primary outcomes. We will separate out effects of omega 3, omega 6 and total PUFA in all analyses (so have 3 separate sets of results, one for omega 3 fats, one for omega 6 and one for total PUFA).

Treatment/control differences in the outcomes will be combined across studies using relative risks (RR) or mean differences (MD) in random effects meta-analysis. Where different scales measuring the same outcome or effect are found random effects meta-analysis will use standardised mean differences. If trials randomised by cluster are identified, the patient numbers would be reduced to an effective sample size as described by Hauck 1991.

For combined outcomes (e.g. combined cardiovascular events) attempts were made to add numbers of individuals experiencing specific outcomes within studies, but only where we were certain that we were not counting individual participants more than once within any one of our review outcome categories. However, individuals may have been counted for more than one of the review outcomes (in separate forest plots).

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. Our primary analyses will assess effects of dietary (dietary advice or supplemental foods such as fortified margarine provided by the study) or supplemental sources (capsules or oils) of total PUFA separately.

**Analysis of subgroups or subsets**

We plan to use subgrouping on primary outcomes to explore effects of increased intake by:

1. Replacement of SFA with PUFA
2. Replacement of MUFA with PUFA
3. For long chain omega 3 fats: At least 150, 250, 400 mg/day from all sources including supplements (above or below each threshold) fish omega 3 dose - low dose 0.4 to 2.4g/day, medium dose 2.5 to 4.4 g/day, and high dose =4.5g/day of combined long chain omega 3 fats
4. For ALA, omega 6 and total PUFA: higher vs lower levels of intake
5. dietary supplemental source– dietary advice, supplemental foods (for example margarine fortified with rapeseed, tins of sardines or oils to use in cooking) provided by the study, or supplements (capsules or oils) provided to take as medicine
6. trial duration - studies with short follow up (12 to 23 months), medium long follow up (24 to 47 months) and long follow up (greater than 48 months)
7. baseline omega 3, omega 6 or total PUFA intake
8. level of baseline medication use including hormone replacement therapy
9. for the total PUFA analyses we will assess and analyse by n3/n6 ratio (for whole diet in intervention and control groups) where possible
10. primary versus secondary prevention of cancers
11. Age
12. Gender
13. Pre and post-menopausal women; women taking hormone replacement therapy
14. Weight (likely to be dichotomous (BMI < or > 25))
15. Ethnicity

**Sensitivity analysis:**

Sensitivity analyses will be used to assess robustness of results to trial quality:

- meta-analysis using fixed, rather than random, effects
- excluding high risk of bias studies

Funnel plots will be used to assess for evidence of small study bias (Egger 1997). Type and frequency of side effects and adverse effects were tabulated (with the other extracted data on adverse effects) and compared between different studies and designs.

The quality of evidence will be rated using GRADE (Grading of Recommendations Assessment, Development and Evaluation, which provides an explicit and comprehensive method to rate quality of evidence in health, GRADE Working Group 2004) using GRADEpro software, and reported in the Summary of Findings table.

**Dissemination plans**

We will publish in appropriate peer reviewed journals

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Conflicts of interest
None known

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Subject indexing assigned by CRD

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Ongoing

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Stage of review at time of this submission

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<th>Activity</th>
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<td>Preliminary searches</td>
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<td>Piloting of the study selection process</td>
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<td>Formal screening of search results against eligibility criteria</td>
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<td>Data extraction</td>
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