

Laetrile treatment for cancer (Review)

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[Intervention Review]

Laetrile treatment for cancer

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ABSTRACT

Background

Laetrile is the name for a semi-synthetic compound which is chemically related to amygdalin, a cyanogenic glycoside from the kernels of apricots and various other species of the genus *Prunus*. Laetrile and amygdalin are promoted under various names for the treatment of cancer although there is no evidence for its efficacy. Due to possible cyanide poisoning, laetrile can be dangerous.

Objectives

To assess the alleged anti-cancer effect and possible adverse effects of laetrile and amygdalin.

Search methods

We searched the following databases: CENTRAL (2014, Issue 9); MEDLINE (1951-2014); EMBASE (1980-2014); AMED; Scirus; CINAHL (all from 1982-2015); CAMbase (from 1998-2015); the MetaRegister; the National Research Register; and our own files. We examined reference lists of included studies and review articles and we contacted experts in the field for knowledge of additional studies. We did not impose any restrictions of timer or language.

Selection criteria

Randomized controlled trials (RCTs) and quasi-RCTs.

Data collection and analysis

We searched eight databases and two registers for studies testing laetrile or amygdalin for the treatment of cancer. Two review authors screened and assessed articles for inclusion criteria.

Main results

We located over 200 references, 63 were evaluated in the original review, 6 in the 2011 and none in this update. However, we did not identify any studies that met our inclusion criteria.

Authors' conclusions

The claims that laetrile or amygdalin have beneficial effects for cancer patients are not currently supported by sound clinical data. There is a considerable risk of serious adverse effects from cyanide poisoning after laetrile or amygdalin, especially after oral ingestion. The risk-benefit balance of laetrile or amygdalin as a treatment for cancer is therefore unambiguously negative.

PLAIN LANGUAGE SUMMARY

Laetrile treatment for cancer

Laetrile is a word created from the first letters of laevorotatory and mandelonitrile and describes a semi-synthetic form of amygdalin. Amygdalin is a compound that can be isolated from the seeds of many fruits such as peaches, bitter almonds and apricots. Both laetrile and amygdalin have a common structural component, mandelonitrile, that contains cyanide.

The lack of laetrile's effectiveness and the risk of side effects from cyanide poisoning led the Food and Drugs Agency (FDA) in the US and the European Commission to ban its use. However, it is possible to buy laetrile or amygdalin via the Internet. As there is no government control of these markets, preparations may not only come from questionable sources but they may also be contaminated. Cancer patients should be informed about the high risk of developing serious adverse effects due to cyanide poisoning after laetrile or amygdalin, especially after oral ingestion. This risk could increase with concomitant intake of vitamin C and in vegetarians with vitamin B12 deficiency.

This systematic review found that there is no reliable evidence for the alleged effects of laetrile or amygdalin for curative effects in cancer patients.

BACKGROUND

Description of the condition

Many surveys have reported that many people suffering from cancer turn towards so-called alternative cancer cures, hoping for an effective therapy. However, few alternative cancer therapies are backed up by encouraging evidence. Some of them are associated with high-risks (Gibbs 2004), and the quality of information about complementary and alternative medicine (CAM) for cancer treatment has the potential to seriously mislead patients (Schmidt 2004). Many websites suggest a variety of alternative cancer cures and most of them advertise and sell such products illegally (Barrett 2011).

Description of the intervention

Amygdalin

Amygdalin is a cyanogenic glycoside plant compound found in the kernels of many fruits and in numerous plants belonging to the genus of *Prunus* (Vetter 2000). Amygdalin consists of a gentiobiose, a disaccharide composed of two units of D-glucose, and mandelonitrile (Kwon 2003). Amygdalin was first isolated in 1830 by two French chemists Robiquet and Boutron-Charlard (Dorr 1978). Orally administered amygdalin is thought to be hydrolyzed into prunasin and glucose by human digestive enzymes and prunasin is further degraded into mandelonitrile in the small intestine. Transformation of mandelonitrile into benzaldehyde and cyanide and the subsequent toxicity is mainly due to gut microflora (Shim 2010).

Laetrile

In the 1950s, an intravenous form of amygdalin was patented and named laetrile, which is an acronym from laevorotatory and mandelonitrile. The form that was patented in the USA, albeit not approved, is a semisynthetic compound consisting of D-glucuronic acid and mandelonitrile, while laetrile made in Mexico is extracted from crushed apricot kernels consists of amygdalin. (Dorr 1978; Fenselau 1977).

Laetrile is prepared for oral as well as for intravenous or intramuscular application. The results of an analysis conducted by the National Cancer Institute (NCI) in order to assess the purity of both oral and injectable amygdalin products indicated that they were substandard by US criteria for pharmaceutical products (Davignon 1978). Other studies also showed the presence of contaminants in both injectable and oral supplements of laetrile (Dorr 1978). Shaffer reported that the FDA deemed that laetrile products were toxic and ineffective and laetrile was consequently banned from US-interstate transportation (Shaffer 1979). However, in 1980 the Associated Press reported that 23 US States had legalized the use of the laetrile within their boundaries and for the treatment of terminal cancer patients (Curran 1980). During the 1970s at least 70,000 Americans had used laetrile (Ellison 1978). Laetrile's proponents consider it to be a "natural cancer cure"; whereas opponents consider "the slickest, most sophisticated, and certainly the most remunerative cancer quack promotion in medical history" (Lerner 1981).

How the intervention might work

Cyanide released from enzymatic degradation of laetrile or amygdalin is believed to be the ingredient responsible for the alleged anti-cancer action. Proponents claim that malignant cells are specifically vulnerable to cyanogenic glycosides because of two characteristics: a higher level of beta-glucosidases and beta-glucuronidase compared to normal cells, which would lead to a more rapid intracellular release of cyanide from laetrile or amygdalin and a deficiency in rhodanese, an enzyme that converts cyanide into the harmless compound thiocyanate. Another theory claims that cancer develops due to the deficiency of a vitamin, named "vitamin B17", which was the name that the chemist E.T. Krebs gave to laetrile (theories reviewed in NCI 2011). Recent in-vitro studies suggested possible anti-cancer effects of amygdalin (Chang 2006; Fukuda 2003; Kwon 2003; Park HJ 2005).

Why it is important to do this review

After a best case series in 1978, the NCI conducted a phase I and phase II trial. Their results suggested that oral ingestion of laetrile or amygdalin raises the risk of cyanide poisoning and that the number of patients who showed a tumor response after the application of amygdalin was minimal: one out of 175 evaluable patients met the criteria for a tumor response (Moertel 1982). Laetrile has been banned by the FDA since the 1980s and it is not authorized for sale as a medicinal product in the European Community (Meijer 2001). Nevertheless, it continues to be manufactured and administered as an anti-cancer therapy (Lilienthal 2014). Over the last years websites have again started promoting and selling laetrile, amygdalin and apricot pits (Barrett 2011) and

questionable claims are made concerning benefits for cancer patients (reviewed in Lilienthal 2014).

OBJECTIVES

To determine the effectiveness and tolerability of laetrile and or amygdalin for the treatment of cancer patients.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs), including cluster and cross-over trials and quasi-RCTs (assigning patients to groups based on date, order of entry, birth date etc.).

Types of participants

Any adult patients with histologically proven malignant diseases of any stage.

Types of interventions

Intervention

Oral or parenteral (intravenous or intramuscular) preparations of laetrile, amygdalin, or from the seed of *Prunus* species.

Control Interventions

Control groups could consist of placebo, conventional standard treatment, or no treatment, or waiting lists.

Types of outcome measures

The outcomes of interest were:

- Overall survival (OS),
- Disease-free survival (DFS) and progression-free survival (PFS),
- Tumor response (parameters for response had to be defined or follow standard criteria (WHO (Miller 1981), RECIST (Therasse 2000)),
- Adverse events related to the intervention.

Search methods for identification of studies

Electronic searches

For the previous version of the review we searched the following databases for the indicated time periods or from inception of the database: The Cochrane Central Register of Controlled Trials (CENTRAL, 2011, Issue 1); MEDLINE (1951-2011); EMBASE (1980-2011); AMED; Scirus; CancerLit; CINAHL (all from 1982-2011); CAMbase (from 1998-2011). For this update we searched The Cochrane Central Register of Controlled Trials (CENTRAL, 2014, Issue 9); MEDLINE (Oct week 3, 2014); EMBASE (2014, week 43); AMED; Scirus; CINAHL (all from 2011-2015); CAMbase (2011-2015). See [Appendix 1](#) for list of electronic search strategies.

Searching other resources

For ongoing trials, we searched the following databases: Clinical Trials of the American Cancer Society (<http://www.cancer.gov>, April 2015), the metaRegister of Controlled Trials (mRCT, <http://www.controlled-trials.com>, April 2015) and the German Cancer Study Register (<http://www.studien.de>, April 2015). In addition, we scanned the bibliographies of all located studies to identify unpublished or on-going trials through correspondence with experts in the field. Finally, we handsearched our own files for further studies.

Data collection and analysis

We downloaded all titles and abstracts retrieved by the searches to a reference management database. We removed duplicates and two review authors independently examined the remaining references (SM, MH). We obtained the full texts for potentially relevant studies and reviewed them for inclusion based on predetermined criteria. We resolved disagreement by discussion.

Methods for future updates

The updated search of this review again did not retrieve any studies which met the inclusion criteria. If eligible trials are identified in further updates, we will apply the review methods reproduced in [Differences between protocol and review](#).

RESULTS

Description of studies

Results of the search

The searches up to Feb 2011 identified 69 potentially relevant references (63 for the original review and 6 for this update). After screening the titles and abstracts, we obtained full publications of 40 references for detailed evaluation. We excluded all 40 for the following reasons: not randomized (1 study), case reports (25 studies), best case series (6 studies), consecutive case series (3 studies), non-consecutive case series (2 studies), benzaldehyde treatment rather than laetrile or amygdalin (2 studies), patients with benign tumors (1 study) ([Characteristics of excluded studies](#)). Searches of trial registries did not identify any ongoing and eligible trials in this area. CENTRAL, MEDLINE and EMBASE searches up to October 2014 and CINAHL, CAMbase and author team topic knowledge up to April 2015 did not identify any studies for inclusion.

Risk of bias in included studies

No study met the inclusion criteria.

Effects of interventions

No study met the inclusion criteria.

DISCUSSION

Summary of main results

There were no RCTs or quasi-RCTs investigating the effectiveness of laetrile or amygdalin for the treatment of cancer. Despite the utilization of laetrile and amygdalin, this systematic review found no evidence for laetrile or amygdalin to be effective as anti-cancer agents.

Overall completeness and applicability of evidence

Not applicable.

Quality of the evidence

Not applicable.

Potential biases in the review process

Strengths of this review include the use of extensive search terms and multiple databases to ensure a comprehensive search. Limitations include the possibility that we overlooked trials with other cyanogenic glycosides, given their large number in the plant kingdom.

Agreements and disagreements with other studies or reviews

As this systematic review found no evidence from RCTs or quasi-RCTs for the use of laetrile or amygdalin in cancer treatment, nothing must be added to the conclusion of an editorial that was written after the publication of a clinical trial of amygdalin for the treatment of advanced cancer from the NCI: "(...) The evidence, beyond reasonable doubt, is that it [laetrile] doesn't benefit patients with advanced cancer, and there is no reason to believe that it would be any more effective in the earlier stages of the disease." (Relman 1982)

Our search strategy was aimed at identifying clinical trials. This approach generates little information about risks. Yet the high risk of developing serious adverse effects from cyanide poisoning after laetrile or amygdalin, especially after oral ingestion, is considerable. This risk could increase with a concomitant intake of vitamin C (Bromley 2005), in people with a genetic predisposition to a diminished capacity to detoxify cyanide (Calabrese 1979b) and in vegetarians with vitamin B12 deficiency (Chan 2006). Practitioners and patients should also be aware that cyanide poisoning could be related to overdosing and to the quality of the products available on the market. Processing conditions are the main factors affecting the quality of some *Rosaceae* seeds (Hu 2002; Hwang 2002), and often laetrile and amygdalin preparations come from questionable sources with no standards of quality or purity. These preparations might be mutagenic (Fenselau 1977) or could contain bacteria (Davignon 1978) and other contaminants and impurities (Dorr 1978).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from RCTs or quasi-RCTs that support the use of laetrile or preparations containing amygdalin in cancer patients. Due to the risk of cyanide poisoning, the use of laetrile or amygdalin should be discouraged.

Implications for research

On the basis of the available data, there is neither scientific nor ethical justification for clinical trials with laetrile or amygdalin in the management of cancer at the moment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ames 1981	Non consecutive case series
Cancer Comm 1953	Consecutive case series
CPW-Rahlstedt 1995	Unpublished consecutive case series
Guidetti 1955	Best case series
Kochi 1980	Benzaldehyde treatment instead of laetrile or amygdalin
Kochi 1985	Benzaldehyde treatment instead of laetrile or amygdalin
Moertel 1981	Non consecutive case series
Moertel 1982	Consecutive case series study
Morrone 1962	Best case series
Navarro 1957	Best case series
Navarro 1959	Best case series
Navarro 1964	Best case series
Sakamoto 1992	Patients with benign tumor
Suehiro 2005	Not randomised. Assessed outcome not included (bowel motility)
Tasca 1959	Best case series

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Electronic search strategies

CENTRAL

#1 MeSH descriptor: [Amygdalin] explode all trees

#2 (amygdalin or amygdaloside or isoamygdalin or neoamygdalin or mandelonitrile or laetrile or laetril or letril or letrile or lactrile)

#3 MeSH descriptor: [Prunus] explode all trees

#4 (prunus or prunasin* or prulaurasin or apricot or peach or almond or vitamin B17 or tao ren or tonin or tounin or persica or pesicae or semen armeniacae amarum or keishi-bukuryo-gan or keishibukuryogan or TJ-25 or nitriloside or sarcacinase or C20-H27-N-011 or C14-H15-N-07)

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Neoplasms] explode all trees

#7 (neoplasm* or cancer* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)

#8 #6 or #7

#9 #5 and #8

MEDLINE Ovid

1 Amygdalin/

2 (amygdalin or amygdaloside or isoamygdalin or neoamygdalin or mandelonitrile or laetrile or laetril or letril or letrile or lactrile).mp.

3 Prunus/

4 (prunus or prunasin* or prulaurasin or apricot or peach or almond or vitamin B17 or tao ren or tonin or tounin or persica or pesicae or semen armeniacae amarum or keishi-bukuryo-gan or keishibukuryogan or TJ-25 or nitriloside or sarcacinase or C20-H27-N-011 or C14-H15-N-07).mp.

5 1 or 2 or 3 or 4

6 exp neoplasms/

7 (neoplasm* or cancer* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*).mp.

8 6 or 7

9 5 and 8

10 randomized controlled trial.pt.

11 controlled clinical trial.pt.

12 randomized.ab.

13 placebo.ab.

14 clinical trials as topic.sh.

15 randomly.ab.

16 trial.ti.

17 10 or 11 or 12 or 13 or 14 or 15 or 16

18 9 and 17

key:

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

sh=subject heading

pt=publication type

ab=abstract

EMBASE Ovid

1 amygdalin/

2 (amygdalin or amygdaloid or isoamygdalin or neoamygdalin or mandelonitrile or laetrile or laetril or letril or letrile or lactrile).mp.
 3 exp Prunus/
 4 (prunus or prunasin* or prulaurasin or apricot or peach or almond or vitamin B17 or tao ren or tonin or tounin or persica or pesicae or semen armeniaca amarum or keishi-bukuryo-gan or keishibukuryogan or TJ-25 or nitrilside or sarcacinase or C20-H27-N-011 or C14-H15-N-07).mp.
 5 1 or 2 or 3 or 4
 6 exp neoplasm/
 7 (neoplasm* or cancer* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*).mp.
 8 6 or 7
 9 5 and 8
 10 crossover procedure/
 11 double-blind procedure/
 12 randomized controlled trial/
 13 single-blind procedure/
 14 random*.mp.
 15 factorial*.mp.
 16 (crossover* or cross over* or cross-over*).mp.
 17 placebo*.mp.
 18 (double* adj blind*).mp.
 19 (singl* adj blind*).mp.
 20 assign*.mp.
 21 allocat*.mp.
 22 volunteer*.mp.
 23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
 24 9 and 23

Search terms for NHS Dialog

NHS Dialog is a portal that provides access to databases such as AMED, CINHALL, EMBASE, and MEDLINE. All the above terms were searched in the same way in the NHS Dialog portal, apart from the truncation symbol *, that has been replaced by \$. In order to limit truncation and avoid the possibility of overflow, a number of characters after the wildcard was also specified.

Search terms for CAMbase CAMbase is a virtual search engine with modern XML-based retrieval-technology, which enables the user to easily find relevant literature of Complementary and Alternative Medicine (CAM) in different resources. The use of CAMbase is optimized in such a way that the user can type in a request as a naturally spoken phrase. It is helpful to complete the sentence.

We used the following sentences:

- Laetrile for cancer
- Vitamin B17 for cancer
- Amygdalin and cancer
- Prunus and cancer

FEEDBACK

Correspondence

Summary

Andrew Vickers, Assistant Attending Research Methodologist
 vickersa@mskcc.org

The authors' state that they: "[have] clearly identified the need for randomised or controlled clinical trials assessing the effectiveness of Laetrile or amygdalin for cancer treatment."

This is to fail completely to understand the nature of oncology research in which agents are tested in randomized trials ("Phase III") only after they have been successful in Phase I and II study. There was a large Phase II study of laetrile (N Engl J Med. 1982 Jan 28;

306(4):201-6) which the authors of the review do not cite, they merely exclude as being non-randomized. But the results of the paper are quite clear:

there was no evidence that laetrile had any effect on cancer (all patients had progression of disease within a few months); moreover, toxicity was reported. To expose patients to a toxic agent that did not show promising results in a single arm study is clinical, scientific and ethical nonsense.

I would like to make a serious recommendation to the Cochrane Cancer group that no reviews on cancer are published unless at least one of the authors either has a clinical practice that focuses on cancer or actively conducts primary research on cancer. My recollection when the Cochrane collaboration was established was that the combination of “methodologic” and “content” expertise was essential. Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Stefania Milazzo and Ezard Ernst

The view that there is no need for further clinical trials of Laetrile seems entirely reasonable. On the other hand, there are many people out there who promote Laetrile. Firstly they cite non-RCT data which, they claim, is encouraging. Secondly they state that the phase 2 study Vickers refers to was totally flawed. Therefore it might be of benefit to lay this issue at rest by conducting a rigorous RCT. If this prevents cancer patients from being misled into using laetrile, lives could be saved.

Contributors

Vickers A

Milazzo S, Ernst E

WHAT'S NEW

Last assessed as up-to-date: 31 October 2014.

Date	Event	Description
20 April 2015	New citation required but conclusions have not changed	Literature searches updated.
20 April 2015	New search has been performed	No studies identified for inclusion.

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 2, 2006

Date	Event	Description
3 August 2011	New citation required but conclusions have not changed	New author added and contact details revised.
17 June 2011	New search has been performed	Update of the literature search and complete revision of the text. No studies identified for inclusion
16 February 2006	Amended	Minor update: 16/02/06 Feedback added: 15/08/06 Response to feedback added: 04/01/07
6 January 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

First version of the review

Draft protocol (SM with contributions from all). Ran searches (SM). Identified relevant titles (SM, SL, KB, EE). Selected eligible trials (SM, SL, KB, EE). Drafted final review (SM with contribution from all).

Updated version of the review 2011

Update of the literature search and revision of the text (SM, MH). Comments on the updated text (EE, SL).

Updated version of the review 2011

Update of the literature search and revision of the text (SM, MH).

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- FP5 project “Concerted Action for Complementary and Alternative Medicine Assessment in the Cancer Field (CAM-Cancer)”, Quality of life and management of living resources programme, European Commission [QLRT- 2001- 00786], Other.
- Cochrane Gynecologic Cancer Group, Bath, UK.
- AG Biologische Krebstherapie, Deutsche Krebshilfe (70-301), Germany.

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- Kompetenznetz Komplementärmedizin in der Onkologie - KOKON, Germany. Förderungsschwerpunkt der Deutschen Krebshilfe e.V. (Projekt-Nr. 109863)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

If in any future update studies are identified for inclusion we will use the following methodology:

Data extraction and management

Data will be independently extracted unblinded to the study authors by at least two review authors using a predefined extraction form. All disagreements will be resolved by discussion.

We will extract the following information : author, year of publication, country and language of publication, funding source, objectives, study design, characteristics of participants including age, gender, number of participants who were eligible, enrolled and completed the study, diagnostic criteria and procedures, presence of intention-to-treat or per protocol analysis, method of sequence generation and randomization, blinding and allocation concealment, numbers and reasons for withdrawals and dropouts, details on intervention (type of preparation, dosage, chemical structure) and control treatment, duration of follow-up, time to event data (we will extract the median or mean survival times and their spread or confidence interval (CI)), dichotomous outcomes (e.g. adverse events, deaths, disease recurrence, disease progression, tumor response; we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at the endpoint in order to estimate a risk ratio (RR), adverse events (type and incidence of events and grades of toxicity).

If necessary, we will contact principal authors for further details of each study.

Assessment of risk of bias in included studies

Two review authors will independently assess methodological quality, using The Cochrane Collaboration 'Risk of bias' tool. We will resolve disagreement by discussion.

Measures of treatment effect

For time to event data, we will extract the hazard ratio (HR) and its variance from trial reports. If these are not presented, we will extract the data required to estimate them using Parmar's methods (Parmar 1998), e.g. number of events in each arm and log-rank P value comparing the relevant outcomes in each arm. If it is not possible to estimate the HR, we will extract the number of patients in each treatment arm who experienced the outcome of interest, in order to estimate a RR.

We will present dichotomous data as RR with corresponding CIs. We will also determine the number needed to treat (for improvement) (NNTB) and the number needed to harm (NNTH) (for adverse events) for statistically significant outcomes.

We will present continuous data as mean differences (MD) for common measurement units or standardized mean differences (SMD) for differing measurement units and different scales, along with corresponding CIs.

Unit of analysis issues

For studies with comparable treatment groups, we will enter data for studies with more than one active treatment arm separately into the meta-analysis and we will evenly divide the control arm data as much as possible between entries.

Dealing with missing data

In instances where information is missing, we will contact study authors to provide the information.

Assessment of heterogeneity

We will quantify heterogeneity with the I^2 statistic (Higgins 2003).

Assessment of reporting bias

We will assess publication bias visually using funnel plots (Egger 1997).

Data synthesis

We will use random-effects models for the primary analyses.

Subgroup analysis and investigation of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003) and by a formal statistical test of the significance of the heterogeneity (Egger 2001).

Sensitivity analysis

We will apply subgroup analyses omitting studies with a high risk of bias.

INDEX TERMS**Medical Subject Headings (MeSH)**

Amygdalin [adverse effects; *therapeutic use]; Antineoplastic Agents, Phytochemical [adverse effects; *therapeutic use]; Neoplasms [*drug therapy]

MeSH check words

Humans