

The prevalence of comorbidities among patients with
cancer based on administrative data: A systematic review
protocol

Plan of work CKO-9

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Management summary

The prevalence of comorbidities among patients with cancer based on administrative data: a systematic review

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Background: People around the world are reaching higher ages. Ageing is associated with the development of chronic diseases, e.g. diabetes mellitus or hypertension. These diseases are not directly life-threatening but can cause difficulties when the patient gets a second disease, e.g. cancer. Studies found that patients with cancer are more likely to have one or more other chronic diseases, also called comorbidities. There are various theories about the relationship between cancer and comorbidities. For example, a comorbidity can be the cause or the result of cancer. Also, several studies have confirmed that the presents of a comorbidity impacts the treatment plan, survival and economic burden of cancer patients. However, no systematic review on the prevalence of comorbidities among cancer patients has been conducted. This is a gap of knowledge that we would like to fill with our systematic review. We will gather chart-based (e.g. from medical records) or claim-based (e.g. from insurance health claims) data for the most representative sample of the population.

Objective: What is the prevalence of comorbidities among cancer patients based on chart-based and claim-based data?

Plan of investigation: A literature search using a search string with thesaurus terms and Boolean operators will be conducted in PubMed, EMBASE, Cochrane Library, CINAHL and Web of Science. Two researchers will independently include or exclude studies based on the selection criteria in two phases. In the first phase the title and abstract of the articles are screened. In the second phase, the full text of the previously included articles will be compared with the selection criteria. The selection criteria used will be:

Inclusion criteria:

- Subject of the study includes cancer, comorbidity and prevalence based on administrative data
- The population studied was eighteen years or older at the time of the cancer diagnosis
- Chart-based or claim-based data is used to identify the presence of a comorbidity
- The comorbidity is present at the same time as the cancer

Exclusion criteria:

- Abstracts not written in English or Dutch
- Articles published before 1990
- Not an observational study

The data from the included articles will be extracted using a pre-made template. For the synthesis of the data we will use a narrative approach and summarize the characteristics of the studies in a 'Summary of findings table'. We will show the distribution of different characteristics of the articles using pie charts and other graphs. We will also look at similarities between different subsets of the data e.g. same type of cancer. We are not planning a meta-analysis because we expect that there will be too much heterogeneity between the data.

Impact: With this systematic review we want to provide insights in the prevalence of comorbidities among cancer patients. These insights are relevant to improve treatment, reimbursement and secondary prevention in cancer patients, as well as to improve health infrastructure in an era of increasing prevalence of chronic comorbidities. And ultimately lead to optimal care for cancer patients battling more than one disease.

Rationale

The life expectancy of people around the world is increasing (1). Reaching a higher age is associated with the appearance of chronic diseases that are not directly life threatening, e.g. hypertension and Diabetes Mellitus type II. Another type of disease that is more prevalent among elderly people is cancer(2, 3). Therefore oncologist and other doctors are often faced with treating patients with one or more chronic diseases, also called comorbidities. A comorbidity is defined as the "co-existence of a disorder in addition to a primary disease of interest" (4). For this study we will look at comorbidities existing at the same time as our primary disease: Cancer. Several studies found that people with cancer are more likely to have a least one other chronic disease at the time they are diagnosed (2, 5, 6). This is associated with increased economic burden, lower quality of life and poorer survival probabilities (5, 7). There are various theories about the association between cancer and comorbidities. First, cancer and the comorbid condition can share the same risk factor e.g. smoking is a risk factor for lung cancer and COPD (8, 9). Second, a comorbidity can cause cancer e.g. chronic hepatitis B increases the chance of development of liver cancer (10). However the comorbidity can also be caused by cancer or the cancer treatment e.g. peripheral neuropathy after chemo-treatment (11). There are some studies that suggest that having a chronic illness can be beneficial because being under the care of a physician can help in the early diagnoses of cancer (12, 13). Other studies suggest that presents of comorbidities cause a delay in diagnosis (14). This shows that there is still lots unknown about the relationship between comorbidities and cancer but the importance of this relationship is well established. Be that as it may, exact numbers about the prevalence of comorbidities among cancer patients are still unknown. There are some studies that tried to examine this for specific cancer type (15-17). But no large systematic review to this date has been performed. The goal of this systematic review is to synthesise the existing literature about the prevalence of comorbidities among cancer patients. These insights are relevant to improve treatment, reimbursement and secondary prevention in cancer patients, as well as to improve health infrastructure in an era of increasing prevalence of chronic comorbidities. And ultimately lead to optimal care for cancer patients battling more than one disease.

When looking at the prevalence of comorbidities, the way the data is conducted is determinative for the outcome. In a review conducted by Sarfati et al. is stated that there is no gold standard to measure comorbidity in the context of cancer. The choice of measurement depends on the study question, population studied and the data available (18). The ways of measurement can roughly be divided into three categories: 1. a patient-based approach, where information about comorbidities is collected by getting information directly from the patient. 2. A chart-based approach, where the information is extracted by using the patients charts and ICD codes. 3. A claim-based approach, where the presents of comorbidities is established by looking at the patients' health insurance claims over a certain period of time (19). For this review we have decided to look at chart- and claim-based articles on comorbidities so that we can take to account a large representative group of the population.

Research question

Objective:

What is the prevalence of comorbidities among cancer patients based on chart-based and claim-based data?

Methods

Criteria for considering studies for this review

The inclusion criteria for this systematic review will be:

- Subject of the study includes cancer, comorbidity and prevalence based on administrative data
- The population studied was eighteen years or older at the time the cancer diagnosis was given
- Chart-based or claim-based data is used to identify the presence of a comorbidity
- The comorbidity is present at the same time as the cancer

The exclusion criteria for this systematic review will be:

- Articles published before 1990
- Articles not written in English or Dutch
- Not an observational study

Types of studies

We will only include observational studies in this review because we are interested in descriptive statistics and do not study an effect of intervention. Given the use of 'prevalence' and 'administrative data' in our search string we expect to find mostly observational studies. Other study types will be excluded.

Types of participants

The participants must meet the follow criteria:

- The diagnosis of cancer must be established by a certified doctor and meet the WHO definition of Cancer
- The presence of a comorbidity is confirmed when it meets the following criteria:
 - 1) A chronic disease must be established by a certified doctor and meet the WHO definition of that particular disease.
 - 2) The chronic disease must be present at the time of the cancer diagnosis or arise after the cancer diagnosis.
- The participant must be eighteen or older at the time the cancer diagnosis was given.

Types of outcome measures

The primary outcome for this study will be descriptive statistics on the prevalence of comorbidities in a representative cancer population.

Method and timing of outcome measurement

We will present a 'Summary of findings table' reporting the following outcomes listed.

Study identification	Population description	Sample size	Type(s) of cancer	Measurement of comorbidity	Prevalence estimate

Search methods for identification of studies

Electronic searches

Studies will be identified with an electronic search of PubMed, EMBASE, Cochrane Library, CINAHL and Web of Science. A search string using thesaurus terms and Boolean operators will be constructed. If we detect additional relevant keywords during the search, we will modify the electronic search strategies. We will only include studies published between 1990-2020 and written in English. The current version of the search string for PubMed and EMBASE is included in the appendix 1. When the search is definitive the search will be translated to other databases.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, (systematic) reviews and meta-analyses.

Data collection and analysis

Selection of studies

Before starting the literature search the selection processes is piloted by applying the inclusion criteria to a sample of papers in order to check that they can be reliably interpreted and that they classify the studies appropriately.

One reviewer will execute the search strategy in the selected databases. The number of potential eligible records will be compared. During our search and selection process we will install and 'MY NCBI report service' for our search string. If during this time any articles regarding our subject are uploaded we will include them in our results. When starting the synthesis of our finding we will turn off this report service. This date will be reported in our final paper.

An initial screening of titles and abstracts against the selection criteria will take place to identify potentially relevant papers. The studies that are rejected will be categorized in under 'clearly not relevant' and 'topic of interest but fails to meet the criteria'. The selection criteria will be:

Inclusion criteria:

- Subject of the study includes cancer, comorbidity and prevalence based on administrative data
- The population studied was eighteen years or older at the time of the cancer diagnosis
- Chart-based or claim-based data is used to identify the presence of a comorbidity
- The comorbidity is present at the same time as the cancer

Exclusion criteria:

- Abstracts not written in English or Dutch
- Articles published before 1990
- Not an observational study

This is followed by screening of the full papers identified as possibly relevant in the initial screening, also done independently by two researchers. When studies are excluded, an explanation will be documented in the list with excluded studies. The selection criteria will be:

Inclusion criteria:

- Subject of the study includes cancer, comorbidity and prevalence based on administrative data
- The population studied has been diagnosed with cancer when older than 18 years.
- Chart-based or claim-based data is used to identify the presence of a comorbidity

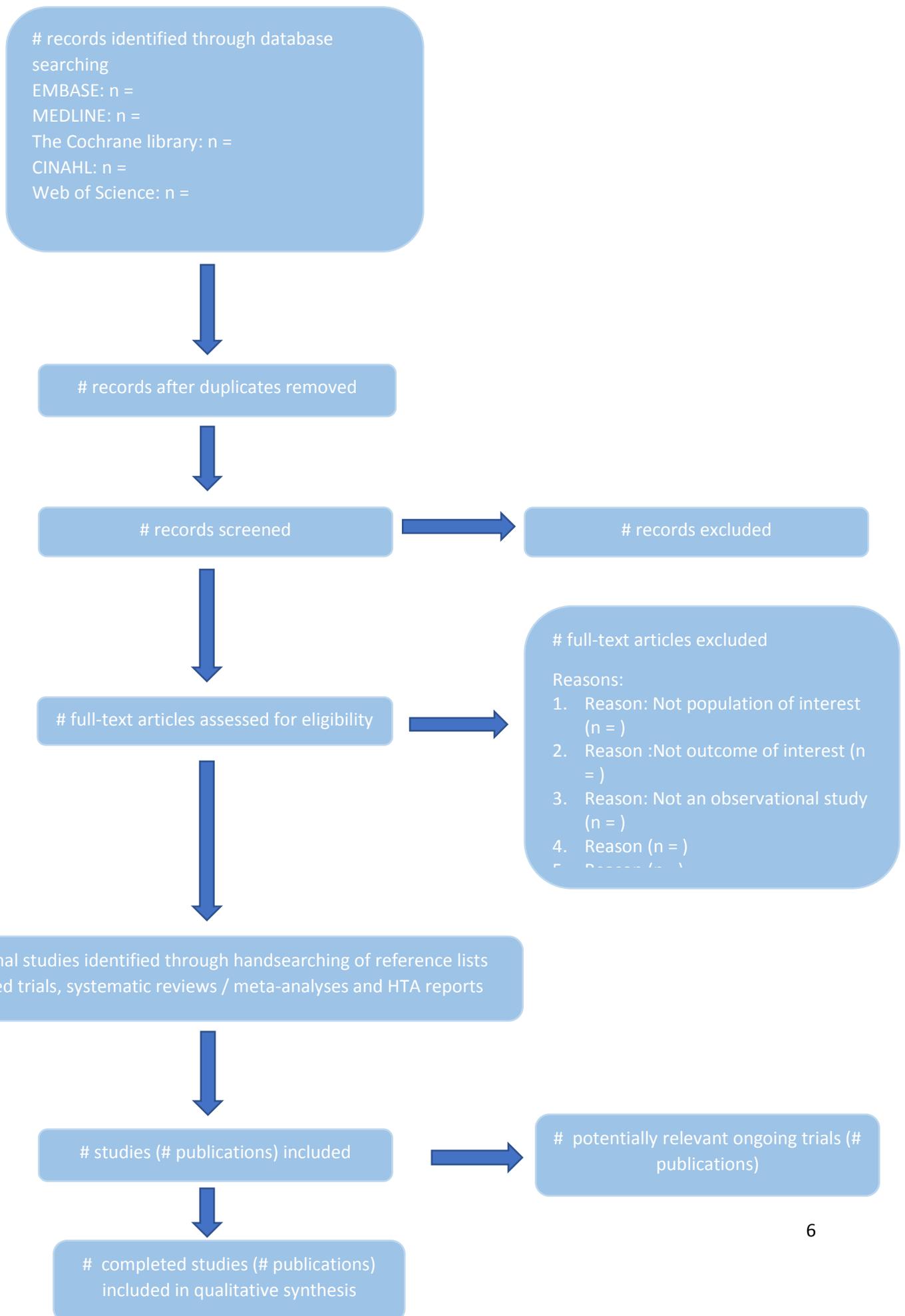
Exclusion criteria:

- Articles not written in English or Dutch
- Not an observational study

If the two researchers are not in agreement about the inclusion of an article, a third researcher will be consulted. The remaining records will be used for the systematic review. The reference list of the remaining records will be checked to see if any relevant studies did not emerge in the literature search.

The documentation of decisions made in the literature search will be done with Rayyan. A flow chart will be included in the final report showing the number of records remaining at each stage. A list of studies excluded from the review will be included in the appendix of the final paper.

Proposed flowchart



Data extraction and management

One reviewer will extract the required data from the included articles using standard extraction templates (appendix 2). Another reviewer will check a random selection of the extracted data for accuracy. The extracted data will include:

- General information
 - Researcher performing data extraction
 - Date of data extraction
 - Identification features of the study
 - Record number
 - Author
 - Article title
 - Citation
 - Type of publication
 - Country of origin
 - Source of finding
- Study characteristics
 - Aim/objectives of the study
 - Study design
 - Retrospect + follow-up time
 - Measurement of comorbidity
 - Study inclusion and exclusion criteria
- Participant characteristics
 - Number of participants
 - Age
 - Gender
 - Type(s) of cancer
 - Type of comorbidities
- Outcome data
 - Prevalence of comorbidities

Dealing with duplicate and companion publications

All records will be uploaded in Endnote. Duplications will be removed. In case of companion publications we will collect all available evidence and use the most complete dataset or in case of doubt the publication with the longest follow-up regarding our primary outcome measurement. After removing all duplications, Rayyan (20) will be used to for the inclusion and exclusion of articles in the following stages.

Dealing with missing data and blinding

Authors of primary studies will be contacted to ask to provide missing or additional data from their study. There will be no blinding of authorship, institutions, journal titles and year of publication, or the results and conclusions of articles. The researchers declare that they have no conflicting interests.

Assessment of risk of bias and quality in included studies

For this study we will not perform a risk of bias or quality assessment. Tools that assess risk of bias or quality of a study, will not be suited or have any additional value, because we don't look at randomised controlled trials or intervention studies. This is because a risk of bias assessment studies systematic deviations in the effect of the study. We are not interested in the effect of the study but only look at the descriptive statistics. We don't expect any bias or quality issues there.

However the external validity of the included studies is relevant for us because we want to assess if the population studied is representative for the general population. This aspect we will discuss in the assessment of our results.

Assessment of heterogeneity

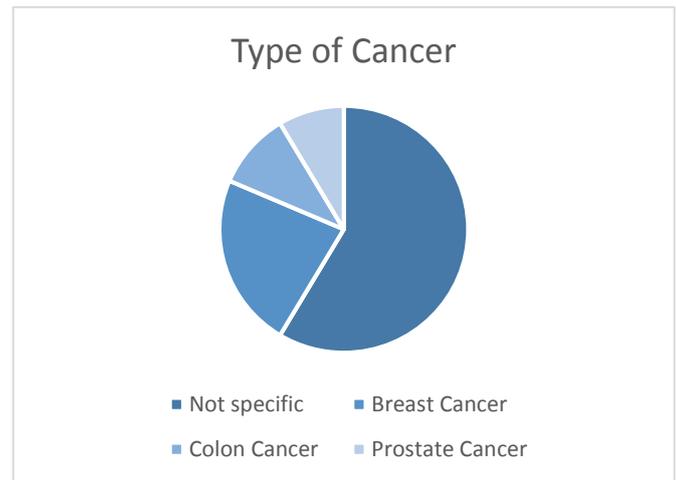
We expect substantial clinical, methodological or statistical heterogeneity. Therefore no meta-analysis is planned. We will also assess the following subgroups for heterogeneity:

- Same type of cancer
- Same types of comorbidities

Data synthesis

For the synthesis of our findings we will use a narrative approach. We will observe the consistency of the prevalence of comorbidity overall and in different groups (e.g. older than >65, specific cancer type). We will construct a clear descriptive summary of the included studies including study type, number of participants, summary of participants (type of cancer, comorbidities) and prevalence of comorbidity using our 'Summary of Findings' table as stated before.

We will report numbers and graphs about the distribution of certain characteristics in the data e.g. type(s) of cancer or measurement of comorbidity. A fictive example of this is shown on the right.



We expect not to be able to perform a meta-analysis because of the heterogeneity between the included articles.

Ethical considerations

This study concerns a systematic literature review and therefore there will be no involvement of bio materials or humans. All references of the literature used will be stated in the article with the correct author(s). There will be no sponsoring and no conflict of interest.

Risk mitigation

Given this internship can only last for twelve weeks, time is limited. Therefore the amount of papers included cannot be unrestricted. The amount of included papers will be critically assessed and a decision will be made to study all the included studies or a subsection of the results. This will be a joint decision made by my supervisor and me. Examples of subsections can be:

- Only include articles with chart-based data
- Only include articles with claim-based data
- Only include articles studying a specific type of cancer

The choice of subsections will depend on the content of the included studies.

Another obstacle in constructing this systematic review could be that a second reviewer hasn't been appointed yet. Conducting a systematic review with only one reviewer will increase the risk of bias of our review. However we are hopeful a second reviewer will shortly be found. There are already several candidates and we expect this to work out.

Time management

Week	1	2	3	4	5	6	7	8	9	10	11	12
Finishing literature study	x	x										
Set up research protocol		x	x	x								
Set up Search string (A)		x	x									
Execute search strategy				x	x	x						
Assess articles for quality				x	x	x	x	x				
Writing the paper												
- Introduction	x	x										
- Methods			x	x								
- Results									x	x		
- Discussion									x	x	x	
Present results												
- Preparation for the presentation											x	x
- Presentation												x
- Finish research report												x

(A) A librarian will be consulted for feedback on the search string

There will be a weekly meeting with my supervisor taking place on Thursday. Here we will discuss the results of the last week, possible deviation from the planning, important goals for the upcoming week and possible hurdles.

SWOT analysis

Time management	(S) – good at planning, works well with deadlines, feels great responsibility for work (W) – not always effective (O) – make a schedule, work with other students doing their research internship (T) - difficulty concentrating when sitting home alone a lot
Organisation of data	(S) – thinking ahead, likes to keep things organised (W) – losing too much time for irrelevant things (O) – working with new organisation tools like Endnote and Rayyan (T) - -
Assessing articles	(S) – motivated to learn a new skill (W) – reading too fast or not careful enough (O) – learning a new skill (T) – Not enough time for supervision
Teamwork	(S) – flexible, open for feedback (W) – not asking for what is needed (O) – learning to express needs, expand the team with PhD student (T) – limited time in schedule supervisor
Writing the article	(S) – persistent, precise (W) – limited previous experience (O) – gaining experience, possible publication (T) – Not enough time

Taking the SWOT analysis into account my personal learning goals will be:

- During this internship I want to spend my time effectively by setting goals for each day and evaluating these at the end of the day and in the weekly meetings with my supervisor
- During this internship I want to learn to assess the quality of the articles using a standardized tool and report on this in the final paper
- During this internship I want to ask for help when needed and ask feedback on the collaboration from my supervisor

Resource used for Research protocol

The CRD's guidance for undertaking reviews in health care (21) and the Cochrane collaboration protocol template (22) were used as resources to set up this protocol.

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Appendices

Appendix I. Search strategies

Search terms and databases
<p>Abbreviations:'*' substitutes one, more or no character, MeSH: medical subject heading (MEDLINE medical index term), Emtree: standardized keywords in Embase, Tiab (PubMed) or .ti.ab.kw (EMBASE): title/abstract or authors keywords</p>
<p>PubMed</p> <p>(Neoplasms [MeSH] OR Cancer [tiab] OR Neoplasm [tiab] OR Neoplasms [tiab] OR Neoplasia [tiab] OR Neoplasias[tiab] OR Tumor [tiab] OR Tumors [tiab] OR Tumour [tiab] OR Tumours [tiab] OR Carcinoma [tiab] OR Carcinomas [tiab] OR Malignancy [tiab] OR Malignancies [tiab])</p> <p>AND</p> <p>(Comorbidity [MeSH] OR Chronic disease [MeSH] OR Comorbid* [tiab] OR Co-morbid* [tiab] OR Multimorbid* [tiab] OR Multi-morbid* [tiab] OR Chronic disorder* [tiab] OR Concomitant disease* [tiab] OR Chronic disease [tiab] OR Chronic diseases [tiab] OR Chronic condition [tiab] OR Chronic conditions [tiab] OR Health condition* [tiab] OR Chronic illness* [tiab] OR Co-occur* [tiab])</p> <p>AND</p> <p>(Prevalence [MESH] OR Epidemiology [MESH] OR Incidence[mesh] OR Epidemiology[subheading] OR Prevalence[tiab] OR Frequency[tiab] OR Frequencies[tiab] OR incidence[tiab])</p> <p>AND</p> <p>(Insurance Claim [MeSH] OR Medical Records [MeSH] OR International Classification of Diseases [MeSH] or Administrative data [tiab] OR Administrative health claims data [tiab] OR Administrative health claim data [tiab] OR chart based [tiab] OR Chart-based [tiab] OR Claim based [tiab] OR Claim-based [tiab] OR claims based [tiab] OR claims-based [tiab] OR claim database [tiab] OR claim databases [tiab] OR claim data [tiab] OR claims data[tiab] OR Comorbidity index [tiab] OR Comorbidity indices [tiab]OR index of Comorbidity [tiab] OR Clinical coding [tiab] OR Medical record [tiab] OR Medical records [tiab] OR Medicare claim [tiab] OR Medicare claims [tiab] OR Cancer database [tiab] OR Cancer databases [tiab] OR Insurance data [tiab] OR insurance claim [tiab] OR insurance claims [tiab])</p>

EMBASE

(Neoplasm [Emtree] OR malignant Neoplasm [Emtree] OR Cancer [.ti,ab,kw.] OR Neoplasm [.ti,ab,kw.] OR Neoplasms [.ti,ab,kw.] OR Neoplasia [.ti,ab,kw.] OR Neoplasias [.ti,ab,kw.] OR Tumor [.ti,ab,kw.] OR Tumors [.ti,ab,kw.] OR Tumour [.ti,ab,kw.] OR Tumours [.ti,ab,kw.] OR Carcinoma [.ti,ab,kw.] OR Carcinomas [.ti,ab,kw.] OR Malignancy [.ti,ab,kw.] OR Malignancies [.ti,ab,kw.]

AND

(Comorbidity [Emtree] OR Chronic disease [Emtree] OR Comorbid* [.ti,ab,kw.] OR Co-morbid* [.ti,ab,kw.] OR Multimorbid* [.ti,ab,kw.] OR Multi-morbid* [.ti,ab,kw.] OR Chronic disorder* [.ti,ab,kw.] OR Concomitant disease* [.ti,ab,kw.] OR Chronic disease [.ti,ab,kw.] OR Chronic diseases [.ti,ab,kw.] OR Chronic condition [.ti,ab,kw.] OR Chronic conditions [.ti,ab,kw.] OR Health condition* [.ti,ab,kw.] OR Chronic illness* [.ti,ab,kw.] OR Co-occur* [.ti,ab,kw.]

AND

(Prevalence [Emtree] OR Epidemiology [Emtree] OR Incidence [Emtree] OR Prevalence [.ti,ab,kw.] OR Frequency [.ti,ab,kw.] OR Frequencies [.ti,ab,kw.] OR incidence [.ti,ab,kw.]

AND

(Health insurance [.ti,ab,kw.] OR Medical Records [Emtree] OR International Classification of Diseases [Emtree] or Administrative data [.ti,ab,kw.] OR Administrative health claims data [.ti,ab,kw.] OR Administrative health claim data [.ti,ab,kw.] OR chart based [.ti,ab,kw.] OR Chart-based [.ti,ab,kw.] OR Claim based [.ti,ab,kw.] OR Claim-based [.ti,ab,kw.] OR claims based [.ti,ab,kw.] OR claims-based [.ti,ab,kw.] OR claim database [.ti,ab,kw.] OR claim databases [.ti,ab,kw.] OR claim data [.ti,ab,kw.] OR claims data [.ti,ab,kw.] OR Comorbidity index [.ti,ab,kw.] OR Comorbidity indices [.ti,ab,kw.] OR index of Comorbidity [.ti,ab,kw.] OR Clinical coding [.ti,ab,kw.] OR Medical record [.ti,ab,kw.] OR Medical records [.ti,ab,kw.] OR Medicare claim [.ti,ab,kw.] OR Medicare claims [.ti,ab,kw.] OR Cancer database [.ti,ab,kw.] OR Cancer databases [.ti,ab,kw.] OR Insurance data [.ti,ab,kw.] OR insurance claim [.ti,ab,kw.] OR insurance claims [.ti,ab,kw.]

Appendix II. Extraction template.

Name researcher:		Date:
Identification study:		
Record number		
Author		
Article title		
Citation		
Type of publication		
Country of origin		
Source of finding		
Study characteristics:		
Aim/objectives of the study		
Study design		
Study inclusion and exclusion criteria		
Participant characteristics:		
Number of participants		
Age		
Gender		
Types of cancer		
Types of comorbidities		
Outcome data		
Prevalence of comorbidities		