Scientific Center for Quality of Healthcare

THE PREVALENCE OF COMORBIDITIES IN PATIENTS WITH BREAST, COLORECTAL, LUNG, PROSTATE AND SKIN CANCER: A SYSTEMATIC REVIEW

Research report internship CKO9

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SUMMARY

Introduction: Patients with cancer are more likely to have one or more other chronic diseases, also called comorbidities. Comorbidities impact the treatment plan, survival and economic burden of cancer patients. We conducted a systematic review to summarize the current literature on the prevalence of comorbidities among the five most common types of cancers.
Methods: Articles reporting the prevalence of comorbidities in breast, colorectal, lung, prostate or skin cancer patients between 1990 and 2020 were identified from PUBMED, MEDLINE, Web of Science, Cochrane and CINAHL. Abstracts were reviewed for eligibility, and data on study design and results were extracted. A quality assessment was executed on all included papers.
Results: 166 articles met the inclusion criteria. 57 articles concerned breast cancer, followed by 49 prostate cancer, 44 lung cancer, 44 colorectal cancer and 7 skin cancer patients. 145 studies used the Charlson Comorbidity index (CCI). Ranges for CCI $\geq$ 1 were 8-45 % for breast cancer, 4-69% for colorectal cancer, 25-81% for lung cancer, 12-45% for prostate cancer and 9-72% for skin cancer.
Conclusion: The prevalence of comorbidities calculated with the CCI ranges between 4-81% and differs between cancer types with lower ranges for breast and prostate cancer and higher ranges for colorectal, lung and skin cancer. The prevalence seemed to increase with age. We found no increase of comorbidity prevalence over time for all cancer types. There was considerable heterogeneity in comorbidity prevalence between different studies.

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INTRODUCTION

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, oncologists 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). This study investigates 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 presence of comorbidities could cause a delay in diagnosis (14).

The importance of the relationship between comorbidities and cancer is well established. However, information relating to the prevalence of comorbidities among cancer patients is still unknown. A number of studies examined prevalence rates 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 the five most common types of cancer: breast, colorectal, lung, skin and prostate cancer. 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 methodology behind data construction is determinative for the outcome. Sarfati et al. 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 four 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. 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) 4. A pharmacy-based approach where drug data is used to identify the presence of certain diseases (20). Analysing our dataset, we distinguished a hybrid chart/claim-based category, where comorbidity data is obtained from national/regional/hospital registries, mostly using ICD or other codes (21-24). Each method has its own strengths and limitations. A patient-based approach allows for the collection of more information on the functional impact, but there are concerns about inaccuracy and under-reporting. A chart-based approach is elaborate but can be time-invasive. A claims-based approach or data from registers can be executed quickly for a large group of patients but misses diagnoses not entered in the comorbidity code fields.

This review is restricted to claim-based articles and articles that use data from registers, in order to evaluate comorbidity prevalence in large groups representative of the population. Limitations of this approach are discussed in our discussion section.

METHODS

SEARCH STRATEGY

Following a previously written study protocol based on The CRD's guidance for under taking reviews in health care (25) and the Cochrane collaboration protocol template (26) an electronic search was carried out in PubMEd, EMBASE, Cochrane Library, CINAHL and Web of Science. The search string (appendix 1) consists of four boxes: 1) neoplasm, 2) comorbidity, 3) Prevalence, index, score, measure, level, number or scale and 4) Administrative data: claim-based or registry data. The terms and their thesaurus terms were combined using Boolean operators AND between boxes and OR between terms in the boxes. Box 3 contained an extra requirement: the terms measure, level and number had to be combined with a variation of terms used for comorbidity to meet the criteria of the box. The search string was executed on the 25th of June.

SCREENING PROCESS

All citations were imported into EndNote X8.2 and the duplicates were discarded. A two-stage screening process was applied to assess whether articles met inclusion criteria, with all articles screened by two independent reviewers (LD and CV). The inclusion and exclusion criteria used in the screening are displayed in table 1.

Inclusion criteria	Exclusion criteria
1. Studies providing data about the prevalence of comorbidities in patients diagnosed with cancer, including previously diagnosed chronic conditions	Studies not providing data about the prevalence of comorbidities in patients diagnosed with cancer
2. Routinely collected prevalence data, derived from registries of health insurance claims databases	Chart- or patient-based prevalence data
3. Population studies is representative for a broad oncological population. Selection based on age or insurance type was permitted.	Studies restricted by type of treatment, race, presence of a certain disease or complication, survival or response to a questionnaire
4. Observational studies	Case reports, randomized controlled trials, systematic reviews and meta-analyses
5. Published between 1990-2020	Published before 1990
6. Published in English or Dutch	Published in other languages than English or Dutch
7. Originating from an OECD-country	Published outside of an OECD-country

Table 1: Inclusion and exclusion criteria used in the selection process

Selection based on age or insurance type was permitted. Also, the study had to provide information on the prevalence of comorbidities. Lastly, prevalence data had to be routinely collected and derived from registries or health insurance claims databases. Studies that collected comorbidity data from medical records or questionnaires (chart-based or patient-based) were excluded.

Titles and abstracts were screened using Rayyan (27). When the title or abstract did not provide information on one or more of the in- or exclusion topics, the study was included for full-text review. Discrepancies were resolved by discussion between the reviewers or, if no consensus was reached, a third reviewer.

Due to the large number of relevant articles found during stage one, we decided to limit our scope to the five most prevalent types of cancer, being breast, colorectal, lung, melanoma and prostate cancer (28).

In the second stage of the review, the full text of all included articles from the first stage were obtained and reviewed independently by two reviewers.

DATA EXTRACTION

A standardized extraction form (appendix) was developed to systematically collect and summarize key data elements from each article. This was done individually by the two reviewers using the Limesurvey application. The title, the name of the first author and year of publication were used to identify the study. The primary outcome was prevalence of comorbidity. Population characteristics such as number of participants, type(s) of

cancer and type(s) of comorbidities were also extracted. All data were extracted directly from the text or calculated from the available information when necessary.

QUALITY ASSESSMENT

To assess whether the included studies reflected on the real world population we conduct a quality assessment using Hoy's risk of bias tool for prevalence studies (29). Modifications were made based on O'Sullivan (30) and Müskens (31) adjusted prevalence tools to tailor the quality assessment tool to our research question. The final quality assessment tool (appendix 1) was filled in independently by two reviewers. Answers from both reviewers were compared. Differences were reported.

DATA SYNTHESIS AND ANALYSIS

As a result of heterogeneity in study designs and diversity of patient populations in the included studies, a formal meta-analysis was not possible. We used summary statistics to describe our main outcomes of interest.

ETHICAL CONSIDERATIONS

This study concerns a systematic literature review, there was no involvement of biomaterials or humans. All references of the literature used are stated in the article with the correct author(s). There was no sponsoring and no conflict of interest.

RESULTS

After duplicates were discarded, a total of 3.070 articles were collected. Title and abstract scrutiny and full-text evaluation led to 164 eligible studies. Details on the selection process are displayed in figure 1.

TYPES OF CANCER

The final set of articles included 164 studies: 57 studies on breast cancer, 49 on prostate cancer, 44 on colorectal cancer, 44 on lung cancer and 7 on skin cancer. Some studies investigated more than one type of cancer and are therefore counted more than once. The majority of the studies originated from the USA. Table 1 shows an overview of all included articles.

REPORTING OF COMORBIDITIES

Comorbidities were reported in three ways: as a count of comorbidities, as a comorbidity index or as a percentage of specific comorbidities. The Charlson Comorbidity Index (CCI) (32) and its adaptations were the most used comorbidity index. Therefore, we decided to use this data to compare the different studies. Data on percentage of specific comorbidities per cancer sort are displayed in appendix 2-6.

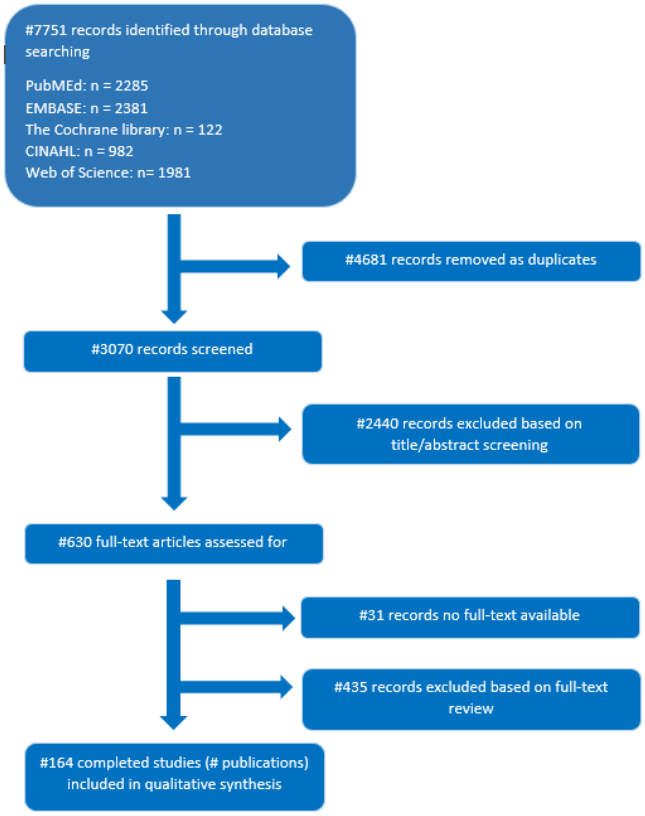


Figure 1: Graphic presentation of the selection process

Of the 165 studies, 144 used the Charlson comorbidity index. The original index contains nineteen categories and was designed to predict 1-year mortality on the basis of a weighted composite score. A score of zero indicates that no comorbidities were found and thus making this index serviceable for our purpose. Another index often used was the Elixhauser Comorbidity Index (ECI), which originally distinguished 30 categories (33). A list of the specific ICD diagnosis codes is used to identify the categories of comorbidities from administrative data (34). Lastly, the C3 comorbidity index was used by two studies. This comorbidity index was developed specifically for a cancer population and excludes conditions that are prevalent in <0.5% of the population.

Author	Year	Country	Type of cancer	Data period	Data Source	Comorbidity measurement
Smith, T. J. (35)	1995	USA	Lung cancer	1985-1989	VCR, HIM, the Medicare Annual Demographic Files, MEDPAR, MADRS, ARF and the 1990 Census Data for Zip Code Level information	CCI
Desch, C. E. (36)	1996	USA	Prostate cancer	1985-1989	VrCR, MEDPAR	CCI
Hillner, B. E. (37)	1996	USA	Breast cancer	1985 - 1989	VrCR, MEDPAR, Medicare Health insurance Master File, Medicare Annual Demographic Files, ARF	CCI
Janssen-Heijnen, M. L. G. (38)	1998	Netherlands	Lung cancer	1993-1995	ECR	CCI
Newschaffer, C. J. (39)	1998	USA	Breast cancer	1986-1988	VrCR, MEDPAR	CCI
Penberthy, L. (40)	1999	USA	Breast, Colorectal, Lung and Prostate cancer	1985 - 1988	VCR, MEDPAR, MADRS, ARF	CCI
Post, P. N. (41)	1999	Netherlands	Prostate cancer	1993-1996	ECR	CCI
De Marco, M. F. (21)	2000	Netherlands	Colorectal cancer	1993-1995	ECR	Percentage/number per comorbidity
Klabunde, C. N. (42)	2000	US	Breast and Prostate cancer	1992-1993	SEER-Medicare	Percentage/number per comorbidity
Du, X. (43)	2001	US	Breast cancer	1991 -1992	SEER-Medicare	CCI
Goodwin, J. S. (44)	2004	USA	Breast cancer	1993-1996	SEER-Medicare	CCI
Osborne, C. (45)	2005	USA	Breast cancer	1991-1995	SEER-Medicare	CCI
Coory, M. (46)	2006	Australia	Lung cancer	1999-2002	Queensland Cancer Registry, computerized discharge abstracts	Percentage/number per comorbidity
Gross, C. P. (47)	2006	USA	Colorectal cancer	1993-1995	SEER-Medicare	Percentage/number per comorbidity
Reyes-Ortiz, C. A. (48)	2006	USA	Skin cancer (Melanoma)	1988-1999	SEER-Medicare	CCI

Du, X. L. (49)	2007	USA	Colon cancer	1992-1999	SEER	CCI
Klabunde, C. N. (50)	2007	USA	Breast, colorectal, lung and prostate cancer	1992 - 1996	SEER-Medicare	CCI
Farjah, F. (51)	2008	USA	Lung cancer	1992-2002	SEER	CCI
Heck, J. E. (52)	2008	USA	Breast cancer	1999	SEER , MedPAR, the Outpatient Standard Analytic File, and the Physician/ Supplier File	CCI
Cooperberg, M. R. (53)	2009	USA	Prostate Cancer	After 1990	Cancer of the Prostate Strategic Urologic Research Endeavor	Number of comorbidities
Ketchandji, M. (24)	2009	USA	Prostate cancer	1992-2002	SEER-Medicare	Percentage/number per comorbidity
Onega, T. (54)	2009	USA	Breast, Colorectal, Lung and Prostate cancer	1998-2002	SEER-Medicare	Number of comorbidities
Onega, T. (55)	2009	USA	Breast, Colorectal, Lung and Prostate cancer	1998-2002	SEER-Medicare	CCI
Davidoff, A. J. (56)	2010	USA	Lung cancer	1997-2002	SEER-Medicare	CCI
Krahn, M. D. (57)	2010	Canada	Prostate cancer	1995 - 2002	OCR	CCI
Pagano, E. (58)	2010	Italy	Lung cancer	2000-2003	Piedmont Cancer Registry of Turin	CCI
Shack, L. G. (59)	2010	England	Colorectal cancer	1997-2005	North West Cancer Intelligence Service, HES	CCI
Singh, H. (60)	2010	Canada	Colorectal cancer	1992 - 2008	Manitoba's population-based databases	CCI
van Steenbergen, L. N. (61)	2010	Netherlands	Colon cancer	2001-2007	ECR	CCI
Berglund, A. (62)	2011	Sweden	Prostate cancer	1997 - 2006	PCBaSe, NPR	CCI
Chavez-MacGregor, M. (63)	2011	USA	Breast cancer	1992-2005	Medicare	CCI
Foley, K. L. (64)	2011	USA	Colon cancer	1999-2002	North Carolina Central Cancer Registry	CCI
Gross, C. P. (65)	2011	USA	Colorectal cancer	1993-2002	SEER-Medicare	Number of comorbidities

Lemeshow, S. (66)	2011	Denmark	Skin cancer (Melanoma)	Since 1943	DCR, DNRP	CCI
Salloum, R. G. (67)	2011	USA	Lung cancer	2000 - 2007	900-physician member, multispecialty, salaried medical group practice in southeast Michigan	Percentage/number per comorbidity
Berglund, A. (68)	2012	Sweden	Prostate Cancer	1997 - 2006	PCBaSe	CCI
Berglund, A. (69)	2012	UK	Lung cancer	2006-2008	Thames Cancer Registry, HES, and UK National Lung Cancer Audit	CCI
Deleuran, T. (70)	2012	Denmark	Lung cancer	2004 - 2009	DCR, DNPR	CCI
Frøslev, T. (71)	2012	Denmark	Skin cancer (Meloma)	2004 - 2009	DCR, DNPR	CCI
Lavelle, K. (72)	2012	England	Breast cancer	1997-2005	English cancer registries + HES	CCI
Fu, A. Z. (73)	2012	USA	Breast cancer	2003 - 2008	MarketScan Commercial Claims and Encounters database	Percentage/number per comorbidity
Lowrance, W. T. (74)	2012	USA	Prostate cancer	1998 - 2005	SEER-Medicare	ECI
Nambudiri, V. E. (75)	2012	USA	Prostate cancer	2001-2004	VACCR, Fee-for-Service Medicare Data	CCI
Nguyen-Nielsen, M. (22)	2012	Denmark	Prostate cancer	2004-2009	DCR, DNPR	CCI
Ording, A. G. (76)	2012	Denmark	Breast cancer	2004-2009	DCR, DNPR	CCI
Ostenfeld, E. B. (77)	2012	Denmark	Colorectal cancer	2004 - 2009	DCR, DNPR	CCI
Schonberg, M. A. (78)	2012	USA	Breast cancer	Since 1992	SEER-Medicare	CCI
Singh, H. (79)	2012	Canada	Colorectal cancer	2004-2009	Manitoba's population-based cancer registry	CCI
Wang, S. (80)	2012	USA	Lung cancer	2003 - 2008	VACCR , Veterans Health Administration National Patient Care Database	CCI
Chastek, B. (81)	2013	US	Colorectal cancer	2005 - 2010	Oncology Management registry, Optum Research Database, Social Security Administration's Death Master File	CCI
Keating, N. L. (82)	2013	USA	Prostate cancer	1992-2007	SEER-Medicare	Percentage/number per comorbidity

Ladjevardi, S. (83)	2013	Sweden	Prostate cancer	1996 - 2008	NPCR + NPR	CCI
Loeb, S. (84)	2013	Sweden	Prostate cancer	1998 - 2011	PCBaSe + NPCR	CCI
van Leersum, N. J (85)	2013	Netherlands	Colorectal cancer	1995-2010	ECR	CCI
Xiao, H. (86)	2013	USA	Prostate cancer	2001 - 2007	FDCS + AHCA	ECI
Bates, T. (87)	2014	England	Breast cancer	2007	ENCR, HES, BCCOM audit and NHS Breast Screening Programme and Association of Breast Surgery audit data	CCI
Beckmann, K. R. (88)	2014	Australia	Colorectal cancer	2003-2008	SACR linked with Public hospital separations and Private hospital separations	CCI
Davidoff, A. J. (89)	2014	USA	Breast and Lung cancer	1997-2007	SEER	CCI
de Decker, L. (90)	2014	France	Breast cancer	2007	FCR (Doubs, Loire-Atlantique, and Tarn)	CCI
Dik, V. K. (91)	2014	Netherlands	Colorectal cancer	2005-2010	ECR, Statistics Netherlands	CCI
Edwards, B. K. (92)	2014	USA	Breast, colorectal, lung, prostate cancer	1992-2005	SEER	CCI
Escribà, J. M. (93)	2014	Spain	Breast cancer	2005, 2008 and 2011	Acute Hospital Discharge Dataset	CCI
Griffiths, R. I. (94)	2014	USA	Breast cancer	2001 - 2005	SEER-Medicare	CCI
Hamza, S. (95)	2014	France	Colon cancer	2004-2009	Registry recording all the digestive tract cancers occurring in Burgundy, France	CCI
Howlader, N. (96)	2014	USA	Prostate cancer	2000 - 2009	SEER-Medicare	CCI
Iachina, M. (97)	2014	Denmark	Lung cancer	2010	Danish Lung Cancer Registry, DNPR	CCI
Jespersen, C. G. (98)	2014	Denmark	Prostate cancer	2002-2010	DCRS, DCR, DNPR, DCDR	CCI
Jespersen, C. G. (99)	2014	Denmark	Prostate cancer	1997-2010	DCR, DNPR	CCI
Seneviratne, S. (100)	2014	New Zealand	Breast cancer	1999 - 2011	NZCR, WBCR	CCI
Tannenbaum, S. L (101)	2014	USA	Colorectal cancer	2007-2011	FCDS, AHCA, diagnosis-related group codes	Number of comorbidities
Tannenbaum, S. L. (102)	2014	USA	Lung cancer	1996-2007	FCDS registry, AHCA	ECI

Tong, L. (103)	2014	US	Colorectal cancer	1992 - 2004	SEER-Medicare	CCI
Barocas, D. A. (23)	2015	USA	Prostate cancer	2010-2012	NCDB	CCI
Bratt, O. (104)	2015	Sweden	Prostate cancer	2001 - 2012	PCBaSe	CCI
Cardwell, C. R. (105)	2015	England	Breast cancer	1998-2009	National Cancer Data repository	Percentage/number per comorbidity
Cetin, K. (106)	2015	Denmark	Breast cancer	1997 - 2011	DCR, DNPR	CCI
Cohen, A. (107)	2015	USA	Prostate cancer	1998-2011	NCDB	CCI
Dinan, M. A. (108)	2015	USA	Breast cancer	2005-2009	SEER-Medicare	Number of comorbidities
Hoffman, R. M. (109)	2015	USA	Prostate cancer	2003 - 2008	VACCR, Medicare	CCI
Islam, K. M. (110)	2015	USA	Lung cancer	2005 - 2009 follow-up until 2010	Nebraska Cancer Registry linked with the Nebraska Hospital Discharge Data	Percentage/number per comorbidity
Jespersen, C. G. (111)	2015	Denmark	Prostate cancer	2003 - 2010	DCR, DNPR	CCI
Morgan, J. (112)	2015	UK	Breast cancer	2002-2010	HES data set icm UK cancer reigstration regions West Midlands, Northern and Yorkshire	CCI
O'Brien, B. (113)	2015	USA	Breast cancer	1996-2007	FCDS, AHCA data and the US Census databases	ECI
Shi, R. (114)	2015	USA	Breast cancer	1998-2006	NCDB	CCI
Unger, J. M. (115)	2015	USA	Prostate cancer	1995-2007	SEER-Medicare	CCI
Beckmann, K. R. (116)	2016	Australia	Colorectal cancer	2003 - 2008	SACR	CCI
Bott, M. J. (117)	2016	USA	Lung cancer	1998-2010	NCDB	CCI
Jakobsen, E. (118)	2016	Denmark	Lung cancer	2000 - 2012	Danish Lung Cancer Registry	CCI
Lin, C. C. (119)	2016	USA	Breast, Colorectal, Lung Cancer	2006-2007	NCDB, SEER-Medicare	CCI
Loeb, S. (120)	2016	Sweden	Prostate cancer	2005-2007	NPCR + PCBaSe	CCI
Møller, H. (121)	2016	England	Breast cancer	2012-2013	NCRAS	CCI

Richards, P. (122)	2016	UK	Breast cancer	2002-2010	UK cancer registry regions (West Midlands, Northern & Yorkshire) icm HES	CCI
Shi, R. (123)	2016	USA	Lung cancer	1998-2011	NCEB	CCI
Tomic, K. (124)	2016	Sweden	Prostate cancer	1998-2012	PCBaSe	CCI
Vehko, T. (125)	2016	Finland	Breast cancer	1998-2008	Finnish Cancer registry , Employment Statistics and Hospital Discharge Register and Special Reimbursement Register	Percentage/number per comorbidity
Xiao, H. (126)	2016	USA	Prostate cancer	2002 - 2007	FCDS, census tract level from the U.S. Census Bureau, public use files for the State of Florida, health provider information by county, AHCA	ECI
Allaire, B. T. (127)	2017	USA	Breast cancer	2003-2010	North Carolina Central Cancer Registry linked to private insurers' enrollment files	CCI
Brungs, D. (128)	2017	Australia	Colon cancer	2006 - 2013	lawNew South Wales clinical cancer registry, registry of Births, Deaths and Marriages, Admitted Patient Data Collection	CCI
Capri, S. (129)	2017	Italy	Breast cancer	2007-2011	Health information systems of the Agency for Health Protection of the Province of Milan, Local cancer registry	CCI
Cassidy, R. J. (130)	2017	US	Rectal cancer	2004-2013	NCDB	CCI
Fallahpour, S. (131)	2017	Canada	Breast cancer	2010 - 2012	OCR, Canadian Institute for Health Information's Discharge Abstract Database	CCI
Fowler, H. (132)	2017	England	Colon cancer	2010- 2013 followed up until 2014	National cancer registry records linked with HES and national bowel cancer clinical audit data	CCI
Jansen, L. (133)	2017	Netherlands	Colorectal cancer	1998 - 2011	ECR and the PHARMO Database Network	Percentage/number per comorbidity
Jasem, J. (134)	2017	USA	Breast cancer	2010 - 2012	NCDB	CCI
Li, S. (135)	2017	USA	Breast cancer	2010-2013	NCDB	CCI

Mateo, A. M. (136)	2017	USA	Breast cancer	2004-2012	NCDB	Number of comorbidities
Migden, M. (137)	2017	USA	Skin cancer (Basal cel carcinoma)	2010 - 2014	Truven Health MarketScan	CCI
Nayak, P. (138)	2017	US	Breast, Colorectal, Lung and Prostate cancer	2001-2010	TCR, Medicare claims data and 2000 US Census files	CCI
Nilsson, J. (139)	2017	Sweden	Lung cancer	2002-2011	Lung Cancer Data Base Sweden, NPRSe, SCR, a Social database and the Cause of Death Register	CCI
Puig, C. A. (140)	2017	USA	Breast cancer	2004-2012	NCDB	CCI
Sinha, S. (141)	2017	USA	Prostate cancer	2004 - 2012	NCDB	CCI
Steuer, C. E. (142)	2017	USA	Lung cancer	1998-2006	NCDB	CCI
Thiels, C. A. (143)	2017	USA	Colorectal cancer	1998 - 2012	NCDB	CCI
Trogdon, J. G. (144)	2017	US	Breast cancer	2003–2008	North Carolina Central Cancer Registry data linked to Medicaid enrolment files	CCI
Yang, D. D. (145)	2017	USA	Prostate cancer	2004-2012	NCDB	CCI
Yang, D. D. (146)	2017	USA	Prostate cancer	2004-2012	NCDB	CCI
Blackmore, T. (147)	2018	New Zealand	Breast cancer	2000 - 2013	Waikato and Auckland Breast Cancer Registers	Number of comorbidities
Busby, J. (148)	2018	England	Breast cancer	1998-2012	NCDR, linked to GP records from the UK Clinical Practice Research Datalink, deprivation indices from census information and death registration data from the Office for National Statistics	Percentage/number per comorbidity
Chen, A. B. (149)	2018	USA	Breast, Colorectal, Lung and Prostate cancer	2007 - 2011	SEER-Medicare	CCI
Cuthbert, C. A. (150)	2018	Canada	Colorectal cancer	2004 - 2015	Alberta Cancer registry	CCI
Di Girolamo, C. (151)	2018	England	Breast, Colon and Lung cancer	2013	NCRAS, Index of Multiple Deprivation for England, Routes to Diagnosis dataset, HES	CCI

Kearney, M. (152)	2018	USA	Skin cancer (Merkel cell carcinoma)	2010 - 2014	BM Watson Health's Truven MarketScan Commercial Claims and Encounters, Medicare Supplemental and Coordination of Benefits datasets of patients	CCI
Kong, A. L. (153)	2018	USA	Breast cancer	2006-2009	SEER-Medicare	Number of comorbidities
Lam, M. B. (154)	2018	USA	Lung cancer	2004-2011	SEER-Medicare	CCI
Lawrenson, R. (155)	2018	New Zealand	Breast cancer	2000 - 2013	Waikato and Auckland Breast Cancer Registers + National Minimum Dataset	C3
Lüchtenborg, M. (156)	2018	Australia, Canada, Norway, UK	Lung cancer	2009-2012	Australia: NSWCR, VCR, New South Wales and Victorian AEDPDC Canada: ACR, OCR, Discharge Abstract Database Norway: the NCR + NPR United Kingdom: English, Northern Irish, Scottish and Welsh registries + HES (England), Patient Administration System (Northern Ireland), SMR-01 data set (Scotland), Patient Episode Data data set (Wales)	CCI + ECI
Mehta, H. B. (157)	2018	USA	Breast, Colorectal, Lung and Prostate cancer	2005-2011	TCR, Medicare	CCI + ECI
Pettersson, A. (158)	2018	Sweden	Prostate cancer	1998-2012	NPCR, NPR	CCI
Rios, J. (159)	2018	USA	Lung cancer	2007-2011	SEER-Medicare	CCI (Klabunde adaptation)
Sineshaw, H. M. (160)	2018	USA	Breast cancer	2010-2013	NCDB	CCI
Soriano, L. C. (161)	2018	UK	Colorectal cancer	2000-2014	The Health Improvement Network	Percentage/number per comorbidity
Tomic, K. (162)	2018	Sweden	Prostate cancer	2007-2014	NPCR linked to the Prescribed Drug Registry, the Patient Registry, the Cause of Death Register, LISA and PCBaSe	CCI
Trofymenko, O. (163)	2018	USA	Skin cancer (Merkel cell carcinoma)	2004 - 2013	NCDB	CCI

Weidner, T. K. (164)	2018	USA	Colorectal cancer	2008-2014	Optum Labs Data Warehouse	CCI
Williams, A. D. (165)	2018	USA	Breast cancer	2005-2014	NCDB	CCI
Concors, S. J. (166)	2019	USA	Rectal cancer	2010-2015	NCDB	CCI
Heilbroner, S. P. (167)	2019	USA	Lung cancer	2007 - 2011	SEER-Medicare	CCI
Jauhari, Y. (168)	2019	England and Wales	Breast cancer	2014 - 2016	NABCOP	CCI
Lewis, G. D. (169)	2019	USA	Breast cancer	2007 - 2012	NCDB	CCI
May, A. (170)	2019	USA	Prostate caner	2010-2015	NCDB	CCI
Morishima, T. (171)	2019	Japan	Lung cancer	2010-2012	Osaka Cancer Registry linked with Japan's Diagnosis Procedure Combination	CCI
Murawski, M. (172)	2019	Japan	Lung cancer	2010-2012	Osaka Cancer Registry linked with Japan's Diagnosis Procedure Combination	ECI
Myint, Z. W. (173)	2019	USA	Prostate cancer	2007-2011	KCR	CCI
Pearson, C. (174)	2019	England	Colorectal and Lung cancer	2014-2015	NCRAS, Public Health England	CCI
Pule, M. L. (175)	2019	Australia	Colorectal cancer	2003-2012	SACR	CCI + C3
Roy, S. (176)	2019	Canada	Prostate cancer	2011 - 2014	ACR	CCI
Te Marvelde, L. (177)	2019	Australia	Colorectal cancer	2008-2014	VCR, Victorian Admitted Episodes Dataset, Medicare Benefits Schedule, Pharmaceutical Benefits Schema	CCC
Ventimiglia, E. (178)	2019	Sweden	Prostate cancer	1992-2014	NPCR, PCBaSe, NPRSe, NCRSe	CCI
Willén, L. (179)	2019	Sweden	Lung cancer	2002-2016	LCBaSe, NPR, Swedish Cancer Registry, LISA and CDR	CCI
Abudu, B. (180)	2020	USA	Skin cancer (Melanoma)	2004 - 2015	NCDB	CCI
Aksenov, L. (181)	2020	USA	Prostate cancer	2010-2015	NCDB	CCI
Chow, Z. (182)	2020	USA	Colon cancer	2007-2012	KCR	CCI
Duma, N. (183)	2020	USA	Lung cancer	2004-2014	NCDB	CCI

Fowler, H. (184)	2020	England	Colorectal and lung cancer	2009-2013	ENCR, HES	CCI
Franck Lissbrant, I. (185)	2020	Sweden	Prostate Cancer	until 2019	NPCR	CCI
Gupta, A. (186)	2020	USA	Colon cancer	2006 -2017	Geisinger Health System cancer registry	CCI
Jauhari, Y. (187)	2020	England and Wales	Breast cancer	2014-2017	NABCOP, NCRAS, HES for England and Patient Episode Database for Wales (PEDW)	CCI
Lin, J. (188)	2020	USA	Lung cancer	1998 - 2007	Department of Defense's Central Cancer Registry and the MHS Data Repository	CCI
Milligan, M. G. (189)	2020	USA	Lung cancer	2004-2013	SEER, MEDPAR and Outpatient Standard Analytical File of the Medicare claims data	CCI
Nilssen, Y. (190)	2020	Norway	Breast, Colorectal, Lung and Prostate cancer	2015 - 2016	Cancer Registry of Norway CRN, Norwegian Patient Registry	CCI
Parise, C. A. (191)	2020	USA	Breast cancer	2000 - 2015	California Cancer Registry, Office of Statewide Health Planning and Development Discharge Data, ambulatory surgery, and emergency department data	ECI
ten Berge, D. M. H. J. (192)	2020	Netherlands	Lung cancer	2008-2014	Netherlands Cancer Registry	CCI
Thurtle, D. (193)	2020	Sweden	Prostate cancer	2000 - 2010	PCBaSE	CCI
Wennstig, A. K. (194)	2020	Sweden	Breast cancer	1992-2012	National Quality Registry for Breast Cancer, NPRSe, LISA	CCI

Table 2: Description of included studies. Abbreviations: ACR - Alberta Cancer Registry, AEDPDC - Admitted Episodes Dataset Patient Data Collection, AHCA - Florida Agency for Health Care and Administration, ARF – Area Resource File (USA), ARF - Area Resource File Medicare, BCCOM - Breast Cancer Clinical Outcome Measures (England), CDR – Cause of Death Register (Sweden), DCDR – Danish Cause of Death Registry, DCR – Danish Cancer Registry, DCRS – Danish Civil Registration System, DLCR – Danish Lung Cancer Registry, DNPR – Danish National Patient Registry, DPC – Diagnosis Procedure Combination (Japan), ECR - Eindhoven Cancer Registry, ENCR – England National Cancer Registry, FCDS – Florida Cancer Data System, FCR – Finnish Cancer Register, FCR – French Cancer Registry, GHSCR – Geising Health System Cancer Registry, HCFA – Medicare Health insurance Master File, HES - Hospital Episode Statistics, HIM - Medicare Health Insurance Master File, KCR – Kentucky Cancer Registry, LCBaSe – Lung Cancer Database Sweden, LISA – Longitudinal Integration Database for Health Insurance and Labour Market Studies, MADRS – Medicare Automated Data Retrieval System, MBS - Medicare Benefits Schedule (Australia), MEDPAR – Medicare Provider Analysis and Review, NABCOP -

National Audit of Breast Cancer in Older Patients, NCCCR - North Carolina Central Cancer Registry, NCDB - National Cancer Data Base, NCDR - National Cancer Registration Database (England), NCR - Norwegian cancer registry, NCR – Netherlands Cancer Registry, NCRAS – National Cancer Registration and Analysis Service (England), NCRAS – National Cancer Registration and Analysis Service (UK), NCRSe – National Cancer Register Sweden, NPCR – National Prostate Cancer Register (Sweden), NPRNo - Norwegian Patient Register, NPRSe – National Patient Register (inpatient) (Sweden), NSWCR – New South Wales Cancer Registry, NWCIS - North West Cancer Intelligence Service (NWCIS), NZCR - New Zealand Cancer Registry, OCR – Ontario Cancer Registry, OLDW - Optum Labs Data Warehouse, OsCR – Osaka Cancer Registry, PBS – Pharmaceutical Benefits Schema (Australia) – prescription fill data, PCBaSE – Prostate cancer Database Sweden à (NPCR and other healthcare registers and demographic databases by use of the unique Swedish personal identity number as previously described + Patient Register, the Prescribed Drug Register, the Swedish Cancer Register, the Cause of Death Register, and the LISA), PCRT - Piedmont Cancer Registry of Turin, PHE – Public health England, QCR – Queensland Cancer Registry, SACR - South Australia Cancer Registry, SCR – Swedish Cancer Register, SEER - Surveillance, Epidemiology, and End Results, TCR - Texas Cancer Registry, VACCR – VA Central Cancer Registry, VAED – Victorian Admitted Episodes Dataset, VCR – Victorian Cancer Registry, VHANPCD – Veterans Health Administration National Patient Care Database, VrCR – Virginia Cancer Registry, WBCR - Waikato Breast Cancer Register, WSCR - Washington State Cancer Registry

BREAST CANCER

The percentage of one or more comorbidities in breast cancer ranged from 8% to 89% across measurement types. 39 studies used the CCI and his adaptations (range 8-45%) (figure 2), two studies used ECI (range 25-89%), one study that used the C3 score (19%) and five studies that counted the number of comorbidities present (range 12-50%). Figure 3 distinguishes age groups. 14 studies looked at a population of 65 or 66 and older (range 14-45%), 2 studies investigated a younger population aged between 18/21 and 64 (range 10-18%), 2 studies restricted their population to over 50 (range 14-17%) and the remaining 22 studies had no age restrictions for their population (range 8-45%).

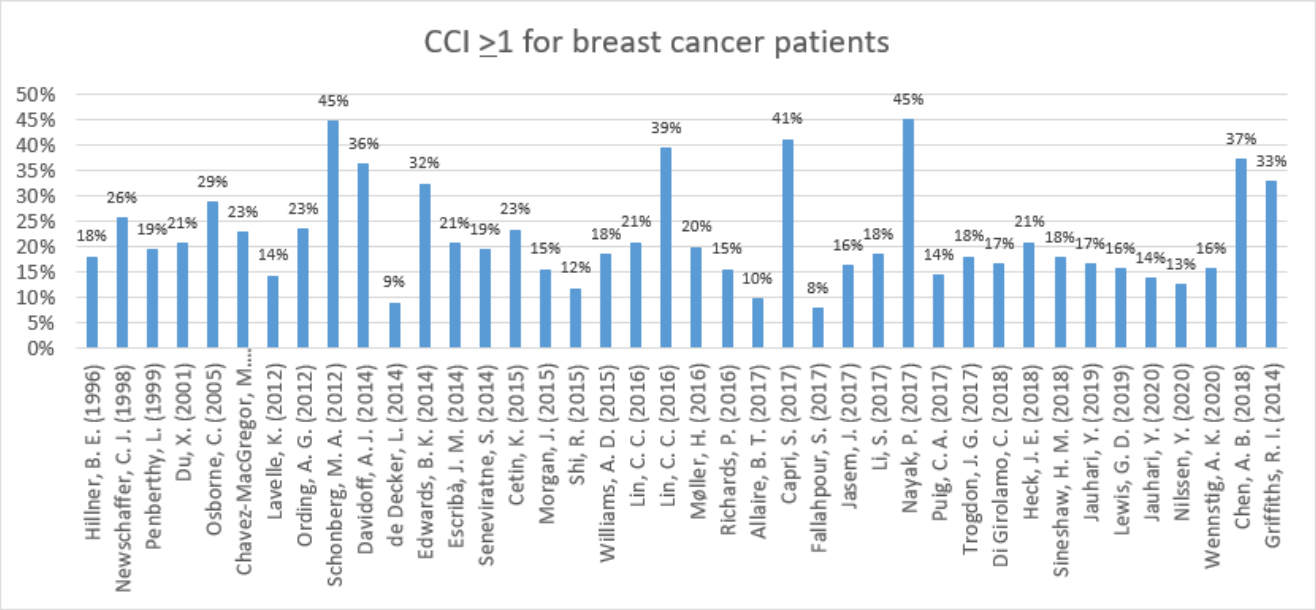
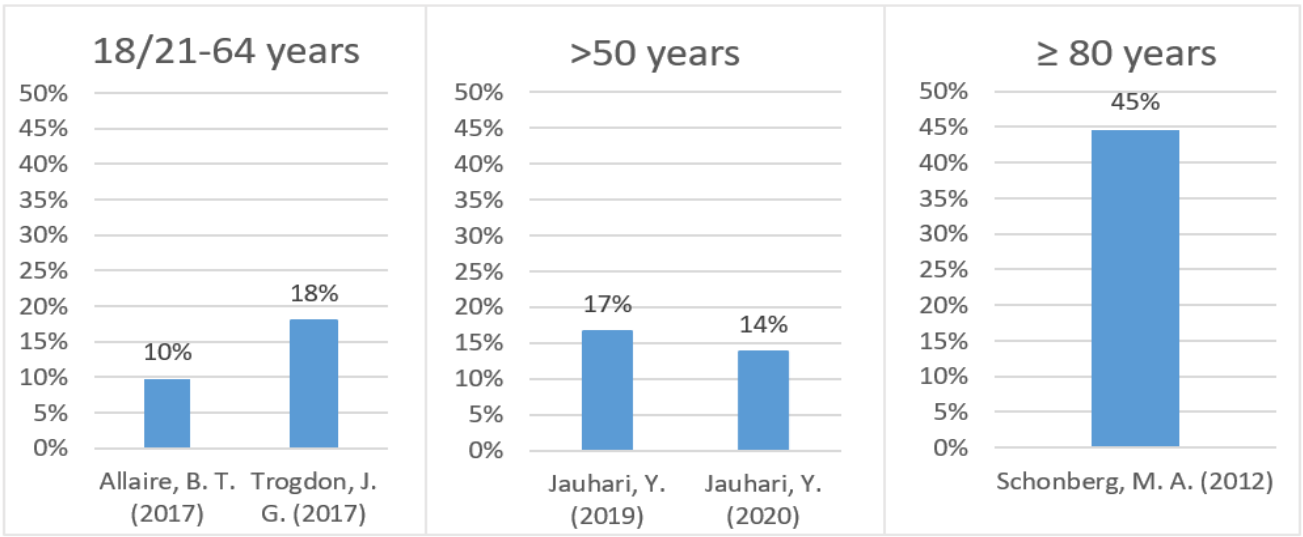


Figure 2: Percentage of breast cancer patients having a CCI of one or more per study



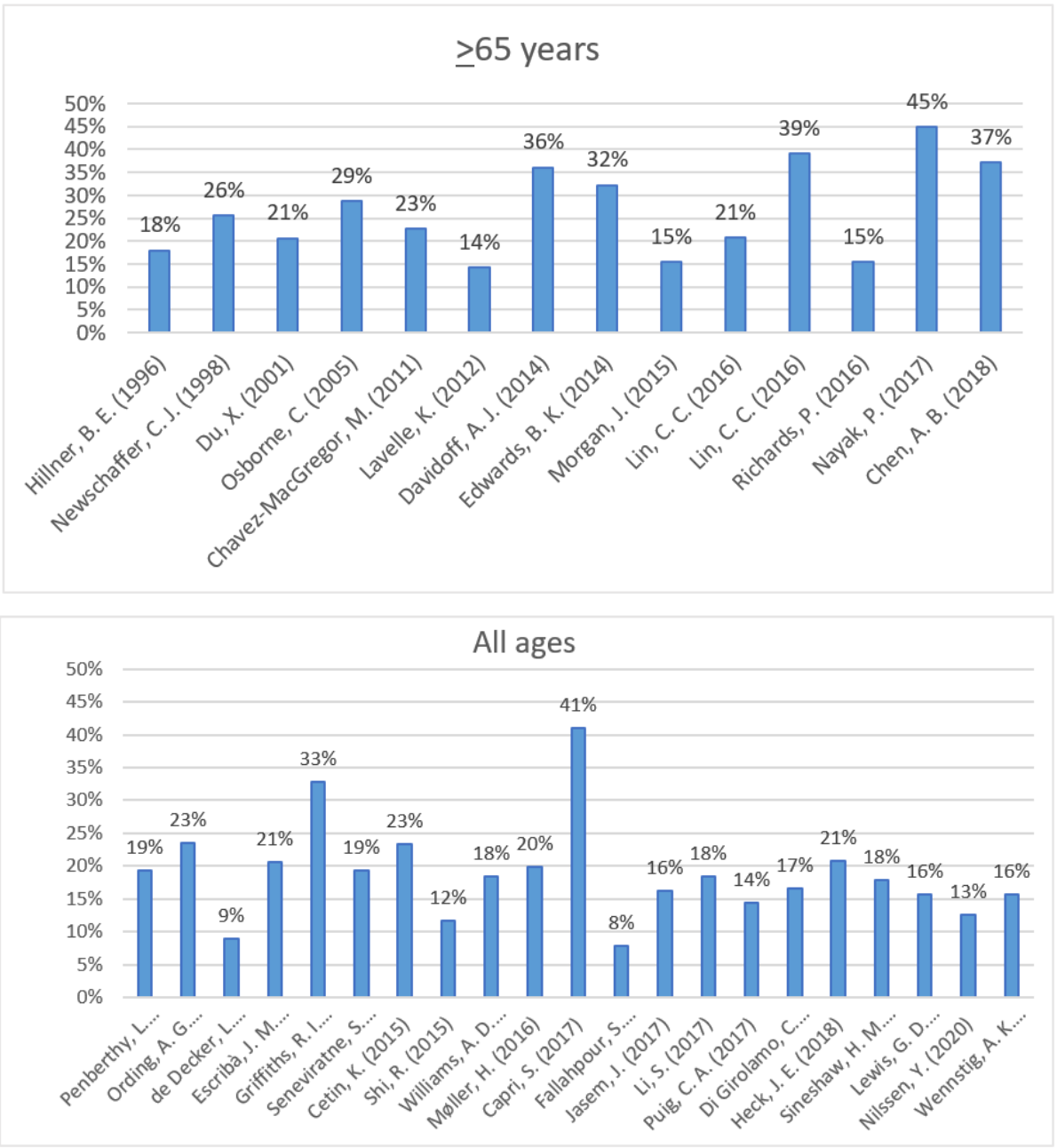


Figure 3: Percentage of breast cancer patients having a CCI of one or more per study stratified by age groups

COLORECTAL CANCER

There were 38 studies that reported the prevalence of comorbidities in colon or rectal cancer patients. The percentage ranged from 4% to 71%. There were 34 studies that used the CCI and his adaptations (range 4% to 69%, figure 4), one study used the ECI (28%), one study used the C3 comorbidity index (33%) and two studies that counted comorbidities (Range 48 to 71%). Of the 34 CCI studies, two studies looked at 50-79/80 year old population (range 30-61%), one study looked at a population >80 years (37%), seven studies investigated a population older than 65/66/67 years (38-52%) and 25 studies had no age restriction (other than some >18/20)(range 4-69%) (figure 5). Of the 34 CCI studies, 19 looked at colorectal cancer, 10 looked at colon cancer alone, 2 only looked at rectal cancer and three studies investigated both types but presented the data for rectal and colon cancer separately (figure 6).

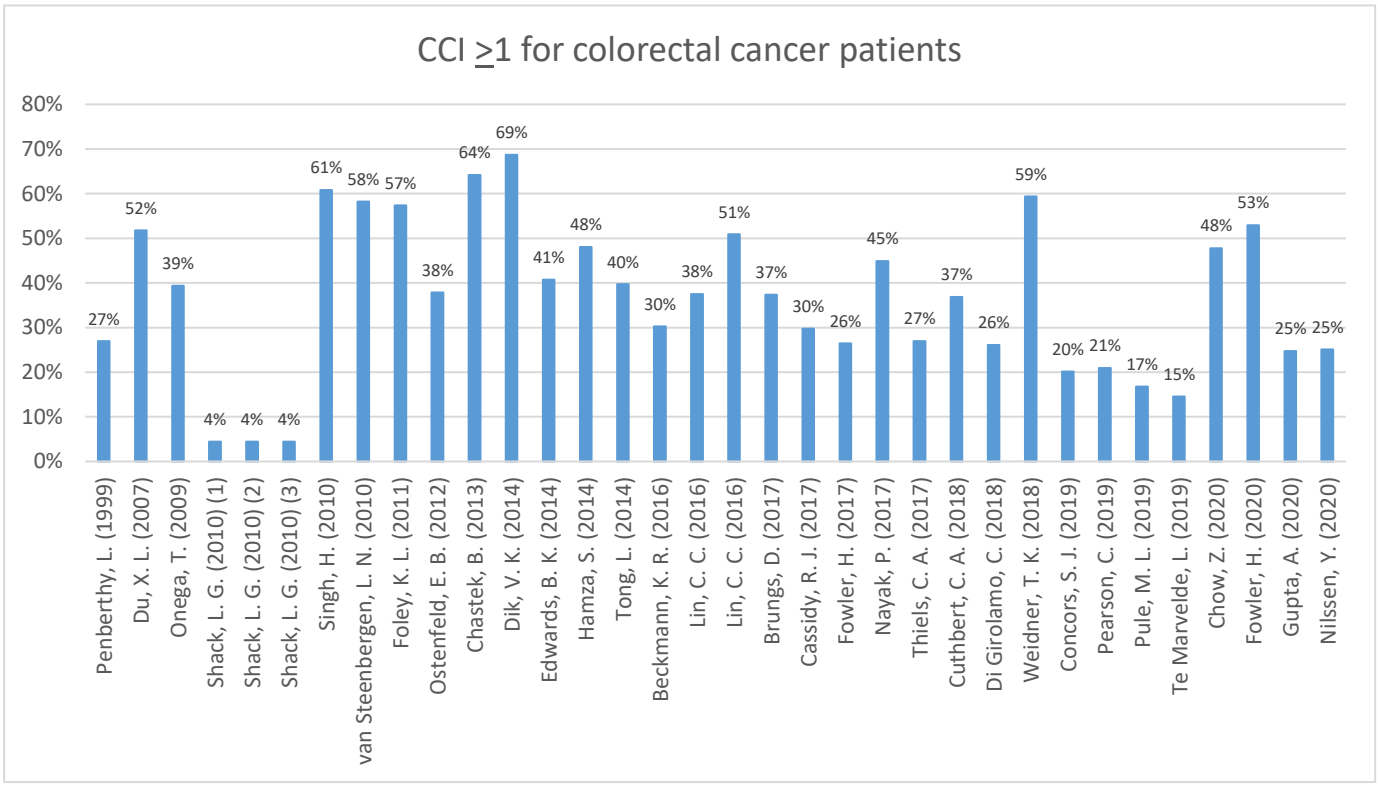
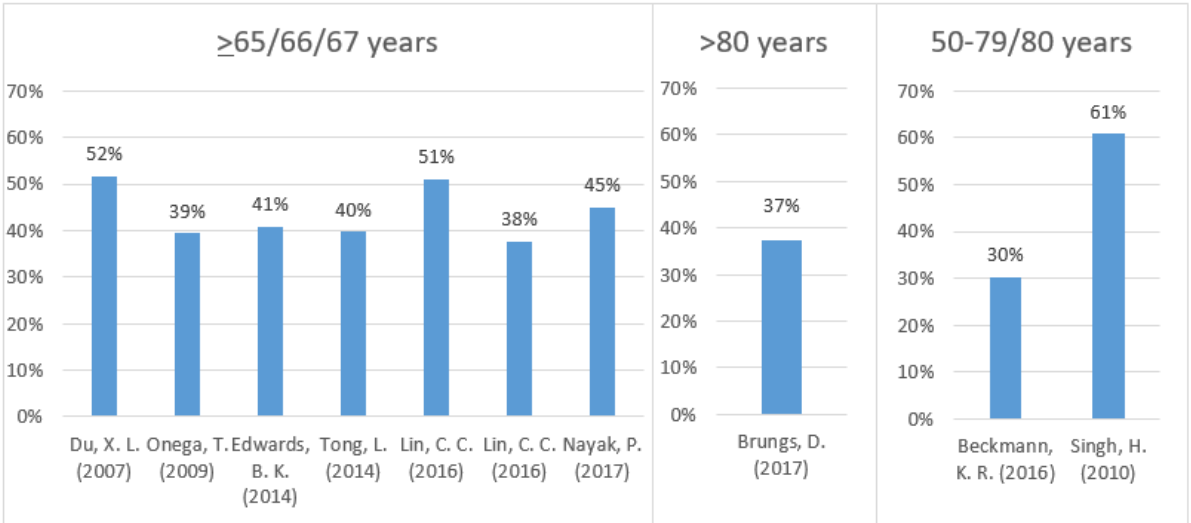


Figure 4: Percentage of colorectal cancer patients having a CCI of one or more per study
Shack (1): Comorbidities present 18-6 months before cancer diagnosis
Shack (2): Comorbidities present before cancer diagnosis
Shack (3): Comorbidities present anytime around cancer diagnosis



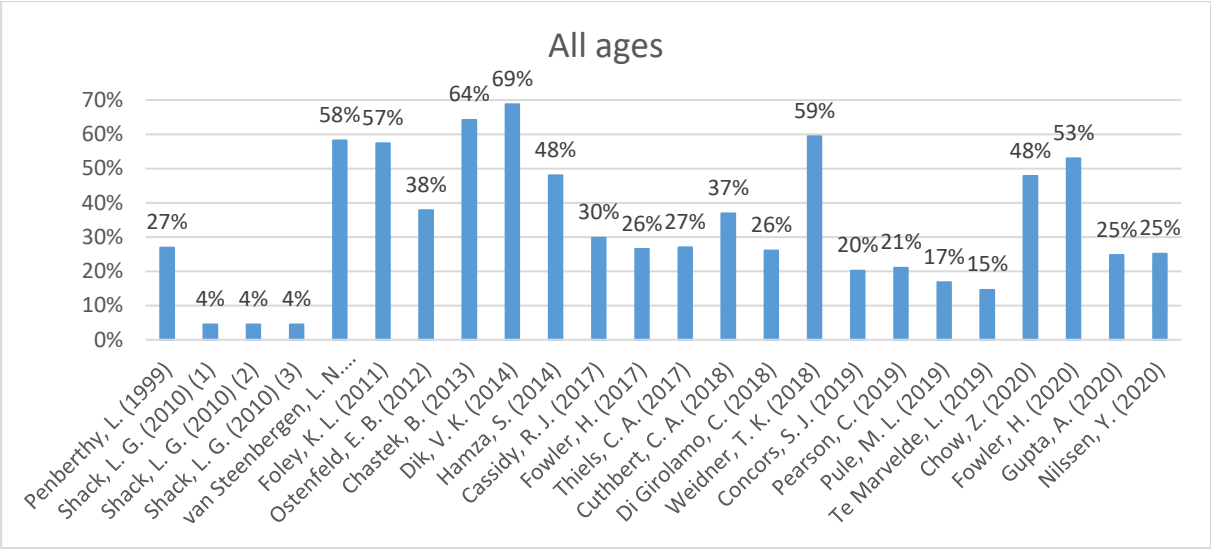
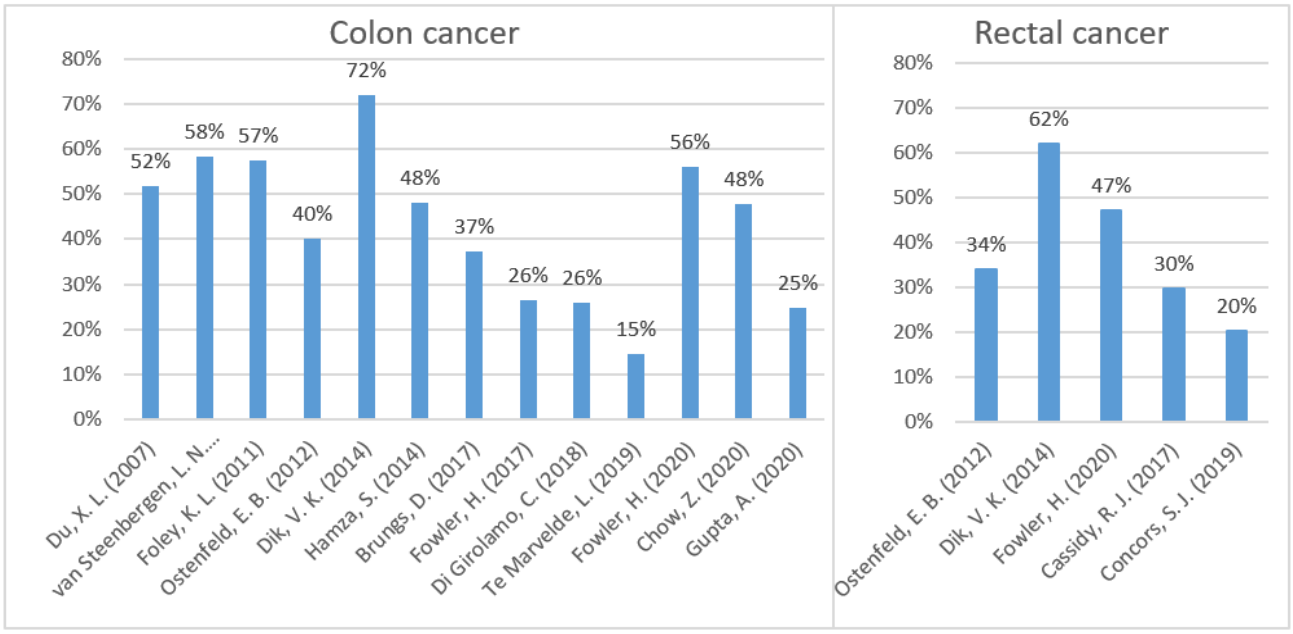


Figure 5: Percentage of colorectal cancer patients having a CCI of one or more per study stratified by age groups
Shack (1): Comorbidities present 18-6 months before cancer diagnosis
Shack (2): Comorbidities present before cancer diagnosis
Shack (3): Comorbidities present anytime around cancer diagnosis



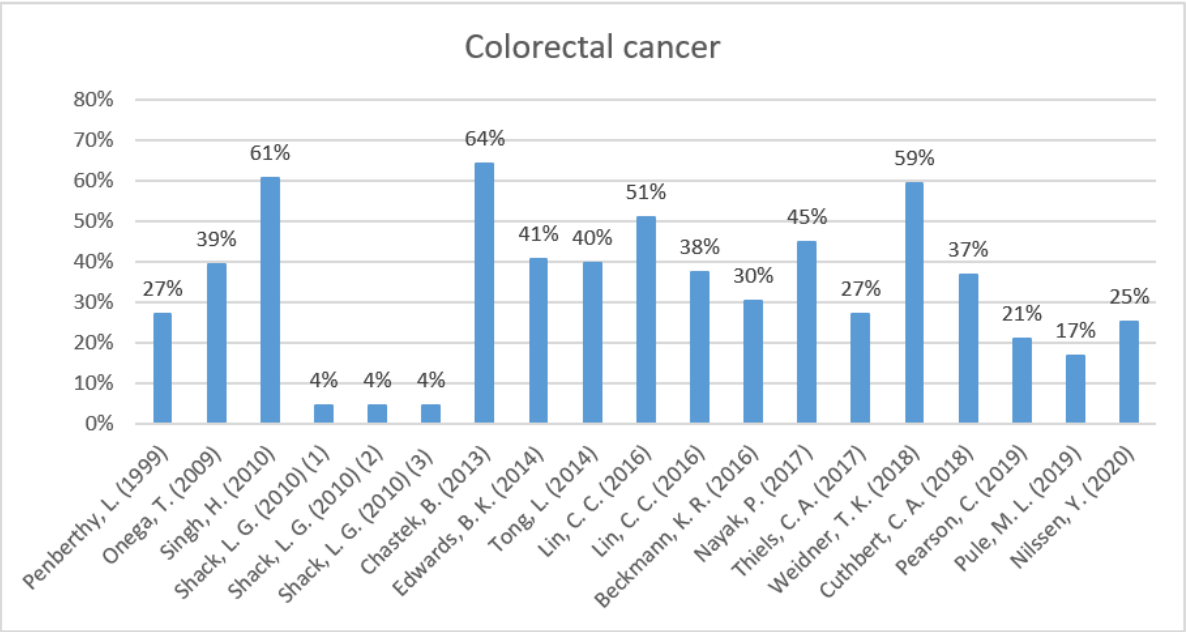


Figure 6: Percentage of colorectal cancer patients having a CCI of one or more per study stratified by cancer type
Shack (1): Comorbidities present 18-6 months before cancer diagnosis
Shack (2): Comorbidities present before cancer diagnosis
Shack (3): Comorbidities present anytime around cancer diagnosis

LUNG CANCER

The percentage of patients with one or more comorbidities ranged from 25% to 95%. 30 studies used the CCI and adaptations to report their findings (range 27-81%) (figure 7). Two studies used the ECI (32-95%) and one study counted the number of comorbidities present (39%). A table of all the results and description of population and measurement can be found in the appendix. Of the CCI studies, eleven investigated an older study population (65/66 years and older) (37-82%), relative to 19 studies having no age restriction besides some only investigating an adult population (18/20+) (25-67%) (figure 8).

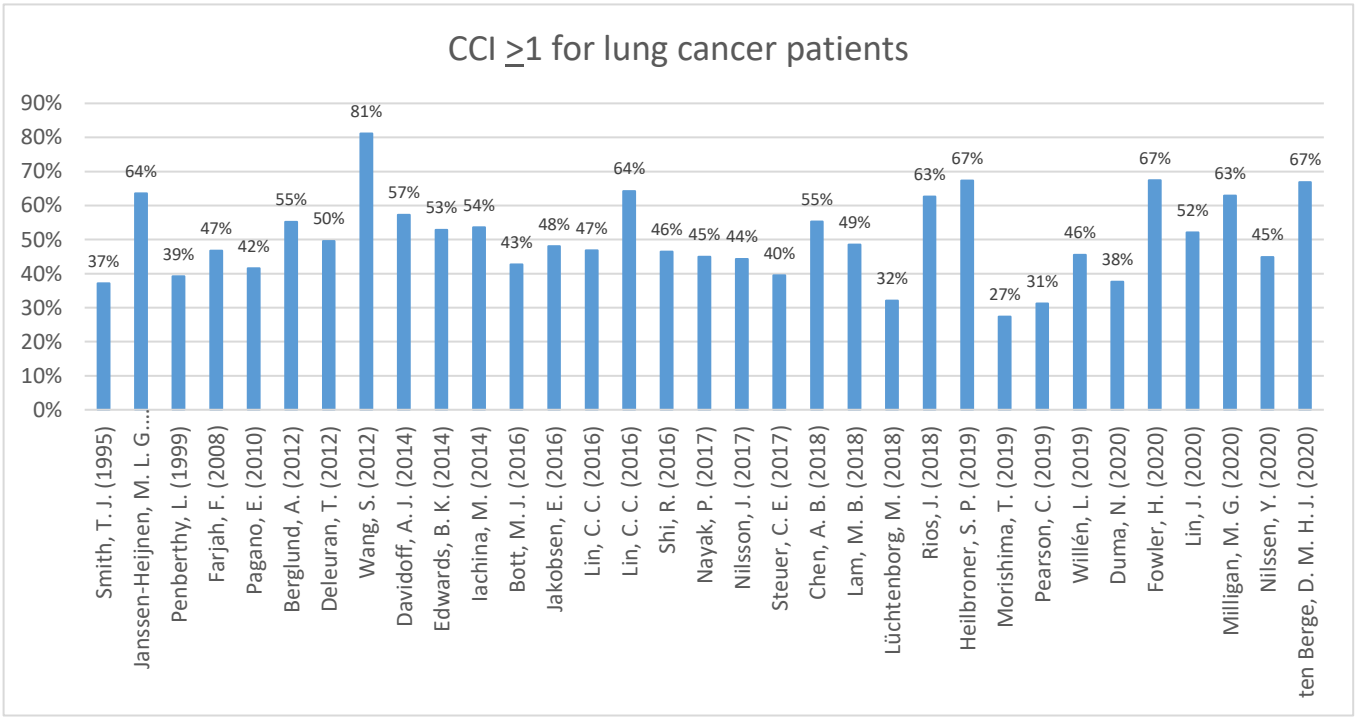


Figure 7: Percentage of lung cancer patients having a CCI of one or more per study

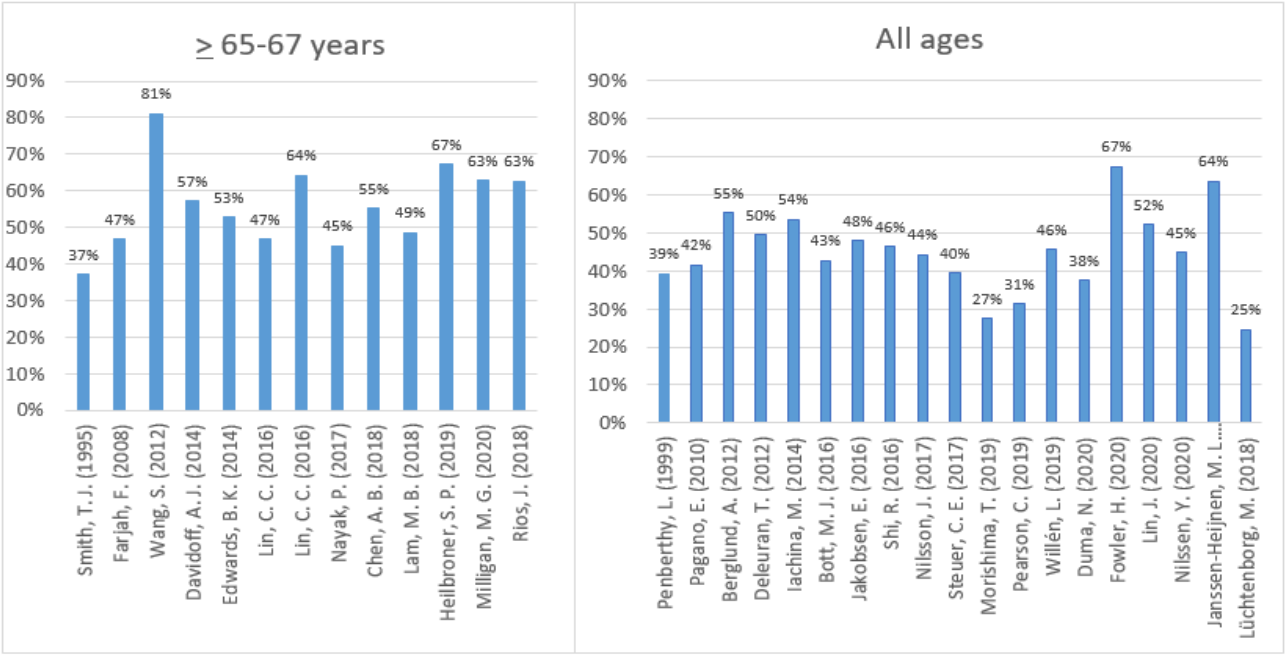


Figure 8: Percentage of lung cancer patients having a CCI of one or more per study stratified by age groups

PROSTATE CANCER

A total of 38 studies assessed the prevalence of comorbidity among prostate cancer patients. The percentage ranged from 12% to 82%. The CCI was used in 36 studies (range 12-45%) (figure 9), the ECI was used in one study (56%) and one study counted the number of comorbidities (82%). When looking at age groups of the CCI studies, five studies limited their population with an age limit (2x <80, 2x <75 and 1x <70)(relatively range 21-22%, range 26-31% and 12%), two studies selected a specific age group (40-99 (20%)and 55-95 years (27%)) and 8 studies looked at 65/66 years and older (24-45%), and the remaining studies had no age limitations (besides an adult population)(10-40%) (figure 10).

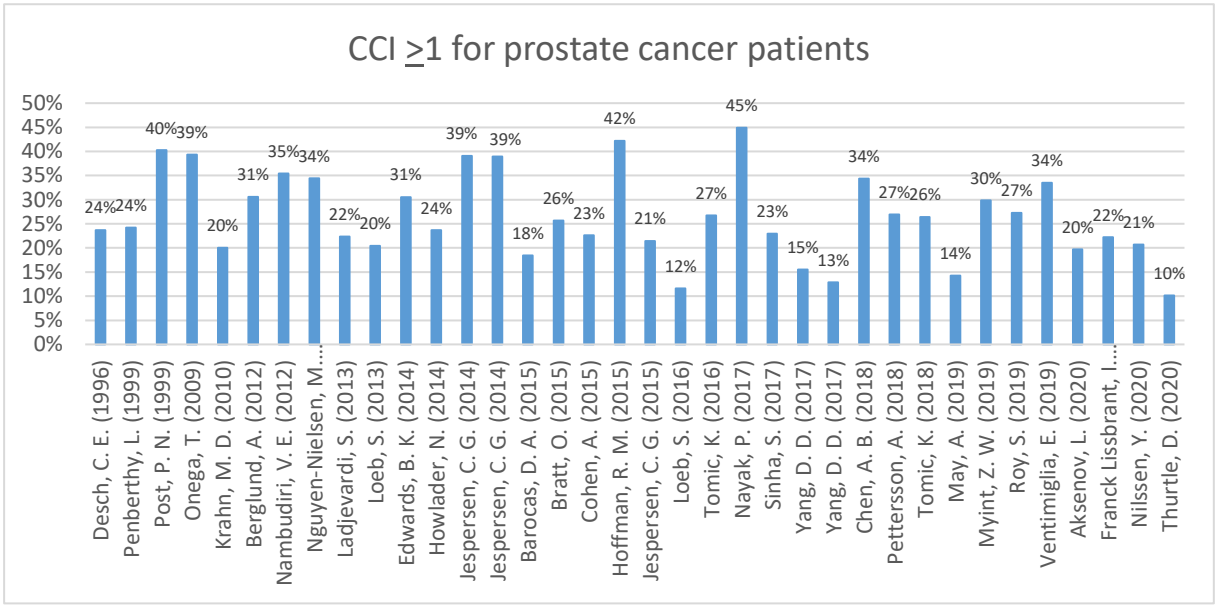


Figure 9: Percentage of prostate cancer patients having a CCI of one or more per study

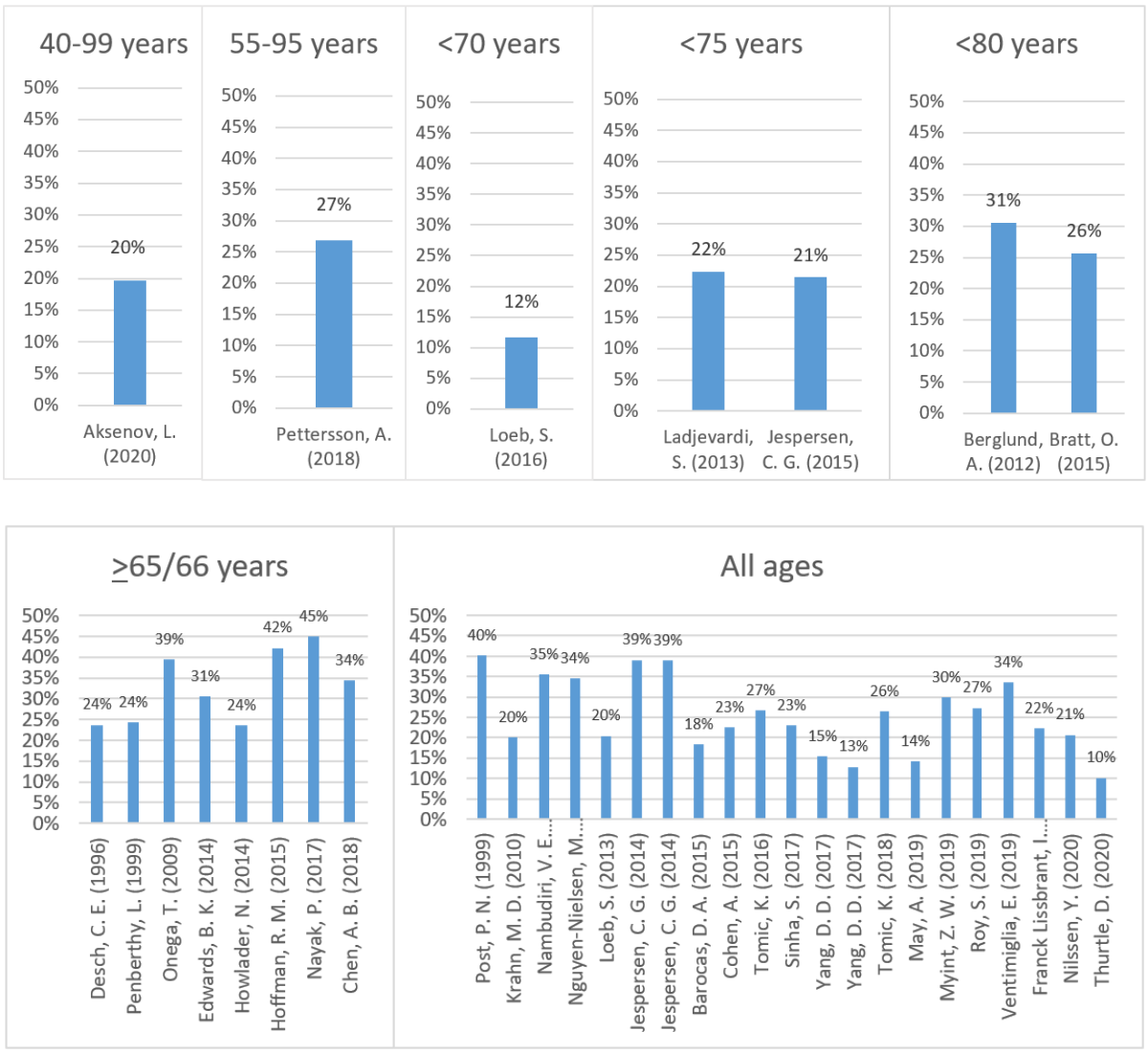


Figure 10: Percentage of prostate cancer patients having a CCI of one or more per study stratified by age groups

SKIN CANCER

Six studies were included that contained data about the prevalence of comorbidities in a population diagnosed with skin cancer. They all used the CCI or adaptations to measure a comorbidity score. The percentage of patients with one or more comorbidity ranged from 9% to 72% (figure 11). Four studies looked at melanoma (range 9-23%) and two studies looked at Merkel cell carcinoma (MCC) (range 24-72%). One study looked at a younger population (26-64 years) (9%)), one looked at an older population (≥65 years) (18%) and four studies applied no age restrictions (24-72%).

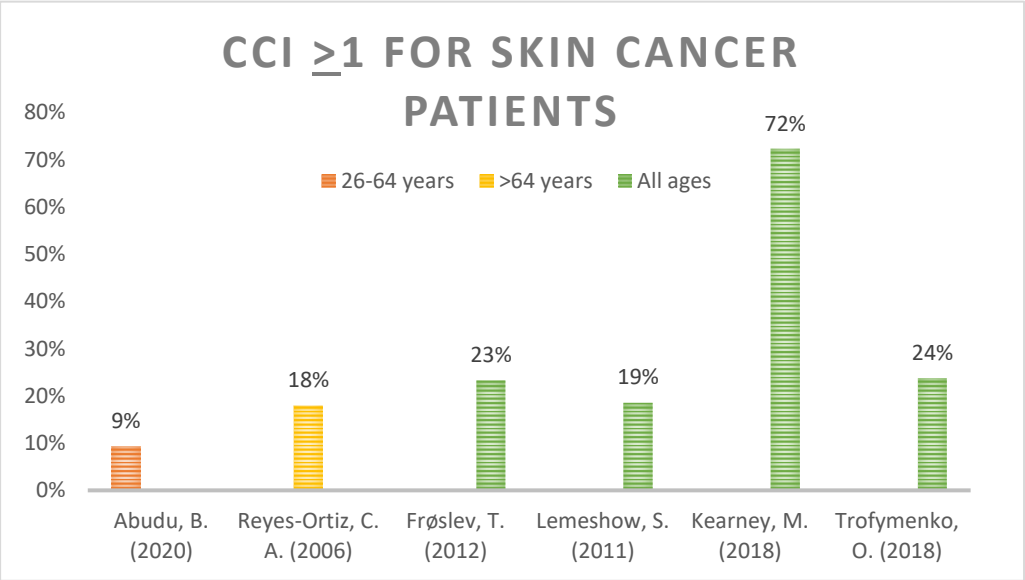


Figure 11: Percentage of skin cancer patients having a CCI of one or more per study stratified by age groups

TYPES OF COMORBIDITIES REPORTED

Tables 4-8 in the appendix show the prevalence of specific comorbidities categorized by type of cancer. Similar disorders were combined under one overarching term e.g. hemiplegia and paraplegia under paralysis. Illnesses that were not of a chronic nature or did not have long-lasting effect were not included in the analyses of the results. If a study only provided prevalence numbers of subpopulations a total prevalence number was calculated. When this was not possible due to missing data the study was excluded from that particular analysis.

QUALITY ASSESSMENT

The methodological quality of each included article was assessed (table 3). Conflicts between the two reviewers are processed as 'yes/unknown' or 'no/unknown'. 38 of the 164 articles scored 'yes' on all items of quality assessment. 64 Articles scores no or unknown on one item, 50 on two items, 10 on three items, one on four items and one on six items.

First author + jaartal	Was the study's target population a close representation of the national population in relation to relevant variables, e.g. disease stage, type of database?	Do the inclusion criteria match the target population, e.g. age, sex, insurance?	Are all eligible participants included in the study?	Was an acceptable case definition used in the study?	Was the same mode of data collection used for all subjects?	Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Free of other biases?
Smith, T. J. (1995)	unknown	yes	yes	yes	yes	yes	yes/unknown
Desch, C. E. (1996)	no/unknown	no/unknown	yes	yes	yes	yes	yes/unknown
Hillner, B. E. (1996)	yes/unknown	no	yes	yes	yes	yes/unknown	yes/unknown
Janssen-Heijnen, M. L. G. (1998)	no	yes	yes	yes	yes	yes	yes
Newschaffer, C. J. (1998)	yes	unknown	yes	yes	yes	yes	yes
Penberthy, L. (1999)	yes/unknown	unknown	yes	yes	yes	yes	yes
Post, P. N. (1999)	no	yes	yes	yes	yes	yes	yes
De Marco, M. F. (2000)	yes	yes	yes	yes	yes	yes	yes
Klabunde, C. N. (2000)	yes	no	no	yes	yes	yes	unknown
Du, X. (2001)	yes	no	yes	yes	yes	yes	yes
Goodwin, J. S. (2004)	yes	no	yes	yes	yes	unknown	yes/unknown
Osborne, C. (2005)	yes	no	yes	yes	yes	yes	yes
Coory, M. (2006)	yes	yes	yes	yes	yes	yes	unknown
Gross, C. P. (2006)	no	no	yes	yes	yes	yes	yes
Reyes-Ortiz, C. A. (2006)	yes	unknown	yes	yes	yes	yes	yes
Du, X. L. (2007)	no	no	yes	yes	yes	yes	yes
Klabunde, C. N. (2007)	yes	no	yes	yes	yes	yes	yes
Farjah, F. (2008)	no/unknown	no	yes	yes	yes	yes	yes
Heck, J. E. (2008)	unknown	no	yes	yes	yes	yes	yes
Cooperberg, M. R. (2009)	no	yes	yes	yes	yes	yes	yes
Ketchandji, M. (2009)	yes	no/unknown	yes	yes	yes	yes	yes/unknown
Onega, T. (2009)	yes	no	yes	yes	yes	yes	yes
Onega, T. (2009)	yes	no	yes	yes	yes	yes	yes
Davidoff, A. J. (2010)	no	unknown	yes	yes	yes	yes	yes
Krahn, M. D. (2010)	yes	yes	yes	yes	yes	yes	yes
Pagano, E. (2010)	no	yes	yes	yes	yes	yes	yes
Shack, L. G. (2010)	yes	yes	yes	yes	yes	yes	yes

Singh, H. (2010)	yes	yes	yes	yes	yes	unknown	yes/unknown
van Steenbergen, L. N. (2010)	no	yes	yes	yes	yes	no	yes
Berglund, A. (2011)	yes	yes	yes	yes	yes	yes	yes
Chavez-MacGregor, M. (2011)	yes	no	yes	yes	yes	yes	yes
Foley, K. L. (2011)	unknown	unknown	yes	yes	yes	yes	yes
Gross, C. P. (2011)	yes	no	yes	yes	yes	yes	yes
Lemeshow, S. (2011)	yes	yes	yes	yes	yes	yes/unknown	yes/unknown
Salloum, R. G. (2011)	no	yes	yes	yes	yes	yes	yes
Berglund, A. (2012)	no	yes	yes	yes	yes	yes	yes
Berglund, A. (2012)	yes	yes	yes	yes	yes	yes	yes
Deleuran, T. (2012)	yes	yes	yes	yes	yes	yes	yes
Frøslev, T. (2012)	yes	yes	yes	yes	yes	yes	yes
Fu, A. Z. (2012)	unknown	unknown	yes	yes	yes	yes	yes
Lavelle, K. (2012)	yes/unknown	yes/unknown	yes	yes	yes	yes	yes
Lowrance, W. T. (2012)	unknown	yes/unknown	yes	yes	yes	yes	yes
Nambudiri, V. E. (2012)	unknown	unknown	yes	yes	yes	yes	yes
Nguyen-Nielsen, M. (2012)	yes	yes	yes	yes	yes	yes	yes
Ording, A. G. (2012)	yes	yes	yes	yes	yes	yes	yes
Ostenfeld, E. B. (2012)	yes	yes	yes	yes	yes	yes	yes
Schonberg, M. A. (2012)	unknown	no	yes	yes	yes	yes	yes
Singh, H. (2012)	yes	yes	yes	yes	yes	unknown	yes
Wang, S. (2012)	unknown	no/unknown	yes	yes	yes	yes	yes
Chastek, B. (2013)	no	no	yes	yes	yes	yes	yes
Keating, N. L. (2013)	no/unknown	no/unknown	yes	yes	yes	yes	yes
Ladjevardi, S. (2013)	yes	no	yes	yes	yes	yes	yes
Loeb, S. (2013)	no/unknown	yes	yes	yes	yes	yes	yes
van Leersum, N. J. (2013)	yes	yes	yes	yes	yes	no	unknown
Xiao, H. (2013)	yes	yes/unknown	yes	yes	yes	yes	yes/unknown
Bates, T. (2014)	yes	yes	yes	yes	yes	no	yes

Beckmann, K. R. (2014)	yes	yes	yes	yes	yes	yes	yes
Davidoff, A. J. (2014)	no	no	yes	yes	yes	yes	yes
de Decker, L. (2014)	unknown	yes/unknown	yes	yes	yes	yes/unknown	yes
Dik, V. K. (2014)	yes	yes	yes	yes	yes	yes	unknown
Edwards, B. K. (2014)	yes	no	yes	yes	yes	yes	yes
Escribà, J. M. (2014)	no	yes	yes	yes	yes	yes	yes
Griffiths, R. I. (2014)	yes	no	yes	yes	yes	yes	yes
Hamza, S. (2014)	no	unknown	yes	yes	yes	yes	yes
Howlader, N. (2014)	yes	no	yes	yes	yes	yes	yes
Iachina, M. (2014)	yes	yes	yes	yes	yes	yes	yes
Jespersen, C. G. (2014)	yes	yes	yes	yes	yes	yes	yes
Jespersen, C. G. (2014)	yes	yes	yes	yes	yes	yes	yes
Seneviratne, S. (2014)	no/unknown	yes	yes	yes	yes	yes	yes
Tannenbaum, S. L. (2014)	yes	yes	yes	yes	yes	yes	yes
Tannenbaum, S. L. (2014)	yes	yes	yes	yes	yes	yes	yes
Tong, L. (2014)	yes	no	no	yes	yes	yes	yes
Barocas, D. A. (2015)	yes	yes	yes	yes	yes	yes	yes
Bratt, O. (2015)	no	yes	unknown	yes	yes	yes	yes
Cardwell, C. R. (2015)	unknown	unknown	yes	yes	yes	yes	yes
Cetin, K. (2015)	unknown	unknown	yes	yes	yes	yes	yes
Cohen, A. (2015)	no	yes	yes	yes	yes	yes	yes
Dinan, M. A. (2015)	unknown	unknown	unknown	yes	yes	yes	yes
Hoffman, R. M. (2015)	yes	no/unknown	yes	yes	yes	yes	yes
Islam, K. M. (2015)	yes	yes	yes	yes	yes	yes	yes
Jespersen, C. G. (2015)	no	yes	yes	yes	yes	yes	yes
Morgan, J. (2015)	no	no	yes	yes	yes	yes	yes
O'Brien, B. (2015)	yes	no	yes	yes	yes	yes	yes
Shi, R. (2015)	yes	yes	yes	yes	yes	yes/unknown	yes/unknown
Unger, J. M. (2015)	no	unknown	yes	yes	yes	yes/unknown	yes

Beckmann, K. R. (2016)	yes	yes	yes	yes	yes	yes	yes
Bott, M. J. (2016)	no	yes	yes	yes	yes	yes	yes
Jakobsen, Erik (2016)	yes	yes	yes	yes	yes	yes	yes
Lin, C. C. (2016)	yes	unknown	no	yes	yes	yes	yes
Loeb, S. (2016)	no/unknown	yes	yes	yes	yes	yes	yes
Møller, H. (2016)	yes	yes	yes	yes	yes	yes	yes
Richards, P. (2016)	unknown	no	yes	yes	yes	yes	yes
Shi, R. (2016)	no	yes	yes	yes	yes	yes	yes/unknown
Tomic, K. (2016)	yes	yes	yes	yes	yes	yes	yes
Vehko, T. (2016)	yes	yes	yes	yes	yes	yes	yes
Xiao, H. (2016)	yes	yes	yes	yes	yes	yes	yes
Allaire, B. T. (2017)	yes	no	yes	yes/unknown	yes	yes	yes
Brungs, D. (2017)	yes	yes	yes	yes	yes	yes	yes
Capri, S. (2017)	no	yes	yes	yes	yes	yes	yes
Cassidy, R. J. (2017)	no	no	yes	yes	yes	yes	yes
Fallahpour, S. (2017)	no	yes	yes	yes	yes	yes	yes
Fowler, H. (2017)	yes	yes	yes	yes	yes	yes	yes
Jansen, L. (2017)	no	yes	yes	yes	yes	yes	yes
Jasem, J. (2017)	no	yes	yes	yes	yes	yes	yes
Li, S. (2017)	no	yes	yes	yes	yes	yes	yes
Mateo, A. M. (2017)	no	yes	yes	yes	yes	yes/unknown	yes/unknown
Migden, M. (2017)	no	no	no	yes	yes	yes	yes
Nayak, P. (2017)	yes	no	yes	yes	yes	yes	yes
Nilsson, J. (2017)	yes	yes	yes	yes	yes	unknown	yes
Puig, C. A. (2017)	unknown	yes	yes	yes	yes	yes	yes
Sinha, S. (2017)	no	yes	yes	yes	yes	yes	yes
Steuer, C. E. (2017)	yes	yes	yes	yes	yes	yes	yes
Thiels, C. A. (2017)	unknown	yes	yes	yes	yes	yes/unknown	yes
Trogdon, J. G. (2017)	yes	no	yes	yes	yes	yes	yes

Yang, D. D. (2017)	no	yes	yes	yes	yes	yes	yes
Yang, D. D. (2017)	no	yes	yes	yes	yes	yes	unknown
Blackmore, T. (2018)	yes/unknown	no	yes	yes	yes	yes	yes
Busby, J. (2018)	yes	no/unknown	yes	yes	yes	yes	yes
Chen, A. B. (2018)	yes	no	yes	yes	yes	yes	yes
Cuthbert, C. A. (2018)	no	yes	yes	yes	yes	yes	yes
Di Girolamo, C. (2018)	yes	yes	yes	yes	yes	yes	unknown
Kearney, M. (2018)	no	no	yes	yes	yes	yes	yes
Kong, A. L. (2018)	yes	no	yes	yes	yes	unknown	yes/unknown
Lam, M. B. (2018)	no	unknown	yes	yes	yes	yes	yes
Lawrenson, R. (2018)	no/unknown	yes	yes	yes	yes	yes	yes
Lüchtenborg, M. (2018)	yes	yes	yes	yes	yes	yes	yes
Mehta, H. B. (2018)	yes	no	yes	yes	yes	yes	yes
Pettersson, A. (2018)	yes	yes	yes	yes	yes	yes	yes
Rios, J. (2018)	yes	no/unknown	yes	yes	yes	yes	yes
Sineshaw, H. M. (2018)	no	yes	yes	yes	yes	yes	yes
Soriano, L. C. (2018)	unknown	yes	yes	yes	yes	yes	yes
Tomic, K. (2018)	yes	yes	yes	yes	yes	yes	yes
Trofymenko, O. (2018)	yes	yes	yes	yes	yes	yes	yes
Weidner, T. K. (2018)	unknown	unknown	yes	yes	yes	yes	yes
Williams, A. D. (2018)	unknown	yes	unknown	yes	yes	yes	yes
Concors, S. J. (2019)	no	yes	yes	yes	yes	yes	yes
Heilbroner, S. P. (2019)	yes	unknown	unknown	yes	yes	yes	yes
Jauhari, Y. (2019)	no	yes	yes	yes	yes	yes	yes
Lewis, G. D. (2019)	no	yes	yes	yes	yes	yes	yes
May, A. (2019)	no	yes	yes	yes	yes	yes	yes
Morishima, T. (2019)	yes	no	yes	yes	yes	yes	yes
Murawski, M. (2019)	yes/unknown	unknown	yes	yes	yes	yes	yes
Myint, Z. W. (2019)	yes	unknown	yes	yes	yes	yes	yes

Pearson, C. (2019)	yes	yes	yes	yes	yes	yes	yes
Pule, M. L. (2019)	yes	yes/unknown	yes/unknown	yes/unknown	yes/unknown	yes/unknown	yes/unknown
Roy, S. (2019)	no/unknown	unknown	yes	yes	yes	yes	yes
Te Marvelde, L. (2019)	yes	yes	yes	yes	yes	yes	yes
Ventimiglia, E. (2019)	yes	yes	yes	yes	yes	yes	yes
Willén, L. (2019)	yes	yes	yes	yes	yes	yes	yes
Abudu, B. (2020)	yes	no	yes	yes	yes	yes	yes
Aksenov, L. (2020)	yes/unknown	no	yes	yes	yes	yes	yes
Chow, Z. (2020)	no	no	yes	yes	yes	yes	yes
Duma, N. (2020)	unknown	unknown	yes	yes	yes	yes	yes
Fowler, H. (2020)	yes	yes	yes	yes	yes	yes	unknown
Franck Lissbrant, I. (2020)	yes	yes	yes	yes	yes	yes	yes
Gupta, A. (2020)	unknown	unknown	yes	yes	yes	yes/unknown	yes
Jauhari, Y. (2020)	no	yes	yes	yes	yes	yes	yes
Lin, J. (2020)	unknown	unknown	yes	yes	yes	yes	yes
Milligan, M. G. (2020)	no/unknown	yes/unknown	yes	yes	yes	yes	yes
Nilssen, Y. (2020)	yes	yes	yes	yes	yes	unknown	yes
Parise, C. A. (2020)	no	yes	yes	yes	yes	yes	yes
ten Berge, D. M. H. J. (2020)	no	yes	yes	yes	yes	yes	yes
Thurtle, D. (2020)	yes	yes	yes	yes	yes	yes	yes
Wennstig, A. K. (2020)	unknown	yes	yes	yes	yes	yes	yes

Table 3: Results of quality assessment of all included articles

DISCUSSION

This review aimed to summarise evidence on the prevalence of comorbidities among oncological patients and distinguish differences between the five most common types of cancer. We found that the prevalence of comorbidities calculated with the CCI ranges between 4-81%, with lower ranges for breast and prostate cancer and higher ranges for colorectal, lung and skin cancer. The prevalence seemed to increase with age, with higher percentages reported in studies that only investigated an older population, with an exception for skin cancer. Higher percentages in older people with colorectal and lung cancer were also found in comparison to breast and prostate cancer. For all cancers types we found no increase of comorbidity prevalence over time. Although this was the expected trend (195). There was a large heterogeneity between the data from the different studies.

Previous studies have reported a similar wide variance in the prevalence of comorbidities. Lee et al. reported a range of 0.4% to 90% of cancer patients with a comorbidity, the highest frequency among patients with lung (35%), breast (20%) or colorectal cancers (20%) (196). Safarti et al. stated that some cancers, such as lung, stomach and liver cancer, are strongly associated with risk factors related to other chronic conditions. For other cancers, e.g. breast and prostate cancer this association is less strong (3). Edwards et al. confirmed this, reporting a comparable prevalence of comorbidity in breast and prostate cancers patients in comparison with cancer-free Medicare beneficiaries 66 years or older, higher frequencies in lung cancer patients and intermediate frequencies for colorectal cancer patients (92). This review, summarizing available evidence on comorbidity prevalence, generally confirms these findings.

However, there is a broad variance in the way comorbidities are measured and what is considered a comorbidity. Using only data from health claims and registries based on ICD-codes it is likely that some diagnoses have been missed. On the other hand, the use of administrative data has enabled us to analyse prevalences based on a broad population representative of the total population, which strengthens the generalizability of study. Still a large variety in percentages is found when analysing the different studies, which resulted in a broad range per cancer type. This variation can partly be explained by differences between countries/populations, measurement tools, review period and data sources. Some studies only used data from patients hospital admissions, other studies also included physician visits and different registers included data derived from hospital discharge records, referral letters and patients history by trained registry personnel. Klabunde et al found that prevalences are higher in physician than in inpatient hospital claims for some but not all conditions (42). Further analyses on the data can explore these differences between the data sources. Part of the variation could also be explained by the review period an article used to assess comorbidities. Some studies collected all disease codes one year before the cancer diagnosis, others used a considerably longer period or looked at all diagnoses present at that moment.

The CCI was the most widely used comorbidity index in our study and allowed us to compare studies and age groups. A limitation of this method is that comorbidities not included in the Charlson's list of nineteen comorbidities where not included in the comorbidity score. This also applies for the other comorbidity indexes. When looking at the categories listed in the ECI one could argue that not all items scored in the index are health conditions or of a chronic nature. Therefore, the total score might overestimate the number of clinically relevant comorbidities present; consequently, this index did not play a major role in analysing the prevalence of comorbidities. However, percentage data on specific comorbidities can be compared to data on specific comorbidities from other studies regardless of the comorbidity measurement used.

Limitations of our research method are that the research protocol was adjusted during the article selection process, limiting the study focus to the five most common types of cancer to keep the amount of papers manageable. Consequently, the search strategy was broader than necessary. In retrospect, a more specific search strategy targeting the five most common cancers would have been preferred. Also, we did not research any grey literature or include expert opinions. Additionally, the references of the included articles were not reviewed for other relevant studies due to the limited time period.

The quality of the included studies was generally high with roughly 62% of the studies scoring 6/7 or 7/7. The quality assessment form was tailored to the purpose of our review by adapting three similar quality assessment forms. However, this specific quality assessment form has not been validated.

In this systematic review we have gathered and summarized the current literature on the prevalence of comorbidities. These findings underline the importance of including comorbidity management in guidelines for cancer treatment. Given that such a large proportion of the oncological population deals with more diseases at once, research on the effect of comorbidities on treatments and their outcome should be prioritized. However, to fully assess the extent of comorbidities in cancer, uniformity in measurement and reporting of comorbidities is required. This could provide physicians with much needed levers to give the best possible personalized care for their patients. Additional analysis on the data can be executed to gain more insights on the distribution of the prevalence of comorbidities and examine the differences between the studies, data sources and countries. In order to tailor cancer treatment to patients and provide patient centered care, uniform information on comorbidity prevalence at a population level is required.

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APPENDIX

APPENDIX 1: SEARCH STRATEGY PUBMED

(Neoplasms [MeSH] OR Cancer* [tiab] OR Neoplas* [tiab] OR Tumor* [tiab] OR Tumour* [tiab] OR Carcinom* [tiab] OR Melanom* [tiab] OR Malignan* [tiab] OR Lymphoma* [tiab] OR Oncolog* [tiab])

AND

(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 condition [tiab] OR Chronic conditions [tiab] OR Health condition* [tiab] OR Chronic illness* [tiab] OR Co-occur* [tiab] OR Chronic morbidit* [tiab])

AND

(index [tiab] OR indices [tiab] OR score [tiab] OR scores [tiab] OR scale [tiab] OR scales [tiab] OR Frequency[tiab] OR Frequencies[tiab] OR prevalence estimate* [tiab]

OR (prevalence [tiab] AND (estimate [tiab] OR comorbidit* [tiab] OR co-morbidit* [tiab] OR multimorbidit* [tiab] OR multi-morbidit* [tiab]))

OR ((measure* [tiab] OR level* [tiab] OR number* [tiab]) AND (comorbidit* [tiab] OR co-morbidit* [tiab] OR multimorbidit* [tiab] OR multi-morbidit* [tiab])))

AND

((Administrative [tiab] AND health claim* data [tiab]) OR International Classification of Diseases [MeSH] OR ICD [tiab] OR International Classification of Diseases [tiab] OR Administrative data [tiab] OR claim [tiab] OR claims [tiab] OR Cancer data* [tiab] OR Insurance data* [tiab] OR Cancer registr* [tiab] OR Cancer register* [tiab])

APPENDIX 2: QUALITY ASSESSMENT

Name of author(s):_____
Year of publication:_____

Name of paper/study:

_____

This tool is designed to assess the risk of bias in population-based prevalence studies. Please read the additional notes for each item when initially using the tool. Note: If there is insufficient information in the article to permit a judgement for a particular item, please answer No (HIGH RISK) for that particular item.

Risk of bias item	Criteria for answers	Additional notes and examples
External Validity		
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. disease stage, type of database?	• Yes (LOW RISK): The study's target population was a close representation of the national population. • No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	The target population refers to the group of people or entities to which the results of the study will be generalised. Examples: • The study was a national registry of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: Yes (LOW RISK). • The study was conducted in one province/city only, and it is not clear if this was representative of the national population. The answer is: No (HIGH RISK). • The study was undertaken in one village/city only and it is clear this was not representative of the national population. The answer is: No (HIGH RISK).
2. Do the inclusion criteria match the target population e.g. age, sex insurance?	• Yes (LOW RISK): The application of the inclusion criteria results in a true or close representation of the target population. • No (HIGH RISK): The inclusion criteria do NOT result in a true or close representation of the target population.	The sampling frame is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: • The sampling frame was a list of almost every individual within the target population. The answer is: Yes (LOW RISK). • The sampling frame was confined to just one particular ethnic group within the overall target population, which comprised many groups. The answer is: No (HIGH RISK).
3. Are all eligible participants included in the study?	• Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	Examples: • All eligible participants are included Yes (LOW RISK) • Part of eligible participant are included No (HIGH RISK)

	• No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	

Internal Validity		
4. Was an acceptable case definition used in the study?	• Yes (LOW RISK): An acceptable case definition was used. • No (HIGH RISK): An acceptable case definition was NOT used.	For a study on cancer, the following case definition was used: "The diagnosis of cancer must be given by an physician or pathological proven." The answer is: • The answer is: Yes (LOW RISK). • The answer is: No (HIGH RISK).
5. Was the same mode of data collection used for all subjects?	• Yes (LOW RISK): The same mode of data collection was used for all subjects. • No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. Examples: • The answer is: Yes (LOW RISK). • The answer is: No (HIGH RISK).
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	• Yes (LOW RISK): the paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of comorbidity). • No (HIGH RISK): the paper dis represent numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: • There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of low back pain. The answer is: Yes (LOW RISK) • In reporting the overall prevalence of comorbidities in an oncological population (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: No (HIGH RISK).
7. Free of other bias?	• Yes (LOW RISK): No other biases are found when examining the paper • No (HIGH RISK): Other biases are found when examining the paper	

APPENDIX 3: BREAST CANCER

Author (year)	Busby, J. (2018)	Cardwell, C. R. (2015)	Fu, A. Z. (2012)	Klabunde, C. N. (2007)	Klabunde, C. N. (2000)	Klabunde, C. N. (2000)2	Lin, C. C. (2016)	Lin, C. C. (2016)2	Mehta, H. B. (2018)	Mehta, H. B. (2018)2	Schonberg, M. A., (2012)	Vehko, T. (2016)
Description	All stages	All stages	All stages, women 18-64 years	All stages, ≥66 years	All stages, ≥66 years	All stages, ≥66 years	Women ≥ 66 years	Women > 66 years	All stages, >66 years	All stages, >66 years	Women ≥80 years with Favorable Breast Tumor (<5cm, LN-, ER+)	All stages, women ≥30 years
Subcategory					Inpatient claims	Physician claims	NCDB	SEER	CCI	ECI		
N=	23669	17880	35057	26377	7471	7471	13823	13823	19082	19082	9932	43439
AIDS/HIV				0,0%			0,0%	0,0%	0,0%			
Alcohol abuse										0,2%		0,3%
Atherosclerosis												0,1%
Atrial fibrillation												2,5%
Blood-loss anemia										0,7%		
Cancer - Other metastatic cancers			1,6%									
Cancer - Other non-metastatic solid tumors			2,9%									
Cancer, except breast cancer											4,0%	6,4%
Cerebrovascular disease	2,7%	3,6%		3,6%	1,4%	1,6%	0,9%	5,4%	4,4%		9,0%	
Chronic obstructive pulmonary disease and asthma												6,1%
Chronic pulmonary disease	11,5%	16,2%	4,4%	7,2%	2,4%	3,9%	6,7%	11,5%	9,1%	10,4%	11,4%	
Coagulopathy										1,4%		
Congestive heart failure	1,5%	1,9%		5,7%	2,3%	2,7%	2,6%	7,1%	6,4%	6,5%	13,5%	3,8%

Connective tissue disease/ rheumatologic disease				1,5%	0,2%	1,2%	1,0%	2,7%	2,3%			
Coronary artery disease												6,3%
Deficiency anemia			3,3%							10,9%		
Dementia				1,1%	0,3%	0,6%	0,2%	1,3%	1,3%		3,0%	1,2%
Depression			2,6%									0,3%
Diabetes	6,2%	5,9%	6,9%	10,2%	2,3%	7,5%	10,8%	20,7%			14,0%	4,9%
Diabetes with complications				1,0%	0,2%	0,5%	4,3%	4,0%	4,3%	5,4%		
Diabetes without chronic complications									16,4%	20,5%		
Drug abuse										0,1%		
Epilepsy												1,0%
Falls											2,1%	
Fluid and electrolyte disorders										6,0%		
GI hemorrhage											3,8%	
Hemiplegia or paraplegia							0,1%	0,3%	0,3%			
Hip fracture											2,4%	
Hypertension			16,7%							58,1%		19,9%
Hypothyroidism			6,3%							16,4%		
Liver disease	0,2%									0,5%		
Mental disorders												3,4%
Mild liver disease				0,2%	0,1%	0,1%	0,1%	0,4%	0,2%			
Moderate or severe liver disease				0,0%			0,1%	0,1%	0,1%			

Moderate or severe renal disease				0,7%	0,4%	0,4%			3,8%			
Mood Disorder											6,1%	
Myocardial infarction	1,1%	1,5%					1,8%	2,1%	1,3%		3,6%	
Myocardial infarction (acute)				0,6%	0,5%	0,3%						
Myocardial infarction (old)				0,8%	0,4%	0,1%						
Neurodegenerative disorders										4,7%		
Nutritional Deficiencies											1,6%	
Obesity										2,1%		
Paralysis				0,4%	0,4%	0,1%				0,7%		
Parkinson's disease											1,3%	0,6%
Peptic ulcer disease	1,0%	2,2%					0,3%	0,6%		0,1%	1,9%	
Peripheral vascular disease	1,1%	1,6%		2,1%	0,5%	1,5%	0,9%	3,5%	3,1%	6,0%	5,2%	
Pneumonia											4,3%	
Psychosis			3,1%							2,6%		
Pulmonary circulation disorders										1,0%		
Renal disease	4,5%	3,0%					0,9%	3,3%				
Renal failure										3,7%	1,4%	
Renal insufficiency												0,1%
Rheumatoid arthritis/collagen vascular diseases			1,9%							3,1%		
Stroke												0,5%
Ulcer disease				0,5%	0,2%	0,4%			0,6%			

Valvular disease	4,5%
Weight loss	1,0%

Table 4: Percentages per comorbidity for studies investigating breast cancer patients

APPENDIX 4: COLORECTAL CANCER

Author (year)	Cuthbert, C, A, (2018)	De Marco, M, F, (1999)	Fowler, H, (2020)	Gross, C, P, (2006)	Jansen, L, (2017)	Klabunde, C, N, (2007)	Lin, C, C, (2016)	Lin, C, C, (2016)	Mehta, H, B, (2018)	Mehta, H, B, (2018)	Shack, L, G, (2010)	Shack, L, G, (2010)	Soriano, L, C, (2018)	Tong, L, (2014)
Description	Stage I-III	All stages	All stages	Stage I-III adeno-carcinoma, ≥67 years	All stages	All stages, >66 years	Carcinoma ≥66 years	Carcinoma ≥66 years	All stages, ≥65 years	All stages, >65 years	All stages	All stages	All stages, 40–89 years	All stages, ≥66 years
							SEER	NCDB	CCI	ECI	Comorbidity measured anytime	Comorbidity measured 18-6 months before diagnosis		
N=	12265	3242	102216	29733	8100	26460	12343	12343	16963	16963	29565	29565	2251	
Abnormal weight loss													2,0%	
AIDS/HIV							0,0%	0,0%	0,0%	0,0%				
Alcohol abuse										0,5%				
Anaemia													5,8%	
Asthma													11,1%	
Atrial fibrillation				16,1%									5,1%	
Bleeding per rectum													6,8%	
Blood-loss anemia										2,4%				
Cardiovascular disease	9,4%	16,0%	10,0%		12,8%									
Cerebrovascular disease		4,0%		10,3%	1,6%	2,0%	7,6%	1,3%	6,0%			2,9%		

Change in bowel habits													3,6%	
Chronic obstructive pulmonary disease	5,5%	8,0%	29,0%	20,9%		5,0%							6,1%	11,5%
Chronic pulmonary disease							15,9%	41,3%	12,1%	13,0%	7,9%			
Chronic renal failure				2,4%										
Coagulopathy										1,7%				
Congestive heart failure			70,0%	18,8%		4,0%	13,5%	9,0%	10,8%	10,5%		3,7%		18,2%
Connective tissue disease/ rheumatologic disease	0,7%					1,0%	2,3%	3,0%						
Deficiency anemia										22,3%				
Dementia	1,2%			3,2%		1,0%	2,0%	0,4%	1,7%			1,0%		
Depression													6,8%	
Diabetes	14,0%	8,0%	14,0%	17,8%	4,5%	6,0%	25,9%	23,1%					13,8%	17,5%
Diabetes with complications						6,0%	5,7%	1,3%	18,8%	6,2%				
Diabetes without chronic complications									4,9%	23,5%				
Drug abuse										0,0%				
DVT/PE													3,1%	
Fluid and electrolyte disorders										8,4%				

GI adenoma																			2,7%	
GORD																			6,0%	
Haemorrhagic stroke																			0,4%	
Heart disease																			2,7%	
Hemiplegia or paraplegia				2,1%		0,0%				0,5%		1,1%								
Hip fracture								0,6%		0,1%										
HIV				6,0%																
Hypercholesterolaemia	0,0%																		4,7%	
Hypertension		14,0%										57,4%							29,3%	
Hypothyroidism					11,6%							11,3%								
IBD																			2,0%	
IHD																			7,4%	
Ischaemic stroke																			1,4%	
Liver disease				1,4%																
Moderate or severe liver disease	1,0%					0,0%		0,6%		0,6%		0,2%		0,6%		0,6%				
Moderate or severe renal disease						1,0%		0,1%		0,2%		5,5%								
Myocardial infarction						1,0%		4,2%		4,1%		2,6%							1,8%	
Myocardial infarction - acute						1,0%														
Neurodegenerative disorders												5,5%				2,6%				
Obesity		42,8%																		

Osteoarthritis													15,2%	
Other		6,0%												
Peptic Ulcer - complicated		42,8%											1,4%	
Peptic ulcer disease	0,1%					1,7%	1,5%			1,6%			2,1%	
Peptic ulcer disease, no bleeding	0,0%		7,8%						0,1%					
Peripheral vascular disease			6,7%		2,0%	6,6%	2,4%	5,3%	8,8%		1,7%			
Previous cancers		15,0%		3,5%										
Psychosis									2,3%					
Pulmonary circulation disorders									1,2%					
Pulmonary diseases														
Renal disease			11,0%											
Renal failure	1,4%					5,6%	3,5%		5,3%					
Rheumatoid arthritis/collagen vascular diseases		14,6%							2,3%				1,2%	
Severe liver disease			2,4%											
TIA	0,2%												1,7%	
Peptic ulcer - Uncomplicated					0,6%			1,3%					0,9%	
Unknown		8,0%							5,5%					
Valvular disease														
Weight loss			3,0%						2,9%					

Table 5: Percentages per comorbidity for studies investigating colorectal cancer patients

HIV = human immunodeficiency virus AIDS= acquired immune deficiency syndrome IBD= inflammatory Bowel Disease IHD= ischemic heart disease TIA = transient Ischemic Attack

Author (year)	Coory, M. (2006)	Fowler, H (2020)	Islam, K. (2015)	Janssen-Heijnen, M, L, G, (1998)	Klabunde, C, N, (2007)	Lin, C, C (2016)	Lin, C, C (2016)2	Mehta, H, B, (2018)	Mehta, H, B, (2018)3	Morishima, T, (2019)	Murawski, M, (2019)	Nilsson, J, (2017)	Salloum, R, G, (2011)	Wang, S, (2012)
	All stages	All stages	All stages	NSCLC, All stages	All stages, ≥66 years	NSCLC, ≥66 years	NSCLC, >66 years	All stages, ≥66 years	All stages, >66 years	All stages	All stages, >25 years	NSCLC , All stages	Stage II-IV, >50 years	NSCLC, All stages
						SEER-Medicare	NCDB	CCI	ECI					
N=	6901	165677	5683	3284	33975	15993	15993	26047	26047	796	16202	24703	994	20511
Acute coronary syndromes	9,2%													
AIDS or HIV					0,0%	0,1%	0,1%	0,1%	0,1%	0,0%		0,0%	1,2%	
Alcohol Abuse									0,8%	8,6%	9,1%			
Aneurysm													6,3%	
Blood-loss anemia									1,0%					
Cancer - Other	5,6%			3,5%						9,0%		13,2%	29,3%	20,8%
Cancer - Solid Tumor without Metastasis										18,0%	16,0%			
Cancer with metastasis												0,6%	7,2%	
Cardiac Arrhythmia											23,8%			
Cardiovascular disease				5,7%									20,6%	
Cerebrovascular disease		10,0%	7,1%	1,1%	3,4%	2,4%	9,5%	7,1%		5,0%		9,0%		13,0%

Chronic bronchitis and emphysema	22,1%												
Chronic liver failure	0,1%												
Chronic pulmonary disease			52,5%		17,3%	32,4%	41,3%	32,3%	34,0%	7,0%	48,8%	12,6%	40,4%	52,3%
Coagulopathy									1,8%		6,2%			
Congestive heart failure	21,6%	11,0%	13,0%		6,1%	7,4%	13,6%	11,7%	11,5%	3,0%	21,9%	7,0%	17,3%	12,7%
Connective tissue disease			2,3%					2,7%		0,0%		2,5%		
COPD		55,0%		5,1%										
Deficiency Anemia									14,7%		4,3%			
Dementia	0,5%		1,0%		0,6%	0,3%	1,5%	1,4%		1,0%		0,5%	1,1%	1,7%
Depression									4,4%		14,3%			
Diabetes	9,0%	19,0%		1,7%	5,9%	23,1%	12,5%						27,3%	25,3%
Diabetes with complications			1,2%		0,6%	4,4%	0,8%	3,9%	5,2%	2,0%	11,5%	1,3%	4,5%	
Diabetes without complications			14,6%					17,0%	20,7%	11,0%	17,9%	7,4%		
Drug abuse									0,1%					
Fluid and Electrolyte Disorders									9,4%		26,3%			
Gangrene													0,7%	
Hemiplegia or paraplegia					0,5%	0,5%	0,5%	0,6%		0,0%		0,4%		
Hypertension	12,8%			3,0%					58,0%					
Hypertension Complicated											11,0%			
Hypertension Uncomplicated											54,8%			

Hypothyroidism							10,5%		9,5%			
Ischemic heart disease											9,1%	
Lipid Metabolism Disorders									39,1%			
Liver disease							0,7%		13,7%		1,5%	
Mild liver disease		3,2%		0,3%	0,6%	0,3%	0,4%		5,0%		1,2%	
Moderate or severe liver disease		0,4%		0,1%	0,1%	0,1%	0,1%		0,0%		0,3%	
Moderate or severe renal disease				0,8%			5,4%					8,0%
Myocardial infarction		6,9%			5,3%	4,1%	3,3%		1,0%		8,1%	5,6%
Myocardial infarction - acute				0,8%								
Myocardial infarction - old				1,2%								
Neurodegenerative disorders							4,7%					
Obesity							1,7%		13,1%			
Other Neurological Disorders									7,7%			
Paralysis		1,6%		0,5%			1,0%		6,2%		1,0%	
Peptic ulcer		1,8%			1,5%	0,7%			4,0%		3,0%	3,5%
Peptic ulcer disease, no bleeding							0,1%					
Peripheral vascular disease	17,0%	8,8%		3,2%	10,7%	3,9%	8,8%	13,1%	2,0%	25,6%	5,7%	13,2%	18,2%
Pneumonia	8,5%											

Psychosis							2,4%					
Pulmonary Circulation Disorders							1,5%		4,2%			
Renal disease		5,8%		6,3%	3,1%			0,0%		1,3%	6,3%	
Renal failure	3,3%						5,5%		16,3%			
Rheumatoid arthritis/collagen vascular diseases							3,3%					
Rheumatologic disease			1,3%	3,0%	1,2%						6,2%	
Stroke	2,7%											
Ulcer disease			0,7%			1,0%						
Valvular Disease							5,4%	7,6%	7,9%			
Weight Loss							3,4%		9,2%			

Table 6: Percentages per comorbidity for studies investigating lung cancer patients

APPENDIX 6: PROSTATE CANCER

Author (year)	Keating, N. L. (2013)	Ketchandji, M. (2009)	Klabunde, C. N. (2007)	Klabunde, C. N. (2000)	Klabunde, C. N. (2000)	Mehta, H. B., (2018)	Mehta, H. B. (2018)	Post, P. N. (1999)	Xiao, H. (2016)	Xiao, H. (2016)	Xiao, H. (2016)
Description	Non metastatic, >65 years	66-84 years	All stages, ≥ 66 years	All stages, ≥ 66 years	All stages, ≥ 66 years	All stages, > 66 years	All stages, > 66 years	All stages	All stages, ≥40 years	All stages, >40 years	All stages, >40 years
				Inpatient claims	Physician Claims	ECI	CCI			Early stage	Late stage
N=	185106	99388	14439	14439	14439	23044	23044	400	11083	9679	1404
AIDS/HIV						0,1%	0,1%		0,1%	0,1%	0,2%
Alcohol abuse						0,1%			1,0%	0,8%	2,6%
Benign neoplasm and in-situ cancer									3,3%	3,3%	2,8%
Bilroth II								1,8%			
Blood loss anemias						0,4%			0,9%	0,7%	2,1%
Brain and other neurological disorders									1,0%	0,8%	2,7%
Cardiovascular								13,9%			
Cerebrovascular accident								3,8%			
Cerebrovascular disease			7,4%	2,0%	1,4%		3,9%				
Chronic obstructive pulmonary disease	19,1%	7,3%									
Chronic pulmonary disease			16,2%	3,3%	4,5%	9,1%	8,1%		9,4%	9,1%	11,4%
Chronic renal insufficiency	13,3%										
Coagulopathy						1,3%			1,4%	1,1%	3,6%
Congenital anomalies									0,5%	1,2%	0,6%

Congestive heart failure	20,0%	3,7%	9,8%	2,3%	2,3%	4,8%	4,7%		2,1%	1,7%	5,0%
Connective tissue disease/rheumatologic disease							1,0%				
COPD								11,0%			
Deficiency anemias						7,5%			5,4%	3,4%	15,0%
Dementia	5,4%		1,3%	0,3%	0,2%		0,5%	0,8%			
Depression									2,1%	0,5%	3,1%
Diabetes	14,2%	9,8%	17,4%	2,0%	6,9%			5,8%	10,9%	11,0%	10,8%
Diabetes with complications			1,5%	0,2%	0,6%	3,7%	2,8%		0,8%	0,7%	1,4%
Diabetes without chronic complications						18,1%	15,4%				
Digestive system disease									16,3%	15,5%	21,7%
Drug abuse						0,1%			0,1%	0,1%	0,4%
Endocrine disorders, nutritional and metabolic, immunity									20,6%	20,1%	24,3%
Fluid and electrolyte disorders						3,8%			5,9%	4,4%	15,7%
Genitourinary system disease									24,5%	24,7%	31,8%
Hemiplegia or paraplegia							0,3%				
Hypertension	30,5%					49,8%			44,5%	44,1%	47,2%
Hypothyroidism						4,9%			2,4%	2,4%	2,8%
Infection									3,9%	3,0%	10,4%
Injury and poisoning									8,6%	8,2%	11,4%
Ischemic heart disease									13,7%	13,4%	15,5%
Liver disease	1,0%					0,4%			0,6%	0,5%	1,1%
Lymphoma									0,6%	0,6%	0,6%
Metastatic cancer									4,1%	2,5%	15,1%

Mild liver disease			0,3%	0,1%	0,1%		0,1%				
Moderate or severe liver disease			0,1%				0,0%				
Moderate or severe renal disease			2,0%	0,5%	0,5%		3,7%				
Musculoskeletal and connective tissue disease									12,6%	11,7%	18,9%
Myocardial infarction		1,7%					1,6%				
Myocardial infarction - acute			2,1%	0,8%	0,3%						
myocardial infarction - old	4,2%		2,9%	0,8%	0,4%						
Neurodegenerative disorders						2,5%					
Obesity	3,8%					1,2%			2,3%	2,3%	2,5%
Other								1,3%			
Other anemias (excluding deficiency anemia and blood loss anemia)									1,5%	1,2%	3,8%
Other circulatory disease (excluding Peripheral vascular disease, ischemic heart disease)									3,5%	3,0%	6,9%
Other mental disorders (excluding depression and psychosis)									1,3%	11,9%	2,3%
Other nervous system and sense organs disorder									3,4%	3,2%	4,8%
Other neurological disorders (excluding Paralysis)									1,4%	1,4%	1,8%
Paralysis	2,7%		1,0%	0,6%	0,9%	0,6%			0,4%	0,3%	1,3%
Peptic ulcer disease	4,6%										

Peptic ulcer disease excluding bleeding						0,0%			0,3%	0,3%	0,3%
Peripheral vascular disease	12,9%	2,0%	4,6%	1,0%	1,2%	5,3%	3,3%		2,0%	1,9%	2,6%
Psychoses						1,2%			0,6%	0,5%	1,3%
Pulmonary circulation disease						0,6%			0,3%	0,3%	0,7%
Renal failure						3,7%			2,2%	1,8%	5,1%
Respiratory disorders									5,0%	4,4%	9,6%
Rheumatoid arthritis/collagen vas						1,3%			0,5%	0,6%	0,6%
Rheumatologic disease	2,2%		1,7%	0,1%	0,6%						
Skin and subcutaneous tissue disease									1,6%	1,2%	3,9%
Other cancer with/without metastasis								9,0%	5,6%	5,7%	4,6%
Stroke	16,6%	3,2%									
Tuberculosis								1,5%			
Ulcer disease			1,5%	0,4%	0,3%		0,5%				
Valvular disease						3,7%			2,9%	2,7%	3,8%
Weight loss						0,9%			0,8%	0,4%	3,1%

Table 7: Percentages per comorbidity for studies investigating prostate cancer patients

APPENDIX 7: SKIN CANCER

Author (year)	Migden, M, (2017)
Type of cancer	Basal cel carcinoma
N=	1694
Myocardial infarction	3,6%
Congestive heart failure	11,0%
Peripheral vascular disease	13,5%
Cerebrovascular disease	13,6%
Chronic pulmonary disease	15,9%
Rheumatic disease	3,2%
Peptic ulcer	1,5%
Diabetes without complications	14,9%
DM with chronic complications	7,0%
Any malignancy	18,2%
Renal disease	11,3%
Mild liver disease	2,9%
Moderate or severe liver disease	0,4%
Hemiplegia or paraplegia	0,7%
AIDS/HIV	0,1%

Table 8: Percentages per comorbidity for studies investigating skin cancer patients