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Associations between comorbidities and advanced stage diagnosis of lung, breast, colorectal, and prostate cancer: a systematic review and meta-analysis

Daniel Boakye[1]; Kathrin Günther[1]; Tobias Niedermaier[2]; Ulrike Haug[3,4]; Wolfgang Ahrens[1,5]; Rajini Nagrani[1]

[1]Department of Epidemiological Methods and Etiological Research, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany

[2]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

[3]Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany

[4]Faculty of Human and Health Sciences, University of Bremen, Bremen, Germany

[5]Institute of Statistics, Faculty of Mathematics and Computer Science, University of Bremen, Bremen, Germany

Correspondence to:

Daniel Boakye, PhD

Department of Epidemiological Methods and Etiological Research,

Leibniz Institute for Prevention Research and Epidemiology – BIPS

Achterstrasse 30

28359 Bremen, Germany

Tel: +4942121856823

Email: boakye@leibniz-bips.de

Daniel Boakye (sec-epi@leibniz-bips.de)

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Abbreviations

ACE-27	Adult comorbidity evaluation – 27
AJCC	American Joint Committee on Cancer
ASD	Advanced stage diagnosis
CCI	Charlson comorbidity index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
OR	Odds ratio
RR	Relative risk
SEER	Surveillance, Epidemiology, and End Results
UICC	Union for International Cancer Control
TNM	Tumor-Node-Metastasis

Abstract

Comorbidities and advanced stage diagnosis (ASD) are both associated with poorer cancer outcomes, but the association between comorbidities and ASD is poorly understood. We summarized epidemiological evidence on the association between comorbidities and ASD of selected cancers in a systematic review and meta-analysis. We searched PubMed and Web of Science databases up to June 3rd, 2021 for studies assessing the association between comorbidities and ASD of lung, breast, colorectal, or prostate cancer. Summary odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated using random-effects models. Also, potential variations in the associations between comorbidities and ASD by cancer type were investigated using random-effects meta-regression. Thirty-seven studies were included in this review, including 8,069,397 lung, breast, colorectal, and prostate cancer patients overall. The Charlson comorbidity index score was positively associated with ASD (stages III-IV) of breast cancer but was inversely associated with ASD of lung cancer ($p_{interaction}$=0.004). Regarding specific comorbidities, diabetes was positively associated with ASD (OR=1.17, 95%CI=1.09-1.26), whereas myocardial infarction was inversely associated with ASD (OR=0.84, 95%CI=0.75-0.95). The association between renal disease and ASD differed by cancer type ($p_{interaction}$<0.001). A positive association was found with prostate cancer (OR=2.02, 95%CI=1.58-2.59) and an inverse association with colorectal cancer (OR=0.84, 95%CI=0.70-1.00). In summary, certain comorbidities (e.g., diabetes) may be positively associated with ASD of several cancer types. It needs to be clarified whether closer monitoring for early cancer signs or screening in these patients is reasonable, considering the problem of over-diagnosis particularly relevant in patients with short remaining life expectancy such as those with comorbidities. Also, evaluation of the cost-benefit relationship of cancer screening according to the type and severity of comorbidity (rather than summary scores) may be beneficial for personalized cancer screening in populations with chronic diseases.

Keywords: comorbidity; chronic disease; advanced stage; late-stage; cancer

Background

Cancer is the second leading cause of death globally [1]. In 2018, there were about 18.1 million new cancer cases and about 9.6 million deaths were attributed to cancer [1]. Alongside improved treatment strategies, early detection has contributed to the improved cancer survival observed in many countries [2].

The incidence of advanced stage diagnosis (ASD, defined as stages III-IV), the main negative prognostic factor regarding cancer survival, of several cancers including breast [3-5] and prostate cancer [6,7] is declining in many countries. However, it is still high for some cancers such as lung and colorectal cancer [8,9]. In the US Surveillance, Epidemiology, and End Results (SEER) data (2008-2017), for example, ASD (regional and distant stages) represented about 70%, 55%, and 36% of all lung, colorectal, and breast cancer cases, respectively [10]. Besides demographic (e.g., ethnicity) and health system-related factors (e.g., insurance and access to screening services) [11-15], patient factors such as comorbidities may also affect ASD. For instance, comorbidities may mask early cancer signs, leading to delayed help-seeking for symptoms and referrals for further investigations [16,17]. Also, hyperinsulinemia and hyperglycemia in diabetic patients may promote tumor growth, leading to ASD [16,18]. By contrast, frequent healthcare visits due to comorbidities may increase the chances for opportunistic screening [19], leading to early detection [20].

It is well documented that cancer patients with comorbidities have poorer prognosis [16,21,22]. Besides directly causing non-cancer death [23] and the fact that comorbid patients utilize cancer treatments less often [16], one of the possible mechanisms by which comorbidities may affect cancer survival is through ASD. In recent decades, several epidemiological studies have investigated the associations between comorbidities and stage at diagnosis, but no study has summarized results in a systematic review or meta-analysis. Assessment of this association is important for understanding the mechanisms underlying the apparent poorer prognosis in cancer patients with comorbidities and for enhanced identification of persons at increased risk of ASD.

Our aim was to systematically review the available literature and perform a meta-analysis on the associations between comorbidities and ASD of the four most common cancer types in the world in terms of incidence (lung, female breast, colorectal, and prostate cancer).

Methods

Search strategy

We systematically searched the PubMed and Web of Science (Core Collection) databases up to June 3rd, 2021 for relevant studies. The following general search strategy was used: (comorbidity OR comorbidities OR multimorbidity OR “chronic diseases” OR “chronic conditions” OR “chronic illness” OR “mental conditions” OR “mental disorders”) AND (((cancer OR tumor OR tumour OR neoplasm OR adenoma OR carcinoma) AND (lung OR colorectal OR colon OR colonic OR rectum OR rectal OR breast OR mammary OR prostate OR prostatic)) AND ((“cancer stage” OR “stage at diagnosis” OR “early stage” OR “late stage” OR “early-stage diagnosis” OR “late-stage diagnosis” OR “advanced stage” OR “early detection” OR “late detection” OR “delayed diagnosis” OR “emergency diagnosis” OR “emergency presentation” OR “early presentation”) OR (“cancer stage at diagnosis” OR “cancer diagnosis”))). Further details of the adaptation of the search strategy for the respective databases are shown in **Table A.1**. We also conducted manual search in the reference lists of articles for additional eligible studies. This review followed the updated PRISMA guidelines [24], and its protocol was registered in PROSPERO (registration number, CRD42020194276).

Eligibility criteria

Studies were eligible for inclusion if they: (i) were published observational studies that assessed comorbidity (summary scores such as the Charlson comorbidity index [CCI] [25], Adult comorbidity evaluation-27 [ACE-27] [26], and Elixhauser method [27] or specific disease conditions that are well known to be associated with health outcomes in cancer patients, namely hypertension, schizophrenia, depression, and those in the CCI (e.g., myocardial infarction, heart failure, peripheral vascular disease, diabetes, renal disease, stroke, chronic obstructive pulmonary disease [COPD], HIV/AIDS, and dementia) and their associations with tumor stage at diagnosis in patients with primary lung, female breast, colorectal, or prostate cancer; (ii) reported risk estimates of the associations (e.g., odds ratios [ORs] or relative risks [RRs]); and (iii) adjusted for at least age. We excluded (i) studies not determining comorbidities before or up to the time of cancer diagnosis; (ii) studies assessing the association between comorbidity and diagnostic delay or un-staged tumor only; and (iii) studies not differentiating between cancer types (**Figure 1**). Also, for studies using the same study population, the less informative or less recent articles were excluded. Moreover, studies published as abstracts or posters only were excluded because their information was not sufficient for quality assessment.

Definition of ASD

We defined ASD as the American Joint Committee on Cancer (AJCC) or Union for International Cancer Control (UICC) TNM (Tumor-Node-Metastasis) stages III-IV, Dukes' stages C-D, or the US SEER regional and distant stages. Correspondingly, early stage was defined as AJCC/UICC stages I-II, Dukes' stages A-B, or the US SEER localized stage. We classified Dukes' stages A, B, C, and D as AJCC/UICC stages I, II, III, and IV, respectively, because the Dukes' stage corresponds with the AJCC/UICC stages. Also, the US SEER localized, regional, and distant stages were classified as AJCC/UICC stages I-II, III, and IV, respectively.

Data extraction and quality assessment

Pre-designed data extraction forms were used by two of the authors (DB and RN) to abstract data from the eligible studies independently. One of the forms summarized the characteristics of the studies, as shown in **Table 1**. The second form summarized the results of each of the studies as well as factors that were adjusted for, as reported in **Tables A.2-A.5**. In case of differential adjustment levels, the most comprehensively adjusted risk estimates were abstracted. We used the Newcastle-Ottawa Scale for cohort studies [28] and the Joanna Briggs Institute Appraisal Tool for cross-sectional studies [29] to assess the quality and risk of bias of the included studies. In brief, the eligible studies were assessed against the following broad domains: (i) representativeness of the study sample, (ii) valid assessment of comorbidities, (iii) reliable assessment of tumor stage, and (iv) adjustment for history of screening in the multivariable analysis. Further details of the quality assessment and corresponding scores are illustrated in **Tables A.6-A.7**. The highest achievable scores were 9 for the cohort studies and 8 for the cross-sectional studies: low scores indicate low quality and high risk of bias. In case of disagreement in the quality assessment between the two authors, consensus was achieved through additional review and comprehensive discussion.

Statistical analysis

Studies that used the same comorbidity score (e.g., the CCI [25]) or assessed the same comorbid conditions were selected for meta-analysis provided their reference categories and ASD definitions allowed for combination of risk estimates. RRs and ORs were treated as equivalent estimates in our data synthesis. For the meta-analysis, we log-transformed the extracted risk estimates and calculated their standard errors indirectly [30]. We then applied the random-effects model [31] to calculate summary ORs and 95% confidence intervals (95%CIs). If a study reported estimates for stratified groups only (e.g., according to severity of comorbid condition), they were first pooled using a fixed-effect model before including them in the main analysis.

We analyzed the associations of the CCI score and specific comorbidities with ASD. Also, we assessed potential variations of the associations between comorbidity and ASD according to cancer type using random-effects meta-regression. In case of statistically significant interactions between comorbidity and cancer type in the association with ASD, subgroup analysis according to cancer type was also performed, as appropriate. Heterogeneity between studies was assessed using the I^2 statistic, where I^2 >50% indicated substantial heterogeneity [32]. Finally, we used the Egger's test to assess potential publication bias aside from visual inspection with the funnel plot [33].

All analyses were conducted with the "meta" package (version 4.12-0) in R (version 4.0.1, R Development Core Team). Statistical tests were two-sided, with a significance level of 5%.

Results

Literature search and characteristics of the included studies

Our electronic search identified 2,861 articles – 1,559 from PubMed and 1,302 from Web of Science (**Figure 1**). After removal of duplicates and full-text review, 37 studies were eligible for inclusion in this review. Of these, 23 studies that used similar ASD definitions, the same comorbidity score and similar reference groups or that investigated the same comorbid conditions were included in the meta-analysis. Of the studies included in this review, the majority were from the US (24/37, **Table 1**). Almost all the included studies were cohort or nested case-control studies (32/37), and the vast majority used data from population-based cancer registries linked to hospital data (33/37). Most of the studies referred to participants diagnosed before 2010 (27/37). Over half of the studies included patients of all ages (21/37), whereas 13 studies included patients aged 65+ years. Half of the studies examined breast cancer only (18/37), 5 examined lung cancer only, four assessed prostate cancer only, one assessed colorectal cancer only, and 9 assessed more than one cancer type. The sample size of the studies ranged from 69 to 1,451,151 patients, with a total of 8,069,397 lung, breast, colorectal, and prostate cancer patients overall. Less than half of the studies (14/37) adjusted for history of cancer screening. The median quality assessment score of the cohort and nested case-control studies was 5/9 (interquartile range, 4-6) and that of the cross-sectional studies was 5/8 (interquartile range, 5-6).

Assessment of comorbidities

The time window for determination of comorbidities was three years prior to cancer diagnosis in about half of the studies (18/37, **Table 1**). Of studies providing specific data on time of determination of comorbidities (24/37), the median time window was 12 (interquartile range, 12-24) months. Most of the studies used information on clinically diagnosed comorbidities (34/37, **Tables A.6-A.7**), and the majority of these studies obtained information on comorbidities from administrative or health claims data (29/34). About half of

the studies investigated comorbidity scores only (18/37; CCI=11, count=4, Elixhauser method=1, and summary [yes/no]=2), 13 studies investigated specific comorbidities only, and 5 studies examined both comorbidity scores and specific comorbidities (**Table 1**).

Assessment of tumor stage

Almost all the studies used summary stage (35/37, **Table 1**), but two studies assessed specific tumor features (e.g., T3/T4 stage) [34,35]. Of the studies using summary stage, the majority analyzed patients with stages I-IV (23/35), whereas 12 studies additionally included stage 0 (in-situ) tumors. ASD was defined as TNM stages III-IV in the majority of the studies (23/35), but three studies defined it as stage IV only [36-38]. Nine studies used various definitions such as stages IIB-IV [13,39,40], IIIB-IV [41], or multiple definitions [42-46].

Meta-analysis

Overall comorbidity quantified by the CCI and ASD

Figure A.1 shows results of our meta-analysis of the association between the CCI score and ASD (1+ vs. 0, 8 studies), overall and by cancer type [13,34,41,47-51]. In the analysis of all cancers combined, we found no association between CCI score and ASD, but meta-regression analysis showed significant interaction between CCI score and cancer type ($p_{interaction}$=0.004). In a subgroup analysis according to cancer type, a positive, non-significant association was observed with ASD of breast cancer (OR=1.19, 95%CI=0.96-1.48; I^2=89%, $p_{heterogeneity}$<0.01) and an inverse association with ASD of lung cancer (OR=0.82, 95%CI=0.76-0.88, I^2=74%, $p_{heterogeneity}$<0.01). There was a high degree of between-study heterogeneity in the associations, but the funnel plot showed no indication of publication bias (Egger's test, p=0.163; **Figure A.2A**).

Cardiovascular diseases and ASD

Our meta-analysis of the associations between various cardiovascular diseases (hypertension=5 studies [42,52-55], myocardial infarction=3 studies [42,48,54], peripheral vascular disease=3 studies [42,48,54], heart failure=3 studies [42,48,53], and stroke=2 studies [42,48]) and ASD of the various cancer types is illustrated in **Figure 2**. Myocardial infarction was associated with 16% lower odds of ASD (OR=0.84, 95%CI=0.75-0.95), with no evidence of between-study heterogeneity (I^2=0%, $p_{heterogeneity}$=0.54). Hypertension was also inversely associated with ASD, but the association was not statistically significant (OR=0.90, 95%CI=0.79-1.03). By contrast, patients with heart failure (OR=1.38, 95%CI=0.94-2.02), stroke (OR=1.22, 95%CI=0.74-2.01), and peripheral vascular disease (OR=1.10, 95%CI=0.90-1.35) tended to have higher odds of ASD, but the associations were not statistically significant.

Diabetes and renal disease and ASD

Our meta-analysis of the association between diabetes and ASD (9 studies) [42,43,48,53,56-59] is shown in **Figures 3**. Diabetes was associated with 17% higher odds of ASD (OR=1.17, 95%CI=1.09-1.26; I^2=70%, $p_{heterogeneity}$<0.01), with no indication of publication bias in the association (Egger's test, p=0.112; **Figure A.2B**). Our meta-analysis of the association between renal disease and ASD (4 studies) [42,48,54,60] with ASD, overall and by cancer type, is shown in **Figure 4**. In all cancers combined, patients with renal disease showed higher odds of ASD, but the association was not statistically significant (OR=1.18, 95%CI=0.91-1.53; I^2=84%, $p_{heterogeneity}$<0.01). Meta-regression analysis showed significant interaction between renal disease and cancer type in the association with ASD ($p_{interaction}$<0.001). Subgroup analysis by cancer type showed a 2-fold increased risk of ASD of prostate cancer (OR=2.02, 95%CI=1.58-2.59; I^2=0%, $p_{heterogeneity}$=0.77) but 16% lower odds of ASD of colorectal cancer (OR=0.84, 95%CI=0.70-1.00; I^2=0%, $p_{heterogeneity}$=0.34).

COPD, HIV/AIDS, liver disease, and dementia and ASD

Figure 5 summarizes results of our meta-analysis of the associations of COPD (4 studies) [42,44,48,55], HIV (5 studies) [45,46,52,55,61], liver disease (2 studies) [42,48], and dementia (2 studies) [42,53] with ASD of the various cancer types. In the analysis of all cancers combined, no association was found for COPD (OR=0.92, 95%CI=0.76-1.11; I^2=81%, $p_{heterogeneity}$<0.01) or for HIV (OR=1.10, 95%CI=0.986-1.23; I^2=67%, $p_{heterogeneity}$<0.0.01). By contrast, patients having liver disease (OR=2.04, 95%CI=1.50-2.79; I^2=0%, $p_{heterogeneity}$=0.51) and dementia (OR=2.24, 95%CI=1.47-3.41; I^2=0%, $p_{heterogeneity}$=0.46) tended to have higher odds of ASD of the various cancer types.

Narrative synthesis of results not included in the meta-analysis

Fourteen studies could not be included in the meta-analysis because of the use of different comorbidity scores and groupings or different ASD definitions (**Table 1**) [20,35-40,62-68]. Of these, 11 assessed comorbidity scores (CCI=4 [20,38,64,68], Elixhauser method=1 [37], count=2 [36,66], and other methods=4 [39,40,62,67]) and three assessed specific comorbidities [35,63,65]. Of the studies using comorbidity scores, comorbidity was inversely associated with ASD in four studies (**Tables A.3-Table A.5**) [36,37,64,66,68]. In one of these studies [64], the association was stronger among patients aged 65+ (vs <65) years. By contrast, positive association between comorbidity, including severe mental illness, and ASD was reported by three studies [38,39,67]. One study, however, found no association between comorbidity and ASD [62].

In another study [20], the association between the CCI score (2+ vs 0-1) and ASD differed by cancer type – a positive association was reported for prostate cancer, whereas an inverse and no association were reported for colorectal and breast cancer, respectively. Results of one study on breast cancer patients suggested that the association between comorbidity and ASD potentially differs by the type of comorbidities included in the summary score [40]. For example, scores derived from non-life threatening comorbidities (e.g., arthritis, peptic ulcer) were inversely associated with ASD, whereas those derived from life-threatening conditions

(e.g., renal disease, liver disease, and heart failure) were positively associated with ASD. Of the studies assessing specific psychiatric comorbidities [63,65], schizophrenia and phobia were inversely associated with ASD, whereas major depression was positively associated with about 10-fold increased odds of ASD of breast cancer [65].

Discussion

We summarized and quantified epidemiological evidence on the associations between comorbidities and ASD of lung, breast, colorectal, and prostate cancer in a systematic review and meta-analysis. Results suggested that the association between comorbidity and ASD differs by type of cancer and by comorbidity. The CCI score was positively associated with ASD of breast cancer but was inversely associated with ASD of lung cancer. Regarding specific comorbidities, diabetes was associated with a higher risk of ASD of all cancer types combined, whereas myocardial infarction was inversely associated with ASD of all cancer types combined. The association between renal disease and ASD differed by cancer type – a positive association was found with prostate cancer and an inverse association with colorectal cancer.

There are several possible mechanisms underlying the observed differential associations by type of cancer and comorbidity. For example, severe comorbidities such as chronic liver disease and heart failure may mask early cancer signs, leading to delayed help-seeking for symptoms by patients as well as delayed referrals for further investigations by clinicians [16,17]. Severe comorbidities may thus be related to ASD via the “competing demand hypothesis” [58], whereby the attention of physicians and healthcare resources are inadvertently diverted from cancer diagnosis to management of comorbidities. Also, illicit drug use [69] and heavy alcohol use [70,71], which are risk factors for liver diseases, are associated with reduced health awareness and lower utilization of preventive health services, which may lead to ASD. By contrast, frequent healthcare visits by persons with comorbidities may increase their chances of being additionally offered cancer screening [19,72], leading to early detection and supporting the “surveillance hypothesis” [20].

For instance, patients with COPD are likely to be screened for lung cancer during their routine follow-up care. Also, patients with chronic renal failure usually undergo lower gastrointestinal endoscopy because of their increased risk of gastrointestinal bleeding [73,74] leading to early detection of colorectal cancer, as observed in our meta-analysis. Even though hypertension and myocardial infarction were also inversely associated with ASD, the association with hypertension was not statistically significant. A possible explanation is that the surveillance effect explaining the inverse association between hypertension and ASD might have been partly concealed in the results of our meta-analysis because many of the included studies had already adjusted for frequency of healthcare visit and screening.

For some cancers such as breast and colorectal cancer, screening programs have been implemented in many countries because of their established benefits of reducing disease-specific mortality. Cancer and comorbidities share common risk factors (e.g., older age and unhealthy lifestyle) and the burden of cancer may be higher in comorbid patients than the general population [75]. Yet, patients with comorbidities utilize cancer screening less often [13,40,72]. Also, among persons with abnormal screening results (e.g., those with positive fecal blood test), evidence suggests that patients with comorbidities are less likely to adhere to follow-up diagnostic procedures (e.g., colonoscopy) [76,77]. This may partly explain the higher risk of ASD observed in patients with comorbidities. However, in two studies reporting results stratified by screening [43,56], the magnitude of the association between diabetes and ASD of breast cancer was comparable in patients with and without prior mammography screening. Also, in three studies [38,40,58], the risk estimates from models with and without adjustment for screening were comparable. These suggest that lower utilization of screening may not fully explain the observed higher risk of ASD in patients with comorbidities.

The apparent lower utilization of screening in persons with (vs. without) comorbidities may be due to the less clear benefits of screening in this population [78]. This is because of the short life expectancy, high risk of death from causes other than cancer, and over-diagnosis of cancer (especially breast cancer) in this population [78,79]. Consequently, in many

countries such as the US, screening is usually not recommended beyond the age of 75 years [80], when comorbidities are common. However, evidence on the cost-benefit relationship of cancer screening according to comorbidity is sparse. The few available studies [81-83] evaluating this relationship based on microsimulation modeling (such as the MISCAN model) suggested that the benefits of screening in patients with comorbidities largely depend on screening history and outcomes and are generally lower than in non-comorbid patients. For example, regardless of screening history and outcome, the benefit of screening was estimated to be lower in persons with than those without comorbidities [81,83]. Nevertheless, for populations without a history of screening, those with severe comorbidities appeared to benefit from screening even at older ages (up to between 80 and 86 years) [81,83].

The modeling studies, however, have several limitations. For example, some of the studies investigated populations with no prior cancer screening only [83] or did not take into account complications of screening [84]. Also, they did not consider relevant psychiatric comorbidities (e.g., schizophrenia) [81-85] that may also impact cancer outcomes. Moreover, they did not consider the type and severity of comorbidity but rather used summary comorbidity scores (e.g., the CCI) that include a broad range of heterogeneous comorbidities. It is thus unclear which comorbid patients benefit from screening. Given the differential association between comorbidity and ASD according to type of comorbidity, with some conditions (e.g., myocardial infarction) being inversely associated with ASD, the use of summary scores alongside the afore-mentioned limitations may have resulted in less accurate estimates of the benefits of screening in the modeling studies. Evaluation of the cost-benefit relationship of screening according to the type and severity of comorbidity may thus be useful for determining which comorbid patients benefit from this intervention. Also, such information may be valuable for refining the stop ages for screening [86], besides the commonly studied factors (e.g., history and outcomes of cancer screening and family history of cancer).

It is possible that comorbidities also affect ASD partly through alteration in physiological processes. For example, besides tumor initiation, hyperglycemia and hyperinsulinemia have also been found to promote tumor growth [16,18], supporting the observed higher risk of ASD in patients with diabetes, even though these characteristics and some chronic diseases might also be signs of an advanced cancer. Whether comorbidities or their treatments affect tumor biology is a research gap. Dedicated studies addressing these important questions could provide further information to elucidate the biological mechanisms linking comorbidities to ASD and to poorer cancer outcomes. Our meta-analysis of two studies demonstrated a 2-fold higher risk of ASD among patients with (vs. without) dementia. A possible explanation may be the limited capacity of those with severe mental illnesses to make health-related decisions [87]. However, given the limited number of studies assessing the relationship between mental illnesses and ASD [42,53,63,65,67], future studies should address this important research gap in order to determine the mechanisms underlying the apparent worse cancer survival in patients with mental illness [88].

The findings of our review also have implications for patient education and referral. For patients whose disease conditions may obscure early cancer signs (e.g., those with diabetes and severe liver disease), it may be important for health professionals to intensify health education and to also enhance referral systems for further examination (e.g., cancer screening). This is particularly relevant, as evidence suggests that utilization of cancer screening [13,40,72] and adherence to recommendations for further cancer investigations [76,77] are lower in populations with (vs. without) comorbidities. However, implementation of this recommendation may be difficult because of logistic reasons, especially in settings where such disease conditions are highly prevalent and in low-income settings where there is limited access to health care resources. Future studies should therefore determine the best approach for optimizing patient education and referral for cancer screening in these patient populations.

Some narrative reviews have partly discussed the association between comorbidity and ASD of cancer [17,89]. However, these studies focused on summary scores [89] and did not distinguish between cancer types [17] or quantify the association in a meta-analysis [17,89]. Also, the inherent bias in narrative reviews (e.g., selection bias due to less explicit eligibility criteria and minimal appraisal of quality and risk of bias of studies) [90] make it difficult to assess the validity of findings from such studies. Moreover, in the narrative reviews, all studies assessing comorbidity and tumor stage were included, irrespective of when comorbidities were determined. Reverse causation (e.g., comorbidities due to cancer or its treatment) may have thus impacted findings from those reviews. Our systematic review and meta-analysis overcame these major limitations. Also, the quality of the included studies was moderate, as evidenced by a median score of 5 out of 9.

Our review has some potential limitations. First, despite our comprehensive literature search in multiple databases, there is still a possibility of having missed other relevant studies such as those on specific comorbidities, as it was not feasible to include the names of specific comorbidities in our search strategy. Second, a third of the studies were from the US (24/37) and the vast majority of them used data from the SEER. There was thus limited evidence from countries other than the US. Also, there were limited numbers of studies assessing the association between comorbidities and ASD in cancers other than breast cancer. Further studies from countries other than the US and on cancer types other than breast cancer are required for a more comprehensive conclusion on the associations between comorbidities and ASD. Third, like all systematic reviews, our results might be affected by selective reporting arising from unpublished eligible studies with non-significant results. However, the funnel plots suggested no publication bias. Second, we were not able to include all the eligible studies in the meta-analysis because of the use of different comorbidity scores and/or groupings. Fourth, there was a moderate degree of heterogeneity in some of the associations, possibly due to variations in the definitions of ASD and/or duration of comorbidities. For example, some of the studies defined ASD as stages IIB-IV [13,44] or IIIB-IV [41], whereas the majority defined it as III-IV.

Also, it is less clear whether the association between comorbidity and ASD also differs by duration of comorbidity. In two of the included studies [43,56], the association between diabetes and ASD of breast cancer appeared to be stronger among patients with a longer history of diabetes, but we were not able to conduct a subgroup analysis according to this factor due to the limited number of studies. Future studies should assess the extent to which the duration of comorbidities is associated with ASD.

Conclusions

Due to the aging population, the prevalence of morbidity and multimorbidity is increasing globally. Findings from this meta-analysis suggest that the associations between comorbidities and ASD differ by type of cancer and comorbidity. Certain comorbidities (e.g., diabetes) were found to be associated with a higher risk of ASD in several cancer types. It needs to be clarified whether closer monitoring for early cancer signs or screening in these patients is reasonable, considering the problem of over-diagnosis particularly relevant in patients with short remaining life expectancy such as those with comorbidities. Also, evaluation of the cost-benefit relationship of cancer screening according to the type and severity of comorbidity (rather than summary scores) may be beneficial for personalized cancer screening.

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Availability of data and code: The data extracted from the individual studies are available in the supplementary Tables 2-5. The analytic code used for the meta-analysis is available from the corresponding author upon request.

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Table 1: Characteristics of the included studies on comorbidities and tumor stage at diagnosis

Author	Year	Country	Design	Sample characteristics				Comorbidity assessment		Advanced stage		Quality score [j]				
				Source (registry)	*Period*	*Size*	*Age (years)*	*Time when comorbidity was determined*	*Comorbidity score/type*	*Definition*	*Prop (%)*	*RE*	*EX*	*O*	*AD*	*Total*
Lung cancer only																
Dalton [41] [k]	2011	Denmark	Cohort	Yes	2001-2008	18,103	30+	Up to 1 yr. to diagnosis	CCI	IIIB-IV	60.0	2	3	1	0	*6*
Berglund [47] [k]	2012	UK	Cohort	Yes	2006-2008	11,328	All	Within 3 yrs. to diagnosis	CCI	III-IV	83.1	2	1	1	0	*4*
Bergamo [63]	2014	USA	Cohort	Yes	1992-2007	95,591	66+	Before diagnosis	Schizophrenia	III-IV	68.1	1	2	2	0	*5*
Lin [48] [k]	2020	USA	Cohort	Yes	1998-2007	4,768	All	Within 3 yrs. to diagnosis	CCI & type	III-IV	56.6	2	2	1	2	*7*
Sanchez [44] [k]	2020	USA	Cohort	Yes	2011-2015	30,198	18+	Within 1 yr. to diagnosis	CCI & COPD	SCLC: II-IV NSCLC: IV	94.6 38.9	1	2	1	0	*4*
Breast cancer only																
Desai [65]	1999	USA	Cohort	Yes	1980-1981	69	38-95	Before diagnosis	Specific type	III-IV	34.8	1	2	1	0	*4*
Vaeth [66]	2000	USA	Cohort	Yes	Multiple [a]	731	40-85	Before diagnosis	Count [f]	III-IV	46.1	2	2	2	0	*6*
Arndt [62]	2001	Germany	Cohort	No	1996-1998	380	18-80	1 yr. before symptoms	Summary	III-IV	47.9	2	1	2	1	*6*
Bradley [64]	2003	USA	Cohort	Yes	1996-1997	816	25+	Up to 1 mo. to diagnosis	CCI	III-IV [g]	47.0	2	1	0	0	*3*
Fleming [58] [k]	2005	USA	Cohort	Yes	1993-1995	17,468	67+	Within 2 yrs. to diagnosis	Specific type	III-IV	28.1	1	2	1	1	*5*
Dalton [34] [k]	2006	Denmark	Cohort	Yes	1983-1999	28,765	<70	Up to 6 mo. to diagnosis	CCI	High-risk [h]	79.8	1	2	1	1	*5*
Badgwell [13] [k]	2008	USA	Cohort	Yes	1996-2002	13,262	80+	Within 1 yr. to diagnosis	CCI	IIB-IV	NR	1	2	2	1	*6*
Yasmeen [40]	2011	USA	Cohort	Yes	1993-2005	107,536	67+	Within 2 yrs. to diagnosis	Count	IIB-IV	13.0	1	2	1	1	*5*
Yasmeen [39]	2012	USA	Cohort	Yes	2000-2006	3,316	67+	Up to 1 mo. to diagnosis	Count	IIB-IV	14.0	1	2	2	1	*6*
Camacho [53] [k]	2015	USA	Cohort	Yes	2007-2008	3,589	27+	Within 2 yrs. to diagnosis	ACE-27 & type	III-IV	15.7	2	2	1	0	*5*
Koroukian [37]	2015	USA	Cohort	Yes	1996-2005	2,177	<65	Before diagnosis	Elixhauser	IV	NR	1	2	1	0	*4*
Lipscombe [43] [k]	2015	Canada	Cohort	Yes	2007-2012	38,407	20+	Before diagnosis	Diabetes	Multiple	NR	2	2	2	1	*7*
Joffe [61] [k]	2018	S. Africa	CS	No	2015-2016	499	18+	Not reported	HIV	III-IV	51.0	1	3	2	0	*6*
Murto [56] [k]	2018	Finland	Cohort	Yes	1995-2013	66,804	All	Before diagnosis	Diabetes	III-IV	41.3	2	3	1	1	*7*
Calip [57] [k]	2019	USA	Cohort	Yes	1999-2014	2,040	52-74	Within 2 yrs. to diagnosis	Diabetes	III	6.7	1	3	2	0	*6*
Overbeek [59][k]	2019	NL	NCC	Yes	2002-2014	7,776	All	Within 4yrs. to diagnosis	Diabetes	III-IV	7.5	2	2	2	0	*6*
Ayeni [52] [k]	2020	S. Africa	CS	No	2016-2018	2,274	18+	At diagnosis	HIV	III-IV	56.1	2	1	1	0	*4*
Ayeni [55] [k]	2021	SSA	CS	No	2014	2,066	18+	At diagnosis	Specific type	III-IV	58.7	2	1	2	0	*5*
Colorectal cancer only																
Arhi [68] [k]	2021	UK	Cohort	Yes	2000-2010	234,009	18+	Within 3 yrs. to diagnosis	CCI	III-IV	52.2	2	2	1	0	*5*
Prostate cancer only																
Fleming [54] [k]	2006	USA	Cohort	Yes	1993-1995	5,076	67+	Within 2 yrs. to diagnosis	Count & type	III-IV	21.5	1	2	0	1	*4*
Carpenter [51] [k]	2010	USA	Cohort	Yes	1994-2002	18,067	65+	Up to 1 yr. to diagnosis	CCI	III-IV	24.0	1	3	2	1	*7*
Raval [35]	2016	USA	Cohort	Yes	2002-2009	103,820	66+	Within 1 yr. to diagnosis	Specific type	T3-T4	5.4	1	2	2	1	*6*
Jaysekera [38]	2019	USA	Cohort	Yes	2004-2007	37,760	70+	Within 1 yr. to diagnosis	CCI	IV	6.1	1	3	2	1	*7*

Table 1 continues on next page

Table 1 (continued): Characteristics of the included studies on comorbidities and tumor stage at diagnosis

Author	Year	Country	Design	Sample characteristics				Comorbidity assessment		Advanced stage		*Quality score*				
				Source (registry)	*Period*	*Size*	*Age (years)*	*Time when comorbidity was determined*	*Comorbidity score/type*	*Definition*	*Prop (%)*	*RE*	*EX*	*O*	*AD*	*Total*
Multiple cancer types																
Gornick [20]	2004	USA	Cohort	Yes	1995	5,242 [c] 5,165 [d] 7,286 [e]	67+	Within 2 yrs. to diagnosis	CCI	BC: III-IV CRC: III-IV PC: IV	25.2 50.7 6.5	1	2	0	1	*4*
Bradley [50] [k]	2007	USA	Cohort	Yes	1997-2000	8,770 [c] 12,318 [e]	66+	Within 1 yr. to diagnosis	CCI	BC: III-IV PC: III-IV	NR	1	2	0	0	*3*
Taneja [60] [k]	2007	USA	Cohort	Yes	1992-1999	404 [b] 259 [c] 325 [d] 261 [e]	All	Within 1 yr. to diagnosis	ESRD	LC: III-IV BC: III-IV CRC: III-IV PC: IV	NR	2	2	1	0	*5*
Koroukian [36]	2011	USA	Cohort	Yes	1997-2001	14,254 [c] 14,954 [d] 14,483 [e]	65+	Within 1 yr. to diagnosis	Count (CCI)	BC: IV CRC: IV PC: IV	NR	1	2	0	0	*3*
Sikka [49] [k]	2012	USA	Cohort	Yes	1996-2000	11,281 [b] 9,030 [d]	66+	Within 1 yr. to diagnosis	CCI	LC: III-IV CRC: III-IV	79.8 61.5	1	2	0	0	*3*
Gurney [42] [k]	2015	NZ	Cohort	Yes	2006-2008	4,540 [c] 4,525 [d]	25+	Within 5 yrs. to diagnosis	C3 index & type	BC: III/IV CRC: III/IV	42.5 69.1	2	2	1	0	*5*
Shiels [45] [k]	2015	USA	CS	Yes	1996-2010	638,755 [b] 710,006 [c] 513,849 [d] 727,381 [e]	All	At diagnosis	HIV	Multiple	NR	2	2	2	0	*6*
Coghill [46] [k]	2019	USA	CS	Yes	2004-2014	1,134,507[b] 1,451,151[c] 786,035[d] 1,137,810[e]	18+	At diagnosis	HIV	Multiple	NR	2	2	1	0	*5*
Cespedes [67]	2020	Spain	NCC	Yes	2010-2016	75 [c] 36 [d]	30+	Before diagnosis	Summary	BC: III-IV CRC: III-IV	NR	2	2	1	0	*5*

Abbreviations: *ACE-27*=Adult comorbidity evaluation-27; *BC*=Breast cancer; *CCI*=Charlson comorbidity index; *COPD*=Chronic obstructive pulmonary disease; *CRC*=Colorectal cancer; *CS*=Cross-sectional study; *C3 index*=Cancer-specific measure of comorbidity; *ESRD*=End-stage renal disease; *LC*=Lung cancer; *Mo*=Months; *NCC*=Nested case-control study; *NL*=The Netherlands; *NR*=Not reported; *NSCLC*=Non-small cell lung cancer; *NZ*=New Zealand; *PC*=Prostate cancer; *Prop*=Proportion of patients with advanced stage tumors; *S. Africa*=South Africa; *SCLC*=Small cell lung cancer; *SSA*=Sub-Saharan African countries (South Africa, Namibia, Nigeria, Zambia, and Uganda); *UK*=United Kingdom; *USA*=United States of America; *Yrs*=Years.

[a] 1984-1985 and 1987-1988.

Number of lung,[b] breast,[c] colorectal, [d] and prostate cancer cases [e]

[f] Comorbidities that predicted functional limitations only.

[g] Un-staged patients were classified as late stage.

[h] High-risk was defined as the presence of at least one of the following features: >20mm tumor size, lymph node positive, histology grade >1, or negative hormone receptor.

[j] Quality assessment of the cohort studies was conducted using the Newcastle-Ottawa scale and that of cross-sectional studies was conducted using the Joanna Briggs Institute Appraisal Tool (RE=Representativeness of sample; EX=Exposure [comorbidity] assessment; O=Outcome [tumor stage] assessment; AD=Adjustment for at least age and history of cancer screening) – higher scores indicate high quality and low risk of bias.

[k] Studies included in the meta-analysis.

Figure 1: Flow diagram showing selection of eligible studies

Note: 14 studies used different advanced stage definition, different comorbidity scores, groupings, and reference groups, or assessed different specific conditions and hence could not be included in the meta- analysis.

Figure 2: Meta-analysis of the associations between cardiovascular diseases and advanced stage diagnosis (III-IV)

Abbreviations: *CI*=Confidence interval; *OR*=Odds ratio; *SSA*=Sub-Saharan African countries (South Africa, Namibia, Nigeria, Zambia, and Uganda); *USA*=United States of America.

The size of data markers indicates the weight of each study in the analysis.

Note: ORs and 95%CIs were calculated indirectly and might differ slightly from the original values (OR < 1.00 indicates lower likelihood of advanced stage diagnosis).

Figure 3: Meta-analysis of the association between diabetes and advanced stage diagnosis (III-IV)

Abbreviations: *CI*=Confidence interval; *OR*=Odds ratio; *SSA*=Sub-Saharan African countries (South Africa, Namibia, Nigeria, Zambia, and Uganda); *USA*=United States of America.

The size of data markers indicates the weight of each study in the analysis.

Note: ORs and 95%CIs were calculated indirectly and might differ slightly from the original values (OR < 1.00 indicates lower likelihood of advanced stage diagnosis).

The study by Lipscombe et al [43] used slightly different definition for advanced stage (stages II-IV).

The study by Lin et al [48] was on lung cancer and that of Gurney et al [42] was on prostate cancer.

Figure 4: Meta-analysis of association between renal disease and advanced stage diagnosis (III-IV), overall and by cancer type

Abbreviations: *CI*=Confidence interval; *OR*=Odds ratio; *USA*=United States of America.

The size of data markers indicates the weight of each study in the analysis.

Note: ORs and 95%CIs were calculated indirectly and might differ slightly from the original values (OR < 1.00 indicates lower likelihood of advanced stage diagnosis).

Meta-regression analysis showed significant interaction between renal disease and cancer type ($p_{interaction}$<0.001).

Figure 5: Meta-analysis of associations of COPD, HIV, liver disease, and dementia with advanced stage diagnosis (III-IV)

Abbreviations: *CI*=Confidence interval; *COPD*=Chronic obstructive pulmonary disease; *OR*=Odds ratio; *S. Africa*=South Africa; *SSA*=Sub-Saharan African countries (South Africa, Namibia, Nigeria, Zambia, and Uganda); *USA*=United States of America.

The size of data markers indicates the weight of each study in the analysis.

Note: ORs and 95%CIs were calculated indirectly and might differ slightly from the original values (OR < 1.00 indicates lower likelihood of advanced stage diagnosis).

Meta-regression analysis showed significant interaction between COPD and cancer type ($p_{interaction}$<0.001).