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Patterns of age disparities in colon and lung cancer survival: a systematic narrative literature review

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ABSTRACT

Objectives To identify patterns of age disparities in cancer survival, using colon and lung cancer as exemplars.
Design Systematic review of the literature.
Data sources We searched Embase, MEDLINE, Scopus and Web of Science through 18 December 2020.
Eligibility criteria We retained all original articles published in English including patients with colon or lung cancer. Eligible studies were required to be population-based, report survival across several age groups (of which at least one was over the age of 65) and at least one other characteristic (eg, sex, treatment).
Data extraction and synthesis Two independent reviewers extracted data and assessed the quality of included studies against selected evaluation domains from the QUIPS tool, and items concerning statistical reporting. We evaluated age disparities using the absolute difference in survival or mortality rates between the middle-aged group and the oldest age group, or by describing survival curves.
Results Out of 3047 references, we retained 59 studies (20 for colon, 34 for lung and 5 for both sites). Regardless of the cancer site, the included studies were highly heterogeneous and often of poor quality. The magnitude of age disparities in survival varied greatly by sex, ethnicity, socioeconomic status, stage at diagnosis, cancer site, and morphology, the number of nodes examined and treatment strategy. Although results were inconsistent for most characteristics, we consistently observed greater age disparities for women with lung cancer compared with men. Also, age disparities increased with more advanced stages for colon cancer and decreased with more advanced stages for lung cancer.
Conclusions Although age is one of the most important prognostic factors in cancer survival, age disparities in colon and lung cancer survival have so far been understudied in population-based research. Further studies are needed to better understand age disparities in colon and lung cancer survival.
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Strengths and limitations of this study

- ► For the first time, we conducted a systematic review of population-based studies relating to differences in cancer survival between middle-aged and older patients, using colon and lung cancer as exemplar cancers.
- ► We limited our search to peer-reviewed original articles and letters to Editors published in English up until 18 December 2020.
- ► We excluded clinical studies and trials due to the strict selection of patients and the common under-representation of older patients in these studies.
- ► We could not conduct any quantitative analysis (such as meta-analysis) because of the vast heterogeneity of the studies included, which prevented us from quantifying the relationship between increasing age and cancer survival.

INTRODUCTION

Poorer cancer survival among older patients has been well documented.[1–6] Although patients with cancer are increasingly surviving their disease thanks to advances in treatment,[2–6] those who are older have not benefitted from these advances to the same degree as their middle-aged counterparts, widening the age-related cancer survival gap.[2 5 7]

From a clinical point of view, cancer management in older patients may be different to that of middle-aged patients due to higher comorbidity levels, polypharmacy, age-related physiological changes and reduced life expectancy.[8] In addition, older adults with cancer are often excluded from randomised clinical trials, limiting the evidence they provide in relation to the benefits and risks of different treatment strategies at older ages.[9 10] Cancer management may also be hindered in older patients with cancer by social factors such as reduced social support[11 12] or healthcare system-related factors such as access to care facilities.

A recent systematic review found that advanced age, low income, low socioeconomic status, presence of comorbidities, advanced stage and poor tumour grade were associated with lower survival among older adults with cancer, while female gender and being married were associated with increased survival.[13] However, the authors did not explore inequalities in cancer survival between age groups, and they excluded studies that included middle-aged patients. They also did not focus on any particular cancer sites. This is important, as it is likely that many factors influence age disparities in cancer survival, and they may vary depending on cancer site.

Worldwide, colon and lung cancers are the most common cancer types diagnosed among adults aged 65 years and older.[14] These two cancer sites have different biology, risk factors and survival outcomes, with colon cancer having a higher 5-year relative survival than lung cancer, ranging from 59% to 71% for colon cancer and 15% to 22% for lung cancer in high-income countries.[7] These cancers also have a different pattern of age inequalities in survival over time. In colon cancer, disparities in cancer survival between older and younger adults is mainly observed in the first year following diagnosis, while in lung cancer, the excess mortality in older adults is mainly observed after 5 years of follow-up.[5 15]

To our knowledge, there has been no attempt to summarise the available literature on age disparities in cancer survival. Thus, in this manuscript we conducted a systematic review of studies that have investigated differences in cancer survival between middle-aged and older patients, using the diverse contexts of colon and lung cancer as exemplars. We aimed to identify (1) patterns of age-related disparities based on patient and clinical characteristics and (2) the potential gaps in knowledge to inform future research.

METHODS AND MATERIALS

We conducted a systematic literature search of Embase, MEDLINE, Scopus and Web of Science. Using a Boolean approach, we searched for articles including the following keywords: cancer, colon, lung, survival and older patients. Online supplemental table 1 shows the search terms that were used. The search strategy was first set up in Embase (online supplemental table 2), and then adapted for the other databases.

We retained all original articles or letters published in English up until 18 December 2020 that included patients diagnosed with colon or lung cancer. Eligible studies were required to report survival across several age groups (of which at least one was over the age of 65) and investigate the impact of increasing age on survival stratified by at least one other characteristic (eg, sex, treatment). We included population-based studies only. We excluded clinical studies and trials due to their strict inclusion criteria and the under-representation of older adults.[9] The PICO criteria for our review are shown in online supplemental table 3.

Study selection

We selected eligible articles using a three-step process: (1) after removal of duplicate records, SP screened all titles to remove irrelevant studies, with a 10% random sample of these verified by VCS. (2) For each study retained after title screening, SP screened all abstracts, with a 10% random sample of these checked by HG. (3) The full-texts of all retained papers were retrieved and assessed twice for eligibility by SP, with a 10% random sample verified by HG. Online supplemental table 4 lists all references not included in the final selection after screening the full text, along with the justification of their exclusion. In addition, SP scanned the reference lists of all included studies for additional relevant studies. If one of the authors referenced a study that met the eligibility criteria, we included it if relevant. The origin of the studies (ie, database search or reference lists) are specified in table 1 for included papers.

Data collection process and data items

For all included studies, SP and HG independently extracted the following information: first author; year of publication; location of data; study objective; cancer type; stage at diagnosis; age at diagnosis; exclusion criteria; cancer diagnosis period; source of cancer data; source of mortality data; measure of age; source of age; sampling; time origin; end of follow-up; survival/mortality metrics; method; sample size; time of follow-up; number of deaths; characteristic(s) studied and their definition.

In cases where an eligible study contained no numerical survival estimates but presented one or more graphs showing survival by age group stratified by another characteristics (eg, sex, stage at diagnosis), SP emailed the corresponding author to request numerical data.[16–21]

SP and HG independently assessed the quality of included studies against selected evaluation domains from the QUIPS tool:[22] study participation; prognostic factor measurement; outcome measurement; and statistical reporting. We adapted the items within each domain to our study. Also, we used selected items among those suggested by Altman *et al*[23] to assess statistical reporting.

Where numerical survival estimates were available, we assessed age disparities in survival by calculating the absolute difference in (overall or relative) survival between middle-aged patients (age groups including the age of 50 when possible, depending on the availability of data) and the oldest age group (age groups including the age of 65 years old or older ages, depending on the availability of data), to give a sense of trends and inform discussion. When survival estimates were available for several periods of cancer diagnosis, we retained estimates for the latest period. Where numerical survival estimates were not available, we described survival curves by age group and the characteristic(s) of interest. For mortality rates, we computed the absolute difference between the mortality rate in the oldest age group with that in the middle-aged age group, again to give a sense of trends and inform discussion. We reported CIs or p values when available.

We collected and logged references in Zotero V.5.0.73. We used the Rayyan free web application for the title and abstract screening.[24] The Preferred Reporting Items

Table 1 Quality assessment of included studies

			(1) Selection bias				(2) Prognostic factor measurement		(3) Outcome measurement	(4) Statistical reporting			
Author, year	**Cancer site**	**Article's source**	**Inclusion criteria**	**Exclusion criteria**	**Time zero appropriately defined**	**Baseline characteristics adequately described**	**Source of age mentioned**	**Definition of determinants studied**	**Source of mortality data mentioned**	**End of follow-up reported**	**Summary of follow-up given**	**Number of deaths given**	**Numerical estimate of survival by age groups in each group of comparison are given**
Criteria			Defined: Criteria mentioned Not defined: No criteria mentioned		Defined and appropriate: Time zero clearly mentioned and appropriately defined Defined and not appropriate: Time zero clearly mentioned but not adapted to the analysis (ie, factors of interest collected after time zero) Not defined: Time zero not clearly mentioned	Yes: Described by age group Partially: Not by age groups No: No description	Yes: The original source is reported No: Not reported	Yes: Reported Partially: Not fully defined (ie, the data source is not described) No: Not reported	Yes: The original source is reported Partially: Not specific enough No: Not reported	Yes: Reported Partially: Not specific enough No: Not reported	Yes: Reported No: Not reported		
Dickman *et al*, 1999[74]	Both sites	References	Defined	Defined	Defined and appropriate	Yes	No	Partially	Yes	Yes	No	No	Yes
Sant *et al*, 2009[75]	Both sites	References	Not defined	Defined	Defined and appropriate	Partially	No	Yes	No	No	No	No	Yes
Mariotto *et al*, 2014[76]	Both sites	Known by SP	Not defined	Not defined	Defined and appropriate	Partially	No	No	No	Yes	No	No	Yes
Innos *et al*, 2015[64]	Both sites	References	Defined	Defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	No	No	Yes
Nur *et al*, 2015[77]	Both sites	References	Defined	Defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	No	No	Yes

Continued

Table 1 Continued

		(1) Selection bias					(2) Prognostic factor measurement		(3) Outcome measurement	(4) Statistical reporting			
Author, year	Cancer site	Article's source	Inclusion criteria	Exclusion criteria	Time zero appropriately defined	Baseline characteristics adequately described	Source of age mentioned	Definition of determinants studied	Source of mortality data mentioned	End of follow-up reported	Summary of follow-up given	Number of deaths given	Numerical estimate of survival by age groups in each group of comparison are given
Yancik *et al*, 1998[26]	Colon	Databases	Defined	Not defined	Not defined	Partially	No	Yes	Yes	Yes	No	Yes	No
van de Schans *et al*, 2007[21]	Colon	Databases	Defined	Not defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	No	No	No
van Steenbergen *et al*, 2010[27]	Colon	Databases	Defined	Not defined	Defined but not appropriate	Yes	Yes	No	Yes	Yes	No	No	Yes
Nedrebø *et al*, 2011[28]	Colon	Databases	Defined	Defined	Not defined	Partially	No	Yes	Yes	Yes	No	No	Yes
van den Broek *et al*, 2011[16]	Colon	Databases	Defined	Not defined	Not defined	Yes	No	Partially	Yes	Yes	No	No	No
Kolfschoten *et al*, 2012[17]	Colon	Databases	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	Yes	No
Majek *et al*, 2013[29]	Colon	Databases	Defined	Defined	Not defined	Partially	No	Yes	No	No	No	No	Yes
Park *et al*, 2013[36]	Colon	Databases	Defined	Not defined	Not defined	No	No	Yes	No	No	No	No	Yes
van Steenbergen *et al*, 2013[30]	Colon	Databases	Defined	Defined	Not defined	Partially	Yes	Yes	Yes	Yes	No	No	Yes
Khan *et al*, 2014[31]	Colon	Databases	Defined	Defined	Not defined	Yes	No	Yes	No	Yes	No	No	Yes
Aan de Stegge *et al*, 2016[32]	Colon	Databases	Defined	Defined	Not defined	Partially	No	Yes	Yes	Yes	Yes	No	Yes
Hines *et al*, 2016[33]	Colon	Databases	Defined	Defined	Defined but not appropriate	Yes	No	Yes	No	Yes	Yes	Yes	Yes

Continued

Table 1 Continued

		(1) Selection bias					(2) Prognostic factor measurement		(3) Outcome measurement	(4) Statistical reporting			
Author, year	**Cancer site**	**Article's source**	**Inclusion criteria**	**Exclusion criteria**	**Time zero appropriately defined**	**Baseline characteristics adequately described**	**Source of age mentioned**	**Definition of determinants studied**	**Source of mortality data mentioned**	**End of follow-up reported**	**Summary of follow-up given**	**Number of deaths given**	**Numerical estimate of survival by age groups in each group of comparison are given**
Aquina *et al*, 2017[34]	Colon	Databases	Defined	Defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Brungs *et al*, 2018[20]	Colon	Databases	Defined	Defined	Not defined	Yes	No	Partially	Yes	Yes	No	No	Yes
Hur *et al*, 2018[35]	Colon	Databases	Defined	Not defined	Not defined	Yes	No	Yes	No	No	No	No	Yes
Mayer *et al*, 2019[37]	Colon	Databases	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	Yes	No
Syriopoulou *et al*, 2019[38]	Colon	Databases	Not defined	Not defined	Defined and appropriate	Partially	No	Yes	No	No	No	No	Yes
Kawamura *et al*, 2020[39]	Colon	Databases	Defined	Defined	Defined but inappropriate	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Pilleron *et al*, 202[41]1	Colon	Databases	Defined	Defined	Defined and appropriate	No	No	Yes	No	Yes	No	Yes	No
Qaderi *et al*, 2020[40]	Colon	Databases	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	No	Yes
Ries *et al*, 1994[49]	Lung	Databases	Defined	Defined	Defined and appropriate	Partially	Yes	Yes	No	No	No	No	Yes
Janssen-Heijnen *et al*, 1998[56]	Lung	Databases	Defined	Defined	Not defined	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Wingo *et al*, 1998[42]	Lung	Databases	Defined	Not defined	Not defined	No	No	Yes	Yes	Yes	No	No	Yes
McDavid *et al*, 2003[58]	Lung	References	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	No	Yes
Janssen-Heijnen *et al*, 2004[59]	Lung	References	Not defined	Defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Sigel *et al*, 2009[50]	Lung	References	Defined	Not defined	Defined but not appropriate	Yes	No	Yes	Yes	Yes	No	No	Yes

Continued

Table 1 Continued

		(1) Selection bias					(2) Prognostic factor measurement		(3) Outcome measurement	(4) Statistical reporting			
Author, year	**Cancer site**	**Article's source**	**Inclusion criteria**	**Exclusion criteria**	**Time zero appropriately defined**	**Baseline characteristics adequately described**	**Source of age mentioned**	**Definition of determinants studied**	**Source of mortality data mentioned**	**End of follow-up reported**	**Summary of follow-up given**	**Number of deaths given**	**Numerical estimate of survival by age groups in each group of comparison are given**
Sagerup *et al*, 2011[73]	Lung	References	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	No	No	No	Yes
Chang *et al*, 2012[43]	Lung	Databases	Defined	Not defined	Defined and appropriate	Yes	No	Yes	Partially	Partially	No	No	Yes
Janssen-Heijnen *et al*, 2012[19]	Lung	Databases	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	No	No
Lin *et al*, 2012[51]	Lung	Databases	Defined	Defined	Defined but not appropriate	Yes	No	Yes	Yes	Yes	No	Yes	No
van der Drift *et al*, 2012[18]	Lung	Databases	Defined	Defined	Defined but not appropriate	Yes	No	Yes	Yes	Yes	No	No	No
Deleuran *et al*, 2013[60]	Lung	References	Defined	Not defined	Defined and appropriate	Partially	Yes	Yes	Yes	Yes	No	No	Yes
Jung *et al*, 2013[44]	Lung	Databases	Defined	Defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	No	No	Yes
Mangone *et al*, 2013[61]	Lung	References	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	No	Yes
Langer *et al*, 2014[52]	Lung	Databases	Defined	Defined	Defined and appropriate	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Eberle *et al*, 2015[47]	Lung	Databases	Defined	Defined	Defined and appropriate	Yes	No	Yes	No	Yes	No	Yes	Yes
Francisci *et al*, 2015[62]	Lung	References	Defined	Defined	Defined and appropriate	Yes	No	Yes	No	Yes	No	No	Yes
Maringe *et al*, 2015[45]	Lung	Known by SP	Defined	Defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	No	No	Yes
Petera *et al*, 2015[46]	Lung	Databases	Not defined	Not defined	Not defined	Partially	No	Yes	Yes	No	No	No	Yes
Driessen *et al*, 2017[53]	Lung	Databases	Defined	Defined	Defined and appropriate	Yes	No	Yes	Yes	Yes	No	No	Yes

Continued

Table 1 Continued

			(1) Selection bias				(2) Prognostic factor measurement		(3) Outcome measurement	(4) Statistical reporting			
Author, year	**Cancer site**	**Article's source**	**Inclusion criteria**	**Exclusion criteria**	**Time zero appropriately defined**	**Baseline characteristics adequately described**	**Source of age mentioned**	**Definition of determinants studied**	**Source of mortality data mentioned**	**End of follow-up reported**	**Summary of follow-up given**	**Number of deaths given**	**Numerical estimate of survival by age groups in each group of comparison are given**
Kinoshita *et al*, 2017[63]	Lung	References	Defined	Defined	Not defined	Partially	No	Yes	No	No	No	No	Yes
Schulkes *et al*, 2017[48]	Lung	Databases	Defined	Defined	Not defined	Yes	No	Yes	Yes	Yes	No	No	Yes
Wang *et al*, 2017[57]	Lung	Databases	Defined	Defined	Not defined	Yes	No	No	No	No	No	No	Yes
Driessen *et al*, 2018[54]	Lung	Databases	Defined	Defined	Defined but not appropriate	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Akhtar-Danesh *et al*, 2019[72]	Lung	Databases	Defined	Defined	Defined and appropriate	Partially	Yes	Yes	Yes	Yes	No	No	No
Driessen *et al*, 2019[55]	Lung	Databases	Defined	Defined	Defined but not appropriate	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Innos *et al*, 2019[78]	Lung	Databases	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	No	Yes
Morishima *et al*, 2019[71]	Lung	References	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	Yes	Yes	Yes
Zhao *et al*, 2019[65]	Lung	Databases	Defined	Defined	Not defined	Partially	No	Yes	Yes	No	Yes	Yes	No
Akhtar-Danesh *et al*, 2020[66]	Lung	Databases	Defined	Defined	Not defined	Partially	No	Yes	Yes	Yes	No	No	No
de Ruiter *et al*, 2020[67]	Lung	Databases	Defined	Defined	Defined but inappropriate	Partially	No	Yes	Yes	Yes	Yes	Yes	Yes
Fan *et al*, 2020[68]	Lung	Databases	Defined	Defined	Defined but inappropriate	Partially	No	Yes	Yes	No	No	No	No
Nguyen *et al*, 2020[69]	Lung	Databases	Defined	Defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	Yes	No	Yes

Continued

Table 1 Continued

		(1) Selection bias					(2) Prognostic factor measurement		(3) Outcome measurement	(4) Statistical reporting			
Author, year	**Cancer site**	**Article's source**	**Inclusion criteria**	**Exclusion criteria**	**Time zero appropriately defined**	**Baseline characteristics adequately described**	**Source of age mentioned**	**Definition of determinants studied**	**Source of mortality data mentioned**	**End of follow-up reported**	**Summary of follow-up given**	**Number of deaths given**	**Numerical estimate of survival by age groups in each group of comparison are given**
Sachs *et al*, 2020[70]	Lung	Databases	Not defined	Not defined	Defined and appropriate	Partially	No	Yes	Yes	Yes	No	No	Yes

for Systematic Reviews and Meta-Analyses guidelines were used for the review,[25] and we registered our review protocol in the International Prospective Register of Systematic Review.

Patient and public involvement

No patients were involved.

RESULTS

We screened 3047 references for eligibility and retained 59 studies (figure 1): 20 studies on colon cancer survival,[16 17 20 21 26–41] 34 studies on lung cancer survival[18 19 42–73] and 5 studies which detailed both colon and lung cancer survival.[64 74–77]

Quality assessment

Essential information to appropriately interpret survival analysis results (ie, the number of events, end of follow-up, numerical estimates of survival) were missing in a substantial proportion of the included studies. For example, 18 studies did not report the time origin from which the survival time had been calculated,[16 20 26 28–32 35 36 42 46 48 56 57 63 65 66] and 12 studies did not indicate the end of follow-up date.[29 35 36 38 46 49 57 63 65 68 73 75] In 47 articles the authors did not report follow-up time,[16–21 26–31 35 37 38 40–49 51 53 57–64 73–77] and the number of deaths were missing in 43 articles.[16 18–21 27–32 35 38 40 42–46 48 49 53 54 57 58 60–64 66 68–70 72–78] Only four studies reported the source of age at diagnosis (from medical records).[27 30 49 72] In 12 studies, the authors did not provide numerical survival estimates.[16–19 21 26 37 41 51 65 66 68 72]

Characteristics of included studies

All studies used population-based cancer registry data. Two studies analysed a random sample of patients.[26 61]

Of the 25 studies examining colon cancer, 6 studies investigated age disparities in colon cancer survival (table 2).[16 17 31 32 34 41 59] Seven studies used data from The Netherlands,[16 17 21 27 30 32 40] and six presented data from the USA.[26 31 33 34 37 76] The remaining studies used data from Estonia,[64] England,[38 77] Japan,[39] Finland,[74] Germany,[29] Korea[35 36] and Australia.[20] One study used data from >20 Europeans countries,[75] and another one from seven high-income countries.[41] Fifteen studies included all cancer stages,[16 17 21 26 28 29 35 36 38 41 64 74–77] four studies restricted their analyses to stage III cancer,[20 27 33 39] five studies to stages I–III[30–32 34 40] and one study to stages II–III.[37] Ten studies included all patients whatever their age at diagnosis,[16 17 27 28 32 34–36 38 74] with the inclusion criterion for age varying widely in the remaining studies. All studies, with the exception of two,[38 41] analysed age at diagnosis using age categories but the number and boundaries of these varied across studies (table 2). Twelve studies presented relative survival (RS) estimates only,[16 28–30 35 36 38 40 64 74–76] seven studies presented overall survival (OS) estimates only[20 21 26 27 32 37 39 72] and two studies used net survival[38 77] (table 2). The remaining studies showed 30-day postoperative mortality rates,[17] the cumulative incidence of death at 5 years,[31] or mortality rates.[33 34]

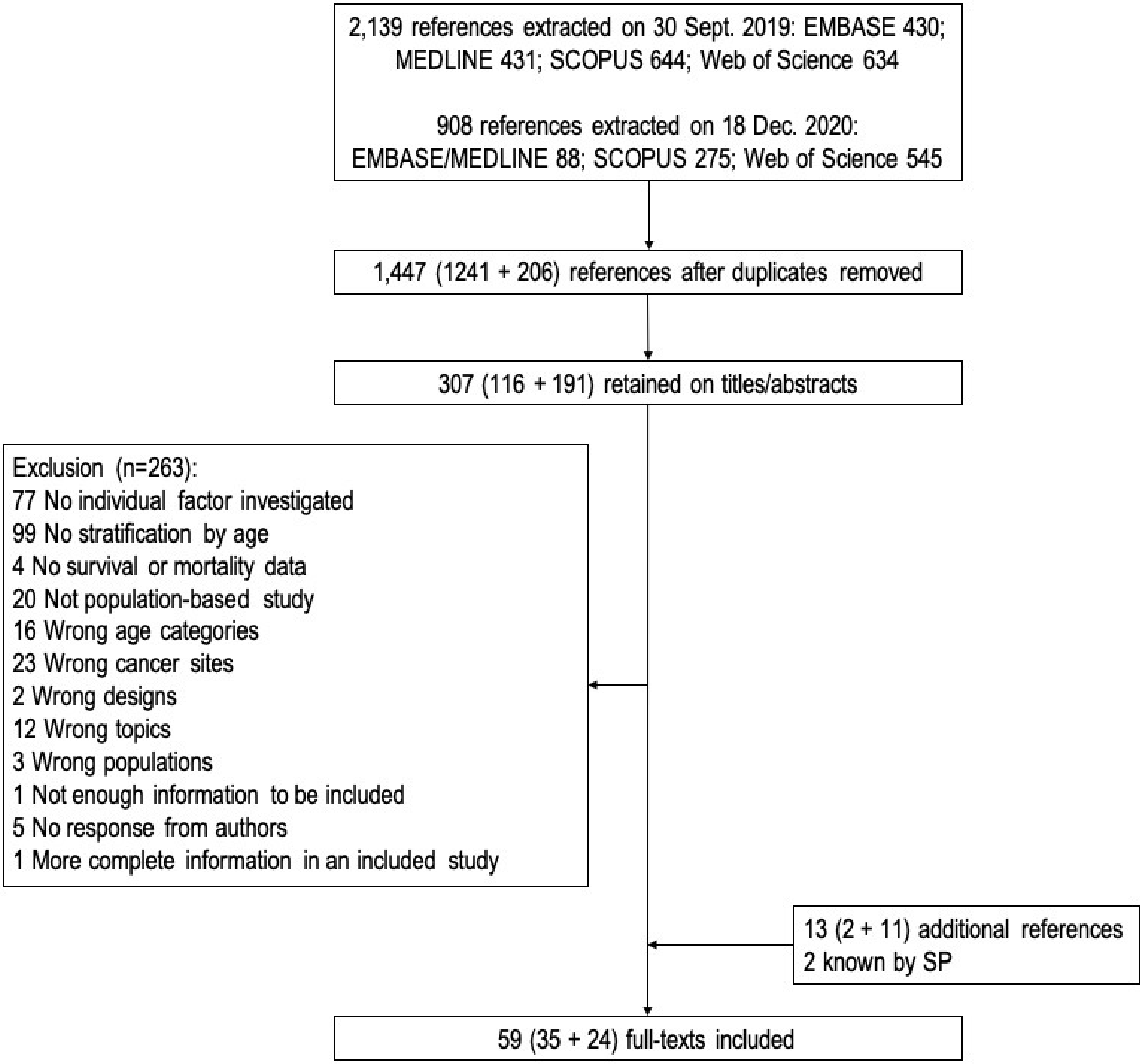

Figure 1 Flow chart of studies' inclusion.

Of the 39 studies that examined lung cancer, 12 studies focused on non-small cell lung cancer (NSCLC),[18 49–55 59 67 68 72] 3 studies on small-cell lung cancer (SCLC),[19 56 57] with the remaining studies investigating all lung cancer cases (table 3). Six studies evaluated age disparities in survival.[46 48 50 53–55] Nine studies analysed data from the Netherlands,[18 19 48 53–56 59 67] 10 studies from the USA[42 49 52 57 58 65 68 76] and the remaining studies presented data from Canada,[66 72] Denmark,[60] Estonia,[64 78] Sweden,[70] Japan,[63 71] Norway,[73] Italy,[61] Finland,[74] Taiwan,[43 51 69] Korea,[44] the Czech Republic,[46] England[45 77] and Germany.[47] Two studies used data from >20 Europeans countries.[62 75] While most studies included all stages at diagnosis, some studies restricted their sample to specific stage(s): stage I cancer,[50 65–68] stages I–IIIa,[51] stages IIIb and IV,[52] stage III[54] and stages I or II.[55] Fifteen studies included patients of all ages at diagnosis,[19 42 43 46 49 50 53 56 57 59 60 68 70 73 74] other studies included patients from the age of 15 (n=11),[18 45 47 58 61–64 75 77 78] 18 (n=7),[48 51 65–67 71 72] 20 (n=3)[44 69 76] or 65.[52 54 55] The studies used age categories that differed widely in terms of number and boundaries. Seventeen studies presented RS estimates only,[18 19 42 44 46 47 49 53 56 58 61 63 64 73 74 76 78] 14 studies OS estimates only,[43 48 51 52 54 55 59 60 66–68 70 72 76] 2 studies net survival,[45 77] 1 study presented cancer-specific survival (CSS) estimates,[57] 3 studies both OS and RS estimates[62 71 75] and 1 study presented OS estimates and CSS.[65] The one remaining study used mortality rates.[69]

Table 2 Factors of age disparities in colon cancer survival

			Patient-related factors					Tumour characteristics			Anti-treatment		Treatment outcome	Others
Author, year	Age categories (years)	Survival metrics	Sex	SES/deprivation	Insurance	Comorbidity	Physical function	Stage	Subsite	Lymph nodes	Chemo therapy	Surgery with or without chemotherapy	Compli cations	Cumulative number of factors
Mariotto *et al*, 2014[76]	20–44; 45–54; 55–64; 65–74; ≥75	RS	No											
Sant *et al*, 2009[75]	15–44; 45–54; 55–64; 65–74; 75–99	OS+RS	No											
Nur *et al*, 2015[77]	15–44; 45–54; 55–64; 65–74; 75–99	Net survival	Yes	Yes										
Dickman *et al*, 1999[74]	30–44; 45–59; 60–74; ≥75	RS	Yes					Yes	Yes					
Majek *et al*, 2013[29]	15–44; 45–54; 55–64; 65–74; ≥75	RS	Yes						Yes					
Innos *et al*, 2015[64]	15–44; 45–54; 55–64; 65–74; ≥75	RS	Yes											
Syriopoulou *et al*, 2019[38]	Continuous	RS		No										
Yancik *et al*, 1998[26]	55–64; 65–74; ≥75	OS						Yes						
van den Broek *et al*, 2011[16]	<65; 65–74; ≥75	RS						Yes						
van Steenbergen *et al*, 2013[30]	15–44; 45–59; 60–74; 75–89	RS						Yes						
Pilleron *et al*, 202[41]1	Continuous	Net survival						Yes						
Qaderi *et al*, 2020[40]	<60; ≥60	RS						Yes						
Park *et al*, 2013[36]	<70; ≥70	RS							No					
Hur *et al*, 2018[35]	<39; 40–49; 50–59; 60–69; ≥70	RS							No					

Continued

Table 2 Continued

			Patient-related factors					Tumour characteristics			Anti-treatment		Treatment outcome	Others
Author, year	Age categories (years)	Survival metrics	Sex	SES/deprivation	Insurance	Comorbidity	Physical function	Stage	Subsite	Lymph nodes	Chemo therapy	Surgery with or without chemotherapy	Compli cations	Cumulative number of factors
Nedrebø *et al*, 2011[28]	<75; ≥75	RS								Yes				
Khan *et al*, 2014[31]	20–49; 50–64; 65–74; 75–84; ≥85	Cumulative Incidence of death at 5 years								Yes				
Aan de Stegge *et al*, 2016[32]	<66; 66–75; >75	OS								Yes				
van Steenbergen *et al*, 2010[27]	<65; 65–74; ≥75	OS									Yes			
Hines *et al*, 2016[33]	40–64; 65–74; 75–84	Mortality rate									Yes			
Brungs *et al*, 2018[20]	<70; ≥70	OS									Yes			
Kawamura *et al*, 2020[39]	<75; ≥75	OS										Yes		
Aquina *et al*, 2017[34]	<65; 65–74; ≥75	Mortality rate											Yes	
van de Schans *et al*, 2007[21]	35–64; ≥65	OS				Yes								
Kolfschoten *et al*, 2012[17]	<70; 70–79; ≥80	Mortality rate												Yes
Mayer *et al*, 2019[37]	<75; 75–84; ≥85	Risk of death					Yes							

OS, overall survival; RS, relative survival; SES, socioeconomic status.

Table 3 Factors of age disparities in lung cancer survival

			Patient-related factors				Tumour characteristics			Anti-cancer treatment					
Author, year	**Age categories**	**Survival metrics**	**Sex**	**SES/ deprivation**	**Ethnicity/ race**	**Comorbidity**	**Stage**	**Histology**	**Tumour size**	**Treatment**	**Chemotherapy**	**Surgery type**	**Surgery versus SBRT**	**Radiation**	**Statin use**
Lung cancer															
Wingo *et al*, 1998[42]	<45; 45–54; 55–64; 65–74; ≥75	RS	No				Yes								
Akhtar-Danesh *et al*, 2020[66]	<60; 60–69; 70–79; ≥80	OS	No												
Nur *et al*, 2015[77]	15–44; 45–54; 55–64; 65–74; 75–99	Net survival	Yes	Yes											
Mariotto *et al*, 2014[76]	20–44; 45–54; 55–64; 65–74; ≥75	RS+OS	Yes			Yes	Yes	Yes							
Dickman *et al*, 1999[74]	30–44; 45–59; 60–74; ≥75	RS	Yes				Yes	Yes							
Eberle *et al*, 2015[47]	15–59; 60–69; 70–79; ≥80	RS	Yes												
Innos *et al*, 2019[78]	15–54; 55–64; 65–74; ≥75	RS	Yes												
Sachs *et al*, 2020[70]	<60; 60–64; 65–69; 70–74; ≥75	OS	Yes												
Francisci *et al*, 2015[62]	15–44; 45–54; 55–64; ≥75	OS+RS	Yes												
Kinoshita *et al*, 2017[63]	15–64; 65–74; 75–99	RS	Yes												
Innos *et al*, 2015[64]	15–44; 45–54; 55–64; 65–74; ≥75	RS	Yes												
McDavid *et al*, 2003[58]	15–44; 45–54; 55–64; 65–74; 75–84; 85–99	RS	Yes												

Continued

Table 3 Continued

			Patient-related factors				Tumour characteristics			Anti-cancer treatment					
Author, year	**Age categories**	**Survival metrics**	**Sex**	**SES/ deprivation**	**Ethnicity/ race**	**Comorbidity**	**Stage**	**Histology**	**Tumour size**	**Treatment**	**Chemotherapy**	**Surgery type**	**Surgery versus SBRT**	**Radiation**	**Statin use**
Sagerup *et al*, 2011[73]	0–49; 50–59; 69–69; 70–79; ≥80	RS	Yes												
Sant *et al*, 2009[75]	15–44; 45–54; 55–64; 65–74; 75–99	OS+RS	Yes												
Mangone *et al*, 2013[61]	15–54; 55–64; 65–74; 75–99	RS	Yes												
Deleuran *et al*, 2013[60]	15–69; 70–79; ≥80	OS	Yes												
Chang *et al*, 2012[43]	<65; ≥65	OS		Yes											
Maringe *et al*, 2015[45]	15–44; 45–54; 55–64; 65–69	NS			Yes										
Morishima *et al*, 2019[71]	<65; 65–69; 70–74; 75–79; ≥80	OS+RS				Yes									
Jung *et al*, 2013[44]	20–49; 50–64; 65–74; ≥75	RS					Yes								
Petera *et al*, 2015[46]	<70; ≥70	Mortality rate+RS					Yes								
Schulkes *et al*, 2017[48]	18–70; 71–84; ≥85	OS					Yes								
Zhao *et al*, 2019[65]	<65; 65–74; ≥75	OS+CSS										Yes			
Nguyen *et al*, 2020[69]	<65; 65–74; ≥75	Mortality rate													Yes
Non-small cell lung cancer															
Janssen-Heijnen *et al*, 2004[59]	<60; 60–69; 70–79; ≥80	OS	No			Yes	Yes	Yes	Yes	Yes					

Continued

Table 3 Continued

	Patient-related factors						Tumour characteristics			Anti-cancer treatment					
Author, year	**Age categories**	**Survival metrics**	**Sex**	**SES/ deprivation**	**Ethnicity/ race**	**Comorbidity**	**Stage**	**Histology**	**Tumour size**	**Treatment**	**Chemotherapy**	**Surgery type**	**Surgery versus SBRT**	**Radiation**	**Statin use**
Akhtar-Danesh *et al*, 2019[72]	<60; 60–69; 70–79; ≥80	OS	No												
Ries *et al*, 1994[49]	<45; 45–64; 65–74; ≥75	RS	Yes				Yes								
Sigel *et al*, 2009[50]	<60;61–69; 70–79; ≥80	RS	Yes												
Driessen *et al*, 2018[54]	65–74; ≥75	OS					Yes			Yes					
Driessen *et al*, 2019[55]	65–74; ≥75	OS					Yes			Yes					
van der Drift *et al*, 2012[18]	<75; ≥75	RS					Yes								
Driessen *et al*, 2017[53]	<70; ≥70	RS					Yes								
Langer *et al*, 2014[52]	65–74; ≥75	OS									Yes				
Lin *et al*, 2012[51]	18–69; ≥70	OS									Yes				
Fan *et al*, 2020[68]	≤65; 65–74; ≥75	OS										Yes			
de Ruiter *et al*, 2020[67]	18–59; 60–79; 70–79; ≥80	OS											No		
Small cell lung cancer															
Janssen-Heijnen *et al*, 2012[19]	45–59; 60–74; ≥75	RS	Yes												
Janssen-Heijnen *et al*, 1998[56]	<70; ≥70	RS					No								

Continued

Table 3 Continued

Author, year	Age categories	Survival metrics	Patient-related factors				Tumour characteristics			Anti-cancer treatment					Statin use
			Sex	SES/deprivation	Ethnicity/race	Comorbidity	Stage	Histology	Tumour size	Treatment	Chemotherapy	Surgery type	Surgery versus SBRT	Radiation	
Wang *et al*, 2017[57]	<50; 50–59; 60–69; 70–79; ≥80	CSS					Yes							Yes	

CSS, cancer-specific survival; OS, overall survival; RS, relative survival; SBRT, Stereotactic body radiation therapy; SES, socioeconomic status.

Age patterns in colon and lung cancer survival

Patterns of age disparities in survival for colon and lung cancers based on patient-related and clinical factors are shown in tables 2 and 3, respectively. The detailed description of each included study is available in the online supplemental tables 5 and 6.

Regarding colon cancer survival, higher age disparities were observed in women with regional or distant cancers,[74] and those with left colon cancer,[29] while the other studies did not find difference across sexes.[64 75 76] Another study suggests that age disparities across sexes differ based on socioeconomic deprivation level of domicile of patients,[77] with higher age disparities in women observed after 1 year in deprived areas only. Age disparities in 5-year net survival were similar across sexes. One study found greater age disparities in deprived areas compared with affluent areas in England,[77] while another study found no difference.[38] In another study, patients' physical function level did not influence age disparities in overall survival.[37] Overall, age disparities were greater as cancer spread or when the cancer stage was unknown,[16 26 30 40 41 74] when lymph nodes were involved[28] or when fewer than 12 nodes were examined.[31 32] While some studies did not show different age patterns in survival based on subsite,[35] others reported smaller age differences for patients with cancer of the distal colon compared with the proximal colon.[36 74] Regarding treatment, the presence of bias precludes accurate interpretation, when studies presented survival data across treatment strategies.[20 27 33 39] One study reported postoperative mortality rates in patients who underwent an elective and non-elective resection.[17] This study showed higher age disparities for men, for those with an American Society of Anesthesiologists score of ≥3, for those with a Charlson comorbidity score ≥2, for those with metastatic disease and for those with hemicolectomy. The study also concluded that complications and sepsis after surgery,[34] as well as the presence of chronic obstructive pulmonary disease at the time of cancer diagnosis,[21] would also likely increase age disparities in colon cancer survival.

Regarding lung cancer survival, women had higher age disparities in survival in the majority of studies.[19 47 49 50 58 60–63 74–78] However, in other studies, no differences were observed in age disparities between sexes[59 66 72 73] and another study found greater age disparities in men who underwent pulmonary resections.[70] We observed no clear pattern for the role of socioeconomic level on age disparities in data from one study,[43] while another suggested smaller age disparities in deprived areas compared with affluent areas.[77] Regarding the role of race/ethnicity, one study reported smaller age disparities in lung cancer survival among black patients compared with white patients in the USA.[42] In comparison, South Asians showed greater age disparities than non-South Asians in the UK.[45] One study suggested tumour size influenced age disparities, with disparities being greater in patients with larger tumours.[59] Age disparities tended to decrease as the cancer spread[42 44 46 49 53 55–57 59 74 76] and were greater in patients with NSCLC than in those with SCLC.[74 76] One study suggested that age disparities were smaller in patients with severe comorbidities than in those without comorbidity,[76] while another study showed greater age disparities with comorbidity,[59] and another showed greater age disparities with comorbidities, but only in patients with localised NSCLC.[59] Again, most studies presenting survival data by treatment group were at high risk of bias.[18 51 54 55 57 65 67 68] The only interpretable study showed that age disparities in overall survival did not differ based on the chemotherapy regimen.[52] A study that focused on the relationship of statin use and survival in patients with lung cancer who received Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) therapy, showed greater age disparities in the statin group than in the non-statin group.[69]

DISCUSSION

This review is the first to bring together the literature on those factors which influence age disparities in cancer survival, using colon and lung cancer as exemplars. While age at diagnosis is an important prognostic factor in cancer survival, few studies, often of suboptimal quality, have specifically focused on the relationship between age and cancer survival, and only one has sought to identify patterns of age disparities in colon or lung cancer survival per se. However, our review showed that (1) the magnitude of disparities in survival between younger and older patients differed greatly and inconsistently based on patient and clinical characteristics; (2) the stage at diagnosis was the sole clinical characteristic that consistently influenced age disparities in survival, however opposite outcomes were seen for colon cancer and lung cancer; and (3) age disparities in lung cancer survival were typically greater in women than in men.

Magnitude of age disparities in survival

While in most studies older patients had poorer survival than middle-aged patients, this was not always the case. For instance, two studies reported no age disparity in cancer survival in patients with cancer of the right colon,[29 35] and other papers showed minimal age disparities in patients with advanced lung cancer,[29] or small-cell lung carcinoma.[74] On the other hand, age disparities were substantial in patients with distant colon cancer[30 74] or those with localised lung cancer,[42 46 49 53 74 76] particularly for patients without comorbidities.[76]

Clinical characteristics of age disparities in cancer survival

The influence of stage at diagnosis on age disparities differed depending on the cancer. Age disparities in colon cancer survival tended to increase with increasing stage of disease,[28 30] while the opposite was observed for lung cancer.[42 46 49 53 74 76] Surgery is the main treatment strategy for patients with colon cancer diagnosed with localised and regional stage disease, while chemotherapy is recommended for metastatic disease.[79] It has been shown that older patients are less likely to receive chemotherapy than younger patients,[80–82] and less intensive therapies are usually recommended for unfit older patients.[83] In lung cancer, older patients with early stage disease, especially those older than 75, are less likely to undergo surgery compared with younger patients.[84] The high lethality of the disease, especially at a more advanced stage, may explain the small difference in survival disparities observed between middle-aged and older patients with metastatic lung cancer.

Comorbidity, the prevalence of which drastically increases with age, is an important prognostic factor in patients with cancer, because it may complicate cancer management.[85] However, our review identified four studies (one for colon cancer and three for lung cancer) reporting data for comorbidity, so few studies prevent us from making any firm conclusions regarding comorbidity and its impact on age disparities in cancer survival. One study suggested that the presence of chronic obstructive pulmonary disease at diagnosis may increase age disparities in survival seen in patients with colon cancer.[21] Two studies showed greater age disparities in lung cancer survival in patients with comorbidity[59 71] while another study suggested that patients without comorbidities showed greater age disparities in survival than those with severe comorbidities.[76] Comorbidity alone is not enough to assess vulnerabilities in older patients with cancer, and comprehensive geriatric assessments (CGA) may be useful in capturing a more nuanced view of health, fitness and physiological ageing.[86] Although less valuable than information derived from CGA, it is now possible in many countries to link cancer survival data to comorbidity information through linkage with administrative hospitalisation data or pharmacy data,[87 88] and thus further studies should be conducted, that describe the role of comorbidities on age disparities in survival, in patients with colon or lung cancer.

Unfortunately, we are unable to draw any conclusions regarding the role of treatment on age disparities in colon and lung cancer survival. Indeed, most studies presenting survival data by treatment group were at high risk of immortal time bias.[27 33 54 55 57] Immortal time bias occurs when survival comparisons are made between groups of patients based on a factor (eg, treatment) that is defined after the start of follow-up (eg, cancer diagnosis date). Patients in the treated group survived long enough to be treated, while others in the untreated group may have died before having that chance. As a consequence, the treatment may be erroneously considered as effective because patients in the treated group have, on average, a better survival than those in the untreated group. In reality, the apparent better survival in the treated group may be the result of the selection of the fittest patients (ie, those who had the better chance to survive). For instance, this bias may be at play in the 2010 study of van Steenbergen *et al* and would explain the higher survival among the oldest age group in the 'no chemotherapy' group,[27] or in the study of Sigel *et al* that reported higher 2-year RS in female patients older than 80 years compared with those younger than 60 years.[50] With a few exceptions,[34 45 52 74 76] the overall quality of studies included in this review was poor. Further high-quality studies are required if we are to better identify the role of treatment as a possible driver of age disparities in cancer survival.

Patient-related factors of age disparities in cancer survival

Only a few studies provided information about patient characteristics. The main patient characteristic examined in the colon cancer studies was sex, and the results were inconsistent.[29 64 74–77] Contradictory results were observed regarding the influence of socioeconomic deprivation level on age disparities in colon cancer survival,[38 77] posing the need for specific research to investigate the potential role of deprivation. However, the included lung cancer studies suggested that the difference in 5-year survival between younger and older patients was wider in women than in men[19 42 47 74] but this was not necessarily the case for 1-year and 3-year survival.[19] In the study by Dickman *et al*, women aged 45–59 years had better 1-year RS than men of the same age; however, women aged 75 years or older had lower 1-year RS than their male counterparts.[74] Even if some evidence suggests a positive effect of sex hormones on survival from NSCLC in women,[89] the implication of sex hormones is still not clear.[90] However, because of the observational nature of the studies included, survival bias may also be an explanation for the difference observed across sexes. In terms of race/ethnicity, age disparities in lung cancer survival seem to be influenced by race/ethnicity in the USA and the UK, but results are inconsistent,[42 45] probably because of differences between healthcare systems, or possible survival bias. Finally, the role of socioeconomic level in age disparities in lung cancer survival is not clear.[43] While sex, ethnicity/race and socioeconomic level are known to influence cancer survival,[91–93] their role in age disparities in cancer survival remain unclear and should be further explored.

Other characteristics may be important in explaining lower survival among older patients. When using observational data, data related to demographics and cancer are the easiest to study. With the exception of comorbidity, geriatric factors (ie, cognition, nutritional status, functional status) are not commonly studied, although these are important considerations in the management of cancer in older adults.[94] Only one of the studies we reviewed investigated physical status and survival.[37] No other factors influencing cancer management (such as performance status) were investigated in the included studies. Other factors, such as physical and financial access to cancer facilities, are likely to be more difficult to measure, and therefore were less likely to be included in this review.

The importance of choice of survival metric in future age disparity studies

Older adults have a higher risk of dying from causes other than cancer than younger adults. While of interest to patients and clinicians,[95] OS measures are of limited value when studying disparities in survival between younger and older patients, mainly because they do not make a distinction between causes of death, and because of the higher risk of background mortality in older patients. Identifying the underlying cause of death may be challenging in older adults who may present with co-existing serious disease, making cancer-specific survival difficult to estimate. When studying the age disparities in survival, it is therefore crucial to take into account this difference in background mortality. Accordingly, relative survival (ie, the ratio of the observed survival among patients with cancer, over the (expected) survival among the general population obtained from national life tables) or net survival (ie, the probability of being alive after a defined period of time in the hypothetical world where one can die only from cancer) are suited to this purpose. However, life tables used to estimate the expected survival should be adequately stratified by likely important factors (eg, comorbidity, smoking status).[96]

Limitations

Our systematic review has limitations. We could not conduct any quantitative analysis (such as meta-analysis) because of the vast heterogeneity of the studies included, which prevented us from quantifying the relationship between increasing age and cancer survival. This is largely a reflection of the quality of the studies included in this review. We did, however, attempt to synthesise the available evidence into the key findings, as discussed above.

Implications

The rapidly increasing number of older patients with cancer[14] has presented a dire need for a better understanding of the drivers of the disparities in colon and lung cancer survival between older and younger patients, ultimately enhancing the probability of patients surviving their cancer regardless of their age. While it is not realistic to believe that survival among older adults can equal that of middle-aged adults, there is more that can be done to minimise age disparities in colon and lung cancer survival—however the current quality of evidence prevents a full understanding of the key drivers of these disparities. As a first step for a better description of age disparities in survival, we encourage authors of future cancer survival studies to systematically present results stratified by age group, even if a study may not specifically focus on age. Geriatric factors that are important when managing cancer in older adults are not routinely captured by administrative data sets. Recent studies used hospitalisation data sets to define frailty or to identify patients with weight loss using general practices codes.[97 98] Further studies of this kind are recommended for other factors (eg, functional status, cognition) and in other countries, and we encourage future cancer survival studies to consider presenting results stratified by age wherever possible. With the growth in the number of older patients with cancer, it is now time to improve the description of cancer survival prospects in this vital group.

CONCLUSION

In this systematic review, we have investigated age disparities in cancer survival using colon and lung cancer—two differing cancer contexts in terms of the likely impact of age on survival—as exemplars. The present review highlights both the lack of knowledge about age disparities in colon and lung cancer survival, and the absence of geriatric variables (eg, cognition, functional status, social support, nutritional status) investigated within current population-based research. With the growth of the use of administrative health data in several (high income) countries and an increased emphasis being placed on data quality, we can expect a more accurate description of age disparities in colon and lung cancer survival in the near future and a subsequent improved understanding of what drives them.

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