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Risk of COVID-19 death for people with a pre-existing cancer diagnosis prior to COVID-19-vaccination: A systematic review and meta-analysis

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Abstract

While previous reviews found a positive association between pre-existing cancer diagnosis and COVID-19-related death, most early studies did not distinguish long-term cancer survivors from those recently diagnosed/treated, nor adjust for important confounders including age. We aimed to consolidate higher-quality evidence on risk of

Abbreviations: COVID-19, coronavirus disease 19; HR, hazard ratio; LMICs, low- and middle-income countries; OR, odds ratio; RR, risk ratio; 95% CI, 95% confidence interval.

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COVID-19-related death for people with recent/active cancer (compared to people without) in the pre-COVID-19-vaccination period. We searched the WHO COVID-19 Global Research Database (20 December 2021), and Medline and Embase (10 May 2023). We included studies adjusting for age and sex, and providing details of cancer status. Risk-of-bias assessment was based on the Newcastle-Ottawa Scale. Pooled adjusted odds or risk ratios (aORs, aRRs) or hazard ratios (aHRs) and 95% confidence intervals (95% CIs) were calculated using generic inverse-variance random-effects models. Random-effects meta-regressions were used to assess associations between effect estimates and time since cancer diagnosis/treatment. Of 23 773 unique title/abstract records, 39 studies were eligible for inclusion (2 low, 17 moderate, 20 high risk of bias). Risk of COVID-19-related death was higher for people with active or recently diagnosed/treated cancer (general population: aOR = 1.48, 95% CI: 1.36-1.61, $I^2 = 0$; people with COVID-19: aOR = 1.58, 95% CI: 1.41-1.77, $I^2 = 0.58$; inpatients with COVID-19: aOR = 1.66, 95% CI: 1.34-2.06, $I^2 = 0.98$). Risks were more elevated for lung (general population: aOR = 3.4, 95% CI: 2.4-4.7) and hematological cancers (general population: aOR = 2.13, 95% CI: 1.68-2.68, $I^2 = 0.43$), and for metastatic cancers. Meta-regression suggested risk of COVID-19-related death decreased with time since diagnosis/treatment, for example, for any/solid cancers, fitted aOR = 1.55 (95% CI: 1.37-1.75) at 1 year and aOR = 0.98 (95% CI: 0.80-1.20) at 5 years post-cancer diagnosis/treatment. In conclusion, before COVID-19-vaccination, risk of COVID-19-related death was higher for people with recent cancer, with risk depending on cancer type and time since diagnosis/treatment.

KEYWORDS
cancer, COVID-19, death, meta-analysis, systematic review

What's new?

Previous reviews have shown a link between cancer and COVID-19-related death, but early studies did not distinguish between long-term cancer survivors and recently diagnosed patients. Here, the authors analyzed higher-quality studies focused on people with active or recently diagnosed cancers. For all/solid cancers together, estimates suggested increased risk of COVID-19-related death for up to 5 years after diagnosis/treatment. Those with lung or hematological cancers had a larger increase in risk, as did those with metastatic cancers. This study provides a key benchmark against which future comparisons can be made, to support evidence-informed decision-making.

1 | INTRODUCTION

Globally, over 6.95 million confirmed deaths have been directly attributed to COVID-19 by 1 October 2023.[1] The estimated excess mortality due to the COVID-19 pandemic is even higher (with WHO estimates of 14.83 million excess deaths to 31 December 2021),[2] likely reflecting non-attributed deaths due to COVID-19 and those resulting from secondary causes such as health services disruptions. Cancer was included among the conditions associated with severe COVID-19 and COVID-19-related death in the WHO Clinical Guidelines for COVID-19, with other conditions including diabetes, hypertension and immunosuppression.[3] A systematic review of the early-stage pandemic literature to 1 July 2020[4] found a positive association between pre-existing cancer diagnosis and COVID-19-related death from studies that adjusted for at least age and sex. However, most of these early studies considered the risk associated with any pre-existing cancer diagnosis (both long-term cancer survivors and those recently diagnosed/treated), without explicitly considering time since diagnosis/treatment or adjusting for important confounders including other conditions associated with COVID-19-related death. Thus, it is important to critically evaluate and consolidate the emergent high-quality evidence on risks of COVID-19-related death for people with cancer, with consideration of how these risks depend on cancer type, stage and time since cancer diagnosis or treatment.

Risks of COVID-19-related death may also depend on the COVID-19 variants in circulation as well as COVID-19 vaccination status. Large-scale COVID-19 vaccination programs were rolled out from December 2020.[5] As people with cancer were prioritized for vaccination in many jurisdictions,[6,7] consolidation of evidence before vaccine availability can provide valuable information that is not confounded by differential vaccine eligibility or uptake. Our systematic review and meta-analysis aim to address these important issues by consolidating pre-COVID-19-vaccination, high-quality evidence for risks of COVID-19-related deaths for people with recent cancer diagnosis/treatment. To our knowledge, this is the first review to specifically consolidate results from studies that have provided risk estimates for active/recent cancer or cancer diagnosed/treated within a specified period, with risk estimates adjusted for at least age and sex. Moreover, we specifically examine how risks depend on time since diagnosis/treatment, and consolidate the available evidence on risks by cancer type and stage.

2 | MATERIALS AND METHODS

2.1 | Search strategy and information sources

For this systematic review and meta-analysis, we searched the WHO COVID-19 Research Database,[8] a comprehensive, multilingual collection of COVID-19 literature amalgamated from a broad range of databases, including Medline, Embase and pre-print servers (eg, medRxiv), on 20 December 2021. We combined text terms for COVID-19, cancer or comorbidities and mortality (Table S1), with no limits on language, date or time period or study design. We completed a search update on 10 May 2023, directly searching Medline and Embase databases (Table S1). This search used the same terms as the original search, and we checked that it identified all 28 studies from the original search that satisfied the review criteria. We then removed title/abstract records that were already screened in the original search by matching on titles and first author, via a two-step process. We first used spaCy, a natural language processing package in Python, to give each pair of titles (one from the search update and one from the original search) a similarity score, using cosine similarity. If the score was a perfect match, the record was already included in the original search. For titles in the search update without a perfect match (due to, eg, formatting of records), to identify records already included in the original search, we performed a manual comparison with titles that had the highest similarity score (checking title and first author were identical).

2.2 | Selection criteria

Studies were included if they examined the effects of active or recent cancer on COVID-19-related or COVID-19-specific mortality in (a) the general population, (b) people with COVID-19 or (c) hospital inpatients with COVID-19. Eligible exposures were cancer described as "active" or "current" by the study or recent cancer (defined as cancer managed, diagnosed or treated in a specific period, eg, <1 year before the study period, allowing for study-specific period definition) or metastatic cancer (which was considered to be active cancer). Study-specific definitions of recent cancer were eligible if referring to cancer diagnosis, treatment or management up to 5 years before study baseline. Eligible outcomes were COVID-19-related or COVID-19-specific deaths (as per study-specific definitions), and in-hospital deaths for studies restricted to hospital inpatients with COVID-19. Eligible comparators were no previous cancer diagnosis ("no cancer"), no cancer described as "active" or "current" by the study ("no active cancer") or no cancer management/diagnosis/treatment within a recent specified period (allowing for study-specific period definition). Comparators that only excluded some cancer type(s)/stage(s) were ineligible. Studies restricted to populations with specific non-cancer health conditions or <100 people with cancer were excluded. We considered studies that reported odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) adjusted for at least age and sex. This systematic review was registered on PROSPERO (CRD42022315719). To focus this review on the pre-COVID-19 vaccination phase, we excluded studies with study periods overlapping wide availability of COVID-19 vaccine in the respective jurisdiction (defined as >10% of the national population having received 1+ doses of a COVID-19 vaccine more than 1 week before the end of the study period).

2.3 | Selection process

Two reviewers independently assessed titles/abstracts and subsequently full-text articles against the pre-specified inclusion criteria, with discrepancies resolved by a third reviewer. We employed a highly collaborative approach, with 37 reviewers from 17 countries involved in the screening of titles and abstracts, and 22 reviewers involved in the assessment of full-texts for inclusion. Reasons for exclusion of full-text articles were recorded.

2.4 | Data extraction

Two reviewers independently extracted study characteristics and results for each included study, with differences resolved by discussion or third-reviewer adjudication. Information extracted included publication status, country, size and source of study population, study period, exposure definition and numbers, comparator definition and numbers, outcome definition, number of people with the outcome for those with and without exposure, the effect estimate and 95% confidence interval (95% CI) and covariates included in analyses. We checked study periods against the availability of COVID-19 vaccination in the respective countries, using the Our World in Data COVID-19 vaccination information (% of people who received at least one dose of COVID-19 vaccine among the total population).[9]

2.5 | Risk of bias assessment

The risk-of-bias for each included study was independently assessed by two reviewers, using a modified version of the Newcastle-Ottawa Scale designed specifically to assess biases in observational cohort

studies[10] (Table S2), with detailed guidance and examples for each rating. Differences were resolved by consensus and where necessary, adjudication by a third reviewer, with group discussion for any aspects that were unclear. The risk of bias was rated low, moderate, high or unclear for each of the following: selection of exposed and unexposed cohorts, co-interventions, exposure status ascertainment, reverse causation, outcome ascertainment, completeness and differences in follow-up, exclusions due to missing exposure or covariate data, adjustment for important confounders or over-adjustment and the reliability of covariate data. Important confounders were pre-specified as age, sex and factors listed as associated with severe COVID-19/COVID-19-related death in the WHO "COVID-19 Clinical management: Living guidance", version 25 January 2021: hypertension, cardiac disease, cerebrovascular disease, chronic lung disease, chronic kidney disease, dementia, mental illness, immunosuppression, HIV, obesity and smoking.[3] Studies that adjusted for an intermediate variable on the causal pathway between having cancer and death, for example, the number of comorbidities including cancer or clinical indicators of COVID-19 severity, were considered at high risk of bias due to over-adjustment.

2.6 | Data synthesis

2.6.1 | Selection of studies and effect estimates for meta-analyses

To avoid data duplication, studies with overlapping samples were identified, and the selection of the study for inclusion in the analysis was based on the following pre-specified criteria in order of priority: number of exposed, population size, representativeness (eg, national vs jurisdictional data), adjustment for important confounders. To assess the sensitivity of our main results to the selection of studies in cases of overlapping data, we repeated meta-analyses using alternative study inclusion.

If a study reported several estimates for different times since diagnosis/treatment, the estimate for the most recent diagnosis/treatment was included in the meta-analysis (eg, estimate for <1 year since diagnosis if estimates for <1 year, 1-5 years and 5+ years were provided; we also carried out dedicated meta-regression analyses to consider the relationship between effect estimates and time since diagnosis/treatment, see below). When a study reported the same effect estimate adjusted in more than one way, the effect estimate adjusted for the most covariates was selected, unless there was a concern about over-adjustment.

2.6.2 | Meta-analyses and meta-regressions

Pooled effect estimates and 95% CIs from generic inverse-variance random-effects analyses were calculated using Stata 17.[11] Meta-analyses were done separately by effect measure (ORs and RRs combined, HRs) and study population (general population, all people with COVID-19, hospital inpatients with COVID-19), as people with and without cancer may have had different risks of developing COVID-19 and of hospitalization. ORs and RRs were pooled together as the absolute risk of death was generally low in both the cancer and comparison groups.[12] We carried out separate meta-analyses by cancer type (pooling overall estimates for any cancers and solid cancers as "any/solid" cancers) and stage (any, metastatic, non-metastatic). Estimates for specific non-hematological cancer types were extracted where available, with no meta-analyses for specific cancer types possible due to different effect measures and study populations. To gain insights into the magnitude of risk increase for COVID-19-related death by time since cancer diagnosis/treatment, random-effects meta-regressions were applied to assess the associations between effect estimates from original studies and the corresponding periods since cancer diagnosis/treatment. Estimates from the same study were treated as independent since existing methods that account for dependency either do not allow covariates to vary within studies,[11] require a sufficiently large number of studies (10+) to estimate robust variances,[13] or require the referent group (ie, people without cancer) to have values of the continuous covariate (ie, time since cancer diagnosis/treatment).[14] In the meta-regressions, the time since diagnosis/treatment for each original estimate was assigned to mid-points of the corresponding period in the corresponding exposure group where possible (eg, 0.5 years for <1 year postdiagnosis/treatment); estimates for 1+ years since diagnosis/treatment were assigned to 2 years, with sensitivity analyses based on 3 and 5 years; estimates for 5+ years since diagnosis/treatment were assigned to 6 years, with sensitivity analyses based on 8 and 10 years.

Statistical heterogeneity was assessed with the I^2 statistic.

There were insufficient studies to undertake pre-specified subgroup analyses (study period 2020 only vs 2020/2021; pre-print only; study country; covariates included in adjustment).

2.7 | Reporting bias assessment

None of the meta-analyses of adjusted effect estimates included 10+ studies, so we did not conduct pre-planned assessments of publication bias using visual inspection of funnel plot asymmetry and Egger's statistical test.[15]

3 | RESULTS

Searches identified 23 773 unique records: 17387 in the original search in December 2021, and 10 461 records in a search update in May 2023, of which 4075 were already included in the original search (Figure 1). In total, 39 studies met the inclusion criteria (Figure 1; Data S2 shows the reasons for exclusion for each article at full-text review). The 39 studies included data from 12 countries (Table 1).[16-54] After exclusion of studies due to overlapping data, 33 studies were included in the quantitative analyses, of which 28 were included in the main analyses (including analyses restricted to

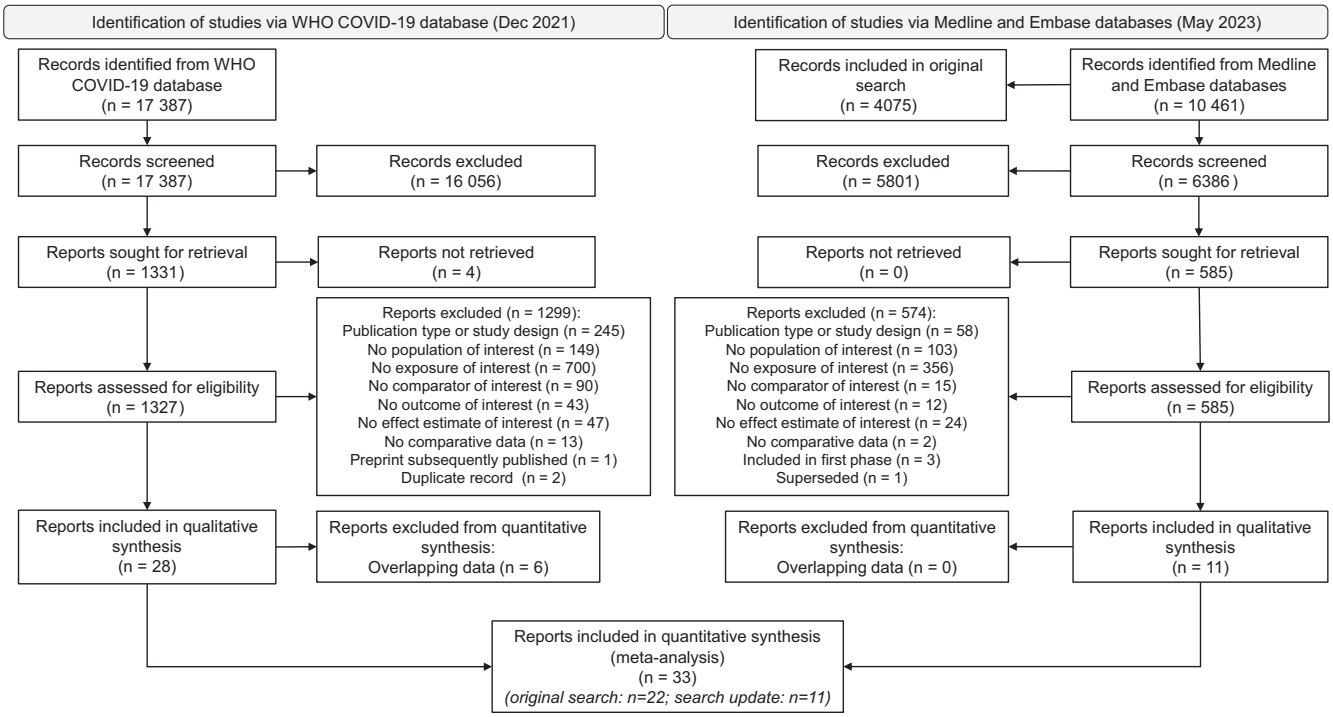


FIGURE 1 Flow diagram based on the PRISMA 2020 flow chart summarizing the article screening process.

cancer types or metastatic/non-metastatic cancers), with data from >27 565 252 individuals including >229 642 people with active or recent cancer. Of these 28 studies, 4 focused on the general population, 9 on all people with COVID-19 and 16 on hospital inpatients with COVID-19 (one study provided results for both the general population and all people with COVID-19). We note that there remain overlaps between data from studies that contributed to different meta-analyses (eg, Bhaskaran 2021 reported ORs of COVID-19-specific death for people with solid cancers, Williamson 2020 reported HRs of COVID-19-related death for people with any cancer, using overlapping data), thus the number of individuals above is a conservative estimate based on the largest study for each country only. Of the 28 studies, 22 provided eligible estimates for any/solid cancers, 6 for hematological cancers (as a group), 4 for specific cancer types; 6 provided eligible estimates for metastatic and 6 for non-metastatic cancers. Of the 28 studies contributing to main analyses, 1 had low, 13 moderate and 14 high risk of bias overall (Figure S1). Risk of bias was low for 1 of 5 studies included in sensitivity analyses, with moderate to high risk for the other 4 studies included in sensitivity analyses (3 moderate, 1 high) and for all 6 studies not included in quantitative analyses due to overlapping data (1 moderate, 5 high). The main sources of bias were limited adjustment for key confounders (only 3 studies[16-18] had low risk rating, with the adjustments used in individual studies detailed in Table S3) and potential over-adjustment.

The results of main analyses are shown in Table 2, with additional supplementary analyses in Table S4 (generally showing robust results for alternative selection of estimates from studies with overlapping data). Analyses of the general population found higher risk of COVID-19-related death for people with any or solid active/recent cancer (aHR = 1.72 [95% CI: 1.50-1.97], 1 study[19]; aOR = 1.48 [1.36-1.61], 3 studies),[20-22] with moderate to high risk of bias of contributing studies due to potentially incomplete adjustment for comorbid conditions (see Figure S1 and Table S3). Based on three of these studies, risk estimates were higher (non-overlapping 95% CIs) for hematological cancers (aHR = 2.80 [2.08-3.77], 1 study[19]; aOR = 2.13 [1.68-2.68], 2 studies).[20,21]

Risk estimate results were similar based on studies of hospital inpatients with COVID-19, with a slightly lower aHR estimate for any/solid cancers (any/solid cancer: aHR = 1.34 [1.19-1.50], 5 studies[23-27]; aOR = 1.66 [1.34-2.06], 8 studies[28-35]; hematological cancer: aOR = 2.20 [1.97-2.46], 1 study[30]). For studies of hospital inpatients with COVID-19, there was moderate to high overall risk of bias in the hazard ratio meta-analysis (moderate risk for one study contributing 52% weight, and high risk of bias for other studies due to exposure measurement or potential over-adjustment), and moderate to high risk of bias in the odds ratio meta-analyses (four studies and 50% weight with moderate and high overall risk of bias each, due to exposure measurement, adjustment for confounders or potential over-adjustment).

Four studies provided risk estimates for specific cancer types (Tables 2 and S5), with multiple studies covering breast, colorectal, lung and prostate cancers and one study covering nine additional cancer types.[16,18,20,37] In three of four studies, risk of COVID-19-related death was elevated for people with lung cancer (eg, aHR = 4.00 [3.50-4.57] for <2 years and 1.70 [1.40-2.07] for 2-5 years after cancer management,[16] compared to people without cancer, low overall

TABLE 1 Characteristics of included studies (with studies identified in the original search shown in white and studies identified in the search update shown in blue).

Study	N	Population	Setting	Period	Exposure definition	Exposure – Cancer type and stage					Comparator	Mortality outcome	Analyses included in
						Any/ mixed	Solid	Hematological	Specific cancer types	Stage			
China													
Chai et al.[35]	664	C19 inpatients	Multiple hospitals	01/20 to 03/20	Cancer treatment <1.25 years ago	X				All	No cancer	In hospital	M, T
Croatia													
Piskac-Zivkovic et al.[33]	4014	C19 inpatients	Single hospital	03/20 to 03/21	Active or current cancer	X				All/Met	No cancer	In hospital	M
England													
Williamson et al.[19]	17 278 392	General population	~40% of population	02/20 to 05/20	Cancer diagnosis <1, 1-4.9, ≥5 years ago		X	X		All	No cancer	C19-related	M
Bhaskaran et al.[21]	17 456 515	General population	~40% of population	02/20 to 11/20	Cancer diagnosis <1, 1-4.9, ≥5 years ago		X	X		All	No cancer	C19-specific	M, T
Galloway et al.[27]	1156	C19 inpatients	Multiple hospitals	03/20 to 04/20	Active or current cancer	X				All	No active cancer	In hospital	M
Navaratram et al.[39]	88 920	C19 inpatients	National	03/20 to 05/20	Cancer management <1 year ago	X				NM/Met	No active cancer	In hospital	NI
Gray et al.[31]	117 438	C19 inpatients	National	03/20 to 09/20	Cancer management <1 year ago	X				NM/Met	No active cancer	In hospital	M
Bottle et al.[40]	74 484	C19 inpatients	National	03/20 to 07/20	Active or current cancer	X				All	No active cancer	In hospital	S
France													
Peron et al.[41]	301	C19 inpatients	Multiple hospitals	03/20 to 04/20	Cancer treatment <5 years ago	X				All	No cancer	In hospital	NI
Bernard et al.[30]	89 530	C19 inpatients	National	03/20 to 04/20	Active or current cancer	X	X	X		NMS/Met	No active cancer	In hospital	M
Ouattara et al.[25]	72 601	Non ICU C19 inpatients	National	01/20 to 06/20	Cancer management <2 years ago	X				All	No active cancer	In hospital	M, T
Semenzato et al.[16]	87 809	C19 inpatients	National	02/20 to 07/20	Cancer management <2, 2-5 years ago				X	All	No cancer	In hospital	M
Italy													
Andreano et al.[42]	18 286	All C19	Jurisdictional	02/20 to 04/20	Cancer management <1, 1-5, 5-10 years ago[a]	X				All	No active cancer	C19-related	M, T
Northern Ireland													
Bucholc et al.[32]	6036	C19 inpatients	National	03/20 to 01/21	Active or current cancer		X			NM	No active cancer	In hospital	M

(Continues)

TABLE 1 (Continued)

Study	N	Population	Setting	Period	Exposure definition	Exposure – Cancer type and stage					Comparator	Mortality outcome	Analyses included in
						Any/ mixed	Solid	Hematological	Specific cancer types	Stage			
Scotland													
Leslie et al.[43]	18 099	All C19	National	03/20 to 07/20	Cancer management <5 years ago	X				All	No active cancer	C19-related	M
South Africa													
Jassat et al.[29]	219 265	C19 inpatients	Multiple hospitals	03/20 to 03/21	Cancer management <5 years ago	X				All	No active cancer	In hospital	M, T
South Korea													
Kang & Kong[44]	3827	All C19	National	01/20 to 04/20	Active or current cancer	X				All	No active cancer	C19-related	NI
Lee et al.[45]	7339	All C19	National	NR to 05/20	Cancer management <3 years ago	X				All	No active cancer	C19-specific	S, T
Choi et al.[46]	7590	All C19	National	NR to 05/20	Cancer management <1.5 years ago	X				NM	No active cancer	C19-related	M, T
Kim et al.[47]	7590	All C19	National	NR to 05/20	Cancer management <3 years ago	X				All	No active cancer	C19-related	M
Cho et al.[48]	7590	All C19	National	NR to 05/20	Cancer management <1.5 years ago	X				All	No active cancer	C19-specific	NI
Spain													
Berenguer et al.[26]	4035	C19 inpatients	Multiple hospitals	NR to 03/20	Active or current cancer	X				All	No active cancer	In hospital	M
Roel et al.[49]	13 206	C19 inpatients	Jurisdictional	03/20 to 05/20	Cancer diagnosis <1, 1-5, >5 years ago[a]	X	X			All	No cancer	C19-related	S, T
Rubio-Rivas et al.[34]	17 122	C19 inpatients	Multiple hospitals	03/20 to 07/20	Active or current cancer	X				All	No active cancer	In hospital	M
Mostaza et al.[22]	41 603	General population All C19 ^ C19 inpatients	Jurisdictional	03/20 to 01/21	Cancer management <5 years ago	X				All	No active cancer	C19-related	M, S, T
Sweden													
Larfors et al.[20]	8 111 041	General population	National	03/20 to 06/20	Active or current cancer[b]	X		X	X	All	No active cancer	C19-related	M, T
USA													
Harrison et al.[50]	31 461	All C19	Multiple hospitals	01/20 to 05/20	Cancer management ≤5 years ago	X				NM/Met	No active cancer	C19-related	M, S

TABLE 1 (Continued)

Study	N	Population	Setting	Period	Exposure definition	Exposure – Cancer type and stage					Comparator	Mortality outcome	Analyses included in
						Any/ mixed	Solid	Hematological	Specific cancer types	Stage			
Chavez-MacGregor et al.[51]	507 307	All C19	Multiple hospitals	01/20 to 12/20	Radiotherapy or systemic therapy <0.25 years ago	X				All	No active cancer	C19-related	M, T
Wang et al.[23]	3273	C19 inpatients	Multiple hospitals	02/20 to 04/20	Active or current cancer	X				All	No active cancer	In hospital	M
Brar et al.[24]	585	C19 inpatients	Multiple hospitals	03/20 to 05/20	Active or current cancer	X				All	No cancer	In hospital	M, T
Alpert et al.[52]	5556	C19 inpatients and hospital attendees	Multiple hospitals	03/20 to 05/20	Active or current cancer	X				All	No active cancer	C19-related	NI
Incerti et al.[36]	13 658	C19 inpatients	Multiple hospitals	02/20 to 05/20	Cancer management <1 year ago	X				NM/Met	No active cancer	In hospital	M, S
Fu et al.[53]	4186	C19 inpatients	Multiple hospitals	03/20 to 05/20	Cancer management <1.2 years ago	X				All	No cancer	In hospital	NI
Rosenthal et al.[38]	35 302	C19 inpatients	Multiple hospitals	04/20 to 05/20	Active or current cancer	X				Met	No cancer	In hospital	M
Isath et al.[28]	1 678 995	C19 inpatients	Multiple hospitals	01/20 to 12/20	Active or current cancer	X				All	No active cancer	In hospital	M
Nolan et al.[17]	54 036	C19 inpatients	Multiple hospitals	02/20 to 12/20	Active or current cancer	X				All	No cancer	In hospital	S
Kim et al.[37]	263 605	All C19	Multiple hospitals	06/20 to 12/20	Cancer diagnosis <1, >1 years ago	X	X	X	X	All/Met	No cancer	C19-related	M, S, T
Chen et al.[18]	116 426	All C19	Multiple hospitals	02/20 to 08/20	Cancer diagnosis <1, >1 years ago			X	X	All	No cancer	C19-related	M
Raez et al.[54]	4870	C19 inpatients	Multiple hospitals	03/20 to 01/21	Active or current cancer	X				All	No active cancer	In hospital	S

Abbreviations: C19, COVID-19; ICU, intensive care unit; M, main meta-analyses (all analyses shown in Table 2, including analyses of specific cancer types or metastatic or non-metastatic cancers); Met, metastatic; NI, not included in any analyses due to data overlap with other studies; NM, non-metastatic; NMS, non-metastatic solid; NR, not reported; S, sensitivity meta-analyses; T, analyses explicitly considering time since cancer management, treatment or diagnosis.

[a]Potentially overlapping periods of years postdiagnosis/treatment are listed here as reported in the original publication, noting overlap would likely be absent/minimal if time since diagnosis/treatment was calculated with sufficient precision ^ aged >75 years.

[b]No chemotherapy <3 months ago.

TABLE 2 Overview of main results (Forest plots for meta-analyses of multiple studies are shown in Figures S2 to S10; sensitivity analyses are shown in Table S4, with forest plots in Figures S11 to S20).

Analysis	Population	Cancer type[a]	Measure of effect	Number of studies	People with cancer[b]: dead	People with cancer: total	Comparator: dead	Comparator: total	Total	Pooled/reported effect estimate (95% CI)	I^2 (p-het)	Risk of bias summary[c]
1	General population	Any	HR	1	220	79 964	9132	16 421 922	17 278 392	1.72 (1.50-1.97)	n/a	1 M
2	All people with COVID-19	Any	HR	1	54	569	171	7021	7590	1.62 (1.19-2.20)	n/a	1 H
3	Hospital inpatients with COVID-19	Any	HR	5	259	10 150	1743	71 500	81 650	1.34 (1.19-1.50)	37% (0.17)	1 M, 4 H
4	General population	Hematological	HR	1	43	8704	10 590	17 178 486	17 187 190	2.80 (2.08-3.77)	n/a	1 M
5	All people with COVID-19	Hematological	HR	1	22	170	3073	115 750	115 920	2.26 (1.48-3.45)	n/a	1 H
6	All people with COVID-19	Lung	HR	1	30	395	3014	114 598	114 628	1.42 (0.99-2.04)	n/a	1 H
7	Hospital inpatients with COVID-19	Breast	HR	1	142	630	5876	39 550	40 180	1.80 (1.52-2.12)	n/a	1 L
8	Hospital inpatients with COVID-19	Colorectal	HR	1	167	615	15 244	86 296	86 911	1.40 (1.20-1.63)	n/a	1 L
9	Hospital inpatients with COVID-19	Lung	HR	1	233	621	13 328	86 887	87 508	4.00 (3.50-4.57)	n/a	1 L
10	Hospital inpatients with COVID-19	Prostate	HR	1	337	1029	8577	44 313	45 342	1.20 (1.08-1.34)	n/a	1 L
11	General population	Any	OR	3	1240	158 311	29 301	25 422 651	25 580 962	1.48 (1.36-1.61)	0% (0.59)	2 M, 1 H
12	All people with COVID-19	Any	OR	5	1199	8271[d]	13 778	556 524[d]	564 795[d]	1.58 (1.41-1.77)	58% (0.05)	4 M, 1 H
13	Hospital inpatients with COVID-19	Any	OR	8	17 837[d]	77 654	295 094[d]	2 022 283	2 099 937	1.66 (1.34-2.06)	98% (<0.001)	4 M, 4 H
14	General population	Hematological	OR	2	140	32 497	21 130	25 257 249	25 406 851	2.13 (1.68-2.68)	43% (0.18)	1 M, 1 H
15	All people with COVID-19	Hematological	OR	1	NR	2224	NR	253 179	255 403	1.48 (1.30-1.68)	n/a	1 M
16	Hospital inpatients with COVID-19	Hematological	OR	1	470	1389	13 057	83 329	84 718	2.20 (1.97-2.46)	n/a	1 H
17	General population	Breast	OR	1	31	32 429	4566	7 901 764	7 934 193	1.0 (0.7-1.4)	n/a	1 H
18	General population	Colorectal	OR	1	50	19 706	4566	7 901 764	7 921 470	1.2 (0.9-1.5)	n/a	1 H
19	General population	Lung	OR	1	34	6537	4566	7 901 764	7 908 301	3.4 (2.4-4.7)	n/a	1 H
20	General population	Prostate	OR	1	96	45 057	4566	7 901 764	7 946 821	1.0 (0.8-1.2)	n/a	1 H
21	All people with COVID-19	Bladder	OR	1	NR	476	NR	253 179	253 655	0.80 (0.63-1.05)	n/a	1 M
22	All people with COVID-19	Breast	OR	1	NR	2143	NR	253 179	255 322	1.08 (0.88-1.32)	n/a	1 M
23	All people with COVID-19	Colorectal	OR	1	NR	794	NR	253 179	253 973	0.91 (0.69-1.19)	n/a	1 M
24	All people with COVID-19	Endometrial	OR	1	NR	291	NR	144 976	145 267	1.62 (0.96-2.74)	n/a	1 M
25	All people with COVID-19	Kidney	OR	1	NR	474	NR	253 179	253 653	1.15 (0.86-1.53)	n/a	1 M
26	All people with COVID-19	Leukemia	OR	1	NR	681	NR	253 179	253 860	1.58 (1.29-1.93)	n/a	1 M

TABLE 2 (Continued)

Analysis	Population	Cancer type[a]	Measure of effect	Number of studies	People with cancer[b]: dead	People with cancer: total	Comparator: dead	Comparator: total	Total	Pooled/reported effect estimate (95% CI)	I^2 (p-het)	Risk of bias summary[c]
27	All people with COVID-19	Liver	OR	1	NR	207	NR	253 179	253 386	2.46 (1.80-3.36)	n/a	1 M
28	All people with COVID-19	Lung	OR	1	NR	887	NR	253 179	254 066	1.85 (1.58-2.17)	n/a	1 M
29	All people with COVID-19	Melanoma	OR	1	NR	409	NR	253 179	253 588	0.96 (0.67-1.38)	n/a	1 M
30	All people with COVID-19	Non-Hodgkin's lymphoma	OR	1	NR	692	NR	253 179	253 871	1.02 (0.78-1.33)	n/a	1 M
31	All people with COVID-19	Pancreatic	OR	1	NR	121	NR	253 179	253 300	1.94 (1.19-3.16)	n/a	1 M
32	All people with COVID-19	Prostate	OR	1	NR	1781	NR	108 203	109 984	0.82 (0.70-0.96)	n/a	1 M
33	All people with COVID-19	Thyroid	OR	1	NR	476	NR	253 179	253 655	0.83 (0.46-1.51)	n/a	1 M
34	All people with COVID-19	Non-metastatic	OR	2	245	2523	1278	36 528	39 051	1.12 (0.65-1.93)	84% (0.01)	1 M, 1 H
35	Hospital inpatients with COVID-19	Non-metastatic	OR	4	3956	13 982	45 466	240 169	254 151	1.39 (1.19-1.63)	88% (<0.001)	2 M, 2 H
36	All people with COVID-19	Metastatic	OR	2	51[e]	1891	1245[e]	284 212	286 103	2.02 (1.74-2.35)	11% (0.29)	1 M, 1 H
37	Hospital inpatients with COVID-19	Metastatic	OR	4	2113[d]	7520	43 924[d]	266 625	274 145	2.50 (1.81-3.45)	94% (<0.001)	3 M, 1 H
	Total across all analyses[e]:				28 969[d]	522 270[d]	556 374[d]	122 281 095	122 803 365			

[a]Meta-analyses of risks for people with any cancer may include estimates based on solid cancers only, for studies where no estimates based on all cancers were available.
[b]Selection of people with cancer was study-dependent, and could include "active" cancer as noted in medical records or cancer diagnosed or treated in a specific period (eg, <1 year). For studies with multiple cancer groups (eg, diagnosed <1 year, 1-5 years or 5+ years before the study period), the effect estimate for the group with most recent cancer diagnosis/treatment was included in the meta-analysis.
[c]Number of studies with high (H), moderate (M) and low (L) overall risk of bias rating. The risk of bias for all studies and domains is shown in Figure S1.
[d]Deaths for both cancer and comparator groups are underestimated as some studies did not report final numbers for adjusted analyses.
[e]Total includes multiple counts of the same studies and people included in different analyses.

risk of bias; and aOR = 3.4 [2.4-4.7] for <4.5 years after cancer diagnosis without chemotherapy in previous 3 months,[20] compared to people with no active cancer, high risk of bias due to adjustment for age and sex only), with a trend for association but no statistical significance in one smaller study with high risk of bias (aHR = 1.49 [0.99-2.04] for <1 year after diagnosis compared to people without cancer[18]; 395 people with lung cancer, vs 621-6357 in other three studies). For breast, colorectal and prostate cancers, evidence was more mixed: one study reported elevated risks for people <2 years after cancer management (aHR = 1.80 [1.52-2.12], 1.40 [1.20-1.63], 1.20 [1.08-1.34], respectively, low risk of bias),[16] with no significant risk increase for people 2 to 5 years after cancer management in the same study[16]; another study found no significant risk increase for people <1 year post-diagnosis (with a decreased risk for prostate cancer, aRR = 0.82 [0.70-0.96], moderate risk of bias),[37] and a third study found no significant risk increase for the broader group of people <4.5 years after cancer diagnosis without chemotherapy in the previous 3 months (high risk of bias).[20] One study that reported on 9 additional cancer types found increased risks for people <1 year after diagnosis of liver cancer (aRR = 2.46 [1.80-3.36]) and pancreatic cancer (aRR = 1.94 [1.19-3.16]), compared to people without cancer (among all people with COVID-19; moderate risk of bias).[37] Our study also found increased risks for people <1 year after diagnosis of leukemia (aRR = 1.58 [1.29-1.93], lower than for analyses of all hematological cancers together as described above; noting that our study also reported lower estimates for other cancers compared to other studies and had unclear risk of bias for several items, see Figure S1).

Pooled effect estimates were higher for metastatic than non-metastatic cancers, with non-overlapping 95% CIs from studies of hospital inpatients with COVID-19 (metastatic cancers: aOR = 2.50 [1.81-3.45], 4 studies[30,31,33,38]; non-metastatic cancers: aOR = 1.39 [1.19-1.63], 4 studies).[30-32,36] There was moderate to high overall risk of bias in these meta-analyses (high risk for 1 of 4 studies and 2 of 4 studies, respectively, all due to potential over-adjustment).

Many of the meta-analyses had high heterogeneity estimates (Table 2), which could not be investigated further due to small numbers of included studies in each analysis.

Plots of risk estimates by time since cancer diagnosis/treatment suggested that risk of COVID-19-related death was highest for people with most recently diagnosed/treated cancers (Figure 2). Consequently, Figure 3 shows the results of meta-regressions to explicitly examine the relationship between risk of COVID-19-related death and time since cancer diagnosis/treatment. Combining information across odds and risk ratio estimates for risk of COVID-19-related death for any/solid cancers across studies of different populations, the fitted estimates yielded an aOR of 1.55 (95% CI: 1.37-1.75) for 1 year post diagnosis/treatment, which was reduced to 1.38 (1.24-1.53) at 2 years and 0.98 (0.80-1.20) at 5 years (Figures 3A,D). Notably, the decline in risk varied between different studies that provided estimates for multiple periods after diagnosis/treatment (Figure 3B,D). The 95% confidence intervals included an aOR of 1 from 3.6 years postdiagnosis/treatment, with a corresponding estimate of 4.4 years from the hazard ratio analysis (Figure 3D), noting that these confidence intervals could not completely capture the non-independence of estimates in the analyses (with some studies contributing estimates for multiple periods post diagnosis/treatment). Based on three studies that provided aORs of COVID-19-related death for hematological cancers, the fitted estimates yielded an aOR of 1.93 (95% CI: 1.26-2.94) for 1 year postdiagnosis/treatment, which was reduced to 1.90 (1.34-2.70) at 2 years and 1.81 (1.07-3.07) at 5 years, with the 95% confidence intervals including an aOR of 1 from 5.5 years post diagnosis/treatment (Figure 3C,D). Results from sensitivity analyses were similar, with higher fitted estimates at 5 years post diagnosis/treatment showing that estimates of excess risk for this subgroup in the main meta-regression may be conservative. For example, in the analysis of aORs for any/solid cancers, fitted aORs at 5 years post diagnosis/treatment were 1.09 (0.93-1.29) and 1.18 (1.02-1.35) when coding original study estimates for 1+ years and 5+ years as 3 and 8 years or 5 and 10 years post diagnosis/treatment, respectively; Table S6). These sensitivity analyses thus also estimated a longer period until the fitted 95% confidence intervals including an aOR of 1 (eg, for aORs for any/solid cancers, at 4.3 and 5.2 years post diagnosis/treatment, respectively; Table S6).

4 | DISCUSSION

Our systematic review and meta-analysis synthesized data on the risk of COVID-19-related death for people with cancer across 28 studies reporting on >27.5 million individuals and >291 271 deaths from 12 countries. The review highlighted the increased risk of COVID-19-related death for people with recently diagnosed/treated cancers. Moreover, we have consolidated the available evidence on risks by cancer type and stage, documenting evidence for higher risk of COVID-19-related death for people with lung and hematological cancers (with mixed evidence for some other cancer types) and for metastatic cancers. While this review focused on higher-quality evidence, the risk of bias assessment also highlighted some remaining limitations in the current evidence, especially comprehensive adjustment for potential important confounders.

Importantly, through focus on the pre-COVID-19-vaccination phase of the pandemic, the data contributing to this review are not confounded by differential COVID-19-vaccine availability for people with and without cancer. With high rates of COVID-19 vaccination in high-income countries, clinical decision-making in these settings largely relates to vaccinated individuals. However, our study can support future work assessing the effects of COVID-19 vaccination in people with cancer for both individual- and population-level outcomes. Moreover, the increased risk of COVID-19-related death for people with recently diagnosed/treated cancers confirms the need to consider these groups for prioritization of COVID-19-vaccination in settings with limited vaccine availability. In particular, there have been substantial inequities in vaccine availability between countries, with ~33% of people in low- and middle-income countries not having received a COVID-19 vaccine and ~40% not fully vaccinated as of 28 August 2023.[9,55] Subject to differences between different SARS-

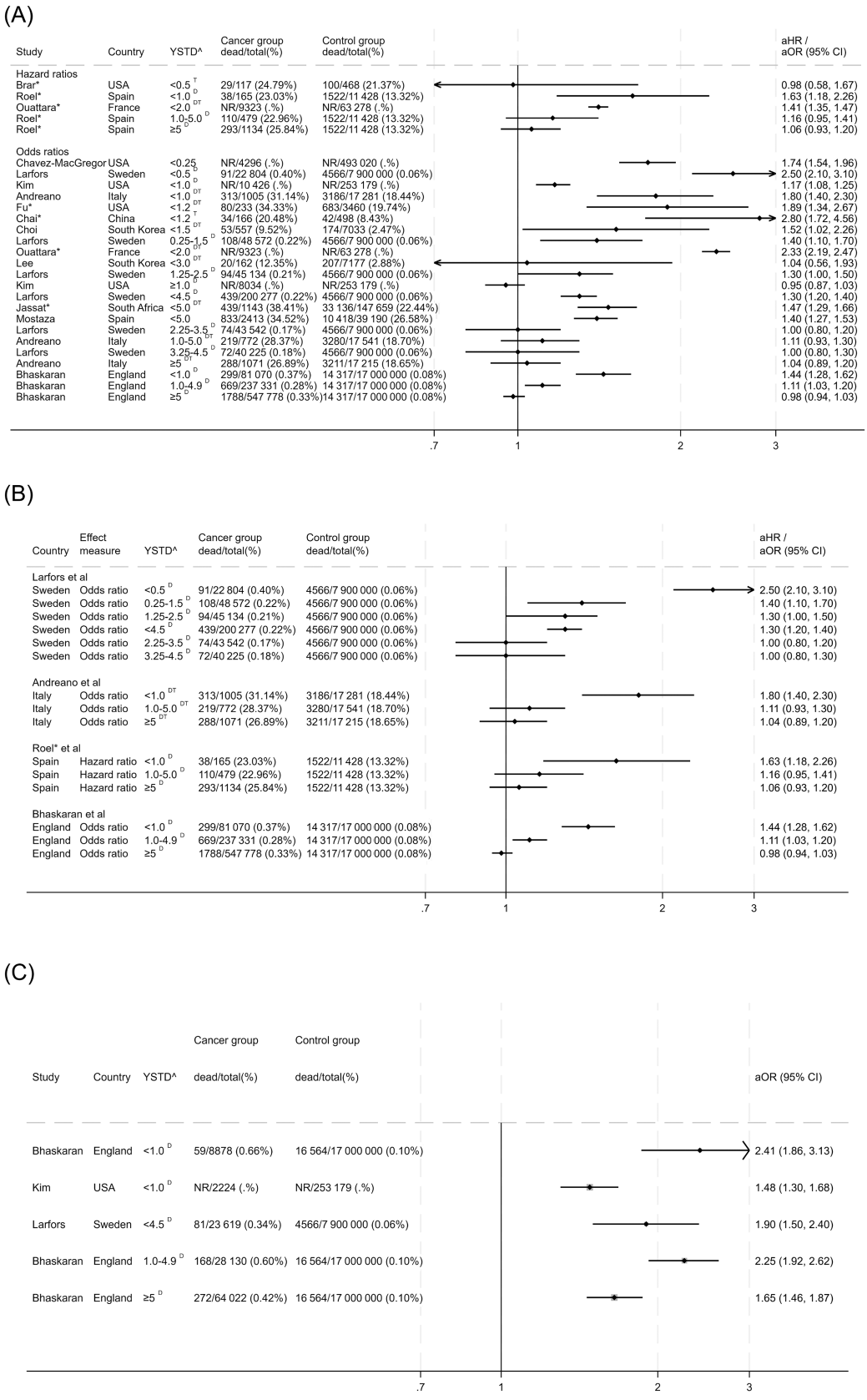
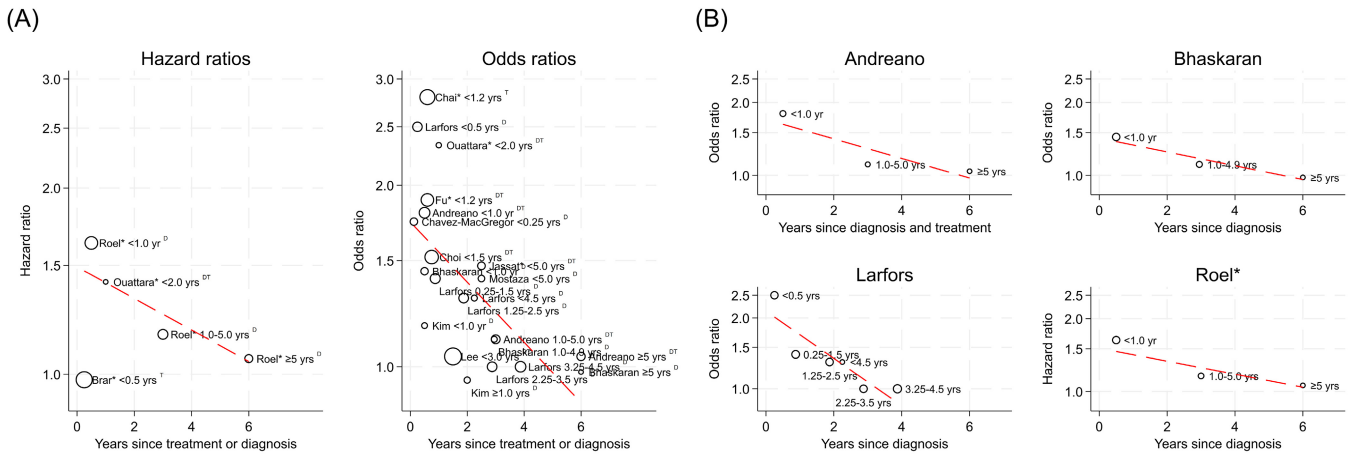


FIGURE 2 Risk of COVID-19-related death by time since cancer diagnosis or treatment. (A) Any/solid cancers. (B) Within-study comparisons, any/solid cancers. (C) Hematological cancers. *Studies of hospital inpatients with COVID-19. aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted rate ratio; CI, confidence interval; D, years since diagnosis; DT, years since diagnosis or treatment; NR, not reported; T, years since treatment.



(D)

Analysis	Resid. I^2	Risk change (aOR/aRR/aHR) per year increase in time since diagnosis/treatment: Estimate (95%CI)	*P*-value	Predicted OR/RR/HR values (95%CIs) at 1, 2, 5 years post diagnosis/treatment: 1 year	2 years	5 years	Minimum years post diagnosis/ treatment with lower limit of predicted value 95%CI being ≤1.00
Any/solid cancers, HRs	11%	0.94 (0.90, 0.99)	.026	1.41 (1.31, 1.51)	1.33 (1.24, 1.42)	1.11 (0.94, 1.32)	4.4
Any/solid cancers, ORs	95%	0.89 (0.84, 0.95)	.001	1.55 (1.37, 1.75)	1.38 (1.24, 1.53)	0.98 (0.80, 1.20)	3.6
Any/solid cancers, Andreano et al	76%	0.91 (0.48, 1.72)	.314	1.55 (0.19, 12.36)	1.41 (0.27, 7.47)	1.07 (0.19, 6.08)	n/a^
Any/solid cancers, Bhaskaran et al	65%	0.94 (0.74, 1.19)	.176	1.33 (0.59, 3.01)	1.25 (0.65, 2.39)	1.03 (0.56, 1.89)	n/a^
Any/solid cancers, Larfors et al	64%	0.79 (0.67, 0.94)	.019	1.70 (1.31, 2.19)	1.35 (1.11, 1.64)	0.67 (0.39, 1.17)	2.4
Any/solid cancers, Roel et al	8%	0.94 (0.65, 1.36)	.281	1.42 (0.32, 6.30)	1.33 (0.41, 4.34)	1.11 (0.53, 2.33)	n/a^
Haematological cancers, ORs	87%	0.98 (0.84, 1.16)	.786	1.93 (1.26, 2.94)	1.90 (1.34, 2.70)	1.81 (1.07, 3.07)	5.5

FIGURE 3 Meta-regression for risk of COVID-19-related death by time since cancer diagnosis or treatment. (A) Any/solid cancers. (B) Within-study comparisons, any/solid cancers. (C) Hematological cancers. (D) Overview of meta-regression estimates. *Studies of hospital inpatients with COVID-19. aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted rate ratio; CI, confidence interval; D, years since diagnosis; DT, years since diagnosis or treatment; n/a^, not applicable, lower limit of 95% CI is <1 for all fitted values; NR, not reported; T, years since treatment.

CoV-2 variants, the results of this review remain relevant in settings without sufficiently widespread, effective COVID-19 vaccination.

Our finding of a higher likelihood of death for people with a pre-existing diagnosis of cancer aligns with findings of evidence syntheses published during the first 12 months of the COVID-19 pandemic.[4,56-61] Similar to earlier reviews,[59,62] our included studies reported an increased mortality risk for people with COVID-19 and hematological cancers. However, earlier literature was characterized by pervasive biases and analytical limitations, including multiple sources of bias (eg, a lack of adjustment for at least age and sex), with many studies having short follow-up periods, small numbers of people with cancer, unclear definitions of cancer status and substantial overlap between data included in different early studies.[59,62] The current review indicates an advancement in the magnitude and quality of evidence being generated.

The studies included in this review reported data relating to COVID-19 cases and associated mortality, focusing on studies that reported estimates for pre-COVID-19-vaccination periods (for the studies identified in this review, predominantly in 2020). During this period, the majority of cases related to earlier strains of COVID-19, inclusive of the initial strain emerging in Wuhan, China, alongside the alpha (first detected in November 2020) and beta (first detected in October 2020) variants.[63] The COVID-19 vaccination rollout commenced in December 2020 in many jurisdictions, albeit with marked variations in the subsequent timing of vaccine program initiation, rollout, prioritization strategies and dosing schedules across countries.[64] As such, our findings are not confounded by the individual or population-level effects of vaccination, including potential mitigation of the risk of death from COVID-19. Future reviews will be needed to address the effect of vaccination, including any effect on COVID-19 mortality risk for populations with cancer.

During the earlier phases of the pandemic, SARS-CoV-2 testing availability was limited due to factors including shortages of reagents and, for many low- and middle-income countries, a lack of well-equipped laboratories with specialized staff.[65] This may be reflected by included studies using COVID-19-related death as an outcome (ie,

deaths from any cause after COVID-19 diagnosis, not just COVID-19-specific deaths). The use of a broader outcome (including in-hospital mortality for hospital inpatients with COVID-19) may have led to cancer deaths contributing to an elevated risk of death being reported within the review, in particular, for metastatic cancers or specific cancers with high mortality (eg, lung, liver or pancreatic cancer). However, for studies of any cancers, this contribution is likely to be relatively small (when considering the general population or all people with COVID-19) given the generally short follow-up period across the included studies (although the follow-up time was not systematically reported in primary studies), and our meta-analyses were carried out separately for different study populations (general population, all people with COVID-19, hospital inpatients with COVID-19), with generally similar results (see Supplementary Text in Data S1 for further discussion of this aspect). The limited follow-up periods highlight a need for long-term data to inform risks of adverse health outcomes for people with cancer over a longer time horizon. This includes a need to understand the impact of treatment disruption and the longer-term health effects of COVID-19, including long COVID, that could lead to adverse health outcomes for people with cancer. Such studies were beyond the scope of this review.

A key component to consider in future longer-term data collection is the inclusion of patient-reported outcomes. Studies to date suggest that for people with cancer, over half of the population experienced long-term effects after their initial COVID-19 diagnosis,[66] with some sequelae persisting in 8% to 10% of patients 6 and 12 months after COVID-19 resolution.[67] More generally, the potential impact of cancer diagnosis and treatment delays and disruptions on quality of life and psychosocial well-being is an important area that needs further study.[68]

There remains a need for more nuanced analyses to increase understanding of any differential impact of COVID-19 on people with cancer, with conflicting evidence on the impact of different patient characteristics to date. For example, existing reviews outlined an increased risk of COVID-19 mortality with advancing age,[57] comparable all-cause mortality between those over 65 years of age with cancer vs those without cancer,[58] and an association between younger age in patients with cancer and SARS-CoV-2 with poorer clinical outcomes.[62] While our review only included estimates adjusted for age and sex, the reporting in original studies did not allow for stratified meta-analyses by these factors, and more research is needed on potential interactions between cancer status and these biological characteristics. Similarly, to understand the potential inequities in COVID-19 outcomes for people with cancer, it will be crucial to consider the impact of societal factors including ethnicity and/or socioeconomic status on risk of COVID-19-related death, as well as their association with availability and uptake of COVID-19 vaccination.

The results of our meta-regression analyses also suggest that more detailed estimates of COVID-19-related death for people 5 to 10 years after cancer diagnosis/treatment would be needed to confirm the extent of risk in this population, including any differences in risk by treatment received (noting that the details on type of cancer treatment were not generally reported in the studies included in this review). The extent of these risks would be of interest vis-a-vis decisions around prioritization of COVID-19 vaccination (both past decisions and future decisions in settings without widespread effective vaccination). For example, the European Society for Medical Oncology statement suggested higher risk for people in the first 5 years after diagnosis[69] based on one of the studies included in this review,[19] with this threshold being compatible with our meta-regression results. Similarly, individuals with cancer up to 5 years post-diagnosis were prioritized for vaccination in Australia (included in phase 1b of the roll-out, alongside those receiving active treatment or with advanced disease),[70] which is also compatible with our results.

More generally, improved granularity is needed in assessing COVID-19 mortality according to cancer stage and treatment. The available evidence for cancer treatment impacts is mixed, with different studies suggesting an increased risk for COVID-19 death while receiving antitumor treatment,[71] no association between receipt of a particular type of oncologic therapy and COVID-19 mortality,[59] or higher risks for patients undergoing chemotherapy and lower risks for those receiving endocrine therapy.[62] Existing large studies have largely used government or third-party data, which cannot be easily on-provided to other researchers and require extensive access approvals (see Data S3). Thus, an individual-level meta-analysis of large studies included in this review was not possible at the current time, and future dedicated consortium efforts would be required to re-analyze the data by cancer stage and/or treatment.

Future analyses may also need to account for the impact of different COVID-19 variants on mortality. Within the period for which data is reported across the studies included in this review, the alpha variant emerged and was both more transmissible and had an increased risk of mortality.[72] The risk of severe outcomes in future periods would also depend on the circulating SARS-CoV-2 variants, alongside the impact of previous SARS-CoV-2 infection and COVID-19 vaccination programs (including original and booster vaccines).[73]

The requisite infrastructure required to undertake high-quality research to determine the impact of COVID-19 on people living with cancer involves access to large-scale collections of rapidly-available data, ideally based on linkages between cancer and immunization registries at the whole-of-population level. Population-based cancer registries provide a vital role in assessing the cancer burden for a country, alongside supporting the monitoring and evaluation of progress in cancer control.[74] As outlined in a previous review by our research team,[4] the provision of real-time information remains a challenge for many population-based registries, and special investments in infrastructure are needed to ensure high-quality near-time record linkage and accurate assessments of health impacts. In recent years, there has been investment in infrastructure and equipment to guide responses to the COVID-19 pandemic.[75] Sustaining the infrastructure that supports data linkages is acknowledged as having value in non-pandemic times, enabling monitoring and insights into diseases, including cancer and, for example, cardiovascular diseases or HIV.[76-78] In particular, there is a need to continue strengthening population-based cancer registries, particularly in low- and middle-income countries (LMICs), with the potential to leverage investments in electronic health information systems to monitor outbreaks.[79] The pandemic has had

profound effects on the health of populations across LMICs, including people living with cancer. The scarcity of data from these settings means that the impact in such settings is not well understood,[80] also noting this review did not identify any eligible study from LMICs.

Irrespective of efforts to determine the impact of COVID-19 on people with cancer, it is critical that health systems are able to support the needs of people with cancer, including equitable access to effective treatments, supportive and palliative care and survivorship care. Care delivery needs to mitigate risks and disruptions to service delivery from the COVID-19 pandemic (and other future emergencies) as a consequence of limited healthcare capacity.

The current analysis has several limitations. We did not consider studies restricted to people with cancer (ie, studies that did not include a comparator of people without cancer). Such studies can provide information on the associations between specific cancer treatment, other health conditions and COVID-19-related deaths (eg, the US National COVID Cohort Collaborative, N3C)[81] and assess the effects of different SARS-CoV-2 strains and vaccination specifically in people with cancer (eg, OnCovid).[82] The selection criteria for the comparators were narrow, excluding studies in which the comparator included some people with active or recent cancer (eg, a study with a comparator of "no active solid cancer" would include active or recent hematological cancer, thus was excluded). Many cancer-specific risk estimates were based on one study only, with relatively small numbers of deaths. Meta-analyses pooled results from studies with different definitions of "active" cancer (with limited information provided in some studies), and studies with different comparators (eg, no cancer history vs no active cancer). The meta-regressions included results from different study populations, exact *P*-values for the slope could not be calculated as the analyses included non-independent results from individual studies (eg, risk estimates for people <1 year, 1-5 years and 5+ years after cancer diagnosis) and the non-independence could not be reflected in confidence intervals for the fitted values. The detailed distributions and median time since cancer diagnosis, treatment or management for included individuals were not systematically reported by primary studies, limiting the information available for the meta-regression. Different titles/abstracts and full-texts were assessed by different reviewers; however, training was provided to align assessment criteria.

Finally, while potential new evidence published from late 2023 was not included, the earlier focus on pre-COVID-19-vaccination avoids confounding of results by differential vaccination status among people with and without cancer, a clear strength of this review. Additional strengths include the rigorous critical assessment of evidence, including a pre-specified list of confounders to include in adjustments based on WHO clinical guidelines, and a highly comprehensive search that aggregated information from a wide range of databases. Thus, our study provides a critical benchmark with importance for future comparisons and evidence-informed decision-making to mitigate risks of death in people with cancer in the era of new COVID-19 variants and new vaccines.

In conclusion, we found evidence of a higher risk of COVID-19-related death for people recently diagnosed with cancer. However, more research is needed on how the risk of COVID-19 death depends on age, sex, as well as cancer type, stage, time since diagnosis, cancer treatment administered and time since treatment, and COVID-19 virus variant, vaccination and treatment. To accurately estimate risks, inform the ongoing public health response, and build resilience to the COVID-19 pandemic, rolling, robust, in-depth analyses of population-wide studies linking cancer and immunization registries remain important. In this context, living systematic reviews will, we hope in future, provide continued consolidation and critical evaluation of up-to-date, high-quality evidence on the impact and mitigation of the COVID-19 pandemic as well as future emergencies.

AUTHOR CONTRIBUTIONS

The work reported in the article has been performed by the authors, unless clearly specified in the text. All authors contributed to interpretation of the data and reviewed the article. Further contributions by individual authors are as follows. **Julia Steinberg:** Conception, methodology, title/abstract screening, risk of bias assessment, drafting of article, coordination/supervision. **Suzanne Hughes:** Conception, methodology, literature search, title/abstract screening, full-text screening, data extraction, risk of bias assessment, drafting of article. **Harriet Hui:** Administration, title/abstract screening, full-text screening. **Matthew J. Allsop:** Full-text screening, risk of bias assessment, drafting of article. **Sam Egger:** Methodology, risk of bias assessment, data analysis, editing of article. **Michael David:** Methodology, data extraction, risk of bias assessment, editing of article. **Michael Caruana:** Methodology, literature search, data curation, data analysis. **Peter Coxeter:** Methodology, title/abstract screening, full-text screening, data extraction. **Chelsea Carle:** Methodology, full-text screening, data extraction, risk of bias assessment. **Tonia Onyeka:** Title/abstract screening, full-text screening. **Isabel Rewais:** Title/abstract screening, full-text screening. **Maria J. Monroy Iglesias:** Title/abstract screening. **Nuria Vives:** Title/abstract screening, full-text screening. **Feixue Wei:** Title/abstract screening. **Derrick Bary Abila:** Title/abstract screening. **Giulia Carreras:** title/abstract screening, full-text screening. **Marilina Santero:** Title/abstract screening. **Emma L. O'Dowd:** Title/abstract screening, full-text screening. **Gigi Lui:** Title/abstract screening, full-text screening. **Musliu Adetola Tolani:** Title/abstract screening. **Maeve Mullooly:** Title/abstract screening, full-text screening. **Shing Fung Lee:** Title/abstract screening. **Rebecca Landy:** Title/abstract screening, full-text screening. **Sharon J. B. Hanley:** Title/abstract screening, full-text screening. **Gemma Binefa:** Title/abstract screening. **Charlene M. McShane:** Title/abstract screening. **Muluken Gizaw:** Title/abstract screening. **Poongulali Selvamuthu:** Title/abstract screening. **Houda Boukheris:** Title/abstract screening, full-text screening. **Annet Nakaganda:** Title/abstract screening. **Isil Ergin:** Title/abstract screening. **Fabio Ynoe Moraes:** Title/abstract screening. **Nahari Timilshina:** Title/abstract screening. **Ashutosh Kumar:** Title/abstract screening. **Diama B. Vale:** Title/abstract screening. **Ana Molina-Barceló:** Title/abstract screening. **Lisa M. Force:** Title/abstract screening. **Denise Joan Campbell:** Data extraction, risk of bias assessment. **Yuqing Wang:** Title/abstract screening, full-text screening. **Fang Wan:** Title/abstract screening, full-text screening. **Anna-Lisa Baker:** Title/abstract screening, full-text screening. **Ramnik Singh:** Title/abstract screening, full-text screening. **Rehana Abdus Salam:** Title/abstract screening, full-text screening. **Susan Yuill:** Full-text screening. **Richa Shah:** Methodology. **Erich V. Kliewer:** Full-text screening. **Felipe Roitberg:** Conception,

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CONFLICT OF INTEREST STATEMENT

Prof. Karen Canfell reports she is co-PI, and A/Prof Michael Caruana reports that he is an investigator, of an investigator-initiated trial of cervical screening, "Compass," run by the Australian Centre for Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity. The ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics. Prof. Canfell is also co-PI on a major implementation program "Elimination of Cervical Cancer in the Western Pacific" which receives support from the Minderoo Foundation and equipment donations from Cepheid Inc. Dr Fabio Ynoe de Moraes reports a previous consulting fee from Câncer em Foco; he also reports honoraria from AstraZeneca and IASLC, both outside of the current work. Dr Lisa M. Force reports funding from the Bill and Melinda Gates Foundation, Conquer Cancer Foundation, St. Jude Children's Research Hospital and the NIH Loan Repayment Program; these are disclosed for transparency and not believed to bias her contributions to this work. Other authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this review were reported in the original articles cited in this review, and are available upon reasonable request to the corresponding author (julia.steinberg@sydney.edu.au).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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