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Review Article

Frequency of arterial thromboembolism in populations with malignancies: A systematic review

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ABSTRACT

Background: Populations with cancer have been documented to have a greater risk of developing venous thromboembolism. The frequency of arterial thromboembolism (ATE) in cancer patients is unclear; while evidence examining this question has grown, it has yet to be systematically summarized. This study aims to systematically review the frequency of ATE in patients with cancer.

Methods: A search of MEDLINE, Embase, CENTRAL, and Web of Science from inception to 28 January, 2019 was conducted. Two independent reviewers screened for eligible studies. Studies comparing the frequency of ATE between populations with cancer and controls were included while studies examining the frequency of ATE in the context of cancer therapies (e.g., chemotherapy, radiotherapy) were excluded. Data corresponding to the follow-up times closest to diagnosis and 1-year follow-up were extracted.

Results

Twelve retrospective cohort studies involving 1,260,237 patients were included. Ten studies concluded increased ATE risk in populations with malignancies. At the time point closest to diagnosis, patients with bladder, breast, colorectal, gastric, lung, non-Hodgkin lymphoma, and pancreatic cancers were at an increased risk. This risk diminished around 1 year after diagnosis except in patients with lung or pancreatic cancers. High heterogeneity within and between studies precluded meta-analysis.

Conclusions: Patients with cancer appear to have an increased risk of developing ATE, with the highest risk immediately after diagnosis and in patients with lung and pancreatic cancers. Better information on the attribu01 risk will require prospective studies that record comprehensive patient characteristics and interventions.

1. Introduction

Patients with cancer are known to experience a greater frequency of thrombotic disease. While interest has primarily focussed on venous thromboembolism (VTE), which is about seven times more common in cancer patients than in patients without cancer, recent studies have highlighted the relationship between cancer and arterial thromboembolism (ATE) [1–4]. Thromboembolism in patients with cancer is associated with the disruption of cancer treatments, economic costs, and increased morbidity and mortality [5–7]. A relationship between cancer and arterial thrombosis has long been suspected [8–11], however understanding of older studies is confounded by specific treatment regimens that may themselves contribute to ATE and by examining only selected cancer types. More recently, matched-cohort studies using population level databases have been conducted investigating the link between incident cancer and ATE. One analysis of the Surveillance Epidemiology and End Results (SEER) database found an increased risk of ATE in patients with cancer, including its components myocardial infarction and ischemic stroke, across a number of cancer types [4]. However, this retrospective study relied on a Medicare linked database, excluded patients under the age of 66 years, used administrative diagnosis codes, and was limited to the United States. Other studies investigating the issue have examined demographically homogeneous populations, relied solely on inpatient data, or analyzed inadequate sample sizes [12–15].

To provide more information on the risk of ATE in a broad cross-section of patients with cancer, we conducted a systematic review of the literature to determine the frequency of ATE, including myocardial

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infarction and ischemic stroke. Our secondary objective was to identify the cancer types associated with the greatest risk for ATE.

2. Methods

This systematic review was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. The protocol of this study was registered before commencement in the Prospective Register of Systematic Reviews (PROSPERO CRD42019115014).

2.1. Search strategy

We searched the following databases covering the period from database inception through Jan 28, 2019: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms such as neoplasm, cancer, myocardial infarction, peripheral arterial disease, and ATE were used (complete search strategy available in supplemental Table 1). The search was designed and conducted with assistance from a medical librarian and input from study investigators. We reviewed the references of published studies and searched grey literature manually to ensure relevant articles were not missed. We did not discriminate full texts by language.

2.2. Eligibility criteria

All inclusion and exclusion criteria were determined *a priori*. Criteria for inclusion of a study were (1) observational, case-control, randomized controlled trial (RCT), or similar study design (2) including patients with any cancer or a particular cancer type (3) reporting the frequency of ATE or any of its components including myocardial infarction, ischemic stroke, and peripheral artery occlusion (4) inclusion of a comparison between patients with cancer and non-cancer controls.

Criteria for exclusion of a study were (1) study design other than those listed above, including case reports, expert opinions, reviews, uncontrolled cohort studies, and basic science papers (2) studies that did not report relevant outcomes such as incidence, prevalence, odds, or risk (3) any study that examined arterial thrombosis and malignancies in a sample restricted to a specific treatment modality (e.g., specific chemotherapy, radiotherapy, or anticoagulation), past history of disease (e.g., CAD, atrial fibrillation), genetic factors, or other factors that may confound the relationship between arterial thrombosis and malignancies (4) population of < 10 patients (5) non-human studies. If a follow-up study of the same patient population was identified, the more recent study was included.

2.3. Study screening and data abstraction

Two reviewers independently (J.Y. and A.L.) screened the searched titles, abstracts, and full texts using a piloted screening form. Discrepancies that occurred at the title and abstract screening stages were resolved by automatic inclusion to ensure that all relevant papers were not missed. Discrepancies at the full-text or data abstraction stage were resolved by consensus between two reviewers and if disagreement persisted, a third reviewer was consulted. Two reviewers independently conducted data abstraction onto a standardized spreadsheet designed *a priori*. The following data were abstracted from included studies: study characteristics (study design, country, year of publication, duration of follow-up, and setting), participant characteristics (mean age, % female, number of patients included, comorbidities), intervention details (stage and type of cancer, duration since diagnosis of cancer, follow-up time points), and outcomes (all-cause mortality, diagnosis of ATE, incidence, prevalence, odds, and risk). Data corresponding to the follow-up times closest to initial diagnosis and closest to 1 year were extracted to allow for comparison over time.

2.4. Risk of bias assessment and certainty of evidence

All studies included in this systematic review were independently assessed for quality in duplicate by 2 reviewers (J.Y. and A.L.). The assessment of methodologic quality was performed using the Newcastle-Ottawa scale [17] for all nonrandomized studies.

2.5. Statistical analysis

Descriptive statistics were calculated to reflect the frequency of outcome measures. We decided *a priori* that any cancer type that was reported on by at least two different studies and for which the frequency of overall ATE was reported would be summarized. A kappa (κ) statistic was used to evaluate inter-rater agreement for study eligibility at all screening stages. According to the guidelines created by Landis and Koch [18], agreement was categorized: 0 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; 0.81 or higher, almost perfect agreement. SPSS statistical analysis software version 25 (IBM, Armonk, NY, USA) was used to calculate the descriptive statistics.

3. Results

3.1. Study identification

The initial literature search yielded 7565 relevant articles. After the removal of duplicate studies, 6871 articles were screened for relevant title and abstracts; 27 articles underwent full-text screening, and 12 full-text articles met the inclusion criteria (Fig. 1). There was substantial agreement between reviewers at the title and abstract stage ($\kappa = 0.74$; 95% CI, 0.61–0.86), and substantial agreement at the full-text screening stage ($\kappa = 0.77$; 95% CI, 0.52–1).

3.2. Study characteristics

Of the 12 studies included, all were retrospective cohort studies with a total participant count of 1,260,237 [4,12,24,25,13–15,19–23]. All studies were published between 2005 and 2018 with the majority being published after 2010. Of the included studies, 9 studies [12–15,21–25] shared a database with at least one other study (Table 1); 5 studies used databases in Sweden (2 Swedish Cancer Register (SCR) [21,22], 2 MigMed 2 [12,13], 1 PCBaSe [19]), 5 studies were conducted using the Taiwan National Health Insurance (NHI) research database [14,15,23–25], 1 study used the UK Biobank [20], and 1 study used the SEER Medicare linked database [4]. Lung cancer was the most frequent cancer studied while ischemic stroke was the most analyzed arterial thromboembolic outcome (Table 2 and 3). No studies analyzed the frequency of peripheral artery disease.

3.3. Methodological quality

Of the 12 studies, we rated 6 studies [4,14,15,23–25] as low risk to bias while 6 studies [12,13,19–22] were high risk of bias (Table 4). Scores varied between 5 and 8 stars. All of the studies were performed retrospectively using population databases where withdrawal from database was considered to be an outcome; as such, the adequacy of follow-up of cohorts section was excluded from risk assessment, making the total maximum score 8. In 5 of 12 studies, the outcome of interest, including MI or ischemic stroke, were not demonstrated to be absent at the start of the study, creating the possibility of information bias. Finally, matching for gender and age occurred in just over half of the included studies (7/12).

3.4. Arterial thromboembolism

Three studies (303,120 patients) reported the overall rate of ATE

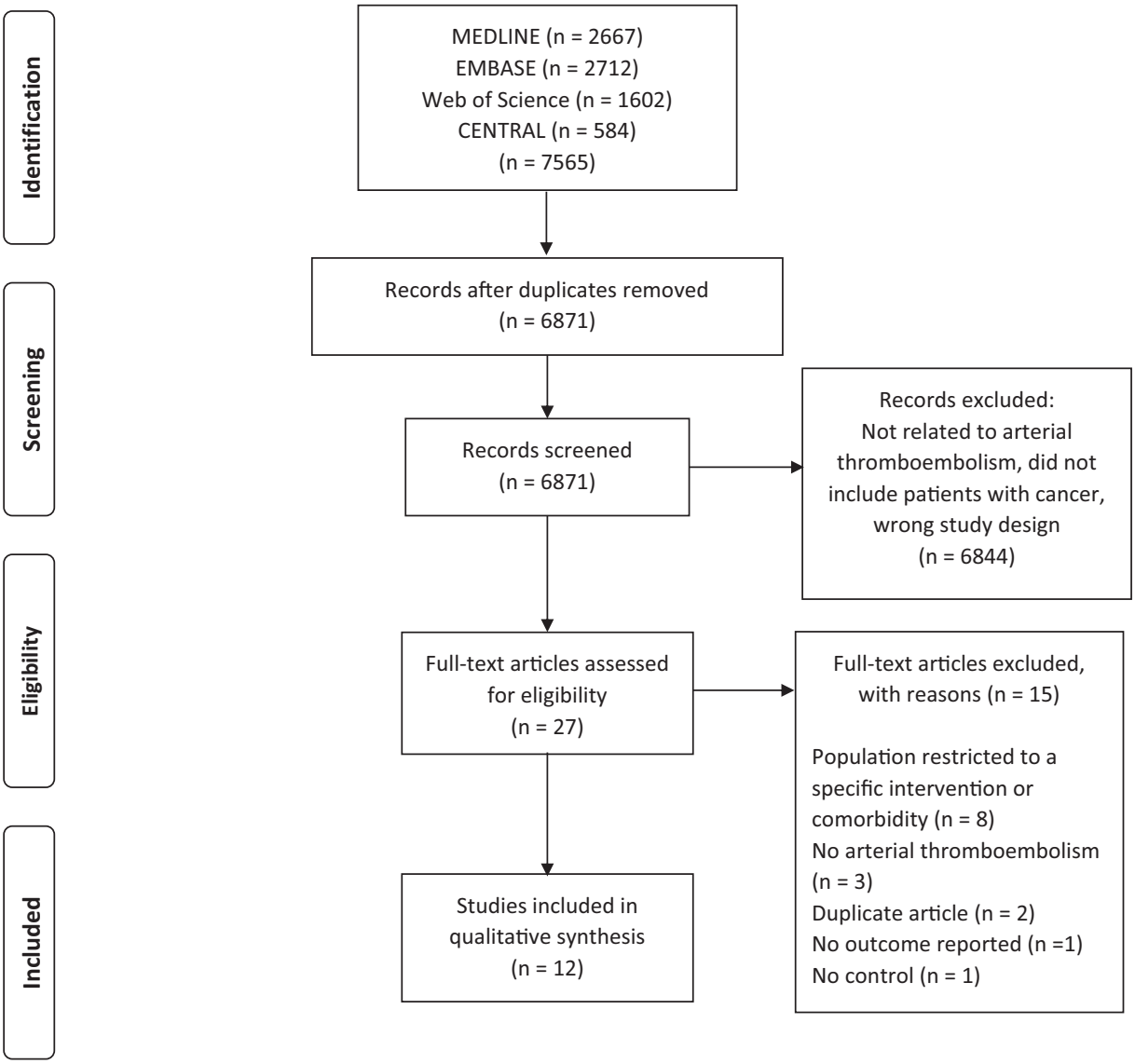

Fig. 1. PRISMA diagram – transparent reporting of systematic reviews and meta-analysis flow diagram outlining the search strategy results from initial search to included studies.

(composite of ischemic stroke and MI) in patients with cancer [4,19,20]. Navi et al. [4], analyzed 279,719 patients from the SEER database and reported that 3.4% (95% CI, 3.4–3.5) of patients with any cancer developed ATE at 3 months compared to 1.1% (95% CI, 1.1–1.1) of controls (hazard ratio [HR] 5.2; 95% CI, 4.9–5.6) (Table 2). Between 3 and 6 months, the risk decreased greatly (HR 1.4; 95% CI 1.3–1.5), and by 9 months to 1 year there was no apparent increment in risk (HR 1.1; 95% CI, 1–1.1) (Table 3). Duarte et al. [20] analyzed 13,972 patients using the UK Biobank, yielding a fully-adjusted odds ratio of 1.9 (95% CI, 1.2–3.2) for the development of ATE in cancer compared to control patients. In both studies, patients with lung cancer experienced the greatest excess risk of ATE, with the study of Navi et al. reporting a hazard ratio of 9.6 (95% CI, 8.4–10.9) at 1 month and 2.2 (95% CI, 1.9–2.5) at 12 months, and the study of Duarte et al. reporting an odds ratio of 8.8 (95% CI, 3.8–20.2) at an unreported follow-up time [1,20]. A third study of Hultcrantz et al. [21] analyzed 9429 patients from the Swedish Cancer Registry, reporting that patients with myeloproliferative cancers experienced an increased risk of ATE (HR 2.0; 95% CI, 1.8–2.2) at 12 months. In total, 10 of 12 included studies [4,12–15,20,21,23–25] reported an increased occurrence of at least one component of ATE in populations with malignancies.

At the time point closest to cancer diagnosis, all included studies reported an increased rate of overall ATE for all cancer types except prostate cancer. At the time point closest to 1 year, only lung and pancreatic cancer patients had an increased rate of ATE.

3.5. Myocardial infarction

Four studies (1,123,611 patients) reported the rate of myocardial infarction in patients with cancer [1,12,20,21]. The study of Navi et al. [1] reported that the excess risk of myocardial infarction was greatest within a month of cancer diagnosis (HR 7.3; 95% CI, 6.5–8.2) compared to 9 to 12 months (HR 1.0, 95% CI 1.0–1.1). Zoller et al. [12] analyzed 820,491 patients from the MigMed 2 database, reporting a standardized incidence ratio of 1.17 (95% CI, 1.16–1.19) for MI in cancer patients compared to the reference population of the total population of Sweden without cancer. Similar results were reported for coronary heart disease (SIR 1.7; 95% CI 1.66–1.75) at 6 months, which persisted at a follow-up interval of over 10 years (SIR 1.07; 95% CI 1.04–1.11).

Among the different cancer types (bladder, colorectal, gastric, lung pancreatic, prostate, and non-Hodgkin lymphoma), studies included in this review reported an excess risk of MI at the time point closest to

Table 1
Study characteristics.

Study	Country	Database	Number of cancer patients	Age (SD)	% Female	Comparison group	Cancer types	Effect of cancer on ATE, MI, or stroke at 1 year (0 = no effect, 1 = harmful)	Cancer treatment type (1 = unspecified, 2 = no treatment, 3 = specified)
Nilsson, 2005 [22]	Sweden	SCR	25,171	63.6 (13.9)	100	Background population	Breast	0 (stroke)	1
Hemelrijck, 2010 [19]	Sweden	PCBaSe	19,526	–	0	Background population adjusted for sex	Prostate	0 (ATE)	2
Chen, 2011 [15]	Taiwan	NHI	52,089	67.2 (12.3)[a]	34[a]	Controls matched for age, sex, and month of cancer diagnosis	Lung	1 (stroke)	1
Zoller, 2012 (MI) [12]	Sweden	MigMed 2	820,491	–	48.1	Background population adjusted for age, sex, time period, SES, geographic region of residence and comorbidities	Combined cancer, breast, lung, prostate, colon, rectal, bladder, non-Hodgkin lymphoma, pancreas, gastric	1 (MI)	1
Zoller, 2012 (Stroke) [13]	Sweden	MigMed 2	820,491	–	48.1	Background population adjusted for age, sex, time period, SES, geographic region of residence and comorbidity	Combined cancer, breast, lung, prostate, colon, rectal, bladder, non-Hodgkin lymphoma, pancreas, gastric	1 (stroke)	1
Chu, 2013 [23]	Taiwan	NHI	1021	52.8 (14.1)[a]	26.5[a]	Controls matched for age and sex	Nasopharyngeal	1 (stroke)	2
Kuan, 2014 [25]	Taiwan	NHI	8810	49[a]	100[a]	Controls matched for age, sex, time of enrollment, and comorbidities	Ovarian	1 (stroke)	3
Kuan, 2015 [24]	Taiwan	NHI	22,530	65[a]	37.8[a]	Controls matched for age, sex, time of enrollment, and comorbidities	Gastric	1 (stroke)	3
Duarte, 2017 [20]	United Kingdom	UK Biobank	13,972	62 (10)	62	Background population adjusted for age, sex, and lifestyle factors (BMI, smoking, frequency of alcohol use, physical activity, and material deprivation)	Combined cancer, lung and trachea	1 (ATE, MI)	1
Navi, 2017 [4]	USA	SEER	279,719	74[a]	52[a]	Controls matched for age, sex, race, SEER registry, and comorbidities	Combined cancer, breast, lung, prostate, colorectal, bladder, non-Hodgkin lymphoma, pancreas, gastric	1 (ATE, MI, stroke)	1
Chan, 2018 [14]	Taiwan	NHI	7479	64.7 (13.2)[a]	41.1[a]	Controls matched for age, sex, and comorbidities	Pancreas	1 (stroke)	1
Hultcrantz, 2018 [21]	Sweden	SCR	9429	72[a]	54[a]	Controls matched for age, sex, and time of diagnosis	Myeloproliferative	1 (ATE, MI, stroke)	1

SEER = Surveillance Epidemiology and End Results-Medicare linked database; SCR = Swedish Cancer Register; NHI = Taiwan National Health Insurance database; SES = Socioeconomic status.
[a] Indicates that matching occurred during the selection of controls.

Table 2
Frequency of arterial thromboembolic events at time closest to cancer diagnosis.

Cancer	Database	Follow-up duration after diagnosis (months)	Number of cancer patients	Measure	All arterial thromboembolic events (95% CI)	Myocardial infarction (95% CI)	Ischemic stroke (95% CI)
All cancer	SEER	0–1 months	279,719	HR	5.2 (4.9–5.6)	7.3 (6.5–8.2)	4.5 (4.1–4.8)
	MigMed 2	< 6 months	820,491	SIR	–	1.17 (1.16–1.19)[a]	1.6 (1.5–1.6)
	UK Biobank	–	13,972	OR	1.9 (1.2–3.2)	–	1.2 (0.9–1.6)
Bladder	SEER	0–1 months	17,637	HR	4.6 (3.5–6)	5.6 (3.6–8.6)	4.1 (2.9–5.8)
	MigMed 2	< 6 months	39,641	SIR	–	1.37 (1.32–1.42)[a]	1.7 (1.5–1.9)
Breast	SEER	0–1 months	62,977	HR	2.3 (2–2.7)	3.8 (2.8–5)	1.8 (1.5–2.2)
	MigMed 2	< 6 months	116,358	SIR	–	0.95 (0.92–0.98)[a]	1.5 (1.3–1.6)
	SCR	< 12 months	25,171	RR	–	–	1.18 (0.97–1.44)
Colorectal	SEER	0–1 months	43,827	HR	6.7 (5.7–7.8)	12.6 (9.5–16.7)	4.6 (3.9–5.6)
	MigMed 2	< 6 months	61,802	SIR	–	1.13 (1.08–1.17)[a]	1.6 (1.5–1.8)
Gastric	SEER	0–1 months	6225	HR	6.0 (4.1–8.9)	11.0 (5.3–22.6)	4.5 (2.9–7.1)
	MigMed 2	< 6 months	22,572	SIR	–	1.18 (1.08–1.30)[a]	1.8 (1.5–2.2)
	NHI	9 years	22,530	HR	–	–	1.11 (1.03–1.19)
Lung	SEER	0–1 months	56,941	HR	9.6 (8.4–10.9)	10.1 (8–12.8)	9.3 (8–10.9)
	MigMed 2	< 6 months	59,644	SIR	–	1.72 (1.61–1.83)[a]	2.2 (1.9–2.4)
	NHI	0–12 months	52,089	HR	–	–	1.43 (1.34–1.51)
	UK Biobank	–	840	OR	8.8 (3.8–20.2)	2.3 (1.4–3.9)	–
Non-Hodgkin lymphoma	SEER	0–1 months	15,669	HR	6.1 (4.6–8.1)	9.1 (5.4–15.6)	4.7 (3.4–6.6)
	MigMed 2	< 6 months	35,974	SIR	–	1.13 (1.07–1.2)[a]	1.6 (1.4–1.8)
Pancreas	SEER	0–1 months	12,279	HR	6.8 (5.1–9.2)	13.9 (7.7–25)	5 (3.6–6.9)
	MigMed 2	< 6 months	19,300	SIR	–	1.53 (1.28–1.81)[a]	2.2 (1.8–2.7)
	NHI	0–6 months	7479	HR	–	–	4.65 (3.62–5.98)
Prostate	SEER	0–1 months	64,164	HR	1.7 (1.5–2)	1.9 (1.5–2.6)	1.6 (1.3–2)
	MigMed 2	< 6 months	139,510	SIR	–	1.18 (1.15–1.2)[a]	1.2 (1.1–1.3)
	PCBaSe	0–6 months	19,526	SIR	0.58 (0.19–1.35)	–	–

OR = odds ratio; HR = hazard ratio; RR = relative risk; SIR = standardized incidence ratio; SEER = Surveillance Epidemiology and End Results-Medicare linked database; SCR = Swedish Cancer Register; NHI = Taiwan National Health Insurance database.
[a] Follow-up duration not reported.

cancer diagnosis. At the time point closest to 1 year after cancer diagnosis, studies reported an excess risk of MI for only lung and pancreatic cancers. Patients with lung cancer were found to have the highest excess risk of MI by 3 databases, including the SEER (HR 2.5; 95% CI 2.1–3), MigMed 2 (SIR 1.72; 95% CI, 1.61–1.83), and UK Biobank (OR 2.3; 95% CI 1.4–3.9) databases. While an analysis of the SEER database found that patients with breast cancer experienced an excess risk of MI at 0 to 1 month after diagnosis (HR 3.8; 95% CI, 2.8–5), there was a protective effect seen at 9 to 12 months (HR 0.7; 95% CI, 0.5–0.8). The MigMed 2 database also found a modest protective effect in patients with breast cancer (SIR 0.95; 95% CI, 0.92–0.98).

Table 3
Frequency of arterial thromboembolic events at time-point closest to 1 year after cancer diagnosis.

Cancer	Database	Follow-up duration after diagnosis (months)	Number of patients	Measure	All arterial thromboembolic events (95% CI)	Myocardial infarction (95% CI)	Ischemic stroke (95% CI)
All cancer	SEER	9–12 months	279,719	HR	1.1 (1–1.1)	1 (1–1.1)	1.1 (1–1.2)
	MigMed 2	6–12 months	820,491	SIR	–	1.17 (1.16–1.19)[a]	1.1 (1.1–1.2)
	UK Biobank	–	13,972	OR	1.9 (1.2–3.2)	–	1.2 (0.9–1.6)
Bladder	SEER	9–12 months	17,637	HR	1.1 (0.9–1.3)	1.2 (0.9–1.7)	1.1 (0.8–1.4)
	MigMed 2	6–12 months	39,641	SIR	–	1.37 (1.32–1.42)[a]	1.2 (1.1–1.4)
Breast	SEER	9–12 months	62,977	HR	0.9 (0.8–1)	0.7 (0.5–0.8)	1 (0.9–1.1)
	MigMed 2	6–12 months	116,358	SIR	–	0.95 (0.92–0.98)[a]	1.2 (1–1.3)
	SCR	< 12 months	25,171	RR	–	–	1.18 (0.97–1.44)
Colorectal	SEER	9–12 months	43,827	HR	1 (0.9–1.1)	1 (0.8–1.3)	1 (0.8–1.1)
	MigMed 2	6–12 months	61,802	SIR	–	1.13 (1.08–1.17)[a]	1.1 (1–1.3)
Gastric	SEER	9–12 months	6225	HR	1.1 (0.8–1.6)	1.0 (0.5–2.0)	1.1 (0.7–1.8)
	MigMed 2	6–12 months	22,572	SIR	–	1.18 (1.08–1.30)[a]	1.0 (0.7–1.4)
	NHI	9 years	22,530	HR	–	–	1.11 (1.03–1.19)
Lung	SEER	9–12 months	56,941	HR	2.2 (1.9–2.5)	2.5 (2.1–3)	2 (1.8–2.4)
	MigMed 2	6–12 months	59,644	SIR	–	1.72 (1.61–1.83)[a]	1.3 (1–1.6)
	NHI	0–12 months	52,089	HR	–	–	1.43 (1.34–1.51)
	UK Biobank	–	840	OR	8.8 (3.8–20.2)	2.3 (1.4–3.9)	–
Non-Hodgkin lymphoma	SEER	9–12 months	15,669	HR	1.2 (1–1.6)	1 (0.7–1.5)	1.3 (1–1.7)
	MigMed 2	6–12 months	35,974	SIR	–	1.13 (1.07–1.2)[a]	1.1 (0.9–1.3)
Pancreas	SEER	3–6 months	12,279	HR	1.7 (1.4–2.2)	2.1 (1.4–3)	1.6 (1.2–2.1)
	MigMed 2	6–12 months	19,300	SIR	–	1.53 (1.28–1.81)[a]	1 (0.6–1.7)
	NHI	7–12 months	7479	HR	–	–	2.01 (1.27–3.19)
Prostate	SEER	9–12 months	64,164	HR	0.8 (0.7–0.9)	0.7 (0.6–0.9)	0.9 (0.8–1)
	MigMed 2	6–12 months	139,510	SIR	–	1.18 (1.15–1.2)[a]	1.1 (1–1.2)
	PCBaSe	7–18 months	19,526	SIR	0.7 (0.35–1.25)	–	–

OR = odds ratio; HR = hazard ratio; RR = relative risk; SIR = standardized incidence ratio; SEER = Surveillance Epidemiology and End Results-Medicare linked database; SCR = Swedish Cancer Register; NHI = Taiwan National Health Insurance database.
[a] Follow-up duration not reported.

Table 4
Modified Newcastle-Ottawa quality assessment scale for cohort studies included in the systematic review.

Study	Selection				Comparability	Outcome		Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcomes of interest were not present at start of study	Comparability of cohorts on the basis of design of the study or analysis	Assessment of outcome	Length of follow-up	
Nilsson, 2005 [22]	1	–	1	1	1	1	1	6
Hemelrijck, 2010 [19]	1	1	1	–	–	1	1	5
Chen, 2011 [15]	1	1	1	1	2	1	1	8
Zoller, 2012 (MI) [12]	1	1	1	–	–	1	1	5
Zoller, 2012 (Stroke) [13]	1	1	1	–	–	1	1	5
Chu, 2013 [23]	1	1	1	1	2	1	1	8
Kuan, 2014 [25]	1	1	1	1	2	1	1	8
Kuan, 2015 [24]	1	1	1	1	2	1	1	8
Duarte, 2017 [20]	1	1	1	–	–	1	1	5
Navi, 2017 [4]	1	1	1	1	2	1	1	8
Chan, 2018 [14]	1	1	1	1	2	1	1	8
Hultcrantz, 2018 [21]	1	–	1	–	2	1	1	6

3.6. Ischemic stroke

Ten studies (1,209,371 patients) reported the rate of ischemic stroke in patients with cancer [4,13–15,20–25]. The excess risk of ischemic stroke was also greatest early after cancer diagnosis. The SEER database (Navi et al.) [4] reporting an increased risk of stroke at one month (HR 4.5; 95% CI, 4.1–4.8); by 9 to 12 months there was no evidence of a persistent increase in the risk of stroke (HR 1.1; 95% CI, 1–1.2). The MigMed 2 database (Zoller et al.) [13] found a SIR of 1.6 (95% CI, 1.5–1.6) at 6 months which reduced to a SIR of 1.1 (95% CI, 1.1–1.2) from 6 to 12 months. A third study of the UK Biobank by Duarte et al. [20] analyzed 13,972 patients but did not find a difference in the risk of stroke at an unspecified time point (OR 1.2; 95% CI, 0.9–1.6).

Among the different cancer types, studies reported an increased rate of ischemic stroke in bladder, colorectal, gastric, lung, pancreatic, and prostate cancer, as well as non-Hodgkin lymphoma at the time point closest to cancer diagnosis. Two of three studies [4,13] also reported an increased rate of ischemic stroke in patients with breast cancer, although one study of the Swedish Cancer Registry by Nilsson et al. did not detect a difference (RR 1.18; 95% CI 0.97–1.44) [22]. At the time point closest to 1 year, studies showed that only patients with lung cancer had a persistent excess risk of ischemic stroke.

3.7. Mortality

Navi et al. [4] analyzed the SEER database and reported mortality of cancer patients who developed ATE compared with those who did not. After adjusting for year of birth, sex, race, SEER registry, comorbidities, and cancer stage, the study reported increased mortality (HR 3.1; 95% CI, 3.0–3.1) in cancer patients who developed ATE.

4. Discussion

In this systematic review of 12 retrospective cohort studies, patients with cancer had an increased risk of developing ATE, including its individual components myocardial infarction and ischemic stroke. The excess risk was highest immediately following cancer diagnosis and had largely returned to baseline by 1 year after diagnosis. Lung and pancreatic cancers appeared to be associated with the highest risk and were the only cancer types that were associated with a persistent increase in the risk of ATE at the time reported closest to 1 year after diagnosis.

Previous investigations have found an increased frequency of ATE in patients with a variety of cancer types including lung, pancreatic, breast, prostate, gastric, colorectal, ovarian, and cervical cancers [3,8–11]. However, limitations of the existing literature include inadequate sample sizes, self-selection bias in studies that use data from patients originally recruited into RCTs, the analysis of demographically homogenous populations in studies that use individual databases, and the absence of cancer free control groups.

Why cancer is associated with arterial thrombosis remains unclear; several hypotheses have been proposed. Cancer can increase platelet reactivity and induce secretion of coagulation factors, leading to hypercoagulability [6]. Endothelial injury can result from angiogenesis, elevated levels of cytokines resulting in a dysfunctional endothelium, and chemotherapy related effects such as those potentially induced by VEGF inhibitors [26]. Decreased mobility in cancer patients and increased plasma viscosity may also lead to stasis and development of thrombosis [27]. Cancer and ATE also share common risk factors including body mass, age, smoking, and comorbidities including diabetes and hypertension. Invasive cancer treatments, bleeding, or thrombocytopenia may require discontinuation of antithrombotics – such as antiplatelet agents predisposing to thrombotic complications. Finally, cancer patients also receive frequent follow-up and increased medical surveillance, potentially leading to a diagnosis of ATE that might otherwise be missed.

Limitations of this study include substantial heterogeneity for all

outcomes, largely because of the different periods analyzed, databases included, and variable outcomes reported by studies, thus precluding meta-analysis. Furthermore, the literature examining the effect of cancer on ATE is limited and found to be at an overall moderate risk to bias. Most studies did not report cancer treatments, antithrombotics, or statin use. All included studies were retrospective and many relied on International Classification of Diseases (ICD) codes. It is possible that cancer types or cases of ATE may be misclassified by physicians particularly given the lack of confirmatory imaging or laboratory data in many databases. The diagnosis of ATE in patients with cancer is particularly difficult because symptoms including chest pain, dizziness, and dyspnea are common in both groups, and diagnostic tools such as coronary angiographies may be avoided in patients with cancer because of a poor prognosis [3]. This could lead to underdiagnoses of ATE. Our analysis is also limited by potential confounding. Risk factors for myocardial infarction and ischemic stroke were not reported in all databases. Cardiovascular risk factors including body mass, diet, and smoking were not reported or adjusted for in the MigMed 2 database [12,13]. Databases did not account for heavy smoking, and it is difficult to determine the extent to which the observed association between lung cancer and ATE is confounded by smoking or other risk factors [28,29]. We also specifically excluded studies examining specific treatment types and thus we were unable to determine whether cancer interventions confounded our observations. Some treatments, including platinum-based agents are well known to increase VTE risk and are used extensively in lung cancer [30,31]. Thus, the association between lung cancer and risk of ATE may be partly attributed to chemotherapy. Selective estrogen receptor modulators including tamoxifen may create similar confounding in patients with breast cancer [32]. There was insufficient data around the risk of ATE and certain hematologic malignancies such as multiple myeloma. Immunomodulatory agents used for treatment of myeloma, including lenalidomide and thalidomide, are well known to increase the risk of ATE but were not considered our analysis [33,34].

It has been thought that patients with cancer may experience an increased risk of ATE, given their elevated risk of VTE [1,2,35]. Our findings suggest that the effect of cancer on ATE risk is weaker than the effect on VTE risk, however our analysis is limited by significant heterogeneity. Aggressive cancers with reduced 1-year survival such as pancreatic cancer appear to be associated with the highest risk of ATE. In contrast, less aggressive cancers, such as breast and prostate cancer, appear to be associated with lower risks of ATE. The increased ATE risk is largely confined to the time immediately following cancer diagnosis. This risk largely returned to baseline by 1 year after diagnosis. This suggests that the increased risk could be a by-product of the cancer itself, with successful treatment eventually diminishing the risk [1]. Additionally, greater prevention and monitoring efforts may have been taken in patients with cancer who had not developed ATE in the time immediately following cancer diagnosis and treatment.

5. Conclusion

Patients with cancer appear to have an increased risk of developing ATE, including myocardial infarction and ischemic stroke. The highest risk was immediately following the time of diagnosis and in lung and pancreatic cancers. Future prospective comparative studies investigating the benefits of prevention strategies for patients with cancer and the identification of at-risk individuals are warranted.

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Declaration of competing interest

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