

APPENDIX

A. Search strategy

PUBMED Search

Search	Query	Result	Time
#1	"urinary bladder neoplasms"[MeSH] OR "Non-Muscle Invasive Bladder Neoplasms"[Mesh] OR "urinary bladder neoplasms"[Tiab] OR "Non-Muscle Invasive Bladder Neoplasms"[Tiab] OR "Invasive Bladder Neoplasms"[Tiab] OR "urinary bladder tumor"[Tiab] OR "bladder cancer"[Tiab] OR "urothelial tumor"[Tiab] OR "Urothelial cancer"[Tiab] OR "Urothelial neoplasm"[Tiab] OR "bladder tumor"[Tiab]	79941	04:59:03 28/04/24
#2	(((((("Prognosis"[Mesh]) OR "Recurrence"[Mesh]) OR "Neoplasm Recurrence, Local"[Mesh]) OR "Disease Progression"[Mesh]) OR "Progression-Free Survival"[Mesh]) OR "Survival"[Mesh] OR (((("Prognosis"[Tiab]) OR "Recurrence"[Tiab]) OR "Neoplasm Recurrence, Local"[Tiab]) OR "Disease Progression"[Tiab]) OR "Progression-Free Survival"[Tiab]) OR "Survival"[Tiab]	357467 5	04:59:23 28/04/24
#3	("DNA Topoisomerases, Type II"[Mesh]) OR "TOP2A protein, human" [Supplementary Concept] OR "TOP2A"[Tiab] OR "Topoisomerase"[Tiab]	23954	04:59:32 28/04/24
#4	#1 AND #2 AND #3	44	04:59:42 28/04/24

Cochrane

Search
Name: TOP2A
Last
Saved: 28/04/2024 16:24:23
Comment:

ID	Search	Result
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees	2345
#2	MeSH descriptor: [DNA Topoisomerases, Type II] explode all trees	55
#3	MeSH descriptor: [Survival] explode all trees	183
#4	MeSH descriptor: [Prognosis] explode all trees	223843

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#5	MeSH descriptor: [Recurrence] explode all trees	16478
#6	MeSH descriptor: [Progression-Free Survival] explode all trees	1462
#7	MeSH descriptor: [Disease Progression] explode all trees	10911
#8	MeSH descriptor: [Progression-Free Survival] explode all trees	1462
#9	Bladder cancer OR Bladder Tumor or Bladder Neoplasm OR Urothelial carcinoma OR urothelial neoplasm OR Urothelial tumor or Non-muscle invasive bladder cancer OR Invasive bladder cancer OR Urinary bladder neoplasm OR Urinary bladder tumor	24983
#10	Prognosis OR Survival OR Recurrence OR Recurrent OR Progressive OR Progression OR Recurrence-Free Survival OR Progression-Free Survival	280708
#11	Topoisomerase OR TOP2A	585
#12	#1 OR #9	25110
#13	#2 OR #11	594
#14	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #10	437949
#15	#11 AND #12 AND #13	13

Database:

Embase Classic+Embase <1947 to 2024 May 10>

#	Query	Results from 11 May 2024
1	exp bladder cancer/	94,169
2	exp bladder tumor/	117,244
3	exp non muscle invasive bladder cancer/	6,944
4	exp muscle invasive bladder cancer/	6,622
5	exp urothelial tumor/	40,715

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6	exp transitional cell carcinoma/	40,036
7	bladder cancer.ab,kf,ot,ti.	67,100
8	bladder tumor.ab,kf,ot,ti.	9,209
9	non muscle invasive bladder cancer.ab,kf,ot,ti.	6,298
10	muscle invasive bladder cancer.ab,kf,ot,ti.	12,469
11	urothelial tumor.ab,kf,ot,ti.	517
12	transitional cell carcinoma.ab,kf,ot,ti.	12,071
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	144,984
14	exp "DNA topoisomerase (ATP hydrolysing)"/	12,641
15	topoisomerase.ab,kf,ot,ti.	24,174
16	TOP2.ab,kf,ot,ti.	672
17	TOP2A.ab,kf,ot,ti.	1,943
18	TOPO2.ab,kf,ot,ti.	54
19	TOPO2A.ab,kf,ot,ti.	117

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20	DNA gyrase.ab,kf,ot,ti.	3,770
21	14 or 15 or 16 or 17 or 18 or 19 or 20	31,444
22	exp prognosis/ or exp cancer prognosis/ or exp recurrent disease/ or exp survival/ or exp cancer specific survival/ or exp cancer free survival/ or exp disease free survival/ or exp disease specific survival/ or exp overall survival/ or exp progression free survival/	2,361,371
23	survival.ab,kf,ot,ti.	1,887,172
24	(recurrent or recurrence).ab,kf,ot,ti.	1,049,839
25	(prognosis or prognostic).ab,kf,ot,ti.	1,295,410
26	22 or 23 or 24 or 25	4,038,040
27	13 and 21 and 26	99

Assessment of study eligibility

Author, year	Title	Reason for exclusion
Fu et al., 2023	Circular RNA Ubiquitin-associated Protein 2 Silencing Suppresses Bladder Cancer Progression by Downregulating DNA Topoisomerase 2-alpha Through Sponging miR-496	No outcome of interest
Galsky et al., 2015	Phase 2 trial of the topoisomerase II inhibitor, amrubicin, as second-line therapy in patients with metastatic urothelial carcinoma	No outcome of interest
Davies et al., 1996	Response to Epirubicin in Patients with Superficial Bladder Cancer and Expression of the Topoisomerase II α and β genes	No outcome of interest
Kim et al., 2010	Clinical Implications and Prognostic Values of Topoisomerase-II Alpha Expression in Primary Non-muscle-invasive Bladder Cancer	No outcome of interest
Kim et al., 2009	TOP2A as a strong predictor for recurrence and progression in primary non-muscle invasive bladder tumor	Duplicate data
Simon et al., 2002	HER-2 and TOP 2A gene amplifications in urinary bladder carcinoma	Duplicate data
Yu et al., 2019	DNA topoisomerase II α and RAD21 cohesin complex component are predicted as potential therapeutic targets in bladder cancer	Study Design

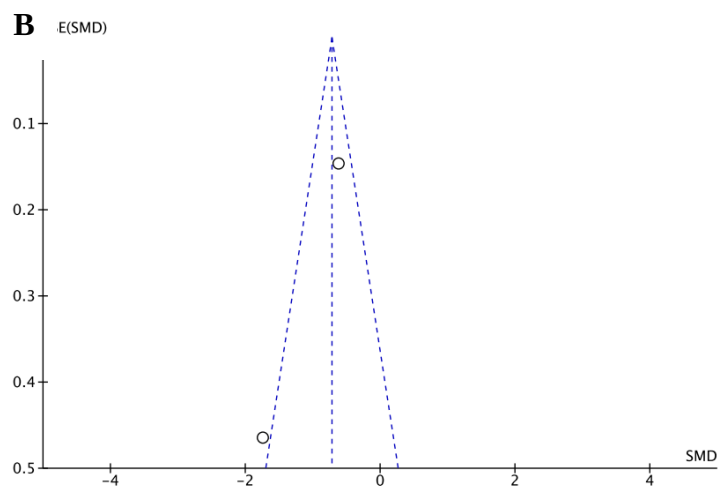
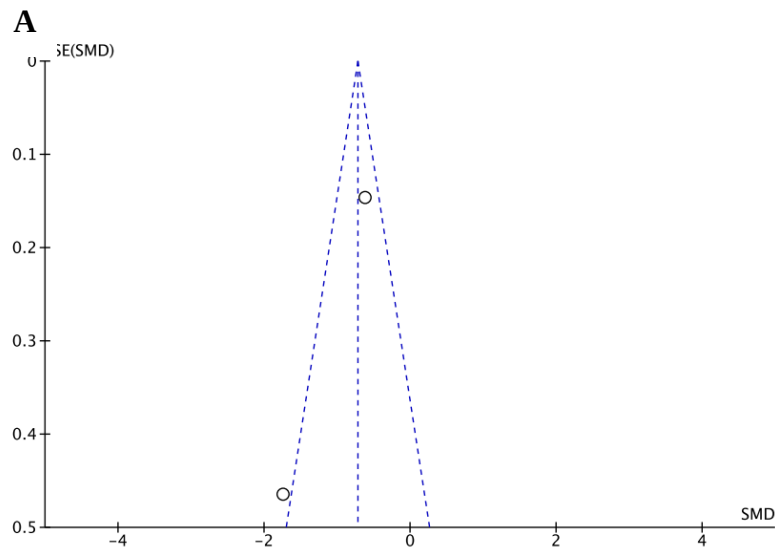
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

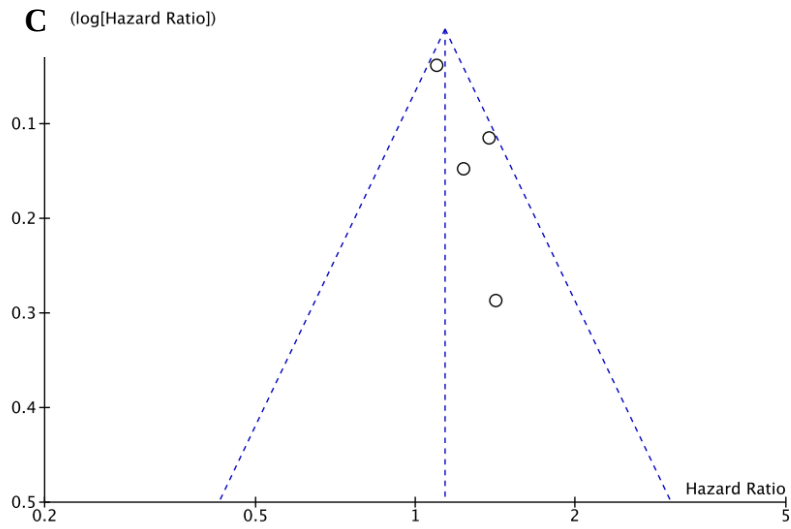
From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

B. SUPPLEMENTARY FIGURES AND TABLES

Supplementary Figure 1. (A) Funnel plot for stage. (B) Funnel plot for grade. (C) Funnel plot for CSS.



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Supplementary Table 1. Risk of bias Newcastle-Ottawa quality assessment scale for cohort studies										
No.	Author (year)	Selection				Comparability	Outcome			Total
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was followup long enough for outcomes to occur	Adequacy of followup of cohorts	
1	Zeng et al (2019)	1	1	1	1	2	1	1	0	8
2	Kruger et al (2005)	1	1	1	1	2	1	1	0	8
3	Nakopoulou et al (2001)	1	1	1	0	1	1	1	1	7
4	Raspollini et al (2016)	1	1	1	1	2	1	1	0	8
5	Liu et al (2022)	1	1	1	1	2	1	1	0	8
6	Simon et al (2003)	1	1	1	0	1	1	1	1	7
7	Koren et al (2002)	1	1	1	1	0	1	0	0	5

Supplementary Table 2. Risk of bias Newcastle-Ottawa quality assessment scale for cross-sectional studies									
No.	Author (year)	Selection				Comparability	Outcome		Total
		Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled	Assessment of outcome	Statistical test	
1	Elkady et al (2018)	1	1	1	0	1	1	0	5
2	Benabdelkrim et al (2014)	1	1	0	0	1	2	1	6