

Table S1: summary of systematic literature search

Database (author)	Date	Search	Hits
Pubmed (JH)	June 28th 2021	<p>("Urinary Bladder Neoplasms"[Mesh] OR ("Neoplasms"[Mesh] AND "Urinary Bladder"[Mesh]) OR "Carcinoma, Transitional Cell"[Mesh] OR ((bladder*[tiab] OR urothelial[tiab] OR muscle invasiv*[tiab] OR non-muscle invasiv*[tiab] OR nonmuscle invasiv*[tiab]) AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR malignan*[tiab] OR carcinom*[tiab])))</p> <p>AND</p> <p>("Biguanides"[Mesh] OR "Metformin"[Mesh] OR "Hypoglycemic Agents"[Mesh] OR metformin*[tiab] OR glucophage[tiab] OR antidiabetic*[tiab] OR anti-diabetic*[tiab] OR biguanide*[tiab] OR buformin[tiab] OR phenformin[tiab] OR hypoglycemic agent*[tiab] OR hypoglycemic drug*[tiab])</p> <p>NOT</p> <p>((("Animals"[Mesh] OR "Animal Experimentation"[Mesh] OR "Models, Animal"[Mesh] OR rat[tiab] OR rats[tiab] OR mice[tiab] OR mouse[tiab] OR dog[tiab] OR dogs[tiab] OR pig[tiab] OR pigs[tiab] OR cow[tiab] OR cows[tiab] OR monkey[tiab] OR monkeys[tiab]) NOT ("Humans"[Mesh] OR human*[tiab]))</p>	307
EMBASE (JH)	June 28th 2021	<p>exp bladder tumor/ or (exp neoplasm/ and exp bladder/) or transitional cell carcinoma/ or ((bladder* or urothelial or muscle invasiv* or non-muscle invasiv* or nonmuscle invasiv*) and (cancer* or neoplas* or tumor* or malignan* or carcinom*)).ti,ab,kw.</p> <p>AND</p> <p>exp biguanide derivative/ or metformin/ or exp antidiabetic agent/ or (metformin* or glucophage or antidiabetic* or anti-diabetic* or biguanide* or buformin or chlorhexedine or phenformin or proguanil or hypoglycemic agent* or hypoglycemic drug*).ti,ab,kw.</p> <p>NOT</p> <p>(exp animal/ or exp animal experiment/ or exp animal model/ or (rat or rats or mice or mouse or dog or dogs or pig or pigs or cow or cows or monkey or monkeys).ti,ab,kw.) not (exp human/ or human*.ti,ab,kw.)</p>	1570
Cochrane library (JH)	June 29th 2021	<p>MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees OR MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees OR (((bladder* or urothelial or muscle invasiv* or non-muscle invasiv* or nonmuscle invasiv*) and (cancer* or neoplas* or tumor* or malignan* or carcinom*)):ti,ab,kw (Word variations have been searched)</p> <p>AND</p> <p>MeSH descriptor: [Biguanides] explode all trees OR MeSH descriptor: [Metformin] explode all trees OR ((metformin* or glucophage or antidiabetic* or anti-diabetic* or biguanide* or buformin or chlorhexedine or phenformin or proguanil or hypoglycemic agent* or hypoglycemic drug*)):ti,ab,kw (Word variations have been searched)</p>	38

Pubmed (BR)	June 28th 2021	((("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields]) OR (non-muscle invasive bladder cancer) OR (muscle invasive bladder cancer)) AND ("metformin"[MeSH Terms] OR "metformin"[All Fields]) OR ("biguanides" [all Fields]) OR "biguanides" [MeSH Terms]) OR "Hypoglycemic Agents" [Pharmacological Action] Filters: humans	288
EMBASE (BR)	June 28th 2021	exp bladder tumor/ or (exp neoplasm/ and exp bladder/) or transitional cell carcinoma/ or ((bladder* or urothelial or muscle invasiv* or non-muscle invasiv* or nonmuscle invasiv*) and (cancer* or neoplas* or tumo* or malignan* or carcinom*)).ti,ab,kw. AND exp biguanide derivative/ or metformin/ or (metformin* or glucophage or biguanide* or buformin or phenformin or proguanil).ti,ab,kw. Limit: humans	607
Cochrane library (BR)	June 29th 2021	((bladder cancer) OR ("bladder neoplasm") OR (muscle invasive bladder cancer) OR (non-muscle invasive bladder cancer)):ti,ab,kw AND ("metformin hydrochloride") OR (metformin) OR ("biguanide")	17
Total			2827
After duplicates removal			1671

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727 *Table S2: Newcastle-Ottawa scale for assessment of quality of included studies - Cohort studies (each asterisk represents if individual criterion within*
 728 *the subsection was fulfilled)*

Quality assessment criteria	Acceptable (*)	Ahn, et al. (2016)	Chen et al. (2015)	Dankner et al. (2019)	Goossens et al. (2015)	Huan et al. (2020)	Lyon et al. (2018)	Mamtani et al. (2014)	Murff et al. (2018)	Nayan et al. (2015)	Neumann et al. (2012)
Selection											
Representativeness of exposed cohort	Representative of average adult in UC population or all-population records	*	*	*	*	*	*	*	*	- only diabetics from 1 center (higher CIS in M cohort)	*
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	*	*	*	*	*	*	*	*	*
Ascertainment of exposure	Health records (with extra control on prescription) or structured interview	*	*	*	*	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study	Incident cases of bladder cancer or recurrent disease	*	*	*	*	*	*	*	*	*	*
Comparability											
Study controls for tumour stage (outcome studies) or age (incidence studies)	Yes	- not in DM patients	*	*	*	- (not in DM subgroup)	*	*	*	*	-
Study controls for at least 3	HbA1c, BMI, other glucose-lowering	-	*	*	*	-	- no data on metformin or other GLD	*	*	-	-

additional risk factors	drugs, other intravesical therapy, smoking history, obesity, comorbidity, tumour stage						use, dosage prescription				
Outcome											
Assessment of outcome?	Independent blind assessment or record linkage	*	*	*	*	*	*	*	*	*	*
Was follow-up long enough for outcome to occur?	Follow-up for >1 year	*	*	*	*	*	*	- median FU of 2 years	*	*	*
Adequacy of follow-up of cohorts	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	-	*	- no statement	*	*	- no statement	* 8% of initiators (n=7,352) left a THIN practice during follow-up.	*	- no statement	-, not described for metformin use
Overall quality score (maximum =9):		6	9	8	9	7	7	8	9	6	6

729 Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be
730 given for Comparability
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Continue Newcastle Ottawa scale for cohort studies

Quality assessment criteria	Acceptable (*)	Oliveria et al (2008)	Richard et al (2018)	Rieken et al (2013)	Rieken et al (2014)	Sung et al (2020)	Tseng et al (2011)	Tseng et al (2014)	Tsilidis et al (2014)	Wang et al *
Selection										
Representativeness of exposed cohort	Representative of average adult in UC population or all-population records	*	-, exclusion of people < 66 y	*	*	*	*	*	*	*
Selection of the non-exposed cohort	Secured records or ICD codes	*	*	*	*	*	*	*	*	*
Ascertainment of exposure	Health records with extra control on prescription	*	*	*	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study	Incident cases of bladder cancer or recurrent disease	*	*	*	*	*	*	*	*	*
Comparability										
Study controls for tumour stage (outcome studies) or age (incidence studies)?	Yes	*	*	*	*	*	*	*	*	*
Study controls for at least 3 additional risk factors	HbA1c, BMI, other glucose-lowering drugs, other intravesical therapy, smoking history, obesity,	-	*	-	-	-	*	*	*	-

	comorbidity, tumour stage									
Outcome										
Assessment of outcome?	Independent blind assessment or record linkage	*	*	*	*	*	*	*	*	*
Was follow-up long enough for outcome to occur?	Follow-up for >1 year	*	*	*	*	*	*	*	*	*
Adequacy of follow-up of cohorts	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	- no statement	- no statement	- no statement	- no statement	- no statement	- no statement	*	- no statement	- no statement
Overall quality score (maximum= 9):		7	7	7	7	7	8	9	8	7

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744 *Table S3: Newcastle-Ottawa scale for assessment of quality of included studies - Case-control studies (each asterisk represents if individual criterion*
 745 *within the subsection was fulfilled)*

Quality assessment criteria	Acceptable (*)	Heidari et al (2016)
Selection		
Is the case definition adequate?	Yes, with independent validation	-, not clear how the case is defined
Representativeness of cases?	Consecutive or obviously representative series of cases	*
Selection of controls?	Controls with bladder cancer or community controls	-
Definition of controls?	No History of disease	*
Comparability		
Study controls for tumour stage?	No	-
Study controls for at least 3 additional risk factors	HbA1c, BMI, other glucose-lowering drugs, other intravesical therapy, smoking history, obesity, comorbidity, tumour stage	-
Outcome		
Ascertainment of exposure?	Secure record, HbA1c levels or fasting glucose levels.	*
Same method of ascertainment of cases/controls?	Yes	*
Non-response rate?	Same rate for both groups	*
Overall quality score (maximum = 9):		5

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752 *Table S4: Revised Cochrane risk-of-bias tool for randomized trials (RoB2)*

Domain	Home et al (2009)	Kahn et al (2006)
Randomization process	Low	Low
Deviations from the intended interventions	High	Low
Missing outcome data	Low	Low
Measurement of the outcome	Some concerns	Some concerns
Selection of the reported result	Some concerns	Some concerns
Overall risk of bias	Some concerns	Some concerns

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