SUPPLEMENTARY TEXT

OVID MEDLINE Search String

((Urologic Neoplasms/ OR exp Ureteral Neoplasms/ OR exp Urethral Neoplasms/ OR exp Urinary Bladder Neoplasms/ OR exp Carcinoma, Transitional Cell/) OR (((Urinary Tract/ OR exp Urinary Bladder/ OR exp Ureter/ OR exp Urethra/) AND (exp Neoplasms/ OR exp Medical Oncology/)) OR ((urinary.af OR urologic.af OR urological.af OR urothelial.af OR urothelium.af OR uroepithelium.af OR urogenital.af OR genitourinary.af OR bladder.af OR bladders.af OR ureteral.af OR ureter.af OR ureters.af OR urethral.af OR urethra.af OR urethras.af OR TCC.af OR "transitional cell".af) AND (neoplasm.af OR neoplasms.af OR tumor.af OR tumors.af OR cancer.af OR cancers.af OR "malignan*".af OR carcinoma.af OR carcinomas.af OR adenocarcinoma.af OR adenocarcinomas.af OR sarcoma.af OR sarcomas.af OR leiomyosarcoma.af OR leiomyosarcomas.af OR adenosarcoma.af OR adenosarcomas.af OR lymphoma.af OR lymphomas.af OR melanoma.af OR melanomas.af OR adenoma.af OR adenomas.af)))) AND (Diabetes Mellitus/ OR Diabetes Mellitus, Type 1/ OR Diabetes Mellitus, Type 2/ OR Diabetes, Gestational/ OR Diabetic Ketoacidosis/ OR Prediabetic State/ OR exp Insulin Resistance/ OR exp Hyperglycemia/ OR exp Glycosuria/ OR Hyperinsulinism/ OR (diabetes OR diabete OR diabetic OR NIDDM OR IDDM OR MODY OR DKC OR "insulin resistant" OR "insulin resistance" OR (metabolic ADJ8 syndrome) OR (metabolic ADJ8 syndromes) OR x-syndrome OR syndrome-x OR syndromes-x OR x-syndromes OR T2DM OR TIIDM OR T2D OR TIID OR T1DM OR TIDM OR T1D OR TID OR hypergylcemia OR hypergylcemias OR hyperglycemic OR hyperglycemia OR glycosuria OR glucosuria OR hyperinsulinism OR hyperinsulinemia OR (glucose ADJ8 intolerance) OR (glucose ADJ8 intolerances) OR "impaired glucose intolerance" OR "impaired glucose intolerances" OR "type 2 DM" OR "type II DM" OR "type 1 DM" OR "type 1 DM" OR "insulin deficiency" OR "insulin deficient" OR LADA).af) AND (exp Survival Analysis/ OR exp Neoplasm Recurrence, Local/ OR cancer specific survival.mp. OR exp Neoplasm Staging/ OR upstaging.mp. OR cancer progression.mp. OR surviv*.mp. OR exp SURVIVAL/ OR exp DISEASE-FREE SURVIVAL/ OR exp SURVIVAL RATE/ OR exp SURVIVAL ANALYSIS/ OR exp RECURRENCE/ OR recur*.mp. OR cancer survival.mp. OR exp Neoplasm Grading/ OR exp Disease Progression/ OR exp Risk Factors/ OR risk factors.mp. OR neoplasm grading.mp. OR disease progression.mp. OR risk factors.mp.)

Supplemental Methods

Data extraction

Data were extracted from studies found to meet inclusion criteria into a Redcap database created for the project, hosted by the University of Southern California. Data items were extracted independently by two reviewers who resolved any inconsistencies by consensus. Captured data described features of the study, independent and outcome variables, covariates, and results.

Specifically, we collected information identifying each report (author last name, publication date, title, and report format) and research approach (location, study design, average duration of follow-up, dates of enrollment and data collection). We also collected numbers of participants with and without diabetes, and the proportion of bladder cancer cases who were female.

Extracted data for bladder cancer included information on type of bladder cancer included (NMIBC, MIBC, both); how cases were identified (ICD code, histology reports, cancer registry); whether cases were limited to urothelial carcinoma; stage

and grade of cancer at diagnosis; presence of carcinoma in situ, lymphovascular invasion, and positive surgical margins; and treatments (radical cystectomy, trans-urethral resection, chemotherapy, radiation etc.).

Extracted data for diabetes mellitus included how diabetes was assessed (physician diagnosis/ICD code, A1C level, fasting blood glucose level, use of antidiabetic medication, etc.), whether the study was restricted to patients with type 2 diabetes and if so how; whether duration of diabetes, glycemic control or antidiabetic medications were addressed in the analysis. If medications were reported, we collected data on whether this information was used as a covariate and/or to classify type of disease (Type 1 or Type 2) and/or to categorize patients for comparisons (i.e., those on metformin vs those not on metformin).

For outcome variables, extracted data included how mortality, recurrence or progression was defined, specific measure of effect (e.g., hazard ratio [HR], odds ratio [OR], rate ratio [RR]) by which the diabetes-outcome association was estimated, specific outcome(s) investigated (all-cause mortality, overall survival, bladder cancer specific mortality, bladder cancer specific survival, recurrence, recurrence free survival, progression, progression free survival) and specific comparison assessed (diabetic vs nondiabetic, type 2 diabetic vs nondiabetic, diabetic on metformin vs nondiabetic, etc.) For use in meta-analyses, we extracted point estimates of effect size, together with upper and lower bounds of the corresponding 95% confidence interval (CI) or the p value if a 95% CI was not provided. We also extracted male- and female-specific estimates of the association if these were reported.

Covariates treated as potential confounders in the study were captured, whether addressed by design (e.g., matching or exclusion) or in multivariate analysis, if this information was provided. Covariates were identified from text and from tables of multivariate results [15-17]. History of smoking tobacco was assessed by recording whether the study measured intensity and/or duration of smoking, reported categories of current/former/never, ever/never, yes/no, used a proxy measure (e.g., diagnosis of chronic obstructive pulmonary disease), or did not measure smoking.

Statistical analyses used for data harmonization

Some papers, instead of presenting a single relative risk (RR) comparing patients with and without diabetes, reported multiple relative risks for subgroups of diabetes patients e.g., used or did not use metformin [18,20], or uncontrolled or controlled diabetes [19]. For these situations, we applied dose-response meta-analysis to estimate a single summary RR for a cumulative incidence model, using the methods described by Greenland and Longnecker [59]. The method takes as input the total number of subjects, the number of cases, and the adjusted relative risk estimate for each patient subgroup. We defined the dose variable as 0 for the diabetes-free reference group and as 1 for each subgroup of patients with diabetes. The summary RR is a weighted average of the adjusted relative risks for all subgroups coded 1, accounting for their correlation estimated from the sample sizes. However, Rieken. et al. [18] only reported the total number of cases instead of the number of cases for each patient subgroup needed for this analysis. As a result, we estimated the number of cases in each subgroup using the total number of cases, the total number of subjects in each subgroup, and the crude RR estimates. Specifically, we computed for each subgroup, the ratio of the number of subjects in the subgroup over the number in the reference category. Then, we summed over patient subgroups, the product of these relative numbers of subjects with the subgroup RR. The inverse of this total was our estimated proportion of cases in the reference category. Multiplying our total number of cases by this estimated proportion gave us an estimate of the number of cases in the reference group. Using this estimate, the estimate of the relative numbers of subjects in each subgroup, and the unadjusted relative risk estimates, we then solved for the estimated number of cases in each of the other patient groups. This provided all the required data (or estimates of it) and we performed the dose-response analysis in R using the adjusted hazard ratios and the reported and estimated sample sizes in each stratum. This provided a single (weighted)

summary estimate of the adjusted RR for diabetes.

Ranc et al. [15] reported their results a little differently. They reported, separately for males and females, HRs for three subgroups of patients with diabetes using patients without diabetes as the reference group. They also provide the numbers of person-years for each stratum and the number of cases in the categories of patients with diabetes. However, the number of cases in the reference group, needed for estimating the covariance between HR estimates for our summary, was not provided. We could estimate the number of cases in the reference category using the person years, the count in the diabetes subgroup with the related HR estimate. We did this for each of the three diabetes groups, finding that the estimates obtained from the two strata with the larger sample sizes were very close to one another (<2%) and the third estimate was rather different. We averaged the two similar estimates of the number of cases and then proceeded with the dose-response analysis of the three sex-specific RRs for diabetes. This was done separately in males and females and was followed by a fixed-effect analysis over sex to estimate the sex-adjusted HR for diabetes.

Lam et al. [17] reported HRs separately by sex, for patients grouped by race and diabetes status. For each sex, the reference category was white patients without diabetes. To estimate the adjusted HR comparing patients with and without diabetes required (1) estimating the race-specific HRs by sex, (2) applying for each sex a fixed effect meta-analysis to average the HRs in whites and in blacks, and (3) applying a fixed effect meta-analysis over stratum of sex, to estimate the sex- and race-adjusted HR for diabetes. The race-specific HRs were computed separately by sex, taking the ratio of the two HRs in blacks, the HR for black patients with diabetes over the HR for black patients without diabetes. The reference category of whites without diabetes cancels from the numerator and denominator and the new HR estimate compares black patients with and without diabetes. The HR for whites was provided in the paper and required no additional manipulation. To summarize over race in a fixed effect meta-analysis required a standard error estimate for the new HR (or logHR). This required estimating the covariance matrix for the logHR estimates. We use the same approach for the dose-response analysis mentioned above to estimate the covariance of logHRs using the stratum-specific numbers of patients and numbers of deaths. Lam et al. [17] reported the number of patients by strata, but they did not report the number of deaths. The study had seven years of follow-up data and we used the sex- and race-specific 5-year survival rates to estimate the number of deaths at five years in categories of sex and race. With an estimate for the number of deaths, we applied the methods in the paragraph above to estimate the number deaths by category of diabetes status. This yielded all the required elements needed to manipulate the HR estimates as described earlier and summarize them with an adjusted HR comparing patients with and without diabetes.