The Association Between Overweight or Obesity and Prognosis of Kidney Cancer: A Study Protocol of An Updated Systematic Review and Meta-Analysis

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Protocol

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Abstract

Introduction: Kidney cancer is among the 10 most common cancers in both men and women. As we know, obesity and overweight is one of the confirmed risk factors. However, several studies found that overweight or obese patients with kidney cancer had a better prognosis than normal weight patients, as known as the “obesity paradox”. Therefore, in this study, we aimed to conduct a systematic meta-analysis of peer-reviewed literature to investigate the association between obesity or overweight and kidney cancer outcomes.

Methods and analysis: Our review will assess case-control or cohort studies on prognosis of kidney cancer patients who are classified as obese, overweight or normal weight before 1 August 2020. Databases to be searched include PubMed/MEDLINE, Scopus, Web of Science and Embase. Two authors will independently conduct eligible studies selection process, perform data extraction and appraise the quality of included studies. Original case-control or cohort studies published in English will be considered for inclusion. The outcomes of interest will be progression-free survival, cancer-specific survival and overall survival. Meta-analyses will be performed to calculate pooled estimates.

Ethics and dissemination: Our study will be based on published data, and thus there is no requirement for ethics approval. The results will be shared through publication in a peer-reviewed journal and presentations at academic conferences.

PROSPERO registration number: CRD42021223347

Strengths And Limitations Of This Study

- This will be the most comprehensive and up-to-date systematic review to sum up the evidence on the association between overweight or obesity and prognosis of kidney cancer.
- We minimize the potential reviewer bias by letting two independent reviewers to screen for eligible studies, extract the data and assess the quality of the included studies.
- We only include papers published in English.
- A considered heterogeneity is anticipated between studies because of differences in study design and length of follow-up.
- The main possible limitation of this study is that most of the studies might use BMI as the criteria of overweight and obese, which cannot precisely definite whether patients are obese or overweight or normal weight, considering the situation of visceral obesity.

1. Introduction

Kidney cancer is among the 10 most common cancers in both men and women. In 2020, about 73,750 new cases of kidney cancer (45,520 in men and 28,230 in women) were diagnosed. About 14,830 people (9,860 men and 4,970 women) died from this disease.¹ In the United States, kidney cancer incidence

rate(age-adjusted to the US Standard Population)have increased at an annual percent change of about 3.4% from 2000 to 2007, 0.7% from 2007 to 2017.² Not only in the United States, the incidence of kidney cancer in other countries should not be underestimated. In China, the estimated age-standardized incidence rates (age adjusted to World Standard Population) in 2020 reached 3.3/100000.³

The lifetime risk for developing kidney cancer in men is about 1 in 46 (2.18%). The lifetime risk for women is about 1 in 79(1.26%).² Renal cell carcinoma (RCC), also known as renal cell cancer or renal cell adenocarcinoma, is the most common type of kidney cancer. About 9 out of 10 kidney cancers are renal cell carcinomas. Scientists have found several risk factors that could make people more likely to develop RCC. Among all risk factors, people who are very overweight have a higher risk of developing RCC. Obesity may cause changes in certain hormones that can lead to RCC. Note-worthily, several studies^{4 5 6} have found that patients who are overweight or obese might have better prognosis than those of normal weight, which is called the “obesity paradox”. However, the findings have been inconsistent. A large cohort of U.S. men and women conducted by Calle et al. in 2003 concluded that increased body weight was associated with increased mortality rates of RCC.⁷ A recent meta-analysis by Kim et al. published in 2020, demonstrated a favorable effect of body mass index (BMI) on kidney cancer outcomes.⁸ However, there were several limitations: First of all, we have found several high-quality researches that Kim missed through our comprehensive search. Secondly, their search was performed between inception and December 2018, however, there are five more researches^{9–13} published since then, and their conclusions are not consistent. Among these studies, Marchioni M et al.¹⁰ and Zhou W et al.¹³ resulted in opposition to the “obesity paradox”. The other three studies^{9 11 12} found better prognosis in patients classified as overweight or obesity. Therefore, it is important to synthesize all the studied we have searched. Also, we have got high-grade clinical data from The Cancer Genome Atlas(TCGA) and The National Cancer Institute’s Clinical Proteomic Tumor Analysis Consortium (CPTAC), through the analysis of these two databases and the combination with results of meta-analysis, we believe that we can get the most comprehensive and convincing conclusions.

2. Objectives

We therefore plan to conduct this systematic review and meta-analysis of epidemiological studies to comprehensively summarize the evidence for the effects of overweight and obesity on the prognosis of kidney cancer. The aim of this proposed study is to determine whether overweight or obesity have a positive effect on the prognosis of kidney cancer and to summarize the current data.

3. Methods And Analysis

This study has been registered on PROSPERO (CRD42021223347) on December 12, 2020.¹⁴ The systematic review will be performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁵ This research protocol is in accordance to the guideline of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015.¹⁶Any

changes or modifications of the methods stated in this protocol will be updated via PROSPERO and reported in the final systematic review itself. One of the cohorts we are going to analyze is from The Cancer Genome Atlas (TCGA), a project jointly initiated by the National Cancer Institute (NCI, National Cancer Institute) and National Human Genome Research Institute (NHGRI, National Human Genome Research Institute) in 2006, which is a very important source of data for cancer researchers. Another cohort is from The National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC), a national effort to accelerate the understanding of the molecular basis of cancer through the application of large-scale proteome and genome analysis, or proteogenomics.

3.1. Eligibility criteria

The Population, Exposure, Comparator and Outcome (PECO) framework will be used to clarify the eligibility criteria.¹⁷

3.1.1. Types of populations

We will include studies which have clear definition of overweight or obesity, while studies doesn't meet this requirement will be excluded. We will also include studies on kidney cancer independently, while those involving other cancers on the same person will be excluded.

3.1.2. Types of exposures

We will include studies which used any classification criteria related to overweight or obesity such as body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and visceral fat area (VFA), etc.

3.1.3. Types of comparators

The included comparator will be patients with normal weight. We will include all these comparisons of overweight or obesity versus normal weight. When overweight or obesity was used as the comparator in original studies, we will use the reciprocal method ($1/x$) to convert the effect estimates of normal weight versus overweight or obesity. We will exclude all other types of comparators.

3.1.4. Types of outcome measures

The primary outcome is overall survival (OS). The second outcomes are cancer-specific survival (CSS) and progression-free survival (PFS). OS is the period from the date of diagnosis to the date of death caused by any reason. CSS is the period from the date of diagnosis to the date of death caused by RCC. Patients who died from causes other than RCC are not counted in this measurement. PFS is the period from the date of diagnosis until the date of the first occurrence of a new tumor event (NTE), which includes progression of the disease, locoregional recurrence, distant metastasis, new primary tumor, or death with tumor. As long as one of these outcomes is available, the study will be included.

3.1.5. Types of studies

We will include a broad set of epidemiological studies that investigate the effects of overweight or obesity to the prognosis of kidney cancer over any period. Eligible study designs include prospective or retrospective cohort study, case-control study, nested case-control study, and case-cohort study. There is no eligible randomized controlled trial or non-randomized intervention study in the preliminary search due to rigorous ethical principles. We will exclude all other study designs such as non-original studies, cross-sectional studies, case series, animal model researches, cell line researches, and other mechanism researches.

3.1.6. Types of effect measures

We will include all these relative effect estimates, including relative risk ratios (RR), hazard ratios (HR), and odds ratios (OR). If one original study reports the effect estimate from two or more alternative models that have not been adjusted or adjusted for different confounding factors, then we will systematically choose the largest adjusted estimate in the model adjusted for more covariates, rather than those from models adjusted for fewer. For example, if a study proposes estimates of the effects from a crude unadjusted model (Model A), a model adjusted for gender (Model B), and a model adjusted for gender, age, and pathological stages (Model C), we will give priority to the estimate from Model C.

3.2. Information sources and search

3.2.1. Electronic bibliographic databases

The following databases will be searched from the database inception to August 1, 2020: PubMed/MEDLINE, EmBase, Web of Science with English published only. Both free-text terms and terms at keyword databases such as Medical Subject Headings (MeSH) and Emtree will be used to define the keywords. For example, 'renal carcinoma', 'kidney carcinoma', 'kidney cancer'. Meanwhile, common terms in the field of prognosis and studies regarding overweight or obesity will be used in our search strategy. Various forms of words, synonyms, plural words, and acronyms for 'cancer of kidney', 'kidney neoplasms', 'BMI' and so on will also be used in varying combinations. Full details of search strategy are presented in **online supplementary file 1**.

3.2.2. Hand-searching and expert consultation

Reference list of all original researches, relevant reviews, editorials, and letters; of relevant reviews, editorials, and letters will be manually searched for additional references. Errata or retractions from eligible studies will be searched on PubMed, and the date when this was done will be reported in the review.

3.3. Study selection

All literature records identified in the search will be imported into the Covidence software¹⁸ and duplicates will be identified and deleted. Afterwards, two authors (SYL and YPL) will independently screen titles and abstracts, only papers considered potentially relevant according to the inclusion criteria will be retrieved for further consideration. Authors will record specific reasons for exclusion in the full-text screening. A

third author (SRW) will resolve any discrepancies. A fourth author (HNJ) will check all procedures before approving the data extraction. The process of study selection will be reported as per PRISMA guidelines.

3.4. Data extraction and data items

Two authors (SYL and YPL) will independently extract data, and a third author (SRW) will resolve conflicts. The extracted data items will include study characteristics (including authors, publication year, study country, participants' age, gender, year of sample collection, and outcome), exposure (including BMI, WC, WHR or VFA, and the definitions of obesity and overweight), study design (including summary of study design, sample size, follow-up period, statistical analysis models used, and effect estimates and corresponding 95% confidence intervals (CIs)), risk of bias (including selection bias, reporting bias, confounding bias). Data will be extracted through a standardized data compilation form (see **online supplementary file 2**) in duplicate to avoid errors. Data will be entered into and managed with the Microsoft Excel software. Pairs of data-extraction forms will be checked for discrepancies. If data are missing or incomplete in any study, we will contact with the authors to obtain such data.

3.5. Risk of bias in individual studies

Two authors (SYL and YPL) will independently assess methodological quality and risk of bias for each study by using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.¹⁹ Any divergences will be resolved by discussion or consultation with a third author (SRW). All quality assessors will trial the ROBINS-I criteria until they have synchronized their understanding and application of the ROBINS-I tool. The ROBINS-I scale covers seven distinct domains: confounding, selection, intervention classification, deviations from intended interventions, missing data, measurement of outcomes and selection of reported results. The risk of bias for each outcome across individual studies will be summarized as a narrative statement, and supported by a risk of bias table presenting domain specific judgements. We will report the study-level risk of bias assessments by domains in a summary table (**online supplementary file 3**).

3.6. Synthesis of results

3.6.1. Quantitative synthesis

In the primary meta-analysis, we will use the maximally adjusted effect estimates and corresponding 95% confidence intervals (CI) to summarize the effect of overweight or obesity on the prognosis of kidney cancer. In order to get more rigorous and conservative results, we will use random effects model, rather than fixed effects model to summarize the effect sizes. The random effects model will assume that there is considerable heterogeneity between studies.

When two or more studies from the same cohort or data source are eligible for inclusion in the meta-analysis, we will prioritize in this order: 1) the study with the highest quality score and the lowest risk of bias; 2) the study with the most credible methods to define overweight or obesity. 3) the study with the

largest sample size; 4) the study with the longest follow-up; 5) the study with the maximal adjustment for relevant potential confounding factors.

Comprehensive Meta Analysis version 2.2.046 (Biostat, Englewood, NJ, USA) will be used for all analyses. Statistical significance was defined as two-sided P-values less than 0.05 in the major meta-analysis. In all subgroup analyses, we will use the Bonferroni method to correct the level of statistical significance.

3.6.2. Heterogeneity inspection

The heterogeneity between studies will be measured by the index of heterogeneity, and Cochran Q-statistics test. Based on the I^2 statistics, an I^2 value of $\leq 50\%$ represents low heterogeneity, 30–50% moderate heterogeneity, 50–75% substantial heterogeneity, and $> 75\%$ considerable heterogeneity. For Q-statistics, heterogeneity will be assumed at a p value less than 0.05. If there is substantial between-study heterogeneity, we will perform meta-regression and subgroup analyses to explore potential sources of the heterogeneity. Meta-regression analyses will be performed according to sample size, year of study publication. Subgroup analyses are elaborated in the section of 3.6.4. Sensitivity analysis.

3.6.3. Publication bias

In order to assess potential publication bias, we will conduct the Begg's and Egger's tests and further rigorously adjust the aggregate results by applying the Duval and Tweedie's trim and fill method. We will also use funnel plots to ascertain presence of publication bias, if ten or more eligible studies are included in our systematic review.

3.6.4. Sensitivity analysis

We will perform a broad set of sensitivity analyses to evaluate the robustness of the findings, as follows:

- We will conduct a sensitivity analysis using fixed-effect models.
- We will combine the minimum adjusted effect estimates and compare these results with the primary results from the maximum adjusted effects using the Confounding RR method, which is defined as the ratio of pooled results of the maximum adjusted to the minimum adjusted data.²⁰ Confounding RRs are used to assess whether the underlying confounders controlled in each individual studies may affect the results.
- To assess the potential impact of residual confounding bias, we will perform an E-value analysis.²¹ E-value shows the minimum strength of association that a hypothetical residual confounding factor would need to have with both the exposure to overweight or obesity and the study outcomes to fully explain the observed effect.
- A sensitivity analysis will be performed by removing the research(or database) with the highest weight to evaluate its impact on the results and to explore potential sources of heterogeneity among studies.
- A sensitivity analysis including only the high-quality studies will be performed.

- We will perform predefined subgroup analyses by geographic area (according to WHO Regions or World Bank Income Country Groups), sample size ($\geq$ median vs. $<$ median), year of study publication and gender (female vs. male), if eligible studies in each subgroup are no less than three. Otherwise, by excluding the subgroup with less than three studies, these afore-mentioned subgroup analyses will be performed as sensitivity analyses
- We will also conduct cumulative meta-analyses based on the sample size of each individual studies from small to large, from the publication year of the study to the latest time.

3.7. Quality of evidence assessment

Critical appraisal of the certainty of each evidence will be useful for dealing with and interpreting conflicting findings. We will use the GRADE approach to grade the quality of evidence as “high”, “moderate”, “low”, or “very low”.²² The GRADEproGDT software online version will be used to summarize the quality of evidence. All authors will jointly assess the quality of evidence of the entire body of evidence.

3.8. Patient and public involvement

No patient or public will be involved in our study directly as we only use data that existed in studies published.

Declarations

Ethics and Dissemination: Ethical approval is not required in this systematic review and meta-analysis of published literature. Results of this review study will be disseminated in peer-reviewed journals and may be presented at relevant international and national conferences to promote knowledge transfer.

Availability of data and materials: Data collected through this systematic review will be managed by the present Research Group. The databases used and/or analyzed during the study will be presented within the manuscript or as supplementary materials. Once published, this systematic review and all the databases analyzed will be freely available in an open-access scientific journal.

Author Contributions: SYL, YPL and SRW conceived and designed this systematic review. All authors developed the selection criteria, risk bias assessment strategy, and data extraction criteria. SYL, YPL and SRW developed the pilot search strategy. SYL and YPL will both be the title, abstract, and full-text reviewers. SRW or HNJ will be the third reviewer that will help resolve any discrepancy. SYL and YPL wrote the initial draft of the protocol. All authors revised the manuscript critically for important intellectual content. All authors approved the final version of the systematic review to be published: All authors. YPL and SRW are the guarantors of the systematic review.

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Conflict of Interest: The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the writing and the publication of this work.

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Supplementary Files

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