Research Article

Cancer Epidemiology, Biomarkers & Prevention

Parity and Kidney Cancer Risk: Evidence from Epidemiologic Studies

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Abstract

Background: Observational studies have reported conflicting results between parity and kidney cancer risk. To our knowledge, a comprehensive and quantitative assessment of the association between parity and kidney cancer has not been reported. Thus, we conducted a systematic review and dose–response meta-analysis of published epidemiologic studies to summarize the evidence of this association.

Methods: Relevant published studies of parity and kidney cancer were identified using MEDLINE (PubMed) database through end of June 2013. Two authors independently assessed eligibility and extracted data. Six prospective and eight case–control studies reported relative risk (RR) estimates and 95% confidence intervals (CI) of kidney cancer associated with parity or parity number. Fixed- or random-effects models were used to estimate summary relative risk.

Results: The summary relative risk of kidney cancer for the parity versus nulliparous was 1.23 (95% CI, 1.10–1.36; $Q = 12.41$; $P = 0.413$; $I^2 = 3.3\%$). In addition, significant association was also found for the highest versus lowest parity number, with summary RR = 1.36 (95% CI, 1.19–1.56; $Q = 8.24$; $P = 0.766$; $I^2 = 0\%$). In the dose–response analysis, the summary per one live birth relative risk was 1.08 (95% CI: 1.05–1.10; $Q = 9.34$; $P = 0.500$; $I^2 = 0\%$), also indicating the positive effect of parity on kidney cancer risk. No evidence of publication bias and significant heterogeneity between subgroups was detected by meta-regression analyses.

Conclusions: In summary, findings from this meta-analysis suggest that ever parity and higher parity number is significantly associated with increased risk of kidney cancer.

Impact: The present results suggest a positive association between parity and kidney cancer risk. *Cancer Epidemiol Biomarkers Prev; 22(12); 2345–53. ©2013 AACR.*

Introduction

The incidence of renal cell cancer, the most common type of kidney cancer, which represents approximately 85% of all kidney cancers (1), has been steadily increasing in the United States and worldwide (2, 3). A recent report also suggested that the incidence rate of kidney cancer has increased rapidly in the past 30 years among the adolescents and young adults in Shanghai, China (4).

Cigarette smoking, obesity, and hypertension are the most established risk factors for kidney cancer in both genders (1, 5). Besides the difference in incidence by gender, a role of hormone-related or reproductive factors in kidney cancer etiology has been hypothesized (1). Animal studies have demonstrated that estrogens can promote or induce kidney cancer development (6). Fluctuating sex hormones have also been shown to make nephrons vulnerable to inflammation and oxidative stress (7).

A recent meta-analysis of epidemiologic studies suggested that women who undergo a hysterectomy have an approximate 30% increased relative risk of subsequent kidney cancer (8), which provided evidence that hormonal and iatrogenic factors might play a role in the etiology of kidney cancer. However, the results of other reproductive factors, including parity, are conflicting, which might be attributed to the limited statistical power to detect those associations. Though previous reviews have focused on this topic (1, 9), to our knowledge, a comprehensive and quantitative assessment of the association between parity number and kidney cancer risk has not been reported. Therefore, to evaluate the relationship between parity and kidney cancer risk, we carried out a dose–response meta-analysis on all prospective and case–control studies published up to June 2013.

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Materials and Methods

Literature search

We carried out a comprehensively literature search using MEDLINE (PubMed) from database initiation until June 31, 2013. The search used the following search key words and medical subject heading terms: (parity OR pregnancy OR live birth OR reproductive OR reproduction OR reproductive factors) and (kidney OR renal cell OR renal) and (cancer OR neoplasm OR carcinoma OR tumor) without limitation. We also reviewed the references of all included studies for additional publications. We followed standard criteria for conducting and reporting meta-analyses (10).

Study selection criteria

Published studies were included if they (i) used a case–control or prospective study design, (ii) evaluated the association between parity and kidney cancer risk, and (iii) presented hazard ratio (HR), odds ratio (OR), or relative risk (RR) estimates with 95% confidence intervals (CI), standard errors (SE), or data necessary to calculate these. When multiple publications from the same study were available, we used the publication with the largest number of cases and most applicable information. After excluding 2,881 and 602 articles based on screening of titles and abstracts, respectively, we identified 20 potentially relevant articles for further full-text review (refs. 11–30; Fig. 1). Two articles were excluded because of duplicate reports from the same study population (24, 27), three articles were excluded because they did not report usable or enough data of risk estimate (20, 29, 30), and one article was excluded because of the use of mortality data (11). One study (21) only reported the highest versus lowest category of parity number and was therefore only included in the parity number and dose–response analysis. As part of the International study of Lindblad and colleagues (21), Mellemgaard and colleagues (23) reported more information, which was included in the analysis of the association between ever parity and kidney cancer risk.

Data abstraction

For each eligible study, 2 investigators (H.-B. Guan and T.-T. Gong) independently performed the eligibility evaluation and data abstraction. The disagreements were discussed and resolved by consensus or by involving a third reviewer (Q.-J. Wu) for adjudication. Data abstracted from each study were author list, year of publication, study region and design, study sample size (number of cases and controls or cohort size), range of follow-up for prospective studies, exposure and outcome assessment including ever parity and parity number categories, study-specific adjusted estimates with their 95% CIs for the ever versus never parity and highest versus lowest of parity number, and factors matched by or adjusted for in the design or data analysis. If multiple estimates of the association were available, we abstracted the estimate that adjusted for the most covariates. If no adjusted estimates were presented, we included the crude estimate. If no estimate was presented in a given study, we calculated it and its 95% CI according to the raw data presented in the article (25, 26).

Statistical analysis

The study-specific adjusted relative risks were used as the measure of association across studies. Because the absolute risk of kidney cancer is low, we assumed that estimates of ORs from case–control studies and risk, rate or HRs from prospective studies were all valid estimates of the relative risk and we therefore report all results as the relative risk for simplicity. For studies that did not use the

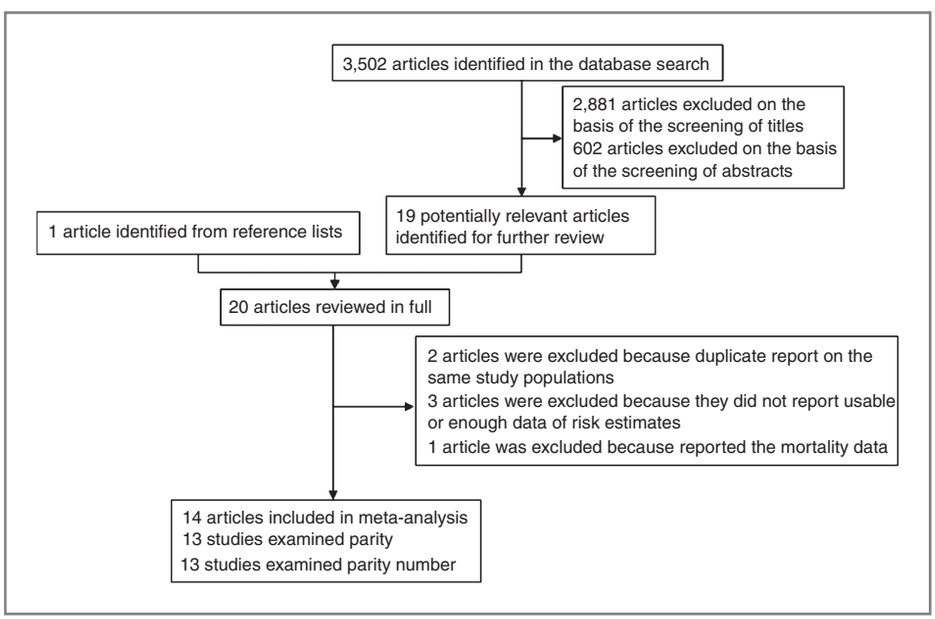

Figure 1. Selection of studies for inclusion in meta-analysis.

category with the lowest parity number as the reference (13, 14, 17, 28), we used the effective count method proposed by Hamling and colleagues (31) to recalculate the relative risks.

For the dose–response analysis, which calculates parity number as continuous variable, we used the method proposed by Greenland and colleagues (32) and Orsini and colleagues (33) to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the relative risks and CIs across categories of the parity number. The method requires that the distribution of cases and person-years of noncases and the relative risks with the variance estimate for at least three quantitative exposure categories are known. For studies that reported the duration by ranges we estimated the midpoint in each category by calculating the average of the lower and upper bound. When the highest category did not have an upper bound, we assumed the length of the open-ended interval to be the same as that of the adjacent interval. When the lowest category did not have a lower bound, we set the lower bound to zero. The dose–response results in the forest plots are presented on the basis of the 1 live birth increments for the parity number.

We evaluated heterogeneity of relative risks across studies by using the Cochrane Q statistic and the I^2 statistic (34). For the Q statistic, a P value less than 0.1 was considered to be representative of statistically significant heterogeneity. I^2 represents the proportion of total variation contributed by between-study variation (34). The summary estimate based on the fixed-effects model (34) for no detected heterogeneity or the random-effects model (35) when substantial heterogeneity was detected. In both methods, the weight of each study depended on the inverse of the variance of log OR, which was estimated by the 95% CI from each study. Subgroup analyses were carried out based on study design (prospective vs. case–control studies), type of controls within the case–control studies (population-based vs. hospital-based controls), exposure assessment (self-administered questionnaire or trained interviewers vs. interviewers or not mentioned), and geographic location (Europe vs. North America). We also stratified the meta-analysis by potentially important confounders [i.e., body mass index (BMI), smoking status, and history of hypertension]. We did not stratify by case assessment because all studies used cancer registries or medical records. Heterogeneity between subgroups was evaluated by meta-regression. A P value less than 0.05 for meta-regression was considered representative of significant statistical difference between subgroups. Finally, we carried out sensitivity analyses excluding one study at a time to explore whether the results were strongly influenced by a specific study.

Publication bias was evaluated via Egger linear regression (36), Begg rank correlation methods (37) and funnel plots. A P value less than 0.05 for Egger or Begg tests was considered representative of significant statistical publication bias. Statistical analyses were performed with Stata (version 11.2; StataCorp). P values were two sided with a significance level of 0.05.

Results

Study characteristics

Characteristics of the 14 included articles (12–19, 21–23, 25, 26, 28) are shown in Supplementary Table S1. The included articles, which represent 5,389 cases and 651,072 noncases, were published between 1974 and 2013 and consist of 6 prospective studies (5 cohort studies; refs. 12, 14, 15, 17, 18) and 1 nested case–control study (19) and 8 case–control studies (13, 16, 21–23, 25, 26, 28). Of the 6 prospective studies, 4 were conducted in the United States (12, 14, 15, 17), and one each in Canada (18) and Sweden (19). Cohort sizes ranged from 37,440 (17) to 283,952 (12), and the number of kidney cancer cases varied from 165 (17) to 1,465 (19).

Of the 8 case–control studies, 3 studies were conducted in the United States (13, 22, 26), 2 in Italy (16, 25), 1 each in Denmark (23) and International cooperation group, which covered multiple countries (21). The number of cases enrolled in these studies ranged from 56 (25) to 608 (21), and the number of control subjects varied from 227 (22) to 5,619 (25). Control subjects were drawn from the general population in 5 studies (13, 21–23, 28), hospitals in 3 studies (16, 25, 26). The highest parity number varied from 3 (16) to more than 6 (21).

Ever versus never parity

Six prospective (12, 14, 15, 17–19) and 7 case–control studies (13, 16, 22, 23, 25, 26, 28) investigated the association between ever parity and kidney cancer risk. The summary relative risk of kidney cancer for the ever versus nulliparous was 1.23 (95% CI, 1.10–1.36), with little heterogeneity ($Q = 12.41$; $P = 0.413$; $I^2 = 3.3\%$; Table 1 and Fig. 2). There was no indication of publication bias with the Egger test (P for bias = 0.214) or with the Begg test (P for bias = 1.000) and no asymmetry was observed in the funnel plots when inspected visually. The 13 study-specific relative risks of the ever versus nulliparous ranged from a low of 1.12 (95% CI, 1.00–1.29; $Q = 8.12$; $P = 0.702$; $I^2 = 0\%$) after omission of the study by Lambe and colleagues (19) to a high of 1.27 (95% CI, 1.14–1.42; $Q = 7.43$; $P = 0.763$; $I^2 = 0\%$) after omission of the study by Molokwu and colleagues (17).

High versus low number of parity

Six prospective (12, 14, 15, 17–19) and 7 case–control studies (13, 16, 21, 22, 25, 26, 28) investigated the association between parity number and kidney cancer risk. The summary relative risk of kidney cancer for the highest versus lowest categories of the number of parity was 1.36 (95% CI, 1.19–1.56), with none heterogeneity was observed ($Q = 8.24$; $P = 0.766$; $I^2 = 0\%$; Table 2 and Fig. 3). There was no indication of publication bias with the Egger test (P for bias = 0.816) or with the Begg test (P for bias = 1.000) and no asymmetry was seen in the funnel plots when inspected visually. In a sensitivity analysis, we sequentially removed one study at a time and reanalyzed

Table 1. Summary risk estimates of the association between ever parity and kidney cancer risk

	No. of studies	Summary RR (95% CIs)	*Q* Statistic	I^2 (%)	P_h[a]	P_h[b]
Overall	13	1.23 (1.10–1.36)	12.41	3.3	0.413	—
Subgroup analyses						
Study design						0.601
Prospective studies	6	1.21 (1.00–1.47)	9.34	46.4	0.096	
Case–control studies	7	1.13 (0.90–1.42)	2.43	0	0.877	
Number of cases						0.440
<250	7	1.10 (0.89–1.36)	7.56	20.6	0.272	
≥250	6	1.27 (1.12–1.44)	3.57	0	0.613	
Exposure assessment						0.115
Self-questionnaire/trained interviewer	11	1.14 (1.00–1.30)	6.78	0	0.746	
Interviewer/not mention	2	1.38 (1.16–1.64)	2.70	63.0	0.100	
Type of control subjects						0.679
Population based	4	1.18 (0.87–1.59)	0.92	0	0.820	
Hospital based	3	1.06 (0.75–1.51)	1.31	0	0.519	
Geographic location						0.126
North America	8	1.12 (0.97–1.30)	7.54	7.2	0.375	
Europe	5	1.34 (1.15–1.56)	2.12	0	0.713	
Primary interest						0.542
Yes	11	1.24 (1.11–1.38)	10.57	5.4	0.392	
No	2	1.01 (0.60–1.71)	1.30	23.2	0.254	
Adjustment for confounders or important risk factors						
BMI						0.110
Yes	9	1.13 (0.98–1.30)	6.56	0	0.584	
No	4	1.37 (1.16–1.60)	2.82	0	0.420	
Cigarette smoking						0.647
Yes	8	1.16 (1.00–1.35)	0.97	0	0.995	
No	5	1.17 (0.84–1.63)	10.35	61.4	0.035	
Hypertension						0.116
Yes	5	1.04 (0.84–1.28)	2.43	0	0.657	
No	8	1.35 (1.10–1.48)	6.55	0	0.477	
BMI, cigarette smoking, and hypertension						0.747
Yes	4	1.14 (0.90–1.46)	0.02	0	0.999	
No	9	1.25 (1.11–1.40)	12.01	33.4	0.151	

[a]*P* value for heterogeneity within each subgroup.

[b]*P* value for heterogeneity between subgroups with meta-regression analysis.

the data. The 13 study-specific relative risks of the parity number ranged from a low of 1.31 (95% CI, 1.13–1.52; $Q = 6.86$; $P = 0.810$; $I^2 = 0\%$) after omission of the study by Lambe and colleagues (19) to a high of 1.41 (95% CI, 1.21–1.64; $Q = 7.37$; $P = 0.769$; $I^2 = 0\%$) after omission of the study by Karami and colleagues (12).

Dose–response analysis

Four prospective (15, 17–19) and 7 case–control studies (13, 16, 21, 22, 25, 26, 28) were included in the dose–response analysis. The summary relative risk per live birth was 1.08 (95% CI, 1.05–1.10), with none of heterogeneity ($Q = 9.34$; $P = 0.500$; $I^2 = 0\%$; Table 2 and Fig. 4). Publication bias was not evident from the Egger test ($P = 0.690$), Begg test ($P = 0.938$), and visual inspection of the funnel plot. In a sensitivity analysis excluding one study at a time, the summary relative risk for kidney cancer ranged from 1.07 (95% CI, 1.04–1.11; $Q = 8.87$; $P = 0.449$; $I^2 = 0\%$), when Lambe and colleagues (19) was excluded, to 1.09 (95% CI, 1.06–1.11; $Q = 6.05$; $P = 0.735$; $I^2 = 0\%$), when Setiawan and colleagues (15) was excluded. In addition, the effect on the results of excluding studies from the dose–response analysis was explored. When the analysis of high versus low parity number was restricted to the studies that were included in the dose–response analysis of the number of parity, the summary relative risk was 1.40 (95% CI, 1.19–1.65; $Q = 7.27$; $P = 0.700$; $I^2 = 0\%$), similar to the original analysis including all studies.

Subgroup analyses

In subgroup analyses of ever parity and kidney cancer risk, all strata showed positive associations, and there was

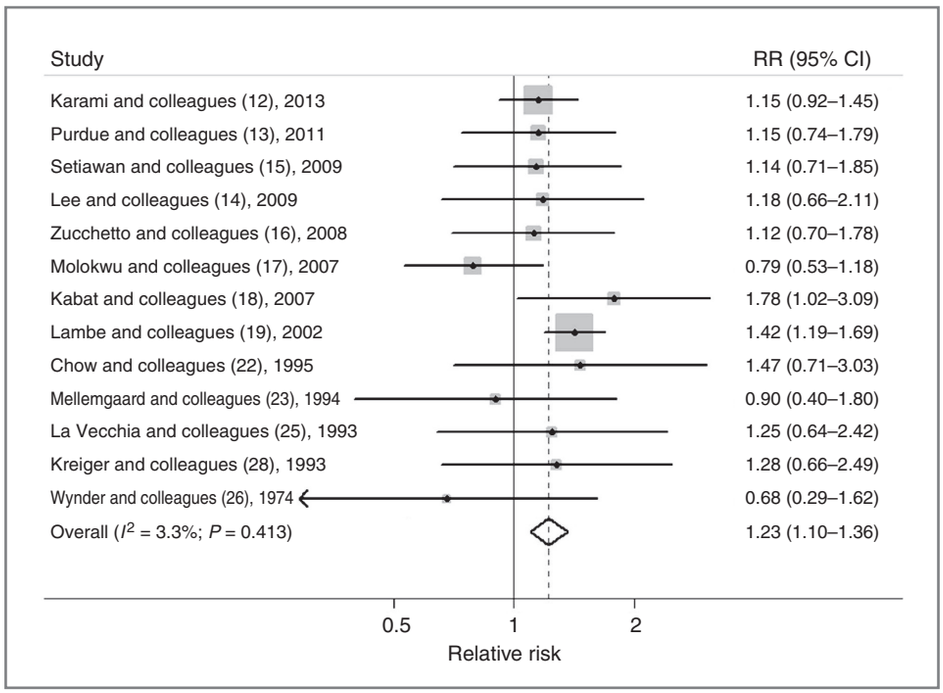

Figure 2. Forest plot (fixed-effects model) of ever parity and kidney cancer risk. The squares indicate study-specific relative risks (size of the square reflects the study-specific statistical weight); the horizontal lines indicate 95% CIs; and the diamond indicates the summary relative risk estimate with its 95% CI.

no evidence of significant heterogeneity between subgroups with meta-regression analyses (Table 1). In the dose–response analyses of the association between parity number and kidney cancer risk, we also found the similar results (Table 2). Similar to the previously study (38), we also performed the subgroup analysis by the primary interest (whether the title or abstract refer to the reproductive factors as their research interest) to focus on whether difference existed. However, the results of the meta-regression hardly support this point and only two studies (26, 28) did not consider the reproductive factors as the primary interest of their research. When stratified by the adjustment for potential confounders, we did not find a significant difference between estimates adjusted and those not adjusted for specific factors (Tables 1 and 2).

Discussion

To our knowledge, this is the first meta-analysis that provides evidence of the association between parity and kidney cancer risk. Findings from this study indicated that ever parity and increased parity number are associated with an increased risk of kidney cancer. Overall, the risk of kidney cancer increased by 23% among populations who ever parity. Furthermore, in the dose–response analysis, the risk of kidney cancer increased by 8% for per 1 live birth.

Although the exact biologic mechanisms underlying the association between parity and increased risk of kidney cancer are not fully understood, several potential mechanisms might have been proposed. Oxidative stress has been hypothesized to be responsible for renal carcinogenesis (39). Renal tubular cells and vascular bed may be more vulnerable to inflammation or oxidative stress through pregnancy-induced physiologic changes such as increases in maternal blood volume, cardiac output, renal plasma flow, glomerular filtration, kidney size, dilation of the renal pelvis, and excess risk of urinary tract infection (7, 40, 41). Anatomic change in the kidney during pregnancy might also contribute to the oxidative stress and inflammation of the nephrons (7, 40). In addition, hormones, either directly or through growth factors, may act as promoters of malignant changes by stimulating renal cell proliferation (42). High doses of potent estrogens have been shown to induce renal cancers in the Syrian hamster (43). The expression of estrogen and progesterone receptors in both normal and malignant renal tissues also suggests that endocrine regulation could directly influence kidney cancer development (44, 45). On the other hand, obesity is a known risk factor for kidney cancer and is associated with pregnancy. Pregnancy-associated weight gain may contribute toward an increased risk of kidney cancer (46, 47).

When we carried out the subgroup analysis by geographic location, significantly positive associations were both observed in Europe and North America. Considering the fact that limited studies from Europe were included, the interpretation of the results should be taken cautiously. We found few studies from Asia and the only one study (11) focused on this topic from Taiwan was excluded because of using mortality data. Compared with the reports from Western countries, Chiu and colleagues (11) was the only study to report that increased parity was associated with a tendency for decreased kidney cancer risk, but without statistical significance. Therefore, more Asian studies should focus on this topic, even

Table 2. Summary risk estimates of the association between parity number and kidney cancer risk

	Highest versus lowest						Dose–response analysis (per 1 live birth)					
	No. of studies	Summary RR (95% CIs)	*Q* Statistic	I^2 (%)	P_h[a] studies	P_h[b] (95% CIs)	No. of statistic	Summary RR (%)	*Q*	I^2	P_h[a]	P_h[b]
Overall	13	1.36 (1.19–1.56)	8.24	0	0.766	—	11	1.08 (1.05–1.10)	9.34	0	0.500	
Subgroup analyses												
Study design						0.941						0.949
Prospective studies	6	1.37 (1.17–1.60)	3.78	0	0.582		4	1.08 (1.04–1.11)	4.27	29.8	0.234	
Case–control studies	7	1.35 (1.04–1.76)	4.45	0	0.616		7	1.08 (1.04–1.12)	5.06	0	0.536	
Number of cases						0.999						0.919
<250	7	1.36 (1.10–1.69)	4.17	0	0.654		6	1.08 (1.03–1.12)	7.15	30.1	0.210	
≥250	6	1.36 (1.15–1.62)	4.07	0	0.539		5	1.08 (1.05–1.11)	2.18	0	0.703	
Exposure assessment						0.303						0.667
Self-questionnaire/trained interviewer	11	1.32 (1.13–1.53)	6.85	0	0.740		9	1.07 (1.04–1.11)	8.53	6.2	0.384	
Interviewer/not mention	2	1.59 (1.17–2.16)	0.22	0	0.636		2	1.09 (1.04–1.13)	0.55	0	0.457	
Type of control subjects						0.254						0.710
Population based	4	1.55 (1.11–2.16)	2.30	0	0.512		4	1.08 (1.04–1.13)	4.26	29.5	0.235	
Hospital based	3	1.08 (0.71–1.66)	0.49	0	0.782		3	1.06 (0.96–1.17)	0.65	0	0.721	
Geographic location						0.295						0.544
North America	8	1.31 (1.11–1.55)	3.75	0	0.808		6	1.07 (1.03–1.11)	7.11	29.7	0.213	
Europe	4	1.39 (1.08–1.79)	2.85	0	0.415		4	1.08 (1.04–1.12)	1.82	0	0.611	
Primary interest						0.648						0.229
Yes	11	1.37 (1.20–1.57)	8.00	0	0.629		9	1.08 (1.06–1.11)	7.65	0	0.469	
No	2	1.14 (0.54–2.42)	0.02	0	0.902		2	1.00 (0.89–1.12)	0.02	0	0.874	
Adjustment for confounders or important risk factors												
BMI						0.568						0.887
Yes	9	1.33 (1.15–1.56)	5.73	0	0.677		7	1.08 (1.04–1.11)	7.16	16.3	0.306	
No	4	1.47 (1.11–1.95)	2.16	0	0.541		4	1.08 (1.04–1.12)	2.11	0	0.550	
Cigarette smoking						0.398						0.324
Yes	8	1.31 (1.11–1.54)	4.84	0	0.679		6	1.06 (1.03–1.10)	6.78	26.2	0.238	
No	5	1.49 (1.18–1.87)	2.62	0	0.623		5	1.09 (1.06–1.13)	1.47	0	0.832	
Hypertension						0.310						0.105
Yes	5	1.25 (1.01–1.54)	1.22	0	0.876		4	1.04 (1.00–1.09)	1.11	0	0.775	
No	8	1.45 (1.22–1.73)	5.89	0	0.533		7	1.10 (1.06–1.13)	4.75	0	0.576	
BMI, cigarette smoking, and hypertension						0.383						0.084
Yes	4	1.25 (1.00–1.58)	1.22	0	0.749		3	1.03 (0.98–1.09)	0.56	0	0.756	
No	9	1.43 (1.21–1.68)	6.20	0	0.625		8	1.09 (1.06–1.12)	5.00	0	0.660	

[a]*P* value for heterogeneity within each subgroup.

[b]*P* value for heterogeneity between subgroups with meta-regression analysis.

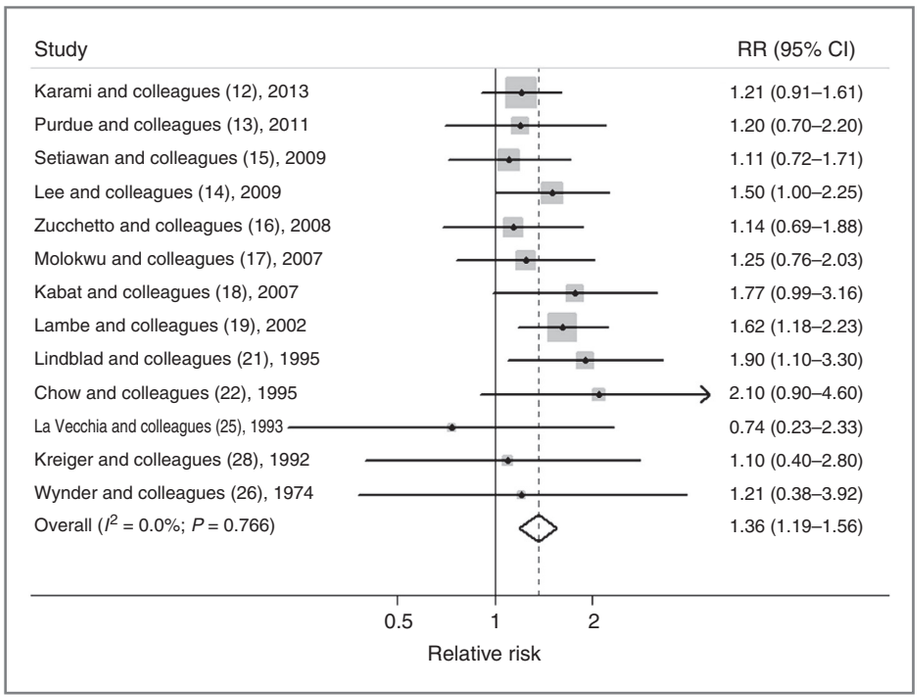

Figure 3. Forest plot (fixed-effects model) of parity number (highest vs. lowest) and kidney cancer risk. The squares indicate study-specific relative risks (size of the square reflects the study-specific statistical weight); the horizontal lines indicate 95% CIs; the diamond indicates the summary relative risk estimate with its 95% CI.

though the incidence of kidney cancer is lower than in Western countries (1).

Our meta-analysis has several strengths. Although the majority of the included studies showed positive association between parity and kidney cancer risk, not all of them (14, 18, 19, 21) showed statistical significance, which could be attributed to the limited statistical power. Our study includes the large sample size of 5,389 cases and 651,072 noncases. This sample size should have provided sufficient statistical power to detect this putative association. In addition, although the summary results demonstrated little heterogeneity, we also carried out a number of subgroups and sensitivity analyses and the results were robust. Several limitations must be addressed. First, as a meta-analysis of epidemiologic studies, the biases (e.g., recall and selection bias) inherent in the original studies

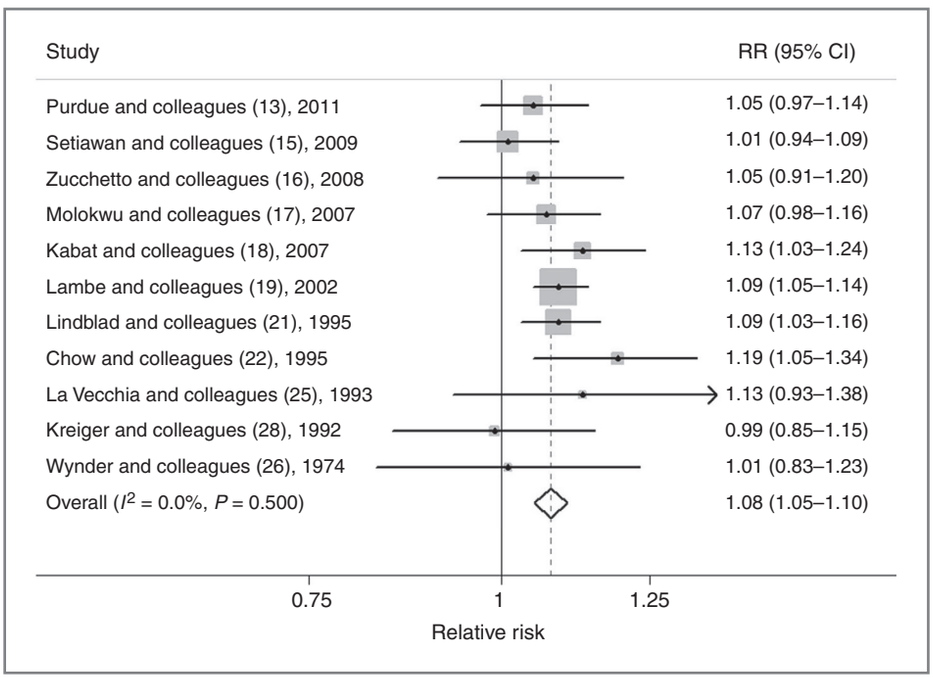

Figure 4. Forest plot (fixed-effects model) of parity number (per 1 live birth) and kidney cancer risk. The squares indicate study-specific relative risks (size of the square reflects the study-specific statistical weight); the horizontal lines indicate 95% CIs; the diamond indicates the summary relative risk estimate with its 95% CI.

could not be avoided. Cohort studies are less susceptible to bias than case–control studies because, in the prospective design, information on exposures is collected before the diagnosis of the disease. Although the results of the meta-regression found no evidence of significant heterogeneity between subgroups by study design and exposure assessment and the results were almost similar in the dose–response analysis (Table 2), we only found the significant results in the prospective studies and the summary association estimates were slightly different in subgroup analyses by exposure assessment (Table 1). It is possible that the relationships reported by case–control studies might have been overstated due to recall or interviewer bias. In addition, considering that some recent epidemiologic studies provided detailed information of adjustment for confounders, whereas some early studies adjusted for fewer factors, we also performed the stratified analysis by the publication year, but the results did not show much difference (data not shown).

Second, parity may be associated with several other factors [e.g., higher exposure to obesity (refs. 46, 47) and more exposure to hypertension (refs. 48, 49)], which were the established risk factors for kidney cancer. Although the results persisted in all the subgroups and the meta-regression analyses did not show statistical significance, difference was still observed among the stratified analyses depending on whether confounders had been adjusted for or not. Similar patterns were also observed among the stratified analyses considering whether adjusted for all the possible confounders/risk factors or not, which might be partly attributed to the limited numbers of studies (Tables 1 and 2). Thus, any further studies should report on analyses that considered these important confounders and adjusted or stratified by other risk factors to be better able to rule out residual confounding.

Third, the summary results are combined from studies conducted with different study design in different populations, and heterogeneity must be considered. Nevertheless, there was little heterogeneity in the overall subgroups and sensitivity analyses of this study. On the other hand, publication bias can be a problem in meta-analyses of published studies; however, we found no statistical evidence of publication bias in this meta-analysis by Egger linear regression and Begg rank correlation methods, and there did not seem to be asymmetry in the funnel plots when inspected visually.

In conclusion, our meta-analysis provided evidence that ever parity and increased parity numbers are associated with an increased risk of kidney cancer. Further research, particularly prospective studies in developing countries, is warranted to report more results. In addition, more studies stratifying the results by different histotypes of kidney cancer and fully adjusting for the confounders should be extended in the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: H.-B. Guan, Q.-J. Wu, T.-T. Gong
Development of methodology: H.-B. Guan, Q.-J. Wu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.-B. Guan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.-B. Guan, Q.-J. Wu, T.-T. Gong
Writing, review, and/or revision of the manuscript: H.-B. Guan, Q.-J. Wu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.-B. Guan, Q.-J. Wu
Study supervision: H.-B. Guan, Q.-J. Wu, T.-T. Gong

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