Int J Clin Exp Med 2016;9(2):952-964
www.ijcem.com /ISSN:1940-5901/IJCEM0013680

Original Article

Parity is a risk factor for hepatobiliary neoplasm: a meta-analysis of 16 studies

Zhifeng Guan[1*], Hongcheng Zhu[2*], Xiaochun Xia[1*], Feng Wang[1], Baixia Yang[1], Yangyang Ge[1], Jing Cai[1]

[1]Department of Radiation Oncology, Nantong Tumor Hospital, Affiliated Tumor Hospital of Nantong University, Nantong 226321, China; [2]Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China. [*]Equal contributors.

Received July 30, 2015; Accepted December 1, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Conflicting results have been reported by studies assessing parity as a risk factor for hepatobiliary neoplasm. Methods: We conducted a meta-analysis of available epidemiologic studies to investigate the association of parity with hepatobiliary neoplasm and calculated dose-response trends using a linear model. Between-study heterogeneity was evaluated using Cochran's *Q* statistic and the I^2 index. Random effects meta-analysis was used to assess the summary relative risk (RR) per child and the 95% confidence interval (CI). Results: Eleven eligible studies including 2021 cases provided data for the meta-analysis. The summary RR of hepatobiliary neoplasm for the highest versus lowest parity number was 2.207 (95% CI = 1.397-3.488), with statistically significant heterogeneity (Q = 95.84, P = 0.000, I^2 = 82.3%). The summary RR of hepatobiliary neoplasm for parous versus nulliparous cases was 1.37 (95% CI = 1.159-1.624, I^2 = 43.8%, P = 0.001). The combined RR of hepatobiliary neoplasm for per live birth was 1.118 (95% CI = 1.032-1.211, I^2 = 77.0%, P = 0.000). We observed a positive association between giving birth to five or more children and hepatobiliary neoplasm risk, with an RR of 2.24 (95% CI = 1.472-3.411, I^2 = 55.6%, P = 0.005). Among the parity numbers considered, five or more was associated with the highest risk of hepatobiliary neoplasm. Elucidating the mechanism underlying this positive association requires further detailed investigation.

Keywords: Parity, hepatobiliary neoplasm, meta analysis, cancer risk

Introduction

Hepatobiliary cancers are highly lethal cancers that comprise a spectrum of invasive carcinomas originating as liver hepatocellular carcinoma, bile duct intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma in the gallbladder and the ampulla of Vater (collectively known as biliary tract cancers). These tumors account for approximately 13% of all annual cancer-related deaths worldwide and for 10%-20% of deaths from hepatobiliary malignancies [1]. Hepatocellular carcinoma (HCC) is an aggressive malignancy that ranks as the fifth most common cancer and the third leading cause of cancer-related mortality worldwide. HCC exhibits substantial geographic variation within each country [2]. Known risk factors for HCC include gender, liver cirrhosis [3], hepatitis B (HBV) or hepatitis C infection, aflatoxin B exposure, alcohol drinking, and cigarette smoking. Prospective epidemiological studies have shown a multiplicative interaction between HBV and aflatoxins in terms of HCC risk [4]. Biliary tract cancers are rare but highly fatal; these cancers include tumors of the gallbladder, extrahepatic bile ducts, and the ampulla of Vater [6]. Biliary tract cancers have notable ethnic and geographic variations [5]. The incidence and mortality rates of biliary tract cancers are relatively high in several central European countries and very high in Northern India, as well as in Chilean Mapuche and American Indian populations. Except for a strong association with chronic cholecystitis and cholelithiasis, little is known about the etiology of biliary tract cancers [6]. Several studies have investigated a possible link between parity and biliary tract cancers or liver cancers using a small sample size. However, these studies reported inconsistent results; some revealed an increased risk of biliary tract cancers and liver cancers, whereas

others found no association. Here we conducted a meta-analysis (including a dose-response study) of available epidemiologic studies to accurately evaluate the association of parity with risk of biliary tract cancers and liver cancers.

Methods

Literature search and eligibility criteria

We performed a comprehensive literature search of the PubMed and Embase databases from the inception of this study to June 2015. We targeted studies that investigated the relationship between parity (defined as the total number of live births) and the risk of biliary tract cancers and liver cancers. To identify related studies on parity, we used the following keywords: "parity", "pregnancy", "live birth", "reproductive", or "reproductive factors"; "liver", "hepatocellular", "hepatoma", "hepatic", "gallbladder", "bile duct" or "biliary"; "cancer", "neoplasm", "carcinoma" or "tumor" and "case-control studies", "case-control", "cohort studies" or "cohort". Articles in any language were considered in the search. Reference lists of the selected papers were also scanned for other pertinent articles. When necessary, we attempted to contact the authors to ask for additional information. Published studies were included if they 1) used a prospective study design; 2) evaluated the association between parity and hepatobiliary neoplasm risk; 3) presented relative risk (RR) or hazard ratio (HR) 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. We excluded non-human, case reports, comparative studies not using an analytical epidemiologic design, or studies not reporting analyses of primary data (e.g., letters, editorials, narrative reviews) and not providing sufficient data. When multiple studies pertained to the same or partially overlapping populations, we used the result with the longest follow-up time or the largest sample size.

Data extraction

For each eligible study, two investigators (ZFG and HCZ) independently performed the eligibility evaluation, data abstraction, and quality assessment. Any disagreements were discussed and resolved by consensus. Further data were extracted from each eligible study. These included the first author, year of publication, geographic region, duration of follow-up or study period, origin of the study population, size of the study population, study design, study-specific adjusted estimates with their 95% CIs for the ever parous versus nulliparous, highest versus lowest number (including nulliparous) of parity, adjusted-RR estimates, 95% CI for incident hepatobiliary neoplasm risk, and confounding variables controlled. If multiple estimates of the association were available, we chose the one that exhibited the greatest degree of control of potential confounders. 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 using the raw data presented in the article. The individual authors were contacted via e-mail if the data of interest were not provided in the publications.

Statistical analysis

Since the absolute risk of hepatobiliary neoplasm is low in humans, the ORs and HRs were considered equivalent to RRs: and we therefore report all results as the RR for simplicity. To control confounding factors to the greatest extent, we extracted the maximally adjusted RRs (95% CI).

We first evaluated the overall effect of parous compared with nulliparous, if the study considered nulliparous as reference, we summed up all the parous categories (number of parity >0) as ever parity in each study together and treated these different categories as different reports. For those studies considering the number of parity of 0 or 1 as reference, we further assessed the effects of different numbers of parity. We first divided the number of parity into three groups (<2, 2-5, ≥5) based on the pre-analysis of the data structure across these eligible articles, and then combined the corresponding data into each group separately. We pooled the RRs for the overall effects of parous and respective effects of different groups in a random effects model, which was previously described by DerSimonian and Laird [36] and which takes into account both within- and between-study variabilities.

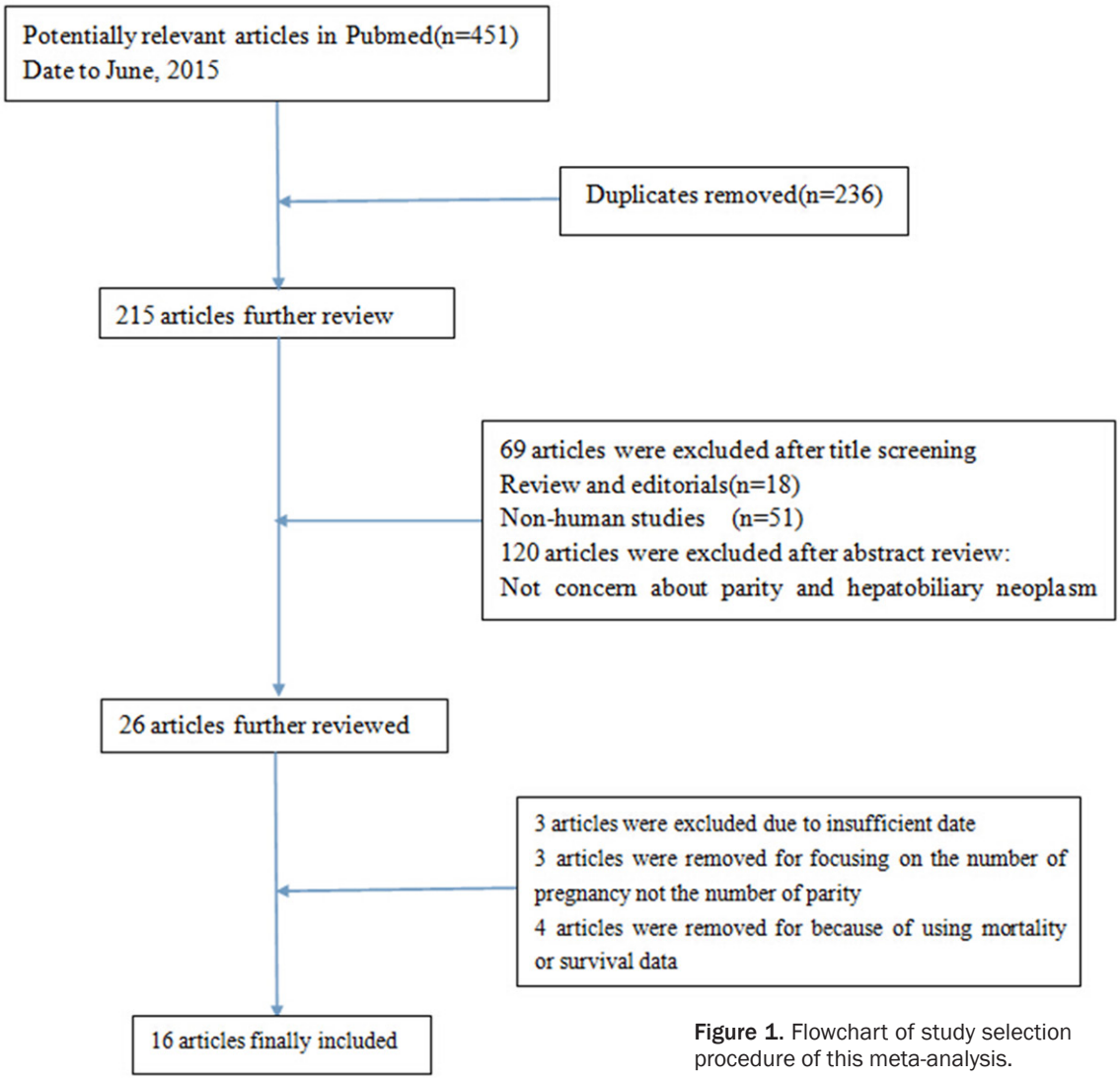

Figure 1. Flowchart of study selection procedure of this meta-analysis.

We quantified the extent of heterogeneity using the Q-test [37] and the I^2 score [38]. We conducted a meta-regression analysis and subgroup analyses to explore the source of heterogeneity. Subgroup analyses were performed, if feasible, based on study design, geographic region, and number of cases. Sensitivity analysis was also performed to assess the influence of each individual report on overall estimates by sequential removal of individual studies. Funnel plots and Egger's test [39] were applied to examine the publication bias. All statistical analyses were conductedusing Stata (version 11.0), the sensitivity and funnel plots, Egger's test were carried by meta section in stata software. The power of our meta-analysis was calculated using PowerV3.0 (http://www.mds.qmw.ac.uk/statgen/dcurtis/software.html).

Results

Study characteristics

Using our search strategy, we identified 215 articles and excluded 189 of them after reviewing their title or abstract. Among the articlesexcluded after reviewing the abstract, 18 were reviews and editorials, 51 were nonhuman studies, and 120 lacked focus on parity and hepatobiliary neoplasm risk. A total of 26 full-text articles were reviewed, of which 3 were excluded because of insufficient data [23-25]. In addition, 3 articles were removed for focusing on the pregnancy number and not on the parity number [30-32], and 4 studies were removed for using mortality or survival data [26-29]. Finally, 1 cohort study [6] and 15 case-

Table 1. Characteristics of eligible studies included in this meta-analysis of parity and hepatobiliary neoplasm risk

Author (Publication year)	Design and Study name	Country	Study period (follow-up years)	N (case)	No. of participants/ controls	Parity	OR (95% CI)	Factors investigated
Anastasia (1992)	HCC	Greece	1976-1984	19	51	0	0.42 (0.04-4.03)	No
						1-2	Reference	
						3-4	1.25 (0.34-4.63)	
						5+	2.86 (0.69-11.84)	
Janet L (1991)	HCC	China	1979-1986	83	596	0	0.7 (0.3-2)	Age, center and year of interview
		Kenya				1-2	Reference	
		Philippin				3-4	2.4 (1.1-5.1)	
		Thailand				5-6	2.6 (1.0-6.5)	
						7+	4.2 (1.5-11.4)	
Ann W (1992)	PCC	USA	1985-1986	72	599	0	Reference	Age at death, race and duration of oral contraceptive use (0, 1-4, 5-9, 5 = 10 years)
						1	1.6 (0.6-4.2)	
						2	2.1 (0.9-4.8)	
						3	1.9 (0.8-4.7)	
						4-5	1.6 (0.5-4.5)	
						6+	2.9 (0.8-11.2)	
Carlo (1992)	HCC	Italy	1984-1991	79	344	0	Reference	Age, education, alcohol consumption, history of hepatitis and oral contraceptive use
						1	2.1 (0.8-5.2)	
						2	2.6 (1.1-6.3)	
						3	3.2 (1.2-8.7)	
						4+	3.5 (1.2-9.9)	
Mats (1993)	PCC	Sweden	1925-1960	60	300	0	Reference	Age
						1	1.01 (0.39-2.60)	
						2	0.52 (0.21-1.31)	
						3	0.55 (0.19-1.56)	
						4	1.01 (0.32-3.18)	
						5	2.35 (0.55-10.00)	
Chyng (2009)	Cohort	Taiwan	1983-2000	202	1420784	1	Reference	Age and HBsAg
						2	0.68 (0.50-0.93)	
						3+	0.63 (0.42-0.92)	
Milena (2010)	HCC	Serbia	2004-2007	13	26	0-2	4.9 (1.1-21.2)	No
						2+	Reference	
Lorelei (2001)	HCC	Greek	1995-1998	50	62	0	Reference	Age, years of schooling, smoking status, alcohol consumption
						1+	1.17 (0.24-5.72)	
M Pandey (2003)	HCC	India	2003	64	165	0	Reference	No
						3+	3.9 (1.4-10.3)	
G Andreotti (2010)	PCC	Shanghai	1985-1986	269	545	0	0.77 (0.20-2.99)	Age, education and body mass index.
						1	Reference	
						2	1.15 (0.63-2.12)	
						3	1.60 (0.83-3.12)	
						4	2.20 (1.09-4.47)	
						5	2.20 (1.01-4.66)	
						≥6	1.70 (0.75-3.74)	
G Andreotti (2010)	PCC	Shanghai	1985-1986	92	586	0	0.98 (0.23-4.25)	Age, education and body mass index
						1	Reference	
						2		
						3		
						4		
						5	1 (0.46-2.20)	
						≥6	1.07 (0.46-2.50)	
A Rehman (2011)	HCC	Pkistan	1988-2007	60	120	≤5	0.61 (0.23-1.65)	No
						5+	0.43 (0.14-1.34)	

Dipanjan (2013)	HCC	Indian	2008-2009	122	122	≤3	Reference	No
						>3	9.06 (4.10-20.35)	
DeAretxabala (1995)	HCC	Chile	1994-1995	50	50	≤5	Reference	Age
						>5	4.2 (1.5-12.8)	
Tavani (1996)	HCC	Italy	1984-1993	31	377	0	Reference	Age and cholelithiasis
						1-2	0.8 (0.3-2.3)	
						3	2.0 (0.6-6.9)	
						>1	1.3 (0.5-3.4)	
						>4	2.9 (0.9-9.6)	
Mats (1993)	CC	Sweden	1925-1960	257	1285	0	Reference	Age through conditional logistic regression
						1	1.12 (0.68-1.84)	
						2	1.42 (0.92-2.18)	
						3	0.97 (0.59-1.59)	
						4	1.51 (0.85-2.70)	
						5	2.00 (0.87-4.62)	
						6+	3.00 (1.13-7.99)	
Mats (1993)	PCC	Sweden	1958-1984	133	665	0	Reference	Age, and mutually for number of births and age at first birth
						1	0.55 (0.30-1.03)	
						2	0.59 (0.35-0.99)	
						3	0.77 (0.43-1.37)	
						4	0.49 (0.19-1.29)	
						5	1.21 (0.30-4.96)	
						6+	0.66 (0.08-5.90)	
Lifang Hou (2005)	PCC	Shanghai	1997-2002	179	493	≤3	Reference	Age at interview and gender
						>3	1.49 (1.03-2. 15)	

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HT, hormone replacement treatment; PCC, population-based case-control; HCC, hospital-based case-control.

control studies [7-11, 13-22] were found eligible for the meta-analysis, with a combined case number of 2021 (**Figure 1**). The characteristics of the 16 included studies are shown in **Table 1**.

Among these studies, six were conducted in Asia [8, 14-17, 22], eight in Europe [7, 10, 11, 13, 14, 18, 20, 21], and two in America [9, 19]. The number of cases per study varied from 13 to 586. Only 12 of the studies provided relative risk estimates adjusted for age (**Table 1**).

Highest versus lowest parity number

In total, 1 cohort study [12] and 15 case-control studies [6-11, 13-22] investigated the association between parity number and hepatobiliary neoplasm risk. Six of the studies [9-11, 15, 21, 22] referred to nulliparous individuals as the lowest category of parity number, whereas three studies [12, 16, 17] referred to one live birth as the lowest parity number. The summary relative risk (RR) of hepatobiliary neoplasm for the highest versus lowest categories of parity number was 2.207 (95% CI = 1.397-3.488), with significant heterogeneity (Q = 95.84, P = 0.000, I^2 = 82.3%; **Figure 2**). Results of Begg's test (P = 0.038 for bias) revealed publication bias, and asymmetry was observed in the funnel plots (data not shown). When the study by Fwu CW et al. [12] was removed, no bias was observed.

We performed, a sensitivity analysis, in which one study was removed at a time and the data was reanalyzed. The 18 study-specific RRs of the parity number ranged from 1.991 (95% CI = 1.287-3.080, Q = 75.44, P = 0.000, I^2 = 78.8%) after omission of the study by Dipanjanet et al. [16] to 2.454 (95% CI = 1.554-3.876, Q = 88.82, P = 0.000, I^2 = 82.0%) after omission of the study by Milena et al. [23].

Parous versus nulliparous cases

Only 12 studies reported the results for parous versus nulliparous individuals, with a total of 48 reports. The summary multivariable-adjusted RR (95% CI) of hepatobiliary neoplasm associated with parity for parous versus nulliparous cases was 1.362 (95% CI = 1.144-1.623; **Figure 3**). This result indicated a positive association between parity and hepatobiliary neo-

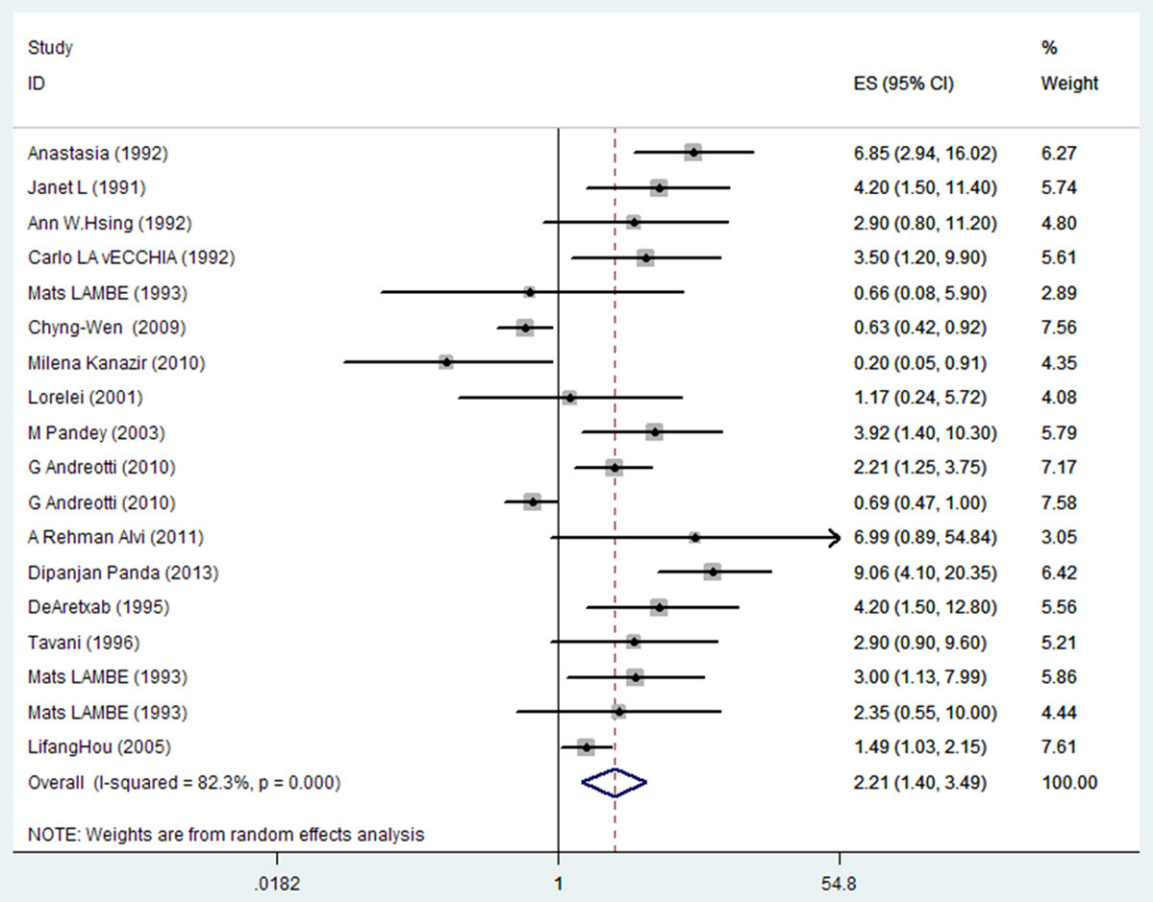

Figure 2. Forest plot of the highest parity number and hepatobiliary neoplasm risk.

plasm risk. Significant between-study heterogeneity was observed among studies (P = 0.001, I^2 = 79.5%). The 48 report-specific RRs of parous versus nulliparous cases ranged from 1.331 (95% CI = 1.12-1.583) after omission of the report by Pandey et al. [15] to 1.495 (95% CI = 1.308-1.708) after omission of the report by Mats et al. [11]. For the sample size of the present meta-analysis, the power to detect an RR of 1.362 was more than 95%.

Different parity numbers

The effects of different parity numbers on hepatobiliary neoplasm risk are presented in **Table 2**. To explore the effects of different parity numbers, we divided the cases into three groups on the basis of parity number; studies that considered a parity number of 0 or 1 were also included as references. A total of 18 reports were assigned to the first group (parity number, 0-2), and the summary multivariable-adjusted RR (95% CI) of hepatobiliary neoplasm associated with 0-2 parity number versus 0 or 1 parity number was 0.988 (95% CI = 0.784-1.246) with I^2 = 43.4% (P_h = 0.026). The second group (3-4 parity number) contained 15 articles, and our analysis yielded, a combined risk estimate of 1.241 (95% CI = 1.015-1.518), with I^2 = 39.3% (P_h = 0.035). The 15 articles in the third group (≥5 parity number) yielded a combined risk estimate of 2.021 (95% CI = 1.529-2.670), with I^2 = 28.5% (P_h = 0.144; **Figure 4**). Sensitivity analysis revealed that the pooled RRs for the first and second groups were similar before and after elimination of the individual reports. In the third group, the 15 report-specific RRs ranged from 1.841 (95% CI = 1.358-2.498) after omission of the report by Stanford JL [8] to 2.448 (95% CI = 1.816-3.299) after omission of the report by Andreotti et al. [16].

Dose-response meta-analysis

The dose-response analysis of parity number and hepatobiliary neoplasm risk involved 16

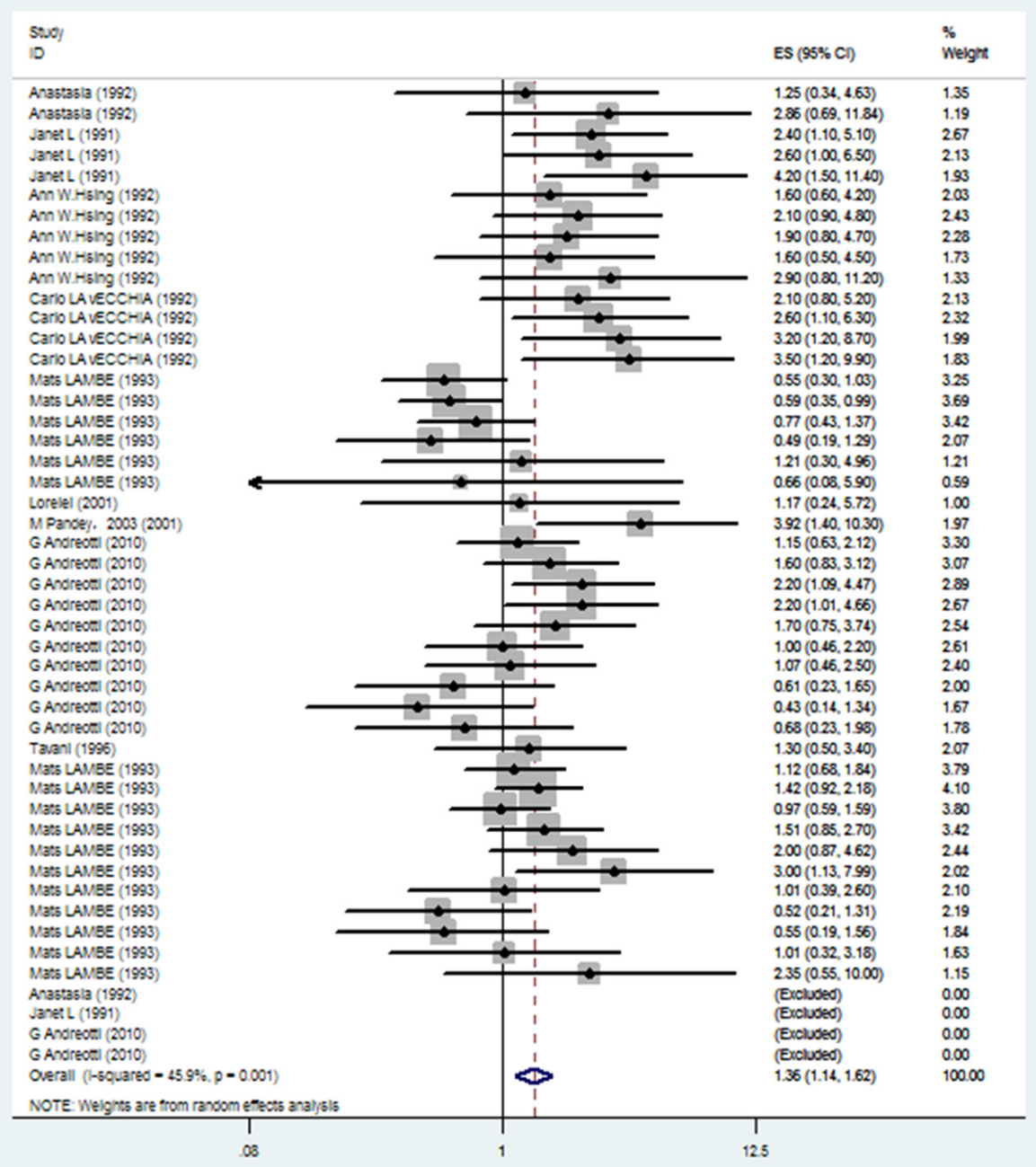

Figure 3. Forest plot of parous and hepatobiliary neoplasm risk.

studies. We did not find a linear association between parity number and hepatobiliary neoplasm risk (P = 0.33 for nonlinearity, I^2 = 25%, P_h = 0.05). The combined relative risk of hepatobiliary neoplasm per live birth was 1.118 (95% CI = 1.032-1.211, I^2 = 77.0%, P = 0.000; **Figure 5**).

Subgroup analysis

In the subgroup analysis of parous versus nulliparous cases, significant positive effects of parous cases on hepatobiliary neoplasm risk were observed in articles published before 2000 (RR = 3.657, 95% CI = 2.517-5.315, I^2 = 70.7%, P_h = 0.000), articles with less than 100 cases (RR = 2.961, 95% CI = 1.709-5.132, I^2 = 53.1%, P_h = 0.024), and articles on American populations (RR = 3.625, 95% CI = 1.577-8.330, I^2 = 0%, P_h = 0.669) (**Table 2**), articles of hepatocellular carcinoma (RR = 1.556, 95% CI = 1.126-2.149, I^2 = 58.7%, Ph = 0.007) (**Table 3**). In the subgroup analysis of the effects of dif-

Table 2. Summary risk estimates of the association between parity number and hepatobiliary neoplasm

	0-2					3-4					>5				
	No. of reports	RR (95% CI)	P	I^2	Ph*	No. of reports	RR (95% CI)	P	I^2	Ph*	No. of reports	RR (95% CI)	P	I^2	Ph*
Overall	18	0.988 (0.784-1.246)	0.918	43.4	0.026	15	1.241 (1.015-1.518)	0.035	39.3	0.059	15	2.021 (1.529-2.670)	0.000	28.5	0.144
Subgroup analysis															
Number of cases															
<100	7	1.459 (0.947-2.248)	0.087	23.3	0.251	5	2.179 (1.408-3.371)	0.000	0.0	0.837	6	1.459 (0.947-2.248)	0.000	0.0	0.944
>100	11	0.854 (0.679-1.075)	0.179	32.5	0.139	10	1.067 (0.851-1.338)	0.575	33.5	0.140	9	0.854 (0.679-1.075)	0.013	28.6	0.190
Location															
Asian	6	0.781 (0.612-0.996)	0.046	0.0	0.722	5	1.558 (1.103-2.199)	0.012	37.3	0.172	6	1.742 (0.955-3.178)	0.07	58.7	0.024
Europe	10	0.980 (0.690-1.390)	0.908	55.1	0.018	9	1.055 (0.815-1.365)	0.685	36.5	0.126	7	2.089 (1.281-3.408)	0.003	0.0	0.787
America	2	1.871 (0.992-3.528)	0.053	0.0	0.678	1	1.900 (0.784-4.605)	0.155	-	-	2	3.625 (1.577-8.330)	0.002	0.0	0.669
Publication period															
<2000 year	13	1.046 (0.770-1.421)	0.772	50.8	0.018	11	1.188 (0.939-1.503)	0.151	43.6	0.060	10	2.611 (1.822-3.741)	0.000	0.0	0.847
>2000 year	5	0.787 (0.612-1.012)	0.083	0.0	0.592	4	1.396 (0.949-2.054)	0.090	38.2	0.183	5	1.320 (0.632-2.758)	0.460	59.3	0.043

*P value for heterogeneity. Abbreviations: OR, odds ratio; CI, confidence interval.

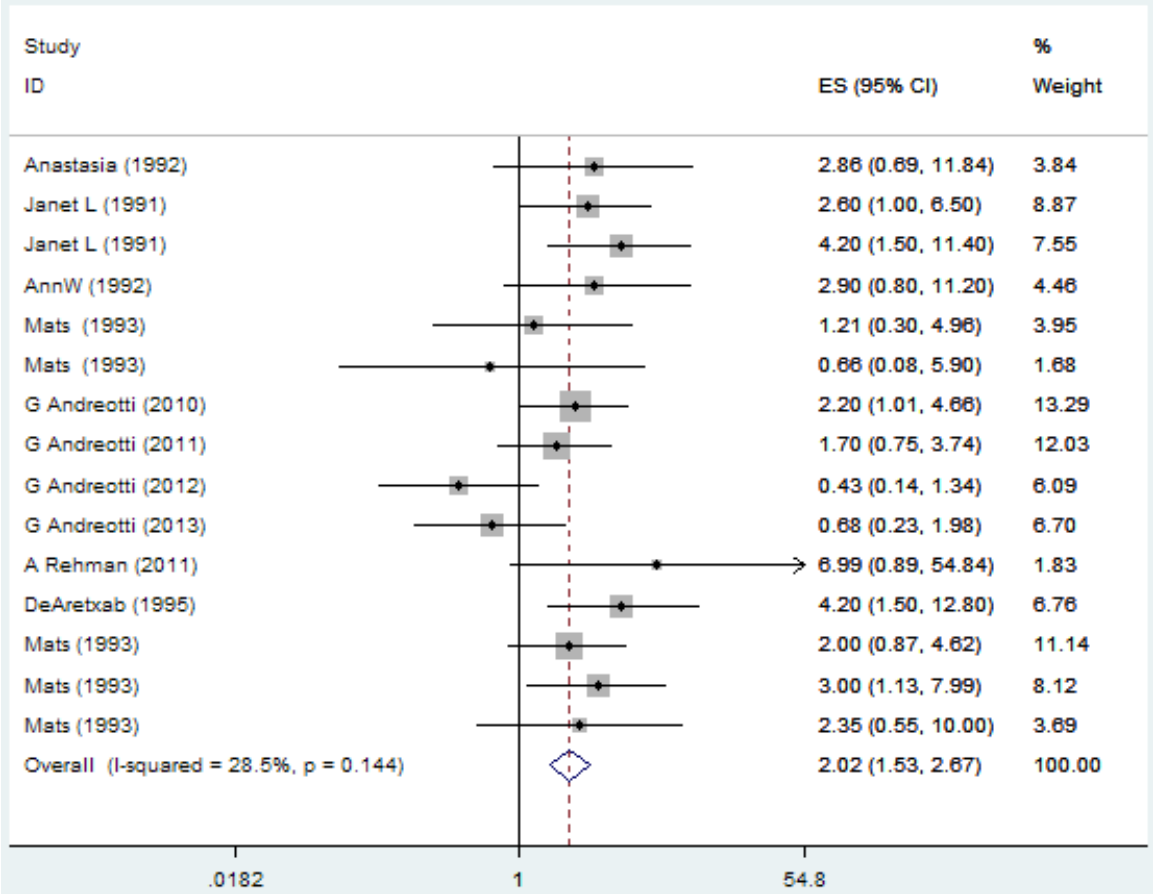

Figure 4. Forest plot of giving birth to ≥5 children and hepatobiliary neoplasm risk.

ferent parity numbers (0-2, 3-4, and ≥5 parity number) on hepatobiliary neoplasm risk, most of the effects were still positive in most strata of the second and third groups. Upon further stratified analysis on the basis of publication period, case number, and study location, the RR values invariably increased with the increase in parity number in various regions. For example, in the subgroup analysis of effects on Asian populations, the summary RR of 0-2 parity number was 0.781 (95% CI = 0.612-0.996, I^2 = 0%, P = 0.722), 3-4 parity number was 1.558 (95% CI = 1.103-2.199, I^2 = 37.3%, P = 0.172), and ≥5 parity number was 1.742 (95% CI = 0.955-3.178, I^2 = 58.7%, P = 0.024) (**Table 2**).

Publication bias

The result of Egger's test did provide evidence of substantial publication bias for parous versus nulliparous cases (P = 0.116), as well as among the first (P = 0.385), second (P = 0.910), and third (P = 0.901) groups. The Begg's funnel plot of parous versus nulliparous cases is presented in **Figure 6**.

Discussion

We systematically reviewed 1 cohort and 15 case-control studies, which included 2021 cases on the association between the number of parity and the risk of liver and biliary tract cancers. An association between endogenous estrogen levels and risk for hepatobiliary neoplasm has been only indirectly investigated to date [33]. Several case-control studies that were conducted both in developed and developing countries have reported a positive association between hepatobiliary neoplasm risk and parity number. The current meta-analysis indicated that parous cases were more positively associated with hepatobiliary neoplasm risk compared with nulliparous cases. Among the parity numbers considered, five or more had the highest risk of hepatobiliary neoplasm. We did not observe a nonlinear or linear rela-

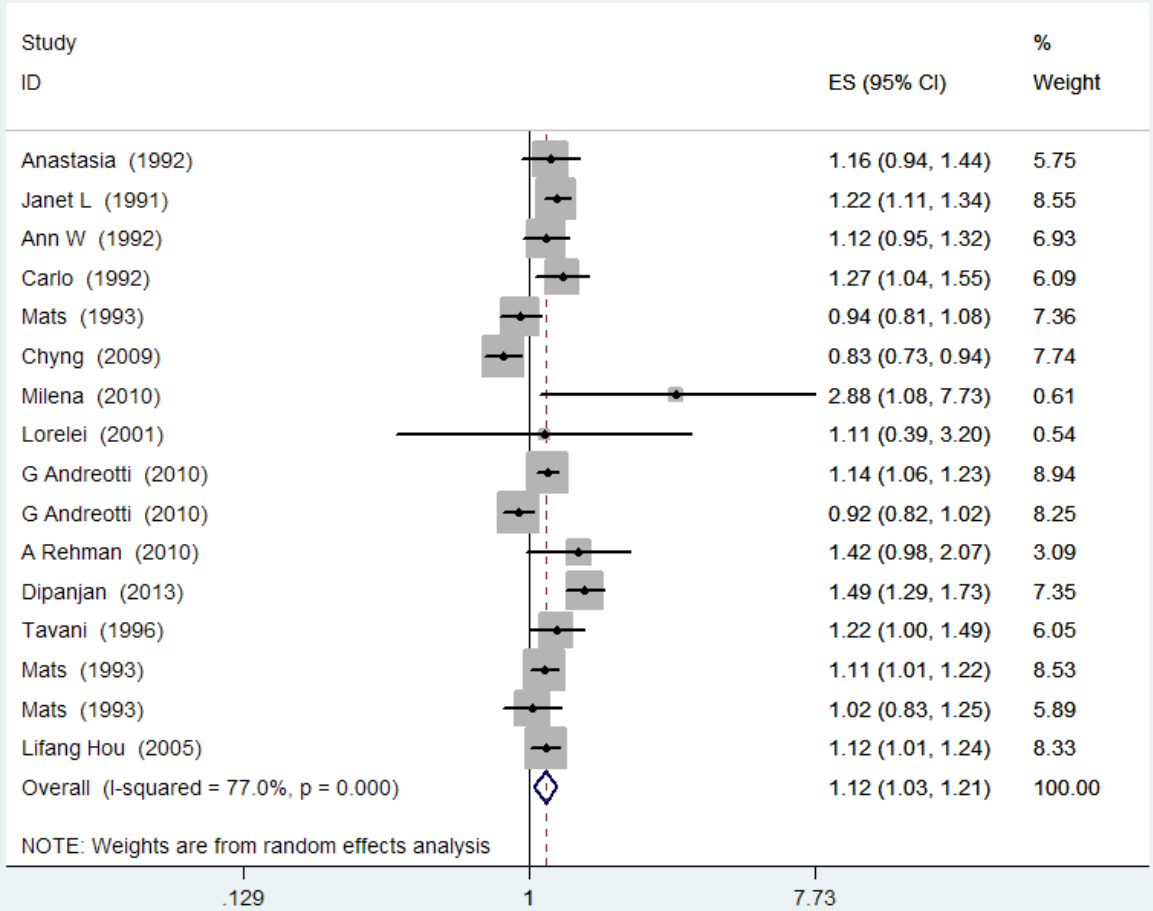

Figure 5. Forest plot of parity number (per 1 live birth) and hepatobiliary neoplasm risk.

Table 3. Summary risk estimates of the association between parity number and hepatobiliary neoplasm

	Highest					Ever				
	No. of reports	RR (95% CI)	P	I^2	Ph*	No. of reports	RR (95% CI)	P	I^2	Ph*
Overall	18	2.207 (1.397-3.488)	0.000	95.84	0.001	44	1.362 (1.144-1.623)	0.001	45.90	0.001
Hepatocellular carcinoma	8	1.639 (0.661-4.062)	0.000	43.89	0.286	21	1.556 (1.126-2.149)	0	58.7	0.007
Biliary tract cancers	10	2.637 (1.513-4.595)	0.000	48.8	0.001	23	1.278 (1.094-1.492)	0.096	29	0.002

tionship between parity number and hepatobiliary neoplasm risk. To the best of our knowledge, this meta-analysis is the first to evaluate in detail the effects of different parity numbers on hepatobiliary neoplasm risk. Our meta-regression analysis revealed that the number of cases might be the major source of between-study heterogeneity. We further performed a subgroup analysis on the basis of publication period, study location, and case number. The between-study heterogeneity was largely removed when the cases were stratified on the basis of publication period. This indicated that publication period mainly contributed to the heterogeneity. In the subgroup analysis of parous versus nulliparous cases, significant stimulatory effects of parity on hepatobiliary neoplasm were identified in articles published before 2000, articles with less than 100 cases, articles involving patients with liver cancer, and articles on American populations. The effects on Asian populations were more significant than those on European populations. However, the results should be interpreted with caution because only a small number of studies (i.e., two) from North America were included. Subgroup analysis of different parity numbers revealed that giving birth to ≥5 children had the

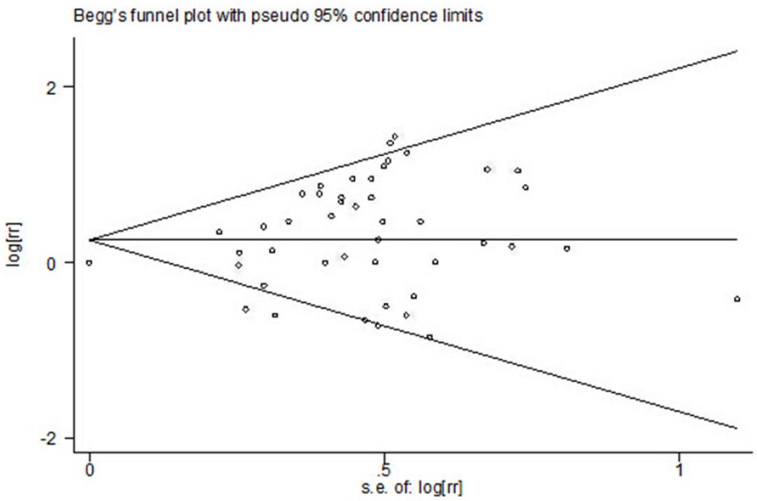

Figure 6. Beeg's funnel plot of parous versus nulliparous.

most positive association with hepatobiliary neoplasm risk in the previously mentioned subgroups. The sample size of articles published before 2000 was smaller than that of articles published on or after 2000. Most studies on liver cancer also had smaller sample sizes than those on biliary tract cancers. Therefore, our detection of significant positive associations might be attributed to the dramatically increased statistical power of the combined small sample size. In a further stratified analysis on the basis of publication period, case number, and study location, the RR values invariably increased with increase in parity number in various regions. In addition, the underlying mechanisms of the geographic variation of the effects of parity on hepatobiliary neoplasm risk are largely unknown and require further investigation.

Race, region, publication period, and research methods may have contributed to the observed inconsistency, in results reported by the articles. To address this issue, a study with a randomized large sample of multiple centers in different regions is necessary. Liver cancer rates in Europe are relatively lower than those in Asia. To date, the main risk factors for HCC are HBV infection, HCV infection, and liver cirrhosis. Other factors include male gender, age, smoking, alcohol intake, and aflatoxin intake, as well as metabolic factors such as a family history of obesity and diabetes, among others. Parity number is an independent factor but not the main factor. Estrogen can inhibit the occurrence and development of hepatocellular carcinoma, obesity, insulin resistance, and liver burden, but its increase during pregnancy may elevate the risk of liver cancer. Some studies have indicated that the level of growth-stimulating factor increases significantly in pregnant women [34]. Compared with tumors in non-pregnant patients, tumors in pregnant patients often grow faster and are easier to metastasize, leading to poorer prognosis. Growth factors are closely related to tumor differentiation, invasion, growth, angiogenesis, and metastasis [35]. Thus, these factors may promote tumor growth and tumorigenesis. This phenomenon is a good example of the complicated relationships between several factors. Data on gallbladder cancer are similarly consistent. Only three related studies on bile duct cancer were found because of the very low incidence of this type of cancer, and the results of these studies are paradoxical. A study with a randomized large sample of multiple centers is warranted in Asia, especially in China, because of the high incidence of hepatobiliary neoplasm in the area.

Our meta-analysis indicated that parous women have higher risk of hepatobiliary neoplasm compared with nulliparous women. Parous women are also likely to have had longer periods of exposure to high levels of circulating estrogens.

Our meta-analysis has several strengths. First, we included one cohort study and 15 case-control studies, which provided us with significant statistical power to detect potential association. The majority of the included studies showed positive association between parity and hepatobiliary neoplasm risk, but not all of them showed statistical significance, which can be attributed to the limits of the statistical power of our study. This study had a large sample size of 2021 cases and 1 427 358 non-cases. Which should have provided sufficient statistical power to detect any putative association. In addition, although the summary results demonstrated heterogeneity, we also conducted a number of subgroup and sensitivity analyses;

whose results were found to be robust. Second, we separately combined the different parity numbers instead of using the highest versus the lowest parity number to control misclassification. Third, we applied the model to adjust for the most established risk factors, which controlled for most of the confounding information.

Despite these advantages, we acknowledge some limitations. First, we did not have access to the primary data from the studies included in this meta-analysis; As a result we could not perform additional adjustments for potential important covariates. Second, a relatively wide range of values was identified as cut-off for the highest parity number; Thus, we could not accurately assign an exposure value to the open-ended category, which might have affected the outcome of our analysis. Third, as a meta-analysis of epidemiologic studies, the biases (e.g., recall and selection bias) inherent in the original studies (e.g., recall and selection bias) could not be avoided. Cohort studies are less susceptible to bias than case-control studies because information on exposures is collected before disease diagnosis in a prospective design. The results of the meta-regression revealed significant heterogeneity between the highest and the lowest subgroups by publication period, among dose-response subgroups by case number, and among dose-response subgroups by adjustment for age or otherwise (**Table 2**). In addition, the relationships reported by the case-control studies might have been overstated because of recall or interviewer bias. Publication bias is a known problem affecting meta-analyses of published studies. Indeed publication biases were detected in our study, suggesting that the entire pooled result may be biased.

In conclusion, the current meta-analysis indicates that parity number is more positively correlated with hepatobiliary neoplasm risk as compared with nulliparous cases. In addition, among the parity numbers considered, ≥5 has the highest hepatobiliary neoplasm risk. Elucidation of the exact mechanism underlying this protective effect still requires further investigation.

Disclosure of conflict of interest

None.

Address correspondence to: Jing Cai, Department of Radiation Oncology, Nantong Tumor Hospital, Affiliated Tumor Hospital of Nantong University, Nantong 226321, China. E-mail: cj7227@sina.com

References

[1] Segura-Lopez FK, Guitron-Cantu A, Torres J. Association between spp. infections and hepatobiliary malignancies: A review. World J Gastroenterol 2015; 21: 1414-1423.

[2] Semela D, Heim M. [Hepatocellular carcinoma]. Ther Umsch 2011; 68: 213-217.

[3] Wiedmann KH. [Liver cirrhosis as a risk factor in hepatocellular cancer]. Internist 1987; 28: 468-476.

[4] Wild CP, Montesano R. A model of interaction: aflatoxins and hepatitisviruses in liver cancer aetiology and prevention. Cancer Lett 2009; 286: 22-28.

[5] Moerman CJ, Bueno-de-Mesquita HB. The epidemiology of gallbladder cancer: lifestyle related risk factors and limited surgical possibilities for prevention. Hepatogastroenterology 1999; 46: 1533-1539.

[6] Tominaga S, Kuroishi T. Biliary tract cancer. Cancer Surv 1994; 19-20: 125-137.

[7] Tzonou A, Zavitsanos X, Hsieh CC, Trichopoulos D. Live born children and risk of hepatocellular carcinoma. Cancer Causes Control 1992; 3: 171-174.

[8] Stanford JL, Thomas DB. Reproductive factors in the etiology of hepatocellular carcinoma. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Cancer Causes Control 1992; 3: 37-42.

[9] Hsing AW, McLaughlin JK, Hoover RN, Co Chien HT, Blot WJ, Fraumeni JF Jr. Parity and primary liver cancer among young women. J Natl Cancer Inst 1992; 84: 1118-1119.

[10] La Vecchia C, Negri E, Franceschi S, D'Avanzo B. Reproductive factors and the risk of hepatocellular carcinoma in women. Int J Cancer 1992; 52: 351-354.

[11] Lambe M, Trichopoulos D, Hsieh CC, Ekbom A, Pavia M. Parity and hepatocellular carcinoma. A population-based study in Sweden. Int J Cancer 1993; 55: 745-747.

[12] Fwu CW, Chien YC, Kirk GD, Nelson KE, You SL, Kuo HS, Feinleib M, Chen CJ. Hepatitis B virus infection and hepatocellular carcinoma among parous Taiwanese women: nationwide cohort study. J Natl Cancer Inst 2009; 101: 1019-1027.

[13] Kanazir M, Boricic I, Delic D, Tepavcevic DK, Knezevic A, Jovanovic T, Pekmezovic T. Risk factors for hepatocellular carcinoma: a case-control study in Belgrade (Serbia). Tumori 2010; 96: 911-917.

[14] Mucci LA, Kuper HE, Tamimi R, Lagiou P, Spanos E, Trichopoulos D. Age at menarche and age at menopause in relation to hepato-

cellular carcinoma in women. BJOG 2001; 108: 291-294.
[15] Pandey M, Shukla VK. Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. Eur J Cancer Prev 2003; 12: 269-272.
[16] Andreotti G, Hou L, Gao YT, Brinton LA, Rashid A, Chen J, Shen MC, Wang BS, Han TQ, Zhang BH, Sakoda LC, Fraumeni JF Jr, Hsing AW. Reproductive factors and risks of biliary tract cancers and stones: a population-based study in Shanghai, China. Br J Cancer 2010; 102: 1185-1189.
[17] Alvi AR, Siddiqui NA, Zafar H. Risk factors of gallbladder cancer in Karachi-a case-control study. World J Surg Oncol 2011; 9: 164.
[18] Panda D, Sharma A, Shukla NK, Jaiswal R, Dwivedi S, Raina V, Mohanti BK, Deo SV, Patra S. Gall bladder cancer and the role of dietary and lifestyle factors: a case-control study in a North Indian population. Eur J Cancer Prev 2013; 22: 431-437.
[19] de Aretxabala X, Riedeman P, Burgos L, Roa I, Araya JC, Echeverría X, Toledo MI, Charles M, Espinoza O, Wenzel C. [Gallbladder cancer. Case-control study]. Rev Med Chil 1995; 123: 581-586.
[20] Tavani A, Negri E, La Vecchia C. Menstrual and reproductive factors and biliary tract cancers. Eur J Cancer Prev 1996; 5: 241-247.
[21] Lambe M, Trichopoulos D, Hsieh CC, Ekbom A, Adami HO, Pavia M. Parity and cancers of the gall bladder and the extrahepatic bile ducts. Int J Cancer J 1993; 54: 941-944.
[22] Hou L, Xu J, Gao YT, Rashid A, Zheng SL, Sakoda LC, Shen MC, Wang BS, Deng J, Han TQ, Zhang BH, Meyers DA, Fraumeni JF Jr, Hsing AW. CYP17 MspA1 polymorphism and risk of biliary tract cancers and gallstones: a population-based study in Shanghai, China. Int J Cancer 2006; 118: 2847-2853.
[23] Parkin DM, Vizcaino AP, Skinner ME, Ndhlovu A. Cancer patterns and risk factors in the African population of southwestern Zimbabwe, 1963-1977. Cancer Epidemiol Biomarkers Prev 1994; 3: 537-547.
[24] Rizvi TJ, Zuberi SJ. Risk factors for gall bladder cancer in Karachi. J Ayub Med Coll Abbottabad 2003; 15: 16-18.
[25] Chow WH, McLaughlin JK, Menck HR, Mack TM. Risk factors for extrahepatic bile duct cancers: Los Angeles County, California (USA). Cancer Causes Control 1994; 5: 267-272.
[26] Plesko I, Preston-Martin S, Day NE, Tzonou A, Dimitrova E, Somogyi J. Parity and cancer risk in Slovakia. Int J Cancer 1985; 36: 529-533.
[27] Chen BK, Yang CY. Mortality from cancers of the digestive system among grand multiparous women in Taiwan. Int J Environ Res Public Health 2014; 11: 4374-4383.
[28] Kvale G, Heuch I, Nilssen S. Parity in relation to mortality and cancer incidence: a prospective study of Norwegian women. Int J Epidemiol 1994; 23: 691-699.
[29] Chen BK, Yang CY. Mortality from cancers of the digestive system among grand multiparous women in Taiwan. Int J Environ Res Public Health 2014; 11: 4374-4383.
[30] Zatonski WA, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst 1997; 89: 1132-1138.
[31] Serra I, Yamamoto M, Calvo A, Cavada G, Baez S, Endoh K, Watanabe H, Tajima K. Association of chili pepper consumption, low socioeconomic status and longstanding gallstones with gallbladder cancer in a Chilean population. Int J Cancer 2002; 102: 407-411.
[32] Yu MW, Chang HC, Chang SC, Liaw YF, Lin SM, Liu CJ, Lee SD, Lin CL, Chen PJ, Lin SC, Chen CJ. Role of reproductive factors in hepatocellular carcinoma: Impact on hepatitis B- and C-related risk. Hepatology 2003; 38: 1393-1400.
[33] Villa E. Role of estrogen in liver cancer. Women's Health 2008; 4: 41-50.
[34] Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, Bossuyt PM, van der Post JA, von Dadelszen P, Mol BW, Pajkrt E; EBM CONNECT Collaboration. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG 2012; 119: 778-787.
[35] Ramchandani D, Weber GF. Interactions between Osteopontin Vascular Endothelial Growth Factor: Implications for Cancer. Biochim Biophys Acta 2015; 1855: 202-22.
[36] DerSimonian R, Laird N. (1986) Meta-analysis in clinical trials. Controlle Clin Trials 1986; 7: 177-188.
[37] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statist Med 2002; 21: 1539-1558.
[38] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
[39] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.