World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i6.784

World J Gastroenterol 2011 February 14; 17(6): 784-788
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Higher parity associated with higher risk of death from gastric cancer

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Supported by A grant from the National Science Council, Executive Yuan, Taiwan, No. NSC-94-2314-B-037-056
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Received: October 14, 2010 Revised: December 27, 2010
Accepted: January 4, 2011
Published online: February 14, 2011

Abstract

AIM: To examine the association between parity and gastric cancer (the cases are almost all premenopausal women) risk in a cohort of young parous women.

METHODS: The study cohort consisted of all women with a record of a first and singleton childbirth in the Birth Register between 1978 and 1987. We tracked each woman from the time of her first childbirth to December 31, 2008. Their vital status was ascertained by linking records to the computerized mortality database. Cox proportional hazard regression models were used to estimate hazard ratios of death from gastric cancer associated with parity.

RESULTS: There were 1090 gastric cancer deaths (85.87% of them were premenopausal) during 33686828 person-years of follow-up. The mortality rate of gastric cancer was 3.24 cases per 100000 person-years. A trend of increasing risk of gastric cancer was seen with increasing parity. The adjusted hazard ratio was 1.24 [confidence interval (95% CI): 1.02-1.50] for women who had borne two to three children, and 1.32 (95% CI: 1.01-1.72) for women with four or more births, when compared with women who had given birth to only one child.

CONCLUSION: These results suggest that higher parity may increase the risk of death from gastric cancer among premenopausal women.

Key words: Gastric cancer; Parity; Mortality; Cohort study

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Chang CC, Chen CC, Chiu HF, Yang CY. Higher parity associated with higher risk of death from gastric cancer. *World J Gastroenterol* 2011; 17(6): 784-788 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i6/784.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i6.784

INTRODUCTION

In Taiwan, gastric cancer (GC) is the fifth leading cause of cancer mortality for males and females[1]. The age-adjusted mortality rate for gastric cancer was 14.1 per 100000 among males and 7.4 among females in 2007. There is

substantial geographic variation in gastric cancer mortality within the country. In most areas, however, its mortality rate is about two-fold higher among men than women[1]. Known risk factors, such as *Helicobacter pylori* (*H. pylori*) infection, tobacco smoking, and low fruit and vegetable intake cannot entirely explain the gender difference[2].

The difference between male-to-female incidence rates is greatest during the reproductive ages, and the rates becomes more similar after menopause; it has been hypothesized that sex hormones play a role in the development or progression of gastric cancer[3]. The influence of sex hormones on gastric cancer risk is supported by the presence of steroid-hormones receptors in the gastric mucosa and gastric cancer tissues[4,5]. In rat experimental studies, there is also a greater preponderance of GC in males compared with females[6,7].

Few epidemiological studies have investigated the association between parity and gastric cancer, and results have been inconsistent. Parity was associated with increased risk of gastric cancer in four studies[8-11]. Three studies found a suggestive inverse relationship, but no significant dose-risk trend[12-14], whereas five others reported no association[15-19].

A previous study on gastric cancer in young individuals indicated that gastric cancer diagnosed in women within two years after delivery was more progressive, and proposed that pregnancy or delivery might accelerate the growth of gastric cancer[20]. Maeta *et al*[21] found that the pathological features of gastric cancer that occurred more frequently in young women were more common among pregnancy-related cases. These results suggested the need for separate analysis of pre- and postmenopausal women when examining the relationship between parity and gastric cancer risk.

Four of the above-mentioned studies, which studied the relationship between parity and gastric cancer risk, were restricted to postmenopausal women[11,12,17,18]. Only one recent Swedish study has examined the relationship between parity and gastric cancer separately for pre- and postmenopausal women[14]. Other studies did not categorize the gastric cancer cases into pre- or postmenopausal because of the lack of sufficient premenopausal gastric cancer cases to support a complete analysis.

The objective of this study was to examine the effect of parity on the risk of gastric cancer in a cohort of 1 292 462 young parous women in Taiwan, followed over a period of 31 years.

MATERIALS AND METHODS

Data source

Registration of births is required by law in Taiwan. It is the responsibility of the parents or the family to register infant births at a local household registration office within 15 d. The Birth Registration System, which is managed by the Department of the Interior, released computerized data on live births since 1978. The registration form, which requests information on maternal age, education, parity, gestational age, date of delivery, infant gender, and birth weight, is completed by the physician attending the delivery. Most deliveries in Taiwan take place in either a hospital or a clinic[22], the birth certificates are completed by physicians attending the delivery, and it is mandatory to register all live births at local household registration offices; therefore the birth registration data are considered complete, reliable, and accurate[22].

Study population

The study cohort consisted of 1 292 462 women with a record of a first and singleton childbirth in the Birth Register between January 1, 1978 and December 31, 1987. Information on any subsequent births was also retrieved from the Birth Register.

Follow-up

Each woman has her own unique personal identification number, which was used to track the women from the time of their first childbirth to December 31, 2008. Their vital status was ascertained by linking records with the computerized mortality database, identifying the date of any deaths.

Statistical analysis

We categorized parity (the number of children recorded in the last childbirth record of each woman registered during follow-up) into three categories: one, two to three, and four or more. We compared selected baseline characteristics of the cohort by parity using χ^2 tests or analysis of variance, as appropriate. Death rates were calculated by dividing the number of deaths from gastric cancer (ICD-9 code 151) by the number of person-years of follow-up. Cox proportional hazard regression models were used to estimate the hazard ratio of death from gastric cancer associated with parity. The 95% confidence intervals (CIs) for the hazard ratios were also calculated. We used two Cox proportional hazard models: an age-adjusted model and a multivariate-adjusted model, which was additionally adjusted for marital status (married, unmarried), years of schooling ($\leqslant 9$, > 9 years), and birthplace (hospital/clinic, home/other). The proportion hazards assumption was assessed for all above-mentioned variables and no violations were observed. Analyses were performed using the SAS statistical package (version 8.02, SAS Institute Inc). All statistical tests were two-sided. Values of $P < 0.05$ were considered statistically significant.

RESULTS

The study cohort was comprised of 1 292 462 primiparous women with complete information. A total of 33 686 828 person-years were observed in this study. The mean follow-up period was 26.09 (standard deviation = 3.28) years. During the follow-up period, 1090 gastric cancer deaths were recorded, yielding a mortality rate of 3.24 cases per 100 000 person-years.

Table 1 presents the baseline characteristics of the study population by parity. Compared with women who had given birth to only one child, women with four or

Table 1 Demographic characteristics of the study cohort (mean ± SD) *n* (%)

	Parity			*P*-value
	1 (*n* = 157207)	2-3 (*n* = 1000977)	4+ (*n* = 134278)	
Age at recruitment (1st birth)	26.38 ± 4.43	24.26 ± 3.22	22.44 ± 2.95	< 0.001
Marital status				
Married	146022 (92.89)	984049 (98.31)	130544 (97.22)	< 0.001
Not married	11185 (7.11)	16928 (1.69)	3734 (2.78)	
Years of schooling				
≤ 9	72090 (45.86)	544098 (54.36)	106330 (79.19)	< 0.001
> 9	85117 (54.14)	456879 (45.64)	27948 (20.81)	
Birth place				
Hospital/clinic	153167 (97.43)	970422 (96.95)	122336 (91.11)	< 0.001
Home/other	4040 (2.57)	30555 (3.05)	11942 (8.89)	

Table 2 Association between parity and hazard ratio of death from gastric cancer over a 31-year follow-up period

Parity	No. of subjects	Follow-up person-years	No. of gastric cancer (per 100000)	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[1] (95% CI)
1	157207	4020271.75	128 (3.18)	1.00	1.00
2-3	1000977	26036992.42	848 (3.25)	1.23 (1.01-1.49)	1.24 (1.02-1.50)
4+	134278	3629563.83	114 (3.14)	1.33 (1.02-1.73)	1.32 (1.01-1.72)
				P = 0.030 for linear trend	*P* = 0.035 for linear trend

[1]Adjusted for age, marital status, years of schooling, and birth place. HR: Hazard ratio; CI: Confidence interval.

more children were more likely to have lower educational level, younger age at first birth, and a lower chance of being born in a hospital or clinic.

Table 2 presents the hazard ratios of gastric cancer mortality by parity. After adjustment for age at first birth, the hazard ratio for gastric cancer death was 1.23 (95% CI: 1.01-1.49) for women who had two to three children, and 1.33 (95% CI: 1.02-1.73) for women with four or more births, when compared with women who had given birth to only one child. In the multivariate-adjusted model, the hazard ratios were only slightly altered. The adjusted hazard ratio was 1.24 (95% CI: 1.02-1.50) for women who had borne two to three children, and 1.32 (95% CI: 1.01-1.72) for women with four or more births, when compared with women who had given birth to only one child. There was a significant increasing trend in the adjusted hazard ratios of gastric cancer with increasing parity (*P* for trend = 0.035).

DISCUSSION

To our knowledge, this is the largest cohort (*n* = 1292462 women) published to date to examine the relationship between parity and gastric cancer risk. In this prospective cohort study, we found a positive association between parity and gastric cancer risk. Our finding of an increased risk of gastric cancer associated with higher parity agrees with some previous studies[8-11], but not with other studies that reported the reverse effect[12-14] or no association[15-19] with parity. Pregnancy elevates serum estrogen levels by about 100 fold[23]. Increasing parity is associated with an overall increase in lifetime exposure to sex hormones. There is experimental evidence that gastric cancer carcinogenesis might be inhibited by estrogens[6,7]. Thus, if estrogens are associated with a reduced risk of gastric cancer, we would expect pregnancy to offer some protection from gastric cancer. Our data did not provide support for this hypothesis.

On the other hand, it has been reported that estrogen stimulates the growth of gastric cancer cell lines[24], and there is evidence that pregnancy or delivery might accelerate the growth of gastric cancer[20]. The mean age at death for gastric cancer was 42.90 ± 7.08 years in this study. The majority of gastric cancer deaths (85.87%) were premenopausal (using age 50 as the cut-off value[14]). Women included in this study tended to be younger (with the large majority of the gastric cancer deaths occurring before menopausal age) than in previous studies. The mean time of gastric cancer was about 14 years after last delivery (age at the birth of the last child = 28.97 ± 4.01; age at the death for gastric cancer = 42.90 ± 7.08). It is possible that these premenopausal gastric cancers were influenced by hormonal conditions caused by the actual events of pregnancy or delivery[17]. Our finding of an increased risk of gastric cancer associated with higher parity may therefore plausibly be related to a short-term increase in risk after a delivery[16]. The incidence of gastric cancer in premenopausal women is low; therefore, such effects are easily lost in overall analyses[17]. Some studies have been restricted to postmenopausal women[11,12,17,18]. To our knowledge, this is the first cohort study to indicate that a positive association between parity and gastric cancer may be only restricted to premenopausal women. However, because there is no consistent evidence to date for an association between parity and risk of death from gastric cancer, the possibility that this is a chance finding must also be considered. Clearly, more work will be needed before the influence of parity on the risk of gastric cancer is understood.

In the event of a death in Taiwan, the decedent's family is required to obtain a death certificate from the hospital or local community clinic, which then must be submitted to the household registration office to cancel the decedent's household registration. The death certificate is required to have the decedent's body buried or cremated. Death certificates must be completed by physicians in Taiwan. It is also mandatory to register all deaths at local household registration offices; thus, the death registration is reliable and complete[22]. The complete population coverage and follow-up made possible by the national identification number has left the study without selection bias. Information bias is also unlikely to be important for parity.

Taiwan is a small island with a convenient communication network. It is believed that all gastric cancer cases had access to medical care. Mortality data rather than data on inpatient cases was used to assess the association between parity and gastric cancer in this study. The mortality of a disease is a function of its incidence and fatality. Gastric cancer has been reported to have the fifth poorest five-year relative survival rate among all cancer sites[25]. Deaths from gastric cancer may therefore be regarded as a reasonable indicator of the incidence of gastric cancer.

Hormone replacement therapy (HRT) has been reported to reduce the risk of gastric cancer in population with higher HRT use[26]. We were unable to adjust for this factor in the current study because of the lack of available data. HRT use is low in Taiwan compared with Western countries[27]; therefore, the confounding effect resulting from this factor should be small, if it exists at all. Furthermore, if the association between this potential confounding variable and the risk of gastric cancer is not as strong as the one that has been observed for parity, adjustment of this variable will not qualitatively change the conclusion.

Cigarette smoking[2] and a family history of gastric cancer[28] have been documented as risk factors for gastric cancer in Taiwan. Unfortunately, there is no information available on these variables for the individual study subjects and, thus, they could not be adjusted in the analysis. However, there is no reason to believe that there would be any correlation between these two variables and parity.

An increased susceptibility to infection by *H. pylori* during pregnancy might affect the increased risk of gastric cancer[29]. We could not adjust for this variable because of the lack of information on *H. pylori* infection. However, it has been reported that most women acquired the infection in childhood rather than during pregnancy[30]. Furthermore, there is no reason to believe that *H. pylori* status would be associated with parity, and, therefore, the estimated effect of parity is likely to be free of a confounding effect of *H. pylori* status.

The birth registration system in Taiwan covers only live births and did not include stillbirths and abortions. Therefore we were unable to examine the possible role of gravidity on the risk of gastric cancer. Our study design only allowed for the study of mortality among parous women. Again, we were unable to examine the possible role of nulliparity on the risk of gastric cancer because the birth registry ascertained births rather than pregnancies. The generalizability of this findings is thus limited. Misclassification of menopausal status may have occurred by using age 50 as the cut-off point. Any effect of this is, however, is probably nondifferential (the misclassification is unlikely to be related to parity) and would probably lead to underestimation of the results.

In summary, we found that there was a trend for increasing parity to be associated with increasing risk for gastric cancer among a cohort of young parous women. This study suggests that the relation between parity and risk of gastric cancer should be considered separately for pre- and postmenopausal women.

COMMENTS

Background

Previous studies that examined this association rarely categorized the gastric cancer cases into pre- or postmenopausal because of the lack of sufficient premenopausal gastric cancer cases to support a complete analysis.

Research frontiers

This study was undertaken to examine the association of parity and gastric cancer (the cases are almost all premenopausal women) risk in a cohort of young parous women.

Innovations and breakthroughs

The results of this study suggest that higher parity may increase the risk of death from gastric cancer among premenopausal women.

Applications

This study suggests that the relation between parity and risk of gastric cancer should be considered separately for pre- and postmenopausal women.

Peer review

The study is worthy of being accepted. The study population is large enough to detect minor differences.

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