Int J Gynecol Cancer 2007, **17**, 32–36

ORIGINAL ARTICLES

Age at first birth, parity, and risk of death from ovarian cancer in Taiwan: a country of low incidence of ovarian cancer

C.-Y. YANG*, H.-W. KUO* & H.-F. CHIU†
**Institute of Public Health, College of Health Sciences and †Institute of Pharmacology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Abstract. Yang C-Y, Kuo H-W, Chiu H-F. Age at first birth, parity, and risk of death from ovarian cancer in Taiwan: a country of low incidence of ovarian cancer. *Int J Gynecol Cancer* 2007;**17:**32–36.

This study was undertaken to examine whether there is an association between parity and age at first birth and risk of ovarian cancer. The study cohort consisted of all women with a record of a first and singleton childbirth in the Birth Register between 1978 and 1984. We tracked women from the time of their first childbirth to December 31, 2003, and their vital status was ascertained by linking records with the computerized mortality database. Cox proportional hazard regression models were used to estimate the relative risks (RR) of death from ovarian cancer associated with parity and age at first birth. There were 322 ovarian cancer deaths during 27,402,995.5 person-years of follow-up. The mortality rate of ovarian cancer was 1.18 cases per 100,000 person-years. A trend of increasing risk of ovarian cancer was seen with increasing age at first birth. The adjusted RR was 0.69 (95% CI = 0.52–0.90) for women who bore two children, and 0.30 (95% CI = 0.21–0.42) for women with three or more births, respectively, when compared with women who had given birth to only one child. There was a significant decreasing trend in the adjusted RR of ovarian cancer with increasing parity. This study provides evidence that parity may confer a protective effect on the risk of ovarian cancer.

KEYWORDS: cohort study, mortality, ovarian cancer, parity, Taiwan.

In Taiwan, ovarian cancer is the 10th leading cause of cancer mortality. The age-adjusted mortality rate for ovarian cancer was 3.04 per 100,000 in 2003[1]. With an incidence of 5.89 per 100,000 women, ovarian cancer is relatively uncommon in Taiwan; however, it has the highest mortality rate among gynecological cancers[2].

Little is known about the etiology of epithelial ovarian cancer, the most common type of malignant ovarian tumor[3]. Several factors have been reported to be associated with ovarian cancer, most notably reproductive and hormonal factors. Use of oral contraceptives (OCs) has consistently been associated with a reduced risk of ovarian cancer, with increasing duration of use linked to greater risk reduction[4–7]. Compared with nulliparous women, parous women have a lower risk of developing ovarian cancer, with a declining trend with increasing number of full-term pregnancies[5–13].

Late age at first live birth has been positively associated with ovarian cancer in some[5,14–16] but not all studies[13,17]. However, one Swedish study found that the risk of ovarian cancer decreased with later age at first birth[9].

The majority of epidemiologic studies have been conducted on high-incidence populations in Europe and North America. The present study was carried out because few epidemiologic studies have been conducted on low-incidence populations such as Asians[13,18–20]. We studied a cohort of women who experienced a first and singleton childbirth between January 1, 1978, and December 31, 1987, to explore further the association between parity, age at first

Address correspondence and reprint requests to: Chun-Yuh Yang, PhD, MPH, Institute of Public Health, College of Health Sciences, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung, Taiwan 80708. Email: chunyuh@kmu.edu.tw

doi:10.1111/j.1525-1438.2007.00804.x

birth, and the risk of ovarian cancer in Taiwan, a country with a relatively low incidence of ovarian cancer.

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 days. The Birth Registration System, which is managed by the Department of 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. Because most deliveries in Taiwan take place in either a hospital or clinic[21] and the birth certificates are completed by physicians attending the delivery and it is mandatory to register all live births at local household registration offices, the birth registration data are considered complete, reliable, and accurate. These data have been used in our previous studies[22–25].

Study population

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

Follow-up

Each women has her own unique personal identification number. Using this number, we tracked each woman from the time of their first childbirth to December 31, 2003, and their vital status was ascertained by linking records with the computerized mortality database, identifying the date of any deaths occurring in this cohort. Since it is mandatory to register death certificates at local household registration offices, the mortality statistics in Taiwan were considered to be highly accurate and complete[26].

Statistics

The person-years of follow-up for each woman was calculated from the date of first childbirth to the date of death or December 31, 2003. Death rates were calculated by dividing the number of deaths from ovarian cancer by the number of person-years of follow-up. Cox proportional hazard regression models were used to estimate the relative risks (RRs) of death from ovarian cancer associated with parity (the number of children recorded in the last childbirth record of each woman registered during follow-up) and age at first childbirth. The 95% confidence intervals (CIs) for the RRs were also calculated. Ovarian cancer is defined according to the International Classification of Disease, Injury, and Causes of Death (ninth revision) (ICD code 183). The variables in the final model included age at first childbirth ($\leq$25, 26–30, $>$30 years), parity (1, 2, 3, or more), marital status (married, unmarried), years of schooling ($\leq$9, $>$9 years), and birth place (hospital/clinic, home/other). Analyses were performed using the SAS statistical package (version 8.2, SAS Institute Inc., Cary, NC). All statistical tests were two sided. Values of $P < 0.05$ were considered statistically significant.

Results

Altogether 1,292,462 primiparous women with complete information were included in the analysis. A total of 27,402,995.5 person-years were observed during the follow-up period from the time of their first childbirth to December 31, 2003. There were 322 ovarian cancer deaths, yielding a mortality rate of 1.18 cases per 100,000 person-years.

Table 1 gives the numbers of person-years of follow-up and ovarian cancer deaths by age at recruitment (age at first birth), parity, marital status, years of schooling, and birth place. The mortality rate was 2.45 among women who had given birth to one child, 1.43 among those who had had two children, and 0.59 among those who had given birth to three or more children.

The multivariate-adjusted RR and 95% CIs are shown in Table 2. A trend of increasing risk of ovarian cancer was seen with increasing age at first birth. The adjusted RR was 0.69 (95% CI = 0.52–0.90) for women who bore two children, and 0.30 (95% CI = 0.21–0.42) for women with three or more births, respectively, when compared with women who had given birth to only one child. There was a significant decreasing trend in the adjusted RR of ovarian cancer with increasing parity (P for trend $<$0.0001).

Discussion

To our knowledge, this is the first prospective study to examine the relationship between parity and age at first birth and the risk of death from ovarian cancer. Previous studies all used case-control designs[5–13].

Table 1. Demographic characteristics of the study cohort

Variables	Number of subjects	Follow-up person-years	Number of deaths from ovarian cancer	Mortality rate (per 100,000 person-years)
Age at recruitment (first birth)				
≤25	859,942	18,528,113.08	152	0.82
26–30	372,895	7,687,356.67	127	1.65
>30	59,625	1,187,525.75	43	3.62
Parity				
1	157,207	3,262,010.42	80	2.45
2	564,727	11,809,326.92	169	1.43
3+	570,528	12,331,658.17	73	0.59
Marital status				
Married	1,260,615	26,721,627.67	316	1.18
Not married	31,847	681,367.83	6	0.88
Years of schooling				
≤9	722,518	15,631,253.58	174	1.11
>9	569,944	11,771,741.92	148	1.26
Birth place				
Hospital/clinic	1,245,925	26,331,337.08	305	1.16
Home/other	46,537	1,071,658.42	17	1.59

In this prospective cohort study, we found that there is a significant protective effect of parity on the subsequent risk of death from ovarian cancer. Our finding of a reduced risk of ovarian cancer associated with the number of parity is in general agreement with previous studies, even in low-incidence population[11,18–19].

Table 2. Association between parity, age at first birth, and RR of death from ovarian cancer over a 26-year follow-up period

Variables	Crude RR (95% CI)	Multivariate-adjusted RR[a] (95% CI)
Age at recruitment (1st birth)		
≤25	1.00	1.00
26–30	2.16 (1.70–2.73)	1.86 (1.45–2.38)
>30	5.00 (3.56–7.02)	3.47 (2.42–4.96)
	$P < 0.0001$ for linear trend	$P < 0.0001$ for linear trend
Parity		
1	1.00	1.00
2	0.58 (0.45–0.76)	0.69 (0.52–0.90)
3+	0.23 (0.17–0.31)	0.30 (0.21–0.42)
	$P < 0.0001$ for linear trend	$P < 0.0001$ for linear trend
Marital status		
Married	1.00	1.00
Not married	0.73 (0.33–1.64)	0.55 (0.24–1.23)
Years of schooling		
≤9	1.00	1.00
>9	1.22 (0.98–1.51)	0.85 (0.68–1.08)
Birth place		
Hospital/clinic	1.00	1.00
Home/other	1.21 (0.74–1.98)	1.61 (0.98–2.65)

[a]Mutually adjusted.

Fathalla[27] proposed that the mechanism of this effect was the interruption of the tearing of the ovarian surface epithelium with each ovulation (the "incessant ovulation" hypothesis). Adami *et al.*[9] proposed that this protective effect is mediated, at least in part, by "clearance" of precancerous cells from the epithelial lining of the ovary and speculated that such an effect might be mediated by placenta or ovarian hormones.

Most studies of the association between ovarian cancer and pregnancies other than live births have reported weak protective effects, often not statistically significant, or no effect at all[28]. A few studies have reported effects similar to a live birth[20,29–30]. 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 ovarian cancer.

Our data takes into account only the effect of the number of children on the risk of mortality from ovarian cancer. The risk progressively declines with each additional birth. However, several studies have reported an increased risk among a subgroup of nulliparous or nulligravid women[5–6,31]. Again, we were unable to examine the possible role of nulliparity on the risk of ovarian cancer because the birth registry ascertained births rather than pregnancies. Nulliparity may reflect an inability to conceive which is linked to an increased ovarian cancer risk[5,32]. It remained to be understood whether nulliparous women are at risk due to the primary basis for their infertility, some correlate of infertility such as the use of ovulation-inducing drugs, a shared genetic susceptibility to ovarian cancer and infertility, or some unrecognized factor[33].

We have found that risk of ovarian cancer increased with increasing age at first live birth after adjusting for parity. This is consistent with previous studies[5,14,16]. However, age at first birth and its relationship to ovarian cancer is still unresolved[4,28]. Older women would be more likely to have accumulated a greater number of transformed ovarian surface epithelial cells than younger women. If a certain proportion of epithelial cells is eliminated during pregnancy, then pregnancy at older ages should, in theory, provide a greater benefit than pregnancy at younger ages in reducing risk of ovarian cancer[17]. One Swedish study confirmed this hypothesis[9]. A recent study by Whiteman *et al*., however, found that a woman's age at her first birth has no independent effect on risk of ovarian cancer. Late age at first birth might reflect selection of women who are able to conceive for a longer time and at older ages; they would constitute a selected population who have healthier ovaries and therefore have a smaller risk of ovarian cancer[9]. Clearly, more work will be needed before the influence of age at first birth on the risk of ovarian cancer is understood.

Mortality data have been widely used to generate epidemiologic hypotheses, despite their inherent limitations[34]. The completeness and accuracy of the death registration system should be evaluated before any conclusion based on the mortality analysis is made. 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 in order to cancel the decedent's household registration. The death certificate is required in order to have the decedent's body buried or cremated. Since the death certificates are required to be completed by physicians and it is mandatory to register all deaths at local household registration offices, the death registration is accurate, reliable, and complete.

Taiwan is a small island with a convenient communication network. It is believed that all ovarian cancer cases had access to medical care. Mortality data rather than data on inpatient cases was used to assess the association between parity, age at first birth, and ovarian cancer in this study. The mortality of a disease is a function of its incidence and fatality. The 5-year survival rate for ovarian cancer has been reported to be as low as 42% in United States and is one of the poorest among all cancer sites[3]. Deaths from ovarian cancer may therefore be regarded as a reasonable indicator of the incidence of ovarian cancer.

In addition to parity, OC use is a well-established protective factor for ovarian cancer[4–7]. We were unable to adjust for this factor in the current study due to the lack of available data. Since the prevalence of OC use is low in Taiwan compared with Western countries[13,35], the confounding effect resulting from this factor should be small if it existed at all. Furthermore, if the association between this potential confounding variable and the risk of ovarian cancer is not as strong as the one that has been observed for parity and age at first birth, adjustment of this variable will not qualitatively change the conclusion. However, we do believe that the risk of ovarian cancer with increasing age at first live birth might be less in countries with more widespread use of OCs.

In summary, we found that there was a trend for increasing parity to be associated with decreasing risk for ovarian cancer. This finding adds evidence to support the hypothesis that parity confers a protective effect on the risk of ovarian cancer. In addition, we found that risk of ovarian cancer increased with increasing age at first birth. More work will be needed before the influence of age at first birth on the risk of ovarian cancer is understood.

Acknowledgment

This study was partly supported by a grant from the National Science Council, Executive Yuan, Taiwan (NSC-94-2314-B-037-056).

References

1 Department of Health, Taiwan (ROC). *Health and vital statistics: I. general health statistics*. Taipei, Taiwan: Department of Health, 2004.
2 Department of Health, Taiwan (ROC). *Cancer registry annual report, 2001*. Taipei, Taiwan: Department of Health, 2004.
3 Schottenfeld D, Frauimeni JF, eds. *Cancer epidemiology and prevention*. New York, NY: Oxford University Press, 1996.
4 Parazzini F, Franceschi S, La Vecchia C, Fasoli M. Review: the epidemiology of ovarian cancer. *Gynecol Oncol* 1990;**43:**9–23.
5 Whittemore AS, Harris R, Itnyre J; the Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;**136:**1184–203.
6 Ness RB, Cramer DW, Goodman MT *et al*. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002;**155:**217–24.
7 Pike MC, Pearce CL, Peters R, Cozen W, Wan P, Wu AH. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertil Steril* 2004;**82:**186–95.
8 John EM, Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer: collaborative analysis of seven US case-control studies. Epithelial ovarian cancer in black women. *J Natl Cancer Inst* 1993;**85:**142–7.
9 Adami HO, Hsieh CC, Lambe M, Trichopoulos D, Leon D, Persson I. Parity, age at first birth, and risk of ovarian cancer. *Lancet* 1994; **344:**1250–4.
10 Purdie D, Green A, Bain C *et al*. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. *Int J Cancer* 1995;**62:**678–84.
11 Mori M, Nishida T, Sugiyama T *et al*. Anthropometric and other risk factors for ovarian cancer in a case-control study. *Jpn J Cancer Res* 1998;**89:**246–53.
12 Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Salmeron-Castro J, Hernandez-Avila M. Reproductive

factors of ovarian and endometrial cancer risk in a high fertility population in Mexico. *Cancer Res* 1999;**59:**3658–62.
13 Yen ML, Yen BL, Bai CH, Lin RS. Risk factors for ovarian cancer in Taiwan: a case-control study in a low-incidence population. *Gynecol Oncol* 2003;**89:**318–24.
14 Negri E, Franceschi S, Tzonou A *et al*. Pooled analyses of 3 European case-control studies: I. Reproductive factors and risk of epithelial ovarian cancer. *Int J Cancer* 1991;**49:**50–6.
15 Polychronopoulou A, Tzonou A, Hsieh C *et al*. Reproductive variables, tobacco, ethanol, coffee and somatometry as risk factors for ovarian cancer. *Int J Cancer* 1993;**55:**402–7.
16 Cooper GS, Schildkraut JM, Whittemore AS, Marchbanks PA. Pregnancy recency and risk of ovarian cancer. *Cancer Causes Control* 1999;**10:**397–402.
17 Whiteman DC, Siskind V, Purdie DM, Green AC. Timing of pregnancy and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2003;**12:**42–6.
18 Shu XO, Brinton LA, Gao YT, Yuan JM. Population-based case-control study of ovarian cancer in Shanghai. *Cancer Res* 1989;**49:**3670–4.
19 Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. Risk factor for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol* 1992;**21:**23–9.
20 Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE, Ross RK. Reproductive, genetic, and dietary risk factors for ovarian cancer. *Am J Epidemiol* 1988;**128:**771–7.
21 Wu SC, Young CL. Study of the birth reporting system. *J Natl Public Health Assoc (ROC)* 1986;**6:**15–27.
22 Yang CY, Cheng BH, Tsai SS, Wu TN, Lin MC, Lin KC. Association between chlorination of drinking water and adverse pregnancy outcome in Taiwan. *Environ Health Perspect* 2000;**108:**765–8.
23 Yang CY, Chiu HF, Tsai SS, Chang CC, Chuang HY. Increased risk of preterm delivery in areas with cancer mortality problems from petrochemical complexes. *Environ Res* 2002;**89:**195–200.
24 Lin MC, Yu HS, Tsai SS *et al*. Adverse pregnancy outcome in a petrochemical polluted area in Taiwan. *J Toxicol Environ Health* 2001;**63:**565–74.
25 Lin MC, Chiu HF, Yu HS *et al*. Increased risk of preterm delivery in areas with air pollution from a petroleum plant in Taiwan. *J Toxicol Environ Health* 2001;**64:**637–44.
26 Yang CY. Calcium and magnesium in drinking water and risk of death from cerebrovascular disease. *Stroke* 1998;**29:**411–4.
27 Fathalla MF. Incessant ovulation: a factor in ovarian neoplasia? *Lancet* 1971;**2:**163.
28 Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. *Clin Endocrinol* 1998;**49:**695–707.
29 Negri E, Franceschi S, La Vecchia C, Parazzini F. Incomplete pregnancies and ovarian cancer risk. *Gynecol Oncol* 1992;**47:**234–8.
30 Casagrande JT, Louie EW, Pike MC, Roy S, Ross RK, Henderson BE. "Incessant ovulation" and ovarian cancer. *Lancet* 1979;**2:**170–3.
31 Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;**331:**771–6.
32 Whittemore AS, Wu ML, Paffenbarger RS *et al*. Epithelial ovarian cancer and the ability to conceive. *Cancer Res* 1989;**49:**4047–52.
33 Rossing MA, Tang MT, Flagg EW, Weiss LK, Wicklund KG. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004;**160:**1070–8.
34 Morgenstern H. Uses of ecologic analysis in epidemiological research. *Am J Public Health* 1982;**72:**1336–44.
35 Chie WC, Chung YL, Huang CS, Chang KJ, Yen ML, Lin RS. Oral contraceptives and breast cancer risk in Taiwan, a country of low incidence of breast cancer and low use of oral contraceptives. *Int J Cancer* 1998;**77:**219–23.

Accepted for publication July 3, 2006