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PRESS

Risk factors for ovarian cancer in Taiwan: a case–control study in a low-incidence population

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Abstract

Objective. We conducted a case–control study to identify risk factors for ovarian cancer in Taiwan, a low-incidence population where the incidence has been on the rise.

Methods. Cases were 86 women (age range 20–75, median 47) drawn from patients with primary, invasive epithelial ovarian cancer diagnosed between 1993 and 1998 in the Taipei metropolitan area, with the following histologic subtypes: 35% serous, 27% mucinous, 21% endometrioid, 15% clear cell, and 2% unspecified adenocarcinoma. Controls were 369 women (age range 20–75, median 44) selected from patients who were hospitalized at the same time for treatment of unrelated diseases. Subjects were interviewed in person regarding sociodemographic and reproductive characteristics, family and medical history, and diet.

Results. A strong inverse relationship of ovarian cancer to each live birth was observed (odds ratio (OR) = 0.43, 95% confidence interval (CI) = 0.20–0.89; OR = 0.30, 95% CI = 0.13–0.69; and OR = 0.18, 95% CI = 0.05–0.62 for parity of 1 or 2, 3–5, and >5, respectively). Menopause was associated with increased risk of disease (OR = 2.15, 95% CI = 1.21–3.83). A trend toward protection was seen with breastfeeding for more than 1 year (OR = 0.55, 95% CI = 0.29–1.01). No dietary factor was associated with an increased disease risk. Milk intake was associated with a decreased disease risk (OR = 0.45, 95% CI = 0.28–0.74).

Conclusion. The strong protective effect of parity was supported by this study, and the decline in parity is likely an important reason for the rising incidence of ovarian cancer in Taiwan. A decreased disease risk was also seen with milk intake. In addition, the difference in the distribution of histologic subtypes in this population compared with high-incidence populations may point to further differences in risk factors.
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Keywords: Ovarian cancer; Case–control study; Risk factors; Diet; Taiwan; Chinese

Introduction

Ovarian cancer is a highly lethal disease with an insidious onset. The incidence of the disease varies widely internationally, with the highest rates in industrialized Western nations and the lowest rate in developing countries and Japan [1]. With an incidence of fewer than 6 per 100,000

women, ovarian cancer is uncommon in Taiwan; however, it has the highest mortality rate among gynecologic cancers [2]. Several risk factors have been reported to be associated with epithelial ovarian cancer, the most common type of malignant ovarian tumor. The most well studied and consistent findings have been reproductive and hormonal factors [1,3–6]. Compared with nulliparous women, parous women have a lower risk of developing ovarian cancer, with a clear trend of decreasing risk with increasing number of live births [3–6]. Use of oral contraceptives (OCs) is also known to decrease the risk of ovarian cancer [1,3,5]. In-

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creased risk is seen in women with a positive family history [1].

Given the fivefold international variation in disease incidence [1] and the increased incidence among women who emigrate from Japan, a low-incidence country, to the United States, a high-incidence country [7,8], dietary factors have been suggested to play a key role in the etiology of the disease [9]. Fat consumption in low-incidence populations has been found to increase disease risk [10,11], but this may not be true for all fats and confounding factors exist [12–14]. A more consistent finding is the protective effect of vegetables and fruits on disease risk [12–15]. Milk, lactose, and its component sugars have been shown to increase risk in some studies [14,16,17], but not others [17–19]. Regarding the association of other protein foods, fish has been found to decrease ovarian cancer risk [15,16,18], but the data are mixed on meat [6,11–16] and eggs [11,13–16].

Many epidemiologic studies have been conducted on ovarian cancer, the vast majority being on high-incidence populations in Europe, and North America. However, data on low-incidence populations such as Asians is sparse, with few recent reports [6,11,12,18,20,21]. Unlike in high-incidence populations where the ovarian cancer incidence is stable [1] or actually decreasing [22], the incidence of the disease in low-incidence populations, including Taiwan, is on the rise [1,2,23,24]. To identify risk factors for ovarian cancer in a low-incidence population, we conducted a hospital-based, case–control study in Taiwan. Reproductive and dietary factors were surveyed in our investigation.

Materials and methods

A case–control study of primary epithelial ovarian cancer was conducted between 1993 and 1998 in the Taipei metropolitan area (north Taiwan). The medical records of all incident cases of primary invasive epithelial ovarian cancer were reviewed to identify newly diagnosed cases, which were taken from hospital pathologic records. Patients with a history of major gynecologic operation including hysterectomy with or without oophorectomy as well as oophorectomy only were excluded. Cases comprised 90 patients (age range, 20–75; median, 47) with newly diagnosed and histologically confirmed cancer. A total of 86 cases (95.6%) with whom contact could be made and who were capable of completing the questionnaire were included in the study. Also, residence in Taiwan for more than 20 years was requisite. Because of the relatively short time from diagnosis to interview for cases (approximately 3–4 months), less than 5% of eligible subjects had died; therefore, no proxy interviews were conducted. The histologic subtypes of the 86 subjects were as follows: 35% serous carcinoma, 27% mucinous carcinoma, 21% endometrioid carcinoma, 15% clear cell carcinoma, 2% unspecified adenocarcinoma.

Controls were selected from patients who were hospital-ized in the same hospitals at the same time for treatment of nonmalignant, nongynecologic conditions, unrelated to hormonal or digestive tract diseases or to long-term modification of diet. Controls were subject to the same surgical exclusions as cases. Four controls were matched to each case by age (± 5 years; age range, 20–75; median, 44), treatment hospital, and date of admission (±4 months). Among controls, 28% were hospitalized for trauma, 30% for nontraumatic orthopedic conditions, 19% for surgical conditions, and 23% for other miscellaneous conditions including medical, eye, nose, throat, and dental disorders. A total of 396 controls were identified and 369 (93.2%) patients were interviewed. An investigator reviewed the medical records of potential control subjects before recruitment. Patients who were very ill were excluded from the interviewing process.

All interviews were conducted in hospital by trained interviewers. Informed consent was obtained from all participating subjects prior to the interview. The questionnaires covered sociodemographic characteristics, including age at diagnosis, ethnicity, education received, marital status, income, height, and weight. Levels of income were grouped into ranges as calculated by the National Executive Yuan of Taiwan [25]. Medical history and family history of disease were solicited. Data on each subject's body weight and height 1 year before the diagnosis for cases and 1 year before the interview for controls were collected and converted into the body mass index (BMI: weight in kilograms divided by the square of the height in meters). Details of each woman's reproductive and contraceptive histories were obtained. Dietary intake history during the 2 years prior to diagnosis or hospitalization (for controls) was elicited. The questionnaire covered the most frequently consumed food groups, including milk, soybean milk, meat, fish, eggs, fruits, and pickled vegetables. Food consumption was reported as weekly frequency.

Data analysis

We used frequency distributions first to review the distributions of responses to the survey parameters. Because of the limited sample size, most potential risk factors were eventually divided into two to four levels for odds ratio (OR) calculation. The strength of association between ovarian cancer and each respective variable was measured in terms of the OR and the 95% confidence interval (CI) using the conditional multivariate logistic regression model, with adjustments for age, income during marriage, and education. In addition, adjustment for the number of live births was made on the analysis of age at first pregnancy, number of incomplete pregnancies, breastfeeding, OC use, and intrauterine device (IUD) use. To calculate the association between diet and disease risk, the food items were classified according to common characteristics, resulting in categories such as pork, fish, chicken, beef, eggs, fruit, and pickled vegetables. Consumption was analyzed as weekly fre-

Table 1
Demographic and socioeconomic characteristics of cases and controls

Characteristic	Cases (n = 86)		Controls (n = 369)		P value[a]
	No.	%	No.	%	
Age					
20–39	29	33.7	163	44.2	
40–49	17	19.8	87	23.6	
50–59	18	20.9	58	15.7	
≥ 60	22	25.6	61	16.5	0.089
Ethnicity					
Fukien	61	70.9	262	71.0	
Hakka	10	11.6	28	7.6	
Aborigine	0	0	5	1.4	
Mainland	15	17.4	74	20.1	0.428
Education					
None	14	16.3	50	13.6	
Primary	33	38.4	141	38.2	
Junior high	18	20.9	92	24.7	
Senior high	10	12.8	37	10.0	
College or higher	11	12.8	49	13.3	0.817
Marriage					
Unmarried	8	9.3	35	9.5	
Married	67	77.9	298	80.8	
Divorced	3	3.5	6	1.6	
Widowed	8	9.3	30	8.1	0.703
Family income during childhood					
Low	17	19.8	72	19.5	
Moderate	62	72.1	263	71.3	
High	2	2.3	18	4.9	
Unknown	5	5.8	16	4.3	0.712
Family income during marriage					
Low	9	10.5	22	6.0	
Moderate	71	82.6	313	84.8	
High	1	1.2	18	4.9	
Unknown	5	5.8	16	4.3	0.191

[a] *P* value for Mantel–Haenszel χ^2 test.

quency levels of 0, 1 or 2, 3–5, and daily consumption. However, due to the small study size, no difference was seen from such analysis (data not shown). Thus, dietary associations were finally analyzed using only yes/no frequency categories. Statistical calculations were performed using the SAS software package [26].

Results

Table 1 summarizes the distribution of demographic and socioeconomic characteristics of the study groups. There were no significant differences between cases and controls. The grading distributions of cases and controls according to various reproductive factors are presented in Table 2. A strong inverse relationship was observed for each live birth and risk of ovarian cancer. Relative to the nullipara, the risk (OR) for ovarian cancer was 0.43 (95% CI = 0.20–0.89), 0.30 (95% CI = 0.13–0.69), and 0.18 (95% CI = 0.05–

0.62) for women whose parity was 1 or 2, 3–5, and more than 5, respectively. Menopausal status was associated with an increased risk of disease (OR = 2.15, 95% CI = 1.21–3.83). Breast-feeding for more than 1 year showed a trend toward protection (OR = 0.55, 95% CI = 0.29–1.01). No other reproductive or menstrual factors, including age at first pregnancy, number of incomplete pregnancies, ages at menarche and menopause, and regularity of periods, were significantly related to the occurrence of ovarian cancer. OC use was associated with a nonsignificant decreased risk (OR = 0.35, 95% CI = 0.08–1.54); however, the rate of ever use was low, only 2.3% for cases and 5.7% for controls. Use of an IUD was not associated with a significant change in risk.

The association of ovarian cancer risk with various dietary factors and BMI is presented in Table 3. In our study, only a small percentage of cases and controls smoked or drank alcohol or coffee, but about one-fourth of the subjects in each group drank tea. However, no dietary factors were significantly related to risk of developing ovarian cancer, except milk intake, which was associated with a decreased risk (OR = 0.45, 95% CI = 0.28–0.74). There was no association of BMI with disease risk.

Discussion

The results of this study support the most consistent finding in the literature: the protective effect of parity on disease risk even in a low-incidence population. Our results show a strong and significant trend of decreasing risk with each live birth. The degree of decreasing risk for each live birth is similar to that seen in other low-incidence studies [6,18,20,21], which is higher than reports from Europe and North America [1,3–5]. The fact that parity is an even stronger protective factor in low-incidence populations such as ours may also be an explanation for the rapidly increasing incidence of epithelial ovarian cancer in Taiwan. The difference in fertility rates between developed and developing nations has been well documented for many years [27]. The higher average parity in developing nations is likely an important reason for the lower incidence of epithelial ovarian cancer in these populations. Since 1950, the average parity per woman of childbearing age in Taiwan has decreased to a nadir of 1.7 in 1998 [28]. Simultaneously, the incidence of epithelial ovarian cancer has risen steadily from a low of 1.26 (per 100,000) in 1979 [29], the first year an official national cancer registry was established in Taiwan, to a high of 5.44 (per 100,000) in 1998, a 4.5-fold increase. This trend of declining parity without a concomitant increase in OC use—unlike in North American and European nations [22]—is, likely an important factor in the increasing incidence of ovarian cancer in Taiwan and other low-incidence populations [24].

The strong association of increasing parity with decreased disease risk has led to the hypothesis of incessant ovulation as a cause of malignant transformation [30]. Fur-

Table 2
Comparison of reproductive risk factors between cases and controls (with adjustments for age, income during marriage, and education)

Characteristic	Cases (n = 86)		Controls (n = 369)		Odds ratio (95% confidence interval)
	No.	%	No.	%	
Number of live births					
0	16	18.6	48	13.0	1.00
1–2	28	32.6	144	39.0	0.43 (0.20–0.89)
3–5	35	40.7	147	39.8	0.30 (0.13–0.69)
>5	7	8.1	30	8.1	0.18 (0.05–0.62)
Age at first pregnancy[a]					
Nulligravida	14	16.3	43	11.7	1.00
<21	12	14.0	58	15.7	1.13 (0.16–7.92)
21–25	46	53.5	143	38.8	1.37 (0.22–8.69)
>25	14	16.3	125	33.9	1.22 (0.21–7.10)
No. of incomplete pregnancies[a]					
0	46	53.5	239	64.8	1.00
≥1	40	46.5	130	35.2	1.42 (0.86–2.32)
Age at menarche					
<14	17	19.8	100	27.1	1.00
14–15	41	47.7	181	49.1	1.27 (0.69–2.37)
16–17	18	20.9	54	14.6	1.58 (0.74–3.39)
>17	4	4.7	23	6.2	0.73 (0.22–2.47)
Unknown	6	7.0	11	3.0	2.10 (0.65–6.81)
Menopause					
Yes	58	67.4	180	48.8	2.15 (1.21–3.83)
No	18	20.9	120	32.5	1.00
Unsure or perimenopause	10	11.6	69	18.7	
Age at menopause[b]					
<45	18/58	31.0	38/180	21.1	1.00
45–50	24/58	41.4	90/180	50.0	0.56 (0.27–1.15)
>50	16/58	27.6	52/180	28.9	0.65 (0.29–1.44)
Breastfeeding (years)[a]					
0	41	47.7	176	47.7	1.00
≤1	8	9.3	42	11.4	0.82 (0.35–1.94)
>1	37	43.0	151	40.9	0.55 (0.29–1.01)
Regularity of periods					
Very regular	64	74.4	287	77.8	1.00
Sometimes irregular	18	20.9	72	19.5	1.14 (0.64–2.06)
Often irregular	4	4.7	10	2.7	1.12 (0.32–3.88)
Ever used oral contraception[a]					
No	84	97.7	348	94.3	1.00
Yes	2	2.3	21	5.7	0.35 (0.08–1.54)
Ever used intrauterine device[a]					
No	63	73.3	302	81.7	1.00
Yes	23	26.7	67	18.3	1.65 (0.95–2.84)

[a] Adjusted for number of live births.
[b] Only 58 case and 180 control subjects could recall their exact age at menopause.

ther support for this theory is the decreased risk seen with breastfeeding and use of OCs [1,3,5], both of which suppress ovulation. Our results show borderline significant protection with breastfeeding for more than one year, a trend that likely would be significant with a larger study population. However, no reduction of risk with OC use was seen, probably due to the low prevalence of use in this population.

Regarding other reproductive risk factors, menopausal status was associated with an increased risk of cancer. However, this positive relationship may not necessarily be a causal one. Rather, it may be that this association points to an earlier common factor that later affects both menopause and disease occurrence. Moreover, there was no relationship between disease risk and age at menopause or age at menarche. Studies to date show divergent results for these risk factors, and the current consensus is that these factors are likely weak predictors of ovarian cancer [1,31]. We also found no association of age at first pregnancy with disease risk, and its relationship to ovarian cancer is still unsettled [1,4,31]. Incomplete pregnancies have been found to have either a slight protective effect [1,3,18] or no association [5,20], as we did. Studies also have shown mixed results regarding menstrual cycle regularity [6,20,21,32], which we have found to have no effect on disease risk.

The inconsistent findings regarding ages at menarche and menopause and other reproductive factors put to question

Table 3
Comparison of dietary risk factors between cases and controls (with adjustments for age, income during marriage, and education)

Characteristic	Cases (n = 86)		Controls (n = 369)		Odds ratio (95% confidence interval)
	No.	%	No.	%	
Smoking					
Yes	5	4.4	23	6.2	1.05 (0.38–2.91)
No	81	94.2	346	93.8	1.00
Alcohol					
Yes	3	3.5	17	4.6	0.71 (0.20–2.51)
No	83	96.5	352	95.4	1.00
Coffee					
Yes	9	10.5	56	15.2	0.73 (0.34–1.56)
No	77	89.5	313	84.8	1.00
Tea					
Yes	25	29.1	125	33.9	0.79 (0.47–1.32)
No	61	70.9	244	66.1	1.00
Milk					
Yes	38	55.8	139	37.7	0.45 (0.28–0.74)
No	48	44.2	230	62.3	1.00
Soybean milk					
Yes	26	30.2	116	31.4	1.12 (0.65–1.90)
No	60	69.8	253	68.6	1.00
Pork > 1/week					
Yes	77	89.5	315	85.4	1.40 (0.65–3.00)
No	9	10.5	54	14.6	1.00
Fish > 1/week					
Yes	55	64.0	246	66.7	0.94 (0.57–1.56)
No	31	36.0	123	33.3	1.00
Chicken > 1/week					
Yes	75	87.2	330	89.4	0.77 (0.37–1.61)
No	11	12.8	39	10.6	1.00
Beef > 1/week					
Yes	18	20.9	73	19.8	0.81 (0.45–1.47)
No	68	79.1	296	80.2	1.00
Eggs > 1/week					
Yes	61	70.9	242	65.6	1.14 (0.67–1.92)
No	25	20.1	127	34.4	1.00
Fruit 1–7 week					
Yes	57	66.3	232	62.9	0.80 (0.48–1.32)
No	29	33.7	137	37.1	1.00
Pickled vegetable > 1/week					
Yes	75	87.2	323	87.5	1.08 (0.53–2.20)
No	11	12.8	46	12.5	1.00
BMI[a] 1 year before diagnosis					
<25	63	73.3	261	70.7	0.77 (0.45–1.33)
≥25	23	26.7	108	29.3	1.00

[a] BMI, body mass index (kg/m^2).

the etiologic theory of incessant ovulation. Moreover, the actual reduction in risk conferred by each pregnancy is statistically much higher than the calculated risk reduction from that duration of ovulation suppression. In addition, the protection from each live birth is not equivalent to a similar duration of ovulation suppression with OC use [32]. Alternative theories have been proposed, the most important of which is that of excessive gonadotropin stimulation leading to malignant transformation [33]. This theory accommodates the effects of parity and OC on disease risk; however, the decreased risk seen with breastfeeding would not fit in. So far, both theories can accommodate only some but not all the epidemiologic data, strongly suggesting ovarian cancer

to be a multifactorial disease. In addition, familial-type ovarian cancer appears to behave biologically differently than non-familial-type cases, further implicating multiple etiologies for the disease [34].

Dietary risk factors for ovarian cancer have been even less consistent than reproductive risk factors. Increased consumption of fat has been cited as a possible cause of the increased incidence of ovarian cancer in immigrants from Asian to Western nations [7,8,10,12,24]. Economic development in the last three decades has been dramatic in Pacific Asian nations, including Taiwan. The per capita daily intake of energy from fat in Taiwan has doubled from 63.5 g in 1970 to 133.1 g in 1990 [35]. Animal meat is a high source

of fat; however, we did not find an increased risk with any type of meat intake. In fact, a study from Japan [6] and a prospective study of diet and ovarian cancer [14] also found no association between risk of disease and either animal meat or fat intake, respectively. Thus, the relationship of fat intake and ovarian cancer remains unresolved.

Although milk and its component sugars have been hypothesized to increase ovarian cancer risk [16], our data as well as studies from Japan [18] show a reduced risk with milk intake. More recent studies out of Italy and the United States, respectively, also did not find any association of milk with disease risk [15,17,19]. Soybean milk, a staple breakfast food unique to the Chinese population, was not found to have an association with disease risk in this study.

The most consistent finding of diet in the literature has been the protective effect of fruit and vegetable intake [8,9,12,14,15]. Our results show a nonsignificant decreased disease risk with fruit intake. However, we did not find any association of disease risk with pickled vegetable intake. The protective effect of vegetables on cancer risk has been hypothesized to be due to antioxidants, vitamins, and other micronutrients [36]. Processing of vegetables may decrease these protective micronutrients. Indeed, in another case–control study, pickled vegetable intake was associated with increased disease risk [11].

The wide range of results from this and other studies on dietary factors suggests caution in interpretation of any analysis, and more evidence is needed before definitive associations with disease risk can be made.

In recent years, an increasing number of studies have shown that epithelial ovarian cancer is not a homogenous entity, and different histologic subtypes may have different etiologies [37]. The histologic subtypes of the cases in this study are markedly different than what has been reported in Caucasian populations [1,31], especially the high incidences of endometrioid and clear-cell subtypes in our population. The breakdown of subtypes in our study is reflective of Taiwan in general, as seen from national tumor registry data over the years [2,29]. Although the case numbers are too small in this study for analysis of risk factor by histologic subtypes, this difference may be another reason for the disparity in incidence rates between this and Caucasian populations.

Certain limitations of this study must be considered. Our study involves a small sample and has a limited power of test, a common drawback of single studies in low-incidence countries. This study also has several limitations of hospital-based case–control studies [38]. Selection bias is possible; however, the enrollment of cases and controls in major teaching and general hospitals of the areas under study and their almost complete participation make the bias less likely. The questionnaire was administered to cases and controls by the same interviewers under similar conditions, thus minimizing any information bias. Very ill individuals were excluded to minimize any recall bias due to severity of the patient's illness, particularly for those with advanced-stage disease. To minimize recall bias on dietary intake, we asked about food intake in the 2 years prior to diagnosis. We were unable to measure the risk association with total intake of nutrients, since only general food groups were surveyed rather than nutrient intake quantity.

In conclusion, the findings in our study support the protective effect of parity on risk of epithelial ovarian cancer, and the rise in incidence in recent years correlates with a continuing decline in parity in Taiwan. Menopausal status was associated with increased disease risk, whereas breast-feeding for more than 1 year showed a trend toward protection. Regarding dietary factors, our finding of a protective effect of milk is consistent with recent studies from other low-incidence populations. A marked difference in histologic subtypes between this and high-risk populations may further contribute to the incidence disparity. This study adds further data to a short list of such studies in populations of low ovarian cancer incidence.

Acknowledgment

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