Population-based Case-Control Study of Ovarian Cancer in Shanghai

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ABSTRACT

A case-control study of 229 ovarian cancer cases (including 172 epithelial tumors) and an equal number of population-based controls was conducted during 1984 to 1986 in Shanghai, China, a low-risk area for ovarian cancer. Similar to studies in high-risk areas, the risk of epithelial tumors was high for nulliparous women (odds ratio, 1.6; 95% confidence interval, 0.8 to 3.2) and decreased with increasing number of livebirths (P < 0.01). Early menarche and late menopause were associated with increased risk, with the trend in risk for age at menarche being statistically significant. In contrast to other studies, oral contraceptive use was not associated with reduced risk, although there was some reduction in risk for those with a prior tubostereolization or intrauterine device use. Risk was also elevated among those reporting a prior ovarian cyst, medroxyprogesterone use, a first degree family history of cancer, and occupational exposure to paint. Risk factors for the nonepithelial tumors were similar to the other cancers, although the power to detect differences was limited.

INTRODUCTION

There is striking international variation in the incidence of ovarian cancer, with the highest age-adjusted rate (15.3/100,000 in Norway) being 5 times that of the lowest (3.2/100,000 in Miyagi, Japan) (1). Among Chinese women, ovarian cancer is relatively infrequent, with the documented incidence being 5.0/100,000 in Shanghai and 5.8 in Hong Kong (2). The incidence of ovarian cancer among Chinese in San Francisco, CA (8.5/100,000), although almost twice that of Chinese women, is still somewhat lower than American white women (12.9/100,000) (2).

These distributions suggest that there might be etiological differences between Chinese and American women. In other areas, reproductive factors have been found to play a major role in the etiology of ovarian cancer, with high parity relating to low risk (1, 3, 4). Oral contraceptive use has also been shown to have a protective effect on ovarian cancer risk (5–8). Other exogenousestrogens, for example, diethylstilbestrol, however, have been found to directly affect risk (1). Although other factors have been suggested to relate to the occurrence of ovarian cancer, their relationship to risk remains less clear. These factors include X-ray exposure (9, 10), viral infections (mumps, rubella, influenza) (1), chemicals (talc, asbestos) (5, 6), and animal fat intake (11). Familial clustering of ovarian cancer has also been noted (12–14).

In order to clarify whether the varying incidence rates between Chinese and American women might relate to etiological differences, we conducted a population-based case-control study in Shanghai during 1984 to 1986.

MATERIALS AND METHODS

Cases consisted of all female residents of the urban Shanghai area, aged 18 to 70 yr, with ovarian cancer newly diagnosed between September 1, 1984, and June 30, 1986. Women with borderline-type ovarian tumors were excluded.

A total of 258 eligible cases was accrued from a population-based cancer register in Shanghai during the study period. Of these, 229 (88.8%) were interviewed, while 21 (8.1%) died before we could contact them, and 8 (3.1%) were untraceable. Clinical and histopathologic data at diagnosis, along with information on treatment and survival, were abstracted from hospital records. Nearly all (94.3%) of the cases were histologically confirmed, with the remainder being diagnosed either through ultrasound (3.1%) or clinical examination (2.6%). Of these tumors, 75.1% were epithelial, 7.4% were germ cell, 7.0% were sex cord, and 7.0% were other or undefined types.

One control was selected from the Shanghai general population by a standard random procedure to match each case within 5 yr of age. For each case, one neighborhood committee was selected from the 1457 committees in the Shanghai urban area, followed by the random selection of one household group (each usually containing 15 to 20 families). Two controls were randomly selected from a household group, with one serving as first control and the other as an alternate. Women with bilateral oophorectomy were replaced with alternative controls. All eligible control women agreed to participate.

Information was collected through direct interviews by trained interviewers. The standard questionnaire covered demographic characteristics, reproductive history, medical history, familial cancer history, personal habits, occupation, and diet.

The measure of association used was the relative risk, as approximated by the OR.2 Stratified analyses were first used to search for potential confounders, followed by conditional logistic regression techniques (15) to derive adjusted odds ratios and 95% CIs. Although a standard model was used for most analyses, alternative models with only pertinent confounding factors produced nearly identical point and interval estimates. A two-tailed test for trend in the logistic analyses was obtained by categorizing the exposure variable, assigning the score j to the jth exposure level of the categorical variable, and treating the scored variable as continuous. The variable, ovulation years, was calculated by both the methods of Risch et al. (16) and Casagrande et al. (17), but since the two methods provided similar results, only those derived by the former method are presented.

RESULTS

In order to control for effects of differing histological patterns, the majority of analyses focused on risk factors for the predominantly occurring epithelial tumors. The epithelial cancer cases and matched controls were found to be comparable in age distribution. The mean age was 49.1 yr for cases and 48.9 yr for controls. Cases tended to be better educated and have higher incomes than controls (Table 1); however, after adjustment for education, income failed to remain as a significant predictor of risk. No significant differences were noted between cases and controls with respect to number of household members, height, average weight, maximum weight, or body mass index (not shown). Fewer cases (93.5%) than controls (96.5%) were ever married.

Nulliparity was associated with a nonsignificantly elevated odds ratio of 1.6 (95% CI, 0.8 to 3.2). Women who had ever been pregnant but had had no livebirths had a slightly lower risk (OR, 1.3; 95% CI, 0.3 to 5.3). The protective effect of parity was significantly related to the number of livebirths (trend...
test, \( P < 0.01 \) but was not related to age at first livebirth (Table 2). A history of a miscarriage or stillbirth was not related to risk, but induced abortions were associated with slight reductions in risk.

Age at menarche was significantly inversely related to risk, with women whose first menses occurred prior to the age of 14 having approximately 4 times the risk of those with menarche at ages 18 and older (Table 3). This effect persisted after adjustment for animal fat intake, a significant determinant of risk in this population (18). Risk increased with the usual length of the menstrual cycle, but the trend was not statistically significant. A total of 51.2% of the cases had ceased menstruating, compared with 48.8% of the controls, resulting in an adjusted odds ratio of 1.0 (95% CI, 0.4 to 2.2). Among the women with a natural menopause, late menopause was linked with a higher risk of ovarian cancer, although there was no distinct trend.

When queried regarding physician-diagnosed menstruation problems (at least 2 yr prior to diagnosis), more cases than controls reported irregular menstruation (OR, 2.7), amenorrhea or relative amenorrhea (OR, 2.6), menorrhagia (OR, 2.8), or dysmenorrhea (OR, 1.2). However, none of these excesses was statistically significant.

The relationship between ovarian cancer and various methods of birth control is summarized in Table 4. A total of 48.3% of the cases and 57.0% of the controls had ever used a method of birth control, resulting in an adjusted odds ratio of 0.8 (95% CI, 0.4 to 1.5). Separate analyses according to ever versus never use of various methods of birth control showed an elevated risk of ovarian cancer associated with oral contraceptive usage (OR, 1.8; 95% CI, 0.8 to 4.1) and a lower risk with tubesterilization (OR, 0.5; 95% CI, 0.2 to 1.1). There was, however, no obvious trend between the risk of ovarian cancer and the duration or years since first use of oral contraceptives, or the years since sterilization. Recomputation of risks using women who had never used any method of birth control as the referent group produced virtually the same point estimates for the various birth control methods but broader confidence intervals.

Since parity, menarche, menopause, and oral contraceptive use were all related to ovarian cancer risk, we attempted to summarize these events by calculating ovulation years (see Table 5 for method of computation). Risk increased with extended periods of ovulation, with women ovulating more than 30 yr having an odds ratio of 1.8 (95% CI, 0.6 to 5.4) compared to those with less than 17 yr. Since ovulation was related to the frequency of menstrual cycles, we also measured the effect of
A total of 14 female diseases and symptoms as well as 18 other diseases occurring at least 2 yr prior to ovarian cancer were examined by calculating odds ratios for jobs held for the longest period of time (Table 7). A total of 24.4% of cases versus 12.2% of controls reported having a hysterectomy, resulting in an adjusted odds ratio of 1.1 (95% CI, 0.1 to 11.9).

A history of ever having smoked was associated with an odds ratio of 1.8 (95% CI, 0.7 to 4.8). There were no differences between cases and controls with respect to drinking or use of hair dyes.

Associations between ovarian cancer and occupation were examined by calculating odds ratios for jobs held for the longest period of time (Table 7). A total of 24.4% of cases versus 12.2% of controls were employed as professional/technical workers, scientists, and research workers, resulting in a crude odds ratio of 2.6 (95% CI, 1.5 to 4.6). However, after adjustment, the odds ratio was reduced to 1.4 (95% CI, 0.6 to 3.3). Chemical workers demonstrated a nonsignificantly elevated risk. No excess risks were found for any of the other occupations examined. Exposure to paint was associated with a nonsignificant elevation in risk (OR, 2.4; 95% CI, 0.9 to 5.9), but other occupational exposures were not related to increased risk.

Similar proportions of cases and controls reported prior pelvic or chest X-ray exposure. Twelve cases and 2 controls had pelvic operations at least 2 yr prior to the diagnosis of ovarian cancer (OR, 5.9; 95% CI, 0.7 to 51.7). Three cases compared to 2 controls reported having a hysterectomy, resulting in an adjusted odds ratio of 1.1 (95% CI, 0.1 to 11.9).

A total of 14 female diseases and symptoms as well as 18 other diseases occurring at least 2 yr prior to ovarian cancer diagnosis was analyzed. No substantial differences between cases and controls were found with respect to childhood viral diseases (mumps, rubella, chicken pox), thyroid or adrenal diseases, hypertension, diabetes, allergies, and benign breast diseases (latter shown in Table 6). However, the risk of ovarian cancer was elevated in women with a history of pelvic infection (OR, 3.0; 95% CI, 0.3 to 30.2), operation for myoma uteri (OR, 3.0; 95% CI, 0.7 to 12.2), or ovarian cysts (OR, 12.0; 95% CI, 2.5 to 57.7). For ovarian cysts occurring less than or equal to 2 yr, 2 to 10 yr, and more than 10 yr prior to diagnosis of ovarian cancer, the odds ratios were 2.7 (95% CI, 0.2 to 30.4), 9.8 (95% CI, 1.2 to 81.0), and 15.3 (95% CI, 1.6 to 150.7), respectively. The association with ovarian cysts was stronger for premenopausal (10 exposed cases versus 0 controls) than postmenopausal women (OR, 5.6; 95% CI, 0.5 to 65.9). Given that women with ovarian cysts might be under better medical surveillance and, hence, have an earlier diagnosis of ovarian cancer, we computed the odds ratios according to the progressiveness of the ovarian cancer. Although the odds ratio for less progressive ovarian cancer was higher (OR, 14.1) than for more progressive cancer (OR, 9.6), both were significant.

An increased risk of ovarian cancer was noted among women with a history of medroxyprogesterone usage (OR, 2.8; 95% CI, 0.9 to 8.5). This association did not appear to be explained by abnormal menstrual symptoms. No distinct trend was observed with years of use, although the number of reported users was limited. Six cases and one control reported using hormones to help them become pregnant (OR, 2.1; 95% CI, 0.2 to 22.7). Use of diethylstilbestrol was associated with an odds ratio of 5.4, although based on only 4 exposed cases. Other hormones, including corticosteroids and testosterone propionate, were not related to increased risk.

A history of pelvic infection was associated with an odds ratio of 1.8 (95% CI, 0.7 to 4.8). There were no differences between cases and controls with respect to drinking or use of hair dyes.

Analyses also examined risk factors for the nonepithelial
The present case-control study, conducted among a low-risk population for ovarian cancer, demonstrated several results for epithelial ovarian cancer consistent with studies in higher risk populations. The elevated risks associated with nulliparity and decreasing risk with increasing parity support previous findings (3–5, 16, 19–23). In line with several studies (3, 6, 24), but in contrast with others (7, 20–22), our study showed that neither age at first livebirth nor age at first pregnancy were significantly related to ovarian cancer. A history of a miscarriage or stillbirth was unrelated to risk, but induced abortions were associated with slight reductions in risk.

The underlying mechanism by which pregnancy confers a protective effect on ovarian cancer risk is unclear. "Incessant ovulation" has received attention as a possible explanation (16, 17, 25, 26), since ovulation exposes the ovarian epithelium to recurrent minor trauma and contact with follicular fluid (27). This hypothesis is supported by findings that an index of ovulatory years (the time from menarche to cessation of ovulation minus the time the ovary is anovulatory or protected) directly relates to ovarian cancer risk (17, 21, 22, 28). Our findings supported this notion, with women ovulating more than 30 yr having nearly twice the risk of those with less than 17 ovulatory yr. Total frequency of ovulation, however, did not appear to affect risk.

Abnormalities in endocrine function have also been hypothesized as an explanation for the association with nulliparity (29). It has been suggested that an unidentified abnormality in endocrine function may predispose women to both infertility and ovarian cancer (3). Of some support for this was our finding that cases more frequently reported irregular menstruation, amenorrhea, and menorrhagia. However, none of the elevations was statistically significant, and the possibility of recall bias cannot be dismissed.

Of note in this study was a strong relationship of risk with early age at menarche, with women having menses prior to age 14 having 4 times the risk of those first menstruating at age 18 or older. Age at menarche has not generally been found to be a risk factor for ovarian cancer (5, 20, 21), although one study did report that cases tended to have slightly earlier ages than controls (17). It would be of interest to examine the relationship in other populations where the range in ages at menarche was as wide as in this population of Chinese women.

We did not find a protective effect of oral contraceptives on ovarian cancer risk as reported in other studies (5, 6, 23, 30, 31). In our study oral contraceptive use was associated with a slight increase in risk, but neither the point estimate associated with ever use nor the trends with extended measures of use was statistically significant. Of note was the fact that excess risk was restricted to short-term (<1 yr) users, suggesting that the effect may relate either to the indications for use or an adverse reaction to use of oral contraceptives, as previously noted (17). Alternatively, the association might reflect the influence of recall bias, lifestyle correlates, or of chance, especially since the number of users was limited.

Our study disclosed that tubosterilization and intrauterine device usage reduced the risk of ovarian cancer. Although the reason for the protective effect associated with intrauterine device usage is unclear, the reduced risk associated with sterilization is consistent with an effect observed among Japanese women (32). However, two other studies did not find such an association (20, 33). It has been suggested that carcinogens can reach the ovary through the fallopian tube (34). Thus, tubosterilization might block the carcinogenic pathway by ligating the tube or terminating the blood supply to the ovary. Furthermore, the lowering of certain hormone levels following tubesterilization might be important (35, 36). Finally, the possibility that the operation allows for screening of abnormal ovaries should not be dismissed, although there was no relation of risk with years since sterilization.

Of note in this study was that a history of ovarian cysts was related to a 12-fold increased risk of ovarian cancer. Risk was highest for cysts diagnosed more than 2 yr prior to diagnosis...
and only significant in premenopausal women. It is possible that women with an ovarian cyst will have better medical surveillance and thus be diagnosed with ovarian cancer at an earlier stage. Although a significant association was found in this study even for those with more aggressive lesions, the possibility of selection bias cannot be totally eliminated.

Previous studies have suggested that oral contraceptives containing only progestogens may enhance the formation of ovarian cysts (37-40). In one study (41), the peripheral serum concentration of progesterone in ovarian tumor patients was found to be elevated, and experimental studies have demonstrated progestosterone treatment can increase the incidence of ovarian cancer in mice (42). It was thus of interest that our study found use of medroxyprogesterone to be associated with a 2.8-fold increased risk of ovarian cancer, implying that progestosterone might mechanistically relate to both ovarian cysts and ovarian cancer.

It has been suggested that women who work in rubber, electrical, and textile industries are at greater risk of ovarian cancer than women employed in other industries (43, 44). Asbestos and talc have also been suggested as risk factors on the basis of several epidemiological (5, 6) and pathological studies (45). The present study did not find any of the hypothesized occupations to relate to risk, but did note that chemical workers had a slightly increased risk of ovarian cancer. Women who were exposed to paint also had a 2.2-fold elevated risk. A few familial clusters of ovarian cancer have been noted (12, 13). In cases studied frequently reported a familial history of cancer of female reproductive organs in general (20) or of cancer of the breast (14). In our study, cases more commonly reported a familial cancer history, although reproductive cancers did not predominate. In addition, the number of familial cancer cases was not large. Thus, it would appear that heredity is not a major contributing factor to the etiology of ovarian cancer in China.

In conclusion, our study showed that epithelial ovarian cancer risk factors among Chinese women and medical factors examined in this study do not solely appear to explain observed geographical patterns of ovarian cancer. Changing incidence rates upon migration support the notion that adopted environmental factors may be etiologically involved. Relationships of ovarian cancer risk with dietary factors (11, 18) may be one possible explanation and should be pursued further as a possible explanation to the varying incidence rates between Chinese and American women.

REFERENCES

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