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Difference in Subjects' and Their Mothers' Parities Among Ovarian Cancer Patients

— A Result of a Case-control Study —

Mitsuru MORI and Hirotsugu MIYAKE
Department of Public Health, Supporo Medical College, Sappor 060, Japan

SUMMARY

An individually age-matched case-control study of ovarian cancer was conducted in Hokkaido, Japan. Forty five women with epithelial-origin ovarian cancer were compared with 2 control groups in terms of the number of their own parities and their mothers' parities. The first control group was comprised of 45 patients admitted to the same gynecologic wards as the cases studied. The second control group was comprised of 45 gynecologic outpatients who were later diagnosed as being without any malignant diseases. Statistically the number of mothers' parities minus subjects' parities was significantly greater among the cases than among controls ($p<0.05$). Moreover, an ascending trend in the relative risks for ovarian cancer was significantly noted in terms of the number of mothers' parities minus subjects' parities ($p<0.01$). That is, ovarian cancer patients who are subfertile are born from relatively fertile mothers. We offer such a possible hypothesis to explain these findings that mothers of ovarian cancer patients possess the specific levels of gonadotropins or sex hormones in sera which do not only make themselves fertile, but also contributes to suppress fetal ovarian development. Prenatally dysfunctional ovaries have been suggested to be predisposed to ovarian cancer.

Key words: Epidemiology, Ovarian cancer, Case-control study, Parity, Maternal factor

INTRODUCTION

The incidence of ovarian cancer has been gradually rising in several parts of the world including Japan (20). From the results of recent epidemiological studies, fewer pregnancies or parities are agreed to be an important risk factor for the disease (5, 10, 12, 23, 25, 28). This finding has been interpreted by two different

inferences (3, 14) : 1) pregnancy or parity protects against ovarian cancer : 2) ovarian dysfunction makes some women both subfertile and prone to ovarian cancer.

We have conducted the case-control study of ovarian cancer since 1979 in Hokkaido, and have reported several risk factors for the disease which were summarized as genetical predisposition and ovarian dysfunction early in life (19). In the present study, we use the data from the second survey which was conducted from 1980 to 1981, in order to further assess the findings concerning the number of subjects' and their mothers' parities among ovarian cancer cases and their controls.

SUBJECTS AND METHODS

This study is an individually age-matched case-control study (2 controls per case). Fifty women with primary ovarian cancer were interviewed at 25 gynecologic wards from November, 1980 to June, 1981 in Hokkaido. Each case of ovarian cancer was pathologically confirmed by the gynecologists in charge and 45 women with epithelial-origin ovarian cancer were referred to as the Case group in this study. Their average age was 49.2 years old (S. D.=12.5 years) and pathological classifications of their cancer were shown in Table 1.

The first control series (Control A group) was comprised of 45 patients admitted to the same gynecologic wards as the cases studied. Their ages were within 3 years of the indexed cases, and they were suffering from a gynecologic complaint other than an ovarian tumor or cyst. Forty-four percent of them had been admitted for cervical cancer, 33% for myoma uteri, 9% for miscarriage and the remainder for various conditions including 4% for prolapsis uteri.

The second control series (Control B group) was comprised of 45 women, and they were identified from outpatients at the Department of Obstetrics and Gynecology, Sapporo Medical College or from women examined for uterine cancer at the Hokkaido Anti-Cancer Association. Their ages were also within 3 years of the indexed cases. Nine percent of them were healthy, 82% were suffering from

Table 1 *Pathological Classification of Ovarian Cancer Patients.*

Pathology	N
serous adenocarcinoma	20
mucinous adenocarcinoma	12
clear cell adenocarcinoma	2
endometrioid adenocarcinoma	1
poorly differentiated	4
unclassified	6
Total	45

inflammation including vaginitis in large part, and the remainder from various other conditions except for a malignant disease, an ovarian tumor, or cyst.

Direct interviews for each woman were conducted by the author, and the data relevant to her parity and her mother's parity were statistically evaluated by means of a 2-way analysis of variance (1). The Mantel-extension method (18, 26) was used to assess trends for the relative risks concerning the number of parities.

RESULTS

The following three items were compared among Case group, Control A group, and Control B group ; 1) the number of subjects' parities ; 2) the number of their mothers' parities ; 3) the number of mothers' parities minus subjects' parities. These comparisions were statistically evaluated by means of a 2-way analysis of variance, and the results were shown in Table 2. The number of subjects' parities among the cases was significantly smaller than among controls ($F=4.65$, D. F.$=2$, 88, $p<0.05$). The number of mothers' parities among the cases tended to be greater than among controls, but not statistically significant ($F=1.86$, D. F.$=2$, 88, $p<0.05$). The number of mothers' parities minus subjects' parities was significantly greater among the cases than among controls ($F=5.11$, D. F.$=2$, 88, $p<0.01$).

The Mantel-extension method was conducted to assess the linear tendency in the relative risks for ovarian cancer concerning the number of parities. As shown in Table 3, a descending trend was significantly observed in the relative risks of the number of subjects' parities ($p<0.05$). Although a trend in the relative risks of the number of mothers' parities was not significant ($p>0.05$), an ascending trend in the relative risks of the number of mothers' parities minus subjects' parities was noted significantly ($p<0.01$). If the number was equal to or more than 5, the relative risk increased to 6.23 (Table 3).

Single women have been identified as a high-risk group for ovarian cancer by

Table 2 *Total Number of Subjects' Parities, Mothers' Parities, and Mothers' Parities minus Subjects' Parities in Three Groups.*

	N	Number of subjects' parities	Number of mothers' parities	Number of mothers' parities minus subjects' parities
Case group	45	87*	273	186**
Control A	45	111	239	128
Control B	45	124	241	117

*: $p<0.05$ **: $p<0.01$ (assessed by a two-way analysis of variance)

Table 3 *Distribution of Case Group and Control Groups in the Number Relevant to Parities.*

(1) Number of subjects' parities

	0	1-2	3-4	5-	N
Case Group	15	15	12	3	45
Controls A&B	10	40	28	12	90
relative risk	1.00	0.25	0.28	0.17	

$x^2=5.85$, $p<0.05$ (by the Mantel-extension test)

(2) Number of mothers' parities

	1-3	4-5	6-7	8-	N
Case Group	7	13	13	12	45
Constmls A&B	21	33	19	17	90
relative risk	1.00	1.18	2.05	2.11	

$x^2=2.64$, $p<0.05$ (by the Mantel-extension test)

(3) Number of mothers' parities minus subjects' parities

	-0	1-2	3-4	5-	N
Case Group	3	9	11	22	45
Controls A&B	17	27	26	20	90
relative risk	1.00	1.89	2.40	6.23	

$x^2=10.05$, $p<0.01$ (by the Mantel-extension test)

recent researchers (5, 7, 9, 16, 19, 23, 24, 30). Therefore, matched triples which included a single woman in each case or indexed controls were excluded to evaluate the results without being confounded by marital status. After these exclusions, the above-mentioned three comparisions were executed by means of a 2-way analysis of variance. As shown in Table 4, statistically the number of subjects' parities among the cases was not significantly smaller than among controls ($F=2.12$, D. F.$=2, 72$, $p>0.05$). Further, the number of mothers' parities tended to be greater among the cases than among controls, but not statistically significant ($F=2.23$, D. F.$=2, 72$, $p>0.05$). However, the number of mothers' parities minus subjects' parities was significantly greater among the cases than among controls ($F=3.59$, D. F.$=2, 72$, $p<0.05$).

The Mantel-extension test was also conducted after matched triples which included a single woman in each case or indexed controls were excluded. As shown in Table 5, a trend was not significantly noted either in the relative risks of the

Table 4 *Total Number of Subjects' Parities, Mothers' Parities, and Mothers' Parities minus Subjects' Parities in Three Groups after Excluding Single Women.*

	N	Number of subjects' parities	Number of mothers' parities	Number of mothers' parities minus subjects' parities
Case group	37	87	236	149*
Control A	37	95	200	105
Control B	37	110	203	93

*: $p<0.05$ (assessed by a two-way analysis of variance)

Table 5 *Distribution of Case Group and Control Groups in the Number Relevant to Parities after Excluding Single Women.*

(1) Number of subjects' parities

	0	1-2	3-4	5-	N
Case group	7	15	12	3	37
Controls A&B	7	32	23	12	74
relative risk	1.00	0.46	0.52	0.25	

$x^2=1.87$, $p>0.05$ (by the Mantel-extension test)

(2) Number of mothers' parities

	1-3	4-5	6-7	8-	N
Case group	5	9	12	11	37
Controls A&B	17	25	17	15	74
relative risk	1.00	1.22	2.40	2.49	

$x^2=3.14$, $p>0.05$ (by the Mantel-extension test)

(3) Number of mothers' parities minus subjects' parities

	-0	1-2	3-4	5-	N
Case group	3	8	8	18	37
Controls A&B	14	23	21	16	74
relative risk	1.00	1.62	1.78	5.25	

$x^2=7.37$, $p<0.01$ (by the Mantel-extension test)

number of patients' parities ($p>0.05$) or in the relative risks of the number of their mothers' parities ($p>0.05$) after these exclusions. However, an ascending trend in the relative risks of the number of mothers' parities minus subjects' parities was

still significantly observed after these exclusions ($p<0.01$). If the number was equal to or more than 5, the relative risk rose to 5.25 (Table 5).

DISCUSSION

Because usage of contraceptives has prevailed in Japan, especially since 1950's, the number of parities have been clearly reduced (13). Therefore, the number of subjects' parities was less than or almost equal to half of the number of their mothers' parities among either Case group, Control A group, or Control B group (Table 1). As we reported previously, ovarian cancer patients tended not to use contraceptive devices and less frequently practiced any kind of contraception (19). Similarly, Nasca *et al.* (23) have reported that ovarian cancer patients were less likely than controls to have ever used nonpermanent birth control methods and they tended to practice contraception less often. Therefore, fewer parities among ovarian cancer patients were not probably brought about by more frequent contraceptions.

From the results of this study, the significantly greater number of mothers' parities minus subjects' parities among ovarian cancer cases was observed and an ascending trend in the relative risks of this number was significantly noted even after excluding single women. It can be assumed, therefore, that subfertile women who are reported with some consistency to be a high-risk group for ovarian cancer are born from relatively fertile mothers. We offer a possible hypothesis to explain this finding as follows; 1) mothers of ovarian cancer patients have the specific endogenous milieu which make them fertile; 2) ovarian-cancer patients are exposed in uterus to this milieu, which would contribute to suppress fetal ovarian development; 3) prenatally dysfunctional ovaries make them both subfertile and prone to ovarian cancer.

There is evidence which supports the theory that congenitally dysfunctional ovaries carry a high risk for ovarian cancer especially of germ cell origins (17, 29). Further, it has been reported that genetic deletion of germ cells in hybrid mice may be a force sufficient for the initiation of a series of events resulting in ovarian tumorigenesis (21, 27). Cramer *et al.* (6) suggested that premature ovarian failure would be associated with high levels of pituitary gonadotropins early in life and might be expected to increase the risk of ovarian cancer. A rise in pituitary gonadotropins brought about by a decrease of ovarian function has been held responsible for experimental ovarian carcinogenesis as well (8, 22).

What kind of maternal endogenous milieu would be expected to be responsible for prenatal ovarian dysfunction predisposed to ovarian cancer, if any? We do not have a clear answer yet, but we would cite some reports pertinent to this question. First, Barlow *et al.* (2) have indicated that deficiency of α-L-fucosidase activity in

sera of females may be a hereditary endogenous condition associated with an increased risk for development of ovarian cancer. Likewise, Kaufman *et al.* (15) reported 18 female cases of hypergonadotrpic hypogonadism with galactosemia. Chen *et al.* (4) added to this report that the toxicity of galactose exerts its primary effect on the oocyte number through interference with oogenesis, which occurs prenatally in human beeings. Besides these reports, it is considered that levels of gonadotropins or sex hormones in sera of females are profoundly associated with both their fertility and prenatal ovarian development of their daughter. It has been reported, for example, that gonadotripins in serum are important in maintaining fertility (11), and that fetal ovarian differentiation is mediated in part by sex hormones derived from the maternal circulation (31).

Ovarian dysfunction occurring in uterus may play an important role for the development of ovarian cancer, although the mechanisms by which maternal endogenous substances suppress fetal ovarian development remain unclear.

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