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Recent Trends in Ovarian Cancer in Niigata Prefecture as Based on Our Ovarian Cancer Registration

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Summary. **On the basis of our ovarian cancer registration from 1983 through 1992, we analysed recent trends in ovarian cancer in Niigata Prefecture. The incidence of ovarian cancer was shown to be rising slightly year by year ($p<0.01$) by a non parametric test, owing primarily to an increase in malignant surface epithelial-stromal tumors. However, sex cord/stromal tumors and germ cell tumors remained rare and almost stable in number of cases ($p<0.05$). We defined a high risk area as a significantly high standardized incidence rate (SIR) area, to which one village and one town were indicated. No high risk area was observed in cities. Among the areas researched, an area in Aikawa Town which was considered to be the highest risk area in Niigata Prefecture showed an age-adjusted incidence rate of 226.6 when calculated by the direct method, a figure 31 times higher than the prefectural rate. By the indirect method, also, a similar result of 197.8 was obtained. In the past 10 years, 10 cases of ovarian cancer have been detected in an area in Aikawa Town, including 9 cases of malignant epithelial-stromal tumors and 1 immature teratoma. All of the 10 patients as well as their parents were born and raised in this area. Furthermore, of the 168 women over 30 years of age in this area with cancer screening, 80% of both them and their parents had been born and raised in Aikawa Town or in this area. To investigate carcinogenic risk factors, a comparison was made as to the number of gravidity, parity, and age at menarche and natural menopause between 364 ovarian cancer cases from our registration, counting 817 cases in women over 30 years of age in Aikawa Town and 3340 controls also aged over 30 in Niigata City who had undergone uterine cancer examination in 1991 and had no ovarian tumor nor operative history. The number of gravidity and parity alone was significantly different between ovarian cancer cases and the control. The breakdown of the 364 patients with ovarian cancer by past history was as follows: 47 cases with sterility (12.9%), 22 cases with cystectomy of an ovarian tumor (6.0%), 9 with total hysterectomy (2.4%), 9 with tubal ligation (2.4%), 13 with endometrial or mammary or rectal cancer (3.6%), which remain to be answered with respect to the etiology and prophylaxis of ovarian cancer. We conclude that further investigation in high risk districts will elucidate these questions.**

Key words—ovarian cancer, registration, incidence rate.

INTRODUCTION

Every year worldwide, 140,000 women develop ovarian cancer, accounting for 4% of all cancers in women today.[1] There is a wide difference in the incidence rate of ovarian cancer in the world. The rate is highest in the Nordic countries, with the lowest is in Japan. A recent report has shown that currently the incidence rate of ovarian cancer in Japan is 4.4 per 100,000 women,[2] and this number is rising.

It must be taken into consideration that a definitive diagnosis of ovarian cancer requires both macroscopic and histopathologic analyses of extractives. Diagnostic imaging, for example, ultrasound sonography, has been used more frequently. However, this is useful only to a limited extent, as there are some cases which cannot be distinguished from cancer metastasis. When a patient dies of advanced ovarian cancer without receiving any medical treatment, she is naturally not diagnosed and her case is therefore not registered. In cases in which interdepartmental communication is insufficient, they may again not be included in the registration, or referrals may not be made. For these and other reasons, even if tumor registration becomes more accurate, we cannot expect to know the actual incidence rate of ovarian cancer in Japan at either the present time or the

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future. With regard to carcinogenic risk factors, despite many investigations, most causes of ovarian cancer remain insufficiently researched, as in the case of other cancers.

In 1983, our department started an ovarian cancer registration with the cooperation of gynecologic hospitals and clinics in Niigata Prefecture. We studied the ovarian cancer registration from 1983 to 1992 and analyzed the recent trends in ovarian cancer in Niigata Prefecture.

MATERIALS AND METHODS

On the basis of the general rules for clinical pathological management of ovarian tumors by Japan Society of Obstetrics and Gynecology and the Japanese Society of Pathology in 1990, we investigated the registration of ovarian cancer between 1983-1992 in Niigata Prefecture, taking into account all primary malignant and borderline cases—(Sertoli-stromal). Staging was assigned according to the FIGO Cancer Committee's new definitions for 1985.[3,4] We calculated the number of borderline and malignant cases in each year, and obtained the crude and age specific incidence rates in Niigata Prefecture on the basis of the annual Niigata Prefecture population statistics. As the basic population, we used the total female population in Niigata Prefecture for each year. Using the direct or indirect method, we determined the age-adjusted incidence rate and the standardized incidence ratio (SIR) for 20 cities and 92 towns and villages. We also obtained the 10-year average of the incidence rate. A high risk area was defined as a significantly high SIR area ($p<0.01$) by chi-square test.

For ovarian carcinogenic risk factors, we exa-

Table 1. Histopathological types of ovarian cancer (1983-1992)

Histopathological type	Total (cases)	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992
Surface epithelial-stromal tumors											
Borderline malignancies											
Serous tumors	20	1	1	3	2	0	4	2	1	5	1
Mucinous tumors	65	9	2	4	7	3	5	9	6	13	7
Malignancies											
Serous tumors	373	32	28	29	47	32	41	39	38	43	44
Mucinous tumors	148	11	13	15	21	13	12	12	10	18	23
Endometrioid tumors	92	7	3	2	5	8	12	16	11	14	14
Clear cell tumors	83	7	5	6	6	9	7	13	13	9	8
Brenner tumors	5	0	1	0	1	0	0	1	2	0	0
Undifferentiated carcinoma	31	5	2	1	4	2	2	1	3	9	2
Mesodermal mixed tumor	5	0	0	0	1	2	1	1	0	0	0
Sex cord/stromal tumors											
Borderline malignancy											
Granulosa-stromal tumors	24	1	0	3	3	3	0	5	5	3	1
Germ cell tumors											
Borderline malignancies											
Immature teratoma	13	2	1	2	1	1	2	1	0	2	1
Carcinoid	2	1	0	0	0	0	0	0	1	0	0
Malignancies											
Dysgerminoma	14	2	0	3	1	0	2	1	1	1	3
Yolk sac tumor	21	2	6	6	1	2	0	2	2	0	0
Mature cystic teratoma with malignant transformation	14	1	2	2	2	2	0	3	0	1	1
Others											
Sarcoma	5	1	0	0	0	0	0	0	1	1	2
Other malignancy	11	0	0	3	2	2	0	1	2	1	0
Total (cases)	926	82	64	79	104	79	88	107	96	120	107

mined gravidity, parity, age at menarche and natural menopause, past operative history. Controls were 3340 women aged over 30 in Niigata City who had undergone uterine cancer examination in 1991 and had no ovarian tumor nor operative history. In addition, we investigated risk factors of ovarian cancer in 817 women aged over 30 years in Aikawa Town, one of the high risk areas, is located.

RESULTS

Histopathological types

As shown in Table 1, the number of cases with ovarian cancer registered between 1983 and 1992 in gynecologic clinics or hospital departments in Niigata Prefecture totaled 926, namely 802 malignant and 124 borderline cases, with a registration rate of virtually 100%. Among 926 cases, 412 cases were treated at gynecologic clinics or hospital departments, 514 cases were referred to us at Niigata University Hospital or major gynecologic hospitals by clinics and other departments (mostly by internal departments). Surface epithelial-stromal tumors were the predominant form of ovarian cancer, accounting for about 90%. Histopathologically, malignant serous tumors were the most typical, accounting for 46.1% of the malignancies. The total number of both borderline and malignant surface epithelial-stromal tumors tended to increase annually according to the results of a non parametric test ($p<0.01$). Also, both early and advanced epithelial-stromal tumors increased annually ($p<0.01$). The cases of sex cord/stromal tumors and germ cell tumors were rare and stable in number.

Table 2. Staging distribution and age of ovarian cancer (1983-1992)

Histologic type	Total (cases)	Stage I	Stage II	Stage III	Stage IV	Age Mean (range)
Surface epithelial-stromal tumors						
Borderline malignancies						48.2
Serous tumors	20	17	2	0	1	46.5(19-76)
Mucinous tumors	65	62	1	2	0	48.7(14-77)
Malignancies						55.8
Serous tumors	370	101	55	162	52	54.7 (15-84)
Mucinous tumors	148	95	14	23	16	51.7(12-91)
Endometrioid tumors	92	46	18	26	2	52.1(29-88)
Clear cell tumors	83	48	18	11	6	52.5(29-86)
Brenner tumors	5	4	0	1	0	67.2(59-86)
Undifferentiated carcinoma	31	0	6	19	6	58.1(35-73)
Mesodermal mixed tumor	5	1	1	3	0	67.8(54-81)
Sex cord/stromal tumors						
Borderline malignancy						
Granulosa-stromal tumors	23	21	0	0	2	55.0(10-84)
Germ cell tumors						
Borderline malignancies						29.3
Immature teratoma	13	12	1	0	0	27.3(10-61)
Carcinoid	2	2	0	0	0	42.0(35-49)
Malignancies						36.5
Dysgerminoma	14	10	1	2	1	31.4(10-68)
Yolk sac tumor	21	11	4	4	2	24.3(9-50)
Mature cystic teratoma with malignant transformation	14	3	5	4	2	59.9(17-80)
Others						
Sarcoma	5	1	0	4	0	50.0(43-72)
Other malignancy	11	0	2	6	3	58.3(35-72)
Total (cases)	922	434	128	267	93	

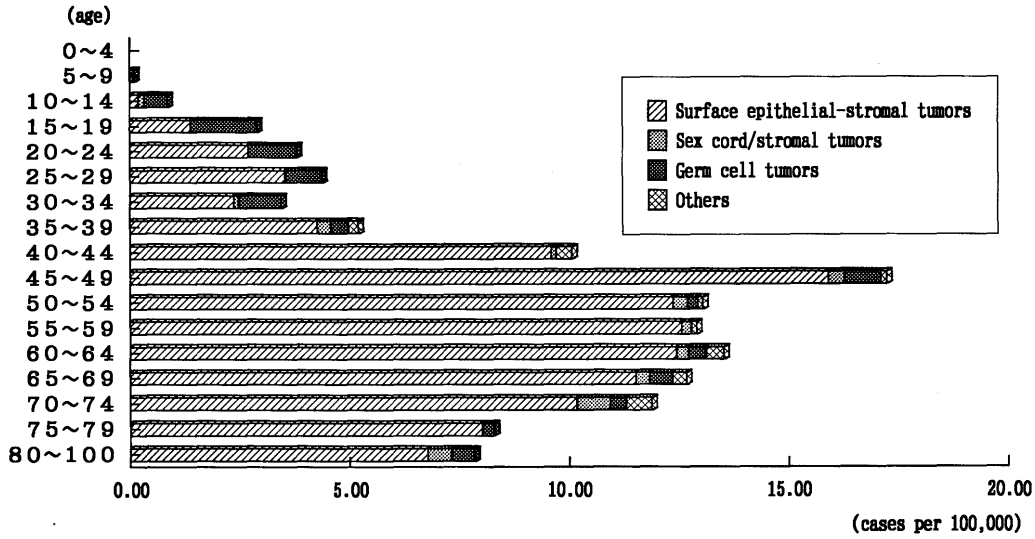

Fig. 1. Age specific incidence rate of ovarian cancer in Niigata Prefecture.

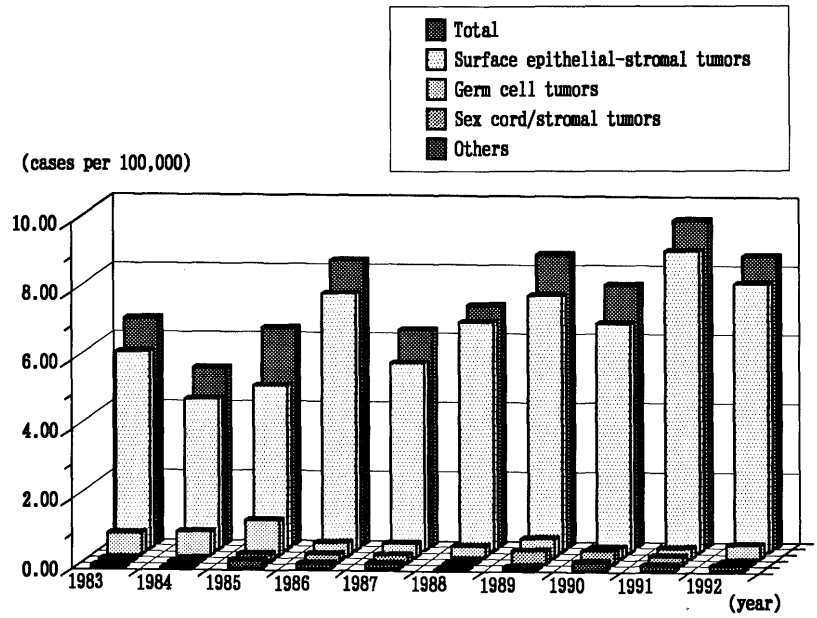

Fig. 2. Crude incidence rate of ovarian cancer in Niigata Prefecture.

Staging distribution and age

As shown in Table 2, in the borderline group, 114 cases were in Stage I, 4 in Stage II, 2 in Stage III, 3 in Stage IV and 3 in an uncertain stage. All of the advanced borderline tumors except for 2 borderline serous tumors were observed in postmenopause. In the malignant group, 320 were in Stage I, 124 in Stage II, 285 in Stage III, 90 in Stage IV and 1 in an uncertain stage, and advanced cancers over Stage II were seen over a wide range of age. Early ovarian cancer accounted for 92.1% of the borderline group which was observed in 39.9% of the malignancies. In undifferentiated carcinomas, malignant mesodermal mixed tumors and malignant serous tumors, the proportion of Stage II or more advanced cases was significantly higher than that of the other surface epithelial-stromal tumors. The average age of surface epithelial-stromal tumors was 58.8 years (12-91), with a peak at ages 45-49. Germ cell tumors showed

an average of 36.5 (9-80), with a peak at 15-19. Among 88 cases (9.5%) of less than 30 years of age, 76 cases (86.4%) were Stage I, including all of the 29 borderline cases and 47 of 59 malignant cases. The breakdown of 12 advanced ovarian cancer (13.6%) in patients less than 30 years of age was 4 cases with serous cystadenocarcinoma, 1 with mucinous cystadenocarcinoma, and 7 with a yolk sac tumor.

Age-specific incidence rate

As shown in Fig. 1, the age-specific incidence rate in patients in their 50s and 60s was almost stable in the surface epithelial-stromal tumors, and no significant difference was noticed in the sex cord/stromal, germ cell, and other tumors.

Crude incidence rate

Fig. 2 demonstrates the change in the crude incidence rate of ovarian cancer in Niigata Prefecture between 1983 and 1992. The surface epithelial-stromal tumors display a tendency to increase slightly year by year while the other groups are almost stable in number.

Age-adjusted incidence rate

The age-adjusted incidence rate in Niigata and Nagaoka, the cities that have the largest numbers of ovarian cancer registration in Niigata Prefecture, were 7.85 and 7.84 per 100,000 women, respectively (Table 3). The table is close to one another and also similar to the overall crude incidence rate in Niigata Prefecture. As high risk areas (=high SIR area, $p<0.01$), Irihirose Village and Aikawa Town were pointed out, while all major cities were excluded.

Area of the highest incidence rate

In Aikawa Town including an area with the highest incidence rate is located, out of 13 cases with ovarian cancer reported during the past 10 years, 10—comprising 6 with malignant serous tumors, 2 with undifferentiated carcinoma, 1 with malignant endometrioid tumors, and 1 with immature teratoma—were from the area, while surrounding villages had no cases. Aikawa Town showed an age-adjusted incidence rate of 226.6, which was the highest in Niigata Prefecture by the direct method, and 31 times higher than the prefectural rate. By the indirect method, also, a similar result of 198.7 was obtained. Of the 168 women over 30 years of age in the area with ovarian cancer screening, 81.4% of both them and their parents were born and raised in Aikawa Town or the area.

For controls, 3340 females in Niigata City aged over 30 with no abnormal gynecological findings nor surgical history were selected, and comparison was made as to the number of gravidity and parity, and age at menarche and natural menopause between the control group, 364 cases from our ovarian cancer registration and 817 cases aged over 30 in Aikawa Town. Gravidity and parity were significantly different between the contorol and ovarian cancer cases by the non parametric test ($p<0.01$) (Table 4). The breakdown of the 373 patients by past history was as follows: 47 cases with sterility (12.9%), 22 cases with ovarian tumor (6.0%), 9 with total hysterectomy (2.4%), 9 with tubal ligation (2.4%), 13 with endometrial cancer or mammary cancer or rectal cancer (3.6%) and 264 without any past medical history (72.5%).

DISCUSSION

As for incidence rate of ovarian cancer, Parazzini et al.[5] have reported that the age-adjusted incidence rate of ovarian cancer in 1978-1982 in Japan was 4.2 per 100,000 women, and that the number was increasing year after year. Tsukuma et al.[6] also predicted that the age-adjusted incidence rate of ovarian cancer in the year 2015 would reach 10.2 per 100,000 women. In Niigata Prefecture, however, our department's registration reveals that the age-adjusted incidence rate rises not suddenly, but rather gradually, as the number of the surface epithelial-stromal tumors in the malignant group increased slightly year after year. These different results can be attributable to incomplete registration rather than the high incidence rate of ovarian cancer in Niigata Prefecture. To further improve the accuracy of our measurement of the incidence rate, the cooperation of all registered institutions located in each area has been requested. Furthermore, laparotomies and histopathological examination are performed at registered institutions to confirm the diagnosis, and metastatic tumors are recorded separately from ovarian cancer development. Moreover, because of the progress in diagnostic imaging and greater attention given to ovarian cancer in other departments, patient referrals are made more frequently from major gynecological hospitals in Niigata Prefecture. The patients are now able to obtain a confirmed diagnosis, and can be treated and registered. For these reasons, the number of diagnostic oversights in ovarian cancer at local institutions is decreasing. However, in some cases at other departments, a confirmed diagnosis is still unattainable due to concurrent pathologies which prevent a laparo-

Table 3. Age-adjusted incidence rate of ovarian cancer in Niigata Prefecture (1983-1992)

City, town, village		Direct method	Indirect method	SIR	City, town, village		Direct method	Indirect method	SIR
Murakami	City	2.75	2.79	0.38	Teradomari	Town	5.56	5.51	0.75
Sekikawa	Village	7.02	6.25	0.85	Yamakoshi	Village	0.00	0.00	0.00
Arakawa	Village	1.72	1.76	0.24	Ojiya	City	5.79	5.73	0.78
Kanbayashi	Village	7.36	6.25	0.85	Kawaguchi	Town	2.25	2.86	0.39
Asahi	Village	2.23	2.57	0.35	Horinouchi	Town	7.71	7.57	1.03
Sanpoku	Town	4.16	3.45	0.47	Koide	Town	9.19	9.04	1.23
Awasima	Village	0.00	0.00	0.00	Yunotani	Village	3.45	3.16	0.43
Shibata	City	7.33	7.57	1.03	Hirogami	Village	2.40	1.98	0.27
Toyosaka	City	8.04	9.41	1.28	Sumon	Village	19.89	18.60	2.53
Toyoura	Town	0.00	0.00	0.00	Irihirose	Village	23.00	27.9	3.80
Yasuda	Town	7.12	7.64	1.04	Yuzawa	Town	4.47	4.41	0.60
Kyogase	Village	5.01	5.44	0.74	Shiozawa	Town	4.63	4.56	0.62
Suibara	Town	9.62	8.97	1.22	Muikamachi	Town	5.76	5.88	0.80
Sasagami	Village	5.54	5.51	0.75	Yamato	Town	11.10	10.88	1.48
Siunji	Town	9.60	10.00	1.36	Toukamachi	City	6.08	6.17	0.84
Seirou	Town	5.91	5.14	0.70	Kawanishi	Town	8.63	7.72	1.05
Kajikawa	Village	18.92	15.37	2.09	Tsunan	Town	6.76	7.50	1.02
Nakajou	Town	6.16	6.32	0.86	Nakazato	Village	2.37	2.57	0.35
Kurokawa	Village	2.59	3.08	0.42	Kashiwazaki	City	6.01	6.25	0.85
Niigata	City	7.85	8.45	1.15	Takayanagi	Town	0.00	0.00	0.00
Niitsu	City	9.68	10.07	1.37	Oguni	Town	8.90	7.72	1.05
Gosen	City	9.19	9.56	1.30	Kariwa	Village	8.14	6.98	0.95
Shirone	City	11.56	12.57	1.71	Nishiyama	Town	6.56	6.32	0.86
Kosudo	Town	13.31	13.23	1.80	Jouetsu	City	5.65	5.81	0.79
Muramatsu	Town	5.13	5.00	0.68	Arai	City	8.08	8.45	1.15
Yokogoshi	Village	10.84	11.91	1.62	Yasuzuka	Town	4.13	3.16	0.43
Kameda	Town	10.09	10.73	1.46	Uragawara	Village	10.55	11.54	1.57
Tsugawa	Town	9.56	10.59	1.44	Matsudai	Town	7.15	5.07	0.69
Kanose	Town	6.25	8.01	1.09	Matsunoyama	Town	6.01	6.69	0.91
Kamikawa	Village	3.91	2.94	0.40	Oosima	Village	0.00	0.00	0.00
Mikawa	Village	6.25	6.91	0.94	Maki	Village	6.08	3.97	0.54
Tsubame	City	9.93	10.81	1.47	Kakizaki	Town	7.03	6.98	0.95
Iwamuro	Village	5.27	9.85	1.34	Oogata	Town	3.60	3.82	0.52
Yahiko	Village	4.72	5.00	0.68	Kubiki	Village	0.00	0.00	0.00
Bunsui	Town	10.84	11.54	1.57	Yoshikawa	Town	2.58	2.57	0.35
Yoshida	Town	10.62	10.81	1.47	Myokoukougen	Town	0.00	0.00	0.00
Maki	Town	8.84	9.04	1.23	Myokou	Village	2.42	6.10	0.83
Nishikawa	Town	8.95	9.19	1.25	Nakagou	Village	3.78	3.23	0.44
Kurosaki	Town	7.36	8.67	1.18	Itakura	Town	5.13	6.03	0.82
Ajikata	Village	3.65	3.97	0.54	Kiyosato	Village	8.34	5.44	0.74
Katahigashi	Village	0.00	0.00	0.00	Sanwa	Village	6.25	8.31	1.13
Tsukigata	Village	0.00	0.00	0.00	Itoigawa	City	0.00	0.00	0.00
Nakanokuchi	Village	6.45	6.32	0.86	Nadachi	Town	2.63	4.41	0.60
Sanjo	City	9.38	10.22	1.39	Oumi	Town	1.49	1.54	0.21
Kamo	City	6.42	6.47	0.88	Nou	Town	9.08	8.31	1.13
Mitsuke	City	8.12	8.97	1.22	Ryotsu	City	7.90	7.79	1.06
Tagami	Town	13.15	14.12	1.92	Aikawa	Town	19.05	16.69	2.27
Shitada	Village	6.13	6.03	0.82	Sawada	Town	2.88	3.23	0.44
Sakae	Town	4.79	5.36	0.73	Kanai	Town	3.60	4.41	0.60
Nakanoshima	Town	2.39	3.60	0.49	Niibo	Village	6.18	9.41	1.28
Nagaoka	City	7.84	8.01	1.09	Hatano	Town	6.05	7.86	1.07
Tochio	City	9.09	8.75	1.19	Mano	Town	9.00	8.53	1.16
Koshiji	Town	7.11	6.84	0.93	Ogi	Town	15.25	15.51	2.11
Mishima	Town	3.15	2.72	0.37	Hamoti	Town	3.43	3.23	0.44
Yoita	Town	8.32	7.72	1.05	Akadomari	Village	10.10	4.70	0.64
Wajima	Village	9.96	10.00	1.36	an area in Aikawa	Town	226.60	198.73	27.02
Izumozaki	Town	7.23	6.98	0.95	Niigata	Prefecture	7.30		

SIR: standardized incidence rate

Table 4. Selected characteristics of ovarian cancer cases and females in Aikawa Town and control (1983-1991)

Characteristic	Cases (n=364)	Aikawa Town (n=817)	Control (n=3340)
Age at menarche			
≦10	1(0.2%)	3(0.4%)	29(0.9%)
11-12	52(14.3%)	68(8.3%)	809(24.2%)
13-14	140(38.5%)	308(37.7%)	1645(49.3%)
15-16	84(23.1%)	306(37.5%)	678(20.3%)
17-18	29(8.0%)	104(12.7%)	132(4.0%)
≧19	9(2.4%)	24(2.9%)	31(0.9%)
Unknown	49(13.5%)	4(0.5%)	16(0.4%)
Age at natural menopause			
≦39	6(1.7%)	11(1.4%)	10(0.3%)
40-44	17(4.7%)	39(4.8%)	36(1.1%)
45-49	67(18.4%)	208(25.5%)	252(7.5%)
50-54	85(23.4%)	301(36.8%)	501(15.0%)
≧55	13(3.6%)	34(4.2%)	47(1.4%)
Gravidity			
0	68(18.7%)	26(3.2%)	107(3.2%)
1	39(10.7%)	26(3.2%)	256(7.7%)
2	91(25.0%)	119(14.6%)	1250(37.4%)
3	60(16.5%)	203(24.8%)	912(27.3%)
4	43(11.8%)	182(22.3%)	487(14.6%)
5	31(8.5%)	118(14.4%)	219(6.6%)
≧6	32(8.8%)	139(17.0%)	95(2.8%)
Unknown	0	4(0.5%)	14(0.4%)
Parity			
0	83(22.8%)	30(3.7%)	168(5.0%)
1	49(13.5%)	49(6.0%)	385(11.5%)
2	125(34.3%)	257(31.5%)	1971(59.0%)
3	55(15.1%)	317(38.8%)	694(20.8%)
4	20(5.5%)	118(14.4%)	83(2.5%)
5	13(3.6%)	29(3.6%)	10(0.3%)
≧6	15(4.1%)	12(1.4%)	3(0.1%)
Unknown	4(1.1%)	5(0.6%)	26(0.8%)

tomy, suggesting that the actual incidence rate could be higher than our present estimate. We suspect that the actual incidence rate is not so very different between Niigata Prefecture and the Nordic countries. In the future, the incidence rate of ovarian cancer in Niigata Prefecture may rise gradually, if diagnostic imaging techniques for the detection of early ovarian cancer further improves and more women undergo examination.

A cancer screening requirement is recommended because of the high incidence rate of gastric, breast and uterine cancers[2] as well as the cost benefit of screening vs. treatment. The 10-year average of ovarian cancer in Niigata Prefecture (1983-1992) is 7.30 per 100,000 women, which is relatively low. Ovarian cancer screening in Niigata Prefecture, except for some high risk areas, is not beneficial in cost. Furthermore, as for age distribution, the ovarian cancer cases under 30 years of age occupies only about 10% of the whole, with those over 40 predominant. Therefore, ovarian cancer screening only for pre- or post-menopausal women is insufficient, as the age distribution of ovarian cancer is widespread.

Of the total of 922 cases of ovarian cancer registered between 1983-1992, we reexamined 443; 304 (81.2%) had continuous lower abdominal discomfort, and only 18 cases (4.1%) examined by chance were cancerous without symptoms. According to our department's investigation, the average period between the time when lower abdominal symptoms were noticed and the first consultation at a hospital was 5.4 months at Stage I, and 6.5 months at Stage II and above. Sixty-seven percent of patients at Stage I and 53% of those at Stage II and above consult a physician within three months, which means that the progress of the disease is associated with the malignancy and the histopathological types of ovarian cancer rather than the time of consultation. However, 13 of the 18 cases with no indicative symptoms were in Stage I, and 14 of them (77.7%) required and received a complete extraction. If ovarian cancer is detected at Stage I, the 5-year survival rate is over 90%. Thus, early detection of ovarian cancer is desirable. While diagnostic imaging by ultrasound sonography may be optimal, it requires considerable time to screen many examinees. Therfore, the best method would be for palpable tumors detectcd by vaginal examination to be further examined by diagnostic imaging.

With regard to cancer clusters, the majority of reports are concerned with leukemia, and few on ovarian cancer have been documented. Mahoney[7] reported 8 cases of ovarian cancers in one New York State area from 1978 to 1988, and drew conclusions of the existence of a cluster based on 7 cases discovered within 0.75 miles of each other, but did not state whether these women and their parents were born and raised in the area. In a city like Niigata, where approximately 10 ovarian cancer cases are diagnosed every year, a similar cluster might exist. SIR in 20 cities, 92 towns and villages in Niigata Prefecture indicates that a high risk area exists at a mountain site. In fact, the age-adjusted incidence rate in this area exceeds that of Northern Europe. Especially, an area in Aikawa Town is the highest risk area in Niigata Prefecture, where ovarian cancer was detected consecutively in 1991 and 1992. Therefore, exami-

nations in the high risk area are extremely important to clarify the etiology of ovarian cancer.

A variety of risk factors have been studied from an epidemiological point of view for a long time: dietary factors,[8] for example, fat, coffee, cigarette and galactose consumption, and gynecologic surgical history,[9] early menopause, estrogen replacement therapy, gravidity and parity, age at menarche and natural menopause,[10] and family history.[11] Most studies report that birth control pills and tubal ligation decrease the risk of ovarian cancer. Among 364 cases in our registration, no habitual consumption of coffee, alcohol, galactose, fat and pills was noticed. For gravidity and parity, the number of nullgravidity and nullparity cases with ovarian cancer was significantly higher than the controls. However, in them, male and tubal factors rather than ovarian dysfunction are the main causes of sterility. Furthermore, among 364 cases in our registration, 81.3% have experienced pregnancy and 77.2% have borne children. Therefore, we cannot conclude that sterility increases the risk of ovarian cancer, and since birth control pills are not so prevalent in Niigata Prefecture, we cannot examine whether they are able to reduce the risk of ovarian cancer. As for tubal ligation, only 2.4% of 364 patients with ovarian cancer underwent surgery. Generally, tubal ligation is not popular with healthy women, and is carried out for purposes of contraception. In terms of age-specific incidences of ovarian cancer, it is overwhelmingly high around menopause; however, some histological types in germ cell tumors develop in young females, and some cases occur a few decades after menopause.

With regard to carcinogenic risk factors, most reports describe a case-control study. Therefore, the evaluation of risk factors differs with the selection of the control group, and the cause-effect relationship for ovarian cancer can not be supported by these studies, which lack agreement in their conclusion. With this view point, it would be impossible to clarify the true causes. Comparison of 3340 controls with 817 females in Aikawa Town showed no significant difference in mean age at menarche and menopause, gravidity or parity. In the area in Aikawa Town, no female had any unusual diet, or consumption of alcohol, tabacco, coffee or pills. In conclusion, for the early detection of ovarian cancer, it seems more practical and economical to search for potential causes by improving the registration accuracy and thus obtain a rate closest to the actual rate, and so discover any clusters. For a geographical cluster study, districts with little change in population are preferable. From the results of the questionnaire we gave to 168 women, 81.4% of the respondents and their parents were originally from the area or Aikawa Town. At the present time, however, it is not clear if these findings are caused by genetic or environment factors. As for genetic factors, we are analyzing the cause-effect relationship from the viewpoint of multi-generational incidence.

Though surface epithelial-stromal tumors are thought to stem from their inclusion cysts, its carcinogenesis is still undefined. Few reports have documented the part of the ovary at which the ovarian cancer originates, malignant changes in ovarian tumor, or the time period between the first and advanced stages. However, we are hopeful that we can shed light on these questions by conducting more frequent medical screening in high risk districts.

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