Ovarian cancer incidence and survival by histologic type in Osaka, Japan

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The incidence of ovarian cancer among Japanese has increased since the 1970s. Histologic diversity is a characteristic of this cancer. However, there has been no population-based study made on the incidence and survival by histologic type. Osaka Cancer Registry's data was used for incidence and survival analyses of ovarian cancer by histologic type in this study. Seven thousand one hundred sixty-seven incident cases were registered during the period 1975 to 1998. According to the IARC's histologic classification, types of ovarian cancer were classified into five categories. Survival analysis was restricted to the reported 2431 cases who lived in Osaka Prefecture (except for Osaka City) and were diagnosed in 1975–1994, since active follow-up data on vital status 5 years after the diagnosis were available. The age-standardized incidence rate of ovarian cancer increased from 4.0 to 5.4 per 100 000 women (standard: world population) in Osaka during the period 1975–1998. Carcinoma, the major histologic category, also increased (from 3.4 to 4.8 per 100 000 women), while sex cord-stromal tumors decreased after 1980 and germ cell tumors remained stable. The 5-year relative survival was 36.4% for ovarian cancer patients diagnosed in 1975–1994. The survival for carcinoma was 38.3%, which was lower than that in sex cord-stromal tumors or germ cell tumors (55.3% and 58.6%, respectively). The increase in the incidence of ovarian cancer was caused by the increase in carcinoma. The relative 5-year survival of ovarian cancer improved over the period, but was different by histologic type. (Cancer Sci 2003; 94: 292–296)

Cancer of the ovary is responsible for 3.4–3.9% of total cancer deaths among Japanese women in 1997–2001. The incidence rate of ovarian cancer in Japan is relatively low as compared with other developed countries: age-standardized incidence rates are less than 7.0 per 100 000 (standard: world population) in Japan, in contrast with a figure of more than 10.0 per 100 000 population in Nordic nations, the United Kingdom, and North America.[1)] There might be a genetic factor that partially protects against the development of ovarian cancer, because racial variation in the incidence of ovarian cancer has already been found in the United States: US-born Japanese had lower rates than white women.[2, 3)]

Trends in the mortality and incidence of ovarian cancer among Japanese however, have been increasing since the 1950s and 1970s, respectively.[4)] Such an increasing trend in the incidence has also been found in England and Wales,[5, 6)] but not in other European countries.[7, 8)] The effect of age on the incidence of ovarian cancer agreed well with that found in previous studies in Japan: the rates increased steadily in older age groups.[4, 5)] Histologic diversity is, however, characteristic of this cancer and a population-based study with respect to histologic type of ovarian cancer has never been reported in Japan. In this paper we have tried to clarify the analysis of incidence and survival of ovarian cancer by histologic type, using the Osaka Cancer Registry's data.

Materials and Methods

Data sources. Individual incidence data on 7167 ovarian cancer cases diagnosed in 1975–1998 were retrieved from the Osaka Cancer Registry's database (WHO: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, code C56). According to the ideas presented in the histologic groups for comparative studies by IARC, histologic types of ovarian cancer were classified into five categories: carcinoma derived from coelomic epithelium, sex cord-stromal tumors, germ cell tumors, other specified cancers and unspecified cancer (Table 1). The proportion of cases registered by death certificate only (DCO) was substantial (25.6–33.5%) in 1975–1998, as was the proportion of cases categorized as unspecified cancer (30.3–46.4%) (Table 2). In order to calculate histologic group-specific incidence rate, subjects in this category were reallocated into other histologic categories (i.e., carcinoma, sex cord-stromal tumors, germ cell tumors and other specified cancers) according to the distributions by age and calendar year at diagnosis.

To obtain information on vital status of registered cases, Osaka Cancer Registry has used the following three steps: 1) collation with annual cancer death file, 2) collation with annual death certificate file in Osaka, and 3) confirmation of the cases' living status by referring to registers in local municipality offices of inhabitants 5 years after the diagnosis. The final step had, however, been conducted only for those residing in Osaka Prefecture (excluding Osaka City) in 1975–1992. Therefore, subjects for survival analysis were restricted to 2431 cases who lived in Osaka Prefecture (except for Osaka City), who were diagnosed in 1975–1994 and had active follow-up information. In addition they met the following criteria:

1) In the case of multiple tumors, only the first was included.
2) Cases registered by DCO were excluded.

The proportion of the DCOs for ovarian cancer was 29.8% in 1975–1994.

The proportion of cases lost to follow-up was 0% 5 years after the diagnosis.

Statistical analysis. Age-standardized incidence rates were calculated by the direct method using the world standard population as the standard. Cumulative observed survival was estimated using the Kaplan-Meier method according to histologic type. Events in this method were defined as dying of all causes. The log rank test was used as a statistical test on the difference between two cumulative observed survival curves. To control differences in age distribution, furthermore, the survival by histologic type was analyzed using the Cox proportional hazards model after adjustment for age at diagnosis. Relative survival was also calculated to adjust the difference in the probability of dying of causes other than cancer among subjects. Relative survival is calculated as the ratio of observed survival to expected survival, which was estimated using the survival probability in the general population of Japan of simi-

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Table 1. IARC's histologic classification in ovarian cancer

1	Carcinoma
1.1	Serous carcinoma
1.2	Mucinous carcinoma
1.3	Endometrioid carcinoma
1.4	Clear cell carcinoma
1.5	Adenocarcinoma NOS (not otherwise specified)
1.6	Other specified carcinoma
1.7	Unspecified carcinoma
2	Sex cord-stromal tumors
3	Germ cell tumors
4	Other specified cancers (include malignant Brenner tumor, mullerian mixed tumor, carcinosarcoma)
5	Unspecified cancer

lar subjects with respect to sex, age, and calendar year of observation. The Ederer method was employed.[9] Differences were considered as statistically significant if P values were less than 0.05 by two-sided test. The statistical package software SPSS (version 10) was used for statistical analysis.

Results

In Figs. 1 and 2, trends in crude and age-standardized incidence rates of ovarian cancer in Osaka, Japan from 1975 to 1998 are illustrated by histologic type. In ovarian cancer, both rates have been steadily increasing since 1975. The crude incidence rate has increased twofold in 1975–1998 (from 4.2 to 8.4 per 100 000 women), while the age-standardized incidence rate has increased less than twofold (from 4.0 to 5.4 per 100 000 women).

Trends differ according to histologic type. For carcinoma, the crude incidence rate showed an upward trend from 1975: it increased approximately twofold in 1975–1998 (from 3.6 to 7.7 per 100 000 women). The age-standardized incidence rate increased less than twofold (from 3.4 to 4.8 per 100 000 women). When we examine the time-trends of carcinoma by the 2 main subcategories: serous and mucinous, the increase was more striking for serous carcinoma than mucinous carcinoma. For sex cord-stromal tumors, both rates steadily decreased from 1980: the crude incidence rate decreased from 0.2 to 0.06 per 100 000 women, while the age-standardized incidence rate decreased from 0.1 to 0.04 per 100 000 women in 1980–1998. For germ cell tumors, both rates remained stable during 1975–1998.

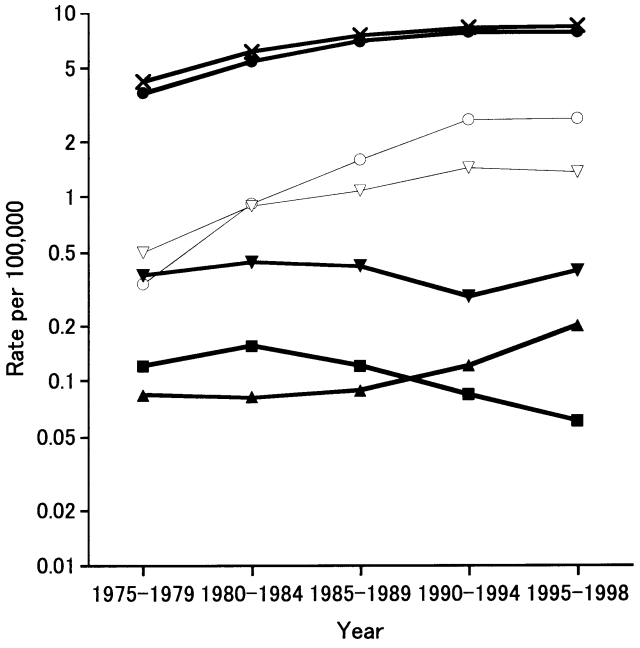

Fig. 1. Trends in crude incidence rates of ovarian cancer by histologic types in Osaka, Japan. The rates of ovarian cancer (×), carcinoma (●), other specified cancers (▲), serous carcinoma (○) and mucinous carcinoma (▽) steadily increased during 1975–1998, whereas that of sex cord-stromal tumors decreased (■). For germ cell tumors (▼), the rate remained stable.

Based on accumulated data in 1975–1998, age-specific incidence rates of ovarian cancer are presented in Fig. 3 according to histologic type. Carcinoma was rare in girls and young women. The incidence rate rose rapidly with increasing age until 45–54 years, after which it plateaued. Serous carcinoma showed higher rates than mucinous carcinoma among those aged 35 years and over, and *vice versa* among those aged under 35. The incidence rate of sex cord-stromal tumors rose with age, and increased approximately threefold in middle age (from 0.04 to 0.1 per 100 000 women). The incidence rate of germ cell tumors peaked at 15–24 years, and leveled off after middle age. For sex cord-stromal tumors and germ cell tumors, the annual incidence rate did not exceed one per 100 000 at any age.

Table 2. Distribution of histologic type and proportions of death certificate only cases in Osaka, Japan

	1975–1979		1980–1984		1985–1989		1990–1994		1995–1998	
	No.	%	No.	%	No.	%	No.	%	No.	%
Carcinoma	405	45.8	808	61.6	1011	61.3	1109	60.9	906	60.3
Serous carcinoma	39	4.4	138	10.5	240	14.6	382	21.0	312	20.8
Mucinous carcinoma	52	5.9	134	10.2	160	9.7	209	11.5	171	11.4
Endometrioid carcinoma	7	0.8	25	1.9	56	3.4	86	4.7	80	5.3
Clear cell carcinoma	9	1.0	39	3.0	62	3.8	103	5.7	104	6.9
Adenocarcinoma NOS	275	31.1	430	32.8	453	27.5	288	15.8	218	14.5
Other specified carcinoma	15	1.7	23	1.8	27	1.6	23	1.3	11	0.7
Unspecified carcinoma	8	0.9	19	1.4	13	0.8	18	1.0	10	0.7
Sex cord-stromal tumors	13	1.5	21	1.6	18	1.1	11	0.6	5	0.3
Germ cell tumors	47	5.3	73	5.6	65	3.9	48	2.6	58	3.9
Other specified cancers	9	1.0	12	0.9	12	0.7	13	0.7	24	1.6
Unspecified cancer	411	46.4	397	30.3	542	32.9	639	35.1	510	33.9
Unspecified morphology	117	13.2	55	4.2	38	2.3	37	2.0	21	1.4
No microscopic verification	294	33.2	342	26.1	504	30.6	602	33.1	489	32.5
Ovarian cancer	885	100.0	1311	100.0	1648	100.0	1820	100.0	1503	100.0
Death certificate only (DCO)	278	31.4	336	25.6	462	28.0	610	33.5	485	32.3

Fig. 4 shows 5-year cumulative survival of ovarian cancer by histologic type. It was 35.2% for subjects diagnosed with ovarian cancer during 1975–1994. The survival for carcinoma was estimated as 37.0%, which was lower than that in sex cord-stromal tumors and germ cell tumors (their 5-year cumulative survivals were 53.9% and 58.3%, respectively). Mucinous carcinoma showed a better 5-year cumulative survival than serous carcinoma (59.0% and 38.5%, log rank test: $P<0.01$). The cumulative survival curves were significantly different between carcinoma and germ cell tumors ($P<0.01$). As compared with that for carcinoma, age-adjusted hazard rate ratios were 0.8 for germ cell tumors (95% confidence interval (CI) 0.6–1.1), and 1.4 for sex cord-stromal tumors (95% CI 0.8–2.4), although the differences were not statistically significant.

Relative 5-year survival is presented in Table 3 according to histologic type and calendar year of diagnosis. In 1975–1994, relative 5-year survival was 36.4% for ovarian cancer, while carcinoma, sex cord-stromal tumors, and germ cell tumors showed a better survival than ovarian cancer. Comparing the periods 1975–1984 and 1985–1994, relative 5-year survivals increased appreciably for ovarian cancer (from 29.1% to 40.9%, $P<0.01$), carcinoma (from 30.9% to 42.1%, $P<0.01$), germ cell tumors (from 46.9% to 69.8%, $P<0.01$), and mucinous carcinoma (from 51.2% to 66.3%, $P<0.05$).

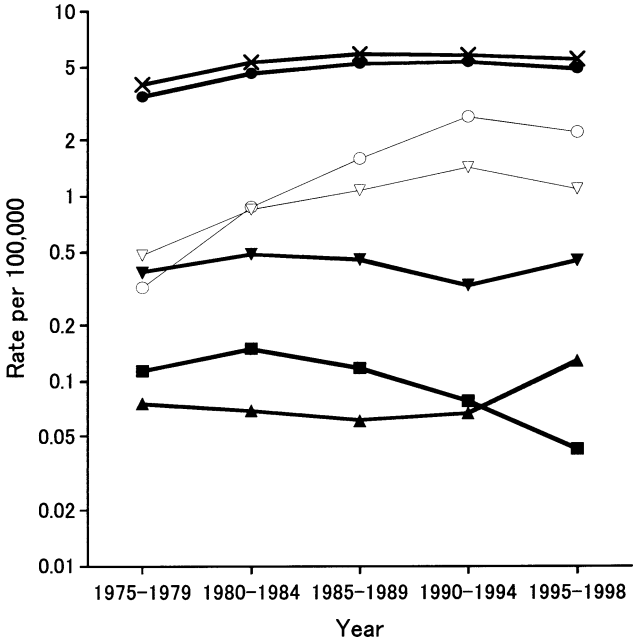

Fig. 2. Trends in age-standardized incidence rates of ovarian cancer by histologic type in Osaka, Japan (standard population: world standard population). The rates of ovarian cancer (×), carcinoma (●), other specified cancers (▲), serous carcinoma (○) and mucinous carcinoma (▽) steadily increased during 1975–1998, whereas that of sex cord-stromal tumors decreased (■). For germ cell tumors (▼), the rate remained stable.

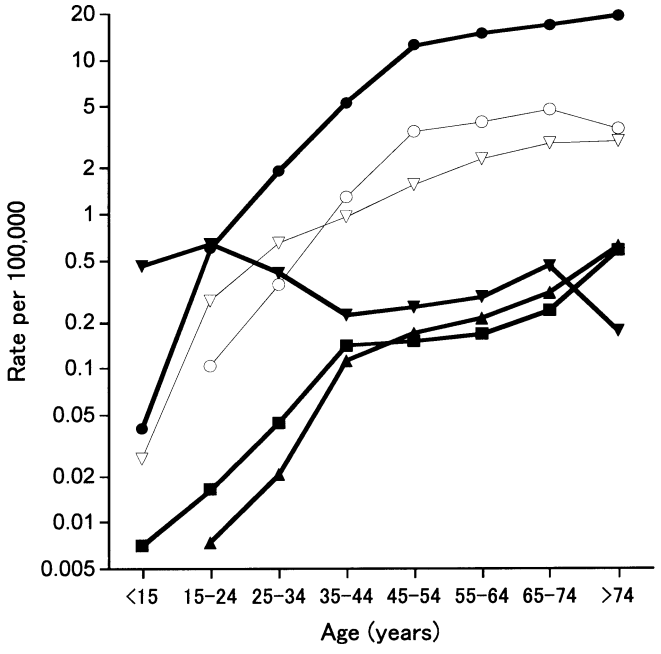

Fig. 3. Age-specific incidence rates of ovarian cancer by histologic type in Osaka, Japan, 1975–1998. The rates of carcinoma (●), sex cord-stromal tumors (■), other specified cancers (▲), serous carcinoma (○) and mucinous carcinoma (▽) rose with increasing age. The rate of germ cell tumors (▼) peaked at 15–24 years, and leveled off after middle age.

Discussion

The age-standardized incidence rate of ovarian cancer increased approximately 1.3-fold (from 4.0 to 5.4 per 100 000 women) in Osaka, Japan from 1975 to1998, which almost matched the mortality trends of ovarian cancer in Osaka.[10] Tamakoshi *et al.*[4] have reported a rise in incidence in Japan from 1975 to 1993. Our present study showed that there has been a rising pattern only in the incidence rate of carcinoma (from 3.4 to 4.8 per 100 000 women). This result suggests that, as both incidence and mortality of ovarian cancer have increased and the incidence of carcinoma is closely approximated by the incidence of ovarian cancer as a whole, the observed changes in incidence of ovarian cancer were caused by the increased rate of carcinoma.

As for relative frequency of ovarian cancer by histologic type in 1988–1992, the proportion of carcinoma in Japan was much less than that in the US[1] (60.9% vs. 88.3%), while proportions of germ cell tumors and unspecified cancer in Japan were more than those in the US (3.3% vs. 2.3% and 34.3% vs.

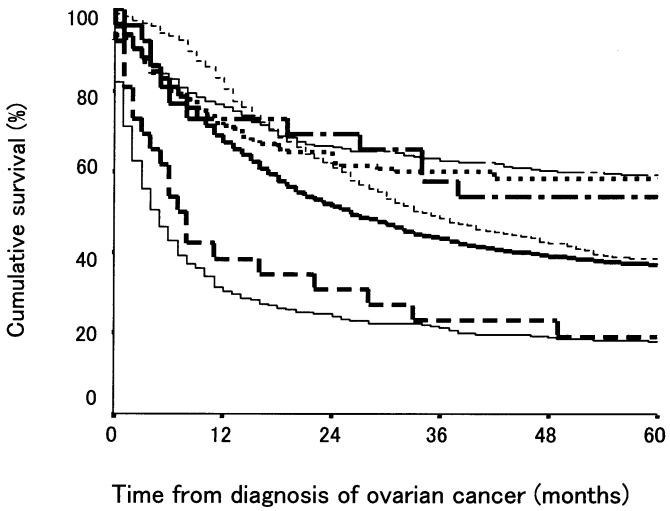

Fig. 4. Kaplan-Meier estimates for cumulative survival of ovarian cancer by histologic type in Osaka, Japan. The 5-year survival for carcinoma (——) was lower than that in sex cord-stromal tumors (—·—), germ cell tumors (·····), serous carcinoma (——) and mucinous carcinoma (——), but not other specified cancers (----) and unspecified cancer (——).

Table 3. Time-trends of relative 5-year survival of ovarian cancer by histologic type in Osaka, Japan

	1975–1984			1985–1994			1975–1994		
	No.	5-year survival	Standard error	No.	5-year survival	Standard error	No.	5-year survival	Standard error
Carcinoma	645	30.9	1.9	1203	42.1	1.5	1848	38.3	1.2
Serous carcinoma	93	39.1	5.3	367	39.6	2.6	460	39.5	2.3
Mucinous carcinoma	102	51.2	5.3	201	66.3	3.5	303	61.3	3.0
Sex cord-stromal tumors	15	62.0	13.1	12	46.3	15.3	27	55.3	10.0
Germ cell tumors	70	46.9	6.2	72	69.8	3.5	142	58.6	4.2
Other specified cancers	13	23.6	12.0	13	15.8	10.2	26	19.7	7.9
Unspecified cancer	194	14.2	2.7	194	24.1	3.3	388	19.1	2.1
Ovarian cancer	937	29.1	1.6	1494	40.9	1.3	2431	36.4	1.0

5.6%). As the proportion of carcinoma among Japanese in the US was similar to that among Americans, the proportion in Japan might be expected to approximate to that in the US in the future.

Through extensive research into the etiology of ovarian cancer, two factors have been suggested to influence the time trends: oral contraceptives (OC) and parity. These factors may reduce the likelihood of ovarian cancer through a decreased number of ovulatory cycles (ovulation hypothesis), and protect women from malignancy by suppressing secretion of pituitary gonadotropins (gonadotropin hypothesis). A protective effect of OCs against the risk for ovarian cancer has been demonstrated.[11–17] Hankinson *et al.*[13] reported that a pooled relative risk of 0.64 was associated with ever-use of OCs, indicating a 36% reduction in ovarian cancer risk. In many Western and other industrialized countries, OCs were widely available, but their use in Japan was minimal. In England and Wales, at young ages, incidence of ovarian cancer has declined in recently years, and this coincided with the introduction and increase in the use of OCs. Thus different patterns of use of OCs may account for the contrasting incidence trends between countries.

The relative risk of ovarian cancer has been reported to decline with increased family size.[6, 14–17] Parity has been investigated by dos Santos Silva *et al.*[6] as a possible determiner of trends in ovarian cancer. They reported that marked declines in fertility were paralleled by the increase in incidence of ovarian cancer for successive cohorts born before 1900. In Japan, birth rate has gradually decreased since 1920, and the increase in incidence of ovarian cancer might in part be attributed to declining parity.

Former reports suggest that prognostic factors predicting survival are: older age, the classification of the International Federation of Gynecology and Obstetrics (FIGO) at initial diagnosis, histologic type, histologic grades and diameter of residual tumor.[18–22] In our results, the 5-year cumulative survivals for carcinoma and germ cell tumors were estimated as 37.0% and 58.3% respectively, and cumulative survival curves were significantly different between these two. In the stage distribution, the proportion of the distant stage for carcinoma (26.6%) was more than that for germ cell tumors (16.9%) although proportions of the unknown stage for carcinoma and germ cell tumors were 7.0% and 16.2%, respectively. It is likely that the lower 5-year cumulative survival was greater in cases with the distant stage at initial diagnosis. On the other hand, age at diagnosis was found to be a strong confounding factor in differences in 5-year cumulative survivals between carcinoma and sex cord-stromal tumors, because the age-adjusted hazard ratio for sex cord-stromal tumors was more than 1.0 as compared with that for carcinoma.

In 1975–1994, relative 5-year survival for ovarian cancer was 43.5% in the US,[23] while it was 36.4% in Osaka, Japan. Age and histological distributions of ovarian cancer cases were somewhat different between the US and Osaka.[1] The proportion of patients aged 60 years and over was 63.0% for the US whites, while it was 41.5% for Osaka Japanese. Remarkably, the frequencies of serous, endometrioid, and mucinous carcinoma were 3.7:1.1:1.0 for the US whites, but 1.6:0.3:1.0 for Osaka Japanese. The proportion of the localized cases was, however, not so different (26.4% in the US[23] vs. 28.9% in Osaka, 1975–1994). In each histologic type except for unspecified cancer, relative 5-year survival in the US was also more than that in Japan: 42.4% vs. 38.3% for carcinoma, 72.9% vs. 55.3% for sex cord-stromal tumors, 83.7% vs. 58.6% for germ cell tumors and 26.0% vs. 19.7% for other specified cancers. Relative 5-year survival for unspecified cancer in Osaka was estimated as less than 20.0%, similar to that in the US. We consider that there was a much greater difference in relative 5-year survival according histologic type between the US and Japan, because 388 subjects in our study (16.0%) were defined as unspecified cancer with/without pathological data, and relative 5-year survival for that category was estimated as only 19.1%. Although the reasons for such survival differences between the US and Osaka were not clear, remarkable difference of survival for germ cell tumors might be explained in part by inappropriate use of effective chemotherapy in Japan, as suggested in the survival analysis on testicular cancer in Osaka.[24]

In conclusion, the age-adjusted incidence rate of ovarian cancer tended to increase in Osaka, Japan during the period 1975–1998, and the increase was explained mainly by the increase in carcinoma of the ovary. The relative 5-year survival of ovarian cancer improved as a whole, but was different by histologic type. Poorer prognosis was also suggested in Japanese ovarian cancer patients than the US cases. Further epidemiologic research on histologic types of ovarian cancer is needed, concerning the effects of the OCs and fertility on incidence of cancer, and the effects of variables (including FIGO stages at initial diagnosis) on survival.

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