Tohoku J. Exp. Med., 2008, **216**, 297-307

Smoking, Earlier Menarche and Low Parity as Independent Risk Factors for Gynecologic Cancers in Japanese: A Case-Control Study

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During recent decades, the incidence of gynecologic cancers, i.e., cancers of the cervix, endometrium and ovary, has increased in Japan. However, risk factors of gynecologic cancers have not been fully clarified in Japan. To investigate common and site-specific risk factors among gynecologic cancers, we conducted a hospital-based case-control study. The cases, i.e., 151 cervical, 103 endometrial and 141 ovarian cancer cases and the controls (n = 2016) were selected from female patients aged 30 and over, who were admitted to a single hospital in Miyagi Prefecture from 1997 to 2003. Information on reproductive factors, exogenous hormone use, and lifestyles including smoking was collected using a self-administered questionnaire. Smoking was significantly associated with an increased risk of cervical cancer. A dose-response relationship with the number of cigarettes per day was also observed (p for trend = 0.004). Older age at menarche was associated with a decreased risk of endometrial and ovarian cancers. For these cancers, the decreased risk was detected with increasing parity number (endometrium, p for trend = 0.0001; ovary, p = 0.0002). There was no significant association between exogenous hormone use and gynecologic cancer risk. The results indicate that smoking is a major risk factor of cervical cancer. In addition, hormonal factors, which are related to early onset of menarche and low parity, are common risk factors for endometrial and ovarian cancers. The increase in female smokers and the decrease in fertility rate may contribute to the increase in gynecologic cancer incidence in Japan. ——— cervical cancer; endometrial cancer; ovarian cancer; reproductive factors; smoking.
Tohoku J. Exp. Med., 2008, **216** (4), 297-307.
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Received September 12, 2008; revision accepted for publication October 22, 2008.
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Over the past several decades, the trends in the incidence of gynecologic cancers have largely changed in Japan. Although Japan is known to be a country of lower risk for cancers of the endometrium and ovary compared with Western countries, the ovarian cancer incidence rate doubled and endometrial cancer incidence rate increased threefold during 1975-2000 (Marugame et al. 2006). Cervical cancer incidence decreased by half during this period, however an increasing tendency in the incidence appeared in recent years (Marugame et al. 2006). Although such trends in the site-specific cancer incidence might have been affected by the improvement of diagnostic procedures and the spread of cancer screening, the distributions of the risk factors in the population, i.e., the changes in lifestyle and behavior in Japanese women, may have larger impacts on the incidence. Previous epidemiologic studies, which have been mainly conducted in Western countries, have shown that reproductive factors and exogenous hormone use may be associated with the risk of endometrial and ovarian cancers (Whittemore et al. 1992; Kelsey et al. 1994; McPherson et al. 1996; Persson 2000). For cervical cancer, human papillomavirus (HPV) infection and lifestyles such as smoking have been described as risk factors (Winkelstein 1990; Zur Hausen 1991; Schiffman et al. 1995). However, it is uncertain whether epidemiologic findings obtained in Western countries may be generalized to the Japanese population. Few epidemiologic studies have been conducted in Japan (Inoue et al. 1994; Hirose et al. 1996; Mori et al. 1998; Hirose et al. 1999; Okamura et al. 2006). Thus, risk factors of gynecologic cancers have not been fully clarified in Japanese population.

To elucidate risk factors of gynecologic cancers, i.e., cancers of the cervix, endometrium and ovary, we carried out a hospital-based case-control study. Since a common protocol is used for collecting data and analyses on each cancer, this case-control study enables us to compare epidemiologic characteristics among gynecologic cancers. We focused on the effects of lifestyles including smoking and alcohol drinking, reproductive factors and exogenous hormone use and assessed common and site-specific risk factors among gynecologic cancers.

Material and Methods

Study design and data collection procedure

In January 1997, we began a questionnaire survey in connection with the present study. Information on lifestyle has been collected from all patients on their first admission to the Miyagi Cancer Center Hospital (MCCH), using a self-administered questionnaire. The questionnaire is distributed to patients on the day of reservation for first admission, i.e., 10-15 days before admission, and collected on the day of actual admission by nurses. The MCCH is located in Natori City, situated in the southern part of Miyagi Prefecture, and functions as a hospital both for cancer and benign disease. Details of the questionnaire survey have already been described elsewhere (Minami et al. 2003; Minami et al. 2008).

The questionnaire covers items on demographic characteristics, personal and family histories of cancer and other disease, general lifestyles before the development of current symptoms including histories of smoking and alcohol drinking, marital status, reproductive history and exogenous hormone use. Items related to the referral base (with and without referral, from screening, other) were also included. The reproductive history included age at menarche, history of pregnancy, age at first birth and parity number. Regarding exogenous hormone use, patients were simply asked whether they had previously used oral contraceptives (OCs) and other exogenous female hormones. Information on HPV infection was not available in this study. Between January 1997 and December 2003, the questionnaire was given to 12,929 first admitted patients and 11,682 responded (response rate 90.4%). This study was approved by the review board of the Miyagi Cancer Center.

Study subjects

Cases and controls were selected from female patients aged 30 and over who responded to the above questionnaire survey. To identify incident cases of cancer, a list of the patients was linked with the hospital-based cancer registry files. The registry records all cancer cases confirmed by clinical, cytological and/or histopathological examination at the MCCH. Patients with carcinoma in situ were excluded in the present study. Consequently, 151 cervical, 103 endometrial, and 141 ovarian cancer patients were identified as cases.

Controls were selected from non-cancer patients

without a past history of cancer. Patients with benign tumors have been classified as non-cancer patients in the present study. Accordingly, 2016 non-cancer patients were identified as controls. The diagnoses among controls were as follows: benign tumor 1112 (55.2%), cardiovascular disease 110 (5.4%), digestive tract disease 288 (14.3%), respiratory tract disease 93 (4.6%), urologic-gynecologic disease 131 (6.5%), other benign disease 161 (8.0%), and no abnormal findings 121 (6.0%). The sites of benign tumors were digestive tract 393, gynecologic organ 321, urologic organ 15, breast 15, bone or connective tissue 272, and other 96. Detailed diagnoses among benign tumors in gynecologic organ were uterine myoma 164, cervical dysplasia 17, endometrial hyperplasia 2, benign ovarian tumor 131 and other 7.

The response rate for each cancer site was 92.1% for cervix, 88.8% for endometrium, and 94.6% for ovary, and that for control group was 90.5%.

Statistical analysis

For each site, odds ratios (ORs) and 95% confidence intervals (95% CIs) for active and passive smoking, alcohol drinking, marital status, reproductive factor and exogenous hormone use were estimated with adjustment for age, year of survey, occupation and other related factors including family history of cancer in parents and siblings, using an unconditional logistic regression model (Breslow and Day 1980). Regarding active smoking, ORs and 95% CIs for age at the start of smoking and the number of cigarettes per day were also estimated. Data on age at natural menopause were incomplete in our database, and therefore not included in the analysis. The cut-off points for reproductive factors were arbitrarily determined, based on the distributions in control subjects.

Results

Table 1 shows distributions of background characteristics in study subjects. Endometrial cancer cases were older than cervical and ovarian cancer cases. Some differences in the distribution of area of residence were observed between cases and controls. About 80% of cases were admitted with referral. Six percent of cervical cancer cases were derived from screening. Some differences in occupational history were also observed between cases and controls. In endometrial cancer cases, for example, the frequency of professional or clerical workers was high.

Table 2 shows ORs and 95% CIs of active and passive smoking and alcohol drinking according to site. The ORs were adjusted for age, year of survey, reproductive factors and other confounding variables, some of which were selected based on the characteristics among the study subjects shown in Table 1. Active smoking was significantly associated with an increased risk of cervical cancer. A significant dose-response relationship between the number of cigarettes per day and OR was also observed (p for trend = 0.004). In women starting smoking before aged 20, high OR for cervical cancer was observed (OR = 3.20). For endometrial cancer, a significant decreased risk associated with passive smoking was found. The small OR was also observed for active smoking (OR = 0.54), however statistically insignificant. Alcohol drinking was significantly associated with a decreased risk of ovarian cancer.

Table 3 shows ORs and 95% CIs of marital status and reproductive factors according to site. The ORs were appropriately adjusted for confounding variables. Unmarried status was significantly associated with an increased risk of cancer in all sites. On the other hand, the analysis limited to married women showed different associations with age at first marriage among the sites; with increasing age at first marriage, cervical cancer risk decreased and risk of endometrial and ovarian cancers increased. Age at menarche was also differently associated with cancer risk among sites; older age at menarche was associated with a decreased risk of endometrial and ovarian cancers (endometrium p for trend = 0.06, ovary p for trend = 0.003). In cervical cancer, no association with age at menarche was observed. Regarding parity history, an elevated risk for nulliparity was consistently observed for all sites. For endometrial and ovarian cancers, a significant decreased risk associated with increasing parity number was observed (endometrium p for trend = 0.0001, ovary p for trend = 0.0002). A similar trend was also observed for cervical cancer, however marginally significant (p for trend = 0.07).

Table 4 shows ORs and 95% CIs of exogenous hormone use. Although no significant association was observed between exogenous hor-

Table 1. Distribution of characteristics in cancer cases and controls.

Category	Controls	Cases		
		Cervix	Endometrium	Ovary
	n = 2016	n = 151	n = 103	n = 141
Age group (years old)				
30-39	170	30	3	13
40-49	409	32	13	32
50-59	429	23	42	44
60-69	515	29	24	30
70 ≤	493	37	21	22
Average age ± SD	58.7 ± 13.6	56.1 ± 16.4	59.4 ± 10.5	55.6 ± 12.8
Area of residence (%)				
Southern Miyagi Pref.	90.6	72.2	83.5	85.8
Other	9.4	27.8	16.5	14.2
Referral base (%)				
Without referral	19.4	8.0	10.7	12.8
With referral	56.5	79.5	80.6	79.4
From screening	16.4	6.0	2.9	1.4
Other	7.7	6.5	5.8	6.4
Occupation (%)				
Professional	6.4	6.0	9.7	3.6
Clerical	16.2	16.6	18.5	17.0
Agricultural	10.9	9.9	7.8	7.8
Industrial	13.4	10.6	16.5	10.6
Other	53.1	56.9	47.6	61.0
Family history of uterine cancer (%)[a]				
Absent	96.8	96.0	97.1	99.3
Present	3.2	4.0	2.9	0.7
Family history of ovarian cancer (%)				
Absent	99.6	99.3	100.0	98.6
Present	0.4	0.7	0	1.4

[a]Uterine cancer includes cancers of all parts in uterus.

mone use and gynecologic cancer risk, the OR for OC use was extremely small in ovarian cancer (OR = 0.46).

Discussion

The present study revealed epidemiologic characteristics of gynecologic cancers, i.e. cervical, endometrial and ovarian cancers in Japanese population. Risk factors for each gynecologic cancer were identified, and similarities and differences in risk factors among the sites were clarified.

Before interpreting the results, methodological problems merit consideration. In hospital-based case-control studies, some methodological problems including both limitations and advan-

TABLE 2. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of smoking habit and alcohol drinking for cervical, endometrial and ovarian cancer

Variable	Controls (n = 2016)	Cervix (n = 151)			Endometrium (n = 103)			Ovary (n = 141)		
		No. of cases	OR	95% CI	No. of cases	OR	95% CI	No. of cases	OR	95% CI
Smoking[a]										
Never	1629	93	1.00		87	1.00		107	1.00	
Ever	314	52	2.25	1.47-3.43	10	0.54	0.26-1.13	27	1.04	0.62-1.72
Age at the start of smoking (years old)[a]										
Never	1629	93	1.00		87	1.00		107	1.00	
25 ≤	127	16	1.94	1.05-3.61	8	1.02	0.45-2.31	12	1.31	0.67-2.59
20-24	119	23	2.49	1.38-4.51	2	0.30	0.07-1.30	8	0.77	0.33-1.81
≤ 19	32	6	3.20	1.22-8.44	0	–[b]		5	1.77	0.57-5.55
Number of cigarettes smoked per day[a]										
Never	1629	93	1.00		87	1.00		107	1.00	
≤ 10	148	21	2.00	1.12-3.58	7	0.81	0.33-1.96	13	1.22	0.63-2.37
11-20	116	22	2.51	1.42-4.56	4	0.48	0.15-1.59	12	1.19	0.58-2.42
21 ≤	123	15	1.56	0.74-3.31	5	0.63	0.19-2.07	9	0.83	0.32-2.16
Trend			p = 0.004			p = 0.18			p = 0.92	
Passive smoking[c]										
With non-smoker husband	441	20	1.00		27	1.00		26	1.00	
With smoker husband	867	53	1.42	0.83-2.42	34	0.54	0.32-0.93	62	0.92	0.58-1.47
Alcohol drinking[d]										
Never	1442	90	1.00		76	1.00		103	1.00	
Ever	463	51	1.40	0.92-2.14	21	0.94	0.54-1.63	29	0.58	0.35-0.96

[a]OR was adjusted for age, year of survey, referral base (from screening, others), area of residence, history of alcohol drinking, family history of index cancer in parents and siblings, occupation (professional or clerical work, other work), age at menarche and number of children.

[b]–: not estimated

[c]Analyses were performed for non-smokers. OR was adjusted for age, year of survey, referral base, area of residence, history of alcohol drinking, family history of index cancer in parents and siblings, occupation, age at menarche and number of children.

[d]OR was adjusted for age, year of survey, referral base, area of residence, smoking history, family history of index cancer in parents and siblings, occupation, age at menarche and number of children.

tages are likely to influence the results. First, we considered problems in selecting cases and controls. Theoretically, eligibility criteria for cases define the source population in case-control studies, from which controls should be selected. Namely, if hospitalized cancer cases are a biased sample of the general population, controls should also be a biased sample in the same way (Rothman and Greenland 1998). In the present study, we selected controls from patients admitted to the same hospital as cases, although in some other studies controls have been selected from patients visiting cancer screening centers. To improve the comparability between cases and controls, statisti-

TABLE 3. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of marital status and reproductive factors for cervical, endometrial and ovarian cancer

Variable	Controls (n = 2016)	Cervix (n = 151)			Endometrium (n = 103)			Ovary (n = 141)		
		No. of cases	OR	95% CI	No. of cases	OR	95% CI	No. of cases	OR	95% CI
Marital status[a]										
Married	1849	137	1.00		84	1.00		124	1.00	
Single	53	11	2.19	1.06-4.53	12	6.18	2.97-12.88	10	2.58	1.22-5.45
Age at first marriage (years)[b]										
≤ 21	423	48	1.00		12	1.00		20	1.00	
22-24	717	38	0.53	033-0.83	34	1.74	0.88-3.42	45	1.32	0.76-2.28
≥ 25	524	35	0.60	037-0.97	28	1.96	0.97-4.00	45	1.83	1.04-3.20
		p = 0.03			p = 0.07			p = 0.03		
Age at menarche (years)[c]										
≤ 12	412	32	1.00		25	1.00		43	1.00	
13-14	732	60	1.42	0.86-2.35	41	0.79	0.45-1.38	57	0.80	0.51-1.26
≥ 15	693	45	1.37	0.75-2.49	32	0.53	0.27-1.03	30	0.39	0.21-0.72
Trend		p = 0.33			p = 0.06			p = 0.003		
Parity history[d]										
Parous	1758	117	1.00		80	1.00		113	1.00	
Nulliparous	132	22	1.96	1.14-3.36	19	3.62	2.04-6.42	22	2.54	1.49-4.33
Age at first birth (years)[e]										
≤ 23	593	52	1.00		21	1.00		34	1.00	
24-26	649	28	0.59	0.35-1.01	38	1.53	0.84-2.77	41	1.13	0.66-1.95
≥ 27	434	29	0.67	0.35-1.26	15	0.92	0.42-2.00	32	1.52	0.83-2.79
Trend		p = 0.12			p = 0.99			p = 0.18		
Parity number[d]										
0	132	22	1.00		19	1.00		22	1.00	
1	170	18	0.79	0.39-1.59	6	0.24	0.09-0.64	17	0.57	0.28-1.17
2	777	38	0.38	0.21-0.69	40	0.32	0.17-0.58	52	0.39	0.22-0.69
≥ 3	726	53	0.58	0.32-1.06	29	0.21	0.11-0.41	38	0.31	0.17-0.57
Trend		p = 0.07			p = 0.0001			p = 0.0002		

[a]ORs were adjusted for age, year of survey, referral base (from screening, others), area of residence, smoking history, history of alcohol drinking, family history of index cancer in parents and siblings, and occupation (professional or clerical work, other work).

[b]Analyses were performed for married women. ORs were adjusted for age, year of survey, referral base (from screening, others), area of residence, smoking history, history of alcohol drinking, family history of index cancer in parents and siblings, and occupation (professional or clerical work, other work).

[c]ORs were additionally adjusted for parity number.

[d]ORs were additionally adjusted for age at menarche.

[e]ORs were additionally adjusted for age at menarche and parity number.

TABLE 4. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of exogenous hormone use for cervical, endometrial and ovarian cancer

Variable	Controls (n = 2016)	Cervix (n = 151)			Endometrium (n = 103)			Ovary (n = 141)		
		No. of cases	OR	95% CI	No. of cases	OR	95% CI	No. of cases	OR	95% CI
Oral contraceptive use[a]										
No	1649	124	1.00		85	1.00		126	1.00	
Yes	97	10	1.20	0.58-2.49	5	1.46	0.55-3.84	3	0.46	0.14-1.50
Use of exogenous female hormones except for oral contraceptive[a]										
No	1636	127	1.00		82	1.00		113	1.00	
Yes	85	4	0.61	0.21-1.75	6	1.25	0.51-3.05	13	1.64	0.82-3.26

[a]ORs were adjusted for age, year of survey, referral base (from screening, others), area of residence, smoking history, history of alcohol drinking, family history of index cancer in parents and siblings, occupation (professional or clerical work, other work), age at menarche and parity number.

cal analyses appropriately controlled background characteristics such as area of residence and referral patterns among study subjects. Second, it is possible that the inclusion of benign tumors in the control group might have distorted the results, since patients with benign tumors may have a background similar to patients with cancers. To resolve this problem, we performed additional analyses as follows: patients with benign tumor in certain sites were excluded from controls for the site and ORs were reevaluated. Exclusion of benign tumors had no effect on the OR (data not shown in tables). Third, it is possible that information bias might have distorted the results. However, since the questionnaires were collected before any definite diagnosis or treatment at the MCCH, there would seem to be minimal recall bias. Fourth, we considered advantages of case-control study methods. Generally, epidemiologists consider cohort studies superior to case-control studies. However, incident cases of gynecologic cancers are relatively young compared with cases in other sites (Marugame et al. 2006). Therefore incident cases of gynecologic cancers may not be completely covered in usual cohort studies targeting middle-aged subjects at baseline. On the other hand, case-control studies can identify younger cases as well as older cases. Thus, case-control studies are regarded a more efficient method for investigating risk factors of gynecologic cancers.

The present study revealed associations of smoking and alcohol drinking with the risk of gynecologic cancers. Tobacco exposure from active smoking significantly elevated cervical cancer risk. A dose-response relationship with the number of cigarettes per day was also observed. Further, women starting smoking at an earlier age may have a higher risk of cervical cancer. On the other hand, a decreased risk associated with passive smoking was observed for endometrial cancer, and a decreased risk associated with alcohol drinking was found for ovarian cancer. In Western countries, similar associations have been observed (Lyon et al. 1983; Baron et al. 1986; Kjaer et al. 1996; Terry et al. 2002; Viswanathan et al. 2005). In Japan, although the evidence is sparse, Hirose et al. have reported the increase in cervical cancer risk among active and passive smokers, and Kato et al. found a decreased risk associated with alcohol drinking in ovarian cancer (Kato et al. 1989; Hirose et al. 1996). These previous and our results indicate that smoking and alcohol drinking may be differently associated with the risk of gynecologic cancers. Biological plausibility suggesting different roles of smoking and alcohol drinking exists as follows. Tobacco products contain more than 50 established or identified carcinogens, some of which may be

involved in the development of cervical cancer (Zaridze et al. 1986). Local immune suppression produced by tobacco smoking, which may enhance HPV persistence, may also affect the development of cervical cancer (Burger et al. 1993). The association between smoking and endometrial cancer risk may be attributed to anti-estrogenic effects of smoking (Terry et al. 2002; Viswanathan et al. 2005). Estrogen may promote the development of endometrial cancer. Smoking may diminish the effects of the estrogen through alteration of the steroid metabolism (Michnovicz et al. 1988). The decrease in ovarian cancer risk associated with alcohol drinking may be explained by the reduction of gonadotropins among alcohol drinkers (Lagiou et al. 2001), although this effect of alcohol intake is still hypothetical (Kato et al. 1989; Kushi et al. 1999). The association between exposure to high levels of gonadotropins and ovarian cancer risk has been proposed by Stadel (Stadel 1975).

The present study also revealed the associations of marital status and reproductive factors with the risk of gynecologic cancers. The increase in risk with increasing age at first marriage and the decrease in risk with increasing age at menarche and parity number were consistently observed for endometrial and ovarian cancers. For cervical cancer, the decrease in risk with increasing age at first marriage was found. Among them, similarities in reproductive risk factors between cancers of the endometrium and ovary have been observed in previous epidemiologic studies from Western countries (Baron et al. 1986; Brinton et al. 1992; Whittemore et al. 1992; Adami et al. 1994; Kelsey et al. 1994; Hankinson et al. 1995; McPherson et al. 1996; Lambe et al. 1999; Greggi et al. 2000; Persson 2000; Riman et al. 2002; Xu et al. 2004; Zhang et al. 2004). Several Japanese studies also support such similarities; Hirose and Okamura showed a decrease in endometrial cancer risk associated with increasing parity number (Hirose et al. 1999; Okamura et al. 2006), and Mori et al. demonstrated the association with parity number in ovarian cancer (Mori et al. 1998). Based on the previous results and ours, hormonal exposures related to menarche and childbirth may mediate the risk of endometrial and ovarian cancers. For example, the elevation of endometrial cancer risk among nulliparous women may be explained by biological mechanisms including continuous exposure to estrogen without progesterone (Key et al. 1988). The protective effect of parity against ovarian cancer may be due to the suppression of pituitary gonadotropins during pregnancy (Stadel 1975). Thus, it is likely that cancers of the endometrium and ovary are hormone-related (Persson 2000). On the other hand, the association with age at first marriage in cervical cancer may reflect the roles of sexual behavior in the development of cervical cancer. Although the present study did not include a detailed analysis of sexual behaviors, the effect of age at first marriage may be comparable to that of age at first sexual intercourse. Sexual behaviors among married women may affect disease progression through HPV infection (Schiffman et al. 1995). Regarding cervical cancer, an increased risk associated with unmarried status and nulliparity was also observed. This observation, which was similar to those in endometrial and ovarian cancers, was inconsistent with the results obtained from previous studies (Hirose et al. 1996; International Collaboration of Epidemiological Studies of Cervical Cancer 2006). We suppose that the effects of marital status and parity on cervical cancer risk in the present study could be explained not by etiological factors but rather by certain factors related to health behaviors; for example, unmarried or nulliparous women, who may be unconcerned about gynecologic diseases, may rarely visit gynecologic clinics and cancer screening centers (Kato et al. 1987; Ikeda et al. 2007). Such women may miss the chance of treating dysplasia or carcinoma in situ and are likely to fall victim to more serious disease, i.e., invasive cancer. Since there has been little epidemiologic evidence showing the associations of reproductive factors with cervical cancer risk in Japan, this interpretation is speculative. However, it seems that the possibility that health behaviors including screening may affect the progression of cervical cancer would not be ruled out.

There was no significant association between

exogenous hormone use and gynecologic cancer risk. However, the analysis of ovarian cancer showed the small OR for OC use. We considered that this finding should be further investigated. In Western countries, the decreased risk associated with OC use has been consistently observed for ovarian cancer (Hankinson et al. 1995; Greggi et al. 2000; Persson 2000; Riman et al. 2002). It is hypothesized that the protection of ovarian cancer by OC use may be due to suppression of plasma pituitary gonadotropins or inhibition of ovulation (Stadel 1975; Persson 2000). From the viewpoints of hormone-related cancers mentioned above, it is plausible that exogenous hormones such as OCs may affect the risk of ovarian cancer.

The trend in gynecologic cancer incidence in Japan may be explained based on the present findings to some extent. In Japan, the prevalence of unmarried and nulliparous women has been increasing, and the total fertility rate has been decreasing (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare 2006; Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare 2007). These characteristics, which are comparable to risk factors of endometrial, ovarian and cervical cancers, may produce a tendency towards an increasing risk of gynecologic cancers in the population. In addition, the prevalence of young female current smokers has been increasing (Ministry of Health, Labour and Welfare 2006), which may contribute to the increase of cervical cancer incidence.

In summary, the present hospital-based case-control study identified common and site-specific risk factors among gynecologic cancers. Smoking was significantly associated with an increased risk of cervical cancer. A dose-response relationship with the number of cigarettes per day was also observed. The increase in risk with increasing age at first marriage and the decrease in risk with increasing age at menarche and parity number were observed for endometrial and ovarian cancers. The increased risk associated with unmarried status and nulliparity were consistently observed for all sites. The results indicate that smoking is a major risk factor of cervical cancer and that hormonal factors related to early onset of menarche and low parity are common risk factors for endometrial and ovarian cancers. Increase in female smokers and decrease in fertility rate may contribute to the increase of gynecologic cancer incidence.

Acknowledgments

The authors are grateful to all staff members of the Miyagi Cancer Center who generously cooperated in this study. Support for the study came in part from a Grant-in-Aid for the Second Term Comprehensive 10-Year Strategy for Cancer Control, the Ministry of Health, Labour and Welfare, Japan. This study was supported in part by a Grant-in-Aid from the Kurokawa Cancer Research Foundation; a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Japan; and a 21st-Century COE Program Special Research Grant (Tohoku University) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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