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A Case-Control Study on Risk Factors for Uterine Endometrial Cancer in Japan

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A case-control study of 143 Japanese women with uterine endometrial cancer and 143 individually age-matched controls was conducted to assess the risk factors for endometrial cancers in Japan. Among the characteristics studied, the following factors were significantly greater in the cases than in the controls: nulliparity (odds ratio for parity 1–3 and ≥4 versus nullipara are 0.40 and 0.02, respectively), obesity (odds ratio: 2.73), hypertension (odds ratio: 2.4), diabetes mellitus (odds ratio: 6.30), and a personal medical history of cancer (odds ratio: 3.06). The present study showed that Japanese women have the same risk factors for endometrial cancer as those reported in Western countries. The recent increase in the incidence of endometrial cancer in Japan may be largely attributed to the decrease in parity.

Key words: Endometrial cancer — Risk factor — Epidemiology — Case-control study

Endometrial carcinoma is at present the second most common malignant tumor of the female genital tract in Japan, and its incidence is increasing, possibly due to westernization of the Japanese life style in the last three decades.[1–3] Japanese have come to show the same characteristics of gynecologic cancer incidence as seen in highly industrialized countries in the West: a high incidence of uterine endometrial cancer and a low incidence of uterine cervical cancer.[4] Therefore, more attention should be paid to endometrial cancer. The recognition of a high-risk group is very beneficial for economical screening for a disease. The elimination of such risk factors is also effective in the prevention of the pertinent malignancy. However, there have been no epidemiologic reports concerning the risk factors for endometrial carcinomas in Japanese women except for one report supported by the Ministry of Health and Welfare, Japan, 10 years ago,[3] in contrast to many reports in Western countries.[5] These circumstances prompted us to design the present case-control study for detection of a group of Japanese women at high risk for uterine endometrial cancers.

MATERIALS AND METHODS

Cases The cases were Japanese women who underwent surgery at the Department of Obstetrics and Gynecology, Osaka University Medical School, between January 1979 and December 1992 and were diagnosed as having histologically confirmed endometrial carcinoma. The medical records 143 cases, aged 22 to 78 years (median age: 53.6 years), were reviewed. The histological diagnoses were performed according to the WHO histological typing system.[6]

Controls For each endometrial carcinoma case, a control was selected from among patients who underwent hysterectomy at the Department of Obstetrics and Gynecology, Osaka University Medical School, for benign gynecologic tumors, including uterine myoma and ovarian cyst, in the same year as the case and who matched the case in terms of age (within 5 years). Endometrial tissues were histopathologically evaluated in detail before making a diagnosis as normal. A total of 143 controls, aged 22 to 79 years (median age: 53.2 years) were thus selected for the present study.

Potential risk factors for endometrial carcinoma (gravida, parity, menstrual status, height, weight, diabetes mellitus, and hypertension), and personal cancer history including double cancers and family cancer histories within 2nd-grade relatives were abstracted from the medical records of the cases and controls. The body mass index (BMI = body weight/height^2) was used as an index of obesity. Obesity and low weight were defined as a BMI of 24 or more and a BMI of less than 20, respectively. Diabetes mellitus was determined by the diagnostic criteria of the Japanese Association for Diabetes Mellitus using the 75-g oral glucose tolerance test. Hypertension was determined by the diagnostic criteria of the Japan Association of Hypertensive Disease.

Statistical analysis The numbers of pregnancies and parity were categorized into three groups: none, from one to three, and more than four. Two dummy variables were used to calculate the odds ratio of these categories

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with reference to no gravidity and no parity. Student's t test was used to compare the mean age between cases and controls. The chi-square test and the chi-square test-for-trend were used to calculate the significance of 2×2 and 2×3 tables, respectively. For univariate analysis, logistic analysis was used to calculate the significance and confidence interval of odds ratios. We adjusted the age to calculate the odds ratios of the variables with more than two categories: i.e., obesity, numbers of pregnancies and parity. Multivariate logistic analysis was performed to calculate the odds and 95% confidence interval of age, numbers of births, diabetes mellitus, hypertension and obesity.

RESULTS

Tables I and II present the distribution of the endometrial cancer cases and the age-matched controls according to age, menarche, menopausal status, number of pregnancies, number of births, other medical complications such as obesity, hypertension and diabetes mellitus, and the medical history of cancer in the individ-

Table I. Distribution of 143 Cases of Endometrial Cancers and 143 Controls According to Age at Diagnosis, Menarche and Natural Menopause

	Cases	Controls	P value
Age (yr)			n.s.
<39	14	13	
$40\leq\ <49$	29	35	
$50\leq\ <59$	56	51	
$60\leq\ <69$	36	37	
$70\leq$	8	7	
Average age (yr$\pm$SD)			
at diagnosis	53.6$\pm$10.8	53.2$\pm$10.9	n.s.
at menarche	14.2$\pm$1.8	14.3$\pm$1.8	n.s.
at menopause	49.3$\pm$3.8	50.2$\pm$2.9	n.s.

Table II. Univariate Logistic Analysis of Odds Ratios and Confidence Interval for Gravidity, Parity, Gravidity without Parity, Obesity, Hypertension, Diabetes Mellitus and Medical History of Cancer

Covariates	Cases	Controls	Odds ratio	95% Confidence interval
Gravidity				
0[a]	37	23		
1–3	63	65	0.48	0.25–0.94
$4\leq$	43	55	0.44	0.20–0.94
Parity				
0[a]	45	26		
1–3	97	101	0.40	0.24–0.81
$4\leq$	1	16	0.02	0.00–0.19
Gravidity without parity				
0[a]	67	61		
1–3	68	77	0.78	0.48–1.27
$4\leq$	8	5	1.48	0.44–4.63
Body mass index[b]				
<20	28	25	1.73	0.90 3.30
$20\leq\ <24$[a]	52	79		
$24\leq$	61	34	2.73	1.58–4.73
Hypertension				
no[a]	124	135		
yes	18	8	2.43	1.02–2.43
Diabetes mellitus				
no[a]	125	140		
yes	17	3	6.30	1.80–21.99
Personal cancer history				
no[a]	122	135		
yes	21	8[c]	3.06	1.32–7.15
Family cancer history				
no[a]	97	94		
yes	46	49	0.92	0.67–1.80

a) Odds ratios were calculated by treating these categories as reference categories.
b) Body mass index (BMI) calculated by using the formula: body weight(kg)/height(m)^2.
c) The sites of other cancers are breast in three, stomach in two, thyroid in two and colon in one patient.

ual and her family. The cases and the controls were similarly distributed with respect to age at diagnosis (respective means of 53.6 and 53.2 years), menarche (14.2 and 14.3 years) and natural menopause (49.7 and 50.2 years). The post- and pre-menopausal statuses were also similarly distributed in both groups.

Table II shows the age-adjusted relative risk of endometrial cancer. Although gravidity was inversely associated with endometrial cancer, with a statistically significant difference, gravidity without delivery did not affect the relative risk at all. With respect to parity, four or more deliveries showed a dramatically reduced relative risk (odds ratio: 0.02). Medical complications such as obesity, hypertension and diabetes mellitus showed odds ratios of 2.73, 2.43 and 6.30, respectively. A personal medical history of cancer was a high risk factor (odds ratio: 3.06). Family cancer history showed no special features, and did not affect the incidence in the present study.

Table III compiles the odds ratios determined by multivariate logistic regression using the number of births, diabetes mellitus, personal cancer history, hypertension, obesity and age as independent variables. Since univariate analysis shows a non-linear relationship between the number of births and the odds ratio of endometrial cancer, cases of up to three deliveries and cases of four or more deliveries were treated as separate categories using two dummy variables. The results are fundamentally similar to those from the univariate analysis. Women with four or more deliveries had the smallest odds ratio (odds ratio: 0.01), while 1–3 deliveries reduced the odds ratio by half (odds ratio: 0.42). Diabetes mellitus and obesity still have significantly high odds ratios even after consideration of other factors. However, hypertension became less significant in the multivariate analysis. A personal history of cancer showed a significantly high odds ratio.

Table III. Multivariate Logistic Analysis of Odds Ratios and Confidence Interval for Parity, Diabetes Mellitus, Personal Cancer History, Hypertension, Obesity, and Age

Covariates	Odds[a] ratio	95% Confidence interval
Parity		
1–3	0.42	0.22–0.79
4≤	0.01	0.001–0.15
Diabetus mellitus	7.75	1.52–40.00
Personal cancer history	2.8	1.13–7.09
Hypertension	1.67	0.57–4.76
Obesity	2.06	1.19–3.57
Age	1.02	0.99–1.05

a) Two dummy variables were used to calculate the odds ratio for the parity number. No parity, no diabetus mellitus, no personal cancer history, no hypertension and no obesity were treated as reference categories. Age was treated as a continuous variable.

DISCUSSION

The incidence of endometrial adenocarcinoma is apparently rising in Japan, having reached half of the incidence of invasive squamous cell carcinoma of the cervix.[1-4] According to the report of Osaka Cancer Registry, which is one of the most reliable sources of data on cancer incidence in Japan, age-adjusted average annual incidence rates have doubled in the past two decades.[4] The reasons for this apparent increase in this tumor are not fully understood. One report suggested that westernization of lifestyle including a change in diet, notably increased fat and animal meat intake, is responsible for the increased incidence of this malignancy in Japanese emigrants to the United States of America (USA).[7] In addition, a significant association between the serum cholesterol level and endometrial cancer has been reported in the USA.[8] Serum cholesterol may promote carcinogenesis of the endometrium possibly by producing hyperestrogenism through peripheral conversion of androstenedione to estrone. Animal protein intake and fat consumption by Japanese have increased in the last three decades,[9] and the latter more than doubled between 1960 and 1985.[10] Dietary factors, especially fat intake, may be involved in the recent increase in endometrial cancer in Japan. Besides dietary factors, multiple risk factors for endometrial cancers have been identified in Europe and North America. Nulliparity, obesity and late menopause have been confirmed as risk factors for developing endometrial cancer by a number of researchers.[5] In the present study, the same risk factors have been identified in Japan.

Most studies from Western countries have demonstrated a three-fold or greater excess risk for nulliparous than for parous women.[5, 11] The present study on Japanese women has also clearly demonstrated that nulliparity is associated with endometrial cancers. In the present study, as normal controls, we selected myoma/ovarian cyst patients who had undergone hysterectomy and were histopathologically evaluated as normal. Uterine myomas or ovarian cysts sometimes induce infertility. Therefore, these parous/gravidic factors could be more important than estimated here if myoma/ovarian cyst-free women were selected as normal controls, though selection bias seems to be minimal. As shown in Table II, gravidity significantly reduced the risk of endometrial cancer but gravidity without deliveries did not affect the risk. This means that parity is important among the reproductive factors. Actually, women with four or more deliveries have a dramatically reduced incidence of this malignancy

(odds ratio: 0.01). The recent increase in the incidence of endometrial cancer in Japan may be largely attributed to this parity factor for the following reasons. The percentage of numbers of deliveries by married women aged 55–59 years between 1962 and 1992 is shown in Fig. 1.[12] Since late 1970, the percentage of women with four or more deliveries has rapidly decreased, and this corresponds with the increase in the incidence of endometrial cancer. In addition, the present multivariate logistic analysis revealed that four or more deliveries is the strongest anticancer factor. Although the precise reason why delivery affects the development of endometrial cancer is unknown, complete evacuation of the endometrial tissue in each delivery, prolonged secretion of progesterone and/or breast feeding after delivery may protect against the development of endometrial cancers. Although we could not examine breast feeding in the present study, some reports from the USA have shown that breast feeding may not be related to endometrial cancer risk.[11, 13] This issue remains to be fully investigated.

Obesity has been a well-recognized risk factor for endometrial cancer in numerous studies.[5, 11, 13–15] It was also confirmed as a risk factor in the present study. Recent research in Western countries concluded that upper-body fat localization is a significant risk factor for endometrial cancer.[16, 17] This may be related to serum hormone-bound globulin (SHBG), which appears to be depressed in women with endometrial cancer.[18] Unfortunately, we could not examine the type of obesity or serum SHBG level. One case-control study reported 10 years ago in Japan did not identify obesity as a significant risk factor.[3] The difference between the present and the previous reports may be due to differences in the samples selected, including the type of obesity or the increased intake of fat by obese Japanese women. In any case, the overall rate of obesity in Japanese females has not changed in the past three decades.[9] Obesity thus seems to be unable to explain the recent increase in the incidence of endometrial cancer in Japan.

Diabetes mellitus and hypertension have also been shown to be risk factors.[5, 11] Diabetes mellitus was associated with endometrial cancers in the univariate as well as multivariate analysis of the present study. Since the controls were selected from patients who had undergone operation for benign disease and were evaluated for diabetes mellitus with the same diagnostic test and criteria as used for the cancer cases, no selection bias was present between the two groups. Diabetes mellitus could reflect a higher serum level of estrone, which may induce endometrial cancer.[11, 15] Hypertension has also been pointed out to be associated with endometrial cancers.[11] However, high blood pressure is prevalent in elderly, obese patients and the present multivariate analysis did not demonstrate a significant odds ratio for hypertension.

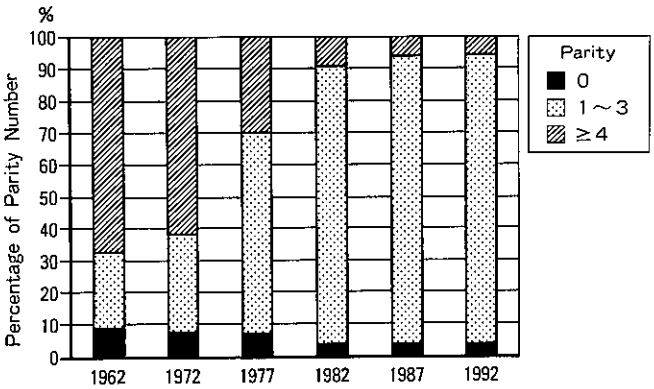

Fig. 1. Percentage of parity number for married women aged 55–59 years in 1962, 1972, 1977, 1982, 1987 and 1992 from the National Census data and Reproductivity Surveys.[12]

Thus, hypertension itself may be less related to endometrial cancer, and this is supported by many studies.[5, 15] However, diabetes mellitus and hypertension may not be responsible for the increased incidence of endometrial cancer since their incidences do not appear to have changed much in the last three decades in Japan.[19, 20]

The ages at menarche and menopause did not differ between the cases and the controls in the present study. Most studies have indicated that the age at menopause is directly related to the risk of developing endometrial cancer, although the age at menarche is less related to endometrial cancer.[11, 13] It was speculated that late menopause may reflect prolonged exposure of the uterus to estrogen stimulation in the presence of anovulatory cycles. The reason why a different result was obtained in the present study is unclear, but endometrial cancers of Japanese women may be less estrogen-dependent. The histopathologic finding that the incidence of poorly differentiated adenocarcinoma is higher in Japan than in the USA may support this speculation.[21]

In the past, discussion concerning the interaction between risk factors and the etiology of endometrial cancer has centered largely around the possible role of estrogen in producing this malignancy. However, recent molecular analysis has led to the conclusion that a carcinoma arises from the accumulation of a series genetic alterations involving activation of proto-oncogenes and inactivation of tumor suppressor genes. These alterations have been observed with endometrial cancers as well.[22, 23] In the present study, family cancer history was not found to be a risk factor, whereas a personal history of cancer was. Thus, familial factors are not important, but environmental factors, including dietary factors, which may induce the accumulation of gene abnormalities in individuals, play a central role in the development of

endometrial cancers. Further studies will be needed to clarify the association between endometrial carcinogenesis and environmental factors, and it may become possible to decrease the incidence of endometrial cancers by modifying these factors. We speculate on the basis of the present study that low parity is one of the most important factors responsible for the recent increase in the incidence of endometrial cancer in Japan, together with environmental factors.

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REFERENCES

1) Masubuchi, K., Nemoto, H., Masubuchi, S., Jr., Fujimoto, I. and Uchino, S. Increasing incidence of endometrial carcinoma in Japan. *Gynecol. Oncol.*, **3**, 335–346 (1975).
2) Tsutsui, A. Epidemiology of endometrial cancer. *Pract. Obstet. Gynecol.*, **37**, 831–839 (1988) (in Japanese).
3) Noda, K. Study of mutiple risk factors for endometrial cancer. *In* "Annual Report of the Ministry of Health and Welfare," pp. 517–530 (1983). Ministry of Health and Welfare, Tokyo (in Japanese).
4) Fujimoto, I., Hanai, A., Oshimura, A., Hiyama, T., Tsukuma, H., Murakami, R., Sobue, T., Tanaka, H. and Ajiki, W. "Cancer Incidence and Mortality in Osaka 1963–1989" (1993). Shinohara Publish., Tokyo.
5) Brinton, L. A. and Hoover, R. N. Epidemiology of gynecologic cancers. *In* "Principles and Practice of Gynecologic Oncology," ed. W. J. Hoskins, C. A. Perez and R. C. Young, pp. 3–26 (1992). J. B. Lippincott Co., Philadelphia.
6) Poulsen, H. E., Taylor, C. W. and Solbin, L. H. Histological typing of female genital tract tumours. *In* "International Histological Classification of the Tumors" (1975). World Health Organization, Geneva.
7) Haenzel, W. and Kurihara, M. Studies of Japanese migrants, I. Mortality from cancer and other disease among Japanese in the United States. *J. Natl. Cancer Inst.*, **40**, 43–68 (1968).
8) Wallace, R. B., Rost, C., Burmeister, L. F. and Pomrehn, P. R. Cancer incidence in humans: relationship to plasma lipids and relative weight. *J. Natl. Cancer Inst.*, **68**, 915–918 (1982).
9) Nutrition Section, Ministry of Health and Welfare. "National Nutrition Survey, 1960–1992" (1961–1993). Daiichi Shuppan Co., Tokyo (in Japanese).
10) Ueshima, H. Changes in dietary habits, cardiovascular risk factors and mortality in Japan. *Acta Cardiol.*, **45**, 311–327 (1990).
11) Elwood, J. M., Cole, P., Rothman, K. J. and Kaplan, S. D. Epidemiology of endometrial cancer. *J. Natl. Cancer Inst.*, **59**, 1055–1060 (1977).
12) Minister's Secretariat, Statistics and Information Department, Ministry of Health and Welfare. "Vital Statistics 1962–1992, Japan Health and Welfare Statistics" (1963–1993). Kosei Tokei-Kyokai, Tokyo (in Japanese).
13) Kelsey, J. L., Livolsi, V. A., Holford, T. R., Fischer, D. B., Mostow, E. D., Schwartz, D. E., O'Connor, T. and White, C. A. A case-control study of cancer of the endometrium. *Am. J. Epidemiol.*, **116**, 333–342 (1982).
14) Henderson, B. E., Casagrande, J. T., Pike, M. C., Mack, T., Rosario, I. and Duke, A. The epidemiology of endometrial cancer in young women. *Br. J. Cancer*, **47**, 749–756 (1983).
15) La Vecchia, C., Decarli, A., Fasoli, M. and Gentile, A. Nutrition and diet in the etiology of endometrial cancer. *Cancer*, **57**, 1248–1253 (1986).
16) Elliott, E. A., Matanokis, G. M., Rosenshien, N. B., Grumbine, F. C. and Diamond, E. C. Body fat patterning in women with endometrial cancer. *Gynecol. Oncol.*, **39**, 253–258 (1990).
17) Austin, H., Austin, J. M., Jr., Partridge, E. E., Hatch, K. D. and Shingleton, H. M. Endometrial cancer, obesity and body fat distribution. *Cancer Res.*, **51**, 568–572 (1991).
18) Armstrong, B. K., Brown, J. B., Clarke, H. T., Crooke, D. K., Hahnel, R., Masarei, J. R. and Ratajczak, T. Diet and reproductive hormones. A study of vegetarian and non-vegetarian postmenopausal women. *J. Natl. Cancer Inst.*, **67**, 761–767 (1981).
19) Ueshima, H. Tatara, K., Asakura, S. and Okamoto, M. Declining trends in blood pressure levels and the prevalence of hypertension, and changes in related factors in Japan. *J. Chron. Dis.*, **40**, 137–147 (1987).
20) Kuzuya, T., Ito, C., Sasaki, A., Seino, Y., Tajima, N., Doi, K., Nunoi, K., Matsuda, A. and Uehara, T. Prevelence and incidence of diabetes in Japanese people compiled from the literature. *J. Jpn. Diabetic Soc.*, **35**, 173–194 (1992) (in Japanese).
21) Silverberg, S. G., Sasano, N. and Yajima, A. Endometrioid carcinoma in Miyagi prefecture, Japan: histopathologic analysis of a cancer registry-based series and comparison with cases in American women. *Cancer*, **49**, 1504–1510 (1982).
22) Trowbridge, D. I., Risinger, J. I., Dent, G. A., Kohler, M., Berchuck, A., McLachlan, J. A. and Boyd, J. Mutations of the ki-ras oncogene in endometrial carcinoma. *Am. J. Obstet. Gynecol.*, **167**, 227–223 (1992).
23) Enomoto, T., Fujita, M., Inoue, M., Rice, J. M., Nakajima, R., Tanizawa, O. and Nomura, T. Alterations of p53 tumor suppressor gene and its association with activation of the c-K-*ras* protooncogene in premalignant and malignant lesions of the human uterine endometrium. *Cancer Res.*, **53**, 1883–1888 (1993).