RESEARCH COMMUNICATION

Risk of Endometrial Cancer Mortality by Ever-use of Sex Hormones and Other Factors in Japan

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Abstract

Objectives: To examine associations of ever-use of sex hormones (EUSH) and other factors with endometrial cancer (EC) mortality through a nation-wide Japan Collaborative Cohort Study. Methods: A total of 63,541 women aged 40-79 years, enrolled in 1988-90 from 45 municipalities of Japan, were followed until 2003 to record their vital status. Using baseline data, the Cox proportional hazard model (age adjusted and multivariate) was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for EC mortality by selected factors, including EUSH. Bivariate analysis was also conducted to establish associations between EUSH and other factors. Results: The mortality rate from EC was 2.6 per 100,000 person-years during the mean follow-up period of 13.3 years. Prevalence rate of EUSH was 5.2%. Significantly increased risk of EC mortality was found for EUSH with both age adjusted (HR=6.43, 95%CI=2.10-19.67) and multivariate (HR=5.33; 95%CI=1.51-18.82) analyses. Bivariate analysis indicated that history of diabetes mellitus, smoking, drinking, and age at first delivery were positively associated with EUSH, whereas age, number of delivery, number of pregnancy, and age at menarche demonstrated inverse links. Conclusions: Our results imply that EUSH may increase the risk of EC mortality among Japanese women. However, further studies with more deaths are needed to validate the results.

Key Words: Endometrial cancer mortality - cohort study - ever use of sex hormones - hormone replacement therapy - Japan

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Introduction

Endometrial cancer (EC) accounted for 198,783 new cases (3.9% of all new cancer cases in women) worldwide in 2002, making this the 7th most common cancer in the world. Because of its favorable prognosis, the number of deaths from this disease was only one-fourth (50,327 deaths, 1.7% of all cancer deaths in women). It is therefore the 13th most common cause of female cancer death worldwide (Parkin et al., 2005). International data indicate that this disease is more prominent in developed than developing countries. Among the developed countries, the incidence rate is relatively low in Japan as compared to the countries of north America and Europe (Parkin et al., 2005; Persson and Adami, 2002; IARC, 2002). International variation in diets, body size, body fat distribution, and exogenous estrogen use may contribute to the observed global differences in the incidence of these hormone-dependent malignancies. For instance, lower prevalence of hormone replacement therapy (HRT) in Japanese community as compared to other countries such as United States (Nagata et al., 1996), and consumption of plant based cuisines which are low in fat and high in fiber that typify the Japanese diets may be some of the reasons of the lower incidence of EC in Japan (Goodman et al., 1997).

Although incidence rates are still low in Japan, several reports (IARC, 2002; Persson and Adami, 2002; IARC 1997; IARC, 1987) have indicated that EC has been increasing gradually over the last few decades. Increasing availability of estrogen to the estrogen sensitive endometrium may increase the risk of EC (Parslov et al., 2000). In Japan, the production of conjugated estrogen, often used for HRT, has increased 2-fold between 1992 and 1993. Pharmaceuticals companies and women's magazines are actively advertising the importance of HRT especially for menopause women (Nagata et al., 1996). Increased life expectancy, a reduction

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in parity, and decreasing trend of breastfeeding practices might be some of the factors that contribute to the increasing trend of EC (Salazar-Martinez et al., 1999; Inoue et al., 1994). Westernization of lifestyle including a change in diet, notably increased fat and animal meat intake, may also be involved in the recent increase in EC in Japan (Inoue et al., 1994).

Various studies reported that uses of unopposed estrogen (Lacey et al., 2005; Emons et al., 2004; Persson and Adami, 2002; Pukkala et al., 2001; Parslov et al., 2000; Persson et al., 1999; Weiderpass et al., 1999; Cushing et al., 1998; Shapiro et al., 1998; Beresford et al., 1997; Pike et al., 1997; Grady et al., 1995; Brinton and Hoover, 1993) are associated with significantly increased risk of EC. Exposure to excessive estrogens, entailing (causing) continued stimulation of the endometrium, appears to be the key mechanism in endometrial carcinogenesis (Persson and Adami, 2002). Some other potential risk factors for EC may include increased BMI, hypertension, diabetes mellitus, nulliparity, non-use of oral contraceptives, decreasing physical activity, and non-smoking (Xu et al., 2004; Persson and Adami, 2002; Jain et al., 2000; Parslov et al., 2000; Salazar-Martinez et al., 1999; Goodman et al., 1997; Inoue et al., 1994; Shu et al., 1993; La Vecchia et al., 1986).

Although various studies, mostly of case-control type, have addressed the associations of EC with hormone use and reported significantly increased risk (Lacey et al., 2005; Emons et al., 2004; Persson and Adami, 2002; Pukkala et al., 2001; Parslov et al., 2000; Persson et al., 1999; Weiderpass et al., 1999; Cushing et al., 1998; Shapiro et al., 1998; Beresford et al., 1997; Pike et al., 1997; Grady et al., 1995; Brinton and Hoover, 1993), except one case-control Japanese study which showed insignificant association (Mizunuma et al., 2001), no cohort study has been conducted in Japan till today and hence these associations are still uncertain from cohort study among Japanese women. To our knowledge, present study is the first prospective cohort study that addressed the associations of EC mortality with ever use of sex hormone (EUSH) and some other potential factors by using the data from the nation-wide Japan Collaborative Cohort (JACC) Study.

Materials and Methods

Study Cohort

The JACC Study for Evaluation of Cancer Risk (sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan) is a large and nation-wide multicenter prospective cohort study which enrolled 127,477 apparently healthy subjects (male=54,032 female=73,445) aged from 16 to 112 years (<40 years=12,295, 40-79 years=110,792, and ≥80 years=3,760) at the time of baseline survey (through questionnaire) during 1988-1990. These subjects were recruited from 45 municipal areas (6 cities, 34 towns and 5 villages) located in 7 districts (out of 8) of Japan, either from general population or at the time of participants' general health check up which was periodically provided by these municipalities. Informed consent from participant was obtained using two strategies either by signing the cover page of the questionnaire (at the individual level which covered majority of the participants) or by explaining the aim of the study and confidentiality of the data (at the group level) to the community leader. Nagoya University School of Medicine approved this study. Details of the study design are described elsewhere (Ohno et al., 2001). Excluding 786 women with past medical history of cancer from 64,327 aged 40-79 years at baseline, present study analyzed a total of 63,541 women.

Baseline survey and questionnaire

At the time of enrollment, the subjects completed a self-administered questionnaire which included demographic characteristics such as age, sex, education, marital status, height and weight; lifestyles factors such as smoking, drinking, physical activity; dietary habits; past medical history of several diseases such as diabetes mellitus, and cancer. Present study, however, analyzed only a partial list of the variables such as age, BMI (<18.5, 18.5-25.0, ≥25.0), smoking (non-smoker, ever smoker), drinking (non-drinker, ever drinker), past history of diabetes mellitus (yes, no), marital status (single, else), number of pregnancies (≤2 versus ≥3), number of deliveries (≤2 versus ≥3), EUSH (yes, no), sports/physical activity (Seldom, ≥1-2 hours/wk), and systolic blood pressure (<130 mmHG, ≥130 mmHG) (shown in Table 1 and 2). The categories of the variables smoking, drinking, pregnancy, and delivery were made in such a way to confirm at least some deaths from EC in each category (for estimation purpose). Here ever smoker (drinker) meant current and ex-smoker (drinker). Although most of the studies used the category of null pregnancy and null delivery, we did not use such category because there was no death from EC in null category.

Follow-up

Follow-up survey was conducted annually until the end of 1999 and 2003 in 3 and 42 areas respectively to determine the vital status of the subjects using resident registration records available in the respective municipalities. For deceased subjects, cause of death was identified from the death certificate, available at each municipality, using International Classification of Disease version 10 (ICD-10). C54 code of ICD-10 was used for EC. For the present analysis, all other subjects (except EC deaths) who alive until the follow-up period or who moved out the study areas or lost to follow-up were considered as censored cases during analysis.

Statistical analysis

Persons-years of follow-up were calculated for each subject from the starting point of the study until the date of death, date of move out of study area, date of lost to follow-up or until the end of follow-up, whichever occurred first. The outcome variable of interest was the EC death. We first used Cox proportional hazard model (PHREG procedure)

to estimate the age adjusted hazard ratio (HR) of EC death including 95% confidence interval (CI) by EUSH and other selected variables. Multivariate Cox model was also used to estimate the HR of EC mortality by some selected variables including EUSH. All the computations were performed using the Statistical Analysis System (SAS) software package version 9.1 (SAS Institute Inc., Cary, NC).

Results

During the mean follow-up period of 13.3 years (standard deviation, SD=2.9 years) based on 63,541 women, the total number of deaths from all causes and move-outs were 7,172 (11.3%) and 2,977 (4.7%) respectively. Twenty two deaths were classified as EC among the total deaths, which provided the mortality rate of 2.6 per 100,000 person-years. The mean age at mortality was 69.0 years with a SD=9.2 years for 22 subjects of EC death.

Table 1 presents the distribution of women, person-years, number of deaths, and HR of EC mortality including 95% CI by some of the potential variables. The prevalence rate of the EUSH was 5.2% among Japanese women. According to univariate analysis for age through Cox model, higher age categories had higher EC mortality (HR=3.6 for age group 50-59; HR=3.2 for 60-69, and HR=4.5 for age group 70-79) compared with reference age (40-49) category. Age adjusted HR showed significant association of EC mortality with single marital status (HR=7.1; 95% CI=1.7-30.8) and EUSH (HR=6.4, 95% CI=2.1-19.7). All other variables such as diabetes mellitus, BMI, physical activity, smoking, drinking, and number of delivery were insignificantly associated with EC mortality.

Table 2 shows the distribution of the rate of EUSH by the selected variables. Significantly inverse association (P<0.0001) between age and the rate of EUSH was found. Lowest age group (40-49) indicated highest rate of EUSH (6.2%) and highest age group (70-79) indicated lowest rate (2.8%). History of DM (P=0.0047), smoking (P<0.0001), and drinking (P<0.0001) were positively associated with EUSH. Lower number of delivery (P<0.0001) and pregnancy

Table 1. Person-years, Number of Deaths, Age adjusted Relative Risk (RR) of Endometrial Cancer including 95% Confidence Interval (CI) due to Selected Variables, JACC Study, 1988-2003

Variables	Category	n[a]	Person-years	Noof deaths	RR	95% CI	P value
Age group	40-49	15391	217332	2	1.00		
(in years)†	50-59	19720	272028	9	3.64	0.79-16.84	0.0983
	60-69	19391	250328	7	3.17	0.66-15.28	0.1498
	70-79	9039	103825	4	4.52	0.83-24.73	0.0816
						P for trend=	0.1172
Past history of	No	52688	708528	19	1.00		
DM	Yes	2363	27987	1	1.64	0.17-9.60	0.8160
Sport activity	Seldom	38376	502391	17	1.00		
(hour/week)	≥1-2	12032	156505	5	1.16	0.41-3.28	0.7769
Body mass	<18.5	3728	46815	1	1.00		
Index (kg/m^2)	18.5-25.0	42143	563614	16	1.42	0.19-10.72	0.7398
	≥25.0	13545	180835	3	0.79	0.08- 7.70	0.8418
Marital status	Else	53529	711458	18	1.00		
	Single	874	11650	2	7.14	1.66-30.80	0.0084
Number of	<3	17865	240191	7	1.00		
pregnancies	≥3	39104	515653	10	0.61	0.17- 1.42	0.3252
Number of	<3	27207	364668	10	1.00		
deliveries	≥3	28924	379066	6	0.49	0.13- 7.33	0.1894
Systolic blood	<130	18678	245803	3	1.00		
pressure (mmHG)	≥130	23740	300337	9	1.89	0.50- 7.15	0.3487
Ever use of sex	No	45310	591603	14	1.00		
hormone	Yes	2359	30556	4	6.43	2.10-19.67	0.0011
Age at first	<25	26284	343096	6	1.00		
delivery (years)	≥25	26299	352015	11	1.74	0.64-4.70	0.2772
Age at menarche	<15	24385	325980	5	1.00		
(in years)	≥15	32922	435703	13	1.56	0.54- 4.54	0.4161
Smoking	Non-smoker	50914	679863	18	1.00		
	Ever smoker‡	4013	52153	1	0.77	0.10- 5.76	0.7924
Drinking	Non-drinker	42442	561384	13	1.00		
	Ever drinker‡	15044	202275	6	1.45	0.55- 3.86	0.4464

[a]Total subjects vary for missing observations; †unadjusted RR shown for age; ‡ ever smokers (drinkers)= current + ex-smokers (drinkers)

Table 2. Ever Use of Sex Hormone by Selected Variables, JACC Study, 1988-2003

Variables	Category	n[a]	% Users	P value
Age group (in years)†	40-44	5851	6.36	<0.001
	45-49	6046	6.02	
	50-54	6908	5.14	
	55-59	8227	4.79	
	60-64	8354	4.92	
	65-69	6209	4.72	
	70-74	3709	2.94	
	75-79	2365	2.58	
Past history of DM	No	40245	4.78	0.0047
	Yes	1777	6.25	
Sport activity (hour/week)	Seldom	34173	4.81	0.0020
	≥1-2	10538	5.47	
Body mass Index (kg/m^2)	<18.5	2807	5.42	0.1369
	18.5-25.0	32317	4.86	
	≥25.0	10388	5.27	
Marital status	Else	43368	4.98	0.3019
	Single	526	3.99	
Number of pregnancies	<3	14166	5.25	0.0147
	≥3	31276	4.72	
Number of deliveries	<3	22112	5.88	<0.001
	≥3	22888	3.88	
Systolic blood pressure (mmHG)	<130	16400	5.73	<0.001
	≥130	20701	4.74	
Age at first delivery (years)	<25	20716	4.31	0.0042
	≥25	21201	4.89	
Age at menarche (in years)	<15	19983	5.54	<0.001
	≥15	25838	4.42	
Smoker	Non	39536	4.76	<0.001
	Ever‡	2809	8.37	
Drinker	Non	33324	4.46	<0.001
	Ever ‡	11001	6.59	

[a]Total subjects vary for missing observations; †unadjusted RR shown for age; ‡ ever smokers (drinkers)= current + ex-smokers (drinkers)

Table 3. Multivariate Analysis for Estimating the HR and 95% Confidence Intervals for Endometrial Cancer Mortality, JACC Study, 1988-2003

Variables	Category	HR	95% CI
Age group (in years)†	40-49	1.00	
	50-59	4.08	0.56 - 41.18
	60-69	8.56	1.05 - 69.84
	70-79	11.99	1.23 -116.61
Body mass Index (kg/m2)	<18.5	1.00	
	18.5-25.0	1.42	0.18 - 11.02
	≥25.0	0.65	0.06 - 7.31
Marital status	Else	1.00	
	Single	13.22	2.99 - 58.48
Ever use of sex hormone	No	1.00	
	Yes	5.33	1.51 - 18.82

(P=0.0147), lower level of systolic blood pressure (P<0.0001), and late age at first delivery (P=0.0042) showed higher rate of EUSH. Multivariate Cox model which included age, BMI, marital status, and EUSH (Table 3) also showed that EUSH (HR=5.3, 95% CI= 1.5-18.8), single marital status, and higher age groups were significantly associated with EC mortality.

Discussion

The prevalence of EUSH was 5.2% among Japanese women aged 40-79 years (based on 1988-90), which was found to be lower as compared to the prevalence of another Japanese study (conducted in 1992) based on women aged 45-64 (Nagata et al., 1996). Our study clearly demonstrated that ever use of hormone was a risk factor for EC among Japanese women. This result is consistent with the findings of many other studies (Lacey et al., 2005; Emons et al., 2004; Persson and Adami, 2002; Pukkala et al., 2001; Parslov et al., 2000; Persson et al., 1999; Weiderpass et al., 1999; Cushing et al., 1998; Shapiro et al., 1998; Beresford et al., 1997; Pike et al., 1997; Grady et al., 1995; Brinton and Hoover, 1993). However, this result contradicted with the result of one Japanese case-control study, which reported the odd ratio (OR)=0.92 (95% CI=0.62-1.35) (Mizunuma et al., 2001). Unopposed estrogen enhances the proliferation of the endometrial tissues which leads to a more frequent occurrence of spontaneous mutations and increase the risk of developing cancer in these tissues (Preston-Martin et al., 1997).

As the estrogen related increased risk can be at least partially prevented by adding progestin to estrogen (Persson and Adami, 2002; Weiderpass et al., 1999; Shapiro et al., 1998; Grady et al., 1995; Voigt et al., 1991), recently progestin has been added to estrogen replacement therapy (ERT) for 5-15 days sequentially or continuously with each ERT (Pike et al., 1997). It is suggested that added progestin counteract estrogenic effects through several mechanisms, including reduction in the estrogen receptor levels, enhancement of estradiol metabolism, regulation of several growth factors, decreased DNA synthesis, and endometrial shedding (Weiderpass et al., 1999; Graham and Clarke, 1997). However, the results regarding the associations between combined estrogen-progestin and EC are inconsistent (Lacey et al., 2005; Hill et al., 2000; Persson et al., 1999; Weiderpass et al., 1999; Shapiro et al., 1998; Beresford et al., 1997; Pike et al., 1997; Grady et al., 1995; Voigt et al., 1991), because evidences showed significantly decreased risk for continuous progestin use with each dose of estrogen (Hill et al., 2000; Weiderpass et al., 1999), sometimes significantly increased risk mainly for fewer days of progestin use (Lacey et al., 2005; Weiderpass et al., 1999; Shapiro et al., 1998; Beresford et al., 1997; Pike et al., 1997) and sometimes no significant association (Persson et al., 1999; Shapiro et al., 1998; Beresford et al., 1997; Pike et al., 1997; Voigt et al., 1991). Although inconsistent, previous studies indicated that the larger the duration of days of addition of progestin to

estrogen in the monthly HRT regimens (in sequential manner), the lower the risk of developing EC (Emons et al., 2004; Persson and Adami, 2002; Pukkala et al., 2001; Parslov et al., 2000; Weiderpass et al., 1999; Beresford et al., 1997; Pike et al., 1997). Comparative findings indicated that continuous addition of progestin is found to more effective than sequential addition of progestin (Emons et al., 2004). Compared with use of unopposed estrogen only, combined therapy was associated with at least 50% reduction in the risk of EC (Shapiro et al., 1998), which is also supported by other studies (Persson and Adami, 2002; Beresford et al., 1997). However, long-term combined therapy (5 years or more) is associated with increased risk of EC (Shapiro et al., 1998; Beresford et al., 1997)

The present study indicated that EUSH was higher among the cohort of younger women than the older women, which may mean that the use of sex hormone among the younger women is more popular than the older women. Liu et al. (2005) also reported that HRT was not a common practice in Japan until the last few decades. This pattern also indicates that hormone use is increasing in Japan, which is supported by Nagata et al. (1996). The reasons are yet to be known. However, one of the reasons may be related to the declining fertility of Japanese women (Inoue et al., 1994). Estrogen levels are generally low during delivery and breastfeeding because of removal of epithelial cells from endometrium during delivery and decreasing endogenic estrogens during breastfeeding, i.e., lower number of deliveries means having higher estrogen levels, which might increase the EC risk (Salazar-Martinez et al., 1999; Inoue et al., 1994). Our data may support this argument because women with higher number of deliveries used significantly less sex hormone ($P<0.0001$) than the women with lower number of deliveries. Secondly, it is a cancer of postmenopausal women, as 91% of cases occur in women aged 50 and older worldwide (Parkin et al., 2005; Parslov et al., 2000). In postmenopausal women, the concentration of plasma estrogen is reduced by 70-80% with respect to pre-menopausal women (Parslov et al., 2000). At menopausal stage, women generally face many menopausal problems such as hot flashes, sweating, vaginal dryness and bladder problems, which are reported to be very common among Japanese women (Anderson et al., 2004). The protective effects of the use of sex hormone for managing the unpleasant menopausal symptoms (Weiderpass et al., 1999; Shapiro et al., 1998; Nagata et al., 1996; Daly et al., 1993) might be another reason. Reducing the risk of diseases such as osteoporosis and cardiovascular diseases through the increasing use of estrogen as well as combinations of estrogen-progestin (McPherson and Mant, 2005; Weiderpass et al., 1999; Beresford et al., 1997; Nagata et al., 1996) including Japan where deaths from heart and cardiovascular diseases are very common (Health and Welfare Statistics Association, 2002) and greater interest of health professionals toward HRT mainly based on American studies (Nagata et al., 1996) may also increase the EUSH.

Although one Japanese case-control study reported that Japanese women have the same risk factors for EC such as nulliparity, obesity, hypertension, diabetes mellitus like the women of western countries (Inoue et al., 1994), which are also supported by many other studies (Xu et al., 2004; Persson and Adami, 2002; Jain et al., 2000; Parslov et al., 2000; Salazar-Martinez et al., 1999; Goodman et al., 1997; Inoue et al., 1994; Shu et al., 1993; La Vecchia et al., 1986), our study failed to show any meaningful association regarding the associations between reproductive factors and EC. However, the direction of associations of EC with diabetes mellitus, pregnancy, delivery, systolic blood pressure, and smoking were similar with other studies. The reasons for such discrepancies are yet to be known. However, differences in life-styles between Japanese and western countries (Goodman et al., 1997), small number of EC deaths, and differences between cohort study (present one) and case-control studies (mentioned above) may produce such inconsistent and insignificant results.

The main advantage of the present study lies in its prospective design with a large cohort size. Naturally cohort study is free from recall bias, which is one of the main limitations of case-control studies. Although the use of hormone in Japan has been increasing particularly as a method of symptom management and protection against osteoporosis and cardiovascular diseases (Nagata et al., 1996), unfortunately the consequences of HRT on EC mortality in Japan has not been investigated till today through any cohort study. To our knowledge, this is the first cohort study in Japan that has investigated such objectives. Thus, the result of the present study may carry some importance and should be taken into account before prescribing this therapy by medical professionals.

Several limitations should be discussed briefly. First, small number of deaths from EC is one of the main limitations, which may limit the statistical power of the study. We did not examine the association between EUSH and EC mortality by deleting the women for which the follow up period was very short, although it is sometimes recommended. Second, the information about the type of used hormone (whether estrogen therapy only, or combined estrogen-progestin), current or past users, and duration of use were not available at baseline. According to previous information, separate analyses are sometimes useful by such categories as the associations differed by these categories. Third, oral contraceptives are generally associated with lower risk of EC (Xu et al., 2004; Jain et al., 2000). However, in Japan the influence of oral contraceptives may not be a factor, because these are rarely used in Japan (Liu et al., 2005). One recent survey indicated that only 7% of the female aged 16-49 would use the low-dose pill if it is approved nationally (Kitamura, 1999). Fourth, a lot of missing information regarding the EUSH may also limit the study findings, particularly if the characteristics differed significantly between the women who provided the information and who did not.

In conclusion, EUSH is a risk factor for EC mortality for Japanese women. Therefore, the women who need HRT

should select lower dose of estrogen. As the continuously combined estrogen-progestin replacement seems to be the safest HRT regimen for the endometrium (Emons et al., 2004; Persson and Adami, 2002), health professionals should recommend continuous use of combined estrogen and progestin throughout the treatment cycle, or recommend sufficient dose of progestin for at least 10-15 days per month. Moreover, health professionals should discuss the associated risk of the use of sex hormone before prescribing as well as should provide information regarding the potential risk factors.

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