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Comparative Case-referent Study of Risk Factors among Hormone-related Female Cancers in Japan

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To assess the impact of reproductive and anthropometric factors as a risk indicator for female cancers in hormone-related organs, i.e., the breast, endometrium and ovary, we conducted a comparative case-referent study using data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. The case group consisted of 1,465, 133 and 99 women who had first been diagnosed as having breast, endometrial and ovarian cancer, respectively. The referents were 25,488 female first-visit outpatients who had not previously been diagnosed with any type of cancer. The odds ratios (ORs) and their 95% confidence intervals (95%CI) were estimated using an unconditional logistic regression model. An inverse association with experience of delivery and a positive association with body mass index (BMI) and with change of BMI after 20 years of age, were observed consistently for all three cancer sites. We observed similar risk and protective factors for breast and endometrial cancer, but the effect of reproduction and overweight condition (BMI≥25) were more prominent in endometrial cancer. Although the present study failed to find site-specific risk factors for ovarian cancer, the results provided evidence that being overweight and/or weight gain in adult life is a common risk factor for all three cancer sites. The results obtained from this study suggested that avoidance of weight gain may reduce the risk of female hormone-related cancers.

Key words: Hormone-related cancer — Reproductive factors — BMI

Although the incidence rates of cancer of the female endocrine target organs, i.e., the breast, endometrium or ovary, are lower in Japan than in Europe and The United States, there has been a marked increase in recent years.[1)] In correlation studies of cancer incidence in different countries, these hormone-related female cancers have shown similar international distributions, which could indicate common etiological factors[2, 3)]. Reproductive factors and obesity have been described as risk factors for all of the above-mentioned cancer sites[4–6)] and seem to play an important role in endocrine-related cancers. Although the breast, endometrium and ovary are target organs for sex hormones, i.e., estrogen and progesterone, the hormonal mechanisms of secretion and metabolism seem to be different, and etiologic factors may vary among the three sites. Therefore, to assess the differences and similarities in the risk of developing cancer among breast, endometrial and ovarian cancers (hereafter referred to as BC, EC and OC, respectively), we conducted a comparative case-referent study using data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. We focused on the impact of reproductive and anthropometric factors as risk indicators for cancers in hormone-related organs in Japanese women.

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SUBJECTS AND METHODS

Data collection The HERPACC study has been conducted since 1988; a self-administered questionnaire survey is completed by first-visit outpatients to the Aichi Cancer Center Hospital. All questionnaires are then collected after having been checked by a trained interviewer for incomplete responses. All the data are loaded into the computer system of the Aichi Cancer Center Research Institute. Details of the questionnaire and data collection procedures have been more fully described elsewhere.[7–10)]

Of first-visit outpatients, totaling 61,475 between January 1988 and December 1995, 5,156 patients were excluded due to interviewer absence, age (younger than 18 years old), or visiting only for consultation. The questionnaire was finally administered to 56,319 patients. Among these, 55,471 (98.5%) completed the questionnaire adequately.

The questionnaire includes items on occupation, medical history, marital status, family history (parents and siblings), smoking and drinking habits, dietary habits,

Table I. Age Distribution of Referents and Cases for the Three Sites of Cancer

Age	Referents		Breast cancer		Endometrial cancer		Ovarian cancer	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
30–39	5,273	(20.7)	172	(11.7)	7	(5.3)	13	(13.1)
40–49	9,799	(38.5)	572	(39.0)	21	(15.8)	26	(26.3)
50–59	6,127	(24.0)	379	(25.9)	50	(37.6)	41	(41.4)
60–69	3,269	(12.8)	255	(17.4)	41	(30.8)	13	(13.1)
70–79	952	(3.7)	75	(5.1)	11	(8.3)	5	(5.1)
80+	68	(0.3)	12	(0.8)	3	(2.3)	1	(1.0)
Total	25,488	(100%)	1,465	(100%)	133	(100%)	99	(100%)
Average age±SD[a)]	48.5±10.7		51.3±10.7		56.6±10.1		51.8±10.5	

a) SD, standard deviation.

sleeping habits, physical exercise, bowel habits, reproductive history. Items on height, current weight and weight at around 20 years old have been added since 1989. Questions on socioeconomic status and education level are not included, because Japanese are, in general, rather reluctant to answer such questions. Inquiries about these items are made prior to the investigation of symptoms, and all the information is collected before diagnoses are made.

Cases and referents The data collected were linked with the hospital-based cancer registry files. Our analysis was restricted to women older than age 30 who visited the hospital between January 1989 and December 1995. Of 4,849 female cancer patients, 1,465, 133, and 99, who were first diagnosed on the basis of histological examination within 6 months of their first visit as having BC, EC and OC, respectively, were recruited as the case group. Their referents were 25,488 female first-visit outpatients who had not previously been diagnosed with any type of cancer. Table I shows referents and cases by age groups.

Statistical analysis Odds ratios (ORs) and 95% confidence intervals (95%CI) for each exposure variable were estimated using an unconditional logistic regression model. The LOGISTIC procedure provided by SAS (SAS Institute, Cary, NC) was used to perform the calculations. Categorizations of the variables used in Tables II and III were determined on the basis of their means and standard deviations. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. We used BMI>25 as the criterion of overweight status.

RESULTS

Age- and BMI-adjusted ORs of reproductive variables for BC, EC and OC are compiled in Table II. An inverse association with later age at menarche, irregular menstruation in the 20s, experience of delivery, number of births and average months of breast feeding was observed for BC. A positive association with being single and later age at first full-term pregnancy was observed among women with BC. We generally observed similar associations for BC and EC. The negative association with experience of pregnancy and number of births was especially marked in EC. The OR for women who had experienced pregnancy was 0.39 (95%CI: 0.25–0.61) for EC and the OR of women who had given birth to more than 3 children when compared to nulliparous women, was 0.36 (95%CI: 0.21–0.60). A trend of decreasing risk with average months of breast feeding in BC was observed, whereas an inverse trend was seen in EC. Experience of pregnancy and parity were associated negatively with OC, though age at first full-term pregnancy and breast feeding did not appear to be a modulator of this association with OC.

Table III gives ORs of anthropometric variables for BC, EC and OC. The estimates presented have been adjusted for age, marital status, age at menarche, menstrual regularity at 20–29 years old, age at first full-term pregnancy and parity. Taller women were found to be at a higher risk of BC and EC than were shorter women. Heavier women were at higher risk of BC and EC than lighter women. The positive association with weight was especially marked in EC (OR=2.18, 95%CI=1.43–3.32 for weight ≥55 kg versus weight ≤49 kg). There appeared to be no evidence of any relation to OC for either height or weight.

BMI is a better measure of adiposity than weight. When BMI was used, positive associations with BC and EC were still observed, while we saw no statistically significant or persuasive trends in OC. Change in BMI, namely, adult weight gain, is known to be more important as an anthropometric determinant of hormone-related cancers. Therefore, we examined the association of early adult body size and subsequent weight gain with the development of BC, EC and OC (Table IV). The women were divided into three groups according to level of change of BMI, and the second group, namely, the no-change group, was used as a reference. Compared with no-change group, the ORs of women who changed at the

Table II. Odds Ratios (ORs)[a)] and 95% Confidence Intervals (95%CI) of Reproductive Variables for Breast, Endometrial and Ovarian Cancer (HERPACC Data: 1989–1995, ≥30 yrs)

	Referents (*n*=25,488)	Breast (*n*=1,465)			Endometrium (*n*=133)			Ovary (*n*=99)		
	No. of referents	No. of cases	ORs	95%CI	No. of cases	ORs	95%CI	No. of cases	ORs	95%CI
Marital status										
Married	23,998	1,356	1.00		124	1.00		93	1.00	
Single	1,146	86	1.52	1.21–1.91**	7	1.63	0.76–3.52	3	0.78	0.25–2.48
Age at menarche (yrs)										
≤12	5,620	312	1.00		17	1.00		13	1.00	
13–14	12,267	665	0.87	0.76–1.00	61	1.22	0.71–2.11	51	1.58	0.85–2.94
≥15	7,330	472	0.84	0.71–0.99*	53	1.05	0.58–1.89	34	1.42	0.71–2.84
Menstrual regularity at age 20–29 yrs										
Regular	19,329	1,165	1.00		106	1.00		76	1.00	
Irregular	5,836	281	0.83	0.72–0.95**	26	0.91	0.59–1.41	21	0.96	0.59–1.56
Pregnancy										
No	2,199	158	1.00		24	1.00		9	1.00	
Yes	23,125	1,299	0.74	0.62–0.88**	108	0.39	0.25–0.61**	89	0.90	0.45–1.78
Age at first full-term pregnancy (yrs)										
≤23	6,287	321	1.00		24	1.00		23	1.00	
24–26	9,571	501	1.10	0.95–1.27	51	1.78	1.09–2.91*	41	1.31	0.78–2.19
≥27	6,466	428	1.40	1.21–1.63**	29	1.50	0.87–2.60	19	0.90	0.49–1.66
Delivery										
No	2,942	202	1.00		28	1.00		13	1.00	
Yes	22,352	1,253	0.77	0.66–0.89**	104	0.44	0.29–0.68**	84	0.81	0.45–1.45
No. of births										
0	2,942	202	1.00		28	1.00		13	1.00	
1	3,259	199	0.87	0.71–1.06	17	0.54	0.29–0.99*	14	0.95	0.45–2.03
2	12,698	694	0.77	0.66–0.91**	56	0.48	0.30–0.76**	48	0.84	0.46–1.56
3+	6,395	360	0.71	0.59–0.85**	31	0.36	0.21–0.60**	22	0.67	0.33–1.33
Breast feeding among parous women										
No	2,009	127	1.00		6	1.00		8	1.00	
Yes	20,315	1,124	0.87	0.72–1.05	98	1.45	0.63–3.33	75	0.89	0.43–1.85
Average months of breast feeding										
never	2,009	127	1.00		6	1.00		8	1.00	
1–5	6,208	347	0.96	0.77–1.18	19	1.26	0.50–3.18	20	0.89	0.39–2.03
6–11	5,950	308	0.85	0.69–1.05	25	1.52	0.62–3.70	27	1.18	0.54–2.60
12+	8,155	468	0.81	0.66–0.99*	53	1.48	0.63–3.49	28	0.70	0.31–1.55
Age at menopause (yrs)										
≤47	1,408	90	1.00		12	1.00		6	1.00	
48–52	4,738	320	1.03	0.81–1.32	36	0.88	0.45–1.69	21	1.05	0.42–2.60
≥53	1,631	136	1.19	0.90–1.57	24	1.50	0.75–3.03	10	1.45	0.52–4.02

a) Adjusted for age and body mass index.
* $P<0.05$, ** $P<0.01$.

highest level of BMI (≥2.50) for BC, EC and OC were 1.20 (95%CI: 1.05–1.37), 1.70 (1.11–2.61), and 1.37 (0.83–2.27), respectively. In these analyses, we were more interested in the independent effect of weight gain and whether this varied with early body size. Thus, we dichotomized at the mean BMI at around 20 years old

Table III. Odds Ratios (ORs)[a)] and 95% Confidence Intervals (95%CI) of Anthropometric Variables for Breast, Endometrial and Ovarian Cancer (HERPACC Data: 1989–1995, ≥30 yrs)

	Referents (*n*=25,488)	Breast (*n*=1,465)			Endometrium (*n*=133)			Ovary (*n*=99)		
	No. of referents	No. of cases	ORs	95%CI	No. of cases	ORs	95%CI	No. of cases	ORs	95%CI
Height (cm)										
≤151	7,665	460	1.00		47	1.00		26	1.00	
151.1–157.9	10,511	609	1.14	1.00–1.30*	55	1.40	0.93–2.11	54	1.81	1.10–2.97*
≥158	7,247	391	1.17	1.00–1.36*	31	1.53	0.93–2.52	19	1.10	0.58–2.08
Weight (kg)										
≤49	8,827	449	1.00		35	1.00		30	1.00	
49.1–54.9	7,755	402	1.07	0.93–1.23	32	1.24	0.76–2.02	34	1.44	0.87–2.38
≥55	8,809	610	1.40	1.23–1.59**	65	2.18	1.43–3.32**	34	1.17	0.70–1.96
Weight at around age 20 (kg)										
≤45	7,369	458	1.00		46	1.00		24	1.00	
45.1–51.9	10,073	548	0.93	0.82–1.06	45	0.85	0.56–1.28	49	1.61	0.98–2.67
≥52	7,789	438	0.96	0.83–1.10	40	0.95	0.62–1.47	25	1.08	0.60–1.91
Body mass index										
<20	5,977	278	1.00		25	1.00		19	1.00	
20–24.9	15,913	916	1.21	1.05–1.40**	71	1.06	0.66–1.69	64	1.25	0.74–2.12
≥25	3,439	263	1.49	1.24–1.78**	36	2.09	1.24–3.53**	15	1.10	0.53–2.27
Body mass index at around age 20										
<20	10,553	602	1.00		51	1.00		34	1.00	
20–22.9	11,347	672	0.99	0.89–1.11	63	1.00	0.69–1.45	54	1.36	0.88–2.12
≥23	3,272	166	0.75	0.62–0.90**	17	0.65	0.37–1.16	10	0.82	0.40–1.68

a) Adjusted for age (continuous), marital status (married, single), age at menarche (≤12, 13–14, ≥15), menstrual regularity (regular, irregular), age at first full-term pregnancy (≤23, 24–26, ≥27) and parity (0, 1, 2, 3+).
* $P<0.05$, ** $P<0.01$.

Table IV. Odds Ratios (ORs)[a)] and 95% Confidence Intervals (95%CI) of Change in Body Mass Index from 20 Years Old for Breast, Endometrial and Ovarian Cancer (HERPACC Data: 1989–1995, ≥30 yrs)

	Referents (*n*=25,488)	Breast (*n*=1,465)			Endometrium (*n*=133)			Ovary (*n*=99)		
	No. of referents	No. of cases	ORs	95%CI	No. of cases	ORs	95%CI	No. of cases	ORs	95%CI
Change of BMI after 20 yrs										
≤0	8,568	418	0.84	0.73–0.96*	38	0.92	0.57–1.48	32	1.06	0.63–1.78
0.01–2.49	8,716	479	1.00		33	1.00		27	1.00	
≥2.50	7,806	541	1.20	1.05–1.37**	59	1.70	1.11–2.61*	38	1.37	0.83–2.27
1) BMI at 20 yrs<20.6										
Change of BMI after 20 yrs										
≤0	2,987	155	0.95	0.78–1.16	11	1.16	0.54–2.52	11	1.08	0.49–2.36
0.01–2.49	5,490	299	1.00		16	1.00		17	1.00	
≥2.50	5,246	356	1.15	0.97–1.35	37	2.06	1.14–3.74*	21	1.09	0.57–2.08
2) BMI at 20 yrs≥20.6										
Change of BMI from 20 yrs										
≤0	5,581	263	0.80	0.66–0.98*	27	0.71	0.38–1.33	21	1.10	0.51–2.36
0.01–2.49	3,226	180	1.00		17	1.00		10	1.00	
≥2.50	2,560	185	1.24	0.99–1.53	22	1.42	0.75–2.68	17	1.87	0.84–4.18

a) Adjusted for age (continuous), marital status (married, single), age at menarche (≤12, 13–14, ≥15), menstrual regularity (regular, irregular), age at first full-term pregnancy (≤23, 24–26, ≥27) and parity (0, 1, 2, 3+).
* $P<0.05$, ** $P<0.01$.

Table V. Summary of Reproductive and Anthropometric Factors for Three Cancers of Women

Factor	Breast	Endometrium	Ovary
Marriage (no vs. yes)	+ +	+	−
Age at menarche (≥15 vs. ≤12)	− −		+
Age at menopause (≥53 vs. ≤47)	+	+	+
Menstrual regularity at age 20–29 yrs (regular vs. irregular)	− −		
Delivery (≥3 times vs. no)	− −	− −	−
Age at first full-term pregnancy (≥27 vs. ≤23)[a)]	+ +	+	
Breast feeding (≥12 mo vs. never)[a)]	− −	+	−
Height (≥158 cm vs. ≤151 cm)	+ +	+	
Weight (≥55 kg vs. ≤49 kg)	+ +	+ +	+
Current BMI (≥25 vs. <20)	+ +	+ +	
BMI at age 20 (≥23 vs. <20)	− −	−	−
Change of BMI after 20 yrs (≤0 vs. 0–2.5)	− −		
Change of BMI after 20 yrs (≥2.5 vs. 0–2.5)	+ +	+ +	+

a) Among parous women.
+, −: OR>1.15, OR<0.85.
+ +, − −: statistically significant (P<0.05).

(BMI=20.6), since the effect of adult weight gain may vary with early weight. Examination of the greater change in BMI categories showed a general increase in the ORs for all three cancer sites irrespective of BMI at around 20 years old. A marked increase in EC was observed in women with lower BMI at around 20 years old (OR=2.06, 95%CI: 1.14–3.74).

The risk trends for reproductive and anthropometric factors are presented in Table V to summarize the relation of reproductive and anthropometric factors to cancers at the three sites.

DISCUSSION

Before drawing conclusions from the present study, certain potential limitations should be considered. One methodological consideration in the present study was the possible bias caused by using hospital-based non-cancer patients as referents. To counter this, we compared lifestyle characteristics of outpatients and the general population, and confirmed that these were not substantially different.[9)] Recall bias was minimized because all data were collected prior to diagnosis. Another methodological study applying the same HERPACC data set showed that ORs based on a large number of referents gave more power and steadier estimates than did the use of matched controls[11)]; therefore, non-cancer individuals were used as referents in this study rather than matched controls.

This study aimed to analyze and to compare the risk for endocrine-related cancers, i.e., BC, EC and OC. We were fortunate to have the opportunity to examine this issue in one of the largest hospital-based case-referent studies. The results suggested that the effects of reproductive and anthropometric factors vary by site to a considerable degree.

This study confirms previously findings of a decrease in hormone-related cancers with increasing parity. Drife suggested three possible explanations for the effect of pregnancy on the risk of BC[12)]: one is that a woman's hormonal state is permanently altered by her first pregnancy; a second possibility is that during the first pregnancy cells that have undergone precancerous change are destroyed, immunologically or otherwise; the third possible explanation is that the breast epithelium itself is permanently changed by pregnancy. There is, however, still no satisfactory explanation of the effect of pregnancy on the risk of BC.

The risk of EC, like that of breast cancer, decreased with increasing parity, while age at first birth did not appear to be an important risk factor in EC. The factor responsible for nulliparity probably characterizes the high EC risk to a greater extent than later age at first full-term pregnancy. A similar situation exists for OC. The OC risk has long been known to be influenced by parity, but it remains unclear whether incomplete pregnancies as well as the timing of pregnancies affects risk. Albrektsen *et al.* reported that the relation of reproductive factors to OC risk may be more complex than previously believed[13)]. Further attention to the biological mechanisms is needed to understand the interrelationship of pregnancy and OC, and such studies also might be useful in advancing our understanding of the association with reproductive factors.

If pregnancy were to reduce directly the risk of hormone-related cancers, the decreasing number of pregnancies among Japanese women recently may partly explain the increasing incidence of these cancers.

In the present study, we observed similar risk and protective factors for BC and EC. The effects of being overweight were more prominent in EC than in BC. Both the breast and the endometrial mucosa are target organs for sex hormones, i.e., estrogen and progesterone. Obesity is associated with an increased extraglandular conversion of androgen to estrogen.[14–16] Also, excess body weight is associated with a diminished capacity of serum sex-hormone-binding globulin and an elevated percentage of serum estradiol in the free state,[16] which may be related to the risk enhancement for BC and EC. This hypothesis does not explain the differences in impact of BC and EC in relation to body size. However, the difference must be due to the different effect of estrogen on breast tissue and on the endometrial mucosa.

Obesity has also been indicated to be associated with the risk of OC, though this has not been confirmed in all studies. In a case-control study on OC in Japan, the OR of OC across increasing quartiles of the heaviest body weight were 1.00, 1.15, 1.71, 2.29.[17] We found the OR for OC of women who showed the highest level of change in BMI (≥2.50) was 1.37 (Table IV). Our study suggested that substantial weight gain from 20 years old is a common risk factor for these three sites of cancers. Prevalence of obesity increases with age, and interventions for overweight control could have an important effect on prevention of female hormone-related cancers.

BC and EC show differences in incidence rates for different age groups. EC is common among postmenopausal women, while BC is also common before the menopause. Prior to the menopause, excess body fat is thought to have little influence on bioavailable estrogen due to the overriding influence of ovarian estrogen production.[18] In the current study, significant associations with late menarche (age 15 or older), and menstrual irregularity in the 20s, were observed for BC. These associations suggest that estrogen stimulus during adolescence and/or early age at reproduction is an important risk factor for BC. In contrast, the influence of the hormonal environment of reproduction at a later age could be more important in developing EC. After the menopause the protective effect of progesterone is lost,[19] and the carcinogenic effect of estrogen is dominant. For most women, weight gain occurs after the menopause and in this period women experience the biological effects of hormonal change.[20] The EC risk increment due to weight gain may be more pronounced among postmenopausal women. The clear-cut effect of being overweight on EC risk and its lesser effect on BC risk suggest the involvement of different etiological mechanisms. Although the overall incidence of EC is lower than that of BC, a larger population of EC than BC cases seems to be attributable to an overweight condition.

The present study failed to find site-specific risk factors for OC. This may be a result of the variety and/or heterogeneity of the histopathological features of OC. There is a need to conduct further studies according to histopathological type. There are two widely accepted theories of OC pathogenesis. Associations between reproductive variables and the risk of epithelial OC have been related to mechanisms involving incessant ovulation[21] and/or exposure to gonadotropin.[22, 23] The former hypothesis predicts that any factor which suppresses ovulation should be protective. The latter hypothesis relates high levels of gonadotropin to an elevated risk of OC. Thus, further explanatory studies will be required to account for the epidemiologic findings.

The present study focused on particular differences in risk impact for BC, EC and OC and yielded clues for a strategy to prevent cancer at these sites. The results obtained from this study provide evidence that an overweight condition and/or weight gain in adult life is a common risk factor in these three sites of cancer. This suggested that avoidance of weight gain may reduce the risk of female hormone-related cancers.

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