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Factors Related to Late Menopause and Early Menarche as Risk Factors for Breast Cancer

Ikuko KATO,[*1] Suketami TOMINAGA[*1] and Tsuguyoshi SUZUKI[*2]
[*1]*Division of Epidemiology, Aichi Cancer Center Research Institute, 1-1, Kanokoden, Chikusa-ku, Nagoya 464 and* [*2]*Department of Human Ecology, School of Health Sciences, Faculty of Medicine, Tokyo University, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113*

To investigate underlying factors of late menopause and early menarche which are regarded as risk factors for breast cancer, we analyzed the relationships between ages at menarche and menopause, and other environmental and physical factors using the data of a population-based survey conducted in Aichi Prefecture, Japan. The analysis on menopause was based on 3,148 women aged 55 or more and the analysis on menarche was based on 16,392 women aged 40 or more. These subjects were grouped into three groups (early, average and late groups) according to their ages at menopause and menarche. Women with late menopause had larger height, weight and body mass index and included more professional, administrative and office workers, more daily fish & shellfish consumers and more women with colorectal cancer history of the mother and less current smokers. Women with early menarche also had larger height, weight and body mass index and more residence in a metropolitan area and consumed more bread, meats, fish & shellfish, vegetables, fruits, milk and black tea and less rice, miso soup and pickles. In a multiple regression analysis, occupation, weight, daily or occasional drinking and daily intake of fish & shellfish were positively and smoking was inversely associated with late menopause, while residence in a metropolitan area, weight and daily intakes of bread, milk and green-yellow vegetables were positively associated with early menarche. These results suggest the importance of underlying factors of early menarche and late menopause in the etiology and prevention of breast cancer.

Key words: Breast cancer — Menarche — Menopause — Risk factor

Breast cancer is a major cancer of females in western countries.[1] The mortality from breast cancer has been increasing, especially in metropolitan areas in Japan, in recent years.[2] Many previous epidemiological studies have shown several risk factors for breast cancer. Reproductive factors such as early menarche,[3–7] late menopause,[6–9] nulliparity and late first birth[5–8] have been considered risk factors for breast cancer. Beside reproductive factors, some environmental factors such as dietary habits, especially high fat intake,[10–12] smoking[13–15] and drinking habits,[15–18] genetic factors which have been studied using family history of breast cancer as an index,[19–21] large body mass,[5–8] high educational level[6, 7] and history of benign breast diseases[22, 23] have been suspected as risk factors for breast cancer. But whether or not these risk factors other than reproductive factors are independent of above-mentioned reproductive factors has been little investigated. Since reproductive factors could be influenced by many other factors, it is necessary to examine the relationships between reproductive factors and other factors. If environmental factors related to reproductive factors are detected, more effective primary prevention of breast cancer may become possible by controlling those factors. Therefore, we examined factors related to late menopause and early menarche as risk factors for breast cancer using the baseline data of a population-based cohort study.

SUBJECTS AND METHODS

A baseline survey for a population-based cohort study on the relationships between various environmental factors and cancer was conducted for the inhabitants aged 40 or more in two areas (one is a ward of a metropolitan area and the other is a city 22 km distant from the metropolitan area) of Aichi Prefecture, Japan, in 1985 using a self-recorded questionnaire. The total number of re-

spondents was 33,538 (15,748 males and 17,790 females) with a response rate of 93%. The female respondents were divided into three groups (early, average and late groups) according to their age at menopause and age at menarche. The analysis on age at menopause was restricted to the women aged 55 or more and women with artificial menopause were excluded from the analysis. Grouping was performed at each five year age-group by setting cutpoints close to the distribution of $\pm$1SD from the mean age at menopause or menarche. Table I shows the number of subjects and mean ages at survey and menopause. Mean age at menopause was 43.3 for the early group, 50.0 for the average group and 54.8 for the late group. Table II shows the number of subjects and the mean ages at survey and menarche. Mean age at menarche was 12.5 for the early group, 14.6 for the average group and 17.2 for the late group. Distributions of other variables in the questionnaire such as dietary habits, smoking and drinking habits, medical history and family history were compared among these three groups by calculating age-adjusted rates based on the age-distribution of the total subjects. Although the information on life-style was taken at the time of the baseline survey when menarche or menopause had already occurred, we used these variables assuming that those habits were relatively constant within individuals even if the absolute values had altered. The test for statistical significance was based on the Mantel-Haenszel chi-square values and the Mantel-extension chi-square test was applied to the test for trend. The step-up multiple regression analysis was used to select independent variables and adjust the effect of each variable.

Table I. Number of Subjects and Mean Ages at Survey and Menopause

Group	No. of subjects	Mean age at survey	Mean age at menopause
Early	955	66.0	43.3
Average	4,203	65.0	50.0
Late	990	65.4	54.8[a]
Total	6,148	65.2	49.7

a) 43 of 990 women who had not had menopause were excluded from calculation.

Table II. Number of Subjects and Mean Ages at Survey and Menarche

Group	No. of subjects	Mean age at survey	Mean age at menarche
Early	3,088	56.4	12.5
Average	10,589	56.5	14.6
Late	2,715	55.2	17.2
Total	16,392	56.3	14.6

Results

Table III shows the relationships between ages at menopause and menarche, and social and physical factors. Residence in a metropolitan area was positively associated with early menarche but was not associated with age at menopause. The rate ratio (RR) of early menarche compared with late menarche was 1.30 ($P<0.01$). As the occupation which women had for the longest duration in their life, professional, administrative and office work was more common in both late menopause groups ($P<0.05$) and early menarche groups ($P<0.01$). Height ($\geqq$158 cm), weight ($\geqq$60 kg) and body mass index (weight/height^2) were positively associated with both late menopause ($P<0.05$) and early menarche ($P<0.01$). Early age at first birth ($\leqq$20 years old) was slightly inversely associated with late menopause ($0.05<P<0.10$). History of hypertension was more frequent in the early menarche group, but history of heart diseases was statistically significantly inversely associated with both late menopause and early menarche. History of diabetes was less frequent in the average menopause group ($P<0.01$). Stomach cancer history of the mother was inversely associated with late menopause and colorectal cancer history of the mother was positively associated with late menopause ($P<0.05$). The RRs for breast cancer history of the mother were also increased in late menopause groups (not significant (NS)). Early menarche was not associated with any type of cancer history of the mother.

The relationships between dietary habits, and menopause and menarche are shown in Table IV. Factors positively associated with late menopause were daily intakes of meats, egg, green-yellow vegetables, other vegetables ($0.05<P<0.10$), fish & shellfish and fruits ($P<0.05$). Daily intake of instant coffee was slightly inversely associated with late menopause ($0.05<P<0.10$). As to early menarche, relatively large rice intake ($P<0.01$), daily intakes of miso soup ($P<0.05$), pickles ($P<0.01$) and instant coffee ($0.05<P<0.10$) were

Table III. Relationships between Ages at Menopause and Menarche, and Social and Physical Factors

Factors (cut point)	Menopause				Menarche			
	Early %[a]	Average RR[b]	Late RR	Mantel-extension χ^2	Late %[a]	Average RR[c]	Early RR	Mantel-extension χ^2
Residence (metropolis)	69.2	1.00	1.00	0.00	56.7	1.14**	1.30**	190.44**
Occupation (professional, administrative, office worker)	16.8	1.22*	1.49**	11.96**	20.7	1.28**	1.55**	78.33**
Height (≧158 cm)	10.5	0.96	1.28*	4.66*	16.0	1.04	1.16**	8.97**
Weight (≧60 kg)	10.6	1.07	1.34*	5.71*	11.5	1.14*	1.30**	17.08**
Body mass index (≧25.0)	15.1	0.99	1.23*	4.21*	13.6	1.02	1.16*	7.50**
Age at first birth (≦20)	11.3	0.91	0.76†	3.24†	5.7	1.27*	1.10	0.35
Medical history								
Hypertension	37.4	1.06	1.08	1.77	25.1	1.06	1.15*	5.79*
Heart diseases	24.5	0.85*	0.83†	3.67†	16.0	0.79**	0.87*	4.15*
Diabetes	17.0	0.65**	0.85	0.97	5.9	0.86	1.08	0.45
Family history of mother								
Stomach cancer	5.9	0.91	0.58*	4.49*	5.4	1.00	0.84	1.27
Colorectal cancer	0.6	2.56†	3.15	4.04*	1.4	1.20	1.26	0.80
Lung cancer	0.9	1.32	1.85	1.74	1.3	0.93	0.98	0.19
Breast cancer	0.2	4.26	3.31	0.71	1.0	0.96	1.27	0.63
Uterine cancer	3.4	1.12	0.71	1.33	3.6	1.02	0.96	0.38

a) Age-adjusted rate.
b) Rate ratio compared with early group.
c) Rate ratio compared with late group.
†$P<0.10$, *$P<0.05$, **$P<0.01$

inversely associated. Conversely, daily intakes of bread, meats, fish & shellfish, egg, green-yellow vegetables, other vegetables, fruits, milk and black tea were statistically significantly positively associated with early menarche ($P<0.01$).

The relationships between smoking and drinking habits and ages at menopause and menarche are shown in Table V. Smoking was strongly inversely associated with both late menopause and early menarche ($P<0.01$). Early menarche was not associated with alcohol drinking except "ume" or medicinal liquor. However, daily or occasional alcohol drinking was positively associated with late menopause ($0.05<P<0.10$). The RRs by type of alcoholic beverages tended to increase for daily intakes of sake, wine and "ume" or medicinal liquor (NS).

Table VI shows the results of a multiple regression analysis. We selected the best five variables except age by using a step-up method. However, for the analysis on age at menarche, variables of smoking, drinking, occupation and medical history, which were usually acquired after menarche, were excluded. Variables of menopause and menarche were trichotomized and the dependent variables except age were dichotomized.

For the variable of late menopause, the positive standardized partial regression coefficients for occupation (professional, administrative and office work), weight (≧60 kg), daily intake of fish & shellfish and daily or occasional alcohol drinking and the negative standardized one for smoking were statistically significant.

For the variable of early menarche, the standardized partial regression coefficients for residence in a metropolitan area, weight (≧60 kg) and daily intakes of bread, milk and green-yellow vegetables were positive and statistically significant.

Discussion

Endogenous hormones are considered to play an important role in the etiology of breast cancer. Exogenous hormones such as menopausal estrogen replacement therapy were also reported to increase the risk of

Table IV. Relationships between Ages at Menopause and Menarche, and Dietary Habits

Factors (cut point)	Menopause				Menarche			
	Early %[a]	Average RR[b]	Late RR	Mantel-extension χ^2	Late %[a]	Average RR[c]	Early RR	Mantel-extension χ^2
Rice (≧4 cups/day)	21.0	0.92	0.91	1.02	23.7	0.90**	0.72**	45.90**
Bread (daily)	42.2	0.97	1.01	0.02	36.7	1.11**	1.28**	56.10**
Meats (daily)	11.7	1.12	1.25†	2.73†	16.7	1.08	1.40**	36.24**
Fish & shellfish (daily)	17.3	1.25**	1.29**	6.14*	18.6	1.09†	1.30**	26.33**
Egg (daily)	29.2	1.15*	1.14	3.39†	33.0	1.03	1.14**	12.62**
Green-yellow vegetables (daily)	49.6	1.05	1.09	3.25†	47.2	1.07**	1.18**	39.75**
Other vegetables (daily)	64.7	1.03	1.06	2.80†	64.5	1.04*	1.08**	16.99**
Fruits (daily)	55.8	1.06	1.09	4.69*	51.1	1.07**	1.16**	38.96**
Miso soup (daily)	53.3	1.01	1.01	0.02	55.3	0.97	0.94*	6.00*
Pickles (daily)	63.7	0.98	0.97	0.97	63.3	0.96**	0.88**	33.32**
Milk (daily)	38.0	1.02	1.09	2.09	33.2	1.09**	1.24**	37.88**
Black tea (daily)	10.1	1.10	1.26	2.47	8.1	1.31**	1.56**	23.36**
Instant coffee (daily)	25.0	0.88*	0.84†	3.11†	29.3	0.96	0.92†	3.71†

a) Age-adjusted rate.
b) Rate ratio compared with early group.
c) Rate ratio compared with late group.
†$P<0.10$, *$P<0.05$, **$P<0.01$

Table V. Relationships between Ages at Menopause and Menarche, and Smoking and Drinking Habits

Factors (cut point)	Menopause				Menarche			
	Early %[a]	Average RR[b]	Late RR	Mantel-extension χ^2	Late %[a]	Average RR[c]	Early RR	Mantel-extension χ^2
Smoking (current smoker)	16.0	0.73**	0.61**	15.15**	17.0	0.75**	0.51**	81.37**
Alcohol drinking (daily or occasional)	19.5	1.13	1.20†	3.56†	28.1	0.98	1.01	0.20
Sake (daily)	1.3	1.03	1.35	0.77	1.1	1.05	1.07	0.03
Wine (daily)	0.4	1.81	1.45	0.29	0.4	1.23	1.71	3.45†
Beer (daily)	2.2	1.02	1.03	0.00	3.9	0.72	0.90	0.98
Ume or medicinal liquor (daily)	0.9	1.57	2.18†	3.47†	0.7	1.38	1.82*	4.31*

a) Age-adjusted rate.
b) Rate ratio compared with early group.
c) Rate ratio compared with late group.
†$P<0.10$, *$P<0.05$, **$P<0.01$

Table VI. Factors Related to Late Menopause and Early Menarche in a Multiple Regression Analysis

	Late menopause			Early menarche		
	Factors	SPRC[a]	*t*-value	Factors	SPRC[a]	*t*-value
1	Occupation (professional, administrative, office worker)	0.048**	3.72	1 Residence (metropolis)	0.094**	12.02
2	Weight (≧60 kg)	0.031*	2.42	2 Weight (≧60 kg)	0.041**	5.35
3	Fish & shellfish (daily)	0.031*	2.46	3 Bread (daily)	0.053**	6.53
4	Smoking (current smoker)	−0.047**	−3.64	4 Milk (daily)	0.039**	4.88
5	Drinking (daily or occasional)	0.032*	2.48	5 Green-yellow vegetables (daily)	0.040**	5.06
	Age	−0.006	−0.48	Age	0.037**	4.76

a) Standardized partial regression coefficient.
*$P<0.05$, **$P<0.01$.

breast cancer,[24–27] though negative results were observed in some studies.[28, 29] Significantly increased levels of plasma estradiol, estrone and prolactin,[30, 31] and a significantly increased percentage of unbound estradiol[32, 33] were reported in breast cancer patients or their daughters. It was also reported that estrogens and prolactin increase the incidence of mammary cancer in animal experiments.[34] Therefore, reproductive factors have been suspected as risk factors of breast cancer.

Early menarche and late menopause are considered to increase the duration of exposure to estrogens.[34] Artificial menopause was reported to reduce the risk of breast cancer.[35, 36] In the present study we detected several factors related to late menopause and early menarche, though these relations do not necessarily indicate causal relationships because in most cases, both menarche and menopause occurred before the survey. In the present study, smoking was associated with early menopause. This was also observed in other studies.[37–40] Moreover, in several case-control and cohort studies[13–15] it was reported that smoking reduced the risk of breast cancer as well as the risk of endometrial cancer.[41, 42] Therefore, these protective effects of smoking may possibly be due to the acceleration of menopause, resulting in a shorter exposure to estrogens.

In contrast to smoking, alcohol drinking was related to delayed menopause in the present study. Recently a positive association between alcohol drinking and breast cancer has been reported in several case-control and cohort studies.[15–18] Although the association was still statistically significant after adjustment of other risk factors for breast cancer in most of the studies, it is possible that drinking increases the risk of breast cancer through the changes of endogenous hormonal levels considering our results and the results of other clinical and laboratory studies.

Although high educational level[6, 7] or high social class[6] has been reported as a risk factor for breast cancer, it is not considered that educational level or social class *per se* affects breast cancer risk. A delay of first birth in women with higher social class was reported.[43] Since professional, administative and office work was associated with late menopause in our study, late menopause may be one of the explanations for the increased risk of breast cancer in women with a high educational level.

Family history of breast cancer has been considered as another important risk factor for breast cancer.[19–21] It is likely that endogenous hormonal levels are similar between mothers and daughters. It was reported that daughters of breast cancer patients had a higher plasma estradiol-plus-estrone level than controls.[30] In the present study, women with late menopause had a higher incidence of family history of breast cancer and colorectal cancer — both hormone-related cancers — in their mothers. This may suggest similar endogenous hormonal pattern between mothers and daughters. But it is not clear which of genetic factors or environmental factors are involved in the similar hormonal pattern, because environmental factors are likely to be shared by family members.

Although the relationship between dietary habits and breast cancer is still inconclusive, westernized dietary habits such as high fat and animal protein diet have been considered as risk factors for breast cancer from international correlation studies and some case-control studies.[10–12] In the present study, early menarche was more strongly associated with dietary habits than age at menopause, though we used dietary habits at the time of the survey. Early menarche was positively associated with western-style foods and inversely associated with Japanese traditional foods. These data suggest that westernized dietary habits may have accelerated menarche. From population-based data the progress of both westernization of dietary habits and acceleration of menarche in Japan have been noted.[43] Protein-rich foods such as meats, egg and fish & shellfish were positively associated with late menopause in our data, but the association was strongest for fish & shellfish. This may be due to the fact that the main source of protein intake was fish & shellfish rather than meats in the subjects for the analysis on menopause, whose mean age at survey was about 10 years older than that of the subjects for the analysis on menarche.

Since it was reported that the westernization of dietary habits occurred earlier in metropolitan areas than in rural areas in Japan,[2] the positive association between early menar-

che and residence in a metropolitan area might reflect a higher degree of westernization of dietary habits.

Although weight and body mass index could change in adults, height, weight and body mass index were all positively associated with early menarche. This suggests that earlier and larger growth leads to acceleration of menarche. It was also reported by Moriyama *et al.* that age at menarche was positively associated with height and the attainment of menarche within the same age groups was positively associated with weight.[44] Although obesity after menopause is considered to increase the risk of breast cancer through the increase of the conversion of androgens to estrogens in fat deposits,[34] our data suggested that large body mass also contributes to the continuation of the menstruation cycle.

The association between early menarche and professional, administrative and office work may reflect higher social class of the families and presumably superior diet, but it is difficult to interpret the strong inverse association between smoking and early menarche.

Summing up the results of the present study, it seemed that menarche was related more closely to dietary factors and menopause was related more closely to other factors such as smoking, drinking and constitutional factors. These results suggest the importance of underlying factors of early menarche and late menopause in the etiology and prevention of breast cancer.

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