A Case-Control Study of Breast Cancer among Japanese Women in Tokyo

Kenji Waka(, Yoshiyuki Ohno°, Sadao Suzuki*, Susumu Watanabet, Goi Sakamoto:!: and Nakako Kubo§

Abstrak

Untuk meneliti faktor. risiko kanker payudara saat in dilakukan penelitian kasus-kontrol pada rumah-sakit di Tokyo, dari tahun 1990 sampai 1991. Informasi mengenai faktor risiko potensial didapat dari kwesioner yang diisi sendiri oleh 5.084 pasien rawat jalan. Dari pasien tersebut didapat 300 kasus /canker payudara, dan dipilih 900 kontrol secara acak yang umunya sesuai. Temuan bermakna adalah: (a) semakin tinggi jumlah kelahiran hidup, semakin kecil risiko pada wanita pramenopause (risiko relatif (RR) yang disesuaikan untuk 3 atau lebih kelahiran hidup terhadap tanpa kelahiran hidup: 0,24; 95% interval kepercayaan (JK) : 0,08 - 0,65); (b) pada wanita pramenopause, siklus haid teratur meningkatkan risiko (RR yang disesuaikan: 2,50; 95% IK : 1,16-5,38), dan peningkatan lama siklus mengurangi risiko (P untuk kecenderungan linier < 0,05); (c) perokok masa kini mengalami peningkatan risiko (1,63; 1,11-2,39) untuk semua wanita, dan (2,73; 1,38-5,39) untuk wanita pasca menopause); (d) wanita yang kegemukan mengalami risiko lebih besar mendapat kanker payudara pasca menopause: RR yang disesuaikan untuk yang berbobot 70 kg atau lebih terhadap yang berbtH>ot 50 kg atau kurang adalah 4,82 (95% IK: 1,53-15,2); (e) semakin tua usia melahirkan anak pertama, semakin tinggi risiko kanker payudara pasca menopause (2,85; 1,16-6,99, dan 3,54; 1,03-12,2 untuk umur 30-34 dan 35 tahun atau lebih). Risiko kanker payudara pra menopause dan pascamenopause tidak berhubungan dengan riwayat kanker payudara pada keluarga, riwayat penyakit payudara jinak, umur saat haid pertama dan menopause, la/etas kebiasaan minum alkohol dan tinggi badan.

Abstract

To explore the risk factors for recent female breast cancer, a hospital-based case-control study was conducted in Tokyo, from 1990 to 1991. Information on potential risk factors was obtained by a self-administered questionnaire from 5.084 out-patients. Of the patients, 300 incident breast cancer cases were recruited, and 900 age-matched controls were randomly selected. Significant findings are: (a) the more the number of livebirths, the smaller the risk in premenopausal women (adjusted relative risk (RR) for 3 or more births relative to none: 0.24; 95% confidence interval (CI): 0.08-0.65); (b) in premenopausal women, regular menstrual cycle increased the risk (adjusted RR: 2.50, 95% Cl: 1.16-5.38), and its increasing duration decreased the risk (P for linear trend <0.05); (c) current smokers experienced an increased risk (1.63, 1.11-2.39 for all women and (2.73; 1.38-5.39) for postmenopausal women; (d) obese women were al a greater risk of postmenopausal breast cancer: adjusted RR for those weighing 70 kg or more relative to those weighing 50 kg or less being 4.82 (95% Cl: 1.53-15.2); (e) the later the age at first livebirth, the higher the postmenopausal breast cancer risk (2.85; 1.16-6.99 and 3.54; 1.03-12.2 for ages of 30-34 and 35 years and more, respectively). Neither premenopausal nor postmenopausal breast cancer risk was independently associated with family history of breast cancer, history of benign breast disease, ages at menarche and menopause, lactation, drinking habits and body height.

Keywords : *breast cancer, risk factor, premenopausal, postmenopausal*

Risk factors incriminated for female breast cancer include family history of breast cancer,[8] history of benign breast disease,[1-4] early menarche,[1,5-12] late menopause,[4,10,11,13] late age at first birth/full-tenn pregnancy,[1,3-6,8,9,12,14,15] and low panty (a small number of full-term pregnancies).[1,6,8,9,10,14] Obesity is also an established risk factor for breast cancer among postmenopausal women.[1,8,11,16,17]

Breast-feeding is reported as a protective factor against breast cancer. Alcohol consumption[2,3,5,6,8,12,18,19] and smoking habits[3,8,19-22] remain to be explored further as significant risk factors of breast cancer.

In Japan, age-adjusted incidence (adjusted by World Population) of breast cancer was 13.5 per 100,000 population in 1975[23] and 24.3 in 1985.[24] This increase is conceivably ascribable to rapidly changing lifestyles among Japanese women. It is, therefore, of impor-

• *Department of Preventive Medicine, School of Medicine, Nagoya University, Nagoya 466, Japan*

t *Department of Surgery, Cancer Institute Hospital, Tokyo 170, Japan*

+ *Department of Pathology, Cancer Institute Hospital, Tokyo 170, Japan*

§ *Department of Public Health, Medical School, Nagoya City University, Nagoya 467, Japan*

tance and significance to explore the recent risk factors for breast cancer among Japanese women.

METHODS

Information on potential risk factors was obtained by a self-administered questionnaire from all out-patients who visited the Department of Breast Surgery, Cancer Institute, Tokyo from May 10, 1990 to May 31, 191. Items surveyed were age, menopausal status, family history of breast cancer, history of benign breast diseas. refillla_!ity and duration of menstrual cycle (for premenopausa l women), ages at mena rche and menopause, age at first birth, number of livebirths, episodes of lactation, smoking and drinking habits, height and weight. These information have been readily collected from all out-patients before examination, that is, prior to diagnosis.

Of the 5,084 female patients during the study period, 314 were newly diagnosed as having breast cancer histologically. Of the 314 breast cancer pa tients, we excluded 11 patients with missing information on inenopa usal status, one patient under 25 years old, and 2 patients with history of other malignant tumors. Thus, 300 incident patients were eligible cases for the prese11t study.

Controls were randomly selected from the remaining 4,770 patients wi thout breast cancer, excluding those with missing information on menopausal status and/or with history of other malignant tumors. Three controls per case were randomly selected, matching each other for age (as nearest as possible). Table 1 shows the age distribution of the study subjects (300 cases and 900 controls), and those related to the menopausal status.

All analyses were performed for premenopausal and postmenopa usal women, sepa rately and totally. Obesity index was calculated as Quetelet's index, defined as weight (in kilogram) divided by the second power of height (in meter).

Unconditional multiple logistic regression analysis[25] was undertaken to obtain RRs adjusted for age and other variables potentially confounded. In the multivariate analysis, study subjects with missing information were also included as an additional category. A linear trend in RRs, derived from the logistic model, was examined by the method of Rothman.[26]

RESULTS

Table 2 shows the RRs obtained by unconditional multiple logistic regression analyses.

After adjusting for other variables (see footnote of Table 2), a significantly increased risk of breast cancer was apparent among premenopausal women, when menstrual cycle was regular (RR: 2.50; 95% Cl: 1.16-5.38). The longer the duration of menstrual cycle, the smaller the risk with statistical significance (*P* for trend <0.05).

Late age at first birth was linked to the risk in postmenopausal women (2.85; 1.16-6.99) and (3.54; 1.03-12.2) for age of 30-34 years, and that of 35 years and older respectively. Number of livebirths was inv erse l y correl a t ed t o b reas t ca nce r ris k i n premenopausal women and all women, independently of other factors (*P* for trend < 0.001 and <0.05, respectively).

Table l.Age Distri butions of Cases and Controls in general and classified by menopausal sta tus

Age	All women				Premenopausal				Postmenopausal			
	Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%
20-29	6	2.0	18	2.0	6	3.5	17	3.5	0	0.0	1	0.2
30-39	25	8.3	75	8.3	25	14.7	71	14.7	0	0.0	4	1.0
40-49	131	43.7	393	43.7	119	70.0	352	72.7	12	9.2	41	9.9
50-59	81	27.0	243	27.0	20	11.8	44	9.1	61	46.9	199	47.8
60-69	40	13.3	120	13.3	0	0.0	0	0.0	40	30.8	120	28.8
70-79	14	4.7	46	5.1	0	0.0	0	0.0	14	10.8	46	11.1
80-	3	1.0	5	0.6	0	0.0	0	0.0	3	2.3	5	1.2
Total	300	100.0	Q00	100.0	170	100.0	484	100.0	130	100.0	416	100.0

Table 2. Adjusted Relative Risks for Breast Cancer in Unconditional Logistic Regression Analysis

	All women		Premenopausal		Postmenopausal	
	RR	95%CI	RR	95%CI	RR	95%CI
Family history or breast cancer						
no	1.00	Reference	1.00	Reference	1.00	Reference
yes	1.29	0.70 - 2.39	1.64	0.70 - 3.83	0.92	0.31 - 2.67
Past history or benign breast disease						
no	1.00	Reference	1.00	Reference	1.00	Reference
yes	0.98	0.65 - 1.46	1.05	0.63 - 1.78	0.73	0.35 - 1.54
Age at menarche						
-12	1.00	Reference	1.00	Rererence	1.00	·Reference
13	1.09	0.72 - 1.63	1.22	0.74 - 2.01	0.90	0.40 - 2.05
14	0.82	0.54 - 1.26	0.79	0.46 - 1.36	0.74	0.32 - 1.71
15-	0.94	0.63 - 1.42	0.93	0.53 - 1.65	0.85	0.40 - 1.77
test for trend		NS		NS		NS
Age at menopause						
-44					1.00	Reference
45-49					0.65	0.29 - 1.45
50-54					0.63	0.30 - 1.36
55-					0.77	0.25 - 2.31
test for trend						NS
Regularity or menstrual cycle						
irregular			1.00	Reference		
regular			2.50	1.16 - 5.38		
Duration or menstrual cycle(days)						
-27			1.00	Reference		
28-29			0.80	0.47 - 1.34		
30-31			0.66	0.34 - *1.28*		
32-			*0.50*	0.10 - 2.58		
test for trend				*P<0.05*		
Age at first livebirth						
-24	1.00	Reference	1.00	Reference	1.00	Reference
25-29	1.03	0.67 - 1.58	0.93	0.51 - 1.69	1.25	0.63 - 2.49
30-34	1.64	0.92 - 2.94	0.94	0.41 - 2.17	2.85	1.16 - 6.99
35-	2.17	0.91 - 5.20	1.08	0.28 - 4.18	3.54	1.03 - 12.2
test for trend		NS		NS		NS
Number of livebirths						
0	1.00	Reference	1.00	Reference	1.00	Reference
1	0.85	0.44 - 1.64	0.52	0.21 - 1.32	1.68	0.57 - 4.98
2	0.78	0.43 - 1.44	0.40	0.17 - 0.95	1.74	0.62 - 4.88
3-	0.61	0.31 - 1.20	0.24	0.08 - 0.65	1.62	0.55 - 4.74
test for trend		*P<0.05*		P<0.001		NS
Lactation						
no	1.00	Reference	1.00	Reference	1.00	Reference
yes	1.08	0.65 - 1.80	1.21	0.59 - 2.50	1.00	0.45 - 2.20
Smoking						
never smoked	1.00	Reference	1.00	Reference	1.00	Reference
ex-smoker	0.91	0.49 - 1.70	0.96	0.42 - *2.20*	0.80	0.28 - 2.32
current smoker	1.63	1.11 - 2.39	1.23	0.75 - 2.03	2.73	1.38 - *5.39*
Alcohol drinking						
no	1.00	Reference	1.00	Reference	1.00	Reference
yes(current)	1.04	0.77 - *1.39*	1.36	0.92 - 2.00	0.71	0.42 - 1.19
Height(cm)						
-149	1.00	Reference	1.00	Reference	1.00	Reference
150-154	1.22	0.78 - 1.92	0.77	0.37 - 1.62	1.81	0.98 - 3.34
155-159	1.13	0.70 - 1.82	0.71	0.34 - 1.49	1.51	0.76 - 2.98
160-	1.46	0.86 - 2.48	1.08	0.49 - 2.37	1.46	0.62 - 3.46
test for trend		NS		NS		NS
Weight(kg)						
-49	1.00	Reference	1.00	Reference	1.00	Reference
50-59	1.18	0.86 - 1.62	1.77	1.12 - 2.80	0.77	0.47 - 1.26
60-69	1.32	0.84 - 2.08	1.59	0.82 - 3.05	1.09	0.54 - 2.21
70-	3.06	1.47 - 6.37	2.76	0.96 - 7.89	4.82	1.53 - 15.2
test for trend		NS		*P<0.05*		NS

• All women: adjusted for age, menopausal status and other variables listed.
  Premenopausal and postmenopausal women: adjusted for age and other variables listed.

Current smokers were at significantly greater risk in all women (1.63; 1.11-2.39) and in post-menopa usal women (2.73; 1.38-5.39).

Women, when weighing 70 kg or more, were also at grea ter risk (RR: 3.06 in all wome n, 2. 76 in premenopausal women, and 4.82 in postmenopausal women). For premenopausal women, a significant trend of increasing risk with increasing weight was detected *(P* for trend <0.05).

Family history of breast cancer, history of benign breast disease, ages at menarche and menopause, lactation, drinking habits and height were not significantly related to breast cancer risk.

DISCUSSION

In our study, there is one important methodologica l limitation. Our control series might more prevalently include women with benign breast disease tha n general female population, because we selected, though randomly, the controls from women who sought for breast examination at the department of breast surgery and were later proved not to have breast cancer. Accordingly, when a potential risk factor for breast cancer is positively associated with the risk of benign breast disease, then the RR obtained for such a factor might be conservative. Conversely, the risk for breast cancer might be over-estimated, when a potential risk factor for breast cancer is negatively linked to the risk of benign breast disease.

Family history of breast cancer is consistently incriminated as a risk factor for female breast cancer.[18] Our failure in finding an association between breast cancer and family history ma y be partly ascribable to the excessive inclusion of women with benign breast disease in our control series, since family history of breast cancer is known to be positivelt associated with the history of benign breast disease.[2,28]

Both early mena rche[1,5,9-12] and late menopause[2,4,10,11,13] are well-established risk factors. In Japa n, however, significant relevance of early menarche and late menopause to breast cancer risk has not always been detected,[8,19] likewise our study.

Decreasing risk of breast cancer with increasing duration of menstrual cycle has been suggested in some studies,[1,29] as did our study. We found a significant association between regular menstrual cycle and an increased premenopausal breast cancer risk, but this was not detected m prev10us stud'les.[19] These two pa rticular findings on menstruation may suggestively

indicate that breast cancer risk appears to be directly related to the cumulative number of regular ovulatory cycles.[29,30]

Late age at first birtWfull-term pre gnancv is known to be linked to breast cancer risk.r.[3-6,8,<11,2,14,15] Our study also detected a significantly larger RR for later age at first birth, particula rly in postmenopausal women.

Several recent studies have noted that frequent full term pregnancy or birth has a protective effect against breast cancer, independently of age at first birtWfull term pregnancy.[1,7,14] In our study also, an independent and significant trend of decreasing risk with increasing number of livebirths was observed, particularly in premenopausal women. This finding may essentially indicate that a recently increasing breast cancer incidence in Japan is partly related to the rapidly declined birth rate.[31]

Premenopausal women who had ever lactated were not found to be at a significantly smaller risk of breast cancer by the multivariate analysis.

An association between smoking habits and breast cancer risk remains inconclusive. Most studies have found no clear assoc1ahon,[3,8,20,22] wh"1le some investigators have suggested an unfavorable effect of smoking habits on breast cancer.[19,21] In the present study, smoking habits was found to be associated with breast cancer risk, likewise a previous study conducted in Nagoya, Japan.[19] The RR for current smokers in our study, particula rly in postmenopausal women, might be over estimated, possibly due to the potentially excessive number of women with benign breast disease in our controls, since benign breast disease was reported as negatively associated with smoking habits in postmenopausal women.[28,32] In our study, we failed to detect dose-response relationship between the number of cigarettes smoked per day and breast cancer risk.

A positive association between alcohol consumf:tion and breast cancer has been reported in many,[3,6,13,18] but not a11,[2,5,18,19] epidem10logical studies. The present study, however, did not show a significa ntly larger RR for current drinkers.

Obese women were at significantly greater risk of postmenopausal breast cancer, which is in food agreement with previous findings.[1,8,1,16,17] In premenopausal women, a significant trend of increasing breast cancer risk with increasing weight was observed. This finding might, however, be attributable to excessive inclusion of benign breast disease in our controls, beca use benign breast disease is more

prevalent in premenopausal women and obesity is negative! associated with the risk of this disease[27,28,3]

Several studies have reported a positive association between height and female breast cancer,[11,34] but we did not find such an association.

CONCLUSION

Our study disclosed the following major findings: (a) the more the number of livebirths, the smaller the female breast cancer risk, particularly in premenopausal women; (b) in premenopausal women, regular menstrual cycle significantly increased the risk, and its increasing duration decreased the risk; (c) current smokers experienced a significantly larger RR, particularly in postmenopausal women; (d) obese women were at a significantly greater risk of postmenopausal breast cancer; (e) the later the age at first livebirth, the higher the postmenopausal breast cancer risk; (f) family history of breast cancer, history of benign breast disease, ages at menarche and menopause, lactation, drinking habits and height were independently not associated with female breast cancer risk.

REFERENCES

1. Yuan JM, Yu MC, Ross RK, Gao YT, Henderson BE. Risk factors for breast cancer in Chinese women in Shanghai. Cancer Res 1988;48: 1949-53.

2. Rosenberg L, Palmer JR, Miller DR, Clarke EA, Shapiro S. A case-control study of alcoholic beverage consumption and breast cancer. Am J Epidemiol 1990;131:6-14.

3. Nasca PC, Baptiste MS, Field NA, Metzger BB, Black M, Kwon CS, et al. An epidemiological case-control study of breast cancer and alcohol consumption. Int J Epidemiol 1990;19:532-8.

4. Segala C, Gerber M, Richardson S. The pattern of risk factors for breast cancer in a southern France population. Interest

5. Simon MS, Carman W, Wolfe R, Schottenfeld D. Alcohol consumption and the risk of breast cancer: a report from the Tecumseh Oimmunity Health Study. J Clin Epidemiol 1991;44:755-61.

6. Ferraroni M, Decarli A, Willett WC, Marubini E. Alcohol and breast cancer risk: a case-control study from northern Italy. Int J Epidemiol 1991;20:859-64.

7. Yoo KY, Tajima K, Kuroishi T, Hirose K, Yoshida M, Miura S, et al. Independent protective effect of lactation against breast cancer: a case-control study in Japan. Am J Epidemiol 1992;135:726-33.

8. Kato I, Miura S, Kasumi F, Iwase T, Tashiro H, Fujita Y, et al. A case-control study of breast cancer among Japanese women: with special reference to family history and reproductive and dietary factors. Breast Cancer Res Treat 1992;24:51-9.

9. Bouchardy C, Le MG, Hill C. Risk factors for breast cancer according to age at diagnosis in a French case control study. J Clin Epidemiol 1990;43:267-75.

10. Yu SZ, Lu RF, Xu DD, Howe GR. A case-control study of dietary and nondietary risk factors for breast cancer in Shanghai. Cancer Res 1990;50:5017-21.

11. Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. Int J Cancer 1990;46:796-800.

12. Gapstur SM, Potter JD, Sellers TA, Folsom AR. Increased risk of breast cancer with alcohol consumption in postmenopausal women. Am J Epidemiol 1992; 136:1221-31.

13. Zaridze D, Lifanova Y, Maximovitch D, Day NE, Duffy SW. Diet, alcohol consumption and reproductive factors in a case-control study of breast cancer in Moscow. Int J Cancer 1991;48:493-501.

14. Ewertz M, Duffy SW, Adami HO, Kvale G, Lund E, Meirk O, et al. Age at first birth, parity and risk of breast cancer: a meta analysis of 8 studies from the Nordic countries. Int J Cancer 1990;46:597-603.

15. la Vecchia C, Negri E, Franceschi S, Parazzini F. Long-term impact of reproductive factors on cancer risk. Int J Cancer 1993;53:215-9.

16. Parazzini F, la Vecchia C, Negri E, Bruzzi P, Palli D, Boyle P, et al. Anthropometric variables and risk of breast cancer. Int J Cancer 1990;45:397-402.

17. Sellers TA, Kushi LH, Potter JD, Kaye SA, Nelson CL, McGovern PG, et al. Effect of family history, body-fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. N Engl J Med 1992;326:1323-9.

18. Howe G, Rohan T, Decarli A, Iscovich J, Kaldor J, Katsouyanni K, et al. The association between alcohol and breast cancer risk: evidence from the combined analysis of six dietary case-control studies. Int J Cancer 1991;47:707-10.

19. Yoo KY, Tajima K, Kuroishi T, Hirose K, Miura S, Murai H, et al. Life-style in relation to the risk of breast cancer. J Epidemiol 1992;2 (Suppl):Sl55-65.

20. Rohan TE, Baron JA. Cigarette smoking and breast cancer. Am J Epidemiol 1989;129:36-42.

21. Chu SY, Stroup NE, Wingo PA, Lee NC, Peterson HB, Gwinn ML, et al. Cigarette smoking and the risk of breast cancer. Am J Epidemiol 1990;131:244-53.
22. Field NA, Baptiste MS, Nasca PC, Metzger BB. Cigarette s.mo\dng and breast cancet. \ntl Epidemio\ 1992;21".842-8.
23. The Research Group for Population-based Orncer Registration. Cancer incidence in Japan, 1975-1979. Osaka: The Osaka Orncer Registry, 1984.
24. Research Group for Population-based Orncer Registration in Japan. Cancer incidence and incidence rates in Japan in 1985-Estimates based on data from seven population-based cancer registries. Jpn J Clin Oncol 1990;20:212-8.
25. Breslow NE, Day NE. Unconditional logistic regression for large strata. In Davis W editor. Statistical Methods in Cancer Research, vol 1. Lyon: IARC, 1980:192-246.
26. Rothman KJ. Modern Epidemiology. Boston: Little, Brown and Company, 1986.
27. Pastides H, Kelsey JL, Holford TR, LiVolsi VA. An epidemiologic study of fibrocystic breast disease with reference to ductal epithelial atypia. Am J Epidemiol 1985;121:440-7.
28. Berkowitz GS, Kelsey JL, LiVolsi VA, Holford TR, Merino MJ, Ort S, et al. Risk factors for fibrocystic breast disease

and its histopathologic components. J Natl Cancer Inst 1985;75:43-50.
29. Olsson H, L.a ndin-Olsson M, Gullberg B. Retrospective assessment of menstrual cycle length in patients with breast cancer, in patients with benign breast dis.ease, and in women without breast disease. J Natl Cancer Inst l983;70:17 -20.
30. Henderson BE, Ross RK, Judo HL, Krailo MD, Pike MC. Do regular ovulatory cycles increase breast cancer risk? Cancer 1985;56:1206-8.
31. Ministry of Health and Welfare of Japan. Vital Statistics of Japan 1991, vol 1. Tokyo: Kousei Toukei Kyoukai, 1993.
32. Berkowitz GS, Canny PF, LiVolsi VA, Merino MJ, O'-Connor TZ, Kelsey JL, et al. Cigarette smoking and benign breast disease. J Epidemiol Community Health 1985;39:308-13.
33. Yu H, Rohan TE, Cook MG, Howe GR, Miller AB. Risk factors for fibroadenoma: a case-control study in Australia. Am J Epidemiol 1992;135:247-58.
34. N, Triaspolitica. "Kanker Payudara: Informasi, Penyebab, Gejala, Stadium Dan Pengobatan." *Mau Nanya Dong Dok*. N.p, 28 June 2017. Web. 30 June 2017. <https://nanyadongdok.blogspot.com/2017/06/kanker-payudara-informasi-penyebab.html>.