To explore risk factors for 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. Following significant findings emerged: (a) A large number of livebirths was associated with a decreased risk in premenopausal women (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 (2.50; 1.16-5.38). (c) Current smokers experienced an increased risk (1.63; 1.11-2.39). (d) Heavy weight was associated with a greater risk of postmenopausal breast cancer: RR for those weighing 70 kg or more relative to those weighing 50 kg or less being 4.82 (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; 3.54; 1.03-12.2 for ages of 30-34 and 35 years and more, respectively). J Epidemiol, 1994; 4: 65-71.
Table 1. Age distribution of cases and controls by menopausal status.

| Age   | All women | Premenopausal | Postmenopausal |
|-------|-----------|---------------|----------------|
| 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  | 11.7| 71  | 11.7| 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| 900 | 100.0| 170 | 100.0| 484 | 100.0| 130 | 100.0| 416 | 100.0|

Table 2. Relative risks (RR) and 95% confidence intervals (CI) of risk factors for breast cancer by menopausal status (1).

| Family history of breast cancer | All women | Premenopausal | Postmenopausal |
|---------------------------------|-----------|---------------|----------------|
|                                  | Cases/   | RR  | 95% CI | Cases/ | RR  | 95% CI | Cases/ | RR  | 95% CI |
| no                              | Controls |     |        | Controls |     |        | Controls |     |        |
| no                              | 275      | 843 | 1.00   | 154     | 452 | 1.00   | 121     | 391 | 1.00   |
| yes                             | 16       | 40  | 1.29   | 1.70-2.39| 11  | 20  | 1.64   | 0.70-3.83| 5   | 20  | 0.92   | 0.31-2.67|
| History of benign breast disease|           |     |        |          |     |        |          |     |        |
| no                              | 261      | 779 | 1.00   | 142     | 409 | 1.00   | 119     | 370 | 1.00   |
| yes                             | 39       | 121 | 0.98   | 0.65-1.46| 28  | 75  | 1.05   | 0.63-1.78| 11  | 46  | 0.73   | 0.35-1.54|
| Age at menarche                 |           |     |        |          |     |        |          |     |        |
| -12                             | 64       | 181 | 1.00   | 1.09    | 0.72-1.63| 27  | 80  | 0.90   | 0.40-2.05|
| 13                              | 76       | 207 | 1.09   | 0.72-1.63| 49  | 127 | 1.22   | 0.74-2.01| 23  | 85  | 0.74   | 0.32-1.71|
| 14                              | 57       | 205 | 0.82   | 0.54-1.26| 34  | 120 | 0.79   | 0.46-1.36| 23  | 85  | 0.74   | 0.32-1.71|
| 15+                             | 99       | 294 | 0.94   | 0.63-1.42| 35  | 89  | 0.93   | 0.53-1.65| 64  | 205 | 0.85   | 0.40-1.77|
| test for trend                  |          |     |        |          |     |        |          |     |        |
| Age at menopause                |           |     |        |          |     |        |          |     |        |
| -44                             |          |     |        |          |     |        |          |     |        |
| 45-49                           |          |     |        |          |     |        |          |     |        |
| 50-54                           |          |     |        |          |     |        |          |     |        |
| 55+                             |          |     |        |          |     |        |          |     |        |
| test for trend                  |          |     |        |          |     |        |          |     |        |
| Regularity of menstrual cycle   |          |     |        |          |     |        |          |     |        |
| irregular                       |          |     |        |          |     |        |          |     |        |
| regular                         |          |     |        |          |     |        |          |     |        |
| Duration of menstrual cycle     |          |     |        |          |     |        |          |     |        |
| (days)                          |          |     |        |          |     |        |          |     |        |
| -27                             |          |     |        |          |     |        |          |     |        |
| 28-29                           |          |     |        |          |     |        |          |     |        |
| 30-31                           |          |     |        |          |     |        |          |     |        |
| 32+                             |          |     |        |          |     |        |          |     |        |
| test for trend                  |          |     |        |          |     |        |          |     |        |
| Age at first birth              |          |     |        |          |     |        |          |     |        |
| -24                             |          |     |        |          |     |        |          |     |        |
| 25-29                           |          |     |        |          |     |        |          |     |        |
| 30-34                           |          |     |        |          |     |        |          |     |        |
| 35+                             |          |     |        |          |     |        |          |     |        |
| test for trend                  |          |     |        |          |     |        |          |     |        |

All women : adjusted for age, menopausal status and other variables listed on the Table 2 and 3.
Premenopausal women and postmenopausal women : adjusted for age and other variables listed on the Table 2 and 3.
NS : not significant.
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Table 3. Relative risks (RR) and 95% confidence intervals (CI) of risk factors for breast cancer by menopausal status (2).

|                      | All women          | Premenopausal       | Postmenopausal      |
|----------------------|--------------------|---------------------|---------------------|
|                      | Cases/ Controls    | RR 95% CI           | Cases/ Controls     | RR 95% CI           | Cases/ Controls    | RR 95% CI           |
| Number of livebirths |                    |                     |                     |                     |                    |                     |
| 0                    | 46 115 1.00        |                     | 34 58 1.00          |                     | 12 57 1.00         |                     |
| 1                    | 46 125 0.85        | 0.44-1.64           | 24 65 0.52          | 0.21-1.32           | 22 60 1.68         | 0.57-4.98           |
| 2                    | 110 357 0.78       | 0.43-1.44           | 68 223 0.40         | 0.17-0.95           | 42 134 1.74        | 0.62-4.88           |
| 3+                   | 42 166 0.61        | 0.31-1.20           | 13 69 0.24          | 0.08-0.66           | 29 97 1.62         | 0.55-4.74           |
| test for trend       | NS                 |                     | NS                  |                     | NS                 |                     |
| Lactation            |                    |                     |                     |                     |                    |                     |
| never                | 62 162 1.00        |                     | 41 86 1.00          |                     | 21 76 1.00         |                     |
| ever                 | 211 670 1.08       | 0.65-1.80           | 112 365 1.21        | 0.59-2.50           | 99 305 1.00        | 0.45-2.20           |
| Smoking              |                    |                     |                     |                     |                    |                     |
| never smoked         | 221 694 1.00       |                     | 123 364 1.00        |                     | 98 330 1.00        |                     |
| ex-smoker            | 15 52 0.91         | 0.49-1.70           | 10 29 0.96          | 0.42-2.20           | 5 23 0.80          | 0.28-2.32           |
| current smoker       | 58 116 1.63        | 1.11-2.39           | 34 79 1.23          | 0.75-2.03           | 24 37 2.73         | 1.38-5.39           |
| Alcohol drinking     |                    |                     |                     |                     |                    |                     |
| no                   | 187 563 1.00       |                     | 93 296 1.00         |                     | 94 267 1.00        |                     |
| yes (current)        | 109 306 1.04       | 0.77-1.39           | 76 180 1.36         | 0.92-2.00           | 33 128 0.71        | 0.42-1.19           |
| Height (cm)          |                    |                     |                     |                     |                    |                     |
| <149                 | 36 136 1.00        |                     | 14 42 1.00          |                     | 22 94 1.00         |                     |
| 150-154              | 102 311 1.22       | 0.78-1.92           | 46 159 0.77         | 0.37-1.62           | 56 152 1.81        | 0.98-3.34           |
| 155-159              | 90 283 1.13        | 0.70-1.82           | 58 180 0.71         | 0.34-1.49           | 32 103 1.51        | 0.76-2.98           |
| 160-                 | 63 146 1.46        | 0.86-2.48           | 47 97 1.08          | 0.49-2.37           | 16 49 1.46         | 0.62-3.46           |
| test for trend       | NS                 |                     | NS                  |                     | NS                 |                     |
| Weight (kg)          |                    |                     |                     |                     |                    |                     |
| <49                  | 91 321 1.00        |                     | 43 177 1.00         |                     | 48 144 1.00        |                     |
| 50-59                | 140 421 1.18       | 0.86-1.62           | 90 225 1.77         | 1.12-2.80           | 50 196 0.77        | 0.47-1.26           |
| 60-69                | 43 120 1.32        | 0.84-2.08           | 23 63 1.59          | 0.82-3.05           | 20 57 1.09         | 0.54-2.21           |
| 70+                  | 17 18 3.06         | 1.47-6.37           | 7 12 2.76           | 0.96-7.89           | 10 6 4.82          | 1.53-15.2           |
| test for trend       | p<0.05             |                     | p<0.05              |                     | NS                 |                     |

All women : adjusted for age, menopausal status and other variables listed on the Table 2 and 3.
Premenopausal women and postmenopausal women : adjusted for age and other variables listed on the Table 2 and 3.
NS : not significant.

cancer, history of benign breast disease, regularity and duration of menstrual cycle (for premenopausal women), ages at menarche and menopause, age at first birth, number of livebirths, episodes of lactation, smoking and drinking habits, height and weight. This information has been collected from all out-patients before examination, that is, prior to diagnosis.

Of the 5,084 female patients who visited the department during the study period, 314 were newly diagnosed as having breast cancer histologically. Of 314 breast cancer patients, we excluded 11 patients with missing information on menopausal 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 present study.

Controls were randomly selected from the remaining 4,770 patients without 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). Almost all the controls (97.6%) were exactly matched for age, while 1.8% and 0.7% of them within ±1-3 and ±4-6 years, respectively. Table 1 shows the age distribution of the study subjects (300 cases and 900 controls) by menopausal status. The mean ages (±standard deviations) of the cases and controls were 50.8±10.7 and 50.7±10.5 years, respectively.

All analyses were performed for premenopausal and postmenopausal women, separately or totally. The RRs by menopausal status were obtained using unconditional multiple logistic regression analysis44) adjusted for age and other variables potentially confounded, irrespective of the matching. Unconditional multiple logistic regression, not conditional one, was also applied to the analysis for all
Table 4. Relative risks (RR) and 95% confidence intervals (CI) for breast cancer according to number of cigarettes smoked per day by menopausal status.

| Number of cigarettes smoked per day | All women (Cases/Controls) | Premenopausal (Cases/Controls) | Postmenopausal (Cases/Controls) |
|------------------------------------|-----------------------------|-------------------------------|-------------------------------|
|                                    | RR 95% CI                    | RR 95% CI                     | RR 95% CI                     |
| 0                                  | 236 746 1.00                 | 133 393 1.00                  | 103 353 1.00                  |
| 1-19                               | 35 74 1.67 1.06-2.63         | 21 54 1.21 0.67-2.19          | 14 20 3.11 1.37-7.10          |
| 20+                                | 18 38 1.44 0.77-2.68         | 12 22 1.54 0.69-3.44          | 6 16 1.68 0.56-5.10           |
| test for trend                     | p<0.05                       | NS                            | p<0.05                        |

All women: adjusted for age, menopausal status and other variables listed on the Table 2 and 3.
Premenopausal women and postmenopausal women: adjusted for age and other variables listed on the Table 2 and 3.
NS: not significant.

RESULTS

Table 2 and 3 summarize the RRs obtained by the logistic regression analyses.

Family history of breast cancer and history of benign breast disease were found neither to increase nor to decrease breast cancer risk, though family history demonstrated somewhat greater relative risk than unity (1.64) in premenopausal women.

Ages at menarche and menopause were not significantly associated with breast cancer risk, though regular menstrual cycle increased the risk in premenopausal women. Decreasing risk of breast cancer with increasing duration of menstrual cycle was also suggested.

Late age at first birth was positively associated with breast cancer risk in postmenopausal women; the RR being 2.85 (95% CI: 1.16-6.99) for age of 30-34 years, and 3.54 (1.03-12.2) for that of 35 years or older. A large number of livebirths was associated with a decreased risk, particularly in premenopausal women; the RR relative to none was 0.40 (95% CI: 0.17-0.95) for 2 livebirths and 0.24 (0.08-0.65) for 3 or more livebirths. “Ever lactated” was found neither to increase nor to decrease the risk.

Current smokers were found to be at an increased risk particularly for postmenopausal breast cancer (RR: 1.63; 95% CI: 1.11-2.39 for all women and 2.73; 1.38-5.39 for postmenopausal women), though the dose-response relationship between the number of cigarettes smoked per day and the risk was not clear (Table 4). Current drinkers were likely to be at an increased risk in premenopausal women (RR: 1.36; 95% CI: 0.92-2.00).

Heavy weight was associated with a significantly greater risk, particularly for postmenopausal breast cancer; the RR for those weighing 70 kg or more relative to less than 50 kg was 4.82 (95% CI 1.53-15.2). No significant association of height with breast cancer risk was detected.

DISCUSSION

When assessing our findings described above, one methodological limitation should be kept in mind.

Our control series might more prevalently include women with benign breast disease than 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. Usually, definite diagnosis is not always made in the clinical practice when malignancy is not suspected. Therefore, we could not systematically exclude women with benign breast disease from our controls. However, patients with histologically confirmed benign breast disease are known to comprise less than 5% among all the patients without breast cancer in the department (unpublished data). Symptomatic (not biopsied) benign breast disease was also known not to be so related to the risk factors for breast cancer as biopsied one45). Since our control series were selected from the patients in the same department where the cases were identified, then study subjects shared similar demographic characteristics each other. The data collection before examination could reduce information biases such as recall one. Therefore, despite the limitation mentioned above, the present control series would be useful as a reference group.

Family history of breast cancer is consistently incriminated as a risk factor for female breast cancer1-13). Our
failure in finding an association with family history may be partly ascribable to excessive inclusion of women with benign breast disease in our control series, since family history of breast cancer is known to be positively associated with history of benign breast disease\(^45\)–\(^47\).

Both early menarche\(^2,10,16–21\) and late menopause\(^7,9,14–17,19,20,22\) are well-established risk factors. In Japan, however, significant relevance of early menarche and late menopause to breast cancer risk has not always been detected\(^13,35,43\) likewise our study.

Decreasing risk of breast cancer with increasing duration of menstrual cycle has been suggested in some studies\(^2,48\), as did our study. We found a significant association of regular menstrual cycle with an increased premenopausal breast cancer risk, but this was not detected in previous studies\(^17,20\). These two particular findings on menstruation may suggestively indicate that breast cancer risk appears to be directly related to the cumulative number of regular ovulatory cycles\(^48,49\).

Many studies have demonstrated that late age at first birth/full-term pregnancy is linked to the risk of breast cancer\(^2,8,11,13,18,21,23–25\). Our study also detected a larger RR for later age at first birth, particularly in postmenopausal women.

Several recent studies have noted that frequent full-term pregnancies or birth has a protective effect against breast cancer, independently of age at first birth/full-term pregnancy\(^2,16,18,21,24,26\). In our study also, a large number of livebirths was independently associated with a decreased risk, 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\(^50\).

Ever-lactated women were not at a significantly smaller risk of breast cancer, when the covariates were adjusted. Since almost studies, which detected the independent protective effect of breast-feeding, examined the relationship between lactation period and breast cancer risk\(^2,12,23\), then further investigations focusing on the period of lactation would be required to assess the effect of lactation more properly.

An association of smoking habits with breast cancer risk still remains to be inconclusive. Most studies have found no clear association\(^3,8,13,27,33,36–38,40\)\(^,\) while some investigators have suggested an unfavorable effect of smoking habits on breast cancer\(^2,13,36,39\). In the present study, smoking habits were found to be associated with breast cancer risk, likewise a previous study conducted in Nagoya, Japan\(^36\). In our study, we failed to detect clear dose-response relationship between the number of cigarettes smoked per day and breast cancer risk. Nevertheless, more detailed studies will be warranted on smoking habits, since our findings certainly indicate a positive association of smoking habits with breast cancer risk in females in Japan.

A positive association between alcohol consumption and breast cancer has been reported in many\(^3,6,8,11,15,21,22,34\), but not all\(^2,10,13,27,33,34\) epidemiological studies. The present study, however, did not show a significantly larger RR for current drinkers. Studies that take an amount of alcohol consumed into consideration will be required to assess this association more properly.

For anthropometric factors, we found women with heavy weight to be at significantly greater risk of postmenopausal breast cancer, which is in good agreement with previous findings\(^2,13,28,30,31\). Several studies have reported a positive association between height and female breast cancer\(^2,28,51\), but we did not find such an association.

In short, our study disclosed the following major findings. (a) A large number of livebirths was associated with a decreased risk, particularly in premenopausal women; (b) In premenopausal women, regular menstrual cycle significantly increased the risk, and its increasing duration suggestively decreased the risk; (c) Current smokers experienced a significantly larger RR, particularly in postmenopausal women; (d) Heavy weight was associated with a significantly greater risk of postmenopausal breast cancer; (e) The later the age at first livebirth, the higher the postmenopausal breast cancer risk; (f) Ages at menarche and menopause, lactation, drinking habits and height were not independently associated with female breast cancer risk.

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