A hospital-based case-control study was conducted to examine changes in odds ratio of risk factors of breast cancer according to age group. Patients aged 30 to 69 years were selected as subjects. Cases were 1,110 female patients with breast cancer diagnosed during 1988 to 1992 at Aichi Cancer Center Hospital. Controls were 20,044 first-visit non-cancer patients during the same period. Logistic model was applied separately to the four age groups (30-39 years, 40-49 years, 50-59 years and 60-69 years at first visit), to estimate odds ratios of reproductive history, family history of breast cancer, body mass index, smoking, and drinking habits. Late menarche tended to give an odds ratio below unity in the age groups older than 50 years. Child birth and age at first delivery were significant risk factors for all four age groups. Odds ratio of having a sister with breast cancer was consistently high among the four age groups, while that of having mother with breast cancer was not. Body mass index over 24 was found to significantly increase the risk in age group 60-69. In age group 40-49, the smoking and drinking habits significantly increased the risk. These findings suggested the attribution of the risk factors to breast cancer could not always be similar among the age groups. J Epidemiol, 1995; 5: 99-105.

Female breast cancer has been increasing in Japan1), along with remarkable changes in life style and reproductive history among Japanese women. The increase was observed similarly in any age groups from 30 to 79 years2). The finding may be attributed to increases in exposures to risk factors in any age groups, but the extent of attribution may differs among age groups.

This paper aims to document the odds ratio of well-established risk factors of female breast cancer according to age group, using data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC).

MATERIAL AND METHODS

Aichi Cancer Center Hospital, which has 500 beds for inpatient care, is located in a residential area of Nagoya in Aichi Prefecture. Population is 2.2 million inside Nagoya and 6.7 million in Aichi Prefecture. About 40% of outpatients of the hospital live in Nagoya city and another 40% live in Aichi Prefecture outside Nagoya. According to the Aichi Cancer Registry covering Aichi Prefecture, 976 cancer patients (5.7% of all reported cases) were reported from Aichi Cancer Center Hospital to the Registry in 1992. During the period from 1988 to 1992, referrals from other hospitals were 14.4% of male first-visit outpatients and 10.0% of female ones. The rest were non-referral patients who suffered from some symptoms or who were advised to visit a hospital after cancer screening at worksite or at a regional center. Approximately 20% of male and 11% of female first-visit outpatients during 1988 to 1992 were found to have cancer.

HERPACC, an epidemiologic research program established at Aichi Cancer Center Hospital in 1987, provided the present study material. Since the details of HERPACC have been described elsewhere3), the outline of the Program is explained briefly. The main database consists of life style data routinely collected from first-visit outpatients by a self-administered questionnaire. It includes questions on occupation, medical history, height, weight,
marital status, family history (parents and siblings), smoking, alcohol, sleeping, physical exercise, history of screening for cancer, stools, female reproductive history (menarche, menopause, pregnancy, delivery, and breast feeding), and dietary habits mainly in terms of intake frequency.

The questionnaire is given to all the new outpatients aged 18 or older (about 8,000 per year) except those who visited after hours, those who refused to participate in the Program, and the aged with problems such as poor visual acuity and illiteracy. Since 1989, more than 99 percent of the eligible outpatients have responded to the questionnaire. As of May 1994, data from 36,944 first-visit patients during 1988 to 1992 were accumulated in a computer of the Division of Epidemiology, Aichi Cancer Center Research Institute.

The questionnaire is handed out on the first day of hospital visit, and collected on the same day by an interviewer who checks it. After a series of examinations, patients with cancer are routinely reported to the office of the Hospital Cancer Registry, from where the reports are sent to the Division of Epidemiology, HERPACC office.

The subjects of this case-control study were selected from the 36,944 outpatients. There were 152 breast cancer cases aged 30-39 years, 447 cases aged 40-49 years, 303 cases aged 50-59 years, and 208 cases aged 60-69 years. The corresponding numbers of the female non-cancer patients were 4,513, 8,299, 4,776, and 2,456, respectively. The age distribution at first visit is shown in Table 1.

Since the diagnoses of the non-cancer patients were not available, we examined medical charts of randomly sampled 1,000 first-visit outpatients classified into the “non-cancer patients”, who visited the hospital during 1988 to 1989. As shown in Table 2, 664 out of 951 patients (69.8%) had no disease, though it was found that eight cancer patients (four with lung cancer, three with stomach

| Table 1. Age at first visit of cases and controls. |
| --- | --- | --- |
| Age | Cases | Controls |
| --- | --- | --- |
| 30-34 | 42 (4.4%) | 1,740 (8.7%) |
| 35-39 | 110 (9.9%) | 2,773 (13.8%) |
| 40-44 | 216 (19.5%) | 4,382 (21.9%) |
| 45-49 | 231 (20.8%) | 3,917 (19.5%) |
| 50-54 | 163 (14.7%) | 2,698 (13.5%) |
| 55-59 | 140 (12.6%) | 2,078 (10.4%) |
| 60-64 | 123 (11.1%) | 1,500 (7.5%) |
| 65-69 | 85 (7.7%) | 956 (4.8%) |
| Total | 1,110 (100%) | 20,044 (100%) |

| Table 2. Diagnosis of randomly sampled 1,000 non-cancer patients who visited Aichi Cancer Center Hospital during 1988 to 1989. |
| --- | --- | --- |
| Breast Clinic | 279 | Gynecology Clinic |
| Fibroadenoma | 21 | Cervical cancer |
| Cysts | 15 | Dysplasia |
| Lipoma | 7 | Polyp of the cervix |
| Lymphadenitis | 1 | Myoma uteri |
| Mastopathy | 35 | Endometriosis |
| Mastitis | 3 | Cysts of the ovary |
| Others | 4 | Others |
| No disease | 194 | No disease |
| Digestive Diseases. Clinic | 309 | Respiratory Diseases. Clinic |
| Stomach cancer | 3 | Lung cancer |
| Polyps | 30 | Benign tumor |
| Stomach/duodenum | 7 | Pneumonia |
| Gallbladder | 32 | Tuberculosis |
| Colon/rectum | 15 | Fibrosis of the lung |
| Gastric/duodenal ulcer | 12 | Other diseases |
| Cholelithiasis | 7 | No disease |
| Liver diseases | 22 | Total |
| Other diseases | 180 | 1,000 |
| No disease | 96 | Cancer |
| Other Clinics | 13 | Other diseases |
| Benign tumor | 25 | No disease |
| Other diseases | 58 | Chart not filed* |

* Medical charts for patients who had made visits to the hospital past six months were not filed in medical chart section.
cancer, and one with cervical cancer) had been included. They were not reported to the Hospital Cancer Registry, because doctors introduced them to other hospitals before treatment, or because they visited to ask for a specialist’s opinion.

We counted hospital visits for 450 out of the 1,000 patients. Eighty patients (17.8%) were only one time visit, 114 (25.3%) were two times, 78 (17.3%) were three times, 41 (9.1%) were four times, and 109 (24.2%) were more than four times. Medical charts of 28 patients (6.2%) were not filed in medical chart section but in reception area. They were regular visitors whose last visit was within six months or so. Consequently, about 60% of first-visit patients visited the hospital three times or less. These findings indicated that majority of the outpatients were disease free inhabitants whose purpose of visit was to be examined whether they had cancer or not.

All the eligible female non-cancer patients were used here as controls to estimate the odds ratios of selected risk factors, because an individual matching method has no advantages in this dataset4). The odds ratios were calculated by unconditional logistic model using SAS Logistic Procedure5).

RESULTS

Distribution of risk factors according to age group

In order to document the distribution of the selected risk factors by age group, data from the non-cancer patients were analyzed.

As shown in Table 3, a marked change in mean age at menarche and its standard deviation were observed. The mean age at menarche was highest in those aged 60-69 years (15.0 years) and lowest in those aged 30-39 years (12.9 years), and the standard deviation was wider in the older age groups.

Child birth variables were classified into five categories. The fifth category “no birth & unmarried” means those who specified “unmarried” and who had not given birth. The fourth category comprises those who specified a marital status other than “unmarried” and those who did not respond to the marital status question. Marital status was ignored for subjects who had given birth. The percentage of females who had first given birth at age 23 or younger was 19.6% in age group 30-39, and 34.4% in age group 60-69. The percentage for “no birth & unmarried” was the highest in age group 30-39, and that for “no birth” was the highest in age group 60-69.

Mother’s history of breast cancer was higher in the younger age groups. However, having at least one sister with breast cancer was not so, because the younger age groups were less likely to have sisters, and their sisters were still young therefore unlikely to have developed breast cancer. Even when the percentage of subjects with at least one sister’s breast cancer history was divided by the percentage of those who had a sister, it was highest in age group 50-59.

On average, women from the younger age groups were taller than those from the older, and body mass index (BMI; kg/m²) before onset and at age 20 was smaller in the younger age groups. Smoking and drinking habits before onset were more prevalent in the younger age groups.

Odds ratio by age group

Table 4 shows the odds ratio and its confidence interval of each risk factor, adjusted for age and year of visit. Except age group 50-59, statistically significant odds ratio was not observed for age at menarche. When age at

| Variable | Age at first visit |
|----------|-------------------|
|          | 30-39 years | 40-49 years | 50-59 years | 60-69 years |
| Number   | 4,513       | 8,299       | 4,776       | 2,456       |
| Mean     | 12.9        | 13.5        | 14.6        | 15.0        |
| S.D.     | 1.25        | 1.34        | 1.69        | 1.90        |
| <14 years | 69.5%       | 51.2%       | 25.1%       | 24.3%       |
| 14-15 years | 28.7%     | 43.2%       | 49.8%       | 37.3%       |
| ≥16 years  | 1.8%        | 5.6%        | 25.1%       | 38.4%       |
| First delivery |           |             |             |             |
| <24 years  | 19.6%       | 24.7%       | 25.5%       | 34.4%       |
| 24-26 years | 36.7%       | 42.5%       | 38.9%       | 29.3%       |
| ≥27 years  | 27.4%       | 23.7%       | 27.2%       | 23.1%       |
| no birth   | 9.2%        | 5.8%        | 5.7%        | 9.5%        |
| no birth & unmarried | 7.1% | 3.4% | 2.7% | 3.6% |
| Family history of breast cancer |          |             |             |             |
| mother    | 1.97%       | 1.55%       | 1.28%       | 0.73%       |
| sisters   | 0.60%       | 1.39%       | 2.32%       | 2.00%       |
| (no sisters) | 36.4%     | 22.0%       | 14.7%       | 15.2%       |
| Height | mean | 156.0 cm | 154.9 cm | 153.1 cm | 151.0 cm |
| s.d. | 4.8 cm | 4.8 cm | 5.0 cm | 5.2 cm |
| BMI before onset | mean | 21.0 | 22.1 | 22.6 | 22.7 |
| ≥24 | 8.4% | 15.8% | 22.6% | 25.1% |
| BMI at age 20* | mean | 20.2 | 20.4 | 20.7 | 21.4 |
| ≥22 | 12.7% | 16.1% | 21.7% | 30.7% |
| Smokers | 17.4% | 11.6% | 8.1% | 6.5% |
| Drinkers with ≥4 times/week | 10.5% | 10.0% | 7.7% | 5.1% |

* Calculated from height at present and weight at age 20
Table 4. Estimated odds ratio and its 95% confidence interval according to age group, adjusted by age and year of visit.

| Variable                        | 30-39 ys | 40-49 ys | 50-59 ys | 60-69 ys |
|---------------------------------|---------|---------|---------|---------|
| Menarche                        |         |         |         |         |
| <14 years                       | 1       | 1       | 1       | 1       |
| 14-15 years                     | 1.21    | 0.83    | 0.70    | 0.91    |
| (0.85-1.71)                     | (0.67-1.01) | (0.53-0.92) | (0.63-1.30) |
| ≥16 years                       | 1.45    | 1.11    | 0.69    | 0.85    |
| (0.52-4.06)                     | (0.75-1.64) | (0.50-0.95) | (0.59-1.23) |
| First delivery                  |         |         |         |         |
| <24 years                       | 1       | 1       | 1       | 1       |
| 24-26 years                     | 1.18    | 1.18    | 1.00    | 1.16    |
| (0.71-1.97)                     | (0.91-1.54) | (0.73-1.37) | (0.79-1.69) |
| ≥27 years                       | 1.67    | 1.52    | 1.36    | 1.57    |
| (1.00-2.79)                     | (1.14-2.02) | (0.98-1.87) | (1.08-2.29) |
| No birth                        | 1.84    | 1.72    | 1.74    | 1.37    |
| (0.96-3.52)                     | (1.14-2.59) | (1.09-2.78) | (0.82-2.29) |
| No birth & unmarried            | 2.21    | 2.82    | 1.45    | 1.59    |
| (1.12-4.34)                     | (1.84-4.32) | (0.73-2.89) | (0.78-3.22) |
| Family history of breast cancer |         |         |         |         |
| Mother                          |         |         |         |         |
| No                              | 1       | 1       | 1       | 1       |
| Yes                             | 0.70    | 1.79    | 0.81    | 2.02    |
| (0.17-2.86)                     | (0.98-3.26) | (0.25-2.59) | (0.59-6.94) |
| Sister (s)                      |         |         |         |         |
| No                              | 1       | 1       | 1       | 1       |
| Yes                             | 2.21    | 2.43    | 1.89    | 2.63    |
| (0.52-9.42)                     | (1.40-4.20) | (1.02-3.47) | (1.31-5.29) |
| BMI before onset                |         |         |         |         |
| <20                             | 1       | 1       | 1       | 1       |
| 20-24                           | 1.16    | 0.92    | 0.85    | 1.05    |
| (0.80-1.69)                     | (0.72-1.16) | (0.63-1.16) | (0.70-1.56) |
| ≥24                             | 1.62    | 0.68    | 1.12    | 2.17    |
| (0.94-2.78)                     | (0.49-0.95) | (0.80-1.57) | (1.46-3.21) |
| BMI at age 20*                  |         |         |         |         |
| <19                             | 1       | 1       | 1       | 1       |
| 19-22                           | 1.33    | 0.82    | 0.80    | 1.29    |
| (0.90-1.96)                     | (0.66-1.03) | (0.60-1.06) | (0.89-1.87) |
| ≥22                             | 1.15    | 0.75    | 0.54    | 0.93    |
| (0.66-1.99)                     | (0.55-1.02) | (0.37-0.79) | (0.62-1.39) |
| Smoking                         |         |         |         |         |
| Non-smokers                     | 1       | 1       | 1       | 1       |
| Ex-smokers                      | 0.91    | 1.40    | 1.18    | 1.14    |
| (0.44-1.89)                     | (0.84-2.36) | (0.65-2.16) | (0.59-2.22) |
| Smokers                         | 0.91    | 1.65    | 0.87    | 1.22    |
| (058-1.42)                      | (1.28-2.13) | (0.55-1.37) | (0.71-2.09) |
| Drinking                        |         |         |         |         |
| Non-drinkers                    | 1       | 1       | 1       | 1       |
| Occasional drinkers             | 0.54    | 1.02    | 1.02    | 1.17    |
| (0.33-0.87)                     | (0.80-1.31) | (0.74-1.42) | (0.73-1.88) |
| Drinkers with ≥4 times/week     | 1.21    | 1.41    | 0.65    | 1.25    |
| (0.75-1.95)                     | (1.06-1.88) | (0.38-1.10) | (0.68-2.32) |

* Calculated from height at present and weight at age 20

Menarche was categorized into two levels (≤13 years and ≥14 years), the odds ratio was 1.22 (95% confidence interval: 95% CI, 0.87-1.71) in age group 30-39, 0.86 (0.71-1.04) in age group 40-49, 0.70 (0.54-0.90) in age group 50-59, and 0.88 (0.64-1.22) in age group 60-69.

The elevated risks for late first delivery or no delivery were observed consistently in all age groups. The finding seemed to be more clear in the younger age groups. When data of the four age groups were combined, the odds ratio was 1.13 for first delivery aged 24 to 26 years, 1.49 for first
delivery aged 27 years or over, 1.61 for no birth, and 2.05 for no birth and unmarried. Based on the combined odds ratio and distribution of delivery history in each age group, the population attributable risk percent (PAR%) was calculated. When the baseline was set to the group whose subjects had first given birth at age 23 years or younger, the PAR% was 23.8% in age group 30-39, 19.5% in age group 40-49, 19.8% in age group 50-59, and 19.8% in age group 60-69. When the odds ratio estimated for each age group was applied, the corresponding PAR% was 29.2%, 23.3%, 13.2%, and 19.0%, respectively.

The mother’s history of breast cancer was not consistent in the odds ratio among the four age groups. Meanwhile at least one sister’s history of breast cancer was consistent, giving a statistically significant odds ratio except in age group 30-39, where there were only two cases having at least one sister with a breast cancer history. The point estimate of the odds ratio ranged from 1.89 in age group 50-59 to 2.63 in age group 60-69.

The estimated odds ratio for BMI over 24 before onset, was significantly high in age group 60-69, and significantly low in age group 40-49, when compared with BMI less than 20. After adjustment for the delivery history by logistic model, both were still significant; OR=2.18, 95% CI: 1.47-3.23 in age group 60-69, and OR=0.71, 95% CI: 0.51-0.99 in age group 40-49. BMI at age 20 was not a significant factor except in age group 50-59. Adjustment for the delivery history did not change the result of BMI at age 20.

Regarding smoking, age group 40-49 with 11.6% of smokers showed an elevated odds ratio (1.65, 95% CI: 1.28-2.13). The value was slightly lower (1.61, 1.24-2.08) with allowance for the delivery history. Since an association was observed between the smoking and drinking habits, the drinking habit was further adjusted, giving an odds ratio of 1.55 (95% CI: 1.19-2.02).

A significantly elevated risk was observed for drinkers who drank at least four times per week in the same age

Table 5. Odds ratio and its 95% confidence interval estimated by a multivariate analysis adjusted each other besides age and year of visit.

| Variable          | Age at first visit |
|-------------------|-------------------|
|                   | 30-39 ys | 40-49 ys | 50-59 ys | 60-69 ys |
| Menarche          |          |          |          |          |
| <14 years         | 1        | 1        | 1        | 1        |
| 14-15 years       | 1.27     | 0.82     | 0.70     | 0.98     |
|                   | (0.89-1.80) | (0.67-1.01) | (0.53-0.92) | (0.68-1.41) |
| ≥16 years         | 1.34     | 1.06     | 0.69     | 0.89     |
|                   | (0.47-3.76) | (0.71-1.67) | (0.49-0.95) | (0.62-1.29) |
| First delivery    |          |          |          |          |
| <24 years         | 1        | 1        | 1        | 1        |
| 24-26 years       | 1.22     | 1.22     | 0.97     | 1.22     |
|                   | (0.73-2.04) | (0.93-1.59) | (0.71-1.34) | (0.83-1.80) |
| ≥27 years         | 1.75     | 1.52     | 1.35     | 1.68     |
|                   | (1.05-2.92) | (1.14-2.03) | (0.98-1.86) | (1.14-2.46) |
| No birth          | 2.15     | 2.00     | 1.63     | 1.54     |
|                   | (1.22-3.76) | (1.43-2.80) | (1.07-2.49) | (0.97-2.44) |
| BMI before onset  |          |          |          |          |
| <20               | 1        | 1        | 1        | 1        |
| 20-24             | 1.21     | 0.95     | 0.86     | 1.07     |
|                   | (0.83-1.77) | (0.75-1.20) | (0.63-1.18) | (0.71-1.60) |
| ≥24               | 1.78     | 0.70     | 1.15     | 2.23     |
|                   | (1.03-3.07) | (0.50-0.98) | (0.82-1.62) | (1.50-3.32) |
| Smoking           |          |          |          |          |
| Non-smokers       | 1        | 1        | 1        | 1        |
| Ex-smokers        | 0.89     | 1.27     | 1.28     | 1.15     |
|                   | (0.42-1.86) | (0.75-2.14) | (0.70-2.36) | (0.58-2.27) |
| Smokers           | 0.88     | 1.57     | 0.90     | 1.23     |
|                   | (0.55-1.41) | (1.20-2.05) | (0.56-1.43) | (0.70-2.16) |
| Drinking          |          |          |          |          |
| Non-drinkers      | 1        | 1        | 1        | 1        |
| Occasional drinkers | 0.54   | 0.98     | 1.00     | 1.17     |
|                   | (0.33-0.87) | (0.76-1.26) | (0.72-1.40) | (0.72-1.90) |
| Drinkers          | 1.23     | 1.23     | 0.65     | 1.22     |
|                   | (0.74-2.02) | (0.92-1.66) | (0.38-1.12) | (0.65-2.29) |
| ≥4 times/week     |          |          |          |          |
The subjects with family history of breast cancer was limited, this variable was not applied. BMI at age 20 was also not included in the model, because it was correlated with BMI before onset, especially in the younger age groups. First delivery was categorized into four levels, combining the fourth and the fifth into one level. The estimates were similar to those in Table 4.

**DISCUSSION**

The differences in the background of non-cancer female patients who visited Aichi Cancer Center Hospital were obvious among the age groups. Although they were not randomly sampled from a general population, the observed differences may also exist in the Japanese female population at large.

There are several methodological problems when we use hospital controls to estimate odds ratio. One of the major problems is the inclusion of factor-related diseases in the adopted controls. As shown in Table 2, majority of the first-visit non-cancer patients in our hospital were not those who were suffering from a chronic disease, but those who were anxious about cancer at a time point of their life. The proportion of patients with factor-related diseases seemed to be much smaller than that of the other hospital controls.

Keeping in mind the methodological problems on hospital controls, the following findings deserved to be mentioned. Late menarche was not a risk factor or risk predictor of breast cancer for age group 30-39. The distribution of age at menarche for those shifted to a narrower and younger range. A small proportion of women with late menarche, e.g., 16 years or older, will make it difficult to estimate the accurate risk for the age group.

The attribution of decreased fertility to increased incidence of breast cancer has been documented by several researchers. Similarlly, decreased fertility and increased breast cancer mortality have been observed in Japan. This paper added a quantitative measure to that attribution according to age group, considering the delivery factor for the four age groups. Since population attributable risk percent is directly influenced by the proportion exposed to risk factor, the estimates should be carefully applied to the whole country of Japan. However, there was no doubt that the attribution of late first delivery were substantial, especially in age group 30-39.

Many studies have shown a family history of breast cancer to be a risk factor of breast cancer. This study showed that the mother's history of breast cancer was not so predictive at present in Japan, but having at least one sister with breast cancer was informative in assessing the risk of breast cancer in any age groups. Since the number of subjects having at least one sister with breast cancer was so small (39 cases and 302 controls in total), the other factors could not be examined among them.

The increased risk attributable to a larger BMI is reported for postmenopausal breast cancer. The increased risk was observed correspondingly for age group 60-69 in this study. The factor may be attributed to the recent increase in breast cancer in Japan.

Most studies have shown that smoking was not a risk factor for breast cancer, but alcohol consumption increased the risk. In this study, age group 40-49 with the largest number of subjects showed a significant value for both of the risk factors, and not for the other age groups. Whether the risk elevation exists truly only in the age group is a very interesting question.

The findings obtained in this case-control study suggested that the influence of the risk factors might be dependent on age at disease occurrence. Although the analysis of premenopausal and postmenopausal breast cancer is very important, age specificity of the risk factors also remains to be studied.

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