

Trends in Benign Breast Tumors in Japanese Women, 1973–1995: Experience of Hiroshima Tumor Tissue Registry

Koji Arihiro^{1,2,3}

¹Hiroshima Tumor Tissue Registry, Hiroshima Prefecture Medical Association, 1-1-1 Kannon Honmachi, Nishi-ku, Hiroshima-shi, Hiroshima 733-8540, ²Department of Clinical Laboratory, Pathology Division, National Hospital Kure Medical Center, 3-1 Aoyama-cho, Kure-shi, Hiroshima 737-0023 and ³Department of Pathology, Hiroshima University Medical Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551

Although some benign breast lesions such as multiple intraductal papilloma have been pointed out as a risk factor for breast cancer, there is little documentation about trends in the incidence of benign tumors of the breast in Japanese women. The author conducted an epidemiological study using data abstracted from the Hiroshima Tumor Tissue Registry file, which includes cases of malignant and benign neoplasms in Hiroshima prefecture between 1973 and 1995. A total of 17 064 cases of female breast tumor were registered in the file between 1973 and 1995. The registration rate for fibroadenoma of the female breast was 19.5 among females and peaked during the 5-year period 1983–1987, while the fibroadenoma registration rate in Hiroshima gradually decreased between 1988 and 1995. The registration rate for intraductal papilloma has risen substantially in Hiroshima, with about a 5-fold increase among females between 1973 and 1995. The mean proportion of fibroadenoma cases accompanied by malignant tumors of the breast was 1.85%, and there was no significant change in the mean proportion between 1973 and 1995 ($P=0.17$). On the other hand, the mean proportion of intraductal papilloma cases accompanied by malignant tumors of the breast gradually rose with about a 14-fold increase among females between 1973 and 1995. The significance of intraductal papilloma as a risk factor for breast cancer may have increased.

Key words: Hiroshima Tumor Tissue Registry — Breast — Benign tumor — Fibroadenoma — Intraductal papilloma

A recent increase in the incidence of and deaths from breast cancer among Japanese women is reported to be owing to changed risk factors among Japanese women.^{1,2} However, there is little documentation about trends in the incidence of benign tumors of the female breast in Japan. The Hiroshima Tumor Tissue Registry was established in 1973 by the Hiroshima Medical Association in collaboration with the Atomic Bomb Casualty Commission (now Radiation Effects Research Foundation). This paper provides a brief description of incidence patterns of benign tumors of the female breast in Hiroshima prefecture during the 23 years from 1973 to 1995.

MATERIALS AND METHODS

Data for the present report were abstracted from the Hiroshima Tumor Tissue Registry file, which includes cases of malignant and benign neoplasms in Hiroshima prefecture. Registration was carried out as described previously.^{3–5} The registry is tumor-based and multiple primary tumors occurring in one person are entered separately. In the case of malignant tumors, not only primary, but also metastatic tumors are registered. Notification is based on a voluntary agreement between the recording

institutes and hospitals. The registry has covered most institutes and hospitals, but not the entire population in Hiroshima prefecture. The number of participant institutes and hospitals was 29 in 1973 at the start of registration and has gradually increased during the 23-year period by 24 to 53 in 1995. While the 29 institutes and hospitals covered most pathological examinations of tumor cases in Hiroshima prefecture in 1973, and a part of the pathological examinations of tumor cases in Hiroshima prefecture has shifted to the other 24 institutes and hospitals during the 23 years, there has not been much change in overall coverage of tumor cases during the period. Some cases are registered repeatedly and from different institutions, thus improving the completeness and accuracy of registration. The histological diagnosis of every case has been reconfirmed by two designated pathologists according to routine registration criteria.^{6,7} There has been little change in the histopathological criteria for the various benign tumors over the 23-year period.

In this study, the author re-examined a representative histological slide of all cases and reconfirmed the histological diagnosis using the same criteria. Subtypes of fibroadenoma such as intracanalicular, pericanalicular, mastopathic and so on were uniformly coded as “fibroadenoma, NOS.” Intraductal papilloma has been defined as a lesion composed of epithelial fronds supported by fibrovascular stroma outside of terminal duct lobular units. In particular,

³To whom correspondence should be addressed.
E-mail: arihiro@hiroshima-u.ac.jp

lesions called epitheliosis or papillomatosis were not classified as intraductal papilloma in this study. The presence of atypia within or adjacent to intraductal papilloma was not evaluated because a registered representative specimen did not always include the whole lesion. The basic information available from the register comprises sociodemographic characteristics of the patient (i.e., age, sex, address), and the primary site and histological type of tumor according to the standard International Classification of Disease for Oncology (ICD-O; World Health Organization, 1990). Passive follow-up data are recorded and each subsequent item of information concerning already registered cases is used to complete the record of that patient. The overall incidence period considered for all breast tumors includes the years 1973 to 1995. Data from the Population Census of Japan were used for the denominators in the calculation of the registration rates per 100 000 population by 5-year age groups. Trends in tumor registration are shown by grouping the data into four 5-year periods and one 3-year period.

For statistical analysis, regression analysis was done using the χ^2 test according to Cochran⁸⁾ and Armitage.⁹⁾

Table I. Histology of Benign Tumors of Breast

Epithelial tumors	
Intraductal papilloma	595 (9.137)
Adenomyoepithelioma	3 (0.046)
Adenoma of nipple	20 (0.307)
Tubular adenoma	14 (0.215)
Adenoma, NOS	48 (0.737)
Mixed connective tissue and epithelial neoplasms	
Fibroadenoma	5492 (84.34)
Juvenile fibroadenoma	20 (0.307)
Benign phyllodes tumor	215 (3.302)
Mesenchymal tumors	
Hemangioma	8 (0.123)
Lymphangioma	2 (0.031)
Fibromatosis	10 (0.154)
Neurofibroma	2 (0.031)
Schwannoma	2 (0.031)
Granular cell tumor	3 (0.046)
Leiomyoma	1 (0.015)
Lipoma	47 (0.722)
Angiolipoma	2 (0.031)
Osteochondroma	3 (0.046)
Myxoma	1 (0.015)
Total	6488
	(%)

RESULTS

All benign and malignant tumors of the female breast

A total of 17 064 cases of female breast tumor were registered in the file between 1973 and 1995. From them the author abstracted 6488 cases of benign breast tumors except for skin tumors localized in the nipple. The age range for the incidence of benign tumors was 1–75 years (median age, 35 years). Fibroadenoma was the most common benign tumor of the female breast, followed by intraductal papilloma (Table I).

The registration rate for all benign tumors of the female breast was 15.3 per year per 100 000 among females during the 5-year period 1973–1977. This rate had increased to 22.2 by the 5-year period 1988–1992 (Fig. 1). The registration rate for fibroadenoma of the female breast was 13.9 during the 5-year period 1973–1977. This rate had increased to 19.5 by the 5-year period 1983–1987, but the fibroadenoma registration rate in Hiroshima has been gradually decreasing over the past 8 years. On the other hand, the registration rate for intraductal papilloma was

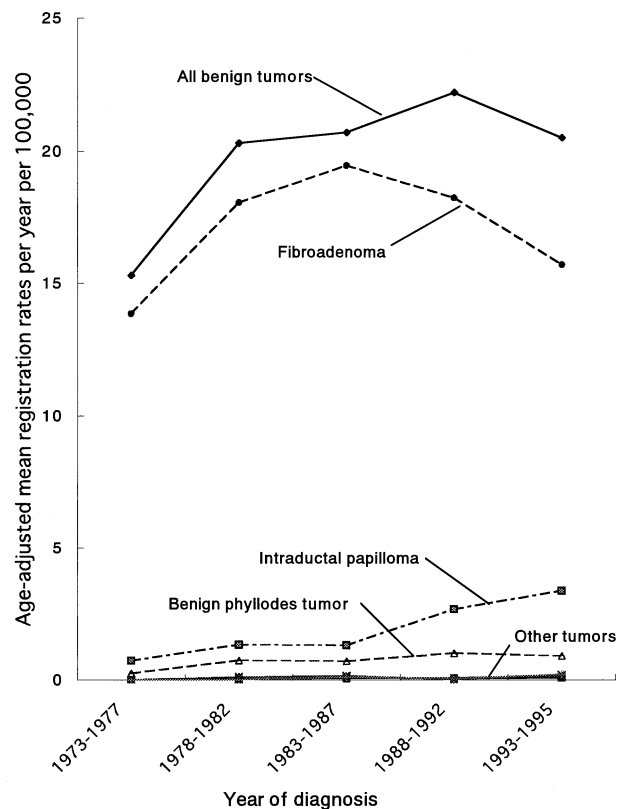


Fig. 1. Trends in age-adjusted registration rates per 100 000 for benign tumors of the female breast by histology, 1973–1995. Other tumors include adenoma of nipple, tubular adenoma, juvenile fibroadenoma and adenoma, NOS.

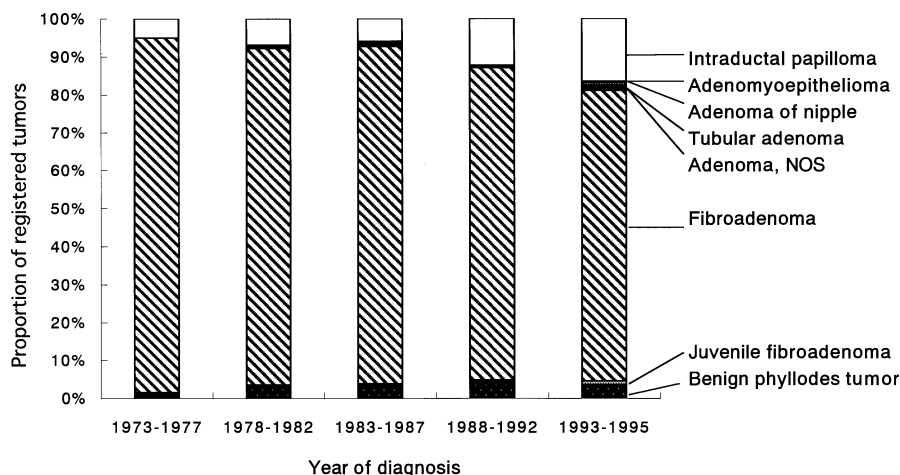


Fig. 2. Proportion of benign tumors of the female breast by histology.

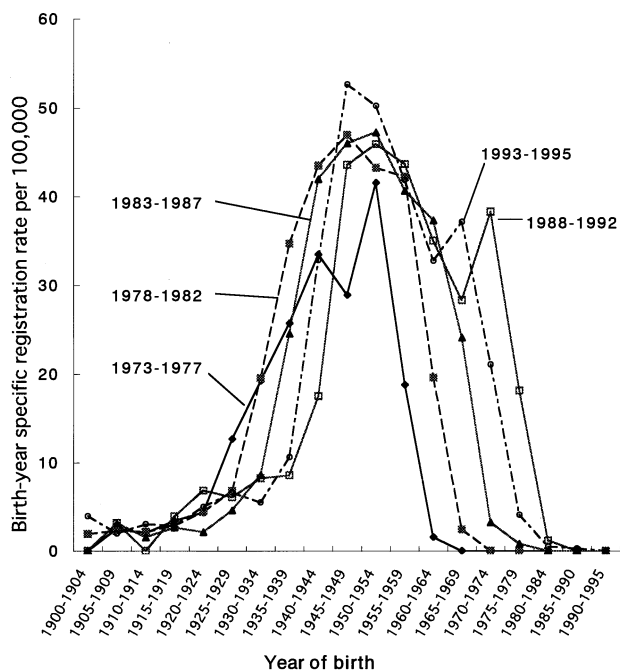


Fig. 3. Trends in birth-year-specific registration rates per 100 000 for benign tumors of the female breast by period of diagnosis.

0.7 during the 5-year period 1973–1977. This rate had increased to 3.4 by the 3-year period 1993–1995, and accordingly, the registration rate for intraductal papilloma has substantially risen in Hiroshima, with about a 5-fold increase in the 23-year period 1973–1995 (Fig. 1).

The proportion of fibroadenoma was 93% among benign epithelial tumors and mixed connective tissue and

epithelial neoplasms during the 5-year period 1973–1977. This had decreased to 78% by the 3-year period 1993–1995 (Fig. 2). On the other hand, the proportion of intraductal papilloma was 5% during the 5-year period 1973–1977. This had increased to 16% by the 3-year period 1993–1995 (Fig. 2).

The highest peak of birth-year-specific registration rate for benign tumors was noted as 1945 to 1954 during every period between 1973 and 1995 (Fig. 3). Another peak of birth-year-specific registration rate was noted as 1965 to 1974 during the 5-year period 1988–1992 and the 3-year period 1993–1995. It seems that the first peak ages involve baby boomers after World War II in Japan and the second peak ages correlate with their daughters' age group.

The diagnosis-period-specific registration rate among 100 000 females who were born between 1945 and 1959 has been higher than 40 since 1978, while the rate among females who were born before 1939 or after 1960 was not so high.

Although the single peak of age-specific registration rate for fibroadenoma was 20 to 24 years in the 5-year period 1973 to 1977, two peaks of age-specific registration rate for fibroadenoma were noted after 1978: the first peak in the 20 to 24 years range and the second peak in the 30 to 39 years range (Fig. 4).

A low peak of age-specific registration rate for intraductal papilloma was 40 to 49 years in the three 5-year periods 1973 to 1987, while a sharp peak was noted in the 5-year period 1988 to 1992 and the 3-year period 1993–1995 (Fig. 5). The peak registration rates for intraductal papilloma were 2.5, 3.6, 3.7, 9.6 and 11.3 among 100 000 females during the periods 1973–1977, 1978–1982, 1983–1987, 1988–1992 and 1993–1995, respectively.

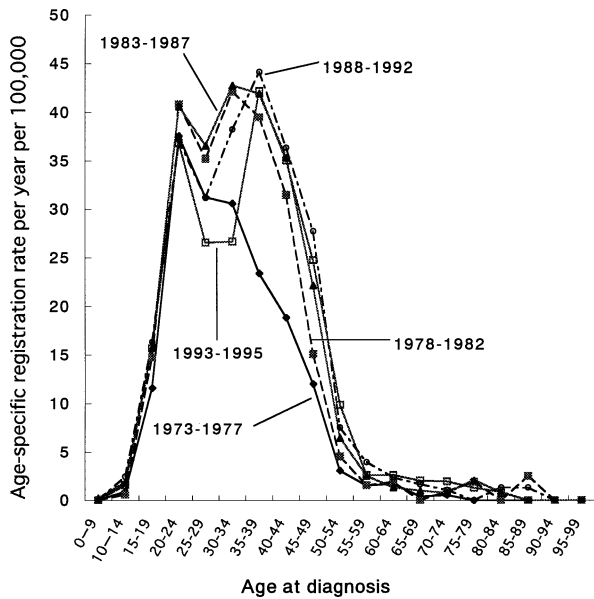


Fig. 4. Trends in age-specific registration rates per 100 000 for fibroadenoma by period of diagnosis.

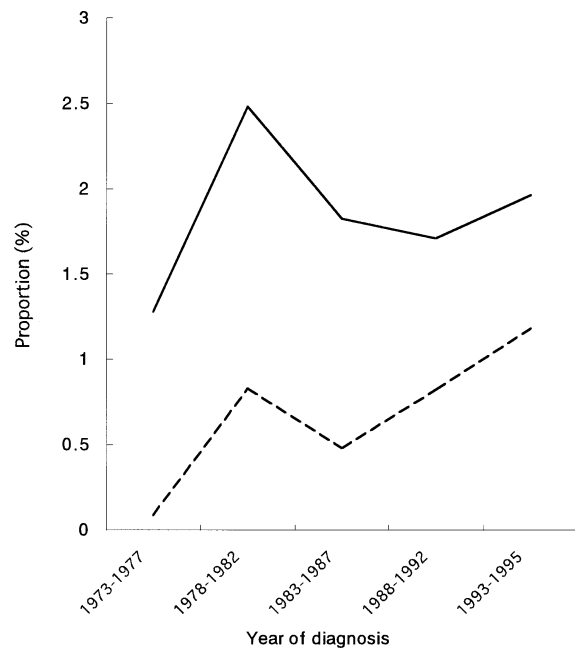


Fig. 6. Proportion of fibroadenoma and intraductal papilloma versus malignant tumor of the breast. There was no significant change in the mean proportion of malignant tumors accompanied by fibroadenoma during the 23 years, 1973–1995 ($P=0.17$). The mean proportion of malignant tumors of the breast accompanied by intraductal papilloma rose significantly with about a 14-fold increase among females during the period 1973–1995 ($P<0.005$). — malignant tumors accompanied by fibroadenoma, --- malignant tumors accompanied by intraductal papilloma.

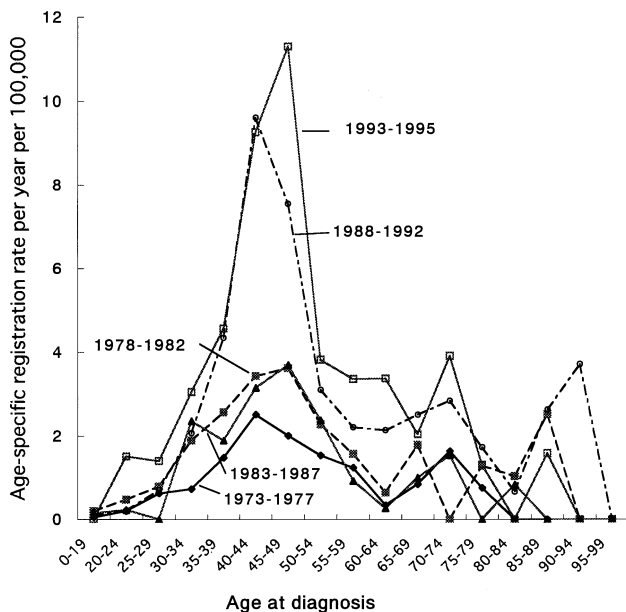


Fig. 5. Trends in age-specific registration rates per 100 000 for intraductal papilloma by period of diagnosis.

The mean proportion of malignant tumors of the breast accompanied by fibroadenoma was 1.85% and there was no significant change in the mean proportion during the 23 years, 1973–1995 ($P=0.17$). On the other hand, the mean

proportion of malignant tumors of the breast accompanied by intraductal papilloma was 0.09% during the 5-year period 1973–1977. This rate rose significantly to 1.18% during the 3-year period 1993–1995 with about a 14-fold increase among females during the period 1973–1995 ($P<0.005$) (Fig. 6).

DISCUSSION

It was found that the registration rate for fibroadenoma of the breast in Japanese females showed a peak during the 5-year period 1983–1987 while it decreased gradually in the period 1988–1992. In previous reports, it was shown that the risk of fibroadenoma was associated with a lower body-mass index, a smaller number of full-term pregnancies,^{10,11} married nulliparae,¹² use of oral contraceptives at an early age (under 20 years),^{10,11,13} women over age 45 years who had ever used oral contraceptives,¹⁴ and a higher socioeconomic status as reflected by income and suburban residence,^{11,15} but there was no evi-

dence of an association with parity, age at first birth,^{12,13)} age at menarche, menopausal status, alcohol consumption or dietary fat intake,⁹⁾ while in multivariate analyses, both duration of cigarette smoking and daily vitamin C intake were shown to have inverse associations with the risk of fibroadenoma.¹⁰⁾ In other reports, it has been pointed out that cigarette smoking is associated with a reduced risk of fibroadenoma, especially in current smokers.^{16,17)} Accordingly, the author speculate that a change of lifestyle is probably associated with the increased registration rate of fibroadenoma during 1973–1987. On the other hand, it has been shown that a fibroadenoma does not require excision unless it is larger than 2 cm in diameter.¹⁸⁾ Non-operative management of fibroadenoma is recommended because spontaneous resolution of fibroadenoma is frequently noted, particularly in women aged 20 years or less.¹⁹⁾ Fine-needle aspiration for cytologic examination and great progress in radiological examination are known to have reduced the number of women subjected to biopsy for benign breast tumors.²⁰⁾ Accordingly, both greater progress in clinical diagnosis without histological examination and the change in management of fibroadenoma are probably associated with the decreased registration rate of fibroadenoma during 1988–1995.

As to the age distribution of fibroadenoma, it has been reported that the incidence rate of fibroadenoma peaks during the twenties.¹²⁾ On the other hand, in other reports a biphasic curve with two peaks between the late twenties and early thirties and between the late forties and early fifties was noted.^{21,22)} In the present report two peaks of age distribution for fibroadenoma were noted in the ages of 20–24 years and in women who were born in the period 1948 to 1952. As we have not yet been able to define why the registration rate of fibroadenoma is highest in women who were born in the period 1948 to 1952, we need to examine these age groups from the viewpoint of social environment as well as biological susceptibility in the future.

With regard to the risk of breast carcinoma, fibroadenoma has been shown to be a long-term risk factor.^{23,24)} On the contrary, a recent study has found that fibroadenoma *per se* is not associated with an increased risk of subsequent breast cancer.²⁵⁾ Although fibroadenoma does share some risk factors with breast cancer, there is insufficient evidence to suggest that it represents a precursor state.¹⁰⁾ As regards the relationship between fibroadenoma

and breast cancer, the present report shows that there was no significant change in the mean proportion of malignant tumors of the breast accompanied by fibroadenoma during the 23 years, 1973–1995. Accordingly, we need to follow up cases of fibroadenoma in the present study and examine whether fibroadenoma is associated with an increase in breast cancer risk.

As for intraductal papilloma, benign intraductal papilloma has been shown to be a risk factor for ipsilateral breast cancer (relative risk=3.33).²⁶⁾ The risk of a woman's developing carcinoma after a biopsy with papillomatous disease including microscopic and macroscopic lesions is 7.4 times that of a normal population of comparable age.²⁷⁾ In another study, development into subsequent carcinomas was noted in six cases (9.4%) of 64 papillomas which were locally excised.²⁸⁾ The real frequency of subsequent carcinoma was suggested to be between 0.4% and 8% by Tavassoli.²⁹⁾ On the other hand it was stressed that multiple papillomas were much more likely to be associated with the concurrent or subsequent development of breast carcinoma, while solitary intraductal papillomas were not.^{30–32)} Additionally, it was indicated that women suffering from papillomas with atypical hyperplasia have a similar or greater cancer risk than others with specifically defined patterns of atypical hyperplasia within the breast parenchyma (a 4- or 5-fold relative risk).^{33,34)} Accordingly, the present finding that the mean proportion of malignant tumors of the breast accompanied by intraductal papilloma has gradually risen may suggest that the significance of intraductal papilloma as a risk factor for breast cancer has increased.

Nevertheless, in the present study the author was unable to evaluate the site of occurrence, multiplicity or singularity, synchronicity or heterochronicity of intraductal papilloma, and the presence or absence of atypical hyperplasia adjacent to intraductal papilloma, and in general, breast carcinoma development is undoubtedly influenced by the presence of other proliferative lesions, which frequently coexist in the same breast, so further evaluation is necessary.

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