

REVIEW ARTICLE

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No increase of breast cancer incidence in Japanese women who received hormone replacement therapy: overview of a case-control study of breast cancer risk in Japan

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Abstract Hormone replacement therapy (HRT) has been considered one of the main risk factors for breast cancer. Studies demonstrating the relationship between HRT and breast cancer incidence were conducted in Western countries and the target populations were mainly Caucasians. Since the Women's Health Initiatives demonstrated that HRT increased the risk of breast cancer with statistical significance, the number of HRT users in the United States has dramatically decreased. A recent case-control study has investigated the relationship between HRT and breast cancer in Japan, and here we review the results of this study to compare any discrepancy in breast cancer risk between Japanese and Western populations. For this case-control study, at seven institutions, women between the ages of 45 through 69 years, with histologically confirmed breast cancer, were selected as the case group. An age-adjusted control group was selected, using hospital-based data, including records of those screened for lung, gastrointestinal, and gynecological cancer. Questionnaires

were administered, and items questioned included various factors related to the incidence of breast cancer: age at diagnosis, body mass index (BMI), smoking habit, age at menopause, birth history, number of births, number of children, history of breast feeding, familial background, and menopausal status. In total, 6183 samples (98.4% of the estimated samples) were put into the database. Data from 276 samples were excluded due to ineligibility. Finally, 5861 samples (3434 cases and 2427 controls) were analyzed. In 3316 cases, 164 (5.0%) patients received hormone-replacement therapy (HRT); on the other hand, 253 (10.7%) of 2355 controls received HRT. The odds ratio was 0.432 (95% confidence intervals [CI], 0.352–0.53), and there was a significantly negative correlation between HRT use and breast cancer. The risk factors in Japanese women showed similar profiles to those in women in Western countries. However, we did find some different profiles of breast cancer risk in the Japanese women. Changing of lifestyle may increase breast cancer risk in Japan.

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Introduction

In Japan, the incidence of breast cancer has recently increased; the age-adjusted rates of breast cancer per 100 000 women were 43.6 in 1998 and 21.7 in 1975. An approximately twofold increase was found during the recent 20 years surveyed. Determination of the breast cancer incidence rate by age revealed the peak age was around 45 to 50 years. Prediction of the age-adjusted incidence rate of breast cancer for 2015 demonstrated that, in Japanese females, breast cancer would show the highest incidence among malignant diseases. In 2001, the age-adjusted death rate of breast cancer was 11.1 per 100 000.¹ A recent report demonstrated that the incidence of breast cancer in hormone-replacement therapy (HRT) users in Japan was not increased.²

In this review, we focus on other well-known risk factors of breast cancer in previously reported studies, and we present an overview of a recent case-control study of breast cancer risk in Japan. We describe the relationship between

breast cancer risk in Japanese women and breast condition, in terms of exogenous and endogenous factors, e.g., genetic factors, food consumption, body weight, body height, and lifestyle, which are involved in the high incidence of breast cancer.

Case-control study of breast cancer risk in Japan

Study population

The target population of women had to be Japanese citizens who were living in Japan. The case group consisted of patients with breast cancer who were aged 45–69 years at breast cancer diagnosis and who were alive and healthy, with complete remission after treatment, in November 2005. Patients with recurrence were excluded. The control group consisted of healthy women without any malignant disease, aged 45–69 years, selected from the records of those who were screened for lung, gastrointestinal, and gynecological cancer.

Questionnaire

A questionnaire was administered to all participants. Questions were asked about endogenous hormone factors; numbers of pregnancies or births; age at menarche; age at menopause; exogenous hormone factors (hormone-replacement therapy [HRT], oral contraceptives); dietary factors; body mass index (BMI—at diagnosis of breast cancer and at age 18 years); lifestyle changes; smoking habit; alcohol intake; physical exercise; educational background (highest level reached); medical history (benign breast disease, breast tumor, breast surgery); and other factors, including breastfeeding, history of breast cancer screening, and family history.

Results

In total, 6183 samples (98.4% of 6282 estimated samples) were collected and input into a database. Finally, 5861 samples (3434 cases and 2427 controls) were eligible and analyzed.

HRT

In 3316 cases, 164 (5.0%) patients received HRT; on the other hand, 253 (10.7%) of 2355 controls received HRT. The odds ratio was 0.432 (95% CI, 0.352–0.53), and there was a significant negative correlation between HRT use and breast cancer.

Body mass index (BMI)

We asked about the current BMI and BMI at age 18 years. Median BMI for all participants was 22.1. In the group with

a BMI of more than 25, the risk of breast cancer was 1.005 (95% CI, 0.986–1.025). The odds ratio of BMI at 18 years was 1.004 (0.734–1.375). There was no statistically significant correlation between BMI and breast cancer in this Japanese population.

Age at menarche

In 3401 subjects in the case group, 1709 patients and in 1192 of 2402 controls, the women were younger than 14 years at menarche. There was no statistically significant correlation between early menarche and breast cancer incidence, but a trend was obtained.

Menopausal status

Of 2835 patients (cases), 2432 (85.8%) were postmenopausal at the time of breast cancer diagnosis, and 1630 (75.7%) of 2152 controls were postmenopausal; 403 patients (cases) and 522 controls were premenopausal. The odds ratio was 1.933 (95% CI, 1.673–2.233). Breast cancer risk was increased in the group of postmenopausal women.

Age at menopause

Of 891 women with breast cancer (patients; cases) 412 (46.2%) were aged more than 50 years at menopause, while 860 in the control group were over 50 years at menopause. On the other hand, 479 patients (cases) and 626 controls were younger than 49 years at menopause. The odds ratio was 0.626 (95% CI, 0.530–0.740). In this Japanese population, age of 50 years or more at menopause reduced breast cancer incidence with statistical significance.

Relative risk of other risk factors

Odds ratios for parity, history of breast screening, alcohol intake, physical exercise, number of births, history of breast feeding, history of benign breast disease, menopausal status, history of breast surgery, family history, smoking, and history of smoking are shown in Table 1.

Discussion

The incidence of breast cancer is highest in Western countries, including North America and Northern Europe, and lowest in Asia and Africa.³ The latest epidemiologic data, reported by Ravdin et al.,⁴ have demonstrated a decrease of breast cancer incidence in the United States. However, in Japan, the incidence rates have still been rising.¹ In addition, the latest report in Japan indicated that breast cancer incidence was highest in the young generation. The peak age-adjusted incidence was between age 40 and 50 years. In Western countries, there is a high incidence of breast cancer in women older than 60 and the incidence shows a trend of

Table 1. Odds ratios for some risk factors for breast cancer

Factor	Category	Odds ratio	95% CI
Parous	Yes	0.542	0.457–0.644
	No	1	
History of breast screening	Yes	0.187	0.165–0.212
	None	1	
Alcohol intake		0.647	0.578–0.724
Physical exercise	Every day	0.307	0.242–0.389
	None	1	0.656–1.017
Number of births	1	2.006	1.402–2.870
	4<	1	0.675–1.304
History of breast feeding	Mixed	0.790	0.649–0.963
	Without breast milk	1	
History of benign breast disease	Yes	1.157	1.017–1.316
	None	1	
Postmenopausal	Yes	1.933	1.673–2.233
	No	1	
History of breast surgery	Yes	1.338	1.075–1.664
	None	1	
Family history	Yes	2.167	1.691–2.778
Breast cancer in sisters	None	1	
Age at first birth	30<	1.551	1.270–1.895
	30 \leq	1	
History of smoking	Present smoker	0.864	0.685–1.088
	Past smoker	1.294	1.080–1.550
	Never smoked	1	

an increase with age.³ Differences in incidences among nations are considered to be related to societal changes occurring with industrialization. Studies of people who have migrated from Japan to the United States have demonstrated that global variations in incidence are caused by environmental factors rather than by genetic factors alone.⁵ Incidence rates of breast cancer are generally increased in second-generation migrants, and the trends increase further in third-generation migrants as they become further acculturated.⁶ These data suggest that environmental and/or lifestyle factors are important factors in breast cancer risk.⁷

A report conducted by a research group to determine whether there was a correlation between HRT use and breast cancer in Japan was the first large-scale study of this field in Japan, and based on their results, breast cancer incidence in Japan has not been increased by HRT.²

In general, a case-control study has some biases that reveal epidemiologic factors and specific risk of disease. However, the data from the case-control study reviewed here provided information on various items for Japanese society from the viewpoint of public health. The sample size of the study was large and approximately 99% of the estimated samples were collected, suggesting that the quality of this study might be enough to estimate breast cancer risk in Japan. The questionnaire used in this case-control study included well-known risk factors;⁸ we analyzed the correlation between these factors and breast cancer risk in the Japanese population.

Risk factors in the Japanese population were similar to those in a previous report.⁹ However, the case-control study reviewed here demonstrated no statistically significant correlation between BMI, early menarche, or late menopause. A high BMI could be an important factor in inducing breast cancer. In Western countries, women with a BMI of more

than 25 kg/m² have been considered to be a high-risk group. There was no statistically significant relationship between BMI and breast cancer risk in Japanese women, as BMI in Japanese women was lower than that in the women in the United States. In fact, the mean BMI in our population was 22.1, compared with 28.5 in women enrolled in the Women's Health Initiative Investigators study.¹⁰ In addition, BMI was not related to an increased risk of estrogen receptor (ER)-negative breast cancer in Japan. The lifestyle of Japanese women has been changing. The style of food consumption has become westernized and high-calorie-intake and high-fat diets in Japanese have been reported, suggesting that BMI may be a risk factor for breast cancer in the near future.

Delaying menarche is possible through physical activity, and possibly by altering diet to avoid overnutrition and animal fats in the prepubertal years.¹¹ The total intake of fat and animal protein has been shown to be significantly correlated with breast cancer mortality in Japan.¹²

In addition, reports have demonstrated that past smokers have a relatively high risk of breast cancer. Other risk factors, including age at birth of the first child, history of benign breast disease, family history, and physical exercise have been correlated with breast cancer risk in Japan, suggesting that Japanese women potentially have breast cancer risks similar to those in Western populations.^{13–21}

Conclusion

In Japan, at present no statistically significantly positive correlation between HRT use and breast cancer has been found. Other risk factors for breast cancer in Japanese

women were similar to those in Western populations. This discrepancy between the Japanese population and Western women in regard to HRT use and breast cancer seemed to suggest a changing lifestyle in Japanese women. We need further investigations and we need to warn our population of the risk factors.

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