SERUM COMPONENTS AND RISK OF CANCER - II

Serum Insulin-like Growth Factors I and II, Insulin-like Growth Factor Binding Protein-3 and Risk of Breast Cancer in the JACC Study

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Abstract

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was planned in the late 1980s as a large-scale cohort study of persons in various areas of Japan. In the present study, we conducted a nested case-control study and examined associations of breast cancer risk with serum levels of insulin-like growth factors I and II (IGF-I, IGF-II), as well as insulin-like growth factor binding protein-3 (IGFBP-3), among women who participated in the JACC Study and donated their blood at the baseline. Sixty-three women who died or suffered from breast cancer were examined. Two or three controls were selected to match each case for age at recruitment and the study area. Controls were alive and not diagnosed as having breast cancer at the diagnosis date of the cases. Associations between the serum IGF-I, IGF-II, IGFBP-3 and breast cancer risk were evaluated using a conditional logistic regression model. In premenopausal Japanese women, IGF-I showed a marginal negative dose-dependent association with the breast cancer risk (trend P= 0.08), but any link disappeared on taking into account IGFBP-3 (trend P= 0.47), which was likely to be inversely associated with the risk. In postmenopausal women, IGFBP-3 showed a marginal dose-dependent association with the risk (trend P= 0.06). Further studies are needed to confirm these findings.

Keywords: Japan Collaborative Cohort Study - nested case-control study - breast cancer - IGF-I - IGF-II - IGFBP-3

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Introduction

The insulin-like growth factor (IGF) system is a key growth regulatory pathway in breast cancer, considered to have direct or indirect influence on neoplasia of the mammary glands (Sachdev et al., 2001). However, relations between the IGF system and breast cancer risk have been mainly discussed with reference to Caucasian women and only very few pertinent epidemiological studies have been performed in Asia (Li et al., 2001; Yu et al., 2002; Hirose et al., 2003).

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by the Ministry of Education, Culture, Sports, Science and Technology (JACC Study) was planned in the late 1980s as a large-scale cohort study surveying Japanese people in various areas of Japan comprehensively and detailing their lifestyles (Ohno et al., 2001; Tamakoshi A et al., 2005). We conducted the present nested case-control study to examine associations of breast cancer risk with serum levels of IGF-I, IGF-II, and IGFBP-3 among women who participated in the JACC Study and donated their blood at the baseline.

Materials and Methods

Study Population

The study population included healthy control subjects in a nested case-control study within a large cohort study (JACC Study). Methods adopted in the baseline survey and follow-up were described in detail elsewhere (Ohno et al., 2001; Tamakoshi A et al., 2005). In brief, the cohort was established from 1988 to 1990, with 110,792 subjects

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(46,465 men and 64,327 women) aged 40-79 years in 45 areas throughout Japan. In most of the study areas, the participants who attended municipal health screening program were enrolled as basic cohort population. At the baseline, information on life style factors were collected by self-administered questionnaires. In 37 areas, blood samples were donated from part of the cohort members at the same time. Proportion of blood donation to the whole subjects was approximately 35%. Informed consent was obtained mainly by having the subjects sign on the cover of the questionnaire, however, the community leaders in some study areas gave the consent for participating in the study on representative of the local residents. Follow-up of the study subjects was subsequently conducted. The whole study design and use of serum was approved by the Ethics Board at Nagoya University School of Medicine, where the central office of JACC Study was located.

Follow-up Survey

Follow-up surveys were conducted using population registries in local municipalities to determine the vital and residential status of the cohort. All deaths until 1997 were ascertained by death certificates from local public health centers in the study areas with the permission from the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications). Causes of death were coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD10) by verifying computer-stored data in the Ministry of Health, Labor, and Welfare. Diagnosis of breast cancer was defined by code C50 in ICD10. The cancer incidences until 1994 were determined by linkage with cancer registries in 24 out of 45 study areas, and primary sites and occurring date were identified.

Cases and Controls

A total of 64 women died or suffered from breast cancer (death cases / incident cases, 19 / 45, respectively). In the present study, 63 cases were available for analysis (death cases / incident cases, 19/44); 24 cases with a premenopausal status at the base line survey (death cases / incident cases, 5/19) and 39 cases with a postmenopausal status (death cases / incident cases, 14/25). Two or three controls were selected to match each case for age at recruitment and the study area. Controls were alive and not diagnosed as having breast cancer at the diagnosis date of the cases. We conducted a nested case control study using these subjects.

Specimen Measurement

Sera were separated from the blood samples at laboratories in each study area and stored at -80˚C until analysis. Then all samples were assayed in 1999 and 2000 by trained staffs at a single laboratory (SRL Inc., Hachioji). Serum levels of IGF-I, IGF-II, and IGFBP-3 were measured by immunoradiometric assay, using commercially available kits (Daiichi Radioisotope Laboratory, Tokyo). Assay methods have been described in detail elsewhere (Ito et al., 2005). The range of reliable measurement for IGF-I, IGF-II, and IGFBP-3 in reference sera was 4-2,000 ng/ml, 10-1,640 ng/ml, and 0.06-10.10 μg/ml, respectively. The intra- and inter- assay precisions obtained using different reference sera for each determination method was as follows: for the IGF-I assay, 2.15-3.53% and 1.12-4.18% of the coefficients variation values, respectively; for the IGF-II assay, 2.74-4.45% and 4.23-5.53%; for the IGFBP-3 assay, 3.16-4.19% and 5.28-8.89%.

Statistical analysis

Data for the premenopausal and postmenopausal status at the base line survey were analyzed separately. Comparison of selected baseline characteristics by case-control status were examined by generalized linear model for continuous variables and $\chi 2$ test or Fisher's exact test for categorical variables. Serum IGF-I, IGF-II, and IGFBP-3 were divided into tertiles based on distribution of serum concentration among the subjects. Associations between these levels and breast cancer risk were evaluated by conditional logistic regression model and odds ratios

Table 1. Baseline Characteristics of the Breast Cancer Cases and Controls by Menopausal Status

	Premenopausal			Postmenopausal		
	Cases (24)	Controls (71)	P- value[c]	Cases (39)	Controls (116)	P-value[c]
Age at recruitment (years)[a]	46.3 ± 5.5	46.9 ± 6.0		60.1 ± 7.7	60.1 ± 7.7	
Age at menarche (years)[b]	14.9 ± 0.3	13.8 ± 0.2	<0.01	14.4 ± 0.4	14.7 ± 0.3	0.52
Age at menopause (years)[b]	-	-		48.2 ± 1.0	49.1 ± 0.7	0.48
BMI (kg/m^2)[b]	22.7±0.8	23.5±0.5	0.35	24.1 ± 0.7	22.8 ± 0.4	0.11
Delivery, ≥3 times, n (%)	5 (20.8%)	29 (40.8%)	0.16	11 (28.2%)	67 (57.8%)	<0.01
History of hormone use, yes, n (%)	1 (4.2%)	5 (7.0%)	1.00	1 (2.6%)	3 (2.6%)	0.46
Family history on cancer, yes, n (%)	9 (37.5%)	22 (31.0%)	0.62	19 (48.7%)	33 (28.4%)	0.03
Sports activity, 1-2 hours / week, n (%)	2 (8.3%)	16 (22.5%)	0.30	12 (30.8%)	29 (25.0%)	0.48
Highest education, ≥18 years old, n (%)	13 (54.2%)	44 (62.0%)	0.67	16 (41.0%)	40 (34.5%)	0.53
Smoking, ever, n (%)	1 (4.2%)	1 (1.4%)	0.60	5 (12.8%)	1 (0.9%)	<0.01
Drinking, ever, n (%)	9 (37.5%)	18 (25.4%)	0.48	9 (23.1%)	29 (25.0%)	0.93
IGF-I (ng/ml)[b]	151.0 ± 11.5	154.4 ± 7.6	0.79	135.6 ± 12.5	143.8 ± 7.6	0.57
IGF-II(ng/ml)[b]	572.0 ± 26.7	628.0 ± 17.7	0.06	640.6 ± 26.5	654.9 ±16.1	0.64
IGFBP-3 (μg/ml)[b]	3.2 ± 0.2	3.3 ± 0.1	0.37	3.3 ± 0.2	3.3 ± 0.1	0.97
IGF-I/IGFBP-3 ratio[b]	47.1 ± 3.5	47.0 ± 2.3	0.98	39.9 ± 3.5	41.4 ± 2.1	0.71

[a]mean ± standard deviation; [b]mean ± standard error; [c]P-value based on generalized linear model for continous variables and $\chi 2$ test or Fisher's exact test for categorical variables

Table 2. ORs and 95% CIs for Breast Cancer Cases by Tertiles of IGF-I, IGF-II, IGFBP-3, and IGF-I/ IGFBP-3

	Tertile 1	Tertile 2	Tertile 3	P trend
IGF-I (ng/ml)	≤120	121-150	≥151	
Cases/controls	7/24	6/23	11/24	
OR[a]	1	0.7 (0.19-2.91)	1.6 (0.53-4.84)	0.40
OR adjusted[b]	1	0.9 (0.20-4.17)	1.2 (0.32-4.09)	0.81
IGF-II (ng/ml)	≤570	571-660	≥661	
Cases/controls	11/22	9/22	4/27	
OR[a]	1	0.9 (0.29-2.51)	0.3 (0.06-1.00)	0.06
OR adjusted[b]	1	0.8 (0.24-2.81)	0.2 (0.06-1.11)	0.08
IGFBP-3 (μg/ml)	≤3.07	3.08-3.52	≥3.53	
Cases/controls	9/23	10/21	5/27	
OR[a]	1	1.1 (0.39-3.22)	0.4 (0.11-1.54)	0.21
OR adjusted[b]	1	0.9 (0.25-3.45)	0.3 (0.05-1.42)	0.12
IGF-I/IGFBP-3	≤38.3	38.4-50.2	≥50.3	
Cases/ controls	5/27	9/22	10/22	
OR[a]	1	2.4 (0.64-8.76)	2.7 (0.75-9.73)	0.14
OR adjusted[b]	1	1.6 (0.38-6.33)	2.0 (0.53-7.70)	0.30

OR, odds ratio; 95% CI, 95% confidence interval; [a]all ORs are matched for age and areas of study; [b]adjusted for age at menarche (continuous), BMI (continuous), delivery (≤2, ≥3, unknown), and family history of cancer (yes, no)

Table 3. ORs and 95% CIs for Breast Cancer Cases by Tertiles of IGF-I, IGF-II, IGFBP-3, and IGF-I/ IGFBP-3 among Postmenopausal Women

	Tertile 1	Tertile 2	Tertile 3	P trend
IGF-I (ng/ml)	≤120	121-150	≥151	
Cases/controls	8/41	17/34	14/41	
OR[a]	1	2.7 (0.98-7.44)	1.9 (0.64-5.92)	0.28
OR adjusted[b]	1	2.8 (0.78-10.3)	2.8 (0.73-10.6)	0.17
IGF-II(ng/ml)	≤580	581-680	≥681	
Cases/controls	12/39	13/40	14/37	
OR[a]	1	1.1 (0.41-2.81)	1.2 (0.47-3.28)	0.65
OR adjusted[b]	1	1.2 (0.35-3.95)	1.2 (0.35-4.03)	0.80
IGFBP-3 (μg/ml)	≤3.00	3.01-3.60	≥3.61	
Cases/controls	9/43	15/36	15/37	
OR[a]	1	2.6 (0.86-7.94)	2.8 (0.82-9.32)	0.12
OR adjusted[b]	1	3.1 (0.80-12.1)	4.7 (0.96-23.4)	0.06
IGF-I/IGFBP-3	≤32.2	32.3-46.1	≥46.2	
Cases/controls	14/38	11/40	14/38	
OR[a]	1	0.7 (0.29-1.89)	1.0 (0.37-2.52)	0.97
OR adjusted[b]	1	1.0 (0.32-3.17)	1.1 (0.34-3.33)	0.91

OR, odds ratio; 95% CI, 95% confidence interval; [a]all ORs are matched for age and areas of study; [b]adjusted for age at menarche (continuous), BMI (continuous), delivery (≤2, ≥3, unknown), and family history of cancer (yes, no)

(ORs) with their corresponding 95% confidence intervals (CIs). Association of IGF-I/IGFBP-3 ratio with breast cancer risk was also examined. ORs for each tertile were calculated using the lowest as reference category, and a test for linear trend was performed to assess statistical significance across the levels by scoring each tertile as 1, 2 and 3.

The associations between the levels of IGFs and breast cancer risk were assessed by mono-variable and multi-variables analysis. Although several potential factors related with breast cancer are known such as reproductive history and age at menarche (Tamakoshi K, et al., 2005), we limited adjusting factors to the following because of the small sample size: for premenopausal status, age at menarche (continuous value), body mass index (BMI) (continuous value), delivery (≤2 times, ≥3 times, and unknown),and family history on cancer (yes, no); for postmenopausal status, age at menopause (continuous value), BMI, delivery, and family history on cancer. All P-values were based on two-sided tests; P-values <0.05 were considered statistically significant. The statistical package SPSS Version 13.0 J was used for the analysis.

Results

Selected baseline characteristics and measured values of IGF-I, IGF-II, IGFBP-3, and IGF-I/ IGFBP-3 ratio are presented in Table 1. Among premenopausal women, mean age at menarche was older, and IGF-II concentration was lower in cases than in controls with marginal significance. Proportion of 3 times delivery was likely to be lower in cases. However, there was no significant difference in other values between cases and controls. Among postmenopausal women, proportion of ≥3 times delivery was significantly lower, and proportions of family cancer history and smoking habit were significantly higher in cases than in controls. Moreover, BMI was likely to be higher in cases. Regarding concentration of serum IGFs and IGFBP-3, there was no significant difference between cases and controls.

Table 2 shows breast cancer risk associated with three categories of serum IGF-I, IGF-II, IGFBP-3, and IGF-I/ IGFBP-3 ratio in premenopausal women. Levels of IGF-I and IGF-I/ IGFBP-3 ratio were not associated with the risk either before or after adjustment for the potential confounding factors. While levels of IGF-II showed a marginal negative dose-dependent association with the beast cancer risk even after adjusted confounders (trend P= 0.08), however, significance disappeared by calculating with IGFBP-3 (trend P= 0.47). Levels of IGFBP-3 were likely to be inversely associated with the risk after adjusted confounders (trend P= 0.12).

For postmenopausal women, levels of IGF-I were likely to be associated with breast cancer risk compared to the lowest. Levels of IGFBP-3 showed a marginal dose-dependent association with the risk in multi-variables analyses (trend P= 0.06) (Table 3). However, IGF-II and IGF-I/ IGFBP-3 ratio were not associated with the risk, either before or after adjustment for the potential confounding factors.

Discussion

Premenopausal women

A nested case-control study found IGF-I to be predictive of breast cancer risk in premenopausal women (Krajcik et al., 2002), and a meta-analysis also showed marginally significant increased the risk (Sugumar et al., 2004). However, in the present study, the IGF-I concentration was not associated with the beast cancer risk. Thus our result was not consistent with the literature. Small sample size might be one of the reasons why we could not find significant association, and the fact that the mean age of subjects was close to menopause may be

another.

Previous epidemiologic studies did not find association between breast cancer risk and IGF-II, although IGF-II as well as IGF-I are the most potent stimulators of cell proliferation in humans (Singer et al., 2004). In contrast, our results showed that serum IGF-II was inversely associated with the risk. However, its significance disappeared by calculating with IGFBP-3. The risk reduced by IGF-I may be owing to effect of IGFBP-3 because IGFs including IGF-II usually bind IGFBP-3, and IGFBP-3 is considered to be inversely associated with the risk as described next .

It is currently known that IGFBP-3 has growth-inhibitory properties (Marshman et al., 2002). Relatively high IGFBP-3 concentration may indirectly reduce cancer risk by binding a greater proportion of circulating IGFs, thereby reducing their bioavailadality and thus inhibiting mitogenic effect (Li et al.. 2001). The present study supported that circulating IGFBP-3 concentration was inversely associated with the risk among premenopausal women. It is also suggested that high level IGF-I and low level of IGFBP-3 may be important in breast cancer development in younger women (Li et al.. 2001), however, our results did not show any relation between IGF-I/ IGFBP-3 ratio and breast cancer risk in premenopausal women.

Postmenopausal women

Among postmenopausal women, serum IGF-I and IGFBP-3 concentration is considered not to be associated with breast cancer risk in several prospective studies (Krajcik et al., 2002.; Keinan-Boker et al, 2003.; Gronbaek et al., 2004). However, our result showed that levels of IGF-I and IGFBP-3 were positively associated with the risk. A matched case-control study conducted in China reported that plasma levels of IGF-I and IGFBP-3 were higher among breast cancer patients than among controls (Yu et al., 2002). It is possible that there were some cases with very early stage of breast cancer in our study and they affected the result. More precise information such as clinical stage is needed to explain the results.

In an earlier prospective study, risk of breast cancer among postmenopausal women increased with increase IGF-II, which was marginally significant (Gronbaek et al., 2004). However, few study found significant association of IGF-II concentration with breast cancer (Krajcik et al., 2002).Our results also showed no association between serum IGF-II concentration and breast cancer risk in postmenopausal women. In the present study, IGF-I/ IGFBP-3 ratio were not associated with the risk of breast cancer.

Limitations of the present study

Several limitations of the present study should be mentioned. First, the number of breast cancer cases was very small in spite of a large scale cohort study. Regarding incident cases, cancer registries were not available in all study areas. Moreover, the cases in the present study included death and incidence together, and menstruation status of the premenopausal cases was not ascertained at the time of diagnosis but rather at the base line survey. It is necessary to examine ORs again using a sufficient number of cases according to medical information at the time of diagnosis. Second, most participants in this cohort were those who attended health screening programs. This means that many participants may be more health-conscious and have better lifestyles than the general population itself. This selection bias could possibly make it difficult to detect breast cancer risk. Third, we could not disregard change of habits and lifestyles over time in each subject. Suzuki et al. reported that the dietary practices of subjects in the JACC Study had changed over five years (Suzuki et al., 2005). Life style has very important effect on serum levels of insulin-like growth factors (Fairey et al., 2003). However, this study is meaningful as one of nested case-control studies conducted in Asia.

In conclusion, in premenopausal Japanese women, IGF-IIshowed a marginal negative dose-dependent association with the breast cancer risk, although significance disappeared by calculating with IGFBP-3, which was likely to be inversely associated with the risk. In postmenopausal women, IGFBP-3 showed a marginal dose-dependent association with the risk. Further studies are needed to confirm these findings.

Member List of the JACC Study Group

The present members and their affiliations in the JACC Study are as follows: Dr. Akiko Tamakoshi (present chairperson of the study group), Aichi Medical University School of Medicine; Drs. Mitsuru Mori & Fumio Sakauchi, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Osaka University School of Medicine; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Michiko Kurosawa, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences; Dr. Naohito Tanabe, Niigata University School of Medicine; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science; Dr. Kenji Wakai, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, National Institute of Health and Nutrition; Dr. Koji Suzuki, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Yasuhiko Wada, Kansai Rosai Hospital; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Nara Women's University; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Dr. Takesumi Yoshimura, Fukuoka Institute of Health and Environmental Sciences; Dr. Yoshihisa Fujino, University

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