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INSULIN-LIKE GROWTH FACTOR (IGF)-I AND IGF-BINDING PROTEIN 3 AND THE RISK OF PREMENOPAUSAL BREAST CANCER: A META-ANALYSIS OF LITERATURE

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Biologic evidence suggests substantial effect of insulin-like growth factor (IGF)-I in mammary cell carcinogenesis. However, controversy remains regarding the association between circulating IGF-I levels and the risk of premenopausal breast cancer in epidemiologic studies. In addition, the association of IGF-binding protein (IGFBP)-3, which binds with and modifies the effect of IGF-I, is unclear. To clarify these associations, we performed a meta-analysis of all the published studies. A systematic review of literature was conducted. Eligible study designs were nested case-control and population-based case-control studies that give estimates for menopausal women. The studies published between January 1990 and March 2003 were obtained from Medline. We obtained 7 studies, consisting of 688 premenopausal incident breast cancer cases and 1,366 controls, for our final evaluation. Summary statistics were odds ratios (ORs) comparing the highest and the lowest levels of IGF-I and IGFBP-3 adjusted for confounders other than IGF-I or IGFBP-3. There was neither evidence of heterogeneity between studies nor evidence of publication bias. The confounders considered and the contrast used for the ORs were the major source of variation. The subjects with higher circulating levels of IGF-I had marginally significant increased risk of breast cancer with an OR of 1.74 (95% CI = 0.97–3.13; $p = 0.06$). No significant difference was observed for IGFBP-3 group (OR = 1.60; 95% CI = 0.84–3.02; $p = 0.15$). In conclusion, we found a marginally significant association between circulating IGF-I levels and the risk of premenopausal breast cancer.

Key words: *IGF-I; breast cancer; meta-analysis; case-control studies; odds ratio*

Insulin-like growth factor (IGF)-I is a member of a family of 2 interacting polypeptide hormone ligands (IGF-I and IGF-II) with close homology to proinsulin.[1] IGF-I stimulates cell proliferation and inhibits apoptosis in many cell types, including human breast epithelium, and there is increasing experimental evidence that this anabolic IGF-I signal may enhance tumor development.[2,3]

Based on the possible biologic significance of IGF on carcinogenicity, several epidemiologic studies have been conducted to assess the association with different kinds of neoplastic diseases such as prostate[4] and colorectal cancer.[5] With regards to breast cancer, several studies have shown that breast cancer patients have higher levels of IGF-I than control subjects.[6-11] There was only one study that was not consistent with this observation.[12] Although not all the studies showed significant association between IGF-I levels and the risk of breast cancer, there appears to be a possible association in premenopausal breast cancer cases.

To examine the association of IGF-I with premenopausal breast cancer, we performed a systematic meta-analysis of all the published studies to determine whether premenopausal breast cancer patients have higher circulating levels of IGF-I than controls. Moreover, as 90% of IGF-I is bound to IGF-binding protein (IGFBP)-3,[13] and because IGFBP-3 has a major role in the bioavailability of IGF-I, we also assessed the association between circulating IGFBP-3 and premenopausal breast cancer.

MATERIAL AND METHODS

Selection of studies

We used Medline (from the January 1990 through March 2003) to identify 31 articles indexed with an MeSH heading of "breast neoplasms or breast cancer" and key words of either "IGF," "insulin-like growth factor," or "insulin-like growth factor-binding protein," in combination with key words of "concentration," "status," "plasma" or "circulating" and "cohort studies" or "case-control studies." We included all the studies reporting odds ratio (OR), comparing the highest category to the lowest as a measure of association and which had a nested case-control or a population-based case-control design. Hospital-based case-control designs and case-only designs were excluded. After preliminary abstract review of 31 studies, we excluded 15 publications due to inappropriate study design. All the 15 studies excluded did not provide any relevant data to estimate ratio measurement for breast cancer risk. All the 15 studies were excluded after detailed examination. Eight out of 15 were designed as case-only studies; of the rest, 3 studies were cohort studies[14-16] and 4 were cross-sectional studies. Three cohort studies were further examined and excluded for the following reasons. Two studies were conducted to evaluate the different endpoints (IGF-I genotype[16] and anthropometry, blood pressure, lipids and so on[14]). Another study was conducted for colorectal cancer.[15] The reference lists of these 31 publications led to the identification of 4 more relevant articles. We further excluded 11 studies due to inappropriate study design after a detailed review of the articles. Two out of 11 studies were excluded for case-only design. Four studies were excluded because they did not provide any value or numbers of subjects to obtain ratio measurement for association. Another 5 studies were excluded because of hospital-based design. As 1 of 9 studies was in the form of abstract[17] and in reality a part of a series of studies, we chose to use the latest published study in the series.[7] One study was excluded because the study was not stratified by menopausal status.[18] Seven studies[6-12] were used for final meta-analysis (Table I). All potentially relevant articles were reviewed by at least 2 independent investigators. The selection process is shown in Figure 1.

Data abstraction

Two investigators using a standard information extraction form independently abstracted the data. Characteristics abstracted from the articles included the name of the first author, location of the study, year of publication, study design, case definition, control

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TABLE I – SUMMARY OF STUDIES INCLUDED IN THE ANALYSIS FOR IGF-I/IGFBP-3 AND RISK OF PREMENOPAUSAL BREAST CANCER

Study	Year	Study design[1]	Cases	Controls	Country	Menopausal status	Result[2]	Matching factor
Bohlke *et al.*[6]	1998	2	94	76	Boston, USA	Pre	NS	Age, precinct of residence
Hankinson *et al.*[7]	1998	1	397	620	Nurses Health Study, USA	Pre/post	S	Age, time of blood collection, month of blood sampling, menopausal status, use of postmenopausal hormone, fasting status, month of blood sampling, use of postmenopausal hormones at the time of blood withdrawal
Toniolo *et al.*[8]	2000	1	287	706	New York, USA	Pre/post	NS	Age at enrollment, time since blood sampling
Kaaks *et al.*[12]	2002	1	513	987	Sweden	Pre/post	NS	Age, subcohort, fasting status, menopausal status, use of pill/exogenous hormones, date at blood donation
Krajcik *et al.*[9]	2002	1	126	126	California, USA	Pre/post	NS	Age, date of examination, duration of follow-up
Muti *et al.*[10]	2002	1	133	503	Italy	Pre/post	S	Age, menopausal status, daylight saving period at recruitment, recruitment center, recruitment period
Yu *et al.*[11]	2002	2	300	300	China	Pre/post	S	Age, date of blood collection, menopausal status

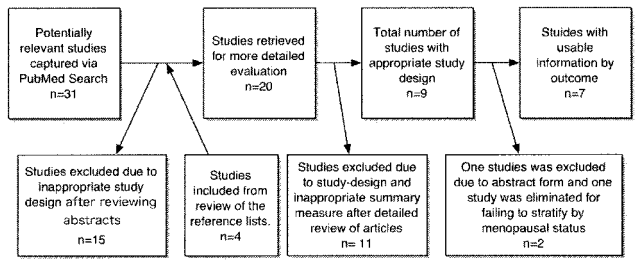

FIGURE 1 – The process of study selection. Thirty-one studies were originally obtained from Medline. After subsequent review, we finally obtained 7 studies for the analysis.

definition, inclusion/exclusion criteria, method of IGF-I and IGFBP-3 measurements, confounding factors that were controlled for by matching or adjustment, mean and standard deviation of IGF-I and IGFBP-3 in each group, menopausal status, odds ratio comparing the highest category to the lowest and its 95% confidence interval.

Statistical analysis

Most of studies provided crude and adjusted OR. Factors adjusted for in the various studies are detailed in Table II. We used the adjusted OR comparing the highest category with the lowest as the principal effect measure in our meta-analysis. The cutoff values for these categories were based on control groups, which better represented the distribution of IGF-I and IGFBP-3 in the general population. The adjusted ORs and their 95% confidence intervals were abstracted directly from the publications. Stata statistical package (version 8, Stata, College Station, TX) was used for the meta-analysis. In addition, we looked for heterogeneity among the studies based on standard methods.[19] We also calculated the between-study variation (τ^2) from the Q-statistic[20] and we obtained τ^2 value of 0 and Q-value of 2.558 (df = 6; $p = 0.862$). This result indicates that there is no between-study variation and that analyses based on fixed-effect model[21] and random-effect model would give completely same results. Therefore, our results presented here can be considered to be independent from type of effect model. The general variance-based method was used to estimate the summary OR and its 95% confidence interval (CI). We also used funnel plots to detect possible publication bias.

RESULTS

In the final analysis, we had a total of 7 case-control studies consisting of 5 nested case-control studies and 2 population-based case-control studies as shown in Table I. Among the 7 studies, 4 studies were conducted in the United States and 3 were done in Sweden,[12] Italy[10] and China.[11] Six studies were conducted for both premenopausal and postmenopausal breast cancer.[7-12] One study focused on premenopausal breast cancer alone.[6] The number of cases and controls ranged from 45 to 513 and 76 to 987, respectively. The total numbers of cases and controls in these studies were 1,895 and 3,711. We selected only premenopausal subjects from each study. The total numbers of cases and controls in our analysis were 688 and 1,366, respectively. After performing the tests for homogeneity for IGF-I and IGFBP-3 separately, we decided to use a fixed-effect model to obtain a summary statistic as the tests were not significant (Q = 2.558 with df = 6, $p = 0.862$ for IGF-I and Q = 3.159 with df = 5, $p = 0.68$ for IGFBP-3). We used the inverse variance weights as already mentioned in weighting the studies.

For IGF-I, the results of our meta-analysis and its graphic plot are presented in Table II and Figure 2. While comparing the highest to the lowest levels of IGF-I in all the studies, the people in the highest strata had a 1.74 (95% CI = 0.972–3.129) times higher risk of developing premenopausal breast cancer. This association was not found to be statically significant ($p = 0.062$). As shown in Table II, the factors adjusted in each study were diverse. The Egger's test did not suggest any publication bias ($p = 0.293$). The Begg's funnel plot is shown in Figure 3.

TABLE I – SUMMARY OF STUDIES INCLUDED IN THE ANALYSIS FOR IGF-I/IGFBP-3 AND RISK OF PREMENOPAUSAL BREAST CANCER (CONTINUED)

Definition of menopause	IGF-I measurement method[3]	IGFBP-3 measurement method	Mean age (SD) cases/ controls	Mean IGF-I (SD) cases/controls (ng/ml)	Mean IGF-BP3 (SD) cases/controls (ng/ml)	Cutoff value for IGF-I (ng/ml)		Cutoff value for IGF-BP3 (ng/ml)	
						Lowest group	Highest group	Lowest group	Highest group
Definition of menopause unclear; based on subjects' report	IRMA	IRMA	NA[4]/NA	NA/NA	NA/NA	≤121.5	≥175.5	≤3,239	≥3,493
Reporting of natural menopause or oophorectomy, at least 56 years (nonsmoker) or 54 years (smoker)	ELISA	ELISA	48.1 (2.8)/ 48.1 (2.8)	204 (NA)/ 184 (NA)	NA/NA	<158	≥207	NA	NA
Definition of menopause unclear; based on subjects' report	RIA	RIA	NA/NA	215.1 (4.89)/ 213.0 (3.01)	3420 (0.06/ 3310 (0.03)	<168.0	>256.0	<2,800	>3,800
Definition of menopause unclear; instead, age < 50 was used as a indicator of premenopausal status	IRMA		NA/NA	166.9 (NA)/ 166.8 (NA)	3697.7 (NA)/ 3625.1 (NA)	NA	NA	NA	NA
Absence of menstrual bleeding for at least 12 months	RIA	IRMA	33.7/34.3	258 (86)/ 244 (90)	2510 (700)/ 2310 (670)	<185	≥308	<1,872	≥2,890
Absence of menstrual bleeding for at least 12 months	IRMA	IRMA	44.8 (5.0)/ 44.4 (4.8)	170.1 (55.2)/ 158.8 (59.8)	3754 (965)/ 3549 (753)	≤115.2	>199.1	≤3,091	>3,986
Definition of menopause unclear; based on subjects' report	ELISA	ELISA	48.5 (8.3)/ 48.4 (8.4)	163[6] (NA)/ 146[6] (NA)	4224[6] (NA)/ 3901[6] (NA)	≤107.5	≥149.6	≤3,698	≥4,395

[1]Study designs: 1, nested case-control study within cohort study; 2, population-based case-control study.–[2]NS and S indicate not significant and significant, respectively. The significance only for premenopausal subjects was considered.–[3]IGF-I and IGFBP-3 measurement method: IRMA, immunoradiometric assay; ELISA, enzyme-linked immunoabsorbent assay; RIA, radioimmunoassay assay.–[4]NA indicates not available.–[6]Median values were applied instead of mean value.

We also examined the possible association of IGFBP-3 and the risk of premenopausal breast cancer as presented in Table II and Figure 4. Because the OR was not available in 1 study,[7] we used 6 studies in our analysis. When we compared the highest to the lowest levels of IGFBP-3, the people in the highest strata had a 1.60 (95% CI = 0.844–3.018) times higher risk of developing breast cancer. But this association was not statistically significant ($p = 0.150$). We used a Begg's funnel plot (plot is not shown) to look for any publication bias. We did not find any significant publication bias ($p = 0.348$).

DISCUSSION

In this meta-analysis, we obtained consistent data suggesting that IGF-I is high in the premenopausal breast cancer population, though we could not demonstrate statistical significance. With regard to the association between IGFBP-3 and premenopausal breast cancer, the data does not seem to suggest an association.

In terms of the biologic mechanism, the IGF family is supposed to play a pivotal role in regulating cell proliferation, apoptosis and transformation.[22] Most circulating IGFs are produced by hepatocytes in response to growth hormone stimulation.[23–25] Circulating IGFBP-3 is produced by hepatic endothelium and Kupffer cells.[24,25] A number of *in vitro* and *in vivo* studies have demonstrated that IGF-I is an effective mitogen in normal epithelial cells and has strong antiapoptotic effects on breast cancer cells.[22,26–28] However, the effect of IGF-I may be modulated by IGFBP-3 in circulation because most of the IGF-I is bound to IGFBP-3 and once bound it is not in its active form. Corresponding results regarding the effect of IGF-I and IGFBP-3 on carcinogenicity were observed in the epidemiologic studies for the risk of prostate cancer[4,29] and colorectal cancer.[5] Previous studies have suggested that using measures such as IGF-I/IGFBP-3 ratio or IGFBP-3 adjusted OR might be more accurate than IGF-I alone in quantifying the association between IGF-I levels and premenopausal breast cancer.[7,30] Although we cannot conclude whether these alternative measures are better than absolute IGF-I level or not, we found that absolute circulating IGF-I was one of the good measures to evaluate the association between IGF-I levels and premenopausal breast cancer.

Possible limitations of our meta-analysis includes relatively small number of studies, different study designs, heterogeneous matching factors, inconsistent OR comparison, different countries and ethnicities, possible publication bias, as well as possible interaction with other biologic and environmental factors. The above limitations might have contributed to the low statistical power of our meta-analysis. The potential difference between case-control studies and cohort studies in terms of influence of existing cancer may limit our interpretation that our results are homogeneous. We cannot rule out potential influence of existing cancer for IGF-I and IGF-BP3 concentrations. It is well documented that ethnic factor contributes to the breast cancer incidence. In our study, we included 1 Swedish, 1 Chinese, 1 Italian and 4 U.S. studies. Therefore, heterogeneity by ethnicity needs to be taken into account when interpreting our data. Heterogeneous matching factors and differential adjustment for confounding factors are other sources of bias. The combined odds ratio was obtained from dissimilar studies. When we compared the highest to the lowest category, 2 studies[6,11] used tertiles, 1 study[7] used quintile, and the other 4 studies[8–10,12] used quartiles. A metaregression analyses regarding the use of these discrepant contrast revealed that the influence of this factor seems limited (data not shown). Regarding statistical model to obtain summary odds ratio, we obtained similar results from random-effect model and from fixed-effect model because the between-study variation was 0. This does not necessarily rule out the effect of heterogeneity between studies; however, one may expect a very limited sway because of it. Finally, we cannot completely rule out possible publication bias, as is often the case with meta-analysis, even though statistical tests deny the existence of it.

Based on our meta-analysis, we suggest some guidelines for future studies. Since circulating IGF-I remains an important factor

TABLE II – SUMMARY OF THE META-ANALYSIS FOR IGF-I/IGF-BP3 AND PREMENOPAUSAL BREAST CANCER RISK

Study	Cases	Controls	OR (95% CI) for IGF-I[1]	Weight for IGF-I, summary OR	OR (95% CI) for IGF-BP3[1]	Weight for IGF-BP3, summary OR	Adjusted factors in the model in original report
Bohlke *et al.*[6]	94	76	1.8 (0.7–4.6)	1.12	0.7 (0.13–3.68)	1.39	Age, body mass index, age at first birth, age at menarche, height, logestradiol, ethnic group, parity, first-degree family history of breast cancer
Hankinson *et al.*[7]	76	105	2.33 (0.50–10.9)	1.61	NA	NA	Year of birth, time of day blood was drawn, fasting status, month of blood sampling, use of postmenopausal hormones at time of blood collection
Toniolo *et al.*[8]	172	486	1.60 (0.53–4.84)	3.14	1.18 (0.38–3.69)	2.96	History of benign breast disease, parity, family history of cancer
Kaaks *et al.*[12]	116	330	0.63 (0.14–2.88)	1.66	1.37 (0.32–5.91)	1.8	Age at menarche, parity, age at first birth
Krajcik *et al.*[9]	66	66	3.49 (0.13–94.1)	0.35	5.28 (0.26–108.4)	0.42	Body mass index and plasma levels of glucose and insulin
Muti *et al.*[10]	69	238	3.12 (0.43–22.8)	0.97	2.31 (0.42–12.7)	1.33	Age, body mass index, socioeconomic status, age at menarche, age at first birth, parity
Yu *et al.*[11]	171	170	2.29 (0.65–8.13)	2.39	3.71 (0.78–17.7)	1.57	Body mass index, age at menarche, age at first birth, total energy intake, waist-to-hip ratio, history of fibroadenoma, family history of breast cancer
Combined	764	1471	1.74 (0.97–3.13)	$p = 0.062$	1.60 (0.84–3.02)	$p = 0.150$	

[1]95% CI presented here were calculated in the meta-analysis.

FIGURE 2 – Graphic representation of the meta-analysis for IGF-I and premenopausal breast cancer. Detailed ORs and weights for each study are shown in Table II. ORs and their 95% CIs in the original studies are shown.

FIGURE 3 – Funnel plot for publication bias in the analysis of IGF-I and premenopausal breast cancer. Each circle indicates the OR of premenopausal breast cancer comparing the subjects in the highest category with the lowest (vertical axis) and the standard error of natural logarithm of OR in each study.

FIGURE 4 – Graphic representation of the meta-analysis for IGF-I and premenopausal breast cancer. One study (Hankinson *et al.*[7]) was excluded due to lack of data for IGFBP-3 in the report. Detailed ORs and weights for each study are shown in Table II. The ORs and their 95% confidence intervals in the original studies are shown.

in premenopausal breast cancer, more studies need to be conducted to discern this association. Considering the biologic evidence of IGF-I in breast cancer carcinogenesis, the studies should ascertain free IGF-I fraction along with IGF-I/IGFBP-3 ratio to address the bioavailability issue of IGF-I. In addition, we should focus on younger subjects (such as age less than 50) because of possible stronger association in this category.[7,8] Uniform adjustment of confounding factors across the studies will help in terms of interpretability and comparability.

In conclusion, we found a marginally significant association between circulating IGF-I levels and the risk of premenopausal breast cancer.

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