Differential effects of insulin-like growth factor-1 CA repeat polymorphism on breast cancer risk along with race: A meta-analysis

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Abstract

Background: Insulin-like growth factor (IGF)-I has been implicated in processes leading to breast cancer initiation and progression. A CA repeat polymorphism in the promoter region of IGF-I may suppress transcriptional activity and be associated with risk of breast cancer. A variety of case–control studies have been published evaluating the association between IGF1 CA repeat polymorphism and breast cancer. However, those published studies yielded contradictory conclusions.

Results: This meta-analysis enrolled eleven studies to estimate the overall breast cancer risk of IGF1 CA repeat polymorphism. There was no significantly breast cancer risk found for pooled ORs among all the models. In the sub-stratified analysis by ethnicity, significantly decreased risks were found among Caucasian (19/19 versus non19/non19: OR = 0.81, 95% CI: 0.70–0.94, P = 0.922; 19/non19 versus non19/non19: OR = 0.86, 95% CI: 0.74–0.99, P = 0.005; dominant model: OR = 0.84, 95% CI: 0.73–0.96, P = 0.871). However, no significantly breast cancer risk was found among Asian and other ethnicities for all the genetic models. Furthermore, in the stratified analysis by case size, significantly decreased risk was found in postmenopausal woman was observed in the comparison of genotype 19/19 versus 19/non19 + non19/non19: OR = 0.89, 95% CI: 0.81–0.99, P = 0.603. In addition, in the stratified analysis by case size, significantly decreased risk was observed in studies whose case size was more than 500 (19/19 versus 19/non19 + non19/non19: OR = 0.92, 95% CI: 0.86–1.00, P = 0.457).

Conclusions: This study suggested that genotype 19/19 of IGF1 CA repeat polymorphism is a decreased risk for developing breast cancer in Caucasian but not in Asian, indicating that the association might be adjusted by race.

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1. Introduction

IGF-I, a peptide hormone with 70 amino acids, plays key roles in regulating cell proliferation, differentiation and programmed cell death (Gockerman et al., 1995), and it is also required for the normal development of the breast (Laban et al., 2003). Various studies have shown that elevated serum levels of IGF-I were associated with increased risks for prostate and premenopausal breast cancer (Hankinson et al., 1998; Renehan et al., 2004). Moreover, in vitro studies have also demonstrated that IGF-I has strong mitogenic and antiapoptotic effects on breast cancer cells (Dunn et al., 1997; Pollak, 1998) and acts synergistically with estrogen to stimulate the growth of breast cancer (Lee et al., 1999; Rasmussen and Cullen, 1998).

Abbreviations: IGF-I, Insulin-like growth factor-1; SE, Standard error; OR, Odds ratio; CI, Confidence interval; HWE, Hardy–Weinberg equilibrium; CA, Cytosine–adenine dinucleotides.

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1 Bangshun He and Yeqiong Xu contributed equally to this work and should be considered as co-first authors.

The IGF-I gene is located on chromosome 12 with 6 exons (D’Ercole, 1996). Studies have indicated that about 38% of variation between person in circulating IGF-I levels is genetically determined (Harrela et al., 1996). In the 5′ untranslated region, the gene contains a polymorphic sequence composed of multiple cytosine–adenine dinucleotides (CA repeats) (Rotwein et al., 1986). Studies have suggested that the polymorphic CA repeats in the promoter region of a gene affect transcription activity and have been associated with plasma IGF-I levels (Rietveld et al., 2004; Rosen et al., 1998), and that the length of CA repeats is inversely correlated with transactivation (Yu et al., 2001).

Among a number of reports, the IGF1 CA-repeat alleles range in sizes from 12 to 23 repeats, and the length of (CA)19 repeats has been shown to have an association between high serum IGF-I levels (Rietveld et al., 2003; Vaessen et al., 2001), while other studies reported the opposite results (Jernstrom et al., 2001a; Rosen et al., 1998). In addition, epidemiological studies have hinted that the association between the length of CA repeats and the level of IGF-I might be a risk factor for cancer (Nam et al., 2003; Wagner et al., 2007), specifically in breast cancer (Al-Ajmi et al., 2012; Cleveland et al., 2006; DeLellis et al., 2003; Figer et al., 2002; Gonzalez-Zuloeta Ladd et al., 2007; Missem...
et al., 2002; Sarkissyan et al., 2011; Slattery et al., 2007; Wagner et al., 2005; Wen et al., 2005; Yu et al., 2001). However, results from these studies were inconsistent, so the strategy including research design, study population and assay characteristics needs to be further investigated.

In consideration of the conflicting role of IGF-I CA repeats in breast cancer, we carried out a meta-analysis on all eligible case-control studies to comprehensively evaluate the role of the IGF-I CA repeats in the risk of breast cancer.

2. Materials and methods

2.1. Identification and eligibility of studies

To identify all articles that examined the association of IGF-I (CA) repeat polymorphism with breast cancer, we conducted a literature search of the PubMed database using the following keywords and subject terms: “breast cancer”, “polymorphism” and “insulin-like growth factor-I” or “IGF-1” (last search was updated on September 2, 2012). References to retrieved articles were screened. Abstracts, case reports, editorials, and review articles were excluded. Additional studies were identified by a hand search of reference of original studies or review articles. Studies included in the current meta-analysis had to follow all the following criteria: (1) a case–control design, (2) evaluation of the IGF-I (CA) repeat polymorphism and breast cancer risk, and (3) contain available genotype frequency.

2.2. Data extraction

Information was carefully extracted from all enrolled references independently by two researchers (Bangshun He and Yeqiong Xu) according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. The following data were considered: author, year of publication, selection and characteristics of cancer cases and controls, control source (population or hospital based), demographics, ethnicity, menopausal status, and genotyping information. Data were extracted separately for each of ethnic groups categorized as Caucasian, Asian or mixed that included more than one ethnic group. Study design was stratified to hospital or population-based studies. Menopausal status was divided to premenopausal and postmenopausal.

2.3. Statistical methods

Crude ORs with 95% CIs were used to assess the strength of association between the IGF-CA polymorphism and breast cancer risk. The pooled ORs were performed for co-dominant model (non19/non19 vs 19/19), dominant model (19/19 + 19/non19 vs non19/non19), and recessive model (19/19 vs non19/non19 + 19/non19), respectively. Fixed-effect model, based on Mantel–Haenszel method (Mantel and Haenszel, 1959), was used when no significant heterogeneity among the studies was found \((P > 0.05)\). Otherwise, a random-effect model was selected. Subgroup analyses, according to menopausal status, ethnicity and case size were also performed. The potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry was tested by Egger’s test (Egger et al., 1997). This meta-analysis was performed using the software STATA version 10.0. All P-values were based on two-sided tests and a P-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of studies

According to our inclusion criteria, a total of eleven eligible papers involving 7047 cases and 12,096 controls were included in the pooled analyses (Fig. 1). Among the eleven papers, one paper (DeLellis et al., 2003) presented in four different populations, so the paper was divided into four studies and one paper (Slattery et al., 2007) presented in two populations which was divided into two studies. There were three studies of Asians, five studies of Caucasians and others (two studies not mentioned, one study of Africans, one study of Latino, one study of Jewish and two of mixed). Direct sequencing was applied in fourteen studies (Table 1). Breast cancers were confirmed histologically or pathologically in most studies. In addition, controls were mainly matched on age, of which ten were population-based. The distribution of genotypes in the controls was consistent with Hardy–Weinberg equilibrium (HWE) in all studies \((P > 0.05)\) except for two studies (Al-Ajmi et al., 2012; Gonzalez-Zuloeta Ladd et al., 2007), whose expected distribution was calculated using the observed data and was found significantly deviated from HWE \((\chi^2 = 88.34, P < 0.001, \chi^2 = 258.22, P < 0.001)\).

3.2. Main results

The main results of this meta-analysis were listed in Table 2. Overall, when all the eligible studies were pooled into the meta-analysis, no significantly decreased breast cancer risk was found for all the models \((19/19 \text{ versus } \text{non19/non19}: OR = 0.91, 95\% \text{ CI: } 0.83–1.00, Z = 1.91, P = 0.057, P = 0.176)\). In the stratified analysis by ethnicity, significantly decreased risks were also found among Caucasian for genotype 19/19 vs non19/non19: OR = 0.81, 95% CI: 0.70–0.94, \(P = 0.922\), 19/19 versus non19/non19: \(OR = 0.86, 95\% \text{ CI: } 0.74–0.99, P = 0.560\) and dominant model: \(OR = 0.84, 95\% \text{ CI: } 0.73–0.96, P = 0.871\) (Fig. 2), while recessive model had a borderline result \((OR = 0.91, 95\% \text{ CI: } 0.83–1.00, Z = 1.92, P = 0.055, P = 0.266)\) (Table 2). However, no significant risk was found among Asian and other ethnicities for all genetic models (Table 2). In the stratified analysis by menopausal status, there was a significant decreased risk for postmenopausal woman for the comparison of genotype 19/19 versus 19/non19 + non19/non19 \((OR = 0.89, 95\% \text{ CI: } 0.81–0.99)\). We also performed meta-analysis for case size. Among case size of studies were more than 500, in which a significant decreased risk of breast cancer was observed for the comparison.
of genotype 19/19 vs 19/non19 + non19/non19 (OR = 0.92, 95% CI: 0.86–1.00, Z = 2.04, P = 0.041, P = 0.457).

3.3. Overall effects for alleles

We also performed a meta-analysis for all enrolled studies to compare IGF-I (CA)19 versus non-(CA)19 allele (Table 2). There was no evidence that (CA)19 allele was associated with the risk of breast cancer in the pooled analysis (OR = 0.98, 95% CI: 0.91–1.05, P = 0.038). At the same time, we performed meta-analysis according to the different ethnicities, and found decreased risk of breast cancer in Caucasian (OR = 0.91, 95% CI: 0.85–0.97, P = 0.684) (Fig. 3). However, there is no significant association between other ethnicities and breast cancer. Menopausal status sub-group analysis revealed no significant association between 19 allele and breast cancer risk either.

3.4. Test for heterogeneity

Heterogeneity was observed in the pooled analysis of the enrolled eleven studies in the genotype heterozygote (P = 0.003) and dominant (P = 0.007) models. The source of the heterogeneity was evaluated for dominant model comparison among subgroups (ethnicity, menopausal status and case size). As a result, ethnicity ($\chi^2 = 7.29$, degree of freedom = 2, P = 0.026) but not menopausal status ($\chi^2 = 0.76$, degree of freedom = 1, P = 0.382) and case size ($\chi^2 = 0.75$, degree of freedom = 1, P = 0.388) was found to contribute to substantial heterogeneity. The heterogeneity was also observed for the comparison of 19 vs non-19 allele (P = 0.038) and the test revealed that the source of the substantial heterogeneity is ethnicity ($\chi^2 = 7.88$, degree of freedom = 2, P = 0.019) but not menopausal status ($\chi^2 = 3.76$, degree of freedom = 1, P = 0.052) and case size ($\chi^2 = 0.03$, degree of freedom = 1, P = 0.873).

3.5. Sensitivity analyses and publication bias

Sensitivity analysis was performed to assess the primary source of the heterogeneity by sequential removal of individual eligible study. The heterogeneity of 19/19 + 19/non19 vs non19/non19 (OR = 0.93, 95% CI 0.80–1.07, P = 0.007) was influenced by Wen et al. (2005). By excluding this study, the heterogeneity was effectively decreased

### Table 1
Characteristics of studies included in the meta-analysis.

<table>
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<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Source</th>
<th>Genotyping method</th>
<th>Menstruation</th>
<th>Genotype (CA)19 ho (CA)19 he Non-(CA)19 ho (CA)19 Non-(CA)19 ho (CA)19 Non-(CA)19 ho (CA)19 Non-(CA)19 ho (CA)19</th>
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<td>PB</td>
<td>DNA sequencing</td>
<td>Premenopause</td>
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<td>NA</td>
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<td>DNA sequencing</td>
<td>Postmenopause</td>
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<td>2002</td>
<td>Israel</td>
<td>Jewish</td>
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<td>PCR-based assay</td>
<td>'NA'</td>
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<td>African</td>
<td>PB</td>
<td>PCR-based assay</td>
<td>Postmenopause</td>
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<td>USA</td>
<td>Asian</td>
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<td>Postmenopause</td>
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* PB: population based.
* HB: hospital based.
* NA: not applicable.
Table 2

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<th>a 19/19 vs non19/non19</th>
<th>19/non19 vs non19/non19</th>
<th>19/19 + 19/non19 vs non19/non19</th>
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</table>

Statistics: **significant results were in bold.**

- a Number of comparisons.
- b P value of Q-test for heterogeneity test.
- c Fixed-effect model was applied.

4. Discussion

Several epidemiologic studies have examined the association between circulating IGF-I and breast cancer, and have found higher levels of circulating IGF-I in cases than controls (Figer et al., 2002; Hankinson et al., 1998; Toniolo et al., 2000), however some studies hold different opinions (Jernstrom and Barrett-Connor, 1999; Petridou et al., 2000). Studies have determined that about 50% of the variability of circulating levels of IGF-I was genetically determined (Harrela et al., 1996; Kao et al., 1994), and a cytosine adenine (CA) repeat in the gene’s promoter region of IGF-1 was associated with plasma IGF-I levels (Rietveld et al., 2004; Rosen et al., 1998). Many studies have assessed the risk of breast cancer according to the carrier ship of the CA19 allele of this polymorphism generating contradicting results (Cleveland et al., 2006; DeLellis et al., 2003; Figer et al., 2002; Gonzalez-Zuloeta Ladd et al., 2007). The result from this meta-analysis indicated that genotype 19/19 of IGF-1 was associated with decreased risk for the occurrence of breast cancer, and non19/non19 was associated with increased risk for breast cancer among postmenopausal woman.

Previous studies of the IGF1 promoter CA repeat polymorphism have generally categorized IGF1 genotype with respect to whether a subject carried a (CA)19 repeat allele or not. Reports have shown inconsistent results for the association between circulating IGF-I levels and (CA)19 repeat allele (Jernstrom et al., 2001b; Rietveld et al., 2003; Rosen et al., 1998; Vaessen et al., 2001) in that the (CA)n repeat was one of the most common forms of naturally occurring repetitive DNA sequences, and it has been regarded that these repeats in the promoter region may suppress transcriptional activity (Tae et al., 1995). Moreover, the length of (CA)n repeats is inversely correlated with transcriptional activity, with up to a 5-fold decrease depending on the number of repeats (Gebhardt et al., 1999). Twin studies (Cleveland et al., 2006; Missmer et al., 2002) have reported a significant inverse association with breast cancer for increasing number of IGF1 (CA)n repeats among premenopausal women. Based on the hypothesis of a functional relevance for the IGF1 (CA)n repeat promoter polymorphism, our results showed that genotype 19/19 of IGF-1 acts as a protective factor for the occurrence of breast cancer among Caucasian population. Moreover, we also observed a different association between genotype 19/19 of IGF-1 and breast cancer for the ethnic. One of the important reasons for the difference is that IGF1 genotype distribution was different according to race and ethnicity. Asian populations carried different genotype distribution with respect to whether a carrier ship of the CA19 allele of this polymorphism generating contradicting results (Cleveland et al., 2006; DeLellis et al., 2003; Figer et al., 2002; Gonzalez-Zuloeta Ladd et al., 2007). The result from this meta-analysis indicated that genotype 19/19 of IGF-1 was associated with decreased risk for the occurrence of breast cancer, and non19/non19 was associated with increased risk for breast cancer among postmenopausal woman.

In the stratified analysis by menopausal status, we observed that genotype 19/19 was a protective factor for breast cancer among postmenopausal women. Some studies have shown that high BMI may be associated with reduced circulating IGF-I levels (Jernstrom et al., 2001a), and a well-established postmenopausal obesity is a risk factor for breast cancer (van den Brandt et al., 2000). For this reason, (OR = 0.89, 95% CI 0.78–1.01, P = 0.099). In the allele comparison, we removed eligible studies one by one. At last, we found that the study conducted by Wen et al. was the main source of the heterogeneity. After excluding this study, the heterogeneity vanished (OR = 0.94, 95% CI: 0.90–0.99, P = 0.203). In view of two studies (Al-Ajmi et al., 2012; Gonzalez-Zuloeta Ladd et al., 2007) which are deviated from HWE, removing them one by one altered ORs (95% CI, p value) to 0.93 (0.80–1.09, P = 0.005) and 0.94 (0.81–1.09, P = 0.006). Funnel plot and Egger’s test were performed to assess the publication bias. The shape of the funnel plot did not indicate any evidence of obvious asymmetry (Figs. 4–8) and the Egger’s test suggested the absence of publication bias (19/19 vs non19/non19: t = 0.73, P = 0.480; 19/ non19 vs non19/non19: t = −0.78, P = 0.449; 19/19 + 19/non19 vs non19/non19: t = −0.37, P = 0.720; 19/19 vs19/non19 + non19/ non19: t = 1.85, P = 0.092; (CA)19 versus non (CA)19 allele: t = 1.48, P = 0.162).
genotype 19/19 may play a protective role in the occurrence of breast cancer among postmenopausal women with obesity. As absence of estrogen is a characteristic of post-menopausal women, and estrogen is also considered as a risk factor for breast cancer. Therefore, synergism of IGF-1 and estrogen should be discussed. According to the previous studies, estrogen has been revealed to regulate IRS-1 expression (Lee 2013).

Fig. 2. Forest plots of effect estimates for cases and controls of eleven individual studies stratified by ethnicity (19/19 + 19/non19 vs non19/non19). For each study, the estimate of OR and its 95% CI is plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.

Fig. 3. Forest plots of effect estimates for cases and controls of eleven individual studies stratified by ethnicity (19 allele vs non19 allele). For each study, the estimate of OR and its 95% CI is plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.
et al., 2006), which is the predominant signaling molecule activated by IGF-1 and insulin (Jackson et al., 1998). Synergism between estrogen and IGF has been shown to have many model systems including breast cancer cells (Stewart et al., 1990). Moreover, Lee et al. (1999) have shown that co-treatment with estrogen and IGF-I causes growth and signaling that are greater than IGF-I alone in the breast cancer cells. And Slattery et al. (2007) have shown that in the absence of estrogen, post-menopausal women and variants of genes associated with increased IGF-1 levels were associated with increased breast cancer risk. These results reinforce the relationship between estrogen and IGF-1 and support their influence on each other in affecting breast cancer risk. However, as the result of this study was carried out by several studies, it should be assessed by further study.

There are still some limitations in this meta-analysis. Firstly, there were only five studies of Caucasian and three studies of Asian in the subgroup analysis. The sample size was not big enough to have substantial power exploring the real association. Secondly, there were only eleven literatures enrolled in this meta-analysis, therefore it should be taken into account that the small number of cases and controls in the performed analysis may result in lack of power in an association analysis. Finally, the detailed information (such as age, sex, and life-style) could not be traced, so that our unadjusted estimates should be confirmed by further studies.

5. Conclusions

In conclusion, our meta-analysis suggested that genotype 19/19 of IGF1 CA repeat polymorphism is a decreased risk for developing breast cancer in Caucasian population but not in Asian and other population, indicating that the association might be adjusted by race. It is necessary to conduct larger sample size studies of the association between IGF1 CA repeat polymorphism and breast cancer risk, eventually leading to our better understanding.

Conflict of interest

The authors declare that they have no competing interests.

Authors’ contributions

BSH and SKW coordinated the meta-analysis, participated in the design of the meta-analysis, participated in the analysis of the results of the meta-analysis, and drafted the manuscript. YQX and YQP participated in the design of the meta-analysis, performed the pre-processing of the data, participated in the meta-analysis, and helped in the analysis of the results of the meta-analysis and drafted the manuscript. RL, TYG,
Fig. 8. Begg’s funnel plot of the Egger’s test of allele comparison for publication bias for 19 allele vs non19 allele in IGF-1 CA repeat polymorphism.

GQS, LG, ZLN, and LPC performed the pre-processing of the data and participated in the meta-analysis. All authors read and approved the final manuscript.

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