RESEARCH ARTICLE

# Growth Hormone 1 T1663A Polymorphism, Recreational Physical Activity and BMI, and Breast Cancer Risk in Chinese Women

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## Abstract

**To evaluate the relationship between the growth hormone 1 (GH1) T1663A polymorphism, recreational physical activity and body mass index (BMI) with reference to breast cancer, we conducted a case-control study with 669 cases of breast cancer and 682 population-based controls in Jiangsu Province, China. A structured questionnaire was used to elicit detailed information. All subjects completed an in-person interview. GH1 genotypes were identified using PCR-RFLP methods. Odds ratios (ORs) were estimated with an unconditional logistic model. The distribution of GH1 genotypes was not significantly different between controls and cases ($\chi^2$=2.576, *P*=0.276). Results of stratified analysis by the participation status of the recreational physical activity showed that the persons with GH1 A allele were at a decreased risk of breast cancer (adjusted-OR=0.66; 95% CI, 0.50-0.87) only among inactive individuals. Stratified analysis by BMI showed that the genotype A/A was associated with a decreased risk of breast cancer only among individuals of the BMI <25 (adjusted-OR=0.80; 95% CI, 0.66-0.98). The findings of this study suggest that recreational physical activity and BMI may modify any association between the GH1 T1663A polymorphism and breast cancer risk.**

**Keywords:** Breast cancer - GH1 genetic polymorphism - recreational physical activity - BMI

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## Introduction

The growth hormone (GH) gene is associated with altered GH production. Human growth hormone-1 (GH1) is a multifunctional hormone, the adequate circulating levels of GH1 is necessary for normal accretion of skeletal and soft tissues (Florini et al., 1996), and GH1 is also believed to be responsible for mammary development (Laban et al., 2003). Concentrations of GH1 change substantially with age, they increase throughout childhood, surge during puberty, and decrease slowly with age thereafter. GH1 underexpress will cause children short in stature (Saggese et al., 2002; Hardin et al., 2006), GH1 overexpress was obverted in progressive proliferative disorder tissue samples compared with normal mammary gland tissue samples (Raccurt et al., 2002),experimental evidence also shows that GH1 overexpress were susceptible to developing mammary tumors in transgenic mice (Cianfarani et al., 1998) and breast cancer were clearly reduced in GH1 gene-deleted mice (Yang et al., 2000).

GH1 regulate expression of the insulin-like growth factors (IGF-I), and IGF-I also influence many physiologic effects of GH1 (Jones et al., 1995; Yu et al., 2000). Evidence shows that GH1/IGF-I axis play a important role in stimulating proliferation and inhabiting apoptosis (Wood et al., 2000; Yu et al., 2000; Sachdev et al., 2001). Epidemiology study indicates that the circulating levels of IGF-I are associated with increased risk of several common cancers (Wolk et al., 1998), including breast cancer (Allen et al., 2005; Fletcher et al., 2005; Al-Zahrani et al., 2006; Lukanova et al., 2006; Schernhammer et al., 2006), but these results are controversial (Kaaks et al., 2002; Schernhammer et al., 2005).

The GH1 gene is located in the human GH gene cluster on chromosome 17q, it has 9 single-nucleotide polymorphisms (SNPs) in the promoter and proximal region and these polymorphisms affect GH1 expression significantly (Horan et al., 2003). GH1 T1663A substitution is located in nontranscribed region (Hasegawa et al., 2000), but it may be related to gene expression or protein dysfunction. Le Marchand et al. (2002) reported that the polymorphism of GH1 T1663A (rs2665802) may affect levels of plasma GH1 and IGF-I, and found a positive association between this polymorphism and colorectal neoplasia. In the previous study, we also have found that the GH1 T1663A A/A genotype can decrease the risk for colorectal cancer (Gao et al., 2010).

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Khoury-Shakour et al. (2008) found that recreational physical activity modifies the association between GH1 polymorphism and colorectal cancer risk. To better understand the association between the polymorphisms of GH1 and risk of breast cancer, we utilized a case-control design, assessed the relationship between GH1 T1663A polymorphisms and breast cancer risk. Furthermore, we also assessed influence of the recreational physical activity and body mass index (BMI) to the association between GH1 T1663A Polymorphism and breast cancer risk.

## Materials and Methods

*Study subjects*

We recruited breast cancer cases using data of the Cancer Registries in Taixing, Wuxi, Jintan and Huian Cities of Jiangsu Province of China, and also recruited cases who visited Jiangsu Province Cancer Hospital from these cities from June 2004 to December 2007. All cases were histopathologically diagnosed as having a primary breast cancer. Physicians at the hospital asked eligible cases to participate in our study, and doctors or nurses interviewed the subjects and collected blood samples from a peripheral vein after obtaining informed consent. Population-based controls were selected from healthy residents in eleven villages or towns of Taixing, Wuxi, Jintan and Huian Cities. Doctors of the public health centers randomly selected one or two controls for each case, after matching for ethnicity and age within 2 years using the records of residents at the local governmental office, and then asked eligible residents for their participation. Interviews and blood collection were performed as for the cancer cases. Totals of 669 cases and 682 controls completed interview, and of these 624 and 624, respectively, provided blood. A few patients and residents refused to taken blood, but the rates for blood sampling were 93.3% for cases and 91.5% for controls. The ethics committee of Jiangsu Province Institute of Cancer Research approved this study.

*Data collection*

A structured questionnaire was used to elicit detailed information on demographic background, socioeconomic status, height and weight, recreational physical activity, menstrual and reproductive history, etc. All subjects completed an in-person interview.

*DNA extraction and genotyping*

Whole blood was collected into EDTA-coated tubes and centrifuged for 15 min, and the buffy coat layer was isolated. Genomic DNA was extracted from 200$\mu$l of buffy coat using a Qiagen QIAamp DNA Blood Mini Kit (QIAGEN Inc., Valencia, CA). The polymerase chain reaction assay used to detect the T-to-A variant at position 1663 (T1663A) in intron 4 of the GH1 gene was a two-step method because of the close homologies that exist between GH1 and the other related genes in the GH cluster (Le Marchand et al., 2002). The first amplification involved denaturation at 94°C for 5 minutes, followed by 30 cycles of 94°C for 30 seconds, 64°C for 30 seconds, and 72°C for 1 minute 30 seconds, and a final extension at 72°C for 10 minutes, using the primers F4 (5-GGCTGACCCAGGAGTCC-3) and R1 (5-AGAAGGACACCTAGTCAGACA-3) to produce a 2176-base-pair (bp) product. Three microliters of this product was further amplified with primer GH1MF2 (5-GAGAAACACTGCTGCCCTCTTTTTAGACG-3) and GH1R2 (5-AAGAGAAGGAGAGGCCAAGC-3) to produce a 180-bp product. The PCR product was subjected to AatII enzyme digestion in 37 °C for 3 hours, and samples were then analyzed by electrophoresis in 3% agarose gels. The T allele was digested with AatII to fragments of 149 bp and 31 bp, whereas the A allele was not digested with AatII. Excluding one subject for whom sufficient DNA was not available or for whom the genotyping assay failed, genotyping data were obtained from 624 cases and 623 controls.

*Data analysis*

Odds ratios (ORs) were used to measure the association of breast cancer risk with GH1 T1663A genotype. Unconditional logistic regression models were used to obtain maximum likelihood estimates of the ORs and their 95% confidence intervals (CIs), after adjusting for potential confounding variables. We calculated adjusted ORs for age, Body Mass Index (BMI), menopausal status, age at menopause and menarche, and parity. BMI was calculated based on weights and heights.The probability of Hardy-Weinberg equilibrium was assessed by the $\chi^2$ test. All the analyses were performed in SAS 8.02 (SAS Institute Inc., Cary, NC). All tests were two-sided, with the significance level of 0.05.

## Results

Comparisons between cases and controls on select demographic factors, menstrual and reproductive history, BMI, and recreational physical activity are presented in Table 1. There were no significant differences between cases and controls in terms of age, BMI and menopausal status. However, significant differences were found for age at menopause and menarche, parity and recreational physical activity.

Table 2 shows the association between the GH1 T1663A polymorphisms, BMI, recreational physical activity and the breast cancer risk. The distributions of GH1 T/T, T/A and A/A genotypes were 37.3%, 47.4% and 15.2% in controls, and 41.7%, 43.7% and 14.6% in breast cancer cases, respectively. The proportional distribution of GH1 T1663A genotypes were not significantly different between controls and breast cancer cases ($\chi^2$=2.576, $P$=0.276). The frequencies of the GH1 A allele were 39% for controls and 36% for breast cancer cases, were in Hardy-Weinberg equilibrium ($\chi^2$=0.004 and =2.056, respectively, $P$ value>0.05). It shows that subjects from population are representative. After adjusted age, BMI, menopausal status, parity, age at menarche and menopause, decreased OR for breast cancer (0.80, 95%CI=0.63-1.01) was observed in persons with GH1 A allele, when compared with GH1 T/T genotype. As compared with the individuals of BMI<25, the individuals of BMI ≥25 had an increased adjusted OR for breast cancer

(1.25, 95%CI: 0.96-1.63), whereas recreational physical activity was found to have a protective effect on breast cancer, the adjusted OR was 0.63 (95% CI, 0.49-0.81).

Stratified analysis by the participation status of the recreational physical activity is presented in Table 3. The allele A was associated with a decreased risk of breast cancer only among inactive individuals, whereas, the same allele was not associated with breast cancer risk among active individuals. As compared with GH1 T/T genotype, the combined group of the GH1 T/A and A/A genotypes were at a decreased risk of breast cancer (adjusted-OR=0.66; 95% CI, 0.50-0.87).

Stratified analysis by BMI is presented in Table 4. The genotype A/A was associated with a decreased risk of breast cancer among group of the BMI <25 (adjusted-OR=0.80; 95% CI, 0.66-0.98). But, the same genotype was

**Table 1. Characteristics Comparison of Cases and Controls (n,%)**

| | Cases(n=669) | Controls(n=682) | Cases(n=624) | Controls(n=624) |
|---|---|---|---|---|
| Age(year) | | | | |
| <40 | 76 (11.36) | 87 (12.76) | 71 (11.38) | 79 (12.66) |
| 40-49 | 226 (33.78) | 229 (33.58) | 211 (33.81) | 208 (33.33) |
| 50-59 | 227 (33.93) | 234 (34.31) | 211 (33.81) | 215 (34.46) |
| ≥60 | 140 (20.93) | 132 (19.35) | 131 (20.99) | 122 (19.55) |
| $\chi^2$ (P) | | 0.98 (0.807) | | 0.81 (0.848) |
| Menopausal status | | | | |
| Postmenopausal | 360 (53.81) | 390 (57.18) | 338 (54.2) | 360 (57.69) |
| Premenopausal | 309 (46.19) | 292 (42.72) | 286 (45.83) | 264(42.31) |
| $\chi^2$ (P) | | 1.56 (0.212) | | 1.57 (0.210) |
| Age at menopause (years) | | | | |
| ≤50 | 202 (56.11) | 283 (72.56) | 201 (59.47) | 281 (78.06) |
| >50 | 158 (43.89) | 107 (27.44) | 137 (40.53) | 79 (21.94) |
| $\chi^2$ (P) | | 22.15 (<0.001) | | 28.15 (<0.001) |
| Menarche | | | | |
| ≤13 | 180 (26.91) | 141 (20.67) | 172 (27.56) | 116 (18.59) |
| `14 | 211 (31.54) | 216 (31.67) | 193 (30.93) | 201 (32.21) |
| `15 | 191 (28.55) | 219 (32.11) | 180 (28.85) | 208 (33.33) |
| ≥16 | 87 (13.00) | 106 (15.54) | 79 (12.66) | 99 (15.87) |
| $\chi^2$ (P) | | 8.45 (0.038) | | 15.31 (0.002) |
| Parity | | | | |
| `0 | 32 (4.78) | 14 (2.05) | 31 (4.97) | 13 (2.08) |
| `1 | 337 (50.37) | 340 (49.85) | 313 (50.16) | 303 (48.56) |
| `2 | 181 (27.06) | 177 (25.95) | 169 (27.08) | 167 (26.76) |
| `3+ | 119 (17.79) | 151 (22.14) | 111 (17.79) | 141 (22.60) |
| $\chi^2$ (P) | | 10.76 (0.013) | | 11.10 (0.011) |
| BMI | | | | |
| ≤22 | 225 (33.63) | 244 (35.78) | 210 (33.65) | 215 (34.46) |
| 22-24.9 | 256 (38.27) | 282 (41.35) | 244 (39.10) | 263 (42.15) |
| ≥25 | 188 (28.10) | 156 (22.87) | 170 (27.24) | 146 (23.40) |
| $\chi^2$ (P) | | 4.88 (0.087) | | 2.59 (0.274) |
| Recreational physical activity | | | | |
| Inactive | 501 (74.89) | 468 (68.32) | 476 (76.28) | 423 (67.79) |
| Active | 168 (25.11) | 214 (31.38) | 148 (23.72) | 201 (32.21) |
| $\chi^2$ (P) | | 6.53 (0.011) | | 11.16 (0.001) |

**Table 2. The Association Between GH1, BMI, Physical Activity, and Breast Cancer Risk**

| | Cases n(%) | Controls n(%) | OR (CI) |
|---|---|---|---|
| GH1 genotypes[a] | | | |
| T/T | 260 (41.7) | 233 (37.3) | 1.00 |
| T/A | 272 (43.7) | 296 (47.4) | 0.81 (0.63-1.03) |
| A/A | 91 (14.6) | 95 (15.2) | 0.81 (0.57-1.14) |
| T/A+A/A | 363 (57.3) | 391 (62.7) | 0.80 (0.63-1.01) |
| BMI[b] | | | |
| <25 | 453 (72.7) | 478 (76.6) | 1.00 |
| ≥25 | 170 (27.3) | 146 (23.4) | 1.25 (0.96-1.63) |
| Regular physical activity[a] | | | |
| Inactive | 476 (76.4) | 423 (67.8) | 1.00 |
| Active | 147 (23.6) | 201 (32.2) | 0.63 (0.49-0.81) |

[a]ORs were adjusted by age, BMI, menopausal status, age at menarche and menopause, parity; [b]ORs were adjusted by age, menopausal status, age at menarche and menopause, parity

**Table 3. The Association of GH1 Genotype with Breast Cancer Risk, by Physical Activity**

| GH1 genotypes | Active | | | Inactive | | |
|---|---|---|---|---|---|---|
| | Cases | Controls | OR (CI) | Cases | Controls | OR (CI) |
| T/T | 53 | 85 | 1.00 | 207 | 148 | 1.00 |
| T/A | 67 | 85 | 1.25 (0.77-2.04) | 205 | 211 | 0.67 (0.50-0.90) |
| A/A | 27 | 31 | 1.17 (0.61-2.25) | 64 | 64 | 0.66 (0.44-1.00) |
| T/A+A/A | 94 | 116 | 1.23 (0.78-1.93) | 269 | 275 | 0.66 (0.50-0.87) |

*ORs were adjusted by age, BMI, menopausal status, age at menarche and menopause, parity

**Table 4. The Association of GH1 Genotype with Breast Cancer Risk, by BMI**

| GH1 genotypes | BMI<25 | | | BMI≥25 | | |
|---|---|---|---|---|---|---|
| | Cases | Controls | OR (CI) | Cases | Controls | OR (CI) |
| T/T | 187 | 171 | 1.00 | 73 | 62 | 1.00 |
| T/A | 206 | 229 | 0.79 (0.59-1.05) | 66 | 67 | 0.84 (0.51-1.37) |
| A/A | 60 | 78 | 0.80 (0.66-0.98) | 31 | 17 | 1.49 (0.74-3.01) |
| T/A+A/A | 266 | 307 | 0.74 (0.57-0.97) | 97 | 84 | 0.98 (0.61-1.55) |

*ORs were adjusted by age, menopausal status,age at menarche and menopause, parity

associated with an increased OR for risk of breast cancer among group of the BMI ≥25 (adjusted-OR=1.49; 95% CI, 0.74-3.01), although the OR value was not statistical significance.

## Discussion

In the previous study, we have found that recreational physical activity can decrease the risk of breast cancer (Gao et al., 2009), and also have found that the GH1 T1663A A/A genotype can decrease the risk of colorectal cancer (Gao et al., 2010). In present study, we found the proportional distribution of GH1 T1663A genotypes were not significantly different between controls and breast cancer cases, however, we found that combined group of the GH1 T1663A T/A and A/A genotypes were at a decreased risk of breast cancer only among the physically inactive individuals.

Ren et al. (2004) investigated the association of breast cancer with four single-nucleotide polymorphisms in GH1 promoter and proximal region in the Shanghai Breast Cancer Study, they found no positive association between GH1 genetic polymorphisms and breast cancer risk. Results of a meta-analysis revealed that GH1 T1663A polymorphism was associated with colorectal cancer risk, but no any association with breast cancer risk (Shi et al., 2014). Our findings are consistent with these study results.

Khoury-Shakour et al. (2008) found that recreational physical activity modifies the association between GH1 polymorphism and colorectal cancer risk, and that the A allele of the GH1 T1663A polymorphism is associated with reduced risk of colorectal cancer only among physically inactive individuals. In present study, our study results on breast cancer are fully consistent with that of Khoury-Shakour S et al in colorectal cancer study.

Body size has been found to be associated with risk of breast cancer in many epidemiological studies. In the previous study, we also have found that the current BMI is associated with an increased risk for breast cancer (Gao et al., 2009). In present study, we found that the GH1 T1663A genotype A/A was associated with a decreased risk of breast cancer among group of the BMI <25, whereas the same genotype was associated with an increased OR for risk of breast cancer among group of the BMI ≥25. During the last decade, the role of GH1/IGF-1-axis has been focused by many researchers (Wagneret al., 2007). The GH/IGF-I axis has a clearly established role in somatic growth regulation. van Heemst D et al. (2005) found that in females, for variant allele carriers of the GH1 SNP, body height was 2 cm lower ($P$=0.007) when compared with wild-type allele carriers, and that genetic variation causing reduced insulin/IGF-1 signalling activation. Ahmad et al. (2011) found that individuals with a GH gene deletion presented short stature and increased body fat, treatment of the recombinant human insulin-like growth factor-I not only promotes increased height velocity, but may be associated with adverse effects on lipids and BMI. Experimental evidence also shows that the adipose tissue was generally smaller in GH transgenic (containing GH1 gene) fish compared to the control, and that the composition of saturated and monounsaturated fatty acids, levels of serum glucose and triacylglycerol were significantly decreased, whereas the composition of polyunsaturated fatty acids was significantly increased in the GH transgenics compared with the wild type fish (Sugiyama M et al., 2012). These study results showed that the GH/IGF-I system is associated with the glucose and lipids metabolism, and may be also indicating an interaction between GH/IGF-I axis and BMI.

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