RESEARCH ARTICLE

Lack of any Association between the Hogg1 Ser326Cys Polymorphism and Breast Cancer Risk: a Systematic Review And Meta-Analysis Of 18 Studies

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Abstract

Background: The human 8-oxoguanine DNA glycosylase (hOGG1) gene may be linked with cancer susceptibility. The aim of this study was to quantitatively summarize any association between the hOGG1 Ser326Cys polymorphism and breast cancer (BC) risk. Materials and Methods: A comprehensive search of the PubMed, Embase, and ISI web of knowledge databases for papers published before 1 October 2016 was conducted. Summary odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were estimated, with fixed-effects or random-effects models when appropriate, to assess any association. Results: A total of 9,434 cases and 10,497 controls from 18 studies were included in this meta-analysis. When the eligible studies were pooled, there was no evidence found for a significant association between the hOGG1 Ser326Cys polymorphism and BC in all genetic contrast models G vs. C (OR=1.19, 95% CI 0.92–1.53), CG vs. CC (OR = 0.97, 95% CI 0.91-1.04, p = 0.46), GG vs. CC (OR = 1.11, 95% CI 0.91-1.35, p = 0.30), GG + CG vs. CC (OR = 0.98, 95% CI 0.92-1.05, p = 0.67), and GG vs. CG + CC (OR = 1.22, 95% CI 0.98-1.52, p = 0.07). According to subgroup analysis, we also did not find a significant association between the hOGG1 Ser326Cys polymorphism and BC risk in Asians and Caucasians considered separately. Conclusions: The current meta-analysis suggests that the hOGG1 Ser326Cys polymorphism is not significantly associated with BC risk.

Keywords: Breast cancer- 8-oxoguanine DNA glycosylase- polymorphism- meta-analysis

Introduction

Breast cancer (BC) is the most common cancer and the leading cause of cancer deaths in women (Neamatzadeh et al., 2015). Global breast cancer incidence has been increasing by more than one million new cases every year; the incidence is significantly higher in developed countries than in developing countries (Torre et al., 2015). Although substantial progress has been made in BC in the past few decades, the underlying molecular mechanism of BC still remains not fully elucidated (Forat-Yazdi et al., 2015; Yao et al., 2015). The vast majority of risk factors associated to breast cancer susceptibility are related to hormonal exposure, either from endogenous sources such as early age at menarche, late age at menopause, late pregnancy or nulliparity, overweight and obesity, or exogenous sources such as the use of hormone replacement therapy (HRT) (Forman et al., 2013). Other risk factors include alcohol intake, radiation exposure, current age, past history of breast cancer and the history of a breast biopsy (Singletary 2003).

DNA damage generated by different carcinogenic agents can be repaired primarily through base excision repair (BER) pathway, composed of many DNA repair genes (Lange et al., 2011). Common polymorphisms in DNA repair genes may alter protein function and the possibility to repair damaged DNA (Ferguson et al., 2015). Defects in DNA repair pathways may lead to genetic instability and carcinogenesis (Roberts et al., 2011). The Human 8-oxoguanine DNA glycosylase (hOGG1) gene is a key gene in the BER pathway and DNA repair process, and the Ser326Cys polymorphism is reported to be a functional variation in the hOGG1 gene. The 1,245 C/G (Ser326Cys) polymorphism of hOGG1 gene is a well-known polymorphism that results in an amino substitution from Serine to Cystein at codon 326 (Wang et al., 2014; Zhang et al., 2014). Lots of functional studies have showed that the Cys allele was associated with the reduced DNA repair activity, thus increased the cancer risk. The Cys326 has lower ability to prevent mutagenesis by 8-OHdG than Ser326 in human cells in vivo (Niu et al., 2014).

Since the original identification of the hOGG1 Ser326Cys polymorphism, a number of studies have investigated the genetic effect of this polymorphism on...
BC susceptibility (Vogel et al., 2003; Rossner et al., 2006; Sangrajrang et al., 2008; Loizidou et al., 2009; Sterpone et al., 2010; Roberts et al., 2011; Kim et al., 2013; Smolarz et al., 2014; Romanowicz et al., 2016). However, the findings are conflicting about the role of the hOGG1 Ser326Cys polymorphism in relation to BC susceptibility. In order to get more accurate results, we performed a meta-analysis. In this study, we intend to explore the possible association between hOGG1 Ser326Cys polymorphism and BC risk. To our knowledge, this is the most comprehensive meta-analysis conducted to date with respect to the association between hOGG1 Ser326Cys polymorphism and BC risk.

Materials and methods

Literature search

We searched all published papers (before 1 October, 2016) in databases of PubMed, Medline, Embase and Google scholar. The keywords were as follows: “OGG1”, “hOGG1”, “polymorphism” and “breast cancer”. Articles not written in English were excluded. Additionally, abstracts and unpublished reports were not included. All of the searched studies were retrieved, and the bibliographies were checked for other relevant publications.

Inclusion and exclusion criteria

Studies included in the current meta-analysis had to meet all the following criteria: (a) evaluation of the Ser326Cys polymorphism and BC risk, (b) case-control studies, (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (95% CI). The exclusion criteria of studies were as follows: (a) not for BC research, (b) only case population, (c) abstract, comment, case reports, letters, and review, (d) duplicate of previous publication and (e) no sufficient data were provided.

Data extraction

Two investigators extracted the data independently, and the results were reviewed by a third investigator. From each study, the following items were noted: first author, year of publication, country, numbers of cases and controls, frequencies of hOGG1 Ser326Cys polymorphism genotypes, and evidence of the Hardy–Weinberg equilibrium (HWE) in controls. If any disagreement were identified through the literature search and selection according to the inclusion criteria. Of these, 13 papers were excluded because of obvious irrelevance by reading the titles and abstracts. Three studies were excluded because of the lack of CC and CG genotype data (Figure 1). Finally, a total of 18 case-control studies with a total of 9434 cases and 10497 controls were included in the meta-analysis (Vogel et al., 2003; Choi et al., 2003; Huang et al., 2004; Cai et al., 2006; Rossner et al., 2006; Zhang et al., 2006; Romanowicz-Makowska et al., 2008; Sangrajrang et al., 2008; Synowiec et al., 2008; Loizidou et al., 2009; Sterpone et al., 2010; Hsu et al., 2010; Roberts et al., 2011; Xie et al., 2013; Kim et al., 2013; Smolarz et al., 2014; Luo et al., 2014; Romanowicz et al., 2016). The characteristics of included studies were summarized in Table 1. All the eligible studies were written in English. The populations came from different countries, including Denmark, Korea, Japan, Taiwan, China, USA, Poland, statistical analysis

The pooled OR and 95%CI were used to assess the association between hOGG1 Ser326Cys polymorphism and BC risk for each case-control study. The pooled ORs were performed for allele model (G vs. C), homozygote model (GG vs. CC), heterozygote model (CG vs. CC), dominant model (GG + CG vs. CC), and recessive model (GG vs. CG + CC). Heterogeneity was evaluated with a chi-square-based Q test among the studies (P<0.10 was considered significant) (Huedo-Medina et al., 2006). When the heterogeneity was present, the random effects model was used to calculate the pooled OR, whereas the fixed effects model was used in its absence (DerSimonian et al., 2007). Sensitivity analysis was performed to assess the stability of the results. The I2 value was used as an index for the heterogeneity test, with values less than 25% indicating low, 25 to 50% indicating moderate, and greater than 50% indicating high heterogeneity. The I2 statistic was used to estimate heterogeneity in the pooled studies (Huedo-Medina et al., 2006). Publication bias was assessed by visual inspection of funnel plots, in which the standard error of log (OR) of each study was plotted against its log (OR). Publication bias was qualitatively assessed by performing Begg’s funnel plots, and it was quantitatively evaluated by Egger’s test. P <0.05 was considered representative of statistically significant publication bias. In addition, an asymmetric plot indicates a possible publication bias (Song 2002). Subgroup analyses were performed according to sample size, ethnicity, source of control, family history status and genotyping method separately. One-way sensitivity analysis was also used to assess the stability of the results by omitting one of the studies each time. All the statistical analyses were performed by comprehensive meta-analysis (CMA) V2.0 software (Biostat, USA). All tests were two-sided, and the P values of < 0.05 were considered statistically significant.

Results

Study characteristic

In total, 47 studies relevant to the role of hOGG1 Ser326Cys polymorphism on cancer susceptibility were identified through the literature search and selection according to the inclusion criteria. Of these, 13 papers were excluded because of obvious irrelevance by reading the titles and abstracts. Three studies were excluded because of the lack of CC and CG genotype data (Figure 1). Finally, a total of 18 case-control studies with a total of 9434 cases and 10497 controls were included in the meta-analysis (Vogel et al., 2003; Choi et al., 2003; Huang et al., 2004; Cai et al., 2006; Rossner et al., 2006; Zhang et al., 2006; Romanowicz-Makowska et al., 2008; Sangrajrang et al., 2008; Synowiec et al., 2008; Loizidou et al., 2009; Sterpone et al., 2010; Hsu et al., 2010; Roberts et al., 2011; Xie et al., 2013; Kim et al., 2013; Smolarz et al., 2014; Luo et al., 2014; Romanowicz et al., 2016). The characteristics of included studies were summarized in Table 1.
in the controls was consistent with HWE in all studies, except one study (Romanowicz-Makowska et al., 2008).

Quantitative synthesis

As shown in Table 2, no significant association between the hOGG1 Ser326Cys and BC risk was observed in any of the genetic models. Overall, no significant associations were found for G vs. C (OR = 1.07, 95% CI 0.95-1.20, p = 0.24), CG vs. CC (OR = 0.97, 95% CI 0.91-1.04, p = 0.46, Figure 2A), GG vs. CC (OR = 1.11, 95% CI 0.91-1.35, p = 0.30, Figure 2B), GG + CG vs. CC (OR = 0.98, 95% CI 0.92-1.05, p = 0.67, Figure 2C), and GG vs. CG + CC (OR = 1.22, 95% CI 0.98-1.52, p = 0.07, Figure 2D).

Subgroup analysis by ethnicity

Subgroup analyses by ethnicity were primarily performed in the Asian and Caucasian populations. Nine case–control studies involving 3,781 cases and 4,207 controls on the relationship between hOGG1 Ser326Cys and BC risk were carried out among Asians and ten ones with 5,653 cases and 6,290 controls were among Caucasians, respectively. Similarly, no statistically significant association was observed in Asians and Caucasians under all genetic models (Table 2).

Heterogeneity analysis and publication bias

The results for heterogeneity analysis among the included studies were summarized in Table 2. The heterogeneity was assessed between each of the studies using the Q test. The between-study heterogeneity among total studies was significant in dominant and homozygote genetic models (I² = 85%, Ph < 0.001; I² = 70%, Ph < 0.001, respectively) (Table 2). No significant
| First author | Country | Ethnicity | Case/Control | Genotype | Allele |
|--------------|---------|-----------|--------------|----------|--------|
| Vogel 2003   | Denmark | Caucasian | 220/224      | CC       | 245    |
| Choi 2003    | Korea   | Asian     | 265/284      | CG       | 209    |
| Huang 2004   | Taiwan  | Asian     | 136/232      | GG       | 209    |
| Cai 2006     | China   | Asian     | 1102/1167    | CC       | 245    |
| Rossner 2006 | USA     | Caucasian | 1041/1093    | CG       | 209    |
| Zhang 2006   | USA     | Caucasian | 1571/1244    | GG       | 209    |
| Romanowic 2008 | Poland | Caucasian | 100/106      | CC       | 245    |
| Sangrajrang 2008 | Thailand | Asian | 506/424 | GG | 209 |
| Synowiec 2008 | Poland | Caucasian | 41/48       | CC       | 245    |
| Loizidou 2009 | Cyprus | Caucasian | 1108/1174    | CC       | 245    |
| Sterpone 2009 | Italy | Caucasian | 43/34       | CC       | 245    |
| Hsu 2009     | China   | Asian     | 401/533      | CC       | 245    |
| Roberts 2011 | USA     | Caucasian | 1054/1887    | CC       | 245    |
| Xie 2012     | China   | Asian     | 630/777      | CC       | 245    |
| Kim 2013     | Korea   | Asian     | 346/361      | CC       | 245    |
| Smolarz 2013 | Poland | Caucasian | 70/70        | CC       | 245    |
| Luo 2014     | China   | Asian     | 194/245      | CC       | 245    |
| Romanowicz 2016 | Poland | Caucasian | 200/200     | CC       | 245    |

Table 1: General Characteristics of Studies Included in the Meta-analysis
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heterogeneity was found in studies among Asians but not Caucasians, indicating that the publications in Caucasians were probably the main source of heterogeneity in the current meta-analysis.

Sensitivity analyses and publication bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. The results suggested that no individual study significantly affected the overall OR dominantly.

Publication bias

In this meta-analysis, we performed funnel plot and Egger’s test to access the publication bias. Funnel plot’s shape of all contrasts failed to indicate obvious evidence of asymmetry, and all the P values of egger’s tests were more than 0.1 providing statistical evidence of funnel plot’s symmetry (Figure. 3). Therefore, the results revealed that publication bias was not significant in this meta-analysis.

Discussion

The presence of 8-oxodG residues, one of the most abundant oxidative products of cellular DNA, leads to GC/TA transversions since it preferentially pairs with adenine instead of cytosine during DNA replication. An increase in 8-oxodG in DNA can contribute to the incidence of different cancer risk (Agnez-Lima et al., 2012).

In this study, we analyzed the data from 18 available case – control studies. The results are conflicting about the role of the hOGG1 Ser326Cys polymorphism in relation to BC susceptibility. Thus far, the association remains not fully understood because of inconsistent results across independent studies. Eight studies found an increased risk for BC associated with the 326Cys allele (Huang et al., 2004; Rossner et al., 2006; Sangrajrang et al., 2008;
especially when inclusive and controversial findings still exist. There were several limitations in our meta-analysis. First, in this meta-analysis, the included 18 studies regarded only Caucasians and Asians, but not other races. Data about other ethnicities, for example, African, should be noticed in the future. Second, because we could not obtain sufficient data from the present publications, in this study, subgroup analyses regarding age, lifestyle, and other factors have not been expressed. Finally, gene – environment interactions were not addressed in our meta-analysis. In addition, it was reported that the combination of hOGG1 Ser326Cys polymorphism with other BER genes such as XRCC1 and APE1 was significantly related to an elevated risk of BC (Sangrajrang et al., 2008; Peng et al., 2014). In addition, several genes including BRCA1, BRAC2, and P53 were identified to significantly mutate in BC patients (Vaclova et al., 2012). Thus, the possible gene – gene and gene – environment interactions may play central roles in the BC pathogenesis and need further confirmation in future studies.

In conclusion, this meta-analysis found that the hOGG1 Ser326Cys polymorphism was not associated with significantly increased risk of BC. However, further studies are warranted to validate the association between the hOGG1 Ser326Cys polymorphism and BC risk with larger sample size and more detailed data.

References

Agniez-Lima L, Melo J, Silva A, et al (2012). DNA damage by singlet oxygen and cellular protective mechanisms. Mutat Res, 751, 15-28.

Cai Q, Shu XO, Wen W, et al (2006). Functional Ser326Cys polymorphism in the hOGG1 gene is not associated with breast cancer risk. Cancer Epidemiol Biomarkers Prev, 15, 403-4.

Choi JY, Hamajima N, Tajima K, et al (2003). hOGG1 Ser326Cys polymorphism and breast cancer risk among Asian women. Breast Cancer Res Treat, 79, 59-62.

DerSimorian R, Kacker R (2007). Random-effects model for meta-analysis of clinical trials, An update. Contemp Clin Trials, 28, 105-14.

Ferguson L, Chen H, Collins A, et al (2015). Genomic instability in human cancer, Molecular insights and opportunities for therapeutic attack and prevention through diet and nutrition. Semin Cancer Biol, 35, 5-24.

Forat-Yazdi M, Neamatrazadeh H, Sheikha M, et al (2015). BRCA1 and BRCA2 common mutations in iranian breast cancer patients, a meta-analysis. Asian Pac J Cancer Prev, 16, 1219-24.

Forman M, Mangini L, Thelus-Jean R, et al (2013). Life-course origins of the ages at menarche and menopause. AHMT, 4, 1–21.

Gu D, Wang M, Zhang Z, et al (2010). Lack of association between the hOGG1 Ser326Cys polymorphism and breast cancer risk, evidence from 11 case–control studies. Breast Cancer Res Treat, 122, 527-31.

Guo C, Han F, Wang H, et al (2012). Meta-analysis of the association between hOGG1 Ser326Cys polymorphism and risk of colorectal cancer based on case–control studies. J Cancer Res Clin Oncol, 138, 1443-48.

Hsu MS, Yu JC, Wang HW, et al (2010). Synergestic effects of polymorphisms in DNA repair genes and endogenous estrogen exposure on female breast cancer risk. Ann Surg
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DOI:10.22034/APJCP.2017.18.1.245

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2012. CA Cancer J Clin, 65, 87-108.

Vaclová T, Milne R, Saucedo-Cuevas L, et al (2012). An evaluation of the genes involved in the Base Excision Repair (BER) pathway as potential phenotypic modifiers of breast cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Res, 72, 90-6.

Vogel U, Nexo BA, Olsen A, et al (2003). No association between OGG1 Ser326Cys polymorphism and breast cancer risk. Cancer Epidemiol Biomarkers Prev, 12, 170-71.

Wang Y, Gao X, Wei F, et al (2014). The hOGG1 Ser326Cys polymorphism contributes to digestive system cancer susceptibility, evidence from 48 case-control studies. Tumor Biol, 36, 1029-38.

Wang Z, Hu J, Cai W, et al (2011). Lack of association between the 8-oxoguanine DNA glycosylase gene Ser326Cys polymorphism and gastric cancer, evidence from a meta-analysis. Asian Pac J Cancer Prev, 12, 3427-31.

Wang Y, Gao X, Wei F, et al (2014). The hOGG1 Ser326Cys polymorphism contributes to digestive system cancer susceptibility, evidence from 48 case-control studies. Tumor Biol, 36, 1029-38.

Xie H, Xia K, Rong H, et al (2013). Genetic polymorphism in hOGG1 is associated with triple-negative breast cancer risk in Chinese Han women. Breast, 22, 707-12.

Yao Y, Hu J, Shen Z, et al (2015). MiR-200b expression in breast cancer, a prognostic marker and act on cell proliferation and apoptosis by targeting Sp1. J Cell Mol Med, 19, 760-69.

Yuan W, Xu L, Feng Y, et al (2010). The hOGG1 Ser326Cys polymorphism and breast cancer risk, a meta-analysis. Breast Cancer Res Treat, 122, 835-42.

Zhang J, Zhou J, Zhang P, et al (2013). A meta-analysis of the association between the hOGG1 Ser326Cys polymorphism and the risk of esophageal squamous cell carcinoma. PLoS One, 8, e56742.

Zhang M, MO R (2014). Association of hOGG1 Ser326Cys polymorphism with colorectal cancer risk, an updated meta-analysis including 5235 cases and 8438 controls. Tumor Biol, 35, 12627-33.

Zhang Y, Newcomb PA, Egan KM, et al (2006). Genetic polymorphisms in base-excision repair pathway genes and risk of breast cancer. Cancer Epidemiol Biomarkers Prev, 15, 353-58.

Zhong D, Chu H, Wang M, et al (2012). Meta-analysis demonstrates lack of association of the hOGG1 Ser326Cys polymorphism with bladder cancer risk. Genet Mol Res, 11, 3490-96.

Zhu S, Zhang H, Tang Y, et al (2012). Polymorphisms in XPD polymorphism and breast cancer risk, a meta-analysis. Breast Cancer Res Treat, 122, 385-42.

Zimmerman M (2010). Impact of Hardy–Weinberg equilibrium deviation on allele-based risk effect of genetic association studies and meta-analysis. Eur J Epidemiol, 25, 553-60.