RESEARCH ARTICLE

X-Ray Repair Cross-Complementing Group 1 (XRCC1) Genetic Polymorphisms and Thyroid Carcinoma Risk: a Meta-Analysis

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Abstract

A number of studies have been conducted to explore the association of XRCC1 polymorphisms with thyroid cancer risk, but the results have been inconsistent. Thus we performed the present meta-analysis to clarify this issue based on all of the evidence available to date. Relevant studies were retrieved by searching PubMed and statistical analysis conducted using Stata software. Nine studies were included in this meta-analysis (1,620 cases and 3,557 controls). There were 6 studies (932 cases and 2,270 controls) of the Arg194Trp polymorphism, 7 studies (1,432 cases and 3,356 controls) of the Arg280His polymorphism and 9 studies (1,620 cases and 3,557 controls) for the Arg399Gln polymorphism. No association of XRCC1 Arg194Trp, Arg280His and Arg399Gln polymorphism with thyroid cancer risk was observed in the overall analysis. However, subgroup analysis revealed: 1) an elevated risk in aa vs AA analysis (OR=2.03, 95% CI= 1.24-3.31) and recessive genetic model analysis (OR=1.93, 95% CI= 1.20-3.08) in the larger sample size trials for XRCC1 Arg194Trp polymorphism; 2) a decreased thyroid cancer risk on subgroup analysis based on ethnicity in Aa vs AA analysis (OR=0.84, 95% CI= 0.72-0.98) and in a dominant genetic model (OR=0.84, 95% CI= 0.72-0.97) in Caucasian populations for the XRCC1 Arg399Gln polymorphism; 3) a decreased thyroid cancer risk on subgroup analysis based on design type in Aa vs AA analysis (OR=0.72, 95% CI= 0.54-0.97) among the PCC trials for the Arg399Gln polymorphism. Our results suggest that the XRCC1 Arg399Gln polymorphism may be associated with decreased thyroid cancer risk among Caucasians and XRCC1 Arg194Trp may be associated with a tendency for increased thyroid cancer risk in the two larger sample size trials.

Keywords: XRCC1 - Arg194Trp - Arg280His - Arg399Gln - thyroid cancer

Introduction

Thyroid cancer is of special concern in endocrinology because it accounts for more than 90% of all endocrine cancers and contributes to more than 50% of all deaths from endocrine cancers (Gilfillan, 2010; Aschebrook-Kilfoy et al., 2011). So far, exposure to ionizing radiation is the only well established risk factor for thyroid cancer, especially when it occurs in early stages of life (Papadopoulou et al., 2009). However, there are evidences that many gene polymorphisms including DNA repair genes influence on thyroid cancer susceptibility (Gudmundsson et al., 2012, Jendrzejewski et al., 2012). X-ray repair cross complementing group 1 (XRCC1), located on chromosome 19q13.2–13.3, with 33 kilobases in length, and encodes a scaffold protein involved in the repair of DNA single-strand break (SSB) formed by ionizing radiation and alkylation damage (Chou et al., 2008). XRCC1 exert its role by interacting with other repair proteins such as OGG1, poly (ADP-ribose) polymerase (PARP), polyadenylation kinase, and proliferating cell nuclear antigen (PCNA) (Hoeijmakers, 2001; Marsin et al., 2003). There have been more than 300 validated SNPs (single nucleotide polymorphism) in the XRCC1 gene, however, only three SNPs have been extensively studied including Arg194Trp, Arg280His and Arg399Gln. The three SNPs have been reported to be associated with many types of cancer, such as lung cancer (Dai et al., 2012), gastric cancer (Chen et al., 2012), breast cancer (Huang et al., 2009) and leukemia (Wang et al., 2012).

There are also some case-control studies conducted to explore the association of SNPs of XRCC1 and thyroid cancer risk (Zhu et al., 2004; Chiang et al., 2008; Siraj et al., 2008; Ho et al., 2009; Sigurdsson et al., 2009; Fard-Esfahani et al., 2011; García-Quispes et al., 2011; Ryu et al., 2011). However, the results were not consistent. For example, Ryu’s study (Ryu et al., 2011) have found that the XRCC1 Arg194Trp Arg/Trp genotype was significantly associated with a decreased risk of papillary thyroid carcinoma compared to that of Arg/Arg genotype (OR with 95 CI: 0.550 [0.308-0.983]), however, no such association was observed in Esfahani’s study (Fard-Esfahani et al., 2011); Quispes’s study (García-
Quispes et al., (2011) have found a positive association (OR = 1.58, 95% CI 1.05–2.46) for XRCC1 Arg280His, however, no such tendency was found in Chiang’s study (Chiang et al., 2008); Akulevich’s study (Akulevich et al., 2009) have found that XRCC1 Arg399Gln polymorphisms was associated with a decreased risk of PTC according to the multiplicative and dominant models of inheritance, however, Siraj’s study (Siraj et al., 2008) found no such association. These inconsistent results failed to clarify the complicated relationship between XRCC1 polymorphism and thyroid cancer risk. To reliably explore the effect of XRCC1 variants (Arg399Gln, Arg280His, and Arg194Trp) on thyroid cancer, we conduct this meta-analysis including all of the evidence to date.

Materials and Methods

Search strategy

Eligible articles were retrieved by searching the PubMed bibliographical database (up to July 30, 2012) using the following combination of keywords: (XRCC1 OR X-ray repair cross-complementing gene 1) AND (thyroid) AND (polymorphism OR polymorphisms OR variants OR variant). In addition, we checked the references in the retrieved articles to avoid missing studies. There was no restriction on language in this search.

Inclusion and exclusion criteria

For an article to be included in this meta-analysis, it must accord to the following criteria: 1) case-control studies evaluating the association between XRCC1 polymorphism and thyroid cancer risk. To reliably explore the effect of XRCC1 variants (Arg399Gln, Arg280His, and Arg194Trp) on thyroid cancer, we conduct this meta-analysis including all of the evidence to date.

Statistical analysis

A predesigned data extraction table was used to extract the data by two independent reviewers. Disagreement was resolved by discussion. The following information was extracted from each included article: journal name, first author, year of publication, area and ethnicity, sample size, design type, inclusion and exclusion criteria, the number of genotypes in both cancer cases and controls, and the results of the studies.

Table 1. Characteristics of Studies Included in XRCC1 Polymorphisms and Thyroid Carcinoma

| Study            | Ethnicity | Country  | Design      | HWE | Total cases | Total controls | Arg194Trp | Arg280His | Arg399Gln | Total cases | Total controls | Cases Controls | Cases Controls | Cases Controls | Cases Controls | Cases Controls | Cases Controls |
|------------------|-----------|----------|-------------|-----|-------------|----------------|-----------|-----------|-----------|-------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Esfahani 2011    | Caucasian | Iran     | HCC         | Yes | 157         | 187            | Arg/Arg(CC) | Arg/Arg(GG) | Arg/Arg(GG) | 116         | 136            | 18             | 20             | 3              | 1              |
| Ryu 2011         | Asian     | Korea    | HCC         | Yes | 111         | 100            | Arg/Arg(CC) | Arg/Arg(GG) | Arg/Arg(GG) | 59          | 73             | 37             | 43             | 9              | 14             |
| Ho 2009          | Caucasian | USA      | HCC         | Yes | 251         | 503            | Arg/Arg(CC) | Arg/Arg(GG) | Arg/Arg(GG) | 203         | 433            | 45             | 69             | 3              | 1              |
| Sigurdson 2009   | Caucasian | Russia   | PCC         | Yes | 25          | 906            | Arg/Arg(CC) | Arg/Arg(GG) | Arg/Arg(GG) | 20          | 665            | —              | —              | —              | —              |
| Chiang 2008      | Asian     | China    | HCC         | Yes | 283         | 469            | Arg/Arg(CC) | Arg/Arg(GG) | Arg/Arg(GG) | 127         | 234            | 119            | 199            | 37             | 36             |
| Zhu 2004         | Asian     | China    | HCC         | Yes | 105         | 105            | Arg/Arg(CC) | Arg/Arg(GG) | Arg/Arg(GG) | 50          | 48             | 52             | 51             | 3              | 6              |
| Esfahani 2011    | Caucasian | Iran     | HCC         | Yes | 170         | 193            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 146         | 173            | 23             | 18             | 1              | 2              |
| Qinipes 2011     | Caucasian | Spain    | HCC         | Yes | 398         | 473            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 337         | 426            | 58             | 44             | 3              | 3              |
| Ho 2009          | Caucasian | USA      | HCC         | Yes | 251         | 503            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 229         | 453            | 22             | 50             | 0              | 0              |
| Akulevich2009    | Caucasian | Russian  | PCC         | Yes | 255         | 593            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 230         | 542            | 25             | 51             | 0              | 0              |
| Sigurdson 2009   | Caucasian | Russia   | PCC         | Yes | 25          | 896            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 24          | 800            | —              | —              | —              | —              |
| Chiang 2008      | Asian     | China    | HCC         | Yes | 283         | 469            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 224         | 349            | 54             | 113            | 5              | 7              |
| Siraj 2008       | Caucasian | Saudi Arabia | HCC     | Yes | 50          | 229            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 33          | 129            | 12             | 79             | 5              | 21             |
| Esfahani 2011    | Caucasian | Iran     | HCC         | Yes | 155         | 190            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 78          | 83             | 60             | 87             | 17             | 11             |
| Ryu 2011         | Asian     | Korea    | HCC         | Yes | 111         | 100            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 87          | 72             | 17             | 19             | 7              | 9              |
| Qinipes 2011     | Caucasian | Spain    | HCC         | Yes | 386         | 474            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 153         | 196            | 186            | 212            | 47             | 66             |
| Ho 2009          | Caucasian | USA      | HCC         | Yes | 251         | 503            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 133         | 220            | 99             | 216            | 19             | 67             |
| Akulevich2009    | Caucasian | Russian  | PCC         | Yes | 255         | 595            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 120         | 233            | 103            | 293            | 32             | 69             |
| Sigurdson 2009   | Caucasian | Russia   | PCC         | Yes | 24          | 892            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 12          | 460            | 10             | 343            | 2              | 89             |
| Chiang 2008      | Asian     | China    | HCC         | Yes | 283         | 469            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 150         | 277            | 110            | 165            | 23             | 27             |
| Siraj 2008       | Caucasian | Saudi Arabia | HCC     | Yes | 50          | 229            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 35          | 142            | 13             | 72             | 2              | 15             |
| Zhu 2004         | Asian     | China    | HCC         | Yes | 105         | 105            | Arg/Trp(CT) | Arg/His(GA) | Arg/AA     | 49          | 57             | 44             | 45             | 12             | 3              |

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heterogeneity. Meanwhile, we assessed heterogeneity with \( I^2 \). \( I^2 > 50\% \) was considered statistically significant heterogeneity. A fixed effect model (Mantel-Haenszel method) was used when there was no heterogeneity among the trials. Otherwise, the random effect model (DerSimonian and Laird method) was used when there was heterogeneity based on a Q-test with \( P < 0.10 \). The potential publication bias was assessed by performance of funnel plot of log[OR] against its standard error (SE), and the degree of asymmetry was tested by Begg’s and Egger’s test (\( P < 0.05 \) was considered a significant publication bias) (Egger et al., 1997). In the control populations, Hardy-Weinberg equilibrium (HWE) was tested. In addition, subgroup analysis for ethnicity (Asian and Caucasian Mixed population), design type (HCC(hospital based case-control study) and PCC(population based case-control study)) and sample size (smaller (total sample<400) and larger (total sample≥400)) was conducted, and influence analysis was performed by omitting each study to find potential outliers. Two authors performed the statistical analysis independently and got the same results.

Results

**Literature selection and study characteristics**

Twelve articles were retrieved from PubMed, three of which were excluded after detailed assessment (one was case report, one was not about thyroid cancer and one was review). Finally, nine studies met the inclusion criteria (1620 cases and 3557 controls). Three of these were conducted in an Asian population (499 cases and 674 controls), six in a Caucasian population (1121 cases and 2883 controls). There were 9 studies with a total of 1620 cases and 3557 controls for Arg399Gln polymorphism, 6 studies with a total of 932 cases and 2270 controls for Arg194Trp polymorphism, and 7 studies with a total of 1432 cases and 3556 controls for Arg280His polymorphism. Genotype distributions in the controls of all studies were in agreement with HWE. The detailed characteristics of the studies are shown in Table 1.

**Quantitative data synthesis**

Table 2 lists the main results of this meta-analysis. For XRCC1 Arg194Trp polymorphism, there was no statistical difference in all contrasts of genotypes based on all included studies (aa vs. AA: OR= 1.22, 95%CI= 0.46-3.23, \( P = 0.69 \); Aa vs. AA: OR=1.05, 95%CI= 0.86-1.29, \( P = 0.63 \); Dominant model: OR=1.26(95%CI= 1.30-2.94, \( P = 0.04 \); Recessive model: OR=1.08(95%CI= 0.86-1.31, \( P = 0.34 \). However, subgroup analysis based on sample size found an elevated risk in aa vs AA analysis (OR=2.03, 95%CI= 1.24-3.31, \( P = 0.01 \)) and recessive genetic model analysis (OR=1.93, 95%CI= 1.20-3.08, \( P = 0.01 \)) in the larger sample size trials. We did not find any significant association in any genetic model among other subgroup analysis. Moreover, meta-regression analysis revealed that sample size was a significant source of between-study heterogeneity.
For XRCC1 Arg280His polymorphism, we did not observe any significant association in all contrasts of genotypes based on all included studies (aa vs. AA: OR=1.00, 95%CI=0.56-1.96, p=0.99; Aa vs. AA: OR=1.03, 95%CI=0.75-1.43, p=0.85; Dominant model: OR=1.01, 95%CI=0.84-1.22, p=0.42; Recessive model: OR=1.08, 95%CI=0.56-2.10, p=0.82). There was also no significant association in any genetic model among subgroup analysis.

For XRCC1 Arg399Gln polymorphism, we did not observe any significant association in all contrasts of genotypes based on all included studies (aa vs. AA: OR=0.99, 95%CI=0.68-1.43, p=0.99; Aa vs. AA: OR=0.91, 95%CI=0.80-1.04, p=0.17; Dominant model: OR=0.92, 95%CI=0.76-1.12, p=0.41; Recessive model: OR=1.03, 95%CI=0.73-1.46, p=0.85). However, we found a decreased thyroid cancer risk in subgroup analysis based on ethnicity in Aa vs AA analysis (OR=0.84, 95%CI=0.72-0.98, p=0.03) and in a dominant genetic model (OR=0.84, 95%CI=0.72-0.97, p=0.02) in Caucasian population, the same tendency was found in subgroup analysis based on design type in Aa vs AA analysis (OR=0.72, 95%CI=0.54-0.97, p=0.03) among the PCC trials.

Tests of heterogeneity

We have found heterogeneities in eight studies: Arg194Trp polymorphism: aa vs. AA analysis (p=0.01), dominant model (p=0.05) and recessive model (p=0.04); Arg280His: Aa vs AA analysis (p=0.03) and dominant model (p=0.06); Arg399Gln: aa vs AA analysis (p=0.02), dominant model (p=0.04) and in recessive model (p=0.04). A random-effects model was adopted in these analysis.

Sensitivity analysis

Influence analysis was conducted to assess the influence of each individual trial on the pooled ORs by sequential omission of individual studies. The results suggested that no individual trial significantly affected the pooled ORs (Figure 1 a,b).

Publication bias

For each of the three SNPs, publication bias was examined by funnel plots qualitatively and estimated by Begg’s and Egger’s tests quantitatively. Taken the Arg399Gln polymorphism for example, the shapes of the funnel plot did not indicate any evidence of obvious asymmetry in dominant genetic model (Figure 2). Moreover, the p values from the Begg’s test (p=0.88) and Egger’s test (p=0.84) were all greater than 0.05, indicating no publication bias.

Discussion

DNA repair mechanisms play essential roles in maintaining the genomic stability which is constantly challenged by endogenous (reactive oxygen species) and exogenous agents (ionizing radiation) (Ming et al., 2012). XRCC1 plays an important role in the DNA repair pathway because it could specifically interact with nicked and gapped DNA, rapidly and transiently responds to DNA damage in cells, thus may serve as a strand-break sensor (Mani et al., 2004). In addition, XRCC1 could interact with many proteins known to be involved in BER andSSBR, so it has been proposed that XRC1 may function as a scaffold protein able to coordinate and facilitate the steps of various DNA repair pathways (Mani et al., 2007). It is widely accepted that alterations in XRC1 may play important roles in the process associated with the etiology of cancers because of the alteration of base excision repair functions (Monaco et al., 2007). The functional significance of XRC1 Arg194Trp polymorphism is due to the location in an evolutionarily conserved region, and the occurrence of chromosomal breaks is largely increased among cases with the Arg/Arg genotype (Vodicka et al., 2007). The Arg280His is located in the PCNA-binding region of XRC1, and could potentially alter the structure
of XRCC1 and its ability to interact with apurinic/apyrimidinic endonuclease (Yan et al., 2009). The XRCC1 Arg399Gln polymorphism is located within a relatively non-conserved region between conserved residues of the BRCA1 COOH terminus domain, and may associated with higher sister chromatid exchange frequency and prolonged cell-cycle delay in response to ionizing radiation (Hu et al., 2001; Matullo et al., 2006).

Our meta-analysis included six studies with a total of 932 cases and 2270 controls for Arg194Trp polymorphism, seven studies with a total of 1432 cases and 3356 controls for Arg280His polymorphism and nine studies with a total of 1620 cases and 3557 controls for Arg399Gln polymorphism. To our knowledge, this is the first meta-analysis evaluated the association between XRCC1 polymorphisms and thyroid cancer risk. Unfortunately, we failed to observe any association between XRCC1 polymorphisms and thyroid cancer risk in the overall analysis based on all of the included studies. However, when we performed subgroup analyses by ethnicity, design type and sample size, we found that: 1) elevated risk in aa vs AA analysis (OR=2.03, 95%CI= 1.24-3.31, p=0.01) and recessive genetic model analysis (OR=1.93, 95%CI= 1.20-3.08, p=0.01) in the larger sample size trials for XRCC1 Arg194Trp polymorphism; 2) decreased thyroid cancer risk in subgroup analysis based on ethnicity in Aa vs AA analysis (OR=0.72, 95%CI= 0.72-0.97, p=0.02) in Caucasian population for XRCC1 Arg399Gln polymorphism; 3) decreased thyroid cancer risk in subgroup analysis based on design type in Aa vs AA analysis (OR=0.72, 95%CI= 0.54-0.97, p=0.03) and in a dominant genetic model (OR=0.84, 95%CI= 0.72-0.97, p=0.02) in Caucasian population for XRCC1 Arg399Gln polymorphism; 4) increased thyroid cancer risk in subgroup analysis based on sample size trials for Arg399Gln polymorphism. In this meta-analysis, we did not observe any association of XRCC1 Arg194Trp polymorphism, Arg280His polymorphism and Arg399Gln polymorphism with thyroid cancer risk in the overall analysis, it may be due to the shortness of available data and the large heterogeneities in the studies. Therefore subgroup analysis based on ethnicity, design type and sample size was conducted to avoid potential bias. We did find a increased thyroid cancer risk associated with the Arg194Trp polymorphism in the larger sample size trials, it may be due to the high statistical power in the larger sample size trials. Previous study have found that the frequency distribution of Arg399Gln allele significantly varied in different ethnicities (Xing et al., 2002; Tumer et al., 2010), so it was essential to conduct a subgroup analysis based on ethnicities. In this subgroup analysis, we also found a decreased thyroid cancer risk associated with the Arg399Gln polymorphism among the Caucasian population. Although our results are suggestive, there are still some limitations in our meta-analysis. First, heterogeneity among the studies, resulting from different design type, ethnicity and sample size or some other factors, may influence the results of the analysis. Although we have conducted subgroup analysis based on these issues, the results may be also biased and the statistical power may be reduced by doing so, thus the results may be interpreted with caution due to a small number of studies. Second, environmental and lifestyle factors may alter the associations between gene polymorphisms and cancer risk. However, the relationship between XRCC1 gene polymorphism and thyroid cancer risk was analyzed without consideration of these interactions because of the lack of sufficient original data, which should be further studied. Third, publication bias may have occurred though the funnel plot did not show it since negative findings were likely to be unreported.

In conclusion, this comprehensive meta-analysis has evaluated all published data currently available on XRCC1 polymorphisms and thyroid cancer risk. This meta-analysis suggest that XRCC1 Arg399Gln polymorphism may be associated with decreased thyroid cancer risk among Caucasian population and the XRCC1 Arg194Trp may be associated with a tendency of increased thyroid cancer risk in the two larger sample size trials. We did not observe any association of XRCC1 Arg280His polymorphism with thyroid cancer. However, our results may be biased because of the relatively small number of objects, therefore, further larger studies should be conducted to validate the conclusion.

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