NQO1 C609T polymorphism and esophageal cancer risk: a HuGE review and meta-analysis

Yanling Hu*a Yuhong Zhang*b Wenwu He*c,d Lei Xian*c Mingwu Chen§c

aMedical Research Center of Guangxi Medical University, Nanning, Guangxi, China
bDepartment of gastroenterology, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China
cDepartment of Cardiothoracic Surgery, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China
dDepartment of Cardiothoracic Surgery, Nanchong Central Hospital, Nanchong, Sichuan, China

* First co-author

§ Corresponding author

Email addresses:

YH: ylhupost@163.com
YZ: yuhool@163.com
WH: wenwu_he@126.com
LX: xianlei59@163.com
MC: chen535@126.com
ABSTRACT

Background

Many studies have been carried out to test the hypothesis that the NQO1 C609T polymorphism might be associated with the risk of esophageal cancer. However, the results were poorly consistent, partly due to genetic or other sources of heterogeneity. To investigate the association between this polymorphism and the risk of esophageal cancer, a meta-analysis was performed.

Methods

We used odds ratios (ORs) with 95% confidence intervals (CIs) to assess the strength of association. The frequency of the putative risk allele in the controls was estimated by the inverse-variance method. Cochran’s Q statistic and the inconsistency index ($I^2$) were used to check heterogeneity. Egger’s test and an inverted funnel plot were used to assess the publication bias.

Results

Our study included eight published case-control studies about the NQO1 C609T polymorphism and esophageal cancer, including a total of 1217 esophageal cancer patients and 1560 controls. Overall, a significant association was found between the NQO1 C609T variant and esophageal cancer under a recessive model (OR=1.647; 95%CI=1.233-2.200). Regarding histological type, more significant evidence was found in esophageal squamous cell carcinoma (ESCC) (OR=2.03; 95%CI=1.29-3.19) than esophageal adenocarcinoma (EAC) (OR=1.61; 95%CI=1.01-2.56) under a recessive model.

Conclusions

The meta-analysis suggests that the NQO1 C609T polymorphism considerably increases the risk of esophageal cancer considerably.
Background

Esophageal cancer is a malignancy of the esophagus, the muscular tube that food passes through from the throat to the stomach. Esophageal tumors usually lead to dysphagia, pain and other symptoms, and are diagnosed with by biopsy. Generally, esophageal cancer has two subtypes, i.e. which are squamous cell cancer and adenocarcinoma. Squamous cell cancer arises from the cells that line the upper part of the esophagus. Adenocarcinoma arises from glandular cells that are present at the junction of the esophagus and the stomach[1].

NAD(P)H quinone oxidoreductase 1 (NQO1) that is a member of the NAD(P)H dehydrogenase (quinone) family and encodes a cytoplasmic 2-electron reductase, which is a cytosolic flavoenzyme that protects cells from oxidative damage[2]. NQO1 catalyzes the reductive activation of quinoid chemotherapeutic agents and environmental carcinogens such as heterocyclic amines, nitrosamines and the condensate of cigarette smoke[3]. The NQO1 T allele has only 2-4% enzymatic activity in comparison to its wild type form. Cells homozygous for the polymorphic NQO1 allele (T/T) express NQO1 mRNA, but they have no detectable NQO1 protein because the mutant NQO1 protein is rapidly degraded by the proteasomal system[4]. However, the activity of the NQO1 enzyme may be influenced by a major polymorphism involving a single C to T substitution at nucleotide 609 of exon 6 in the NQO1 cDNA that causes a Pro187Ser amino acid change[5].

Some studies have shown that this polymorphism in the NQO1 gene affects NQO1 protein encoding. Compared to the homozygous wild-type (C/C), the NQO1 protein encoded by the heterozygous phenotype(C/T) is decreased by approximately three-fold. In addition, the homozygous mutant (T/T) phenotype causes a complete lack of enzyme activity [3, 5-7]. The NQO1 C609T polymorphism has been associated with the risk of various cancers such as renal cancer[8], lung cancer[9, 10] and esophageal cancer[11-13]. However, the results of some studies on the effect of the NQO1 C609T polymorphism on esophageal cancer are debatable. Meta-analyses are usually useful when many studies point more or less in the same direction, but every single study does not have sufficient power to show a significant result. Therefore, a meta-analysis of these studies was undertaken to investigate the association of the NQO1 C609T polymorphism with susceptibility to esophageal cancer.

Methods

Search strategy and data extraction

All original studies published in English on the NQO1 C609T polymorphism and esophageal cancer were considered in our meta-analysis. HuGENet, Embase and Pubmed were completely searched up to August 8 2011, using the following terms: (“esophageal cancer” or “esophagus” or “ESCC” or “EAC” or “oesophagus”) and (“polymorphism” or “SNP” or “allele” or “variant”) and (“NQO1” or “NAD(P)H: quinone oxidoreductase 1” or “NAD(P)H dehydrogenase, quinone 1” or “DHQU”).

Included studies must fit the following criteria: (1) sufficient data regarding allele frequency; (2) an association analysis between the NQO1 C609T polymorphism and esophageal cancer risk; (3) independent case-control studies.

Data extraction

The following information was extracted by three investigators (Y-L H, W-W H and Y-H Z) from each study: the first author, year of publication, country, race, sample size, outcome, characteristics of controls,
case and control diagnostic criteria, genotyping method, allele frequencies, genotypes distribution in cases and controls, pathology status of esophageal cancer and the esophageal cancer risk factors. Results were compared, and different opinions were resolved by a discussion.

**Statistical analysis**

Hardy-Weinberg equilibrium (HWE; $P \geq 1e-03$) and chi-square test method were used to test the distribution of genotypes in control group of each study. The frequency of the putative risk allele in the controls was estimated by the inverse-variance method [14-16]. Cochran’s Q statistic and the inconsistency index ($I^2$) were used to check heterogeneity[17]; if $P>0.10$ and $I^2<25\%$, heterogeneity did not exist among studies[18]. If there was no heterogeneity, logistic regression with fixe effects was used to evaluate the overall gene effect; otherwise, random-effects model was used. To determine the overall gene effect, the model that includes the gene was compared with the model without the gene. If the overall gene effect was statistically significant, further comparisons of OR1 (AA vs. aa), OR2 (Aa vs. aa), and OR3 (AA vs. Aa) were explored with A as a risk allele. We selected the genetic models according to the following criteria[18]:

- If $OR_1 = OR_2 \neq 1$ and $OR_3 = 1$, the dominant model was selected.
- If $OR_1 = OR_3 \neq 1$ and $OR_2 = 1$, the recessive model was accepted.
- If $OR_2 = 1/OR_3 \neq 1$ and $OR_1 = 1$, the overdominant model was taken.
- If $OR_1 > OR_2 > 1$ and $OR_1 > OR_3 > 1$ (or $OR_1 < OR_2 < 1$ and $OR_1 < OR_3 < 1$), the codominant model was adopted.

Finally, the results were pooled again under the appropriate genetic model.

Egger’s test and an inverted funnel plot was used to assess the publication bias[20]. HWE was checked in the control group of the eligible studies by the chi-square test ($p \leq 0.001$). Sensitivity analysis was performed including studies that deviated from HWE. Statistical tests were performed using STATA software, version 11.1 (Stata Corporation, USA). All $P$ values were two-sided.

**RESULTS**

**Study inclusion and characteristics**

Thirteen abstracts in total were retrieved from the HuGENet, Embase and Pubmed databases. Ten relevant studies that described the association between $NQO1$ C609T and esophageal cancer were identified. However, after reading the full text, we excluded two studies of these ten articles that overlapped [21, 22]. Finally, eight studies met the inclusion criteria and were included [11-13, 23-27]. Among these included article, five studies were about Caucasians [11, 23, 24, 25] and three studies were about Asians [11, 26, 27]. All included studies were case-control designed, comprising 1217 cases and 1560 controls.

Among the included articles described in Table 1, four studies selected esophageal cancer patients based on endoscopy or histological diagnosis [11, 23, 24, 27], while the other four articles [12, 13, 25, 26] selected cases that underwent esophagectomy without prior radio- and/or chemotherapy. All the controls were recruited in the same period as the cases. However, the source of the controls for each study was not similar. In the included studies, five studies[12, 13, 25-27] selected healthy persons as controls, while three reports [11, 23, 24] chose hospital patients as controls.

In addition, among these eligible studies, two studies included three populations which selected from ESCC patients [13, 24], four articles selected cases from EAC patients [12, 23, 25, 26]; the but other two studies did not clarify the histological type [11, 27].
Meta-analysis database

Overall, the eligible studies included 1124 cases and 1510 controls which were genotyped. The prevalence rates of TT in C609T variants was 19.1% in controls of Asian descent, which was more frequent than 4.1% in the controls of Caucasian descent. The prevalence rates of CT for controls of Caucasian and Asian decent were 45.5% and 31.7%, respectively. For histological type, the prevalence rates of TT were 8.6% and 7.3% in controls of ESCC and EAC patients, while CT were 40.9% and 34.0% in controls of ESCC and EAC patients, respectively. The genotype distribution and all the P-values for HWE testing are shown in Table 2 and Table 3.

Main results, subgroup analyses

NQO1 C609T polymorphism and ethnic group

The results of the included studies regarding the association between the NQO1 C609T polymorphism and esophageal cancer were conflicting, as seen in Table 1. Hamajima et al. [11], Rahden et al. [25], Zhang et al. [27] and Marjani et al. [24] showed no significant association with esophageal cancer. However, the other four studies showed a significant association with esophageal cancer [12, 13, 23, 26]. All included studies were in HWE.

After sensitivity analysis, Hamajima et al. [11] and Martino et al. [23] had the highest sensitivity, and were removed because the controls included no healthy people, determined by reading the full text. After removing these two articles, the phenotyped samples contained 974 cases and 1226 controls.

Using the inverse variance fixed effects model, the ORs of the pooled NQO1 T allele frequencies were 1.32 (95% CI: 1.08-1.62) for Caucasians and 1.32 (95% CI: 1.08-1.60) for Asians. In total, the summary OR for all the studies was 1.32 (95% CI: 1.15-1.52). It was shown that the T allele was related to susceptibility to esophageal cancer.

According to the principle of genetic model selection by Thakkinstian[15], the recessive model was determined. The summary result showed a significant relationship between the NQO1 C609T polymorphism and esophageal cancer (Fig. 1) from the meta-analysis of the phenotype studies. For the recessive model, the overall pooled odds ratio by using a fixed effect model was 1.65 (95% CI: 1.23-2.20). The ORs for Caucasians and Asians were 2.03 (95% CI: 1.14-3.61) and 1.53 (95% CI: 1.10-2.14). Through heterogeneity analysis, we found no evidence for heterogeneity among studies (for the recessive model, I^2=0.0%, P=0.48). In addition, Egger’s test showed that publication bias was not significant under the recessive model(P=0.69).

NQO1 C609T polymorphism and histological type of esophageal cancer

Six case-control articles which reported the association between the NQO1 C609T polymorphism and the histological type of esophageal cancer were included in our research, but their results were are debatable. For EAC, Martino et al. [23] and Zhang et al. [26] showed a significant association with EAC, but Rahden et al. [25] showed no significant association. For ESCC, Sarbia et al. [12] and Zhang et al. [13] showed a significant association with ESCC, but Marjani et al. [24] showed no significant association with ESCC. After removing this study, the histological type phenotyped samples contained 868 cases and 1120 controls.

The recessive model was selected according to the principle of Thakkinstian[15]. The summary result from the meta-analysis of the phenotype studies indicated a significant relationship between the NQO1 C609T polymorphism and histological type of esophageal cancer (Fig 2). For the recessive model, the overall pooled odds ratio by using the fixed effect model was 1.82 (95% CI: 1.32-2.52). The ORs of ESCC
and EAC were 2.03 (95% CI: 1.29-3.19) and 1.61 (95% CI: 1.01-2.56). Through heterogeneity analysis, we found no evidence for heterogeneity among studies (for the recessive model, $I^2=0.0\%, P=0.44$). Finally, Egger’s test showed that publication bias was not significant under the recessive model ($P=0.74$).

In order to test whether the heterogeneity of the sample might affect the results of the meta-analysis, we performed additional analysis. We only used the samples from Germany and China to test the ethnicity effect. The ORs of Germany and China were 1.68 (95% CI: 1.13-2.51) and 1.96 (95% CI: 1.36-2.82). There was no obvious difference in the results from Caucasian and Asian patients.

**DISCUSSION**

Main findings

*NPQ1* acts as an imperative part of cellular antioxidant defense by detoxifying quinines, and can prevent the formation of reactive oxygen species. *NPQ1* gene mutations are linked to tardive dyskinesia which is an increased risk of hematotoxicity after exposure to benzene, and susceptibility to various forms of cancer. Many studies have been carried out to test the hypothesis that the *NPQ1* C609T polymorphism might associate with the risk of esophageal cancer, but the results were controversial. This meta-analysis, involving a total of 1217 esophageal cancer patients and 1560 controls from eight case-control studies, examined the association of one polymorphisms of the *NPQ1* gene with esophageal cancer risk. The OR of the pooled *NPQ1* T allele frequencies for all the studies was 1.32 (95% CI: 1.15-1.52). In addition, significant evidence was found for an association between the *NPQ1* C609T variant and esophageal cancer under the recessive model (OR=1.647; 95% CI=1.233-2.200). Marjani *et al.* [24] found that *NPQ1* expression in esophageal tutor tissue occurs in relation to the underlying *NPQ1*1*2 allele (C609T) genotype, and is elevated as the T allele emerges in the genotype.

A heterogeneity evaluation is always conducted in statistical analysis in meta-analysis. However, low statistical power was found during heterogeneity testing [28]. Therefore, several subgroup meta-analyses were performed according to ethnicity, control source and case classification. In racial subgroups, there was a statistically significant association between the *NPQ1* polymorphism and esophageal cancer. However, the ORs were not obviously different between Caucasians and Asians. In the subgroup analysis of histological type, the overall pooled ORs under the recessive model for ESCC and EAC were 2.03 (95% CI:1.29-3.19) and 1.61 (95% CI: 1.01-2.56), respectively. The results suggest that the *NPQ1* C609T polymorphism considerably increases considerably the risk of esophageal cancer, especially in ESCC patients.

**Limitations**

The results of this meta-analysis should be interpreted with some degree of caution, because there were limitations in our analysis.

First, selection bias was a possible major source of heterogeneity from uncontrolled confounding and bias inherent in the study design. For example, there was not an identical criterion for cases and controls among all included articles.

Second, different genotype ratio may be have a potential to impact on the outcomes. The rate of the TT genotype was very low in Caucasian subjects (fewer than 10% of all Caucasian studies), but showed a moderate distribution in Asians (more than 15% in all Asian studies).
Third, we only considered the \textit{NQO1} C609T polymorphism with the risk of esophageal cancer in this study. However, there may be a possible interaction between the \textit{NQO1} C609T polymorphism and other environmental factors.

Conclusions and implications for future research

In conclusion, the present meta-analysis provides information on the \textit{NQO1} C609T polymorphism and the considerably increased considerably the risk of esophageal cancer, especially in ESCC patients. However, this paper did not assess gene-to-gene and gene-to-environment interactions on \textit{NQO1} C609T and esophageal cancer. Therefore, a larger study with thousands of subjects and tissue-specific biochemical and biological characterizations are highly recommended in the future.

Authors’ contributions

YH collected the literature, developed the statistical model, carried out the software implementation, and drafted the manuscript. WH collected the literature, read the full text and checked the model and results. YZ collected the literature, read the full text and drafted the manuscript. XL helped with discussion in theoretical developments, as well as in drafting the manuscript. MC helped with discussion both in theoretical development and English copyediting.

Acknowledgements

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References


Fig. 1 - The forest plot describing the meta-analysis with a fixed-effect recessive model (TT versus CT + CC) for the association of NQO1 C609T polymorphism with esophageal cancer. Each study is depicted with size inversely proportional to its variance, accompanied by the respective 95% confidence intervals. Values of OR > 1, implied an increased risk for esophageal cancer with the TT genotype.
Fig. 2 - The forest plot describing the meta-analysis with a fixed-effect recessive model (TT versus CT + CC) for the association of NQO1 C609T polymorphism with ESCC and EAC. Each study is depicted with size inversely proportional to its variance, accompanied by the respective 95% confidence intervals. Values of OR > 1, implied an increased risk for esophageal cancer with the TT genotype.
Table 1 - The studies summary of NQO1 C609T polymorphism with Esophageal cancer.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Investigator</th>
<th>Year</th>
<th>Country</th>
<th>Race</th>
<th>Eligible subjects</th>
<th>Characteristic</th>
<th>Source of controls</th>
<th>Method</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>ESCC</td>
<td>EAC</td>
</tr>
<tr>
<td>[11]</td>
<td>Hamajima et al.</td>
<td>2002</td>
<td>Japan</td>
<td>Asian</td>
<td>102</td>
<td>241</td>
<td>The patients were invited to participate in the present study by doctors in charge. They were enrolled between March 1999 and December 2000 at Aichi Cancer Center Hospital.</td>
<td>Controls were sampled from patients at Aichi Cancer Center Hospital during the same period as for the cases; participants in a Helicobacter pylori eradication program without a history of cancer who underwent gastroscopy.</td>
</tr>
<tr>
<td>Study</td>
<td>Authors</td>
<td>Year</td>
<td>Country</td>
<td>Ethnicity</td>
<td>Cases</td>
<td>Controls</td>
<td>Study Type</td>
<td>Methods</td>
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<td>[13]</td>
<td>Zhang JH et al.</td>
<td>2003</td>
<td>Germany</td>
<td>Caucasian</td>
<td>257 252 257 0</td>
<td>All ESCC patients that underwent esophagectomy without prior radio- and/or chemotherapy between 1978 and 1998 in the Department of Surgery of the Heinrich Heine University, Duesseldorf.</td>
<td>The healthy controls from the German Caucasian population were unrelated blood donors from the same region as the ESCC patients.</td>
<td>Population-based PCR-RFLP</td>
</tr>
<tr>
<td>[26]</td>
<td>Zhang JH et al.</td>
<td>2003</td>
<td>China</td>
<td>Asian</td>
<td>317 306 193 124</td>
<td>All ESCC patients that underwent esophagectomy without prior radio- and/or chemotherapy between 2001 and 2002 in the Fourth Affiliated Hospital, Hebei Medical University.</td>
<td>The healthy controls from the northern Chinese population were unrelated blood donors from the same region as the ESCC patients.</td>
<td>Population-based PCR-RFLP</td>
</tr>
<tr>
<td>[25]</td>
<td>Rahden et al.</td>
<td>2005</td>
<td>Germany</td>
<td>Caucasian</td>
<td>140 260 0 140</td>
<td>The patients that underwent Healthy volunteers</td>
<td>Healthy volunteers</td>
<td>Hospital-based PCR</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Country</td>
<td>Ethnicity</td>
<td>Cases</td>
<td>Controls</td>
<td>Study Description</td>
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</tr>
<tr>
<td>[27] Zhang WC et al.</td>
<td>2006</td>
<td>China</td>
<td>Asian</td>
<td>106</td>
<td>106</td>
<td>The patients were diagnosed for primary esophageal cancer by pathology or endoscopy between 2003–2004, they were Han Chinese person. The healthy controls from the same region without digestive system disease and any history of cancer.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[23] Martino et al.</td>
<td>2007</td>
<td>UK</td>
<td>Caucasian</td>
<td>141</td>
<td>93</td>
<td>0</td>
<td>141</td>
<td>The patients were diagnosed based on endoscopic and histological evidence. Control individuals had been recruited from a dyspepsia endoscopy list, 44 of these (47%) reported reflux-related symptoms, such as heartburn and/or regurgitation.</td>
</tr>
<tr>
<td>[24] Marjani et al.</td>
<td>2010</td>
<td>Iran</td>
<td>Caucasian</td>
<td>93</td>
<td>50</td>
<td>93</td>
<td>0</td>
<td>The criteria for enrollment patients were an age of at least 18 years and be resident of the study area at registration time, with no concurrent or previous history of other cancer in any organ.</td>
</tr>
</tbody>
</table>

Annotation: The “*” representative the study samples have not be classified to EAC or ESCC.
Table 2 – Frequency of NQO1 C609T polymorphism in different populations included in a meta-analysis.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Investigator</th>
<th>Year</th>
<th>Sample size(%)</th>
<th>Race</th>
<th>Cases(%)</th>
<th>Controls(%)</th>
<th>P value for HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11]</td>
<td>Hamajima et al.</td>
<td>2002</td>
<td>343(10.47)</td>
<td>Asian</td>
<td>36.3</td>
<td>51.0</td>
<td>12.7</td>
</tr>
<tr>
<td>[12]</td>
<td>Sarbia et al.</td>
<td>2003</td>
<td>313(9.55)</td>
<td>Caucasian</td>
<td>49.2</td>
<td>47.5</td>
<td>3.3</td>
</tr>
<tr>
<td>[13]</td>
<td>Zhang JH et al.</td>
<td>2003</td>
<td>509(15.54)</td>
<td>Caucasian</td>
<td>71.2</td>
<td>21.8</td>
<td>7.0</td>
</tr>
<tr>
<td>[13]</td>
<td>Zhang JH et al.</td>
<td>2003</td>
<td>499(15.23)</td>
<td>Asian</td>
<td>26.4</td>
<td>47.7</td>
<td>25.9</td>
</tr>
<tr>
<td>[26]</td>
<td>Zhang JH et al.</td>
<td>2003</td>
<td>623(19.02)</td>
<td>Asian</td>
<td>32.3</td>
<td>44.4</td>
<td>23.4</td>
</tr>
<tr>
<td>[25]</td>
<td>Rahden et al.</td>
<td>2005</td>
<td>400(12.21)</td>
<td>Caucasian</td>
<td>65.0</td>
<td>30.0</td>
<td>5.0</td>
</tr>
<tr>
<td>[27]</td>
<td>Zhang WC et al.</td>
<td>2006</td>
<td>212(6.47)</td>
<td>Asian</td>
<td>26.4</td>
<td>46.2</td>
<td>27.4</td>
</tr>
<tr>
<td>[23]</td>
<td>Martino et al.</td>
<td>2007</td>
<td>234(7.14)</td>
<td>Caucasian</td>
<td>68.1</td>
<td>30.5</td>
<td>1.4</td>
</tr>
<tr>
<td>[24]</td>
<td>Marjani et al.</td>
<td>2010</td>
<td>143(4.37)</td>
<td>Caucasian</td>
<td>54.8</td>
<td>37.6</td>
<td>7.5</td>
</tr>
</tbody>
</table>
Table 3 – Frequency of NQO1 C609T polymorphism in ESCC and EAC patients included in a meta-analysis.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Investigator</th>
<th>Year</th>
<th>Histological type</th>
<th>Cases(%)</th>
<th>Controls(%)</th>
<th>P value for HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>CT</td>
<td>TT</td>
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<tr>
<td>[12]</td>
<td>Sarbia et al.</td>
<td>2003</td>
<td>EAC</td>
<td>49.2</td>
<td>47.5</td>
<td>3.3</td>
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<tr>
<td>[13]</td>
<td>Zhang et al.</td>
<td>2003</td>
<td>ESCC</td>
<td>71.2</td>
<td>21.8</td>
<td>7.0</td>
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<tr>
<td>[13]</td>
<td>Zhang et al.</td>
<td>2003</td>
<td>ESCC</td>
<td>26.4</td>
<td>47.7</td>
<td>25.9</td>
</tr>
<tr>
<td>[26]</td>
<td>Zhang et al.</td>
<td>2003</td>
<td>EAC</td>
<td>32.3</td>
<td>44.4</td>
<td>23.4</td>
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<tr>
<td>[25]</td>
<td>Rahden et al.</td>
<td>2005</td>
<td>EAC</td>
<td>65.0</td>
<td>30.0</td>
<td>5.0</td>
</tr>
<tr>
<td>[24]</td>
<td>Marjani et al.</td>
<td>2010</td>
<td>ESCC</td>
<td>54.8</td>
<td>37.6</td>
<td>7.5</td>
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