Association of hOGG1 Ser326Cys, ITGA2 C807T and TNF-A -308G>A Polymorphisms with the Risk of NPC

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is a rare form of cancer. NPC is the 4th most common cancer in Malaysia and the incidence rate for Malaysian Chinese is exceptionally high compared to other races. NPC is considered as a relatively radiosensitive tumor and patients diagnosed at early stages tend to survive longer compared to those who have advanced disease. Given that early symptoms of NPC are non-specific, and that the nasopharynx is relatively inaccessible, less invasive screening methods such as biomarker screening might be the key to improve NPC survival and management.

Methodology: A matched case-control study was conducted to investigate the effect of hOGG1 Ser326Cys, ITGA2 C807T and TNF-α -308G>A polymorphisms on the risk of nasopharyngeal carcinoma and all-cause survival. hOGG1 gene encodes for a DNA glycosylase, a protein that is involved in DNA repair. ITGA2 is the alpha subunit of the transmembrane receptor integrin and is mainly responsible for cell-cell and cell-extracellular matrix interaction. TNF-α is a cytokine that is released by immune cells during inflammation. Restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) was used to process DNA genotyping studies involving all aforementioned gene polymorphisms. Conditional logistic regression was used for the analysis of NPC risk on gene polymorphisms, controlling for cigarette smoking, salted fish and alcohol consumption.

Results: Conditional logistic regression showed that NPC cases were more likely to ever consume salted fish during childhood compared to controls (OR=1.80, 95% CI=1.32-2.46, p<0.01). Individuals with previous smoking history were also at higher risk of NPC (OR=1.96, 95% CI=1.37-2.81, p<0.01). No significant difference was found between NPC cases and controls for alcohol consumption. No significant association was observed between hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A polymorphisms with NPC risk.

Conclusion: None of the aforementioned polymorphisms showed significant association in increasing NPC risk individually.

Keywords: hOGG1 Ser326Cys; ITGA2 C807T; TNF-A -308G; NPC; Polymorphism

Introduction

Nasopharyngeal carcinoma (NPC) is a rare cancer commonly develops around the lateral wall of nasopharynx. The NPC annual frequency is less than 1 per 100,000 populations in most parts of the world [1]. But there are exceptions where Chinese living in Guangdong province of Mainland China and South-East Asia as well as natives from Arctic region (Alaska and Greenland) experience a much higher NPC risk compared to the rest of the world [2]. NPC is the 4th most common cancer in Malaysia [3]. Given the increasing number of NPC cases per year and the fact that many cases are diagnosed at an advanced stage [4], it is important to find ways of ensuring early diagnosis and prompt treatment. This is a challenge as the nasopharynx is not easily visualized and accessed. Finding potential biomarkers for NPC screening is one of those ways in which a susceptible population could be identified early, which will then help physicians in early detection and treatment of NPC.

Several environmental factors have been shown to be associated with increased risk of NPC. EBV infection [5], consumption of salted fish at an early age [6,7], Constant occupational exposure to wood dust [8] and long-term cigarette smoking [9], are examples of risk factors implicated in NPC carcinogenesis. In addition, normal cellular metabolic processes are also capable of producing hydroxyl radicals that can cause oxidative damage to DNA [10]. The role of reactive oxygen species (ROS) has been implicated in different stages of tumorigenesis [11]. One of the most common mutagenic byproduct resulting from oxidative damage is 8-oxo-7,8-dihydroguanine (8-oxoG), which is a G to T transversion causing agent [12]. Human 8-oxoguanine DNA glycosylase 1 (hOGG1) is the primary enzyme responsible for excision of 8-oxoG through base excision repair (BER) [13]. Short-patch BER removes 8-oxoG through the action of DNA glycosylase and AP lyase followed by the re-synthesis of DNA by DNA polymerase β [14].

As it is implicated above, hOGG1 protein is the initator of BER because of its ability to identify the damaged base. It is thus possible that the presence and functionality of hOGG1 protein will directly affect the level of BER activity. The work of Kohno et al. [15] supported such postulation by showing that the ability of hOGG1 protein to suppress...
spontaneous mutagenesis varied among polymorphic genotypes in an *E. coli* strain. In the study, a polymorphism in exon 7 of *hOGG1* gene resulted in a serine to cysteine amino acid change. *hOGG1*-Ser326Cys (wild type) ability to suppress mutagenesis is stronger than *hOGG1*-Cys326 [15]. Several studies on association of *hOGG1* Ser326Cys polymorphism with various cancers have substantiated these findings by demonstrating that *hOGG1*-Cys326 conferred higher risk of cancer [16-19]. For NPC, the findings showed inconsistent results. Cho et al. [20] have demonstrated that polymorphism of *hOGG1* gene (Ser326Cys) is associated with altered risk of NPC (OR=1.6, 95% CI=1.0-2.6). Laantri et al. [21] on the other hand showed that polymorphism of *hOGG1* gene (Ser326Cys) was not associated with NPC risk (OR=1.22, 95% CI=0.77-1.90) [21].

Apart from DNA repair, transmembrane receptor integrins are also important in carcinogenesis. These transmembrane glycoproteins are mainly responsible for mediating cell-cell and cell-extracellular matrix (ECM) interactions [22]. Integrins are heterodimeric and consist of 2 transmembrane glycoproteins (α and β) that are non-covalently bound together [23]. Integrins are involved in almost every aspect of carcinogenesis, from cell differentiation, cell proliferation, and angiogenesis to metastasis [24-26]. Integrin α2 is a collagen receptor that is mainly expressed on platelets and epithelial cells [27]. Integrin α2β1 was found to facilitate integrin-mediated attachment to collagen type I during the metastasis of breast cancer cells to bone [28]. The binding of collagen 1 to α2β1 integrin was also shown to promote the malignant phenotype of pancreatic ductal adenocarcinoma [29]. There is indication that ITGA2 C807T polymorphism, a silent nucleotide change in position 807 (TTC/TTT, rs1126643), might be associated with increased susceptibility to cancer. This hypothesis is supported by the findings of significant associations between ITGA2 C807T with increased risk of colorectal and breast carcinoma [30,31].

Chronic or recurrent inflammation is an endogenous process in human body that was observed to have a causative role in promotion and progression of human tumours [32]. Numerous mediators released during dysregulated chronic inflammation have been linked to induce cell growth and invasion at the same time promoting mutagenesis and angiogenesis [33]. Tumor necrosis factor alpha (TNF-α) is one of the earliest cytokine produced in inflammatory process [34]. TNF-α is the key mediator for inflammation and is secreted mainly by macrophages [35]. TNF-α protein was observed to be an endogenous tumor promoter in *vivo* [36]. Significant associations were found between the variant -308A allele and susceptibility to malignant tumors [32,35,37-39]. Although ITGA2 C807T and TNF-α-308G>A polymorphisms are not extensively studied in relation to NPC, variant genotypes of both polymorphisms have been shown to carry increased risk for a number of cancers. Together with the evidence indicating the possible roles for both genes in carcinogenesis, ITGA2 C807T and TNF-α-308G>A could potentially serve as screening targets in the early detection of NPC.

No study to date, has explored the association of *hOGG1* Ser326Cys, ITGA2 C807T and TNF-α-308G>A polymorphism with NPC risk in Malaysia. In the present study, we describe results from a case-control study conducted in Malaysia (300 cases and 562 controls) investigating role of *hOGG1* Ser326Cys polymorphism and NPC susceptibility.

### Materials and Methods

#### Ethics statement and study design

This study was approved by the Medical Research Ethics Committee of the Ministry of Health, Malaysia (Appendix) and funded by the Science Fund, Ministry of Science, Technology and Innovation (MOSTI; Project code: 04-11-08-625RF).

#### Study population

The design of a matched case-control study was selected in the present study because the incidence of NPC varies substantially between different subjects in terms of age, gender and ethnicity. The cases in the present study were NPC patients who were admitted to the public hospitals while matching controls were recruited from the same hospitals where the cases have been recruited. NPC patients were recruited from the Departments of Radiotherapy and Oncology while controls were from the general medical clinics and wards. Inclusion criteria for cases include those who were histologically confirmed NPC patients diagnosed from year 2009 onwards in two public hospitals and above 18 years of age. Individuals without prior history of cancers were recruited as controls. All controls were matched to the cases by age (±3 years), gender and ethnicity. Personal information on demographic factors, smoking status, alcohol and salted fish consumption were collected at recruitment. Smoking status and alcohol consumption were divided into 2 categories: Never/ever smoked and never/ever consumed alcohol. For salted fish consumption, classification used was never/ever consumed salted fish during childhood. Written informed consent was obtained from eligible cases and controls prior to the enrollment into the study. We assumed the exposure rate of TNF-α-308G>A polymorphism in controls at 18% [40] and estimated that this polymorphism could increase NPC risk by 100%. Using the formula adopted by Schlesselman [41] on matched case-control study, with two-sided alpha level of 0.05, 229 matched pairs was needed to attain a power of 90% to detect a 100% increase in NPC risk in the proportion of patients exposed with TNF-α-308G>A polymorphism. 300 histologically confirmed NPC cases and 562 controls were available for analysis at the end of the study.

#### DNA extraction and genotyping

2 ml of venous blood was obtained from every research subject. Fresh blood was immediately placed into an EDTA-coated vacutainer. Filled EDTA tube was stored on ice and transferred back to laboratory in the university to be processed. DNA was extracted from the blood using QIaAmp® DNA mini kit (QIAGEN, Venlo, Netherlands) and immediately stored in minus 20°C freezer until further use. *hOGG1* Ser326Cys, ITGA2 C807T and TNF-α-308G>A polymorphisms were assessed by using RFLP-PCR (Restriction Fragment Length Polymorphism). Forward and reverse primers used for the PCR were listed in Table 1.

For *hOGG1* Ser326Cys polymorphism, the outcome of the PCR was a 302 bp product. The composition of a total 25 μl PCR reaction was 12.5 μl of GoTaq® Green Master Mix (Promega, Wisconsin, USA), 0.5 μl of each primer (from working concentration of 10 μm), 0.5 μl of genomic DNA, and the remaining was topped up with nuclease free water. The PCR thermal profile used was initial denaturation at 95°C for 5 min, 32 cycles of 95°C for 30s, followed by 63°C for 30s and 72°C for 30s, then ended with final extension of 72°C for 5 min. PCR yield from previous PCR was then digested by the restriction enzyme *Fnu4HI* (New England Biolabs, Ipswich, USA). After the digestion, homozygous

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Forward primer (5’-3’)</th>
<th>Reverse primer (5’-3’)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>hOGG1</em> Ser326Cys (rs1052133)</td>
<td>CTT CCA CCT CCC AAC ACT GTC AC</td>
<td>GTG CCT GCC CTT TGA GGT AGT C</td>
</tr>
<tr>
<td>ITGA2 C807T (rs1126643)</td>
<td>GTG TTT AAC TGG ACC ACA TAT</td>
<td>ACC TTG CAT ATT GAA TTG CTT</td>
</tr>
<tr>
<td>TNF-α-308G&gt;A (rs1800629)</td>
<td>AGG CAA TAG GTT TGG AGG GCC AT</td>
<td>ACA CTC CCC ATC CTC CTC GCT C</td>
</tr>
</tbody>
</table>

Table 1: Sequence of forward and reverse primers used in RFLP-PCR.
Ser/Ser showed only a single 302 bp product while homozygous Cys/Cys was fully digested into two different products that were 186 bp and 116 bp in size. Samples were identified as heterozygous Ser/Cys if 3 products of different sizes appeared in the gel.

For ITGA2 C807T polymorphism, 115 bp product was generated at the end of the PCR protocol. The PCR composition used was 25 μl PCR reaction consisting of 12.5 μl of GoTaq® Green Master Mix (Promega, USA), 1.0 μl of each primer (from working concentration of 10 μM), 0.5 μl of genomic DNA, and the remaining component was nuclease free water. The PCR thermal profile adopted was as follows: 95°C for 5 min, 35 cycles each of 95°C for 30 s, followed by 55°C for 30 s and 72°C for 30 s, with final extension of 72°C for 5 min. The resulting PCR products were digested by restriction enzyme TaqI (New England Biolabs, Ipswich, US). Homozygous CC was fully digested into 2 products that were 92 bp and 23 bp in size after the excision by the restriction enzyme. For homozygous TT, no digestion occurred and only a single 115 bp product was visible. All 3 products of different sizes were observed for heterozygous CT.

For TNF-α -308G>A polymorphism, 117 bp PCR product spanning the promoter region of TNF-α from -238 to -308 was generated using the respective forward and reverse primers. The PCR composition used was 25 μl PCR reaction consisting of 12.5 μl of GoTaq® Green Master Mix (Promega, USA), 0.5 μl of each primer (from working concentration of 10 μM), 0.5 μl of genomic DNA, and the remaining component was nuclease free water. The PCR thermal profile used as follows: 95°C for 5 min; 95°C for 30 s, 62°C for 30 s and 72°C for 30 s for 35 cycles; followed by 72°C for 5 min. Restriction enzyme Ncol (New England Biolabs, Ipswich, US) was utilized to excise the PCR products from the previous PCR run. Gel image of homozygous G/G showed only 2 products with 95 bp and 22 bp in size. Homozygous A/A was identified when the gel image showed a single product at 117 bp while samples showing all 3 products were identified as heterozygous G/A.

All digested PCR products were visualized under UV light after separation using electrophoresis on 3% ethidium bromide stained agarose gel. For quality control, 10% of the total PCR products were sent for DNA sequencing to confirm the results of RFLP-PCR for every agarose gel. For quality control, 10% of the total PCR products were separated using electrophoresis on 3% ethidium bromide stained agarose gel. For quality control, 10% of the total PCR products were sent for DNA sequencing to confirm the results of RFLP-PCR for every agarose gel. For quality control, 10% of the total PCR products were sent for DNA sequencing to confirm the results of RFLP-PCR for every agarose gel.

**Statistical analysis**

Relative frequencies were used to describe variables studied including socio-demographic and exposure data using SPSS version 21. Deviation from Hardy Weinberg equilibrium (HWE) was tested using Court Lab Calculator on controls [42]. Conditional logistic regression (STATA 10) was used to estimate adjusted odds ratio (ORs) and 95% confidence interval (CI) for NPC risk, controlling for cigarette smoking, alcohol and salted fish consumption during childhood. A p-value less than 0.05 was considered as statistically significant.

**Results**

**Characteristics of the study population**

300 NPC cases and 562 controls were available for analysis in the present study. Mean age (± SD) for NPC cases and controls were 52.8 (± 10.9) and 53.5 (± 11.0) years respectively while the male to female ratio was roughly 3:1. Majority of the subjects were ethnic Chinese (71.0% NPC cases vs. 70.3% control) while 28.0% of NPC cases and 28.8% of controls were Malays. The socio-demographic characteristics together with the distribution of cigarette smoking, alcohol consumption, salted fish consumption during childhood are shown in Table 2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (%)</th>
<th>Control (%)</th>
<th>χ² (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>52.8 (10.9)</td>
<td>232 (77.3)</td>
<td>68 (22.7)</td>
</tr>
<tr>
<td></td>
<td>53.5 (11.0)</td>
<td>425 (75.6)</td>
<td>137 (24.4)</td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td>0.32 (0.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td>Chinese 213 (71.0)</td>
<td>396 (70.3)</td>
<td>0.27 (0.97)</td>
</tr>
<tr>
<td></td>
<td>Malay 84 (28.0)</td>
<td>162 (28.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 3 (1)</td>
<td>5 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking, N (%)</td>
<td>Never 146 (48.7)</td>
<td>358 (63.7)</td>
<td>18.21* (0.00)</td>
</tr>
<tr>
<td></td>
<td>Ever 154 (51.3)</td>
<td>204 (36.3)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption, N (%)</td>
<td>Never 161 (53.7)</td>
<td>366 (65.1)</td>
<td>10.81* (0.00)</td>
</tr>
<tr>
<td></td>
<td>Ever 139 (46.3)</td>
<td>196 (34.9)</td>
<td></td>
</tr>
<tr>
<td>Salted Fish consumption during childhood, N (%)</td>
<td>Never 103 (34.3)</td>
<td>270 (48.0)</td>
<td>14.98* (0.00)</td>
</tr>
<tr>
<td></td>
<td>Ever 197 (65.7)</td>
<td>292 (52.0)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.01

Table 2: Characteristics of the study population.

For hOGG1 Ser326Cys polymorphism, 15.7% of NPC cases were Ser/Ser carriers, 53.7% of them were with heterozygous Ser/Cys and the remaining 30.6% were having Cys/Cys genotype. The proportion of homozygous Ser/Ser carriers was slightly higher in the controls (19.0%) while 50.2% and 30.8% of the controls were having heterozygous Ser/Cys and homozygous Cys/Cys genotypes, respectively. For ITGA2 C807T polymorphism, 57.0% of NPC cases were carrying homozygous C/C genotype whereas 34.3% and 8.7% of the remaining cases were heterozygous C/T and homozygous T/T carriers, respectively. For the controls, 51.4% carried the C/C genotype while 38.6% and 10.0% of the remaining controls were heterozygous C/T and homozygous T/T carriers, respectively. For TNF-α -308G>A polymorphism, 81.3% of NPC cases were carriers of homozygous G/G genotype while the remaining cases were carriers of the G/A and A/A genotypes (18.7%). For the controls, the percentage of homozygous G/G carriers was slightly higher (84.7%) while 15.3% of the remaining carriers were carrying heterozygous G/A and homozygous A/A genotypes.

Chi-square analysis showed that NPC patients were more likely to ever consume salted fish during childhood compared to controls (χ²=14.98, p<0.01). Study participants with previous smoking history were more likely to develop NPC (χ²=18.21, p<0.01). Individuals with previous smoking history and 95% confidence interval (CI) for NPC risk, controlling for cigarette smoking, alcohol and salted fish consumption during childhood. A p-value less than 0.05 was considered as statistically significant.

**Allelic and genotypic frequencies of hOGG1 Ser326Cys, ITGA2 C807T and TNF-α -308G>A polymorphisms with the risk of NPC**

The distribution of hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A and XPD Lys799Gln polymorphisms in controls did not deviate from Hardy-Weinberg equilibrium (Table 3). Conditional logistic regression showed that NPC cases were more likely to ever consume salted fish during childhood compared to controls (OR=1.80, 95% CI=1.32-2.46, p<0.01). Individuals with previous smoking history were also at higher risk of NPC (OR=1.96, 95% CI=1.37-2.81, p<0.01). No significant difference was found between NPC cases and controls for alcohol consumption. No significant association was observed between hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A polymorphisms with NPC risk (Table 4).

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Table 3: Allelic and genotypic frequencies of hOGG1 Ser326Cys, ITGA2 C807T, and TNF-α -308G>A polymorphisms (HWE test).

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th>Adjusted OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hOGG1 Genotypes</td>
<td></td>
<td>N= 562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser/Ser</td>
<td>107 (19.0)</td>
<td>107 (19.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Ser/Cys</td>
<td>282 (50.2)</td>
<td>282 (50.2)</td>
<td>1.42 (0.95-2.13)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cys/Cys</td>
<td>173 (30.8)</td>
<td>173 (30.8)</td>
<td>1.28 (0.81-2.02)</td>
<td>0.29</td>
</tr>
<tr>
<td>ITGA2 Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>289 (51.4)</td>
<td>289 (51.4)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>C/T</td>
<td>217 (38.6)</td>
<td>217 (38.6)</td>
<td>0.78 (0.56-1.08)</td>
<td>0.13</td>
</tr>
<tr>
<td>T/T</td>
<td>56 (10.0)</td>
<td>56 (10.0)</td>
<td>0.74 (0.43-1.42)</td>
<td>0.26</td>
</tr>
<tr>
<td>TNF-α Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>476 (84.7)</td>
<td>476 (84.7)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>G/A</td>
<td>82 (14.6)</td>
<td>82 (14.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>4 (0.7)</td>
<td>4 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alleles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser</td>
<td>1034 (92.0)</td>
<td>1034 (92.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cys</td>
<td>90 (8.0)</td>
<td>90 (8.0)</td>
<td></td>
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</tr>
</tbody>
</table>

Table 4: hOGG1 Ser326Cys, ITGA2 C807T and TNF-α -308G>A polymorphisms and the risk of NPC.

Discussion

Results from the present study did not show any significant relationship between the aforementioned polymorphisms and the odds of developing NPC. We did however show that cigarette smoking and consumption of salted fish at age younger than 10 were associated with increased odds of NPC. The finding from the present study showed that hOGG1 Ser/Cys and Cys/Cys genotype carriers increased NPC risk by 1.42-fold (0.95-2.13) and 1.28-fold (0.81-2.02), respectively after adjusting for age, gender, ethnicity, cigarette smoking, alcohol and salted fish consumption during childhood. Judging from the results, lower boundary of the confidence interval for Ser/Cys genotype was very close to the 1 while the upper boundary of 2.13 indicated a more than 100% increase in NPC risk. Similar results were observed in Cho et al. [20] study where Ser/Cys genotype was significantly associated with NPC risk (OR=1.8, 95% CI=1.1-2.9). The finding from Xing et al. [42], also showed that Cys/Cys genotype significantly increased oesophageal cancer risk by 1.9-fold (95% CI=1.3-2.6). The effect sizes of hOGG1 Ser326Cys polymorphism in both studies are comparable with the finding from the present study. It is thus possible that with an increase in sample size, hOGG1 Ser326Cys polymorphism might be significantly associated with NPC risk. There is a possibility of a type II error in this part of the analysis probably due to insufficient power.

hOGG1 Ser326Cys polymorphism has been shown to be significantly associated with other cancers, namely nasopharynx [20], esophageal [43], lung [44] and prostate cancer [45]. The ability of wildtype hOGG1 Ser326 to suppress mutagenesis was found to be stronger than the variant hOGG1 Cys326 [15]. An in-vitro study also reported that hOGG1 Cys326 protein has lower mutation suppressing activity in human cells compared to its Ser326 counterpart [46]. In addition, homozgyous Cys/Cys variant showed a nearly 2-fold lower enzymatic reaction compared to the wildtype homozgyous Ser/Ser [47]. In a study involving nitric oxide induced stress condition, hOGG1 Cys326 variant was found to be more susceptible to oxidation compared to the Ser326 wildtype [48]. Increased level of 8-oxoG, which is the primary target of hOGG1 DNA glycosylase was observed in lung [49] and oesophageal cancer [50]. Observation for a period of time has shown spontaneous development of lung adenoma/carcinoma in 18-month-old OGG1-KO mice was associated with the increased accumulation of 8-oxoG [51]. A positive correlation between hOGG1 mRNA expression and urinary excretion of 8-oxoG levels has been reported [52]. The evidence suggested that hOGG1 mRNA expression could serve as a biomarker of exposure to oxidative damage [52].

In the present study, study subjects who were G/A+A/A carriers showed a 1.43-fold (95% CI=0.97-2.11) increase in NPC risk compared to those having G/G genotype. The effect size of the polymorphism found in the current study is comparable with findings from several meta-analyses. For cervical cancer, TNF-α G/A+AA carriers were found to significantly increase cancer risk by 1.25-fold (95% CI=1.01-1.54) [53]. Similar result has been observed in gastric cancer where subjects having GA/AA genotypes were associated with a 35% increase in cancer risk (95%=1.14-1.60) [54,55]. Ma et al. has shown that genotypes GA/ AA were significantly associated with increased prostate cancer risk (OR=1.53, 95% CI=1.09-2.15). It is biologically plausible that TNF-α -308G>A polymorphism might be clinically associated with NPC risk.

TNF-α is a pro-inflammatory cytokine that plays an essential role in inflammation, which has been implicated in enhancing tumorigenesis [56]. Several pro-tumor properties of TNF-α have been suggested, such as induction of pro-malignant chemokines, matrix metalloproteinases, cell adhesion molecules and angiogenic mediators [57]. Mocellin et al. [58] have shown that dysregulation and overproduction of TNF-α as induction of pro-malignant chemokines, matrix metalloproteinases, cell adhesion molecules and angiogenic mediators [57]. Mocellin et al. [58] have shown that dysregulation and overproduction of TNF-α as induc20.1222020-00314
inhibit carcinogen-induced cytotoxicity, which resulted in the increase of mutated cells that were susceptible to malignant transformation [61]. TNF-α was also reported to promote cancer development through inducing DNA instability by increasing the production of ROS in the cells [62].

The finding of the present study suggests a potential causative role of hOGG1 Ser326Cys polymorphism in the initiation of NPC. In addition, the effect of aberrant TNF-α expression arising from the -308 G>A polymorphism could have contributed to increased NPC risk. As NPC is considered a relatively radiosensitive tumor, patients diagnosed and treated in the early stages tend to survive longer compared to those with advanced disease [63]. The 5-year disease-free survival and overall survival for NPC patients diagnosed in the early stages who received radiotherapy were 84.7% and 84.2% respectively [63]. Early detection is therefore important due to the fact that symptoms related to NPC in the early stages are usually non-specific. The development of an accurate NPC screening tool such as screening for biomarkers is important in contributing to the early detection of the disease [64]. The predictive effect of hOGG1 Ser326Cys and TNF-α -308 G>A polymorphisms on NPC risk should be validated in future studies. If significant, the aforementioned polymorphisms could potentially serve as diagnostic markers in future to develop customized approaches in screening modalities for high risk populations susceptible to NPC.

Conclusion

Overall, the finding from the present study suggests potential causative role of hOGG1 Ser326Cys and TNF-α -308 G>A polymorphisms in the initiation of NPC despite none of the aforementioned polymorphisms showed significant association. Evidence from previous studies has supported the hypothesis that variation in BER activity due to hOGG1 Ser326Cys polymorphism might give rise to the accumulation of 8-oxoG and subsequently confer increased risk of NPC and other cancers. The effect of aberrant TNF-α expression arising from the -308 G>A polymorphism on tumor promotion could have contributed to the significant association between the -308G>A polymorphism with increased NPC risk.

References


