UNIVERSITI PUTRA MALAYSIA

ASSOCIATION OF GENE POLYMORPHISMS AND XPD EXPRESSION ON RISK OF NASOPHARYNGEAL CARCINOMA AND SURVIVAL AMONG MALAYSIANS

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By

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ASSOCIATION OF GENE POLYMORPHISMS AND XPD EXPRESSION ON RISK OF NASOPHARYNGEAL CARCINOMA AND SURVIVAL AMONG MALAYSIANS

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April 2017

Chairman: **Lye Munn Sann, MBBS, MPH, DrPH**
Faculty: **Medicine and Health Sciences**

Nasopharyngeal carcinoma (NPC) is a rare form of cancer across the world except in certain areas such as Southern China, Hong Kong and Malaysia. 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 with 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. A matched case-control study was conducted to investigate the effect of hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A and XPD Lys751Gln polymorphisms on the risk of nasopharyngeal carcinoma and all-cause survival. The association of XPD Lys751Gln polymorphism with XPD mRNA expression was investigated in order to substantiate the finding of significant association between XPD Lys751Gln polymorphism with NPC risk. A number of genes with their respective polymorphisms were shown in past studies to be associated with various cancers. hOGG1 and XPD genes encode for a DNA glycosylase and a DNA helicase respectively; both are proteins that are 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. In the present study, NPC cases and controls were matched by age, gender and ethnicity. 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. Quantitative real-time PCR was utilized to process the XPD expression. $2^{-\Delta\Delta Ct}$ relative expression fold-change method was chosen for the analysis of expression study. Linkage disequilibrium and haplotype analysis were conducted to explore the association of allele combinations arising from all

aforementioned gene polymorphisms with NPC risk. Kaplan-Meier survival function, log-rank test, and Cox regression were used to investigate the effect of gene polymorphisms on the all-cause survival of NPC. XPD homozygous wildtype Lys/Lys genotype was associated with increased NPC risk (adjusted OR=1.65, 95% CI=1.09-2.50). No association was found between ITGA2 and TNF-α polymorphism on NPC risk. Lys/Lys genotype of XPD polymorphism was associated with reduced XPD expression. Interaction between gene polymorphisms showed that Ser/Gln (hOGG1-Ser^{326}/XPD-Gln^{751}) (adjusted OR=2.18, 95% CI=1.00-4.75), Ser/T (hOGG1-Ser^{326}/ITGA2-T^{807}) (adjusted OR=1.48, 95% CI=1.02-2.16) and G/Gln (TNF-α-G^{308}/XPD-Gln^{751}) (adjusted OR=1.59, 95% CI=1.07-2.35) allelic combinations conferred higher risk of NPC. 5-year survival rates for ITGA2 807 C/C, C/T and T/T carriers were 55 %, 50 % and 43 %, respectively. The application of XPD Lys751Gln and ITGA2 C807T polymorphisms in early NPC detection and prognostic prediction for NPC survival is not warranted at the current moment and the finding should be subjected to further validation and testing involving studies with larger sample size.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

HUBUNGAN DI ANTARA POLIMORFISME GEN DAN EXPRESI XPD ATAS RISIKO KANSER NASOFARINKS DAN PELUANG HIDUP DI GOLONGAN RAKYAT MALAYSIA.

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Kanser nasofarinks (NPC) merupakan sejenis kanser yang jarang berlaku di seluruh dunia, kecuali di negara-negara tertentu seperti Southern China, Hong Kong dan Malaysia. NPC merupakan kanser ke-4 kerap berlaku di Malaysia dan kadar kejadian NPC bagi Cina Malaysia adalah paling tinggi berbanding dengan kaum lain. NPC dianggap sebagai kanser agak radiosensitif dan peluang hidup pesakit NPC pada peringkat awal kanser adalah lebih lama berbanding mereka yang mengalami penyakit peringkat lanjutan. Tanda-tanda awal penyakit NPC adalah tidak spesifik dan kawasan nasofarinks adalah agak tersembunyi. Oleh itu, pemeriksaan yang kurang invasif seperti pemeriksaan biomarker mungkin menjadi satu kaedah diagnosis yang penting untuk meningkatkan peluang hidup dan tahap pengurusan pesakit NPC. Satu kajian kes-kawalan dipadankan telah dijalankan untuk mengkaji kesan polimorfisme hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G> A dan XPD Lys751Gln atas risiko kanser nasofarinks dan peluang hidup pesakit NPC. Kaitan di antara polimorfisme XPD Lys751Gln dengan expresi XPD mRNA telah disiasat untuk menyokong pemerhatian hubungan yang ketara antara polimorfisme XPD Lys751Gln dengan risiko NPC. Polimorfisme gen-gen di atas masing-masing telah ditunjukkan dalam kajian pada masa lalu untuk berkaitan dengan pelbagai jenis kanser. hOGG1 dan XPD gen merupakan gen yang berkaitan dengan glycosylase DNA dan helicase DNA; kedua-duanya adalah protein yang terlibat dalam pembaikan DNA. ITGA2 adalah subunit alfa daripada reseptor transmembran integrin dan tanggungjawab utamanya adalah untuk perhubungan antara sel-sel dan sel-matriks sel. TNF-α adalah sitokin yang dihasilkan oleh sel-sel pertahanan badan semasa inflamasi. Dalam kajian ini, kes-kes NPC dan kawalan telah dipadankan mengikut umur, jantina dan kumpulan etnik. RFLP-PCR telah digunakan untuk memproses kajian genotyping DNA yang melibatkan semua polimorfisme gen yang dinyatakan di atas. Regresi logistic bersyarat telah digunakan untuk analisis risiko NPC bersama dengan polimorfisme gen, dan analisis telah dikawal dengan sejarah merokok, pengambilan ikan masin dan minuman keras peserta. Kuantitatif transkripsi terbalik PCR telah digunakan untuk memproses expresi XPD.

Kaedah $2^{-\Delta\Delta Ct}$ expresi relatif telah digunakan untuk kiraan perubahan dalam expresi XPD. Hubungan dan analisis haplotype polimorfisme gen-gen telah dijalankan untuk meneroka kaitan di antara semua haplotype daripada semua polimorfisme gen yang dinyatakan di atas dengan risiko NPC. Fungsi survival Kaplan-Meier, ujian log-pangkat, dan Regresi Cox telah digunakan untuk mengkaji kesan polimorfisme gen di atas peluang hidup pesakit NPC. XPD wildtype homozygous Lys/Lys telah dikaitkan dengan peningkatan risiko NPC (OR= 1.65, 95 % CI= 1.09-2.50). Tiada kaitan didapati antara polimorfisme hOGG1, ITGA2 dan TNF-α dengan risiko NPC. Genotype Lys/Lys polimorfisme XPD telah didapati berkaitkan dengan pengurangan expresi XPD. Interaksi antara polimorfisme gen menunjukkan bahawa Ser/Gln (hOGG1-Ser326/XPD-Gln751) (OR= 2.18, 95 % CI = 1.00-4.75), Ser/T (hOGG1-Ser326/ITGA2-T807) (OR= 1.48, 95 % CI= 1.02-2.16) dan G/Gln (TNF-α-G308/XPD-Gln751) (OR= 1.59, 95 % CI= 1.07-2.35) telah memberikan risiko yang lebih tinggi untuk NPC. Kadar peluang hidup 5-tahun pesakit NPC untuk ITGA2 807 C/C, C/T dan T/T adalah 55 %, 50 % dan 43 %. Kegunaan polimorfisme XPD Lys751Gln dan ITGA2 C807T dalam pengesanan NPC pada peringkat awal dan penunjuk untuk meramalkan peluang hidup pesakit NPC tidak sah pada masa sekarang dan penemuan tersebut harus disahkan dengan kajian yang melibatkan sampel saiz yang lebih besar.

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8-oxoG	8-oxo-7,8-dihydroguanine
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AP	Apurinic/apyrimidinic
APE1	AP endonuclease 1
Bcl-2	B cell lymphoma 2
BER	Base excision repair
CACS	Cancer anorexia-cachexia syndrome
CAD	Caspase activated dnase
CAK	Cdk-activating kinase
CAS	Crk-associated substrate
CDC42	Cell division control protein 42 homolog
cDNA	Complementary-DNA
cFLIP	FLICE/caspase-8 inhibitory protein
CI	Confidence interval
CIITA	Class II major histocompatibility complex transactivator
CLPTM1L	Cleft lip and palate transmembrane protein 1-like protein
CRK	Adaptor protein CRK
CTD	Carboxy terminal domain
CYP	Cytochrome
DISC	Death signaling inducing complex
DMBA	7,12-Dimethylbenz[a]anthracene
EA	EBV early antigen
EBNA-1	EBV nuclear antigen-1
EBV	Epstein-Barr virus
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
EMT	Epithelial mesenchymal transition
ERCC1	Excision repair cross-complementation group 1
ERK	Extracellular signal-regulated kinase
FA	Fluorescence antibody
FADD	Fas associated protein with death domain
FAK	Focal adhesion kinase
FAS	Apoptosis stimulating fragment
FEN1	Flap endonuclease 1
FGF	Fibroblast growth factor
GG-NER	Global genome-NER
GSTM	Glutathione S-transferase Mu 1
HGF	Hepatocyte growth factor
hHR23B	Human Rad23 homolog
HNSCC	Head and neck squamous cell carcinoma
hOGG1	Human 8-oxoguanine glycosylase
HWE	Hardy-Weinberg equilibrium
IAP	Inhibitor of apoptosis protein
IKB	Inhibitor of kappa B
IKK	Inhibitor of NF-κB kinase

IL	Interleukin
ITGA2	Integrin α2
JNK	c-Jun-terminal kinase
LD	Linkage disequilibrium
LT	Lymphotoxin
MAPK	Mitogen activated protein kinase
MAT1	Menage à trois
Mcl-1	Induced myeloid leukemia cell differentiation protein 1
MDM2	Mouse double minute 2 homolog
MEK	Mitogen activated-protein kinase kinase
MHC	Major histocompatibility complex
MLCK	Myosin-light-chain kinase
MMP	Matrix metalloprotease
MnSOD	Manganese superoxide dismutase
MRI	Magnetic resonance imaging
NER	Nucleotide excision repair
NFAT3	Nuclear factor of activated T-cells 3
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	Non-Hodgkin's lymphoma
NIK	NF-κB-inducing kinase
NPC	Nasopharyngeal carcinoma
NSCLC	Non-small cell lung cancer
OR	Odds ratio
OS	Overall survival
RF-C	Replication factor C
RIP1	Receptor interacting protein 1
ROS	Reactive oxygen species
P53	Tumor protein p53
PAK	P21-activated kinase
PBS	Phosphate-buffered saline
PCNA	Proliferating cell nuclear antigen
PI3K-AKT	Phosphoinositide 3-kinase-protein kinase B
PLAD	Pre-ligand assembly domain
qRT	Quantitative real time
RAF	Serine/threonine protein kinase
RF-C	Replication factor C
RFLP	Restriction fragment length polymorphism
RGD	Arg-Gly-Asp
ROS	Reactive oxygen species
RPB1	DNA-directed RNA polymerase II subunit
SAD	Synapses of amphids defective
SATB-1	Special AT-rich binding protein 1
SODD	Silencer of death domain
SSB	Single-stranded break
sTNF	Soluble tumor necrosis factor
TACE	TNF-α converting enzyme
TC-NER	Transcription coupled-NER
TFIIH	Transcription factor II H
TNF-α	Tumor necrosis factor-alpha

TNF-R	Tumor necrosis factor receptor
TNM	Tumor, Node, Metastasis
TRADD	TNFR-associated death domain protein
TRAF	TNF receptor-associated factor
VCA	EBV capsid antigen
VEGF	Vascular endothelial growth factor
XPB	Xeroderma pigmentosum group B
XPC	Xeroderma pigmentosum group C
XPD	Xeroderma pigmentosum group D
XPF	Xeroderma pigmentosum group F
XPG	Xeroderma pigmentosum group G
XRCC1	X-ray repair cross-complementing protein 1

CHAPTER 1

INTRODUCTION

1.1 Background

Nasopharyngeal carcinoma (NPC) commonly originates in the Fossa of Rosenmüller (Tabuchi *et al.*, 2011). It is a rare malignancy in most parts of the world with the annual incidence less than 1 per 100,000 population (Chang & Adami, 2006). According to the International Agency for Research on Cancer, there were 84,400 new NPC cases and 51,600 deaths in 2008 (Jemal *et al.*, 2011). However, the annual incidence of NPC in places such as Southeast Asia, Southern China and Hong Kong is very high compared to the rest of the world (Cao *et al.*, 2011; Chang & Adami, 2006; Forman *et al.*, 2014). Incidence of NPC is more than 20 per 100,000 population among males residing in Southern China while NPC incidence in Singapore and Penang, Malaysia is 10.9 and 8.5 per 100,000 population respectively (Chang & Adami, 2006; Forman *et al.*, 2014). In Malaysia, NPC is the 4th most common malignancy (Zainal Ariffin & Nor Saleha, 2011). NPC is often overlooked due to its status of being a rare cancer, but in Malaysia, the incidence of NPC is increasing from being the 6th most common carcinoma in 2003 to the 4th in 2007 despite the growing public awareness of the disease (Lim *et al.*, 2008; Zainal Ariffin & Nor Saleha, 2011).

Evidence from past studies indicates that factors other than genetic predisposition are responsible in the etiology of NPC. Chinese offspring who have migrated to western countries were observed to have progressively lower NPC incidence (Sun *et al.*, 2005). Environmental factors such as salted fish consumption, cigarette smoking and wood dust exposure were observed to increase NPC risk in a number of studies (Armstrong *et al.*, 2000; Vaughan *et al.*, 1996; Yu *et al.*, 1986). Epstein-Barr virus (EBV) infection was also found to be closely associated with undifferentiated histological subtype of NPC regardless of patients' ethnic origin (Niedobitek *et al.*, 1996).

NPC is considered as a relatively radiosensitive tumor, and NPC patients diagnosed in the early stages tend to survive longer compared to those with advanced disease (Chang *et al.*, 1998). 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 (Chang *et al.*, 1998). Early detection is therefore important due to the fact that symptoms related to NPC in the early stages are usually non-specific. Early manifestation of NPC as nasal symptoms can be confused with other benign conditions, namely rhinitis, sinusitis, deviated nasal septum or nasal polyp (Lu *et al.*, 2010). Another symptom of NPC such as unilateral hearing loss due to serous otitis media is also not NPC-specific (Lu *et al.*, 2010).

A delay in diagnosis as much as 6 months is still seen in 70 % of the NPC patients despite the combined application of physical examination, biopsy, diagnostic imaging and

serological tests (Prasad, 2000). Similarly, 13.3% of NPC patients with occult primaries at presentation were misdiagnosed using the current standard procedures for NPC diagnosis (Prasad *et al.*, 1983). Hence, the development of an accurate NPC screening tool such as screening for biomarkers is important in contributing to the early detection of the disease (Tabuchi *et al.*, 2011). Biomarker is defined as a characteristic that is objectively measured and monitored as an indicator of either normal biological processes or pathogenic processes (Strimbu & Tavel, 2010). In general, biomarkers can be categorized into 2 groups; biomarkers of exposure, which are used in prediction of cancer risk, and biomarkers of disease, which are used in screening for early detection, diagnosis and monitoring of disease progression (Mayeux, 2004). Genetic biomarkers could be useful in early NPC detection because a highly valid biomarker of exposure enables risk profiling of the susceptible population since birth. The screening of molecular biomarkers in cancer prediction has already been adopted in other malignancies such as breast and ovarian carcinoma (Brooks, 2009; Kobayashi *et al.*, 2012).

Despite NPC being a carcinoma that is manageable by radiotherapy, 20-30% of NPC patients still experience distant metastasis after combined intensity-modulated radiotherapy and chemotherapy (Kam *et al.*, 2004). Thus far, there are very few prognostic biomarkers in NPC that accurately predict the recurrence of disease. The clinical prognostic markers that are commonly in use to predict NPC recurrence are tumor staging and tumor volume or tumor size (Lu *et al.*, 2010). The use of anti-EBV antibodies is limited in this regard because they are essentially a host response to viral tumor antigens. The lack of prognostic effect of antibody assays is thought to be attributable to individual differences in the immune response to various antigens. The antibody titer was shown to remain persistently high in most patients in remission after treatment (Fan *et al.*, 2004; Lu *et al.*, 2010; Shao *et al.*, 2004). It is difficult to ascertain a reliable cutoff value in the differential diagnosis of recurrence or remission (Lu *et al.*, 2010). Genetic biomarkers however, could be useful as a prognosticator due to the fact that the genetic profile of an individual is qualitative rather than quantitative, and it does not fluctuate from time to time. A highly valid genetic prognostic biomarker allows risk profiling of the susceptible population since birth and enables accurate prediction of recurrence and remission of a particular disease.

Deoxyribonucleic acid (DNA) in human cells is constantly exposed to various endogenous and exogenous carcinogens from the surrounding environment (Swenberg *et al.*, 2011). Polycyclic aromatic hydrocarbons and nitrosamines are examples of exogenous carcinogens that human cells are exposed to during ingestion of salted fish and smoking of cigarette (Hecht, 1999; Ward *et al.*, 2000). Normal cellular metabolic processes in the human body were shown to be capable of producing endogenous carcinogens such as hydroxyl radicals that can cause oxidative damage to DNA (Demple & Harrison, 1994). Accumulation of DNA damage was linked to neoplastic transformation of normal cells if they were unrepaired (Coleman & Tsongalis, 2001). Guanine is the nitrogenous base that is most susceptible to oxidation due to its low redox potential, forming 8-oxo-7,8-dihydroguanine (8-oxoG) (Aguiar *et al.*, 2013). 8-oxoG is known to be a G:C to T:A transversion causing agent which generates DNA double-stranded breaks in a subsequent reaction if it is unrepaired (Aguiar *et al.*, 2013; Cheng *et al.*, 1992).

Human 8-oxoguanine DNA glycosylase 1 (hOGG1) is the primary enzyme responsible for the removal of 8-oxoG through base excision repair (BER) (Nash *et al.*, 1997). As an initiator of BER, hOGG1 DNA glycosylase protein is essential in both recognizing the DNA damage and also removal of the affected guanine base from the sugar backbone (Kim & Wilson, 2012). Cys^{326} allele of hOGG1 Ser326Cys polymorphism has been shown to be significantly associated with increased risk of orolaryngeal cancer (Elahi *et al.*, 2002), gastric cancer (Ni *et al.*, 2012), breast cancer (Xie *et al.*, 2013a) and hepatocellular carcinoma (Yuan *et al.*, 2012). However, a solitary bladder cancer study suggested otherwise by showing that hOGG1-Ser^{326} carrying increased risk instead (Ma *et al.*, 2012). In addition, hOGG1 Ser326Cys polymorphism was found to be significantly associated with survival of lung, bladder and pancreatic cancer (Ha *et al.*, 2011; Li *et al.*, 2007; Shen *et al.*, 2007). For the case of NPC, Cho and colleagues (2003) have reported that hOGG1 Ser326Cys polymorphism is associated with increased risk of NPC (OR= 1.6, 95% CI= 1.0-2.6) while contradicting results was shown in Laantri's (2011) study featuring the same cancer (OR= 1.22, 95% CI= 0.77-1.90).

Besides BER, nucleotide excision repair (NER) is another important DNA repair mechanism which is responsible for preserving the integrity of human genome (Hoeijmakers & Bootsma, 1994; Sancar *et al.*, 2004). NER removes bulky DNA adducts and UV-induced photoproducts via the action of transcription factor II H (TFIIH) complex (de Laat *et al.*, 1999). Xeroderma pigmentosum group D (XPD) gene encodes for a 5'-3' DNA helicase which is a member of TFIIH complex (Marteijn *et al.*, 2014). XPD is responsible for the unwinding of the double-helical DNA damaged region in 5'-3' direction during NER and also basal transcription (Marteijn *et al.*, 2014; Tirode *et al.*, 1999). The importance of XPD in NER is clearly shown by the fact that TFIIH complex is unable to excise the damaged DNA in the absence of XPD (Kuper *et al.*, 2014). Several studies reported significant associations between Lys751Gln polymorphism with the development of cancers, namely chronic myeloid leukemia (Banescu *et al.*, 2014), lung cancer (Hung *et al.*, 2008), skin cancer (Lehmann, 2001) and prostate cancer (Yang *et al.*, 2013) while other studies on cancers such as head and neck cancer (Hu *et al.*, 2012), prostate cancer (Mi *et al.*, 2012) and colorectal cancer (Moghtit *et al.*, 2014) did not. Studies on head and neck, lung, breast and colorectal cancer have shown significant associations between XPD Lys751Gln polymorphism and patients' survival (Farnebo *et al.*, 2015; Pare *et al.*, 2008; Tengstrom *et al.*, 2014; Tiseo *et al.*, 2012). As for NPC, Yang and colleagues have found that Lys allele (wildtype) was significantly associated with increased cancer risk (Yang *et al.*, 2007). Hence polymorphisms of DNA repair genes hOGG1 Ser326Cys and XPD Lys751Gln could be potentially useful in NPC screening as both polymorphisms have been implicated in the past to confer higher risk of NPC (Cho *et al.*, 2003; Yang *et al.*, 2007).

Apart from DNA repair, transmembrane receptor integrins are important in carcinogenesis. These transmembrane glycoproteins are mainly responsible for mediating cell-cell and cell-extra cellular matrix (ECM) interactions (Yu *et al.*, 2000). Integrins are heterodimeric and consist of 2 transmembrane glycoproteins (α and β) that are non-covalently bound together (Campbell & Humphries, 2011). Integrins are involved in almost every aspect of carcinogenesis, from cell differentiation, cell proliferation, metastasis to angiogenesis (Abram & Lowell, 2007; Evans *et al.*, 2009; Rathinam & Alahari, 2010).

Integrin α2 is a collagen receptor that is mainly expressed on platelets and epithelial cells (Ding *et al.*, 2015). Integrin α2β1 was found to facilitate integrin-mediated attachment to collagen type I during the metastasis of breast cancer cells to bone (Lundstrom *et al.*, 1998). The binding of collagen I to α2β1 integrin was also shown to promote the malignant phenotype of pancreatic ductal adenocarcinoma (Armstrong *et al.*, 2004). There is evidence indicating 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 (Gerger *et al.*, 2009; Langsenlehner *et al.*, 2006).

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 tumors (Saenz-Lopez *et al.*, 2008). Numerous mediators released during dysregulated chronic inflammation have been linked to induce cell growth and invasion at the same time promoting mutagenesis and angiogenesis (Coussens & Werb, 2002). Tumor necrosis factor alpha (TNF-α) is known as one of the earliest cytokine produced in inflammatory process (Warzocha *et al.*, 1998). TNF-α is a key mediator for inflammation and is secreted mainly by macrophages (Feng *et al.*, 2014). TNF-α protein was observed to act as an endogenous tumor promoter *in vivo* (Komori *et al.*, 1993). This observation has been substantiated by the finding from a knock-out mouse study where the essential role of TNF-α in carcinogenesis was revealed (Knight *et al.*, 2000).

Significant associations were found between the variant -308A allele and susceptibility to malignant tumors, namely hepatocellular carcinoma (Akkiz *et al.*, 2009; Feng *et al.*, 2014; Ho *et al.*, 2004) and prostate cancer (Oh *et al.*, 2000; Saenz-Lopez *et al.*, 2008). In addition, TNF-α -308G>A polymorphism was shown to be associated with survival of several cancers, namely B-cell lymphoma, non-Hodgkin lymphoma, chronic lymphocytic lymphoma (Juszczynski *et al.*, 2002; Lech-Maranda *et al.*, 2013; Tarabar *et al.*, 2014). Although ITGA2 C80T 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 namely breast (Langsenlehner *et al.*, 2006), gastric (Chen *et al.*, 2011a), lung (Shih *et al.*, 2006) and liver (Ho *et al.*, 2004). Together with the evidence indicating the possible roles for both genes in carcinogenesis, which is discussed in the next chapter, ITGA2 C807T and TNF-α-308G>A could potentially serve as screening targets in the early detection of NPC.

1.2 Objectives

General objective: To investigate the association between hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A and XPD Lys751Gln polymorphisms and the risk of NPC, as well as all-cause survival in Malaysian population.

Specific objectives:

1. To determine the sociodemographic (age, gender and ethnicity) and environmental exposures (cigarette smoking, alcohol consumption and salted fish ingestion during childhood) for cases and controls.
2. To determine the genotypes of hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A and XPD Lys751Gln polymorphisms for cases and controls.
3. To determine the clinical characteristics (TNM stage, all-cause survival, 5-year overall survival) for cases.
4. To test the hypothesis that hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A and XPD Lys751Gln polymorphisms are associated with increased risk of NPC, controlling for cigarette smoking, alcohol consumption and salted fish ingestion during childhood.
5. To test the hypothesis that XPD mRNA expression level is different between NPC cases and controls.
6. To test the hypothesis that XPD Lys751Gln polymorphism is associated with variations in XPD mRNA expression.
7. To test the hypothesis that the interactions between hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A and XPD Lys751Gln polymorphisms are associated with increased NPC risk.
8. To test the hypothesis that hOGG1 Ser326Cys, ITGA2 C807T, TNF-α -308G>A, XPD Lys751Gln polymorphisms and TNM staging affect the all-cause survival of NPC, controlling for cigarette smoking, alcohol consumption and salted fish ingestion during childhood.

1.3 Hypotheses

1. hOGG1 Ser326Cys, ITGA2 C807T, TNF-α-308G>A and XPD Lys751Gln polymorphisms are associated with increased risk of NPC after adjusting for age, gender, ethnicity, cigarette smoking, alcohol consumption and salted fish consumption during childhood.
2. XPD mRNA expression is different between NPC cases and controls.
3. XPD Lys751Gln polymorphism is associated with XPD mRNA expression.
4. Interactions between hOGG1 Ser326Cys, ITGA2 C807T, TNF-α-308G>A and XPD Lys751Gln polymorphisms are associated with increased risk of NPC after adjusting for age, gender, ethnicity, cigarette smoking, alcohol consumption and salted fish consumption during childhood.
5. hOGG1 Ser326Cys, ITGA2 C807T, TNF-α-308G>A, XPD Lys751Gln polymorphisms and TNM staging significantly affect the all-cause survival of NPC after adjusting for cigarette smoking, alcohol consumption, and salted fish consumption during childhood.

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LIST OF PUBLICATIONS

Lye MS, Visuvanathan S, Chong PP, Yap YY, Lim CC, Ban EZ (2015) Homozygous Wildtype of XPD K751Q Polymorphism Is Associated with Increased Risk of Nasopharyngeal Carcinoma in Malaysian Population. PLoS ONE 10(6): e0130530. doi:10.1371/journal.pone.0130530

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