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VITAMIN D RECEPTOR AND ADIPOKINE GENE POLYMORPHISMS AND RISK OF NASOPHARYNGEAL CARCINOMA AMONG MALAYSIANS

NURULASSIKIN BINTI SULONG ABDUL RAHMAN

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By

NURULASSIKIN BINTI SULONG ABDUL RAHMAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

May 2017

DEDICATION

This thesis is dedicated to my beloved parents, Sulong Abdul Rahman Mat and Masitah Noh, my wonderful husband, Nasrulridza Yusuf, my brother, Saifulnizam and my sister, Nursyuhada who have supported me in pursuing this master's degree and for their encouragement for me to accomplish my study.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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

Nasopharyngeal carcinoma (NPC) is a relatively rare malignancy in most parts of the world. However, NPC is a cancer which is common in Asia including Malaysia. NPC is the fourth most common cancer in Malaysia and shows high rates among the native people of Sarawak as well as the Chinese and the Malay populations. The distinctive racial/ethnic and geographic distribution of NPC worldwide suggests that both environmental factors and genetic traits contribute to its development. This study is aimed to conduct a molecular epidemiological study on single nucleotide polymorphisms (SNPs) of Vitamin-D receptor (VDR) and adipokine genes and risk of NPC among Malaysians. A matched case-control study was conducted in Hospital Kuala Lumpur (HKL) and Hospital Pulau Pinang (HPP). A total of 600 subjects consisting of 300 case patients and 300 controls were recruited in this study. Genomic DNA was extracted from blood and genotyped using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. The genotype frequencies in case and control groups were estimated by direct gene counting from the gel images and analyzed using SPSS. There was no significant difference found in VDR BsmI, VDR TaqI, VDR ApaI, VDR FokI, IL6R Asp358Ala, LEPR Gln223Arg, ADIPOQ +45 T>G and PAI-1 4G/5G polymorphisms and risk of developing NPC between the NPC case and control subjects. The findings indicate that VDR and adipokine gene polymorphisms do not contribute as risk factors for NPC development among Malaysians. Further studies in a larger population must be carried out to reach a more reliable conclusion. However, there are three significant findings of two SNP interactions: VDR ApaI C/A and VDR TaqI T/C (OR=2.629); IL6R 358 Ala/Ala (variant) and LEPR 223 Arg/Arg (variant) (OR=2.085); and VDR ApaI C/A and IL6R 358 Ala/Ala (OR=3.817). Three out of five findings of three SNP interactions showed higher risks of NPC: VDR ApaI C/A, VDR TaqI T/C and LEPR Arg/Arg; IL6R 358 Asp/Ala, LEPR 223 Arg/Arg and VDR FokI T/C; and VDR BsmI A/G, VDR ApaI C/A and VDR FokI T/C with OR from 1.718 until 3.655. The other two results showed protective effects in

NPC: LEPR 223 Gln/Arg, ADIPOQ +45 T/G and VDR FokI T/C; and LEPR 223 Arg/Arg, ADIPOQ +45 T/G and VDR FokI C/C with OR of 0.181 and 0.458, respectively. One of the three findings of 4 SNP interactions showed a higher risk of NPC: VDR BsmI A/G, VDR ApaI C/A, VDR FokI T/C and IL6R 358 Asp/Ala with OR=10.039. The other two results showed protective effects of NPC: LEPR 223 Gln/Arg, ADIPOQ +45 T/G, VDR FokI T/C and PAI-1 5G/4G; and LEPR 223 Arg/Arg, ADIPOQ +45 T/G, VDR FokI C/C and PAI-1 4G/4G with OR=0.147 and OR=0.193, respectively. In a survival analysis for LEPR Gln223Arg, Arg/Arg carriers had a higher overall survival time and better prognosis in NPC than those with Gln/Gln and Gln/Arg genotype carriers. This result suggests that the polymorphism LEPR Gln223Arg may be used as a molecular marker for progression and prognosis of NPC although more studies need to be conducted to achieve a more reliable conclusion due to controversial findings in other types of cancer.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

POLIMORPHISME GEN BAGI VITAMIN D RESEPTOR DAN ADIPOKINE DENGAN FAKTOR RISIKO KANSER NASOPHARINK DALAM KALANGAN RAKYAT MALAYSIA

Oleh

NURULASSIKIN BINTI SULONG ABDUL RAHMAN

Mei 2017

Pengerusi: **Profesor Dato' Lye Munn Sann, MBBS, MPH, DrPH**
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Kanser nasofarinks adalah barah yang jarang berlaku di seluruh dunia. Walaubagaimanapun, kanser nasofarinks adalah kanser yang kerap berlaku di Asia termasuklah Malaysia dan merupakan kanser keempat yang paling kerap berlaku di Malaysia. Kes kanser nasofarinks menunjukkan kadar yang tinggi dalam kalangan Bumiputera Sarawak serta populasi kaum Cina dan Melayu di Malaysia. Pembahagian kedudukan geografi serta kaum/etnik yang khusus bagi NPC di seluruh dunia menunjukkan bahawa kedua-dua faktor persekitaran dan genetik menyumbang kepada perkembangan kanser nasofarinks. Kajian ini bertujuan untuk menjalankan penyelidikan epidemiological molekul ke atas polimorfisme nukleotida tunggal (SNPs) pada gen reseptor vitamin D (VDR) dan adipokine dan risiko ke atas kanser nasofarinks di Malaysia. Kajian kes-kontrol yang dipadankan telah dijalankan di Hospital Kuala Lumpur (HKL) dan Hospital Pulau Pinang (HPP). Sebanyak 600 subjek yang terdiri daripada 300 pesakit kes dan 300 kontrol telah direkrut dalam kajian ini. Genomik DNA telah diekstrak dari darah dan telah digenotip menggunakan reaksi berantai polimerase-polimorfisme panjang fragmen restriksi (PCR-RFLP). Frekuensi genotip bagi setiap kes dan kontrol diambil secara terus dari gambar elektrophoresis gel dan dianalisa menggunakan SPSS. Tiada keputusan signifikan telah dijumpai dalam polimorfisme VDR BsmI, VDR TaqI, VDR ApaI, VDR FokI, IL6R Asp358Ala, LEPR Gln223Arg, ADIPOQ +45 T>G dan PAI-1 4G/5G dan risiko menghidapi kanser nasofarinks antara pesakit kes dan pesakit kontrol. Hasil kajian telah menunjukkan bahawa gen polimorfisme VDR dan adipokine tidak menyumbang kepada faktor risiko perkembangan kanser nasofarinks dalam kalangan rakyat Malaysia. Walaubagaimanapun, tiga keputusan signifikan telah dijumpai pada interaksi yang melibatkan dua SNP: VDR ApaI C/A dan VDR TaqI T/C (OR=2.629); IL6R 358 Ala/Ala (varian) dan LEPR 223 Arg/Arg (varian) (OR=2.085); dan VDR ApaI C/A dan IL6R 358 Ala/Ala (OR=3.817). Tiga daripada lima keputusan yang melibatkan tiga interaksi SNP telah menunjukkan

risiko kanser nasofarinks yang lebih tinggi: VDR ApaI C/A, VDR TaqI T/C dan LEPR Arg/Arg; IL6R 358 Asp/Ala, LEPR 223 Arg/Arg dan VDR FokI T/C; dan VDR BsmI A/G, VDR ApaI C/A dan VDR FokI T/C dengan OR antara 1.718 dan 3.655. Dua keputusan yang lain menunjukkan kesan perlindungan dalam kanser nasofarinks: LEPR 223 Gln/Arg, ADIPOQ +45 T/G, VDR FokI T/C dan PAI-1 5G/4G; dan LEPR 223 Arg/Arg, ADIPOQ +45 T/G, VDR FokI C/C dan PAI-1 4G/4G dengan OR=0.147 dan OR=0.193, mengikut urutan masing-masing. Dalam analisa peluang hidup, pembawa genotip Arg/Arg mempunyai peluang masa hidup yang lebih tinggi dan ramalan penyembuhan yang lebih baik dalam kanser nasofarinks berbanding pembawa genotip Gln/Gln dan Gln/Arg. Keputusan ini menunjukkan bahawa polimorfisme LEPR Gln223Arg boleh digunakan sebagai penanda molekul untuk perkembangan dan prognosis kanser nasofarinks walaupun lebih banyak kajian perlu dijalankan bagi mencapai kesimpulan yang lebih pasti atas sebab keputusan kajian yang bersifat kontroversi pada jenis kanser yang lain.

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I certify that a Thesis Examination Committee has met on 3 May 2017 to conduct the final examination of Nurulassikin binti Sulong Abdul Rahman on her thesis entitled "Vitamin D Receptor and Adipokine Gene Polymorphisms and Risk of Nasopharyngeal Carcinoma among Malaysians" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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LIST OF ABBREVIATIONS

NPC	Nasopharyngeal carcinoma
$1,25(OH)_2D_3$	Dihydroxycholecalciferol or dihydroxyvitamin D_3 or calcitriol
ADAM	A disintegrin and metalloproteinase
ADIPOQ	Adiponectin
ADIPOR	Adiponectin receptor
AJCC	American Joint Committee on Cancer
AKT	Protein kinase B
Ala	Alanine
AMPK	Adenosine monophosphate-activated protein kinase
Arg	Arginine
Asp	Aspartic acid
ASR	Age incidence rate
Bcl-2	B-cell lymphoma 2
bp	Base pair
CDK2	Cyclin dependent kinase 2
CI	Confidence interval
CTF	C terminal fragment
df	Degree of freedom
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
FAK	Focal adhesion kinase
Gln	Glutamine
GLOBOCAN	Global Cancer
Gly	Glycine
gp	Glycoprotein
Grb-2	Growth factor receptor-bound protein 2
GSK3β	Glycogen synthase kinase 3β
GWAS	Genome-wide association studies
HKL	Hospital Kuala Lumpur
HLA	Human leukocyte antigen
HPP	Hospital Pulau Pinang
HR	Hazard ratio
HSP27	Heat shock protein 27
HWE	Hardy-Weinberg Equilibrium
IgA	Immunoglobulin A
IGF-1	Insulin-like growth factor 1
IgG	Immunoglobulin G
IL-6R	Interleukin-6 receptor
Ile	Isoleucine
ILK	Integrin linked kinase
Indel	Insertion/deletion

JAK	Janus kinase
JNK	c-Jun N-terminal kinase
LD	Linkage disequilibrium
LEPR	Leptin receptor
mAb	Monoclonal antibody
Mac-2 BP	Mac-2 binding protein
MAPK	Mitogen-activated protein kinase
MAPKAPK	MAP kinase activated protein kinase
Met	Methionine
mRNA	Messenger ribonucleic acid
mTOR	Mechanistic target of rapamycin
OR	Odds ratio
OS	Overall survival
PAI-1	Plasminogen activator inhibitor-1
PARP	Poly ADP ribose polymerase
PCR	Polymerase chain reaction
PI3K	Phosphoinositide 3-kinase
pp38	Phosphorylated 38
RANKL	Receptor activator of nuclear factor kappa-B ligand
RFLP	Restriction fragment length polymorphism
ROCK	Rho-associated kinase
ROS	Reactive oxygen species
SD	Standard deviation
SERPINs	Serine protease inhibitors
sIL-6R	Soluble interleukin-6 receptor
SNP	Single nucleotide polymorphism
SOCS3	Suppressor of cytokine signalling 3
STAT	Signal transducer and activator of transcription
TF2B	Transcription factor 2B
Thr	Threonine
TNM	Tumour, Node, Metastasis staging system
t-PA	Tissue-type plasminogen activator
TYK	Tyrosine kinase
u-PA	Urokinase-type plasminogen activator
VDR	Vitamin D receptor
VDREs	Vitamin D response elements
VDUP1	Vitamin D upregulated protein 1
VEGF	Vascular endothelial growth factor
X^2	Chi-square

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Nasopharyngeal carcinoma (NPC) is a malignant tumour that arises from the epithelial cells, lining a recess along the lateral wall of the nasopharynx named "Fossa of Rosenmuller' (Prasad, 1996; Tabuchi et al., 2011) as shown in Figure 1.1. It is one of the most rapidly developing tumours of the head and neck and comprises more than two thirds of all tumours arising in the nasopharynx (Prasad, 1996).

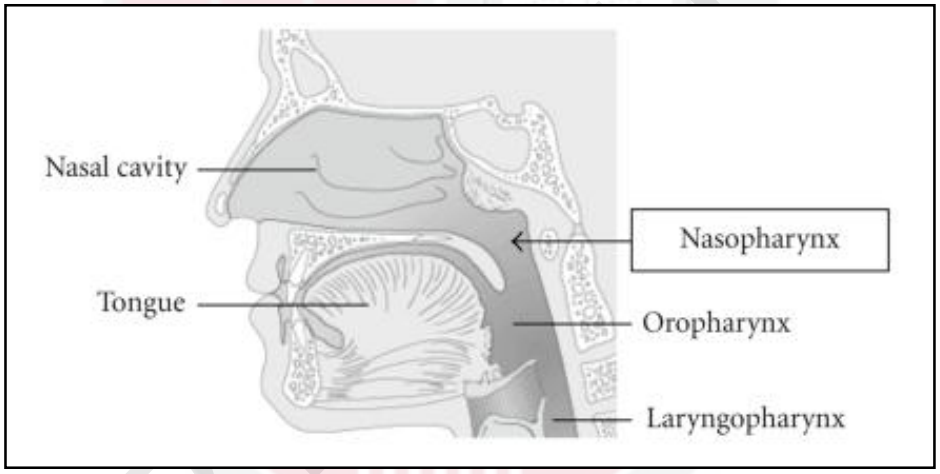

Figure 1.1: Anatomic site of NPC (adapted with permission from Zhou et al. (2007))**.**

The first presenting complaints were symptoms that represented the main reason for seeking medical advice. The first presenting symptoms reported by NPC patients in Malaysia include swelling in the neck (neck mass), blood-stained nasal or postnasal discharge, aural discomfort which included impairment of hearing with or without tinnitus in one ear, and intracranial symptom; either headache or cranial nerve palsy (Prasad & Pua, 2000; Tiong & Selva, 2005). NPC is diagnosed using a combination of a clinical examination, imaging, serological markers and histology (Prasad & Pua, 2000).

According to World Cancer Report 2008, NPC is a relatively rare malignancy in most parts of the world (Anusha et al., 2012; Tabuchi et al., 2011). NPC accounts for 2% of all head and neck squamous cell carcinoma, with an incidence of 0.5

to 2 per 100,000 population in the United States (Tabuchi et al., 2011; Zhou et al., 2007). However, NPC has a well-defined geographical distribution, primarily affecting people from Southern China and Southeast Asia (Anusha et al., 2012; Pua et al., 2008). NPC shows high incidence rates among Cantonese in the Guangdong Province, Southern China and Hong Kong, and among Sarawak, Borneo native people (Anusha et al., 2012; Devi et al., 2004).

Malaysia is a country with diverse ethnic backgrounds. The three major racial groups are the Malays, Chinese and Indians. Malaysia is considered as one of the regions with intermediate risk for NPC but the risk actually differs among the different ethnicities (Anusha et al., 2012). The highest risk is the Chinese, many of whom originate from the Southern Provinces of China followed by the Malays; intermediate risk, and the low risk Indians (Anusha et al., 2012). A study by Devi et al. (2004) showed that the Bidayuh people of Sarawak, East Malaysia were 2.3-fold (31.5/100,000 age-adjusted incidence rate (ASR)) at higher risk of NPC in males and 1.9-fold (11.8/100,000 ASR) higher risk in females when compared to the Sarawak average (13.5/100,000 ASR and 6.2/100,000 ASR for males and females, respectively). Bidayuh people were also exposed to about 50% higher risk than that in Hong Kong population which was the highest recorded by any population-based registry for the same period (21.4/100,000 ASR and 8.3/100,000 ASR for males and females, respectively (Devi et al., 2004). Among 13 states in Malaysia, Kelantan, Kedah, Terengganu and Malacca are the only ones where NPC was not listed in the five most common cancers in year 2007 (Omar & Tamin, 2011).

The National Cancer Registry Report 2007 has provided the information on cancer occurrence in Peninsular Malaysia, Sabah and Sarawak. According to this report, cancer is the third most common cause of death in Malaysia after heart diseases and diseases of pulmonary circulation; and septicaemia (Omar & Tamin, 2011). NPC is a highly prevalent cancer in Malaysia. NPC is the fourth most common cancer among Malaysians, being the third most common among males and eleventh among females (Omar & Tamin, 2011). NPC incidence is more than two-fold higher in males than in females (Omar & Tamin, 2011). On the other hand, the Chinese population recorded the highest incidence rate (10.9 and 3.5 per 100,000 population for males and females, respectively) compared to the Malay population (3.0 and 1.3 per 100,000 population for males and females, respectively) and the Indian population (1.1 and 0.9 per 100,000 population for males and females, respectively) (Anusha et al., 2012; Omar & Tamin, 2011).

Patients with NPC commonly present at advanced stages, with the percentage of 34% at stage III and 32% at stage IV resulting in poor prognosis (Abdullah et al., 2009; Omar & Tamin, 2011). The late presentations of NPC, at the stages of III and IV, which are in the Tumour, Node, Metastasis (TNM) staging system, have greatly affected patient survival (Tiong & Selva, 2007). The five-year survival for stages I and II are 95% and 85%, respectively, whereas those in stages III and IV are 55% and 45%, respectively (Tiong & Selva, 2007). In

Malaysia, most of the NPC cases belong to the non-keratinizing carcinoma (Pua et al., 2008).

Radiotherapy is the primary treatment given to NPC patients at all stages upon diagnosis (Abdullah et al., 2009). Radiotherapy uses high energy radiation to kill the cancer cells. For NPC patients with advanced stages III and IV, a combination of chemotherapy and radiation is given to enhance the effectiveness of radiotherapy (Abdullah et al., 2009). The combination of radiotherapy and chemotherapy prolonged the survival rate of patients at an advanced stage of NPC (Abdullah et al., 2009).

The distinctive ethnic and geographical distribution of NPC worldwide suggests that both genetics and environmental factors be partly responsible for the cause of the disease (Anusha et al., 2012; Pua et al., 2008). Elevated antibody levels against the Epstein-Barr virus (EBV) (Hsu et al., 2009; Lo et al., 2004; Young et al., 1988; zur Hausen et al., 1970), genetic factors, human leukocyte antigen class I (HLA-1) genotypes (Chang & Adami, 2006; Lu et al., 1990; Tabuchi et al., 2011), consumption of salt-preserved fish (Armstrong et al., 1998) and cigarette smoking (Hsu et al., 2009) are believed to be involved in the NPC tumourigenesis. However, the molecular mechanism of NPC pathogenesis is not fully elucidated yet.

A better understanding of the molecular mechanism of NPC is important for establishing more effective prevention, diagnostic, treatment and prognostic approaches. In this study, a multi-centric matched case-control study was performed to better address the interactions between vitamin D receptor (VDR) and adipokine (interleukin-6 receptor, leptin receptor, adiponectin and plasminogen activator inhibitor-1) gene polymorphisms with the risk of developing NPC in Malaysian population.

1.2 Problem Statement

Based on the Malaysia Cancer Statistics 2007 (Omar & Tamin, 2011), the incidence of NPC in Malaysia was 900 cases. The age-specific incidence rate (ASR) for female was 2.3 per 100,000 population and 6.4 per 100,000 population for male. As the majority of NPC cases were detected at advanced stages of III and IV, genetic biomarkers could provide a window into the nasopharyngeal early detection and prognosis in the future.

Both environmental and genetic factors have been identified to contribute to the NPC development. The single nucleotide polymorphisms (SNPs) of vitamin D receptor (VDR), interleukin-6 receptor (IL6R), leptin receptor (LEPR), and adiponectin (ADIPOQ); and insertion/deletion (indel) polymorphism of plasminogen activator inhibitor-1 (PAI-1) had been well studied in other types of

cancer. VDR and ADIPOQ genes are involved in anti-cancer mechanisms while IL-6R, LEPR and PAI-1 genes are involved in pro-cancer mechanisms. However, to the best of my knowledge, there are no publications on these gene polymorphisms in NPC in Malaysian population. Therefore, a hospital-based case-control study was conducted to explicate the potential association between these polymorphisms and the risk of developing nasopharyngeal carcinoma among the Malaysian population.

1.3 Significance of the Study

NPC is a highly prevalent cancer in Malaysia, being the fourth most common cancer among Malaysians and the third most common among males. Determination of the potential susceptible genes of NPC is crucial in elaborating our understanding of the biological and aetiological mechanism involved in the NPC development.

To the best of my knowledge, the association between genetic polymorphisms of the VDR, ADIPOQ, LEPR, IL-6R AND PAI-1 genes with nasopharyngeal carcinoma have not yet been studied in the Malaysian population. Given the unresolved gaps in the understanding of genetic risk factor of NPC, there is a clear need for further study in this area. The SNPs of VDR, IL6R, LEPR, and ADIPOQ; and indel polymorphism of PAI-1 could be potentially useful as markers to predict the risk of developing NPC, to detect NPC at an earlier stage, and thus contribute to the mortality rate of NPC.

1.4 Hypothesis

In this study, it is hypothesized that single nucleotide polymorphisms of VDR, IL6R, LEPR and ADIPOQ genes; and insertion/deletion of PAI-1 gene are significantly associated with the risk of developing NPC in patients diagnosed in Hospital Kuala Lumpur and Hospital Pulau Pinang.

1.5 Objectives

1.5.1 General objective

The main objective of this study is to conduct a molecular epidemiological study to determine if there is an association between single nucleotide polymorphisms (SNPs) of vitamin D receptor (VDR), interleukin-6 receptor (IL-6R), leptin receptor (LEPR), adiponectin (ADIPOQ) and insertion/deletion (indel) polymorphism of plasminogen activator inhibitor-1 (PAI-1) and the risk of nasopharyngeal carcinoma among Malaysians.

1.5.2 Specific Objectives

1. To determine the genotypic and allelic frequencies of genetic polymorphisms VDR BsmI G/A (rs1544410), VDR TaqI T/C (rs731236), VDR ApaI C/A (rs7975232), VDR FokI T/C (rs2228570), IL6R Asp358Ala (rs2228145), LEPR Gln223Arg (rs1137101), ADIPOQ +45 T>G (rs2241766) and PAI-1 -675 4G/5G (rs1799889) in the Malaysian NPC and control subjects.
2. To determine the association of the genetic polymorphisms of VDR BsmI G/A, VDR TaqI T/C, VDR ApaI C/A, VDR FokI T/C, IL6R Asp358Ala, LEPR Gln223Arg, ADIPOQ +45 T>G and PAI-1 -675 4G/5G and the risk of developing NPC in cases when compared with the controls.
3. To determine the association between the genotype interactions of the selected polymorphisms and the risk of NPC.
4. To determine the association between the haplotype of the selected polymorphisms and the risk of NPC.
5. To determine the linkage disequilibrium between the selected polymorphisms in NPC.
6. To determine the association between these gene polymorphisms and the survival of NPC patients.

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