UNIVERSITI PUTRA MALAYSIA

ASSOCIATION OF CIRCULATING NUTRITIONAL MARKERS, DIETS, LIFESTYLE, WORKPLACE AND ENVIRONMENTAL EXPOSURES WITH NASOPHARYNGEAL CARCINOMA IN TWO PUBLIC HOSPITALS IN MALAYSIA

VAIDEHI ULAGANATHAN

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By

VAIDEHI A/P ULAGANATHAN

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Chairman : Professor Dato' Lye Munn Sann, MBBS, MPH, DrPH
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Malaysia is one of the Asian countries with a high incidence of nasopharyngeal carcinoma (NPC) with age-specific incidence rate (ASIR) of 7.2 per 100,000 population. Nutritional factors as well as workplace and environmental exposures have been implicated as risk factors of NPC. This case-control study was conducted to determine the association between circulating nutritional markers, diet, lifestyle factors, workplace and environmental exposure with risk and survival of NPC in the search for markers to predict risk and prognosticate survival for this disease. A total of 300 histologically confirmed NPC cases and 300 matched (age, gender, ethnicity) cancer-free controls from two local hospitals were recruited from 2012 to 2016. An interviewer-administrated questionnaire was used to capture information on socio-demographic background, dietary intake, physical activity, smoking, alcohol consumption and workplace and environmental exposures. Anthropometry measurements were taken directly after interview. The fasting blood sample was collected by a trained and qualified paramedic from respective hospitals and analyzed using relevant analysis in the laboratory. Clinical characteristics were obtained from patients' medical records. The overall survival of NPC was 63.7% with 79.3% complete remission. Vigorous physical activity (AOR = 1.58, 95% CI = 1.09, 2.31), ex-smoking habit (AOR (quitted ≤ 2 years) = 4.69, 95% CI = 1.63, 13.5) and alcohol consumption (AOR (once a week) = 3.10, 95% CI =1.22, 7.91) significantly increased the risk of NPC. A medium consumption of high-protein dietary pattern was protective against NPC risk (AOR (Q2 vs Q1) = 0.44, 95% CI = 0.25, 0.76), while a high consumption of high-salted and processed food dietary pattern increased the risk of NPC (AOR (Q4 vs. Q1) = 9.75, 95% CI = 4.66, 20.38). Consumption of high vegetables and fruits dietary pattern showed no association with risk of NPC. Workplace exposures to leather, cloth, textiles or carpet (AOR (≥

5 days/week) = 12.03, 95% CI = 1.39, 104.4) and dust, smoke, fumes or gases (AOR (≥ 5 days/week) = 2.50, 95% CI = 1.54, 4.07) significantly increased the risk of NPC. Environmental exposure to disinfectants or biocides significantly increased the risk of NPC (AOR = 2.84, 95% CI =1.21, 6.68). Advanced NPC stage (AOR (Stage 4C) = 5.64, 95% CI =1.13, 28.2), treatment with chemotherapy alone (AOR = 5.58, 95% CI = 2.30, 13.50) and low serum leptin level (AOR (Q1 vs. Q4) = 9.61, 95% CI = 3.36, 27.47) significantly increased risk of NPC mortality. In conclusion, the generation of risk models in this study based on these factors would not only increase understanding of NPC aetiology, but could potentially contribute to planning and implementation of clinical and public health interventions.

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

HUBUNGAN DI ANTARA PENANDA PEMAKANAN, DIET, GAYA HIDUP, PENDEDAHAN DI TEMPAT KERJA DAN PERSEKITARAN TERHADAP KARSINOMA NASOFARINKS DI DUA HOSPITAL AWAM DI MALAYSIA

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Malaysia adalah salah satu daripada negara Asia yang mempunyai kadar tertinggi karsinoma nasofarinks (NPC) dengan kadar insiden umur sebanyak 7.2 per 100 000 orang dalam populasi. Faktor pemakanan, pendedahan di tempat kerja dan persekitaran berhubungkait terhadap peningkatan faktor risiko dengan NPC. Kajian kes-kawalan telah dijalankan untuk menentukan hubungan antara petanda-petanda darah pemakanan, gaya hidup, pendedahan di tempat kerja dan persekitaran terhadap NPC. Sejumlah 300 orang pesakit NPC yang disahkan berdasarkan laporan histologi dan 300 orang pesakit kawalan yang bebas kanser dipadankan (umur, jantina, etnik) di dua buah hospital awam dari tahun 2012-2016. Borang soal selidik digunakan oleh penemuduga untuk mengumpul maklumat mengenai latar belakang sosio-demografi, pengambilan makanan, aktiviti fizikal, tabiat merokok, pengambilan minuman keras, pendedahan di tempat kerja dan persekitaran semasa sesi temu duga dengan pesakit. Ukuran antropometri diukur semasa sesi temuduga. Sampel darah pesakit yang telah berpuasa dikumpulkan oleh paramedik yang berkelayakan dan terlatih dari setiap hospital dan diuji di makmal menggunakan ujian-ujian yang berkaitan. Ciri-ciri klinikal didapati daripada rekod perubatan pesakit. Hasil kajian mendapat penglibatan dalam aktiviti fizikal yang lasak (AOR = 1.58, 95% CI = 1.09, 2.31), tabiat bekas perokok (AOR (berhenti $\leq$ 2 tahun) = 4.69, 95% CI = 1.63, 13. 5) dan pengambilan minuman keras (AOR (sekali seminggu) = 3.10, 95% CI = 1.22, 7.91) berhubungkait dengan peningkatan risiko NPC. Pengambilan corak makanan yang tinggi dengan kandungan protein pada tahap yang sederhana adalah faktor perlindung terhadap risiko NPC (AOR (Q2 vs Q1) = 0.44, 95% CI = 0.25, 0.76), manakala pengambilan corak makanan yang tinggi dengan makanan masin dan diproses pada tahap yang tinggi meningkatkan risiko NPC (AOR (Q4 vs Q1) = 9.75, 95% CI = 4.66, 20.38). Pengambilan corak makanan yang tinggi kandungan sayur dan buah-buahan tidak menunjukkan sebarang hubungan dengan risiko NPC.

Pendedahan yang kerap kepada kulit, kain, tekstil atau permaidani (AOR (≥ 5 hari / minggu) = 12.03, 95% CI = 1.39, 104.4) dan pendedahan kepada debu, asap, wasap atau gas (AOR (≥ 5 hari / minggu) = 2.50, 95% CI = 1.54, 4. 07) di tempat kerja meningkatkan risiko NPC. Pendedahan persekitaran kepada pembasmi kuman atau biosid meningkatkan risiko NPC (AOR = 2.84, 95% CI = 1.21, 6.68). NPC di peringkat akhir (AOR (peringkat 4C) = 5.64, 95% CI = 1.13, 28.2), rawatan kemoterapi (AOR = 5.58, 95% CI = 2.30, 13.50) dan serum leptin yang rendah (AOR (Q1 vs Q4) = 9.61, 95% CI = 3.36, 27.47) telah meningkatkan risiko kematian dalam kalangan pesakit NPC. Kesimpulannya, hasildapatan yang menunjukkan faktor-faktor yang menjurus kepada risiko peningkatan dan etiologi terhadap NPC dapat membantu dalam merancang intervensi klinikal dan kesihatan umum.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

BF%	Body fat percentage
BMI	Body mass index
Ca	Calcium
CI	Confidence Interval
DNA	Deoxyribonucleic acid
FBG	Fasting blood glucose
HDL-C	High density lipoprotein cholesterol
HKL	Hospital Kuala Lumpur
HPP	Hospital Pulau Pinang
IL-6	Interleukin-6
LDL-C	Low density lipoprotein cholesterol
MET	Metabolic Equivalent
Mg	Magnesium
MOSTI	Ministry of Science, Technology and Innovation
MREC	Ministry of Health Research & Ethics Committee
NCR	National Cancer Registry
NMRR	National Medical Research Registry
NPC	Nasopharyngeal carcinoma
OR	Odds ratio
OS	Overall survival
PAI-1	Plasminogen activator inhibitor-1
TC	Total cholesterol
TG	Triglycerides
TNFA	Tumour necrosis factor
VD	Vitamin D
WC	Waist circumference
WHO	World Health Organization
WHR	Waist hip ratio
CRP	C-reactive protein
EBV	Epstein-Barr Virus
RT-PCR	Reverse transcriptase-polymerase chain reaction
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography and computed tomography
ASIR	Age-specific incidence rate
MOH	Ministry of Health
HIV	Human Immunodeficiency Virus
IHME	Institute for Health Metrics and Evaluation
ASR	Age-standardized incidence rates
UICC	International Union Against Cancer
AJCC	American Joint Committee on Cancer
MAKNA	National Cancer Council Malaysia
IMRT	Intensity-modulated radiotherapy
NCCN	National Comprehensive Cancer Network
CCRT	Concurrent chemo-radiotherapy
SMART	Simultaneous Modulated Accelerated Radiation Therapy

UKMMC	University Kebangsaan Malaysia Medical Centre
HR	Hazard ratio
USM	UniversitiSains Malaysia
TSCC	Tongue squamous cell carcinoma
SCC	Squamous cell carcinoma
MMP-9	Matrix-metalloproteinases-9
LMP-1	Latent membrane protein-1
HNSCC	Head and neck squamous cell carcinoma
NO	Nitric oxide
ROS	Reactive oxygen species
CACS	Cancer anorexia-cachexia syndrome
ESCC	Esophageal squamous cell carcinoma
GLUT1	Glucose transporter proteins 1
ME1	Malic enzyme 1
NADPH	Nicotinamide adenine dinucleotide phosphate
G6PD	Glucose-6-phosphate dehydrogenase
ATP	Adenosine triphosphate
25(OH)D	Serum 25-hydroxyvitamin D
PTH	Parathyroid hormone
NMHS	Nashville Men's Health Study
INHANCE	International Head and Neck Cancer Epidemiology
PA	Physical activity
EMT	Epithelial-mesenchymal transition
ASCO	American Society of Clinical

CHAPTER 1

INTRODUCTION

1.1 Background

One of the most challenging public health problems of the 21st century is cancer. The word "cancer" was coined by the father of medicine, Hippocrates, an ancient Greek physician. Hippocrates used the Greek words, *carcinos* and *carcinoma* to describe tumours, thus calling cancer "*karkinos*" (Fayed, 2009). Cancer is a term used for disease in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems (National Cancer Institute, 2010). When cells become old or damaged, they die and are replaced with new cells but sometimes this orderly process goes wrong. The genetic material (DNA) of a cell can become damaged or changed, thus resulting in mutations that affect normal cell growth and division. When this happens, cells do not die when they should and new cells form when the body does not need them. The extra cells may form a mass of tissue called a tumour (National Cancer Institute, 2015).

In the year 2012, nearly 32.6 million people were living with cancer and according to GLOBOCAN there were 14.1 million new cancer cases reported. This number of new cancer cases is estimated to accelerate up to 24 million in the next two decades. A higher cancer incidence was noticed among men (with 7.4 million) compared to women (with 6.6 million). More than 8.2 million cancer deaths were reported especially in the less developed countries. This situation might escalate because of limited accessibility to health care in low and middle-income countries which has insufficient prevention, diagnoses and treatments for cancer. On the other hand, adoption of lifestyles that are known to increase cancer risk, such as smoking, poor diet, and physical inactivity, fewer pregnancies and increased aged population are also linked with the increased incidence and death due to cancer (GLOBOCAN, 2012).

In Malaysia, cancer was the 4th leading cause of death accounting from 10.4% in 2008 to 13.62% in 2014 of total deaths after diseases of the circulatory system, diseases of the respiratory system and certain infectious and parasitic diseases. Nevertheless, the incidence of cancer was also found to have increased two-fold from 9.34% cases to 18.21% within four years (2010 – 2014) (Ministry of Health Malaysia, 2014). This transition, almost similar as reported in economically developed countries which urged Malaysia to take immediate action in order to prevent and control cancer threat. The five most common cancers among the population of Malaysia in 2012 were breast, colorectal, lung, cervix uteri and prostate cancer (GLOBOCAN, 2012).

According to National Cancer Registry (2007), nasopharyngeal carcinoma (NPC) is considered a very rare cancer worldwide but it is the fourth most common cancer and the incidence among Chinese males in Malaysia was among the highest in the world (ASR = 10.9) (Zainal, Arifin, Salehah, 2007). In East Malaysia, NPC is the most common cancer in Sarawak males and third most common cancer in Sabah male population (Khoo and Phua, 2013). NPC is a tumour originating in the nasopharynx, the uppermost region of the pharynx ("throat"), behind the nose where the nasal passages and auditory tubes join the remainder of the upper respiratory tract. NPC is a distinct disease process from squamous carcinoma that affects other sites of the pharyngeal mucosal space. It is a locally aggressive neoplasm that has a high incidence of neck nodal disease (Yu et al, 2010). The lesion is often situated in a relatively large and inert space where only air and mucus are in transit. NPC can be dormant for a long time causing few primary symptoms such as neck swelling or nasal blockages (Kataki et al, 2011).

NPC is associated with many etiological factors, including Epstein-Barr virus (EBV) infection (Suliman 2015; Chai et al, 2012; Klein, Klein, & Kashuba, 2010), genetic factors (Hildesheim & Wang, 2012) environmental exposure (Jia et al, 2012; Ekburanawat et al, 2010), occupational exposure (Viegas et al, 2010), dietary factors (Turkoz et al, 2011; Sharma et al, 2011; Ekburanawat et al., 2010; Jia et al, 2010;) and other lifestyle factors (Sharma et al, 2011; Turkoz et al, 2011). Recently, some circulating micronutrient (McCullough et al, 2010) and inflammatory markers (Chang et al, 2011) also have been linked with the prognosis of NPC.

Genetic factors were known to be important in determining the propensity of cancer development, however there is strong evidence that cancer incidence is mainly due to the environment, lifestyle and the food that we eat (Roberts, 2011). Lifestyle and behavioral changes, such as sedentary lifestyle, lack of physical exercise, smoking and tobacco use and alcohol consumption have contributed to a dramatic increase in the occurrence of various type of cancers (Cao et al, 2010). As the prevalence of modifiable cancer risk factors increases in developed and developing countries, the global prevalence of cancer may be expected to increase markedly (Ekburanawat et al, 2010) with a subsequent increase in NPC especially in NPC-endemic area.

Foods are consumed in various characteristic combinations that deliver a variety of nutrients, which can have either synergistic or interactive metabolic action. For this reason, it is often difficult to separate out the specific effects of nutrients or foods. In nutritional epidemiology, dietary patterns were suggested as a more appropriate approach in assessing the risk of developing various types of cancers when certain food groups are consumed rather than analysing the benefits or harms of specific food items or micronutrients (Halpin et al, 2010). As dietary pattern looks beyond the single nutrient or food and attempts to capture the broader picture of diet, it can be more easily interpreted or translated into dietary recommendations for the public (Jacobs & Orlich, 2014).

An increased risk of NPC in relation to workplace exposure such as formaldehyde and wood dust have been reported in some population-based studies although the evidence is inconsistent (Bachand, Mundt, Mundt, & Montgomery, 2010; Zhang, Xu, Shen & Zhu, 2014). NPC mortality was found doubled among workers in wood related industries and printing occupations (Zhang et al, 2014). To the best of our knowledge, no recent study has been conducted to investigate the risk of NPC in relation to various workplace exposures in Malaysia. Therefore, it is very important to investigate the relationship and interaction between workplace, environmental exposure and nutritional factors in improving NPC treatment and to reduce its incidence in Malaysia.

Chronic inflammation is thought to promote carcinogenesis and may predispose an individual to cancer. Inflammatory markers such as adiponectin, leptin, interleukin-6 (IL-6), tumour necrosis factor alpha (TNFA), plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein (CRP) were initially identified as a serum factor inducing necrosis of transplanted tumorus in mice through inflammatory mechanism (Carswell et al. 1975). It has been proven that some of these inflammatory markers play an essential role in host defense against infectious diseases, whereas their uncontrolled, excessive production may cause organ dysfunction (Raychaudhuri et al, 2009). Adiponectin acts as pro-inflammatory agent which exhibits insulin-sensitizing, pro-apoptotic, anti-atherogenic, anti-inflammatory, and anti-proliferative properties in tumour cells. Leptin plays a major role in the chronic pro-inflammatory state that is seen in atherosclerosis and certain cancers such as colorectal cancer. In humans, leptin is an independent risk factor for neoplasms, and the levels are correlated with C-reactive protein, plasma triglycerides, and fasting plasma glucose levels (Paz-Filho et al, 2012).

Recent findings suggest that blockade of IL-6 signalling and reduced production of circulating IL-6 are effective in treating experimental models of autoimmune and inflammation-associated cancer (Neurath & Finotto, 2011). There is also evidence suggesting that blood level of TNFA is increased in solid tumours (Brown et al, 2008) and some reports have suggested that it might act as an endogenous tumour promoter *in vivo* (Balkwill, 2009). Meanwhile, PAI-1 is also found involved in angiogenesis, thus it may contribute to inflammation-driven tumour cell growth, invasion, and metastasis (Hursting and Dunlap, 2012). CRP was proposed as an important marker in chronic inflammation which might have an aetiological role in cancer (Shrotriya, Walsh, Bennani-Baiti, Thomas & Lorton, 2015).

Studies have suggested that inflammation creates a tissue microenvironment where the reactive oxygen and nitrogen species released by inflammatory cells could cause potentially malignant DNA alterations (Paz-Filho et al, 2012), and that some inflammatory cytokines such as IL-6 and TNFA and proteins in chronic inflammation promote tumour growth (Neurath & Finotto, 2011). Therefore, it seems likely that the regulation of these inflammatory markers may be involved in cancer pathogenesis and progression especially in an inflammation-associated cancer such as NPC.

Micronutrients block initiation and suppress promotion and progression of cancer. Deficiency in micronutrients causes chromosomes to break and contribute to increased risk of cancer (Prado et al, 2010). Vitamin D (25-dihydroxyvitamin D), has been the interest of studies since 1980s as an anti-proliferation and pro-differentiation agent. Recent findings indicate that vitamin D is a pro-apoptotic agent and an inhibitor of cell migration and angiogenesis, supporting its potential role in cancer prevention and cure. Even more recently it was also implicated in the control of programmed cell death (McCullough et al, 2010). Vitamin D has been shown to up-regulate TNFA through the inflammation mechanism. Vitamin D has growth-suppressing and anticancer properties where it induces apoptosis in cancer cells by modulating TNFA (Mullin & Dobs, 2007). A meta-analysis reported that a number of epidemiologic studies have shown the suppressing effects of vitamin D on cancer risk (Bischoff-Ferrari, 2014). Some studies have provided strong evidence for the protective effects of vitamin D against colorectal cancer (Lee et al, 2011) and breast cancer (Kim and Jee, 2014). Recently, animal and human studies indicated that high calcium intake might decrease levels of parathyroid hormone and 1,25(OH) vitamin D. Both parathyroid hormone and 1,25(OH) vitamin D inhibit lipogenesis and stimulate lipolysis. This subsequently reduces the vitamin's cancer protective effect unless extra amounts of Vitamin D are supplemented (Chen et al, 2010).

Magnesium deficiency seems to be carcinogenic, and in case of solid tumours, a high level of supplemented magnesium inhibits carcinogenesis. Studies have found that less Mg^{2+} binding to membrane phospholipids of cancer cells, than to normal cell membranes and frequently complicates therapy with some anti-cancer drugs (Castiglioni & Maier, 2011). To date low magnesium level has been associated with colon (Chen, Pang, & Liu, 2012), breast (Park, Parker, Boardman, Morris & Smith, 2011) and lung cancer (Li, Kaaks, Linseisen & Rohrmann, 2011). High magnesium and calcium levels have been linked to reduced risks of colon cancer, but studies have also shown that high calcium levels inhibit the absorption of magnesium (Daniells, 2008). Changes in intracellular zinc have been observed in a number of different cancers and often accompanied by parallel alterations in the expression of different zinc transporter especially in breast cancer (Taylor, Gee & Kille, 2011) and colon cancer (Tayyem et al, 2015). Meanwhile, folate serves as a methyl donor for DNA methylation, an epigenetic modification known to be dysregulated in carcinogenesis, and its genetic-association with NPC risk has been found to be convincing (Cao et al, 2010).

As important as inflammation markers and circulating micronutrients, post-diagnosis anthropometry measurements such as body mass index (BMI) was reported descriptively in several studies among NPC patients and further treated as one of potential confounders. Research on the association of BMI solely on NPC is scarce (Liu et al, 2012). Equivalently, researches on factors such as waist circumference (WC), waist-hip ratio (WHR) and body fat percentage (BF %) in association with NPC risk were few.

Recent studies have shown that higher level of BMI, WC, WHR or BF% predisposes to an inflammatory condition and that fat behaves as an immune endocrine tissue. It has been shown that adipokine produced from fat tissue has autocrine, paracrine and endocrine effects. Adipose tissue acts as an endocrine organ secreting inflammatory mediators such as TNFA, IL-6 which enhance inflammation signalling which leads to DNA damage and enhance cellular proliferation (Renehan, Zwahlen & Egger, 2015). Invariably, adiposity and inflammation have been found to play key roles in the aetiology of other cancers; therefore, it is important to measure their effect on NPC risk and prognosis too. Nonetheless, recent studies have suggested that BMI influenced prognosis in patients with advanced stage of NPC, who were treated with chemotherapy (Huang et al, 2013). Therefore, WC, WHR and BF% also might have their own prognostic value and also influence the survival of NPC patients.

1.2 Problem Statement

Cancer is a multifactorial disease resulting from complex interaction between genetics, environments, dietary and lifestyle. Several systemic biomarkers have been identified as an indicator for cancer initiation. Each of these factors may have modest risk on NPC which showed an increased risk less than twofold in multivariable analysis (OR < 2) (Wang et al, 2016). Evidence for a causal role of various workplace exposure, diet and lifestyle behaviours is inconsistent especially in NPC endemic areas (Jia & Qin, 2012). Inflammatory markers are statistically linked with impairment of protective effect of certain micronutrients, which contribute a modest risk of NPC (Hsu et al, 2012). However it is still unknown whether these inflammatory markers are related to low status of circulating micronutrients and affect the prognosis of NPC.

Previous studies have demonstrated that some products from the latent and lytic cycles of EBV infection could be detected in NPC and that these products could induce production of inflammatory markers (Takada, 2012), making the roles of circulating inflammatory markers in patients with NPC an urgent issue to be investigated. Nonetheless, only a few studies have reported on the levels of single or several inflammatory markers as blood markers for NPC (Chang et al, 2011). Additionally, a previous study has reported on the expression of inflammatory markers by reverse transcriptase-polymerase chain reaction (RT-PCR) and has shown that expression of some of these genes was elevated in NPC tumour tissues. However, to the best of our knowledge; no previous study has analyzed the circulating inflammatory markers for NPC detection or prediction of survival.

While previous studies have mostly focused on food items that are related to NPC risk, studying micronutrients could offer advantages mainly through providing better understanding of underlying mechanisms of disease (Ali, 2014). According to Jessri et al (2011), the aetiology of a particular cancer is closely related to the type of nutrient intake, thus the focus of research should be such. Furthermore, animal studies found that marginal-to-moderate micronutrient deficiency can be

compensated or exacerbated by other factors influencing inflammatory and oxidative stress; therefore, it is hypothesised that similar mechanisms in humans could significantly contribute to the occurrence of chronic inflammation and further lead to cancers (Ali, 2014). However, the impact of a wide range of macro- and micronutrient residual (energy adjustment) intake and their levels in blood in the aetiology of NPC has not been examined in our high-risk population.

There are unresolved gaps in understanding of NPC involving modifiable and non-modifiable risk factors. However, there is a clear need for a population based epidemiologic studies to elucidate how modifiable risk factors such as environmental, lifestyle and nutritional risk factors interact to influence the development of NPC, prognosis and survival (Jia et al, 2012). Nevertheless, for a complex disease like cancer, especially NPC which is geographical and genetic specific, studying the association of single factors provides limited information compared to multiple factor approaches in predicting risk (Lakhanpal et al, 2015)

Biopsy of the nasopharyngeal mass caused discomfort to the NPC patients, while the cost of more accurate imaging modalities such as MRI or PET/CT scan are excessively high and this often results in delay of diagnosis and treatment of NPC. Therefore, using a non-invasive and cost-effective method such as biomarkers to diagnose NPC might be more accurate and might be able to predict the clinical outcome which would have a major impact on clinical practices (Andersson et al, 2014). It is expected that death due to NPC will have reduced if there is development of the ability to identify aberrant changes in the normal anatomy, histology, metabolomics, physiology and fundamental biochemistry of the nasopharynx (Takada, 2012). This goal can only be attained by the development and characterization of a cluster of biomarkers as an additional strategy aimed at early detection, thereby ultimately leading to early diagnosis of NPC without obvious clinical signs or metastasis, and permissive of promising cure.

Most of the previous epidemiological studies were conducted to identify viral or genetic risk factors which confer a higher risk of NPC. To systemically evaluate non-viral and non-genetic risk factors in the development of NPC in a high-risk population, a hospital-based matched case-control study was conducted to address the association of diets, lifestyle factors, workplace and environmental exposures with risk and survival of NPC. Clinical characteristics, inflammatory markers, circulating micronutrients and anthropometry profile during recruitment may impact the progress of the cancer (Jia et al, 2012), but whether these profiles can influence the overall survival for this high-risk population remains unknown.

1.3 Significance of the study

There are many research findings on the effect of inflammation on cancer but the evidence that links the effect of inflammation on NPC is limited. Findings from this study will add new knowledge to the existing literature on the relationship between lifestyle factors, dietary patterns, work place and environmental exposures with risk of NPC through inflammation mechanism especially in Malaysian population. In addition, inflammatory markers, circulating micronutrients, and anthropometry measurements status may add more evidence on their associations with NPC mortality.

Data on nutritional factors are very important to predict the development and to indicate plausible biological mechanisms of NPC. If these modifiable risk factors found to be significant predictors, they can be improved with dietary intervention. Detection of nutritional imbalance can be done easily, non-invasive and predicted to be a cost-effective approach to rapidly identify individuals at a "high risk" for NPC. Therefore, discomfort by biopsy of the nasopharyngeal mass and high cost of MRI or PET/CT scan for diagnosis of NPC can be reduced.

The interaction or generation of risk model between well-established risk factors of NPC may provide an opportunity to rationalize health services in terms of better screening, treatment and management options. These services are to be delivered and coordinated to those with cluster of risk factors rather than having to separate the care into different services addressing as an individual risk factors to reduce the risk of chronic diseases. Data obtained is critical for future studies to determine whether there is a single pathophysiologic mechanism underlying this cluster of risk factors which will be useful as biomarker for NPC risk assessment, screening, prognosis and treatment. If a single mechanism can be explained then, this study may present opportunities for the development of therapeutic options with efficacy in treating multiple traits simultaneously.

In addition, the outcomes from this study may assist dietitians or Ministry of Health in developing nutrition and lifestyle intervention for high-risk groups. Other than that, they also can use this outcome to increase the awareness of nutritional risk factors and prevent the development and recurrence of NPC. Data on workplace and environmental exposures can be used as evidence to provide clear implications on risk assessment, formulation of workplace policy, and appropriate engineering of safeguards to help reduce the incidence of workplace cancers.

There is a known association between inflammation markers, micronutrients, diet, lifestyle as well as workplace and environmental exposure with other cancers but to the best of our knowledge, the relative contribution of these multiple factors simultaneously to the risk of NPC and survival of NPC cases has not been previously evaluated. Thus, the present study contributes original information to the literature

and is the largest study to date evaluating the association between those variables with the risk and survival of NPC cases. This study provides new data on the association of those variables with overall survival in NPC cases.

1.4 Research Questions

1. What are the clinical characteristics of NPC cases in terms of

    a. Presenting signs and symptoms
    b. Clinical staging
    c. Histology type
    d. Treatment received
    e. Late toxicity
    f. Response to treatment
    g. Survival

2. Is there any difference between cases and controls in terms of

    a. Socio-demographic background (age, gender, ethnicity, dialect group, educational background, occupation, household income, marital status)
    b. Inflammatory markers (adiponectin, leptin, interleukin-6 (IL-6), tumour necrosis factor alpha (TNFA), plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein (CRP))
    c. Circulating micronutrients (vitamin D, magnesium, calcium, calcium magnesium ratio, zinc and folate)
    d. Anthropometry measurements [body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR) and body fat percentage (BF %)]
    e. Lifestyle factors (physical activity, smoking status and alcohol consumption)
    f. Dietary patterns
    g. Workplace and environmental exposures (smoke, dust and other particulate materials)

3. Are (a) socio-demographic background (b) lifestyle factors, (c) dietary patterns and (d) workplace and environmental exposures associated with risk of NPC?

4. Are (a) clinical characteristics (b) inflammatory markers (c) circulating micronutrients (d) anthropometry measurements, (e) lifestyle factors (f) dietary patterns and (g) work place and environmental associated with survival of NPC?

1.5 Research Hypotheses

1. There are significant differences between cases and controls in terms of

    a. Socio-demographic background (age, gender, ethnicity, dialect group, educational background, occupation, household income, marital status)
    b. Inflammatory markers (adiponectin, leptin, interleukin-6 (IL-6), tumour necrosis factor alpha (TNFA), plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein (CRP))
    c. Circulating micronutrients (vitamin D, magnesium, calcium, calcium magnesium ratio, zinc and folate)
    d. Anthropometry measurements [body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR) and body fat percentage (BF %)]
    e. Lifestyle factors (physical activity, smoking status and alcohol consumption)
    f. Dietary patterns
    g. Workplace and environmental exposures (smoke, dust and other particulate materials)

2. Socio-demographic background, lifestyle factors, dietary patterns, workplace and environmental exposures are significantly associated with risk of NPC.

3. Presenting signs and symptoms, clinical staging, histology type, treatment received, late toxicity, response to treatments, socio-demographic background, inflammatory markers, circulating micronutrients, anthropometry measurements, lifestyle factors, dietary patterns, workplace and environmental exposures are associated with survival of NPC.

1.6 General Objective

To investigate the relationship between socio-demographic background, inflammatory markers, circulating micronutrients, anthropometry measurement, lifestyle factors, dietary patterns, workplace and environmental and risk of NPC and survival

1.6.1 Specific Objectives:

1. To describe the following clinical characteristics of NPC cases

    a) Presenting signs and symptoms
    b) Clinical staging
    c) Histology type
    d) Treatment received
    e) Late toxicity
    f) Response to treatment
    g) Survival

2. To determine and compare the following factors between case and control

    a) Socio-demographic background (age, gender, ethnicity, dialect group, educational background, occupation, household income and marital status)
    b) Inflammatory markers (adiponectin, leptin, interleukin-6 (IL-6), tumour necrosis factor alpha (TNFA), plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein (CRP))
    c) Circulating micronutrients (vitamin D, magnesium, calcium, zinc and folate]
    d) Anthropometry measurements [body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR) and body fat percentage (BF %)]
    e) Lifestyle factors (physical activities, smoking status and alcohol consumption)
    f) Dietary patterns
    g) Workplace and environmental exposures (smoke, dust and other particulate materials)

3. To determine estimates of risk of NPC associated with

    a) Lifestyle factors
    b) Dietary patterns
    c) Workplace and environmental exposures

4. To determine association between survival of NPC patients with

    a) Presenting signs and symptoms
    b) Clinical staging
    c) Histology type
    d) Treatment received
    e) Late toxicity and response to treatments
    f) Inflammatory markers
    g) Circulating micronutrients
    h) Anthropometry measurements

i) Lifestyle factors
j) Dietary patterns
k) Workplace and environmental exposures

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BIODATA OF STUDENT

The student was born on 10th June 1985 in Alor Star, Kedah. She received her education at Sekolah Kebangsaan Teluk Kechai, Kuala Kedah, Kedah and then furthered her secondary education at Sekolah Menengah Jenis Kebangsaan Keat Hwa, Alor Star. Upon completion her secondary education in 2005, she was offered to do Bachelor of Science (Biomedicine) Hons in Management and Science University which she successfully completed in 2009. She completed her Master in Science in Nutritional Science in Universiti Putra Malaysia in 2012. At present, she is pursuing her interest in the field of clinical nutritional by furthering her studies in Doctor of Philosophy. She is also life member of Nutrition Society of Malaysia since 2009 and Malaysian Vegetarian Society since 2016.

She have presented posters in several scientific conferences includes local and international. She was awarded Gold medal for abstract and poster presentation during Scientific Cancer Research Exhibition in Conjunction with World Cancer Day 2011 for her presentation entitled "Obesity as a risk factor for colorectal Cancer". She was awarded younger investigator award in Clinical Nutritional Conference in 2012.

LIST OF PUBLICATIONS

Books

Educational module for students: Creating a healthier nutrition environment in secondary schools ISBN 978-967-15219-0-8 (2017)

Educational module for teachers and parents: Creating a healthier nutrition environment in secondary schools ISBN 978-967-15219-2-2 (2017)

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Research Articles

Published

Ulaganathan, V., Kandiah, M*, Zalilah, M. S., Faizal, J. A., Fijeraid, H., Normayah, K., ... & Othman, R. (2012). Colorectal cancer and its association with the metabolic syndrome: a Malaysian multi-centric case-control study. *Asian Pacific Journal of Cancer Prevention*, *13*(8), 3873-3877. [PUBLISHED]

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Vaidehi Ulaganathan, Munn- Sann Lye*, Su- Peng Loh, Yoke- Yeow Yap, Mirnalini Kandiah, Eng- Zhuan Ban, Nurulassikin Sulong Abdul Rahman. Association of serum 25-hydroxyvitamin D with nasopharyngeal carcinoma: a multi-centric hospital based case-control study in Malaysia. *BMC Nutrition and Metabolism*

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