

CHAPTER I

INTRODUCTION



BACKGROUND AND RATIONALE

1. Geographical Distribution of Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a rare tumor in most parts of the world, with annual age-standardized incidence rates typically below 1 per 100,000 people/year in both sexes.¹ Although, it is seen in all parts of the world, there are variations in incidence among different population groups. The tumor occurs most often in Southern Chinese who reside in Guangdong Province, at an incidence rate 30-50 per 100,000 people / year. Other ethnic groups showing higher incidences are Eskimos of the Arctic region and some North and East Africa population.²⁻³ In contrast, NPC is a rare disease in North America and Europe with an age-adjusted incidence rate below 1 case per 100,000-people/year.⁴ An intermediate incidence is observed in Southeast Asia (3-10 per 100,000 people/year) such as Malay, Thai, and Vietnamese.⁵

2. Etiological Factor of Nasopharyngeal Carcinoma

Epstein - Barr virus

Epstein - Barr virus (EBV) is an important factor in the development of NPC. A link between EBV and NPC was first suggested on the basis of serological studies showing elevated antiviral antibody titers in NPC patient. Both IgG and IgA antibodies directed against the early antigen-diffuse (EA-D) and viral capsid antigen (VCA). IgG antibody titers to VCA and EA-D are significantly raised in the serum of both NPC patients and healthy controls, whereas IgA antibodies to EBV are only rarely detected in healthy controls.^{6,8} Thus, EBV-IgA antibodies have more specificity than IgG antibodies. A number

of large population-based screenings using these serological markers have been tentatively applied and proven significant for early NPC detection.⁹ Subsequently, EBV DNA has been shown to permanently infect NPC tumor cells by EBV nucleic acid hybridization studies.⁶ In addition, analysis of the terminal repeat length of EBV genome in NPC suggested that the viral DNA was clonal arising from a single viral particle. Because EBV presents in virtually all NPC including preinvasive nasopharyngeal lesions, EBV infection is an early event in NPC development. Therefore, EBV is the most important etiologic factor of NPC.¹⁰⁻¹²

Environmental Factors

Dietary habits have been advocated for many years to explain high incidence rates in some populations. Several case – control studies conducted among Southern Chinese have indicated an association between the consumption of salted fish, especially during weaning, and the risk of developing NPC.¹³⁻¹⁶ More previous studies in China and Tunisia have suggested that the consumption in early youth of salted and preserved foods other than salted fish is also associated with an increased risk of NPC.^{15,17-18} Salted fish has a high level of secondary amines. These amines are believed to interact with nitrate salts used as preservatives and lead to the formation of N-nitroso compounds, which are possibly organotrophic for the nasopharynx.¹⁹ This has been demonstrated in vivo by Yu et al. who induced malignant nasal cavity tumors in rats fed salted fish.²⁰ Interestingly, salted fish from Southern China contain a significant amount of volatile nitrosamines, as do the salted fish commonly eaten by Greenland Eskimos and the preserved foods eaten by Tunisian people, two other populations with high NPC incidence.²¹ Additionally, a case-control study in Northeast Thailand demonstrated an association between the consumption of sea-salted fish at least once a week versus never in adult life was a significant

risk factor for NPC (OR=2.5, 95% CI=1.2-5.2).²² A number of environmental factors, dictated by diet and / or lifestyle, may therefore contribute to NPC risk.

Race and Genetic Susceptibility

Racial factors would seem obvious, owing to such a specific geographical distribution of NPC. The disease is found most frequently among Chinese individuals in Southern China. Emigrant Chinese populations in several countries continue to show a higher incidence of NPC than the respective indigenous populations. For example, in the immigrant Chinese population in North America, NPC incidence is falling with time and is lower in the second generations, though still well above typical Caucasian rates.⁴ In addition, cancer incidence in East and Southeast Asian migrant to Australia has been found to a 30-fold higher risk of dying from NPC in the first 2 decades of residence, falling to nine fold after 30 years since 1975-1995.²³ Thus, Chinese people who live in other countries have changed their lifestyle; the prevalence of NPC is still higher than indigenous populations and tends to further decrease in subsequent generation. Interestingly, multiple cases of NPC occurring in first-degree relatives have documented in diverse populations, and there are a number of reports showing familial NPC in western countries.^{3, 24-25}

3. Incidence and Important of Nasopharyngeal Carcinoma in Thailand

Nasopharyngeal carcinoma is an epithelial-originated malignancy occurring with a high incidence in Chinese individuals especially in Southern China. The tumor occurs moderately often in Thai people.⁵ In addition, the incidence of NPC at King Chulalongkorn Memorial Hospital as reported by record and statistic was the tenth in the ten leading sites of cancer for both sexes in 1998.²⁶ Interestingly, there are many Chinese people who have immigrated and permanently lived in Thailand for 2 to 3 generations, resulting in

a mixed population of Thai and Chinese people. From clinical observation, we had observed at least one-third of NPC patients were Chinese in origin.

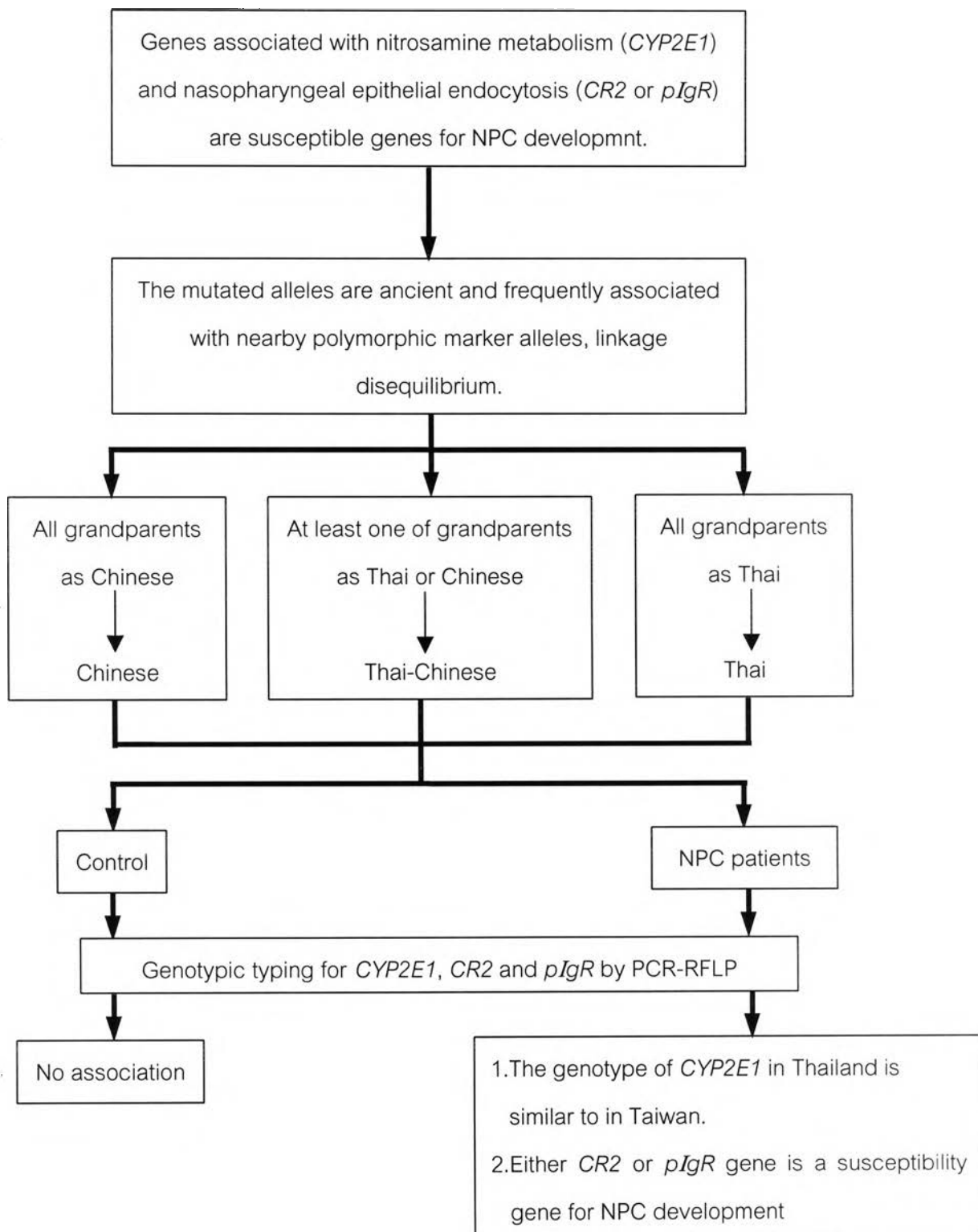
4. Conclude Hypothesis

Hereditary, environmental factors and EBV are the causes of NPC development. Study in Taiwan has proved the association between a host gene, *CYP2E1*, which interact with NPC promoter, nitrosamine, and NPC. The first aim of this thesis is to study if the genotype of *CYP2E1* in Thailand, both Thai and Chinese in origin is similar to the Taiwanese data. More importantly this study will explore whether the variation in capacity of host nasopharyngeal epithelium to be infected by EBV is the hereditary factor for NPC development. In other word, this thesis studies the association between *CR2* or *pIgR* alleles, candidate nasopharynx EBV receptors, and NPC development. Additionally, this linkage disequilibrium data will provide a clue to indicate mechanism how EBV enters the epithelium.

Objective

1. To study the association between *CYP2E1* polymorphism and NPC development in Thailand.
2. To establish PCR-RFLP techniques for *CR2* and *pIgR*.
3. To study the association between *CR2* or *pIgR* RFLP alleles and the relative risk of NPC development.

Conceptual Framework



Assumption

Both NPC patients and healthy blood donors were interviewed and separated into three groups, that is Thai, Chinese and Thai-Chinese based on their grandparents' ethnic origin. With their ancestors including the great grandparents originating from China, all subjects were considered Chinese. With their ancestors originating from Thailand, all subjects were considered Thai. Those subjects with mixed Thai / Chinese ancestors were defined as Thai-Chinese.

Limitation

Some sample populations were excluded because of lacking precise information regarding ethnicity.

Operational definition

Linkage disequilibrium is the tendency for certain alleles at two linked loci to occur together more often than expected by chance. For example, marker locus M with M^a and M^b is linked to disease locus D and it is found that the mutant allele at D occurs on the chromosome as M^b more often than expected with in a certain population.²⁷

Expected Benefit

If the susceptibility genes of NPC development are found, we can use that knowledge to study mechanism of disease and clinical application such as screening and prevention.

Research Methodology

1. Sample collection

Case: Nasopharyngeal carcinoma patients at King Chulalongkorn Memorial Hospital and National Cancer Institute of Thailand

Control: Healthy blood donors at Thai Red Cross

2. Process of study

- blood collection
- DNA extraction
- Polymerase Chain Reaction (PCR) for quantitative increasing by DNA
- Restriction Fragment Length Polymorphism (RFLP) for detecting polymorphism of studied gene
- Agarose gel electrophoresis

3. Data collection and analysis