CHAPTER I

INTRODUCTION

1. Background and Rationale

Cancer in children under 15 years old is rare, accounting for less than 1% of all malignancies diagnosed each year in developed countries (Coleman *et al.*, 1999; Draper, 1995). Childhood cancers tend to differ from those diagnosed in adults in terms of their site of occurrence, histological, appearance, and clinical behavior --- growing rapidly, being aggressively invasive, and being more responsive to chemotherapy (Miller, 1995). Leukemia are the most common cancer to effect children, accounting for between 25% and 35% of all childhood cancers (Parkin *et al.*, 1988). Leukemia, the number one disease killer of children less than 14 years of age in the world, represents around 53 % of all cancers cases among children in the age group in Thailand (table 1) and around 31% in Unites states (Zahm SH, 1995). Acute lymphoblastic leukemia (ALL) is the most frequent form of cancer affecting children, represents around 78 % of all leukemia (Smith *et al.*, 1999). The incidence of leukemia is lower in children than adult, with approximately 3250 children and adolescents younger than 20 years of age diagnosed each year in the US, of which 2400 are acute lymphoblastic leukemia (ALL).

Table 1 Age-standardized incidence of childhood cancer (per million) Thailand and comparison registries (Smith M *et al*, 1999; Greaves M, 1999).

Country, year	Leukemia	All sites
Thailand, 1988-1994	27.9	70.7
Thailand, 1995-1997	36.9	93.0
Thailand, ThaiPOG 2003	42.6	79.7
USA, SEER (White 1975-1995)	37	149
China (Tianjin), 1981-1992	40.3	105
Japan, 1980-1992	38.5	116.3
Philippines, (Manila &Rizal) 1983-1992	48.1	100.8
Singapore, (Chinese) 1983-1991	51.0	129.2

Leukemia is a heterogeneous disease, characterized by the dysregulated proliferation of blood precursor cells of myeloid or lymphoid origin (Woo MH *et al*). It can be classified as acute (low level of differentiation) or chronic (high level of differentiation) and can be further classified by cytogenetic subtype. For example, t(12;21) which generates the TEL-AML1 fusion gene occurs in 25% of patients with common ALL (cALL). Translocation t(1;19) and high hyperdiplody (>50 chromosome) are also common in childhood ALL (Greaves M, 1999). The major cell-type categories (acute lymphoblastic leukemia [ALL], chronic lymphoblastic leukemia [CLL], acute myeloid leukemia [AML], acute monocytic leukemia [CML], and chronic myeloid leukemia [CML] were distinguished in eighth revision of the International Classification of Diseases (ICD) (WHO, 2002).

Acute lymphoblastic leukemia (ALL), the malignant transformation of a B-lineage or T-lineage lymphocytic precursor, is the most common diagnosis in pediatric oncology (Greaves MF, 1986). The cause of ALL remain unclear. It is thought to represent the culmination of evolution of an abnormal clone through successive genetic changes. ALL may be considered a complex disease in which the individual's risk of cancer represents a cumulative effect of a series of low-penetrance genes combined with the external factors. A variety of environmental factors were identified to be

associated with the risk of ALL (Jang-Ming Lee *et al.*, 2001). Cigarette smoke exposure is known to have a carcinogenic effect on various organs, and maternal smoking during pregnancy is known to have deleterious outcomes for both the mother and fetus, such as, increasing the risk of obstetric complications, intrauterine growth retardation, and other adverse health impacts (Pirkle, 1988). The main hazard of smoking cigarettes is that it has been linked to major diseases, such as cancer (Pryor, 1987). The connection between smoking and these diseases is oxidative stress (OS), a condition in which macromolecules, such as lipids, proteins, and DNA are damaged by the reactive oxygen species (ROS). Therefore, exposure to cigarette smoke may increase the risk of DNA damage, which could become permanent mutations leading to cancer (Pryor, 1993).

DNA repair process monitors and repairs these DNA alterations using the complex mechanisms. The repair systems include base excision repair (BER), nucleotide excision repair (NER), mismatch repair, and double strand break repair depending on the type of the damaged DNA (Mohrenweiser, Jones IM., 1998). The BER process replaces a single damaged nucleotide with a normal residue. X-ray repair cross-complementing group1 (*XRCC1*) forms protein complexes with DNA ligase III and DNA polymerase beta to repair gaps left during BER process (Wilson SH., 1998; Sancar A., 1994; Lindahl T. et al., 1997). The *XRCC1* is a critical enzyme for this repair pathway and being alive. Mice lacking the *XRCC1* activity show a fatal phenotype (Wilson DM, Thompson LH., 1997). The NER pathway primarily removes bulky DNA lesions from UV radiation or adducts produced by chemical carcinogens (Sancar A., 1994; Lindahl T. et al., 1997). This process also involves a large number of proteins. Defects in the NER pathway are known to be associated with three diseases, including xeroderma pigmentosum (XP), Cockayne's syndrome, and trichothiodystrophy (Sancar, 1994; Benhamou S, 2000).

Additionally, the relationship between genetic polymorphisms and cigarette smoke exposure has not been demonstrated for ALL. We will examine that interaction between genetic polymorphisms of *XRCC1* gene and cigarette smoke exposure as risk for acute lymphoblastic leukemia in Thai children.

2. Research questions

Primary Question

- Is there a relationship between genetic polymorphisms of *XRCC1* gene and Thai children with ALL?

- Is there a relationship between cigarette smoke exposure and Thai Children with ALL ?

- What is the frequency of *XRCC1* gene polymorphisms in Thai children with ALL?

Secondary Questions

- Do the interaction between genetic polymorphisms of *XRCC1* gene and cigarette smoke exposure increases risk for acute lymphoblastic leukemia in Thai children ?

3. Objectives

The aim of this study is

1. To examine the relationship between genetic polymorphisms of *XRCC1* gene and Thai children with ALL.
2. To examine the relationship between cigarette smoke exposure and Thai children with ALL.
3. To characterize of *XRCC1* gene polymorphisms in Thai poppulation.
4. To examine the interaction between genetic polymorphisms of *XRCC1* gene and cigarette smoke exposure and the risk for acute lymphoblastic leukemia in Thai children.

4. Hypothesis

The risk of ALL in Thai children is associated with polymorphisms of *XRCC1* gene and cigarette smoke exposure.

5. Keywords

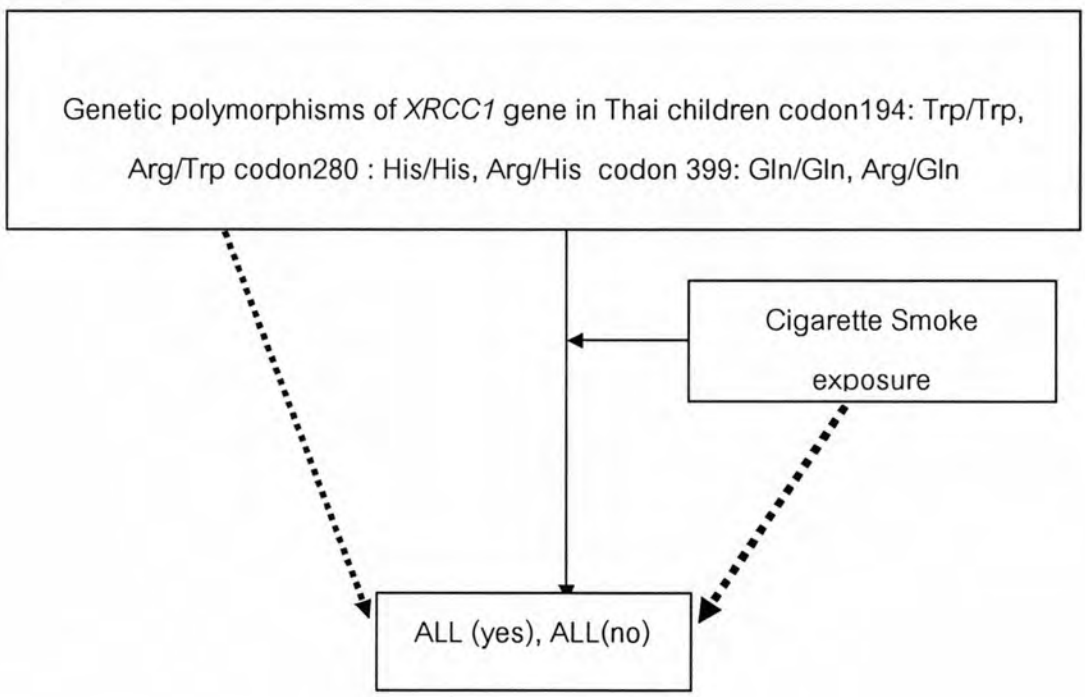
Acute lymphoblastic leukemia

DNA repair

Genetic polymorphisms

XRCC1

6. Conceptual Framework



7. Expected benefit and application

1. Know interaction between genetic polymorphisms of *XRCC1* gene and cigarette smoke exposure as risk for acute lymphoblastic leukemia in Thai children will be useful for genetic diagnosis between pregnancy and advise mother to avoid cigarette smoke exposure.

2. Data base of genetic polymorphisms of *XRCC1* gene in Thai children.