CHAPTER V

CONCLUSION AND DISCUSSION

Hereditary genetic defects lead to a markedly increased risk for cancer. The various agents that cause DNA damage include certain wavelengths of radiation such as gamma rays, X-rays, UV rays, highly reactive oxygen radicals produced during normal cellular respiration as well as by other biochemical pathways, environmental carcinogens and certain chemotherapeutic agents. DNA repair systems act to maintain genomic integrity in the face of environmental insults, cumulative effects of age, and general DNA replication errors. While deficiencies in DNA repair result from mutations in genes leading to loss of DNA repair protein, genetic polymorphisms may lead to alteration in the structure of DNA repair enzyme and thus modulate cancer susceptibility (Lunn R.M., *et al.*, 1999). Xeroderma pigmentosum, a disease involving defects in the nucleotide excision pathway of DNA repair, was one of the earliest documented examples of genetic predisposition to cancer (Cleaver J.E., 1995). Defects in the DNA mismatch repair process have been identified as a causative factor for familial colon cancer (Kolodner R.D., 1995).

Studies have shown DNA repair associated genes and those involved in maintaining genomic integrity to be crucial factors required in preventing mutations that lead to cancer and/or inherited disease (Radman M., *et al.*, 1995; Bohr V.A., 1995). Inter individual variation in DNA repair capacity has been observed using various lymphocyte assays. In these studies, a reduced DNA repair capacity was seen to constitute a statistically significant risk factor for cancer (OR from 1.6 to 10.0 in various studies) including lung and breast cancer (Spitz M.R., *et al.*, 1997; Helzlsouer K.J., *et al.*, 1996; Knight R.D., *et al.*, 1993; Wei Q., *et al.*, 1996; Scott D., *et al.*, 1994). Another observation has been that the phenotype of reduced repair capacity of one pathway appears to be independent of the phenotype for another pathway. Mutations and polymorphisms have been identified in many genes coding for DNA repair enzymes, e.g. *XRCC1, XRCC3, XRCC5, XPD*, etc. (Price E.A., *et al.*, 1997; Dunphy E.J., *et al.*, 1992).

Studies in mice have shown that absence of *XRCC1* activity to be embryo-lethal, it is assumed that the three human *XRCC1* variants do not cause a complete loss of protein function. The Arg194Trp and Arg28OHis amino acid substitution reside in the linker region separating the DNA polymerase ß domain from the poly (ADP-ribose) polymerase interacting domain. The Arg399Gln change occurs in the C-terminal side of the PARP-interacting domain and within an identified BRCT domain (Dunphy E.J., *et al.*, 1992).

This study looked at the distribution of three genetic variants— codon 194 Arg/Trp on exon 6, codon 280 Arg/His on exon 9, codon 399 Arg/Gln on exon 10— of the *XRCC1* gene among childhood ALL cases and normal controls by matched case control study. Our data demonstrated that *XRCC1* polymorphisms had effect on the risk of ALL in Thai children. The *XRCC1* codon 194 is associated with a increased risk of ALL (heterozygous OR=2.00, 95% CI=1.14-3.53). The codon 280 polymorphism was not found to be significantly higher in frequency in ALL cases compared to controls, while in the case of codon 399 polymorphism, either homozygous Gln/Gln variant as well as the heterozygous Arg/Gln variant alleles showed a significantly increased (or higher) risk of developing AL L (heterozygous OR=3.17, 95% CI=1.42-7.06, homozygous OR=2.94, 95% CI=1.73-5.00).The *XRCC1* codon 399 has been shown to be a genetic risk in a variety of adult solid tumors. Yu *et al.* studied the association between *XRCC1* 194 and 399 polymorphisms, and esophageal squamous cell carcinoma (ESCC) risk in a Chinese population. They have shown that codon 399 significantly increases the risk of ESCC. In Indian children, *XRCC1* codon 399 have an increased risk of ALL, but the effect of codon 194 is not clearly apparent.

There have been several reports on the association between *XRCC1* polymorphisms and DNA damage. Have studied the DNA repair ability of three *XRCC1* polymorphisms using aflatoxin B1-DNA (AFB1-DNA) adducts and erythrocyte glycophorin A (GPA) variants as markers, and demonstrated that the *XRCC1* 399Gln allele is associated with higher levels of both AFB1-DNA and GPA NN mutations. In contrast, individuals carrying at least one XRCC1 194 Trp alleles are more likely to have non-detectable level of AFB1-DNA adducts (Lunn *et al.*). These data suggest that *XRCC1* codon 399 is associated with reduced DNA repair capacity and support the

results that that individuals with *XRCC1* codon 399 have a higher risk of several types of cancers including childhood ALL.

The cigarette smoke exposure, led to the suggestion that in utero and postnatal exposures to various biological, physical, and chemical factors may be important determinants of childhood ALL. The previous studies, they show an indication of an association between DNA damage and cigarette exposure in children (Adel *et al.*, 2007). In this study, cigarette smoke in these analyses estimated for active and passive exposure. We can not show that the cigarette smoke exposures in this study, active and passive exposure, were associated increased risk of childhood ALL in Thai population. However, these results may be affected by simultaneous exposure to other confounders, such as, health status of children that has deteriorated over time and other factors. Thus, the finding that there is an association between cigarette smoke exposure and ALL should be interpreted with caution, in particular it should not be taken as proof that the increased risk of ALL is related to the cigarette smoke alone.

To the best of our knowledge, the present match case-control study is the first report of association of the *XRCC1* polymorphisms with ALL risk in the population characterized, and determined prevalence of cigarette smoke exposure in childhood ALL in Thai population, the matched case-control study seems better than the case-control study, because of sex and age matched.

In conclusion, this study demonstrated an effect of *XRCC1* polymorphisms on the risk of childhood ALL in a Thai population. For the maternal cigarette smoke exposure factor, the cigarette smoke exposure not showed association with increased risk for this disease. In contrast, the *XRCC1* 194 and *XRCC1* 399 associated with increased risk for this disease. Thus, the study of the association between environmental carcinogens involved in DNA repair pathway and genetic polymorphism causing leukemogeneis is warranted as well as potentially in the incidence of the disease in susceptible individuals.