CHAPTER II

REVIEW AND RELATED LITERATURE

Acute lymphoblastic leukemia

Leukemia is the most common cancer in children, accounting for between 25% and 35% of all childhood cancers (Parkin *et al.,* 1988). A larger number of haematological malignancies are seen in boys compared to girls, the greatest differences being observed for lymphomas where between two-thirds and three-quarters are male (Parkin *et al.*, 1988; UK Childhood Cancer Study Investigators, 2000). Although a few cases are associated with inherited genetic syndromes, the cause of ALL remains largely unknown. Many environmental factors (e.g. exposure to pesticide, parental use of benzene and tobacco) have been investigated as potential risk factors, but none has been definitively shown to cause of acute lymphoblastic leukemia (Coustan *et al.,* 1998). Children with leukemia generally present with signs and symptoms that reflect bone marrow infiltration and extramedullary disease. Because lymphoblasts replace the bone marrow (Figure 2 and 3), patients present with signs of bone marrow failure, including anemia, thrombocytopenia, and neutropenia.

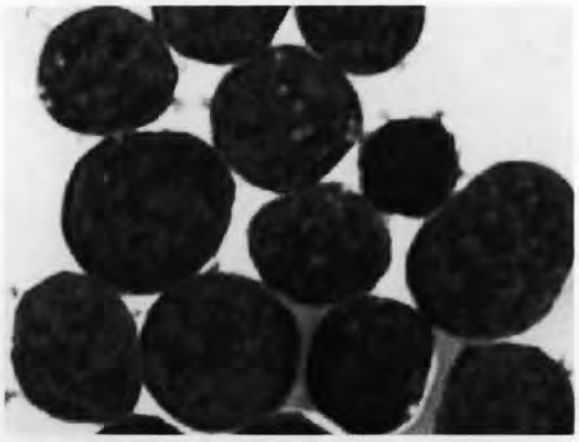

Figure 2 Bone marrow aspirated from a child with T-cell acute lymphoblastic leukemia. The marrow is replaced with lymphoblasts of various sizes. No myeloid or erythroid precursors are seen. Megakaryocytes are absent (1000X).

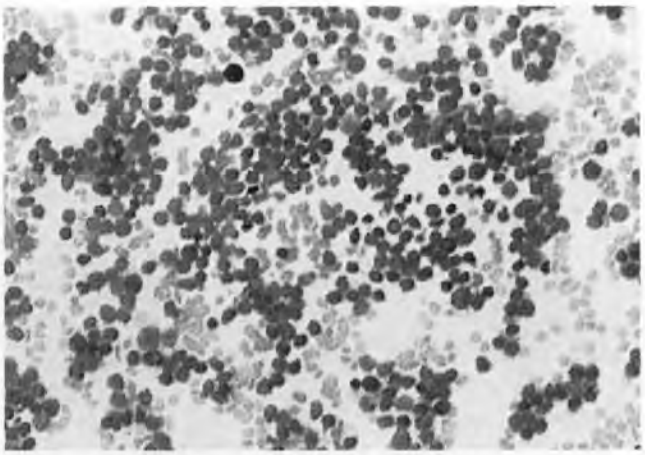

Figure 3 A bone marrow aspirate from a child with B-precursor acute lymphoblastic leukemia (100X).

Childhood leukemia in Thailand was reported in a by Thai Pediatric Oncology Group (ThaiPOG) in 2003. ThaiPOG is a collaborative network for registry new cancer cases from all clinical centers that treat childhood cancer in Thailand. The incidence of childhood cancers was determined from the cancer registrations collected from 18 pediatric cancer centers around the country. The incidence was compared with similar analyses done at cancer registries in Asia, Europe and the USA.

Between January - December 2003, 999 newly diagnosed cases of childhood cancer were registered. Of these patients, 566 (56.7%) were boys and 433 (43.3%) were girls, male: female ratio = 1.3: 1. Classification the cancer type by International Classification of Childhood Cancer (ICCC), acute leukemia is the most common malignancy in children 53% of all cases and 73.5% of acute lymphoblastic leukemia (ALL), 22.5% were acute non-lymphoblastic leukemia (ANLL) shown in Table 1. The incidence of leukemia 42.6 : 1,000,000 person-year (Figure 4), 43.7 for males and 41.5 for females (Europe and North America, where rates generally ranged from 48 to 74 for males and 32 to 46 for females), 31.8 for ALL and 9.2 for ANLL, ALL: ANLL = 3.3:1. Leukemia is the most in 0-4 years old patients shown in Figure 5 (Khuhaprema *et al.*, 2007).

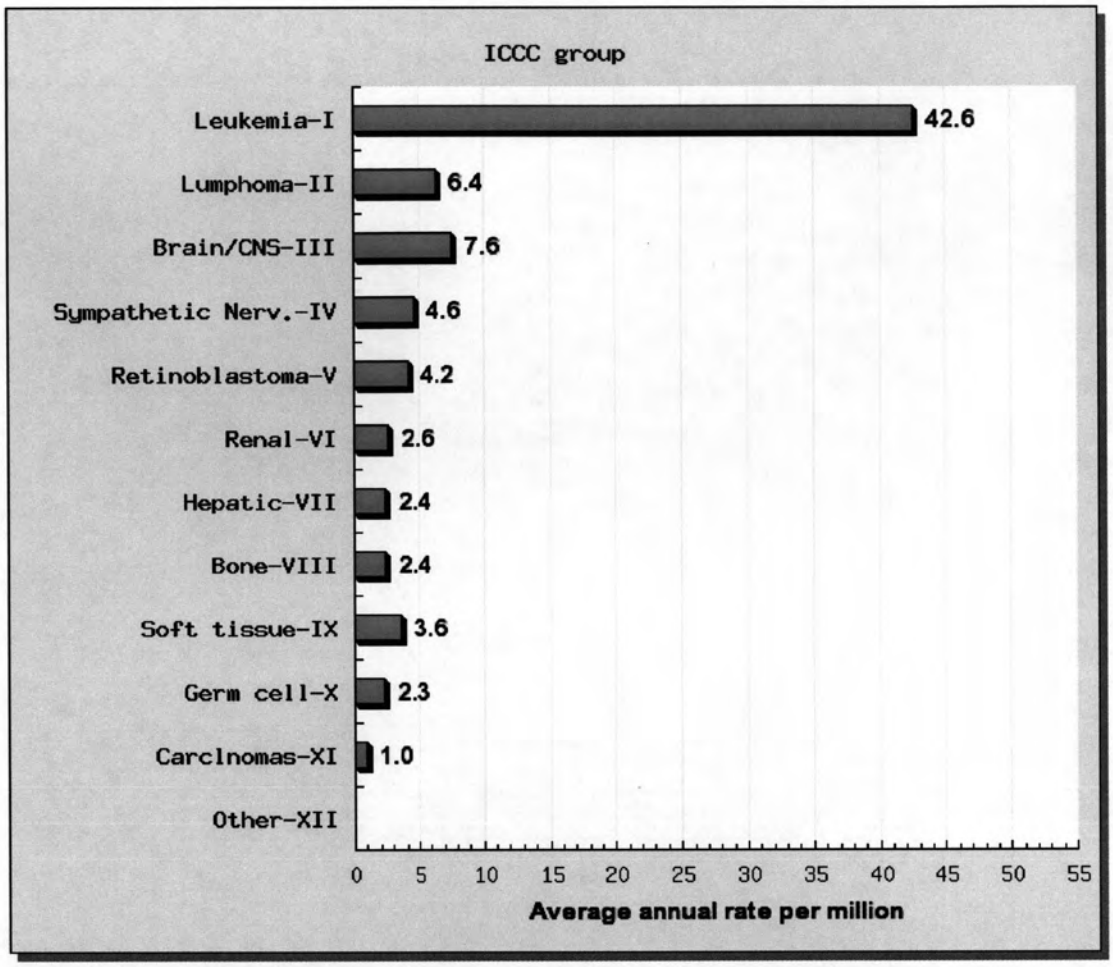

Figure 4 Age-adjusted incidence rates for childhood cancer by ICCC group, age<15, both sexes, 2003 (Khuhaprema *et al.*, 2007).

Table 1 Incidence of Cancers in Childhood, Both Sexes, THAILAND 2003 (Khuhaprema *et al.*, 2007).

	NUMBER OF CASES					RELATIVE FREQUENCY (%)			RATE PER MILLION						
	< 1	1-4	5-9	10-14	All	M/F	Overall	Group	0-4	5-9	10-14	Crude	ASR	Cum.	%MV
I. LEUKEMIAS	**38**	**207**	**148**	**136**	**59**	**1.1**	**53.0**	**100.0**	**62.8**	**31.1**	**28.6**	**39.4**	**42.6**	**612.5**	**100.0**
Acute lymphoid (ALL)	18	172	118	81	389	1.2	38.9	73.5	48.7	24.8	17.0	29.0	31.8	452.5	100.0
Acute non-lymphocytic (ANLL)	17	28	28	46	119	0.9	11.9	22.5	11.5	5.9	9.7	8.9	9.2	135.5	100.0
Chronic myeloid (CML)	2	6	2	8	18	1.3	1.8	3.4	2.0	0.4	1.7	1.3	1.4	20.5	100.0
Other specified	1	1	0	1	3	2.0	0.3	0.6	0.5	0.0	0.2	0.2	0.3	3.5	100.0
II. LYMPHOMAS	**2**	**15**	**39**	**34**	**90**	**3.1**	**9.0**	**100.0**	**4.4**	**8.2**	**7.1**	**6.7**	**6.4**	**98.5**	**94.4**
Hodgkin's disease	0	3	13	7	23	6.7	2.3	25.6	0.8	2.7	1.5	1.7	1.6	25.0	100.0
Non-Hodgkin lymphomas	1	7	16	20	44	2.4	4.4	48.9	2.0	3.4	4.2	3.3	3.1	48.0	93.2
Burkitt's lymphoma	1	4	5	1	11	1.8	1.1	12.2	1.3	1.1	0.2	0.8	0.9	13.0	100.0
Miscellaneous lymphoreticular neoplasms	0	0	1	1	2	1.0	0.2	2.2	0.0	0.2	0.2	0.1	0.1	2.0	100.0
Unspecified	0	1	4	5	10	9.0	1.0	11.1	0.3	0.8	1.1	0.7	0.7	11.0	80.0
III. BRAIN &SPINAL NEOPLASM	**5**	**22**	**45**	**30**	**102**	**1.1**	**10.2**	**100.0**	**6.9**	**9.5**	**6.3**	**7.6**	**7.6**	**113.5**	**66.7**
Ependymoma	2	0	3	0	5	-	0.5	4.9	0.5	0.6	0.0	0.4	0.4	5.5	80.0
Astrocytoma	0	5	8	12	25	1.1	2.5	24.5	1.3	1.7	2.5	1.9	1.8	27.5	84.0
Primitive neuroectodermal tumors	1	9	16	6	32	0.7	3.2	31.4	2.6	3.4	1.3	2.4	2.5	36.5	90.6
Other gliomas	2	4	14	6	26	0.9	2.6	25.5	1.5	2.9	1.3	1.9	1.9	28.5	46.2
Unspecified	0	4	4	6	14	2.5	1.4	13.7	1.0	0.8	1.3	1.0	1.0	15.5	14.3
IV. NEUROBLASTOMA	**8**	**30**	**11**	**2**	**51**	**0.9**	**5.1**	**100.0**	**9.7**	**2.3**	**0.4**	**3.8**	**4.6**	**62.0**	**94.1**
V. RETINOBLASTOMA	**9**	**33**	**0**	**0**	**42**	**2.2**	**4.2**	**100.0**	**10.8**	**0.0**	**0.0**	**3.1**	**4.2**	**54.0**	**90.5**
VI. RENAL TUMORS	**5**	**16**	**6**	**2**	**29**	**1.1**	**2.9**	**100.0**	**5.4**	**1.3**	**0.4**	**2.2**	**2.6**	**35.5**	**89.7**
Wilms' tumor	4	15	4	1	24	1.2	2.4	82.8	4.9	0.8	0.2	1.8	2.2	29.5	87.5
renal carcinoma	1	0	2	1	4	1.0	0.4	13.8	0.3	0.4	0.2	0.3	0.3	4.5	100.0
Other specified	0	1	0	0	1	-	0.1	3.4	0.3	0.0	0.0	0.1	0.1	1.5	100.0
VII. HEPATIC TUMORS	**6**	**13**	**1**	**7**	**27**	**1.1**	**2.7**	**100.0**	**4.9**	**0.2**	**1.5**	**2.0**	**2.4**	**33.0**	**74.1**
Hepatoblastoma	6	13	0	1	20	0.7	2.0	74.1	4.9	0.0	0.2	1.5	2.0	25.5	75.0
Hepatic carcinoma	0	0	1	6	7	6.0	0.7	25.9	0.0	0.2	1.3	0.5	0.4	7.5	71.4
VIII. MALIGNANT BONE TUMOR	**0**	**3**	**9**	**24**	**36**	**1.4**	**3.6**	**100.0**	**0.8**	**1.9**	**5.0**	**2.7**	**2.4**	**38.5**	**100.0**
Osteosarcoma	0	2	6	21	29	1.4	2.9	80.6	0.5	1.3	4.4	2.2	1.9	31.0	100.0
Ewing's sarcoma	0	1	3	3	7	1.3	0.7	19.4	0.3	0.6	0.6	0.5	0.5	7.5	100.0
IX. SOFT TISSUE SARCOMAS	**4**	**15**	**13**	**13**	**45**	**2.0**	**4.5**	**100.0**	**4.9**	**2.7**	**2.7**	**3.4**	**3.6**	**51.5**	**100.0**
Rhabdomyosarcoma	3	11	7	8	29	1.9	2.9	64.4	3.6	1.5	1.7	2.2	2.4	34.0	100.0
Fibrosarcoma	0	1	3	3	7	6.0	0.7	15.6	0.3	0.6	0.6	0.5	0.5	7.5	100.0

	NUMBER OF CASES					RELATIVE FREQUENCY (%)			RATE PER MILLION						
	< 1	1-4	5-9	10-14	All	M/F	Overall	Group	0-4	5-9	10-14	Crude	ASR	Cum.	%MV
Other specified	1	3	3	2	9	1.3	0.9	20.0	1.0	0.6	0.4	0.7	0.7	10.0	100.0
X. GERM CELL TUMORS	**2**	**5**	**7**	**18**	**32**	**1.5**	**3.2**	**100.0**	**1.8**	**1.5**	**3.8**	**2.4**	**2.3**	**35.5**	**90.6**
Intracranial germ cell	1	1	3	10	15	2.8	1.5	46.9	0.5	0.6	2.1	1.1	1.0	16.0	93.3
Other & non-gonadal germ cell	0	0	1	2	3	0.5	0.3	9.4	0.0	0.2	0.4	0.2	0.2	3.0	66.7
Gonadal germ cell	1	4	3	5	13	0.9	1.3	40.6	1.3	0.6	1.1	1.0	1.0	15.0	100.0
Gonadal carcinoma	0	0	0	1	1	-	0.1	3.1	0.0	0.0	0.2	0.1	0.1	1.0	0.0
XI. CARCINOMAS	**1**	**2**	**3**	**8**	**14**	**1.8**	**1.4**	**100.0**	**0.8**	**0.6**	**1.7**	**1.0**	**1.0**	**15.5**	**100.0**
Thyroid	0	0	0	3	3	-	0.3	21.4	0.0	0.0	0.6	0.2	0.2	3.0	100.0
Nasopharyngeal	0	0	1	4	5	-	0.5	35.7	0.0	0.2	0.8	0.4	0.3	5.0	100.0
Skin	0	0	1	0	1	-	0.1	7.1	0.0	0.2	0.0	0.1	0.1	1.0	100.0
adrenocortical carcinoma	1	1	0	0	2	-	0.2	14.3	0.5	0.0	0.0	0.1	0.2	2.5	100.0
Other and unspecified	0	1	1	1	3	0.5	0.3	21.4	0.3	0.2	0.2	0.2	0.2	3.5	100.0
XII. OTHER & UNSPECIFIED NEOPLASMS	**0**	**0**	**0**	**2**	**2**	**-**	**0.2**	**100.0**	**0.0**	**0.0**	**0.4**	**0.1**	**0.1**	**2.0**	**50.0**
Other unspecified	0	0	0	2	2	-	0.2	100.0	0.0	0.0	0.4	0.1	0.1	2.0	50.0
TOTAL	**80**	**361**	**282**	**276**	**999**	**1.3**	**100.0**	**100.0**	**113**	**59.3**	**58.0**	**74.5**	**79.7**	**1,151**	**94.0**

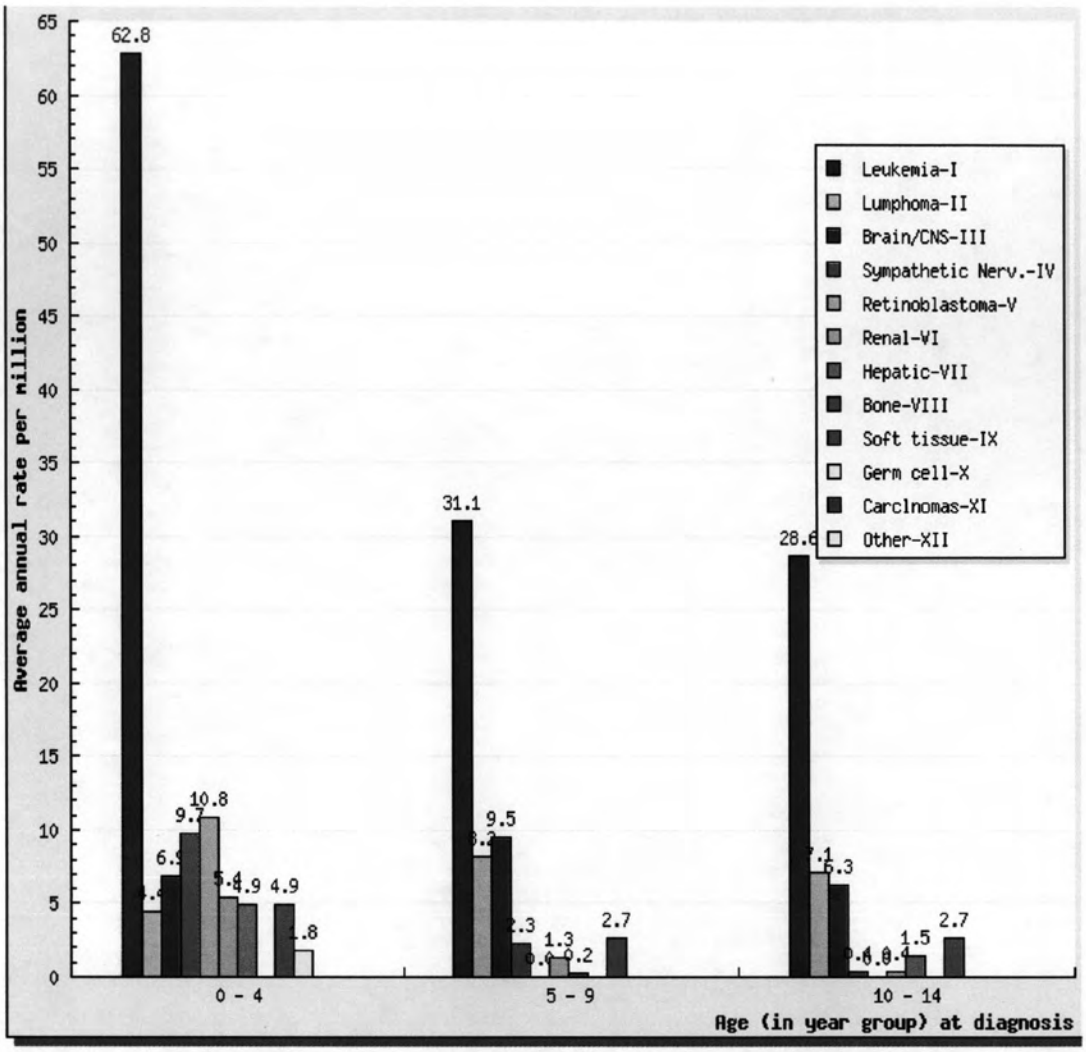

Figure 5 Age-adjusted incidence rates for childhood cancer by age & ICCC group, 2003 (Khuhaprema *et al.*, 2007).

Subtypes of ALL are frequently characterized by morphology of blast cells in bone marrow, immunophenotyping, genetic alterations, including point mutations and deletions, as well as chromosome translocations, including chimeric or fusion genes and change in chromosome number (hyperdiploidy or hypodiploidy) (Look *et al.*, 1997; Ross *et al.*, 2003). Subgroup-directed prognosis, therapy, minimal residual disease monitoring and innovative drug treatment of acute leukemia. The recent World Health Organization (WHO) classification, which is also summarized in Table 2.

Table 2 Acute Lymphoblastic Leukemia Subtypes

WHO classification of lymphoid malignancies (part 1: non-Hodgkin types)	
B cell	T cell
Precursor B cell neoplasm Precursor B lymphoblastic leukemia/lymphoma (precursor B cell acute lymphoblastic leukemia)	Precursor T cell neoplasm Precursor T lymphoblastic lymphoma/leukemia (precursor T cell acute lymphoblastic leukemia)
Mature (peripheral) B cell neoplasms B cell chronic lymphocytic leukemia/small lymphocytic lymphoma	Mature (peripheral) T cell neoplasms T cell prolymphocytic leukemia
B cell prolymphocytic leukemia	T cell granular lymphocytic leukemia
Lymphoplasmacytic lymphoma	Aggressive NK cell leukemia
Splenic marginal zone B cell lymphoma (? villous lymphocytes)	Adult T cell lymphoma/leukemia (HTLV-I+)
Hairy cell leukemia	Extranodal NK/T cell lymphoma, nasal type
Plasma cell myeloma/plasmacytoma	Enteropathy-type T cell lymphoma
Extranodal marginal zone B cell lymphoma of MALT type	Hepatosplenic T cell lymphoma
	Subcutaneous panniculitis-like T cell lymphoma
Mantle cell lymphoma	Mycosis fungoides/Sry syndrome
Follicular lymphoma	Anaplastic large cell lymphoma, primary cutaneous type
Nodal marginal zone B cell lymphoma (? monocytoid B cells)	Peripheral T cell lymphoma, not otherwise specified (NOS)
Diffuse large B cell lymphoma	Angioimmunoblastic T cell lymphoma
Burkitt's lymphoma/Burkitt cell leukemia	Anaplastic large cell lymphoma, primary systemic type

Subtypes of the leukemia classified by immunophenotyping. Approximately 80% of childhood ALL involve lymphoblasts with phenotypes that correspond to those of B-cell progenitors. These cases can be identified by their cell-surface expression of 2 or more B-lineage–associated antigens, CD10, CD19, CD20, CD22, CD34 and HLA-DR (Giordano *et al.*, 2003) (Figure 6 A). T-cell ALL is identified by the expression of T-cell–associated surface antigens CD3, CD5, CD7 and negative HLA-DR (Figure 6 B).

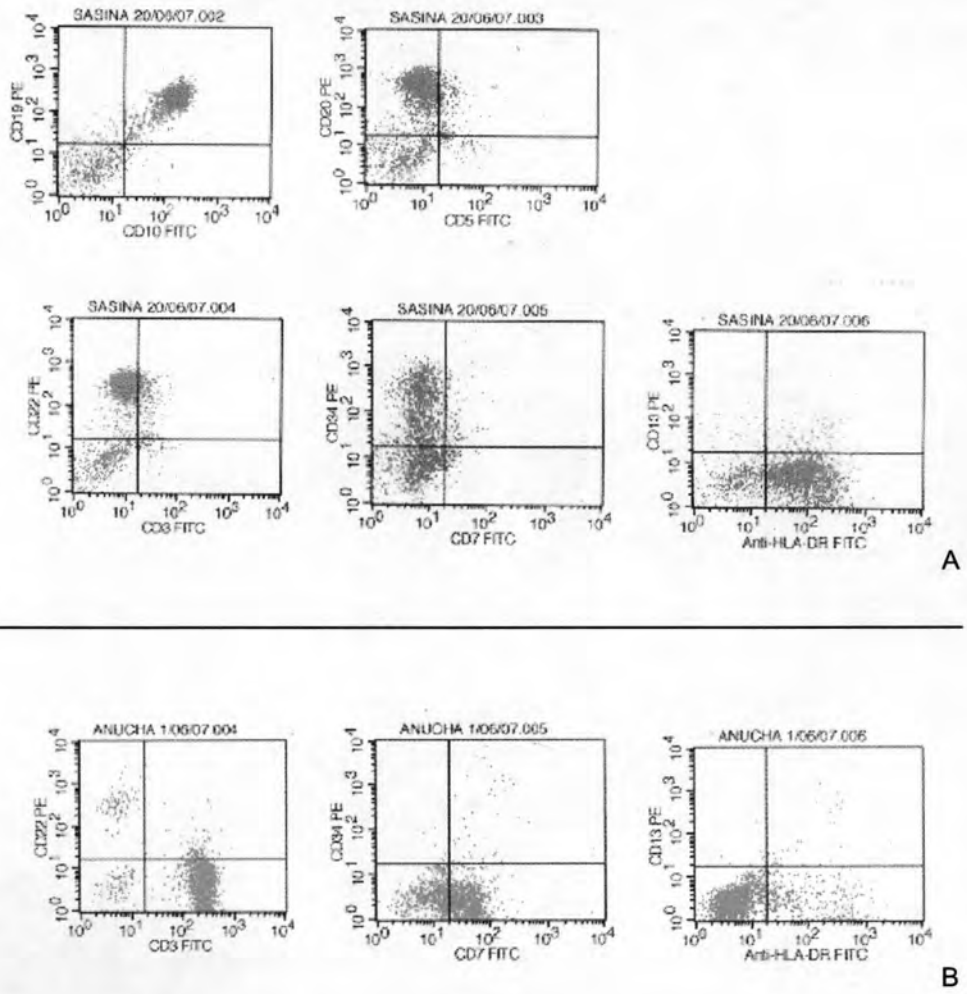

Figure 6 A representative immunophenotyping by flow cytometry of acute lymphoblastic leukemia (ALL): (A) B-cell ALL and (B) T-cell ALL.

Xenobiotic-metabolizing enzymes (Detoxification enzymes)

Xenobiotic-metabolizing enzymes also known as detoxification enzymes or drug-metabolizing enzymes are called mixed-function oxidase or monooxygenase and containing many enzymes including cytochrome P450, NAD(P)H quinone oxidoreductase and other components. The hepatic cytochrome P450s (*CYP)* are multigene family of enzymes that play a critical role in the metabolism of many drugs and xenobiotics with each cytochrome isozyme responding differently to exogenous chemicals in terms of its induction and inhibition. For example, *CYP1A1* is particularly active towards polycyclic aromatic hydrocarbons (PAHs), activating them into reactive intermediates those covalently bind to DNA, a key event in the initiation of carcinogenesis (DeAnn *et al.*,1999). The carcinogenic potency of PAHs, and other carcinogens and the extent of binding of their ultimate metabolites to DNA and proteins are correlated with the induction of cytochrome P450 isozymes (Salah A *et al.*, 2000).

Phase II drug-metabolizing enzymes such as glutathione S-transferase, aryl sulfatase and UDP-glucuronyl transferase inactivate chemical carcinogens into less toxic or inactive metabolites (Salah A *et al.*, 2000). Many drugs change the rate of activation or detoxification of carcinogens by changing the activities of phases I and II drug-metabolizing enzymes. The balance of detoxification and activation reactions depends on the chemical structure of the agents, and is subjected to many variables that are a function of this structure, or genetic background, sex, endocrine status, age, diet, and the presence of other chemicals. It is important to realize that the enzymes involved in carcinogen metabolism are also involved in the metabolism of a variety of substrates, and thus the introduction of specific xenobiotics may change the operating level and the existence of other chemicals (DeAnn *et al.*, 1999). The mechanisms of modification of drug-metabolizing enzyme activities and their role in the activation and detoxification of xenobiotics have been show in Figure 7

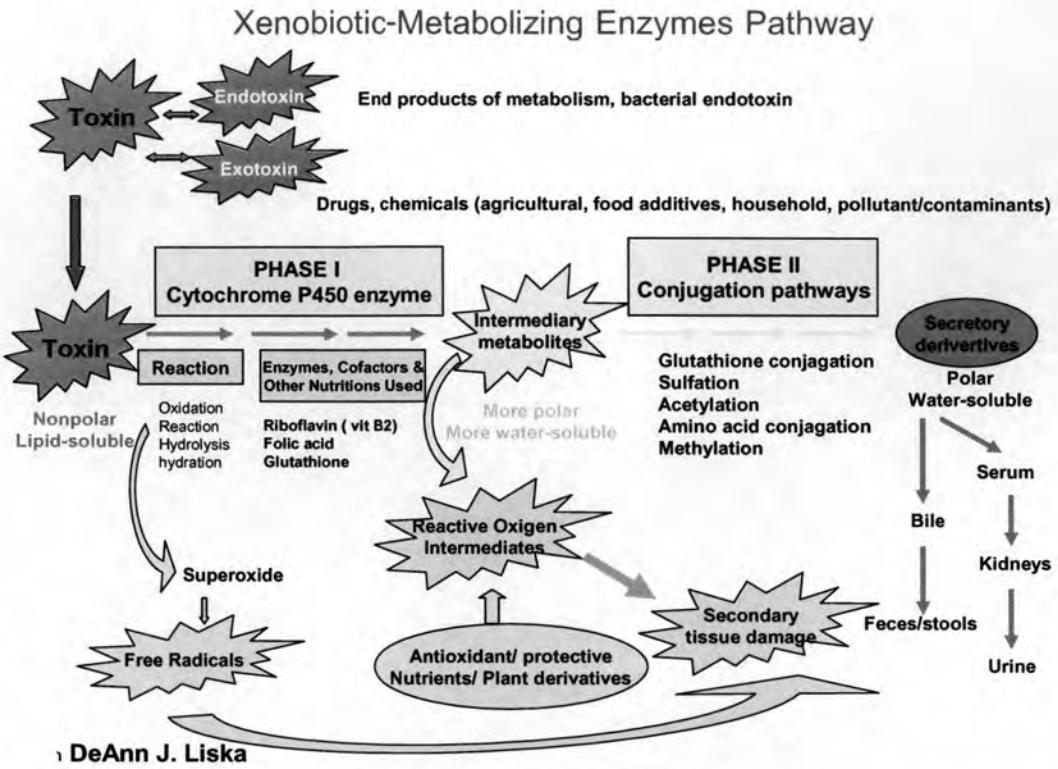

Figure 7 Xenobiotic-metabolizing enzymes pathway or detoxification pathway (modified from DeAnn *et al.*, 1999)

Cytochrome P-450 *(CYP)*

CYP1A1 gene as subfamilies of enzyme cytochrome P450 located on chromosome 15q22-q24, comprises 7 exons and 6 introns and spans 5,810 bp (Kawajiri *et al.*, 2000). *CYP1A1* is a key enzyme in phase I bioactivation of xenobiotic. It contributes to aryl hydrocarbon hydroxylase activity, catalyzing the first step in the metabolism of a number of polycyclic aromatic hydrocarbons (PAHs), such as tobacco carcinogen benzo[a]pyrene, to their ultimate DNA-binding forms (Mcmanus *et al.*, 1990). It also involved in estrogen metabolism, catalytic the hydroxylation of 17β-estratrdiol at C-2 position. In the human, *CYP1A1* is under the regulatory control of the aryl hydrocarbon receptor, a transcriptional factor that regulates gene expression (Masson *et al.*, 2005).

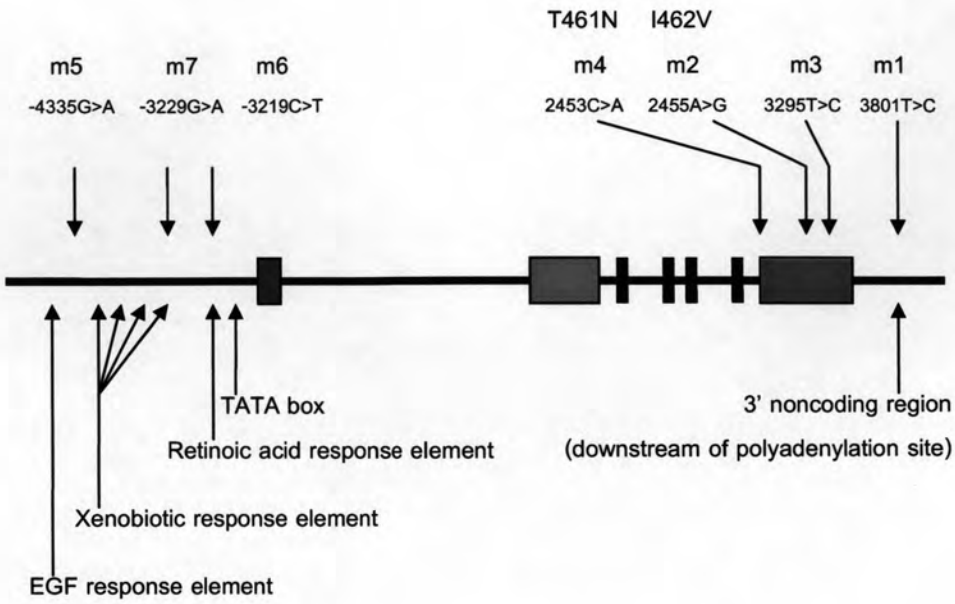

Figure 8 Genetic polymorphisms of *CYP1A1* gene (Hayashi *et al.*, 1991)

Several mutations in *CYP1A1* have been described, and *CYP1A1*2A* (3801T→C) polymrphisms have been study in relation to childhood ALL in Canada. In India the study of *CYP1A1**2A (m1) and *2B (m2) (3801T→C and 2455A→G) (Bale *et al.*, 1987) have been frequency 42.4% and 37.3%, increased risk of childhood ALL (Joseph *et al.*, 2004). The 3801T→C polymorphism located in 3' noncoding region (downstream of polyadenylation site). Polymorphism of 2455A→G arise in exon 7 and result in the animo acid change Isoleucine→valine (Ile462Val) at the residue 462 in the heme binding region (Figure 8) (Hayashi *et al.*, 1991). The previous study found the combined between *CYP1A1* polymorphism and *GSTT1* deletion as the protected risk in childhood ANLL (Belta *et al.*, 2003).

NAD(P)H: Quinone Oxidoreductase 1 (*NQO1)*

NQO1 as subfamilies of NAD(P)H Quinone Oxidoreductase 1 is located on chromosome 16q22.1. The gene spans approximately 17 kb and has 6 exons. *NQO1* is important enzyme in the metabolism of xenobiotics. It may act as either a detoxification or activation enzyme, depending on the substrate. For example, it catalyzes the two-electron reduction of quinoid compounds to the readily excreted hydroquinones, preventing the generation of free radicals and reactive oxygen, thus protecting cells from oxidative damage (Wiernels *et al.,* 1999). Alternatively, *NQO1* is known to catalyze the activation of some environmental procarcinogens present in tobacco smoke, such as benzo-(a)-pyrene quinone, nitroaromatic compounds and heterocyclic amines.

A polymorphism exists as a C→T substitution at nucleotide 609 in the exon 6 *(NQO1*2)*, resulting in a missense mutation in codon 187 from Proline to Serine (Figure 9). This polymorphism has been associated with reduced enzymatic activity or no enzyme function and shown to be present in 5% of African, 15% of Caucasian, 20% of Asian (Traver *et al.,* 1997; Danial *et al.,* 2002). In previous studies, an increased risk of myeloid leukemia (Larson *et al.,* 1999) and urothelial cell and bladder carcinoma (Schulz *et al.*, 1997) were associated with 609C→T polymorphisms. *NQO1* polymorphisms 609C→T (*NQO1**2) and 465C→T (*NQO1**3) were found to be associated with an increased risk of childhood ALL in Canada (Krajinovic *et al.,* 2002).

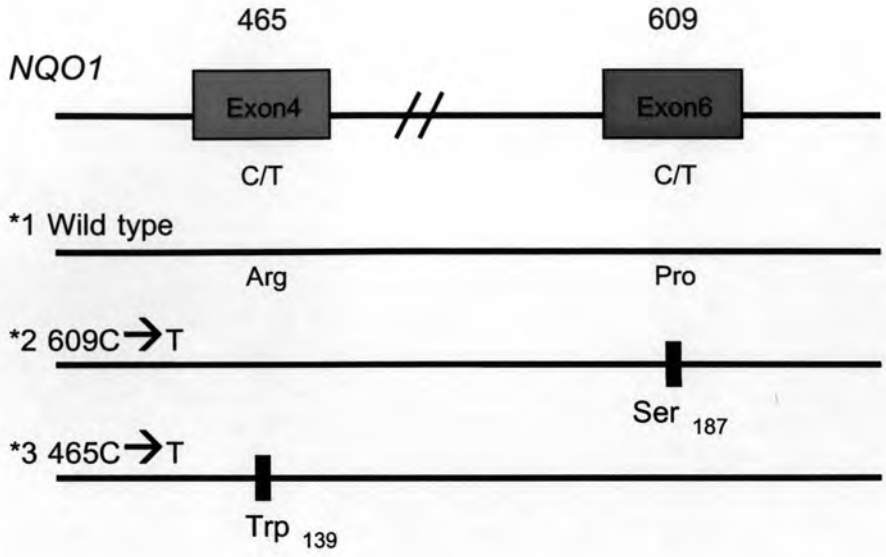

Figure 9 Genetic polymorphisms of *NQO1* gene. Two C → T transitions at position 609 (Pro to Ser replacement at codon 187) and 465 (Arg to Trp replacement at codon 139) define variants *NQO1*2* and *NQO1*3*, respectively (modified from Krajinovic *et al.*, 2002).

Glutathione-S-Transferase (*GSTs)*

The glutathione transferases (*GSTs*; also known as glutathione-S-transferases) are major phase II detoxifcation enzymes found mainly in the cytosol. In addition to their role in catalyzing the conjugation of electrophilic substrates to glutathione (GSH), these enzymes also carry out a range of other functions. They have peroxidase and isomerase activities, they can inhibit the Jun N-terminal kinase (thus protecting cells against H_2O_2-induced cell death), and they are able to bind non-catalytically to a wide range of endogenous and exogenous ligands (Bolt et al., 2006). Cytosolic *GSTs* of mammals have been particularly well characterized, and were originally classified into Alpha (*GSTA*), Mu (*GSTM*), Pi (*GSTP*) and Theta (*GSTT*) classes on the basis of a combination of criteria such as substrate, inhibitor specificity, primary and tertiary structure similarities and immunological identity (Salah A *et al.*, 2000).

Polymorphisms in genes coding for enzymes involved in protection against oxidative stress have been implicated in the predisposition of individuals to disease states such as cancer (Francesco *et al.*, 2004; Krajinovic *et al.*, 1999). In the case of the Mu class, four allelic variants at the *GSTM1* locus have been identified in the human population (Bolt and Their *et al.*, 2006; Stacy *et a*l., 2001). The null allele is homozygous deletion of *GSTM1*, present in 35-61% of the human population (40-61% of Japanese, 58% of Taiwanese, 35-52% of European, 43-51% of American) , which may predispose certain individuals to greater risk from toxic xenobiotics. For the theta class, the null *GSTT1* is homozygous deletion is present in around 20% of the human population (51% of Japanese, 53% of Taiwanese, 13-22% of European, 13-36% of American) (Stacy *et al.*, 2001).

The *GSTM1* locus has been mapped on chromosome 1p13.3, while the *GSTT1* locus exists on chromosome 22q11.2. Persons with homozygous deletions of either the *GSTM1* or the *GSTT1* locus have no enzymatic functional activity of the respective enzyme (Stacy *et al.*, 2001). Similar to *GSTM1, GSTM2, GSTM3, GSTM4* and *GSTM5* genes have all been mapped to human chromosome 1. The close physical proximity of the *GSTM1* and *GSTM2* loci, sharing a 99% nucleotide sequence identity over 460 nucleotides of 3' untranslated mRNA, has led to the concept that the *GSTM1-null* allele results from unequal crossing-over (Pearson *et al.*, 1993). A mapping of the *GSTM* gene cluster revealed that the *GSTM1* gene that consists of 8 exons is flanked by two almost identical 4.2-kb regions. On this basis, the *GSTM1* deletion polymorphism is caused by a homologous recombination process involving both repeats (Figure 10) (Xu *et al.*, 1998; Parl *et a*l., 2005).

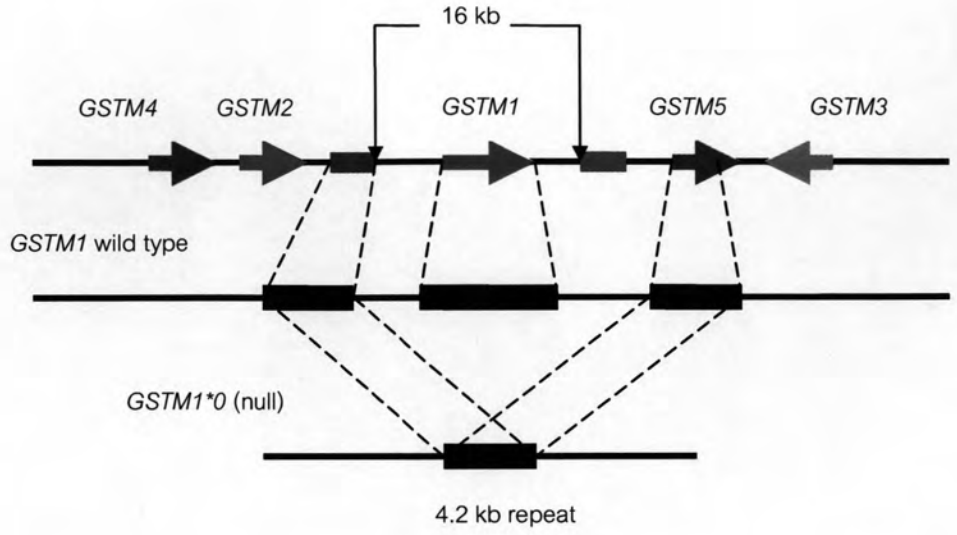

Figure 10 Structure of the *GSTM1* homologous recombination of 4.2 kb repeat causing deletion (Parl *et al*., 2005).

Similarly, the *GSTT1* gene is part of the *GSTT* gene cluster at chromosome 22q11.2. The *GSTT1* gene, consisting of 5 exons, is embedded in a region with intensive homologies and flanked by two 18 kb regions, HA3 and HA5, which are more than 90% homologous. In their central portions these two regions share a 403 bp sequence with 100% identity (Xu *et al.*, 1998). The *GSTT1* deletion is caused by a homologous recombination of these 403 bp repeats. This results in a 54 kb deletion that contains the entire *GSTT1* gene (Figure 11) (Parl *et al.*, 2005).

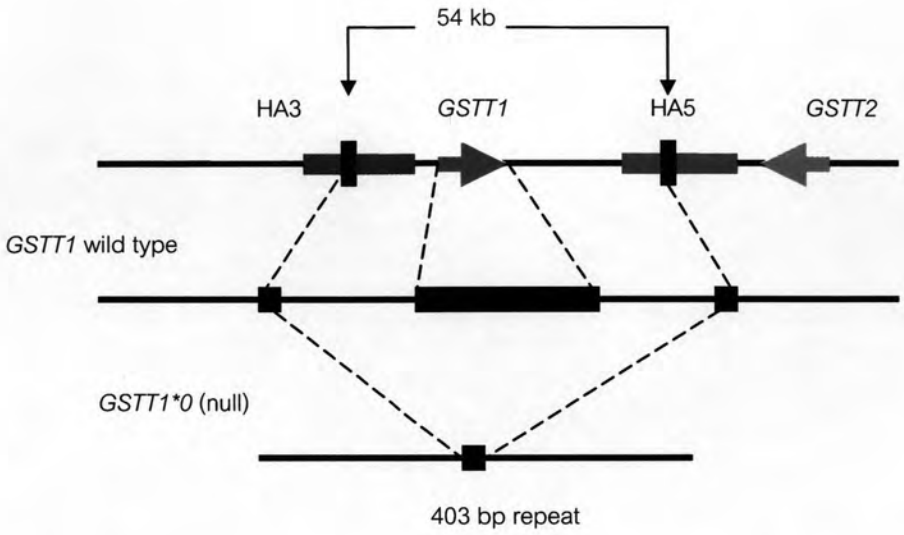

Figure 11 Structure of the *GSTT1* homologous recombination of 403 kb repeat cause deletion (Parl *et a*l., 2005).

GSTM1 null genotype is present in 60% in European, 40% in Asian and 20% in African (Andrew *et al.*, 2000). The polymorphism of *GSTM1* null genotype is significantly associated with cancers. In Turkey children 55% of ALL and 61.3% of ANLL were has *GSTM1* null. *GSTM1* null genotype were shown to be associated with increased risk for childhood ALL in India and Thailand (Joseph *et al.*, 2004; Pakakasama *et al.*, 2005). *GSTT1* null genotype of childhood ALL were present 20.9% in Thailand and Turkey and were not associated with increased risk of ALL, but the combination of *GSTM1* and *GSTT1* null genotype associated with increased risk of childhood ALL in India (Joseph *et al.*, 2004; Pakakasama *et al.*, 2005; Balta *et al.*, 2003).

Pesticides

Pesticides are substances that are used to prevent, repel, or destroy pests or organisms that compete for food supply, adversely affect comfort, or endanger human health. Several classes of compounds are used for this purpose. More than 20,000 pesticide products with nearly 900 active ingredients are registered for use as insecticides, miticides, herbicides, rodenticides, nematocides, fungicides, fumigants, wood preservatives, and plant growth regulators. Pesticides are ubiquitous in the environment.

There are multiple ways of classifying pesticides.

Classified by using

1. Bactericides for the control of bacteria
2. Fungicides for the control of fungi and oomycetes
3. Herbicides for the control of weeds
4. Insecticides for the control of insects - these can be Ovicides (substances that kill eggs), Larvicides (substances that kill larvae) or Adulticides (substances that kill adult insects)
5. Miticides or Acaricides for the control of mites
6. Molluscicides for the control of slugs and snails
7. Nematicides for the control of nematodes
8. Rodenticides for the control of rodents

Pesticides are used to control organisms which are considered harmful. For example, they are used to kill mosquitoes that can transmit potentially deadly diseases like malaria. They can also kill bees, wasps or ants that can cause allergic reactions. Insecticides can protect animals from illnesses that can be caused by parasites such as fleas. Pesticides can prevent sickness in humans that could be caused by mouldy food or diseased produce. Herbicides can also kill invasive weeds in

parks and wilderness areas which may cause environmental damage (Helfrich *et al.*, 2007).

Classified by chemicals into 5 groups

1. Organochlorine Insecticides e.g. DDT and Aldrin
2. Organophosphate Insecticides e.g. Dichlorvos, Propoxur, Methyl parathion, Parathion and Malathion
3. Carbamate Insecticides e.g. Methomyl and Cabaryl
4. Pyrethroid Insecticides, which synthsis from pyrethrin from pyrethrum or chrysanthemum flower e.g. Permethrin and Cypermethrin
5. Botanical Insecticides e.g. nicotine and rotenoids.

However, pesticides can prevent sickness in human from many organisms but pesticides may cause many human diseases, including childhood leukemia and childhood cancers (Zahm and Ward *et al.*, 1998; Claire and Scott *et al.*, 2007). The previous study in Thailand, case - control study was conducted in Bangkok and two rural regions of Thailand, they found the most regular use of Dichlorvos/ Propoxur that the household pesticides used in Thailand but do not increase the risk of aplastic anemia (Kaufman *et al.*, 1997). The studies of gene or environmental and risk of cancers are not enough to explain the cause of disease, so we have to study association between gene-environmental interaction. For example, the previous study in Parkinson's disease (PD) and *NQO1* and *MnSOD* genes polymorphism Taiwan, they found that the exposure to pesticides associated with the combined *MnSOD/NQO1* variant genotype was significantly associated increased risk of PD (Chin-Shih Fong *et al.*, 2006). And the study of North California Childhood Leukemia Study (NCCLS), they found the exposure to indoor pesticides during pregnancy and the first year of life increased risk of leukemia, the inactivating *NQO1* 609C→T polymorphism is positively associated with leukemia arising in the first 1-2 years of life (Smith T *et al.*, 2004).