CHAPTER 1

INTRODUCTION

Cancer has been the leading cause of death in 20 large world areas with geographic variation (Parkin *et al*., 2005). Breast cancer remains the leading cause of death from cancer in females worldwide with 411,000 annual deaths, followed by cervix cancer with 274,000 annual deaths. The annual mortality rates ranged from 27 per 100,000 women in Northern Europe to 4 per 100,000 women in Asia (Parkin *et al*., 2005). Age-standardized incidence rates (ASR) for breast cancer are high in most of the developed areas (except for Japan) such as in North America (99.4 per 100,000), Northern Europe (82.5 per 100,000), Southern Africa (33.4 per 100,000), Japan (32.7 per 100,000), South-Eastern Asia (25.5 per 100,000) and China (18.7 per 100,000). Incidence rates of breast cancer are increasing in most countries, and the changes are usually greatest where rates were previously low. Since the estimates for 1990, there has been an overall increase in incidence rates of about 0.5% annually. At this rate of growth, there would be around 1.4 million new cases in 2010. In Thailand, breast cancer is the third cancer-related mortality cause in Thai women, after liver and lung cancers, with estimated incidence rate (age-standardized rate, ASR) of 7.0, 13.5 and 16.3 in 1985, 1990 and 1993, respectively (Cancer Statistic Bangkok, 1985 ; Vatanasapt *et al*., 1995 ; Chindavijak and Martin, 1999). Breast cancer in men is very rare in Thailand, with the ASR of around 0.1 or less (Chindavijak and Martin, 1999).

The cause of breast cancer is still unclear. There are many risk factors associated with the breast cancer development such as age, reproductive factors, body size/obesity, alcohol, physical activity, exogenous hormones (oral contraceptives and hormone replacement therapy), diet and genetic factors (Nkondjock and Ghadirian, 2004). Approximately, five to ten percentage of all breast cancer is due to genetic predisposition with autosomal dominant pattern of inheritance (Newman *et al*., 1988 ; Claus *et al*., 1996 ; Xu and Solomon, 1996). The major breast cancer susceptibility gene, *BRCA1* gene (MIM# 113705), has been identified (Miki *et al*., 1994).

Germline mutation of *BRCA1* gene accounts for approximately 20-50% of hereditary breast cancer (Martin and Weber, 2000). Inherited mutations of the *BRCA1* gene are involved in 80-90% of familial breast-ovarian cancer (Easton *et al*., 1993 ; Ford *et al*., 1994 ; Easton *et al*., 1995 ; Couch *et al*., 1997). The lifetime risk of breast cancer conferred by a *BRCA1* mutation has been estimated to be 56-85% (Ford *et al*., 1994 ; Couch *et al*., 1997 ; Ford *et al*., 1998)

The *BRCA1* is a tumor suppressor gene localized on chromosome 17q21. The gene consists of 5592 base pairs in 22 exons that encode a 220 kDa protein comprising of 1,863 amino acids and 2 non-coding exons. The BRCA1 protein is functionally characterized into 3 major domains including RING domain, nuclear localization signal domain (NLS) and BRCA1 C-terminal domain (BRCT domain) (Welcsh *et al*., 2000). The BRCA1 has multiple functions in the cell. It has DNA -binding and nuclear localizing regions and interacts with TP53, RB, ATM, BRCA2 and other proteins involved in DNA repair and transcriptional regulation. It also appears to suppress estrogen-mediated proliferation of breast epithelial cells. Thus, the *BRCA1* is important in embryonic proliferation of tissues. Also, inactivation of the *BRCA1* can lead to defective DNA damage repair, abnormal centrosome duplication, G2-M cell cycle checkpoint defects, growth retardation, increased apoptosis, genetic instability and tumor formation in specific target tissues (Deng and Scott, 2000). In sporadic breast cancer, inactivation of the *BRCA1* gene may suggest that there are alternative mechanisms. It may contribute to the allelic loss at the *BRCA1* locus and epigenetic hypermethylation of the *BRCA1* promoter (Dobrovic and Simpfendorfer, 1997 ; Staff *et al*., 2003).

At present, over 1,500 distinct mutations, polymorphisms and variants of the *BRCA1* gene have been discovered. The observed mutations are classified into 3 major types including frame-shift (49.9%), missense (28.6%) and nonsense (10.9%) mutations. The majority of these are frameshift or nonsense mutations causing premature translation termination (BIC, 2004). *BRCA1* mutations span the whole *BRCA1* gene. A large proportion of mutations appears in exon 11, which comprises 60% of the gene (Hedenfalk *et al*., 2002). Genetic testing methods have been used to detect *BRCA1* mutations, including direct sequencing (DS),

single-stranded conformational polymorphism (SSCP), heteroduplex analysis (HA), denaturing high performance liquid chromatography (DHPLC), protein truncation test (PTT), dideoxy fingerprinting assay (DDF), denaturing gradient gel electrophoresis (DGGE) and allele-specific oligonucleotide hybridization (ASO) (Xu and Solomon, 1996). However, each technique has some advantages and disadvantages. Therefore, identification of mutations has to be carried out by a combination of detection methods.

Recently, unprecedented *BRCA1* mutations associated with familial and isolated early-onset breast and ovarian cancer in Thai patients have been reported (Patmasiriwat *et al*., 2002). They include *BRCA1* T320G, 744ins20, 3300delA, C3271G and IVS20+78 G>A. These mutations have been identified in the patients in the central region of Thailand including Bangkok.

Thus, the present study is aimed to identify mutations of the *BRCA1* gene in Thai breast cancer patients, who residing in the southern part of Thailand.