Polymorphism Thr241Met of the XRCC3 Gene and Lack of Association with Colorectal Cancer Susceptibility Risk among Malaysian Population: A Preliminary Report

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ABSTRACT

Background: **The genesis of colorectal cancer (CRC) involves a series of steps in which environmental and/or endogenous carcinogens interact with genetic factors and induce or promote cancer development. Genetic polymorphisms in DNA repair genes may influence individual variation in DNA repair capacity and may be associated with a high risk of developing cancer. Studies on the association between DNA repair gene polymorphisms and CRC appear to be limited and nil from Malaysia.**

Objective: **To examine the polymorphism at codon 241 of the X-Ray Cross Complementing group 3 (XRCC3) in 118 CRC cases and 118 normal controls and to investigate the associated risk of this polymorphism for CRC susceptibility.**

Material and Method: **Peripheral blood from the study subjects were collected in EDTA tubes, genomic DNA extracted and XRCC3 Thr241Met genotyped by using PCR-RFLP technique using *Nla III* restriction enzyme. The resulting genotypes were categorized into wildtype homozygous (Thr/Thr), heterozygous (Thr/Met) and homozygous variant (Met/Met).**

Results and conclusion: **The distribution of genotypes (Thr/Thr, Thr/Met and Met/Met) among CRC cases (83%, 16%, 1% respectively) was not significantly different from those among controls (79%, 21%, 0% respectively). On examining the association between the variant genotypes and CRC risk, the variant genotype either single or in combination did not show significant association with CRC susceptibility risk suggesting that the XRCC3 codon 241 polymorphism does not convey moderate increase in susceptibility to CRC in Malaysian population. Lack of association could be attributed to the small sample size, interaction of other polymorphic DNA repair genes and also low frequency of variant allele for the polymorphism studied in this population.**

KEY WORDS

colorectal cancer, DNA repair gene, XRCC3, polymorphism, susceptibility risk

INTRODUCTION

Colorectal cancer (CRC) is the second to fourth most common cancer in developed countries. Worldwide, 875,000 or more people are diagnosed with CRC annually (De la Chapelle, 2004). CRC represents a complex, multifactorial disease and its etipathogenesis include environmental factors such as dietary factors, life style habits and carcinogen exposure on one hand and genetic predisposition on the other hand (de Jong *et al.*, 2002; De la Chapelle, 2004). Growing evidence suggest that genetic predisposition acts via a combination of high risk variants in a set of low and medium penetrance genes. Humans, who are routinely exposed to mutagens and environment carcinogens such as aromatic amines via diet (through overcooked, charred and preserved meat) and polycyclicaromatichydrocarbon (PAH) from tobacco smoke, are at an increased risk of CRC (Norat *et al.*, 2002). These chemicals when consumed can produce DNA adducts and lead to DNA damage (Vinies *et al.*, 1996). In order to protect the genome against the deleterious effects of carcinogens present in the diet as well as environment, the human body has evolved a host of metabolic enzymes, DNA repair enzymes and other protective enzymes (Yeh *et al.*, 2005).

DNA repair plays a significant role in protecting the genome from damage by endogenous and environmental agents. Distinct pathways, each involving numerous factors, have evolved to perform DNA repair (Friedberg *et al.*, 2002). Genes involved in nucleotide excision repair (NER), recombination repair (RR), base excision repair (BER) and mismatch repair (MMR) pathways have critical roles in protection against cancers. Genetic variations in some DNA repair gene in each of these pathways in the normal population appears to influence cancer susceptibility in exposed individuals (Berwick and Vinies, 2000; Goode *et al.*, 2002). A large number of single nucleotide polymorphisms (SNPs) in DNA repair genes have been determined among individuals. Polymorphisms in DNA repair genes and differences in repair capacity between individuals have been widely documented.

X-Ray Cross Complementing group 3 (XRCC3) gene which is located at chromosome 14q32.3, and related to Rad51, is required for the information of the protein complex necessary for homologous recombination repair (HRR) of Double Strand Break (DSB) and cross-links. XRCC3 plays a key role in maintaining chromosomal integrity and preventing mutations, chromosomal instability and carcinogenesis

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