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ORIGINAL PAPER

Gender-specific association of *NFKBIA* promoter polymorphisms with the risk of sporadic colorectal cancer

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Abstract The inhibitory protein IκBα, encoded by the *NFKBIA* gene, plays an important role in regulating the activity of nuclear factor-kappa B, a transcription factor which has been implicated in the initiation and progression of cancers. This study aimed to evaluate the association of *NFKBIA* −826C>T (rs2233406) and −881A>G (rs3138053) polymorphisms with the risk of sporadic colorectal cancer (CRC) in Malaysian population. A case–control study comprising 474 subjects (237 CRC patients and 237 cancer-free controls) was carried out. The polymorphisms were genotyped from the genomic DNA of the study subjects employing PCR–RFLP, followed by DNA sequencing. The association between the polymorphic genotypes and CRC risk was evaluated by deriving odds ratios (ORs) and 95 % confidence intervals (CIs) using unconditional logistic regression analysis. The two polymorphisms were in complete and perfect linkage disequilibrium ($D' = 1.0$, $r^2 = 1.0$). Overall, no statistically significant CRC risk association was found for the polymorphisms ($P > 0.05$). A similar lack of association was observed when the data were stratified according to ethnicity ($P > 0.05$). However, stratification by gender revealed a significant inverse association between the heterozygous genotype of the polymorphisms and the risk of CRC among females (OR 0.53, 95 % CI 0.29–0.97, $P = 0.04$), but not among males ($P > 0.05$). In conclusion, the heterozygous genotype of the polymorphisms could contribute to a significantly decreased CRC risk among females, but not males, in the Malaysian population.

Keywords Colorectal cancer · Genetic association · *NFKBIA* · Sporadic · Susceptibility · Variation

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Introduction

Colorectal cancer (CRC) accounts for a significant burden of cancer-related morbidity and mortality. Worldwide, it is the third most common cancer in men and the second most common cancer in women [1]. The incidence of colorectal cancer has been increasing over the past decade, especially in developing countries, and in Malaysia, it has emerged as the most common type of cancer among men [2]. The multifactorial nature of the disease suggests that its occurrence is not only due to environmental factors (such as lifestyle and dietary habits), but also a result of genetic factors as well as the interaction between the two [3, 4].

Among the genetic factors, mutations in high penetrance genes, such as *APC*, represent a strong determinant for the pathogenesis of the disease. However, such mutations accounts for only a small proportion of all CRC cases [5], and attempts to identify similar high penetrance genes have been unsuccessful. Therefore, researchers have shifted their attention to the identification of a panel of low penetrance genes, which could modestly modulate the risk of CRC individually, but contribute to a significant risk modification effect when acting together [6–8]. Such low penetrance genetic variations are relatively common in the