

## RESEARCH ARTICLE

# ***XRCCI* Gene Polymorphism, Diet and Risk of Colorectal Cancer in Thailand**

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### Abstract

**Background:** Colorectal cancer (CRC) is one of the most common cancers worldwide. This study aimed to investigate the interaction between the presence of a polymorphism of the *XRCCI* gene and known risk factors for colorectal cancer in Thailand. **Materials and Methods:** A hospital-based case-control study was conducted in Thailand. The participants were 230 histologically confirmed new cases and 230 controls matched by sex and age and recruited from the same hospital. Information about demographic characteristics, life style, and dietary habits was collected using structured interviews, and blood samples were taken which were used for the detection of a homozygous and heterozygous polymorphisms of *XRCCI*. Associations were assessed using multiple conditional logistic regression. **Results:** In the univariate analysis, factors found to be significantly associated with an increased risk for CRC were the presence of the *XRCCI* AA homozygote (OR= 4.95; 95% CI: 1.99-12.3), a first degree family history of cancer (OR= 1.74; 95% CI: 1.18-2.58), and a high frequency of pork consumption (OR= 1.49; 95% CI: 1.00-2.21). Intakes of fish fruit and vegetables appeared to be protective factors, but the associations were not statistically significant. In the multivariate analysis only the *XRCCI* AA homozygote polymorphism and a family history of cancer emerged as risk factors (OR= 4.96; 95% CI: 1.90-12.95 and OR=1.80; 95% CI: 1.18-2.72, respectively). **Conclusions:** While the *XRCCI* AA homozygote and a family history of cancer were found to be associated with an increased risk of CRC, none of the dietary intake variables were clearly identified as risk or protective factors. There is a need for further research to determine the reasons for this.

**Keywords:** *XRCCI* polymorphism - risk factors - colorectal cancer - Thailand

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### Introduction

Globally, colorectal cancer (CRC) is the third most common cancer in males and the second most common cancer in females, and it ranks as the fourth most frequent cause of cancer death in males and the third in females (Ferlay et al., 2013). There has been a remarkable decrease of the CRC rate in Western countries, but it seems to be increasing in some countries in Asia (Sung et al., 2005; Yee et al., 2009), also in Thailand (Ferlay et al., 2013). The incidence of CRC in Thailand now ranks the disease as the third most common cancer in males and the fifth in females (Ferlay et al., 2013). It is known that CRC is related to dietary habits, especially those associated with a Western lifestyle (De Stefani et al., 2011; De Stefani et al., 2012; Durko and Malecka-Panas, 2014).

People around the world, including those living in Asian countries, appear to be increasingly following a pattern of Western food consumption practices, which are associated with a growing incidence of chronic

diseases and colorectal cancer, and this also appears to be happening in Thailand. Particular food cultures or dietary patterns may increase the risk of developing colorectal cancer (Navarro, 2005; Randi et al., 2010; Makambi et al., 2011; Magalhaes et al., 2012).

CRC is a complex disease, which results from both genetic and environmental factors (Wang et al., 2010). It is estimated that 65-85% of cases are sporadic, and the rest are hereditary and familial (Kabzinski et al., 2010). Dietary risk factors for CRC in a Thai population have been explored in previous studies. Sriamporn et al. (2007) reported that red meat (beef and/or pork) was a risk factor for colorectal cancer; alcohol was also a risk factor, but only in the univariate analysis. In a subsequent study of colon cancer (Promthet et al., 2010), the roles of beef and pork were investigated separately, and neither emerged as a risk factor; alcohol was a risk factor, but only at the lower level of consumption. For rectal cancer (Promthet et al., 2012), pork, but not beef, was a risk factor, and there was no association with alcohol.

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The roles of both genetic and environmental factors as risk factors for CRC are in need of further study. Humans are routinely exposed to mutagenic and carcinogenic chemicals via smoking, over-cooked food and other sources, all of which can lead to DNA damage when DNA adducts occur and lead to carcinogenesis (Wang et al., 2010). However, DNA damage can be reversed by DNA repair pathways. Unfortunately, deficiencies in DNA repair have been associated with an individual susceptibility to cancer, and polymorphisms of DNA repair genes may lead to the increased risk of CRC. The x-ray repair cross-complementing group 1 (*XRCC1*) gene was initially discovered through its role in repairing DNA damage caused by ionizing radiation and plays an important role in base excision repair (BER) and single-strand break repair processes (Khan et al., 2013; Nissar et al., 2013), and *XRCC1* polymorphisms have been studied as potentially connected with susceptibility to the occurrence of various cancers (Kabzinski et al., 2010).

Three coding polymorphisms of the DNA repair gene *XRCC1* have been identified in humans (Arg 194Trp, Arg280His, and Arg399Gln). *XRCC1* gene codon 399 (exon 10, base G to A, amino acid Arg to Gln, dbSNP no. rs25487) is a common and non-conservative amino acid which may alter *XRCC1* function (Yi et al., 2013). Despite the fact that polymorphisms of the *XRCC1* have been widely examined and relate to several types of cancers (Zhao et al., 2012; Yi et al., 2013), their roles in CRC in a Thai population have not been established.

The aim of this case-control study was to investigate the associations of the *XRCC1* DNA repair gene and its polymorphisms with the risk of CRC in a Thai population and to explore ways in which any of these associations are modified by various potential environmental factors.

## Materials and Methods

### *Subjects and data collection*

This was a hospital-based case-control study, in which 230 new cases of colorectal cancer were recruited between October, 2002, and October, 2006, from Srinagarind Hospital, the main teaching facility of the Faculty of Medicine, Khon Kaen University, and from the Regional Hospital of Khon Kaen Province. Each case was matched with one control by gender, age ( $\pm 3$  years) and province of residence. All of cases were from Khon Kaen Province or neighboring provinces. The diagnosis of colorectal cancer was confirmed histologically in all cases. The controls were hospital patients suffering from a variety of disorders such as inflammation and diseases of the eyes or genitourinary system, and all patients with any form of cancer or any disorder of the digestive system were excluded. All participants gave their informed consent for inclusion in the study.

The research project was approved by the Khon Kaen University Ethics Committee for Human Research (reference no. HE561328 dated September 9, 2013), and this was based on the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation.

Each participant was interviewed by one of two trained

interviewers using a structured questionnaire, which was in two sections. The first section was composed of items related to demographic variables and socioeconomic status, history of illnesses, history of cancer in first degree relatives, and smoking habits.

The second part was essentially a semi-quantitative food and beverage intake frequency questionnaire. There were nine food item categories, and each item was designed to elicit information about frequency of consumption (daily, weekly, monthly, and less than once a month). Beverage items covered the consumption of alcoholic drinks and coffee. For each type of alcoholic drink questions were asked about whether or not the participant consumed the beverage, the frequency of drinking it, and the amount consumed per occasion. For coffee, the participants were simply classified as drinkers or non-drinkers.

For the analysis of cigarette smoking, the participants were categorized as smokers or non-smokers. Smokers were defined as those who had smoked at least one type of cigarette per day for six months. An average number of cigarettes per year was computed on the basis of all smoking periods reported, and participants were then dichotomized into 'low' and 'high' smokers using the median number smoked per year by the controls. In calculating the average number of cigarettes smoked annually, no distinction was made between filter and non-filter cigarettes, but a correction factor of 1.5 was used where subjects had smoked the longer Yamuan home-made cheroot (annual filtered/non-filtered cigarettes plus 1.5 annual number Yamuan smoked).

Alcohol beverage drinking was categorised into two groups: drinkers were defined as those who consumed at least one type of alcohol beverage (beer, Thai rice wine or Sato and white or red whiskey and whiskey) at least once a month, and those who did not meet this criterion were categorized as non-drinkers. The level of alcohol consumption of each drinker was calculated in terms of alcohol units with a unit of alcohol defined as 10 milliliters (or approximately 8 grams) of ethyl alcohol. The number of units of alcohol in a drink was determined by multiplying volume of the drink (in milliliters) by its alcohol percentage and dividing by 1,000. The average daily amount of alcohol consumed was measured in terms of grams of per day with the units of alcohol content (% alc/vol) based on 5.0% for beer, 7.0% for Sato, 40% for white whiskey, and 35% for red whiskey. The averages were calculated and converted into units of alcohol per day. The participants were able to be further categorized as non-drinkers and drinkers of  $\leq 0.5$  units per day or  $> 0.5$  units per day.

The levels of dietary intake of total vegetables, total fruits, fish, beef, pork, and poultry were measured on the basis of frequency of daily consumption in the previous year, and participants were categorized as low or high consumers of these items using the median daily consumption in the controls.

The levels of intake of vegetable oil, pork oil, and coconut milk were categorised on the basis of frequency of consumption: never, sometimes, and always. The degree of spiciness of foods (non- or a little spicy, medium, and

very spicy) was determined according to the judgment of the individual participants.

#### Laboratory methods

Specimen collection and DNA extraction, blood samples (buffy coat fractions) of the cases and their matched controls were extracted for genomic DNA analysis using a standard technique at the Nagoya City University Medical School, Nagoya, Japan. Buffy coat fractions were available for 230 (100%) of the eligible colorectal cancer cases and were available for 230 matched-controls. Genomic DNA was extracted from buffy coat fractions using the standard protocol of Genomic DNA Mini Kit with Proteinase K (Geneaid Biotech).

#### PCR amplification and genetic polymorphisms detection

PCR amplification and polymorphism detection were performed in the Microbiology Laboratory at the Faculty of Medicine, Khon Kaen University, Thailand. The real-time polymerase chain reactions with high resolution melting analysis (Real-time PCR-HRM) technique for the XRCC1 polymorphism were performed in a 96-well plate in the LightCycler® 480 Real-time PCR system. Of those with DNA samples, genotyping was successfully carried out for 95% (484 out of 508) of all samples for XRCC1.

The amplification of XRCC1 G399A used two primers; [F]: 5'-AGT GGG TGC TGG ACT GTC-3' and [R]: 5'-TTG CCC AGC ACA GGA TAA-3', HRM data were analyzed using the LightCycler 480® Gene Scanning Software version 1.5 (Roche). Normalized and temperature-shifted melting curves carrying a sequence variation were evaluated and compared with the wild-type sample. Sequence variations were distinguished by the different shapes of melting curves for each genotype. Melting peaks of sequence variation were analyzed and compared with the wild-type sample. Different plots were distinguished by different melting peaks for each genotype. To improve the genotyping quality and validation, genotyping of 10% of random samples was confirmed by the PCR with the restriction fragment length polymorphism technique (PCR-RFLP).

#### Statistical analysis

The observed number of each genotype was compared with the expected values based on the Hardy-Weinberg principle. The differences between the frequency of occurrence of the alleles and genotypes in the groups were analysed by a  $\chi^2$ -test. The associations between colorectal cancer and potential risk factors were assessed using odds ratios (ORs) with a 95% confidence interval (95%CI) derived from a conditional logistic regression and McNemar's test. In the univariate analysis, crude ORs were computed for each independent variable. Those exposure variables found to be significantly ( $p$ -value<0.25) associated with colorectal cancer in the univariate analysis and those with no significant association in the present analysis, but which were found to have statistically significant associations in the reviewed literature, were included together in a multiple conditional logistic regression analysis with backward elimination.

All analyses were conducted using STATA (Version 10.0). Except for the process of selecting variables to be included in the multivariate analysis, statistical significance was set as  $p$ <0.05.

## Results

Table 1 shows the distribution of the general characteristics of cases and controls. Most of the participants were male, aged 45 years or more, did not attend school beyond primary level, and were employed as farmers or agricultural workers. Similar distributions for cases and controls were found on the unmatched variables.

The results of the univariate analyses for the genetic and dietary variables are shown in Table 2. The prevalence of the A allele of the XRCC1 G399A polymorphism among the case and control groups was exactly the same (45%). The XRCC1 GA heterozygous genotype appeared to be a risk factor for CRC when compared with the GG wild-type, but was not statistically significant (OR=1.29; 95%CI: 0.89-1.89). However, the XRCC1 AA homozygote was significantly associated with an increased risk of CRC (OR=4.95; 95%CI: 1.99-12.3). While a statistically significant increased risk was also associated with a family history of cancer (OR=1.74; 95%CI: 1.18-2.58), the apparently increased risks related to smoking, alcohol consumption, and drinking of coffee were not statistically significant. Regarding dietary intakes, a high frequency of pork consumption was found to have a statistically significant association with an elevated risk of CRC (OR=1.49; 95%CI: 1.00-2.21), but the increased risks associated with high frequencies of eating beef and poultry were not statistically significant (OR=1.20; 95%CI: 0.81-1.77, and OR=1.45; 95%CI: 0.98-2.15, respectively). High frequencies of eating fish, fruits, and vegetables appeared to be protective factors for CRC, but were not statistically significant.

Table 3 shows the results of gene-environment interaction of the XRCC1 gene polymorphisms. A

**Table 1. Characteristics of Colorectal Cancer Cases and Controls**

| Variables      | Cases                   |     | Controls |      |        |
|----------------|-------------------------|-----|----------|------|--------|
|                | n=230                   | %   | n=230    | %    |        |
| Sex            | Male                    | 125 | 54.4     | 125  | 54.4   |
|                | Female                  | 105 | 45.6     | 105  | 45.6   |
| Age (years)    | < 45                    | 55  | 23.9     | 55   | 23.9   |
|                | 45-55                   | 64  | 27.8     | 65   | 28.2   |
|                | 56-65                   | 72  | 31.3     | 71   | 30.9   |
|                | > 65                    | 39  | 17       | 39   | 17     |
|                | Mean (SD)               | 54  | (11.3)   | 53.9 | (11.4) |
| Marital status | Single                  | 7   | 3        | 17   | 7.4    |
|                | Married                 | 187 | 81.7     | 169  | 73.8   |
|                | Separated, widowed      | 35  | 15.3     | 43   | 18.8   |
| Occupation     | Agriculture, farmer     | 154 | 67.5     | 153  | 67.4   |
|                | Office, technical work  | 21  | 9.2      | 22   | 9.7    |
|                | Professional work       | 25  | 11       | 28   | 12.3   |
|                | Others                  | 28  | 12.3     | 24   | 10.6   |
| Education      | ≤ Primary school        | 175 | 76.4     | 185  | 80.8   |
|                | ≥ Secondary school      | 54  | 23.6     | 44   | 19.2   |
| XRCC1 G399A    | GG                      | 102 | 44.4     | 126  | 54.8   |
|                | GA                      | 101 | 43.9     | 97   | 42.2   |
|                | AA                      | 27  | 11.7     | 7    | 3      |
|                | GA or AA (any A allele) | 128 | 55.7     | 104  | 45     |

statistically significant association was found between the risk of CRC and the presence of both a family history of cancer and the *XRCC1* GA heterozygous genotype (OR=2.23; 95%CI: 1.12-4.13). Statistically significant associations were also found in those who had *XRCC1* GA heterozygous genotype combined with a low alcohol intake ( $\leq 0.5$  unit per day) or a high frequency of pork

**Table 2. Univariate Analyses of Environmental and Dietary Variables**

| Variables                          | Cases<br>n % | Controls<br>n % | OR (95% CI)       | p-value |
|------------------------------------|--------------|-----------------|-------------------|---------|
| <i>XRCC1</i> G399A                 |              |                 |                   |         |
| GG                                 | 102 44.4     | 126 54.8        | 1                 | 0.0005  |
| GA                                 | 101 43.9     | 97 42.2         | 1.29 (0.89-1.89)  |         |
| AA                                 | 27 11.7      | 7 3             | 4.95 (1.99-12.3)  |         |
| Family history of cancer           |              |                 |                   |         |
| No                                 | 144 62.6     | 172 75.1        | 1                 | 0.005   |
| Yes                                | 86 37.4      | 57 24.9         | 1.74 (1.18-2.58)  |         |
| Smoking                            |              |                 |                   |         |
| Nonsmoker                          | 124 53.9     | 131 57          | 1                 | 0.235   |
| Smoker                             | 106 46.1     | 99 43           | 1.5 (0.76-2.95)   |         |
| Average no. of cigarettes per year |              |                 |                   |         |
| Nonsmoker                          | 124 53.9     | 131 57          | 1                 | 0.418   |
| Low (36-5475)                      | 75 32.6      | 67 29.1         | 1.61 (0.78-3.31)  |         |
| High (>5475)                       | 31 13.5      | 32 13.9         | 1.35 (0.63-2.9)   |         |
| Alcohol drinking                   |              |                 |                   |         |
| Nondrinker                         | 118 51.3     | 122 53          | 1                 | 0.628   |
| Drinker                            | 112 48.7     | 108 47          | 1.13 (0.70-1.81)  |         |
| Units of alcohol per day           |              |                 |                   |         |
| Nondrinker/<1per month             |              |                 |                   |         |
|                                    | 134 58.3     | 153 66.5        | 1                 |         |
| $\leq 0.50$                        | 36 15.6      | 27 11.8         | 1.71 (0.95-3.11)  |         |
| $>0.50$                            | 60 26.1      | 50 21.7         | 1.56 (0.94-2.57)  |         |
| Coffee                             |              |                 |                   |         |
| No                                 | 157 68.3     | 169 73.5        | 1                 | 0.205   |
| Yes                                | 73 31.7      | 61 26.5         | 1.31 (0.86-1.98)  |         |
| Beef (average times/day)           |              |                 |                   |         |
| Low ( $\leq 0.03$ )                | 123 53.5     | 132 57.4        | 1                 | 0.37    |
| High (>0.03)                       | 107 46.5     | 98 42.6         | 1.20 (0.81-1.77)  |         |
| Pork (average times/day)           |              |                 |                   |         |
| Low ( $\leq 0.5$ )                 | 146 64.3     | 168 73          | 1                 | 0.047   |
| High (>0.5)                        | 81 35.7      | 62 27           | 1.49 (1.00-2.21)  |         |
| Poultry (average times/day)        |              |                 |                   |         |
| Low ( $\leq 0.2$ )                 | 149 64.8     | 168 73          | 1                 | 0.06    |
| High (>0.2)                        | 81 35.2      | 62 27           | 1.45 (0.98-2.15)  |         |
| Fish (average times/day)           |              |                 |                   |         |
| Low (<2)                           | 212 92.2     | 211 91.7        | 1                 | 0.862   |
| High ( $\geq 2$ )                  | 18 7.8       | 19 8.3          | 0.94 (0.78-1.86)  |         |
| Vegetables (average times/day)     |              |                 |                   |         |
| Low (<2.5)                         | 129 56.1     | 126 54.8        | 1                 | 0.753   |
| High ( $\geq 2.5$ )                | 101 43.9     | 104 45.2        | 0.94 (0.62-1.41)  |         |
| Fruits (average times/day)         |              |                 |                   |         |
| Low (<0.6)                         | 120 52.2     | 116 50.4        | 1                 | 0.669   |
| High ( $\geq 0.6$ )                | 110 47.8     | 114 49.6        | 0.91 (0.60-1.39)  |         |
| Spicy food (level)                 |              |                 |                   |         |
| Non or less spicy                  | 31 13.7      | 37 16.2         | 1                 | 0.313   |
| Medium spicy                       | 106 46.7     | 116 50.6        | 1.16 (0.64-2.1)   |         |
| Very spicy                         | 90 39.6      | 76 33.2         | 1.152 (0.81-2.84) |         |
| Vegetable oil (frequency)          |              |                 |                   |         |
| Never                              | 6 2.6        | 13 5.7          | 1                 | 0.147   |
| Sometime                           | 7 3          | 10 4.3          | 1.33 (0.36-4.93)  |         |
| Always                             | 217 94.4     | 207 90          | 2.39 (0.89-6.46)  |         |
| Pork oil (frequency)               |              |                 |                   |         |
| Never                              | 196 85.2     | 201 87.8        | 1                 | 0.539   |
| Sometime                           | 5 2.2        | 6 2.6           | 0.83 (0.25-2.73)  |         |
| Always                             | 29 12.6      | 22 9.6          | 1.39 (0.76-2.55)  |         |
| Coconut milk (frequency)           |              |                 |                   |         |
| Never                              | 62 26.9      | 61 26.5         | 1                 | 0.085   |
| Sometime                           | 97 42.2      | 116 50.4        | 0.82 (0.50-1.33)  |         |
| Always                             | 71 30.9      | 53 23.1         | 1.41 (0.80-2.50)  |         |

**Table 3. Interaction between *XRCC1* G399A and Others Environmental Factors**

| Variables                                       | Case<br>n (%)          | Control<br>n (%) | OR (95%CI)         | p-value |
|---|------------------------|------------------|--------------------|---------|
| <i>XRCC1</i> Family history of cancer           |                        |                  |                    |         |
| GG  | No 65 (28.3)           | 93 (40.6)        | 1                  | 0.0006  |
|   | Yes 37 (16.1)          | 32 (14)          | 1.54 (0.88-2.68)   | 0.129   |
| GA  | No 63 (27.4)           | 74 (32.3)        | 1.19 (0.76-1.86)   | 0.45    |
|   | Yes 38 (16.5)          | 23 (10)          | 2.23 (1.12-4.13)   | 0.011   |
| AA  | No 16 (6.9)            | 5 (2.2)          | 4.59 (1.57-13.39)  | 0.005   |
|   | Yes 11 (4.8)           | 2 (0.9)          | 7.46 (1.57-35.57)  | 0.012   |
| <i>XRCC1</i> Smoking                            |                        |                  |                    |         |
| GG  | Nonsmoker 59 (25.7)    | 77 (33.5)        | 1                  | 0.006   |
|   | Smoker 43 (18.7)       | 49 (21.3)        | 1.46 (0.65-3.28)   | 0.352   |
| GA  | Nonsmoker 53 (23)      | 51 (22.2)        | 1.43 (0.84-2.43)   | 0.186   |
|   | Smoker 48 (20.9)       | 46 (20)          | 1.63 (0.77-3.46)   | 0.205   |
| AA  | Nonsmoker 12 (5.2)     | 3 (1.3)          | 4.89 (1.32-18.04)  | 0.017   |
|   | Smoker 15 (6.5)        | 4 (1.7)          | 6.95 (1.71-28.16)  | 0.007   |
| <i>XRCC1</i> Average no. of cigarettes per year |                        |                  |                    |         |
| GG  | Nonsmoker 59 (25.6)    | 77 (33.5)        | 1                  | 0.016   |
|   | Low 32 (13.9)          | 37 (16.1)        | 1.48 (0.63-3.49)   | 0.367   |
|   | High 11 (4.8)          | 12 (5.2)         | 1.43 (0.51-4.0)    | 0.493   |
| GA  | Nonsmoker 53 (23)      | 51 (22.2)        | 1.45 (0.85-2.47)   | 0.171   |
|   | Low 33 (14.4)          | 29 (12.6)        | 1.82 (0.8-4.16)    | 0.154   |
|   | High 15 (6.5)          | 17 (7.4)         | 1.36 (0.54-3.41)   | 0.511   |
| AA  | Nonsmoker 12 (5.2)     | 3 (1.3)          | 4.93 (1.33-18.2)   | 0.017   |
|   | Low 10 (4.4)           | 1 (0.4)          | 16.99 (1.9-148.7)  | 0.011   |
|   | High 5 (2.2)           | 3 (1.3)          | 3.22 (0.59-17.4)   | 0.175   |
| <i>XRCC1</i> Alcohol drinking                   |                        |                  |                    |         |
| GG  | Nondrinker 59 (25.6)   | 70 (30.4)        | 1                  | 0.008   |
|   | Drinker 43 (18.7)      | 56 (24.4)        | 1.03 (0.55-1.89)   | 0.936   |
| GA  | Nondrinker 49 (21.3)   | 49 (21.3)        | 1.23 (0.71-2.14)   | 0.467   |
|   | Drinker 52 (22.6)      | 48 (20.9)        | 1.38 (0.76-2.53)   | 0.293   |
| AA  | Nondrinker 10 (4.4)    | 3 (1.3)          | 3.87 (1.02-14.73)  | 0.047   |
|   | Drinker 17 (7.4)       | 4 (1.7)          | 6.15 (1.65-22.96)  | 0.007   |
| <i>XRCC1</i> Units of alcohol per day           |                        |                  |                    |         |
| GG  | Nondrinker/<1per month |                  | 1                  |         |
|   | 65 (28.3)              | 85 (36.9)        |                    |         |
|   | $\leq 0.50$ 13 (5.7)   | 16 (7)           | 1.32 (0.55-3.14)   | 0.533   |
|   | $>0.50$ 24 (10.4)      | 25 (10.9)        | 1.57 (0.77-3.22)   | 0.216   |
| GA  | Nondrinker/<1per month |                  | 1                  |         |
|   | 59 (25.7)              | 65 (28.3)        |                    |         |
|   | $\leq 0.50$ 18 (7.8)   | 8 (3.5)          | 3.72 (1.43-9.69)   | 0.007   |
|   | $>0.50$ 24 (10.4)      | 24 (10.4)        | 1.45 (0.73-2.89)   | 0.29    |
| AA  | Nondrinker/<1per month |                  | 1                  |         |
|   | 10 (4.3)               | 3 (1.3)          | 4.28 (1.11-16.56)  | 0.035   |
|   | $\leq 0.50$ 5 (2.2)    | 3 (1.3)          | 2.49 (0.44-14.13)  | 0.302   |
|   | $>0.50$ 12 (5.2)       | 1 (0.4)          | 20.58 (2.48-170.4) | 0.005   |
| <i>XRCC1</i> Coffee                             |                        |                  |                    |         |
| GG  | No 70 (30.5)           | 94 (40.9)        | 1                  | 0.002   |
|   | Yes 32 (14)            | 32 (13.9)        | 1.47 (0.79-2.72)   | 0.219   |
| GA  | No 73 (31.9)           | 70 (30.4)        | 1.44 (0.91-2.29)   | 0.122   |
|   | Yes 27 (11.8)          | 27 (11.7)        | 1.34 (0.72-2.49)   | 0.351   |
| AA  | No 13 (5.7)            | 5 (2.2)          | 3.32 (1.14-9.72)   | 0.028   |
|   | Yes 14 (6.1)           | 2 (0.9)          | 16.99 (2.16-133.6) | 0.007   |
| <i>XRCC1</i> Beef (average times/day)           |                        |                  |                    |         |
| GG  | Low 54 (23.5)          | 70 (30.4)        | 1                  | 0.002   |
|   | High 48 (20.9)         | 56 (24.4)        | 1.19 (0.68-2.09)   | 0.533   |
| GA  | Low 54 (23.5)          | 56 (24.4)        | 1.29 (0.76-2.21)   | 0.349   |
|   | High 47 (20.4)         | 41 (17.8)        | 1.55 (0.88-2.73)   | 0.131   |
| AA  | Low 15 (6.5)           | 6 (2.6)          | 3.58 (1.25-10.3)   | 0.018   |
|   | High 12 (5.2)          | 1 (0.4)          | 17.0 (2.1-137.4)   | 0.008   |
| <i>XRCC1</i> Pork (average times/day)           |                        |                  |                    |         |
| GG  | Low 64 (27.8)          | 90 (39.1)        | 1                  | 0.002   |
|   | High 38 (16.5)         | 36 (15.7)        | 1.39 (0.79-2.44)   | 0.257   |
| GA  | Low 66 (28.7)          | 73 (31.7)        | 1.25 (0.77-2.04)   | 0.366   |
|   | High 35 (15.2)         | 24 (10.4)        | 1.99 (1.07-3.68)   | 0.029   |
| AA  | Low 19 (8.3)           | 5 (2.2)          | 5.10 (1.79-14.5)   | 0.002   |
|   | High 8 (3.5)           | 2 (0.9)          | 6.18 (1.22-31.4)   | 0.028   |
| <i>XRCC1</i> Poultry (average times/day)        |                        |                  |                    |         |
| GG  | Low 80 (34.8)          | 111 (48.3)       | 1                  | 0.0004  |
|   | High 22 (9.6)          | 15 (6.5)         | 1.81 (0.91-3.61)   | 0.093   |
| GA  | Low 79 (34.3)          | 83 (36.1)        | 1.31 (0.86-1.99)   | 0.216   |
|   | High 22 (9.6)          | 14 (6.1)         | 2.01 (0.98-4.12)   | 0.057   |
| AA  | Low 20 (8.7)           | 7 (3)            | 3.75 (1.45-9.71)   | 0.006   |
|   | High 7 (3)             | 0                |                    |         |
| <i>XRCC1</i> Fish (average times/day)           |                        |                  |                    |         |
| GG  | Low 98 (42.6)          | 117 (50.9)       | 1                  | 0.004   |
|   | High 4 (1.7)           | 9 (3.9)          | 0.52 (0.15-1.73)   | 0.283   |
| GA  | Low 91 (39.6)          | 89 (38.7)        | 1.22 (0.81-1.83)   | 0.343   |
|   | High 10 (4.4)          | 8 (3.5)          | 1.33 (0.51-3.51)   | 0.559   |
| AA  | Low 23 (10)            | 5 (2.1)          | 6.11 (2.06-18.1)   | 0.001   |
|   | High 4 (1.7)           | 2 (0.9)          | 2.21 (0.39-12.2)   | 0.364   |



**Table 3 (continued). Interaction between XRCCI G399A and Others Environmental Factors**

| Variables                            |      | Case<br>n (%) | Control<br>n (%) | OR (95%CI)       | p-value |
|--------------------------------------|------|---------------|------------------|------------------|---------|
| XRCCI Vegetables (average times/day) |      |               |                  |                  | 0.006   |
| GG                                   | Low  | 59 (25.6)     | 64 (27.8)        | 1                |         |
|                                      | High | 43 (18.7)     | 62 (27)          | 0.80 (0.47-1.37) | 0.417   |
| GA                                   | Low  | 59 (25.6)     | 58 (25.2)        | 1.21 (0.72-2.03) | 0.464   |
|                                      | High | 42 (18.3)     | 39 (17)          | 1.14 (0.65-1.99) | 0.649   |
| AA                                   | Low  | 11 (4.8)      | 4 (1.7)          | 3.52 (0.93-13.4) | 0.065   |
|                                      | High | 16 (7)        | 3 (1.3)          | 5.31 (1.46-19.3) | 0.011   |
| XRCCI Fruits (average times/day)     |      |               |                  |                  | 0.007   |
| GG                                   | Low  | 56 (24.4)     | 69 (30)          | 1                |         |
|                                      | High | 46 (20)       | 57 (24.8)        | 0.98 (0.55-1.73) | 0.94    |
| GA                                   | Low  | 55 (23.9)     | 45 (19.5)        | 1.72 (0.97-3.06) | 0.064   |
|                                      | High | 46 (20)       | 52 (22.6)        | 1.04 (0.60-1.80) | 0.887   |
| AA                                   | Low  | 9 (3.9)       | 2 (0.9)          | 5.30 (1.09-25.6) | 0.038   |
|                                      | High | 18(7.8)       | 5 (2.2)          | 5.09 (1.60-16.1) | 0.006   |

consumption (OR=3.72; 95%CI: 1.43-9.69, and OR=1.99; 95%CI: 1.07-3.68, respectively).

Table 4 shows the adjusted ORs and 95%CIs from the multivariate analysis. A family history of cancer remained as a statistically significant risk factor for CRC in the multivariate analysis (OR=1.80; 95%CI: 1.18-2.74) as did the XRCCI AA homozygote (OR=4.96; 95%CI: 1.90-12.95). None of the dietary intake variables, including the frequency of pork consumption, were significantly related to the risk of CRC.

## Discussion

The objective of this study was to investigate risk factors for colorectal cancer in a population of Northeast Thailand in terms of gene polymorphisms, lifestyle, and dietary habits. This is the first analytic study to include features of XRCCI gene polymorphisms as possible risk factors in a population of Thailand, which is a low-risk area for colorectal cancer.

The prevalence of the A allele at codon 399 of XRCCI in the control group (45%) was consistent with other studies in Thailand (42-59%) (Kietthubthew et al., 2006; Sangrajrang et al., 2008; Settheetham-Ishida et al., 2011), XRCCI and its polymorphisms have been studied as potential risk factors for various cancers (Kietthubthew et al., 2006; Kabzinski et al., 2010; Khan et al., 2013; Yi et al., 2013; Zhang et al., 2014), including CRC (Wang

et al., 2010; Yin et al., 2012; Zhao et al., 2012). Our present study found no association between the XRCCI gene heterozygous polymorphism (G399A) and the risk of colorectal cancer. This is consistent with the negative findings of the cohort study of a Singapore Chinese population (Stern et al., 2007) and previous case-control studies (Brevik et al., 2010; Kabzinski et al., 2010; Engin et al., 2011; Gsur et al., 2011; Yin et al., 2012; Przybylowska et al., 2013). The negative finding has also been confirmed in several meta-analyses (Jiang et al., 2010; Liu et al., 2013; Yi et al., 2013). The positive finding that the XRCCI homozygous A allele was associated with a higher risk of CRC is also consistent with previous case-control studies (Brevik et al., 2010; Kabzinski et al., 2010; Engin et al., 2011; Gsur et al., 2011; Przybylowska et al., 2013).

The finding of an association between a family history of cancer in first degree relatives and the risk of CRC confirms those of our previous case-control studies in Thailand (Sriamporn et al., 2007; Promthet et al., 2010). The finding is also consistent with a case-control study in South-east Siberia (Zhivotovskiy et al., 2012), a report that a first degree family history of CRC in those undergoing colonoscopy was associated with the finding of pathologically significant lesions (Castiglione et al., 2012) and the outcome of a study involving a network of 13 case-control studies conducted across various parts of Italy and Switzerland (Turati et al., 2013). With regard to diet, the present study found no statistically significant associations between various dietary intakes and the risk of CRC. Although the consumption of beef and pork appeared to increase the risk for CRC, the relationships were not statistically significant.

However, these non-significant apparent relationships were inconsistent with the positive findings of one of our previous case-control studies, which reported that meat (beef and/or pork) intake was associated with an increased risk for CRC (Sriamporn et al., 2007). This non-significant result is also inconsistent with the positive findings of a case-control study in Uruguay, a country which leads the world in the production of beef. The study reported that a meat-based dietary pattern, which was rich in saturated fat, animal protein, cholesterol, phosphorus and nutrients originating in red meat, was associated with an increased

**Table 4. Multivariate Analyses of Potential Risk Factors**

| Variables                   | Cases               |     | Controls |     | Crude OR<br>(95% CI) | Adjusted OR<br>(95% CI) | p-value           |
|-----------------------------|---------------------|-----|----------|-----|----------------------|-------------------------|-------------------|
|                             | n                   | %   | n        | %   |                      |                         |                   |
| XRCCI G399A                 | GG                  | 102 | 44.4     | 126 | 54.8                 | 1                       | 0.0012            |
|                             | GA                  | 101 | 43.9     | 97  | 42.2                 | 1.29 (0.89-1.89)        | 1.28 (0.86-1.90)  |
|                             | AA                  | 27  | 11.7     | 7   | 3                    | 4.95 (1.99-12.3)        | 4.96 (1.90-12.95) |
| Family history of cancer    | No                  | 144 | 62.6     | 172 | 75.1                 | 1                       | 0.007             |
|                             | Yes                 | 86  | 37.4     | 57  | 24.9                 | 1.74 (1.18-2.58)        | 1.80 (1.18-2.74)  |
| Beef (average times/day)    | Low ( $\leq 0.03$ ) | 123 | 53.5     | 132 | 57.4                 | 1                       | 0.11              |
|                             | High ( $> 0.03$ )   | 107 | 46.5     | 98  | 42.6                 | 1.5 (1.02-2.20)         | 1.42 (0.92-2.19)  |
| Pork (average times/day)    | Low ( $\leq 0.5$ )  | 146 | 64.3     | 168 | 73                   | 1                       | 0.173             |
|                             | High ( $> 0.5$ )    | 81  | 35.7     | 62  | 27                   | 1.49 (1.00-2.21)        | 1.35 (0.87-2.09)  |
| Poultry (average times/day) | Low ( $\leq 0.2$ )  | 149 | 64.8     | 168 | 73                   | 1                       | 0.059             |
|                             | High ( $> 0.2$ )    | 81  | 35.2     | 62  | 27                   | 1.45 (0.98-2.15)        | 1.67 (0.97-2.86)  |
| Fruits (average times/day)  | Low ( $< 0.6$ )     | 120 | 52.2     | 116 | 50.4                 | 1                       | 0.228             |
|                             | High ( $\geq 0.6$ ) | 110 | 47.8     | 114 | 49.6                 | 0.91 (0.60-1.39)        | 0.75 (0.47-1.20)  |

risk of CRC whereas a carbohydrate pattern was not, and a plant-based pattern was protective (De Stefani et al., 2012). Similarly, case-control studies in Jordan and India also support a positive connection between red meat consumption and CRC (Ganesh et al, 2009; Arafa et al, 2011).

A large prospective study conducted across 10 European countries found that the consumption of red and processed meat was associated with an increased risk of CRC, but red meat on its own was not related (Norat et al., 2005). A nested case-control prospective study from the Netherlands found that red meat intake increased the risk of CRC in men, but not in women (Tiemersma et al., 2002). However, in cohort studies involving only male subjects a study of white males in the USA (Hsing et al., 1998) was unable to show any statistically significant association between red meat intake and the risk of CRC, and a Finnish study (Pietinen et al., 1999) found that the consumption of meat or processed meat was not associated with an increased risk of CRC. Many meta-analysis studies have confirmed this association between CRC and meat intake (Sandhu et al., 2001; Norat et al., 2002; Larsson and Wolk, 2006; Sadri and Mahjub, 2006; Huxley et al., 2009; Alexander et al., 2010; Alexander et al., 2011; Chan et al., 2011; Magalhaes et al., 2012).

Regarding the role of fish, the large cohort study conducted in 10 European countries (Norat et al., 2005) found that the consumption of fish was inversely associated with the risk of CRC. This finding was confirmed in a subsequent meta-analysis (Wu et al., 2012), but the outcome of a multicentre controlled trial in the Netherlands and the UK suggests that fish consumption does not markedly change apoptotic and mitotic rates in the colonic mucosa. For poultry, our results suggested a positive relationship between intake and the risk of CRC, but this finding failed to reach statistical significance. In the large European cohort study, poultry consumption was shown to be unrelated to CRC (Norat et al., 2005). In terms of the consumption of fruits and vegetables, the current study found no statistically significant associations with CRC, although both appeared to be protective factors. The lack of a relationship between CRC and fruit and vegetable intakes was confirmed in the Finnish study (Pietinen et al., 1999), but total fruit and vegetable consumption and especially fruit intake were found to be protective factors in a Swedish cohort of women receiving mammography screening (Terry et al., 2001).

Regarding alcohol, the results of present study are consistent with those of our previous study (Sriamporn et al., 2007) which found no relationship between alcohol use and CRC in a multivariate analysis. However, in the Siberian case-control study mentioned earlier (Zhivotovskiy et al., 2012) the use of alcohol in general and, more specifically, the drinking of beer and hard liquor were all strong risk factors for CRC. Interestingly, the consumption of wine was not associated with an increased risk, and the drinking of at least one glass per week appeared to be a protective factor.

Our present study found no association between smoking and CRC risk. Similarly, no statistically significant relationship was found in the US cohort study

of white males (Hsing et al., 1998). However, a smoking history of more than 15 years duration was associated with increased risk in the Netherlands cohort study (Tiemersma et al., 2002). A positive association between smoking and the elevated risk of CRC was also confirmed by the large cohort study of 10 European countries (Leufkens et al., 2011), by the Netherlands cohort study (Tiemersma et al., 2002), by the Siberian case-control study (Zhivotovskiy et al., 2012), and in a meta-analysis (Huxley et al., 2009).

One important limitation of this study is the potential for recall bias. This problem is a frequently mentioned problem in case-control studies and arises here because colorectal cancer cases may tend to recall factors related to their disease better than controls, especially factors about life style or behavioral factors. However, for genetic factors, this bias cannot happen since there are no changes in the genotype after conception.

In conclusion, while the *XRCC1* AA homozygote and a family history of cancer were found to be associated with an increased risk of CRC, none of the dietary intake variables were clearly identified as risk or protective factors. However, there appears to be a considerable degree of inconsistency between the findings of previously reported studies regarding dietary risk factors for CRC, and there is a need for further research to determine the reasons for this.

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