RESEARCH ARTICLE

Lack of Association between an *XRCC1* Gene Polymorphism and Colorectal Cancer Survival in Thailand

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Abstract

<u>Background</u>: Colorectal cancer (CRC) is one of the most common causes of death worldwide and in Thailand. The X-ray repair cross-complementary protein 1 (*XRCC1*) is required for efficient DNA repair. The effects of this gene on survival in colorectal cancer remain controversial and have not been reported in Thailand. The aim of this study was to investigate the association of the *XRCC1* gene with survival of colorectal cancer patients in a Thai population. <u>Materials and Methods</u>: Data and blood samples were collected from 255 newly diagnosed and pathologically confirmed CRC patients who were recruited during the period 2002 to 2006 and whose vital status was followed up until 31 October, 2014. Real-time PCR-HRM was used for genotype identification. The Kaplan-Meier method, the log-rank test, and Cox proportional hazard regression were used to estimate cumulative survival curves and compare various survival distributions and adjusted hazard ratios. <u>Results</u>: Most of the cases were males, and the median age was 55 years. The median survival time was 2.43 years. The cumulative 1-, 3-, 5-, 7-, and 10 year survival rates were 76.70%, 39.25%, 26.50%, 16.60% and 3.56%, respectively. After adjustment, female gender, ages 50-59 and ≥ 60 years, tumour stage III+IV, a signet-ring cell carcinoma, and poor differentiation had significant associations with increased risk of CRC death. While the *XRCC1* Arg/Arg homozygote appeared to be a risk factor for CRC death, the association was not significant. <u>Conclusions</u>: The genetic variant in the *XRCC1* may not be associated with the survival of CRC patients in Thailand. Further studies are needed to verify our findings.

Keywords: *XRCC1* polymorphism - survival - colorectal cancer - Thailand

Introduction

Colorectal cancer (CRC) is the third-most common cancer in the world, and in 2012 there were estimated to have been more than 746,298 newly diagnosed cases and more than 373,639 deaths due to the disease globally (Ferlay et al., 2015). In Europe and the United States of America the colorectal incidence rates are trending down (Rahib et al., 2014; Malvezzi et al., 2015), but in Asia the rates are trending up (Pourhoseingholi, 2012). This is also the case in Thailand where CRC is the fifth most common of all malignant tumors, and the age-standardized incidence rates (ASR) are estimated to be 15.2 per 100,000 for males and 10.1 per 100,000 for females (Khuhaprema & Srivatanakul, 2008; Ferlay et al., 2015).

It is known that CRC is a multifactorial disease, which involves predispositional and environmental factors. While the eating of vegetables and fruit is a protective factor, the consumption of raw or over-cooked red meat,

drinking alcohol, smoking and lack of physical activity are risk factors, particularly when there is a defective DNA repair gene. The X-ray repair cross-complementary protein 1 (*XRCC1*) is a single nucleotide polymorphism (SNP) which was initially discovered through its role in the repair of DNA damage caused by ionizing radiation (Brem and Hall, 2005). However, SNPs in *XRCC1* may impair the efficiency of *XRCC1* in DNA repair activity, especially in base excision repair (BER) and single-strand break repair processes. The presence of a SNP in *XRCC1* is also relevant to cancer (Shen et al., 2011). The polymorphisms of the *XRCC1* gene in humans consist of Arg 194Trp, Arg280His and Arg399Gln. Many studies have suggested that *XRCC1* Arg399Gln is associated with either increased or decreased risk for several types of cancers (Goode et al., 2002; Zhou et al., 2003; Yi et al., 2013), and *XRCC1* Arg399Gln has been shown to increase the risk for CRC (Yeh et al., 2007; Kabziski et al., 2010; Yin et al., 2012; Zeng et al., 2012; Tian et

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al., 2013; Poomphakwaen et al., 2014; Dai et al., 2015). Differences in survival rates in CRC depend on factors called clinicopathological characteristics; these comprise tumor site, stage of the disease (TNM, Dukes' staging system), histological type, histological grading, type of treatment and sites of any metastases site (Elsaleh et al., 2000; Laohavinij, Maneechavakajorn & Techatanol, 2010; Zhang et al., 2010).

While the potential association of ***XRCC1*** polymorphisms with survival has been studied in a variety of cancers (Yoon et al., 2005; Bewick et al., 2006; Liu et al., 2007; Miao et al., 2012; Putthanachote et al., 2014), only a few studies have investigated the association between ***XRCC1*** Arg399Gln and survival in colorectal cancer, and the results of these remain controversial. In addition, no study has been published about the role of ***XRCC1*** polymorphisms in CRC survival among Thai people.

The purpose of this study was to investigate the association between ***XRCC1*** Gene polymorphisms and colorectal cancer survival in a Thai population.

Materials and Methods

Subjects and data collection

This is a retrospective cohort study in which the subjects were a consecutive series of newly diagnosed CRC patients admitted during the period from October, 2002, to October, 2006, to Srinagarind Hospital, the main teaching facility of the Faculty of Medicine, Khon Kaen University, and to Khon Kaen Regional Hospital. All had been diagnosed in accordance with the International Classification of Diseases for Oncology (ICD-O, 3rd edition, 1st revision), and all diagnoses were histologically confirmed.

When CRC cases with multiple primary malignant tumors were excluded, 255 patients were recruited, and all were followed up until death or the end of the study (31 October, 2014). Survival time was defined as the time elapsing between diagnosis and either death or the end the study. Information about prognostic factors known from previous studies to be related to the CRC patients was retrieved from medical records; these prognostic factors were age at diagnosis, gender, tumor site, stage of the disease (TNM, Dukes' staging system), histological type, histological grading, and type of treatment. The ***XRCC1*** genotypes were retrieved from laboratory records (laboratory procedures described below).

The vital status of each patient was monitored from medical records and by linkage with the death registry of the Thai national statistics database.

Laboratory methods

Whole blood samples (3-5ml) were taken from all the recruited CRC patients, and these were centrifuged at 3,000 rpm for 15 minutes to separate plasma, buffy coat and red blood cells. All specimens were kept at -20°C at the Cancer Unit in the Faculty of Medicine, Khon Kaen University. The genomic DNA was extracted from the buffy coat at Nagoya City University Medical School, Japan.

PCR amplification and detection of genetic polymorphisms

A real-time polymerase chain reaction with high resolution melting technique (Real-time PCR-HRM) was performed in order to identify the ***XRCC1*** polymorphisms. DNA amplification was performed in a 96-well plate in a LightCycler® 480 Real-Time PCR System. The amplification of ***XRCC1*** Gln399Arg gene used two primers, forward: 5´- AGT GGG TGC TGG ACT GTC-3´ and reverse:5´- TTG CCC AGC ACA GGA TAA-3´. The HRM data were analyzed using the LightCycler® 480 Gene Scanning software version 1.5 (Roche) in the Department of Microbiology, Faculty of Medicine, Khon Kaen University. To assess and validate genotyping quality, a PCR-restriction fragment length polymorphism analysis (PCR-RFLP) was performed in approximately 10% of random samples.

Statistical analysis

Categorical data were reported as numbers and percentages, and continuous data were summarised in the form of means with standard deviations or medians with ranges (minimum : maximum). Observed survival rates were calculated from a Kaplan-Meier survival curve, and the rates were presented as percentages of patients who were alive after a certain period of time with 95% confidence intervals (95% CIs).

The log-rank test was used to compare the survival distributions in two or more groups. The associations between survival and the various prognostic factors were analysed using Cox proportional hazard regression models with the results reported in terms of crude and adjusted hazard ratios (HRadj) and their 95%CIs. Factors reaching a $p<0.25$ level of significance in the univariate analysis in the initial model and other factors found to have significant association with CRC survival in previous studies were included as candidate variables a multivariate analysis using backward elimination.

All analyses were conducted using Stata version 10.0 (Stata Corp LP, 2007). Except for the process of selecting variables to be included in the multivariate analysis, statistical significance was set as $p<0.05$.

Ethical Consideration

The study was approved by the Khon Kaen University Ethics Committee for Human Research (reference number: HE581400).

Results

Characteristics of CRC patients

The general and pathological characteristics of the 255 CRC patients are summarised in Table 1. Most of the cases were males, and the median age was 55 years. The most common tumor site, stage and treatments were the colon (NOS), stage III, and surgery, respectively. By far the most frequently reported histological type of malignancy was adenocarcinoma, and for most patients the tumor cells were graded as well-differentiated. Regarding the prevalence of ***XRCC1*** polymorphisms, Arg/Arg were found slightly more often than Gln/Arg.

Table 1. Distribution of Demographic and Pathological Characteristics of Colorectal Cancer Patients

| Variables	Number(255)	%
Gender		
Male	136	53.33
Female	119	46.67
Age(years)		
< 50	93	36.47
50-59	75	29.41
≥ 60	87	34.12
Median (Min:Max)	55 (26:75)	
Tumour site		
Cecum	11	4.31
Appendix	1	0.39
Ascending colon	9	3.53
Hepatic flexure of colon	6	2.35
Transverse colon	4	1.57
Splenic flexure of colon	3	1.18
Descending	8	3.14
Sigmoid colon	37	14.51
Overlapping lesion of colon	1	0.39
Colon, NOS	54	21.18
Rectosigmoid junction	29	11.37
Rectum, NOS	92	36.08
Stage of deisease		
Stage I	27	10.59
Stage II	42	16.47
Stage III	78	30.59
Stage IV	77	30.2
Unknown stage	31	12.16
Histological type		
Adenocarcinoma	237	92.94
Mucinous adenocarcinoma	6	2.35
Signet-ring carcinoma	12	4.71
Histological grading		
Well differentiated Grade	159	62.35
Moderately differentiated	56	21.96
Poorly differentiated	40	15.69
XRCC1 G399A genotype		
Arg/Arg	119	46.67
Gln/Arg	106	41.57
Gln/Gln	30	11.76
Types of treatment		
Surgery only	53	20.78
Radiation only	2	0.78
Chemotherapy only	4	1.57
Supportive treatment only	21	8.24
Combined treatment	175	68.62
Combined treatment*	Number (153)	
S+C/R	129	84.31
S+R+C	24	15.69

*exclude patients who acquired supportive care; S, Surgery; C, Chemotherapy; R, Radiotherapy

Survival rate of CRC patients

For the 255 CRC cases, the overall follow-up person-time was 570 person-years, and the overall mortality rate was 28 per 100 person-years (95% CI= 24.17 to 32.92). The cumulative 1-,3-,5-,7-, and 10 years survival rates were 76.70%, 39.25%, 26.50%, 16.60% and 3.56%, respectively (Table 2). Figure 1 shows the median survival time of all CRC patients, which was 2.43 years (95% CI: 1.88 to 2.83). The survival times by stage of disease, histological type and *XRCC1* polymorphisms are presented in Figures 2-4. When the stages were

Table 2. Survival Rate of Colorectal Cancer Patients After Diagnosis

Survival time	Survival rate (%)	95% CI
1 year	76.70	70.61-81.70
3 years	39.25	32.36-46.07
5 years	26.50	19.87-33.58
7 years	16.60	10.51-23.90
10 years	3.56	0.74-10.32
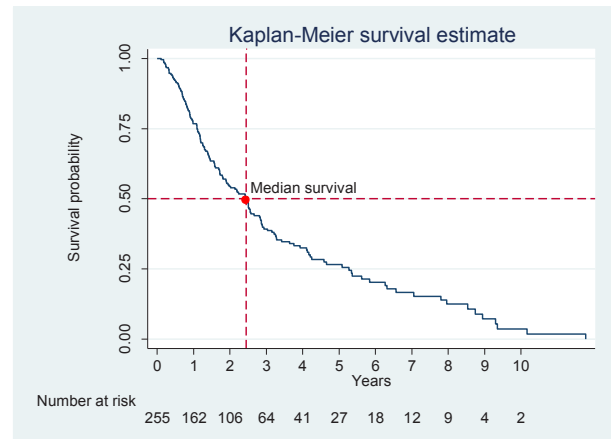
Figure 1. Overall Survival Curve of Colorectal Cancer
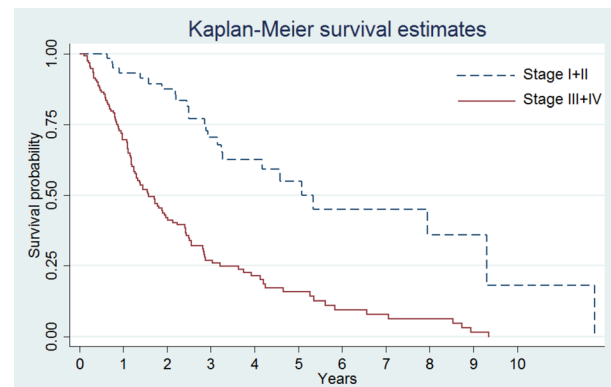
Figure 2. Survival Curve of Colorectal Cancer by Stage of Disease
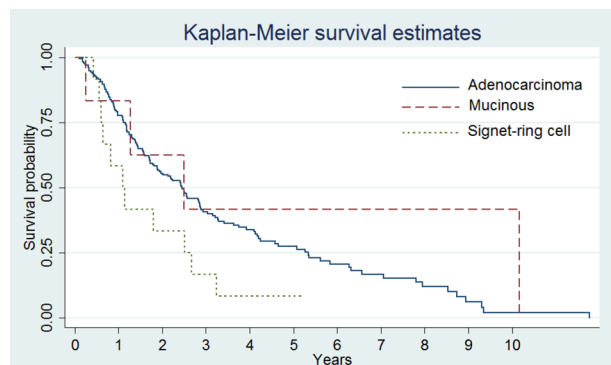
Figure 3. Survival Curve of Colorectal Cancer by Histological type

grouped as stage I+II and stage III+IV, the median survival times were 5.08 years and 1.57 years, respectively. The median survival times for the histological types of adenocarcinoma, mucinous and signet-ring cell were 2.45, 2.50 and 1.09 years, respectively. The median survival times for patients with the Arg/Arg, Gln/Arg and Gln/

Table 3. Factors as Effected to Survival of Colorectal Cancer (Multivariate Analysis)

Variable	Number (%)	Median time (Months) 95% CI	Crude HR (95% CI)	Adjusted HR (95% CI)	p-value
Gender					0.005
Female	119 (46.7)	1.56 (1.20-2.23)	1	1	
Male	136 (53.3)	2.86 (2.45-3.75)	0.59 (0.43-0.82)	0.58 (0.40-0.85)	
Age (years)					0.017
< 50	93 (36.5)	2.54 (1.90-3.92)	1	1	
50-59	75 (20.4)	2.01 (1.55-3.20)	1.20 (0.80-1.79)	1.91 (1.19-3.06)	
≥ 60	87 (34.1)	1.97 (1.30-2.89)	1.47 (1.01-2.14)	1.59 (1.01-2.51)	
Tumor site					-
Colon	163 (64.0)	2.49 (1.88-2.86)	1	-	
Rectum	92 (36.0)	2.40 (1.29-2.88)	1.03(0.74-1.43)	-	
Stage of disease					<0.001
Stage I+II	69 (30.8)	5.08 (3.24-9.30)	1	1	
Stage III+IV	155 (69.2)	1.57 (1.24-2.01)	3.54(2.27-5.53)	3.17 (1.99-5.05)	
Histological type					0.081
Adenocarcinoma	237 (93.0)	2.45 (1.89-2.86)	1	1	
Mucinous adenocarcinoma	6 (2.3)	2.50 (0.25-NA)	0.65(0.23-1.82)	2.14 (0.66-6.98)	
Signet-ring carcinoma	12 (4.7)	1.09 (0.55-2.66)	2.00(1.10-3.70)	2.47 (1.08-5.62)	
Histological grading					0.066
Well differentiated Grade	159 (62.4)	2.54 (2.18-3.26)	1	1	
Moderately differentiated	56 (22.0)	1.90 (1.30-3.20)	1.14 (0.77-1.68)	1.32 (0.85-2.06)	
Poorly differentiated	40 (15.6)	1.16 (0.77-2.42)	2.18 (1.43-3.34)	1.74 (1.07-2.80)	
XRCC1 G399A genotype					0.23
Arg/Arg	119 (46.6)	2.20 (1.60-2.81)	1	1	
Gln/Arg	106 (41.6)	2.55 (1.58-3.75)	0.87 (0.62-1.22)	0.87 (0.60-1.27)	
Gln/Gln	30 (11.8)	2.67 (1.56-6.31)	0.71 (0.43-1.20)	0.58 (0.31-1.11)	
Types of treatment					0.127
Surgery	224 (87.8)	2.50 (2.01-2.89)	1	1	
Non-surgery	31 (12.2)	0.83 (0.58-1.10)	2.37 (1.52-3.67)	1.52 (0.89-2.58)	
Combined treatment*	Number (201)				-
Surgery only	53 (26.4)	2.89 (2.18-5.33)	1	-	
S+C	124 (61.7)	2.13 (1.70-2.83)	1.39 (0.90-2.16)	-	
S+C+R	24 (11.9)	2.50 (1.33-3.75)	1.37 (0.68-2.77)	-	

*exclude patients who acquired supportive care; S, Surgery; C, Chemotherapy; R, Radiotherapy; p-value from Partial likelihood ratio test

Table 4. Final Multivariate Model for Hazard of Death in CRC Patients

Variable	Adjusted HR	95% CI	p-value
Gender			0.007
Female	1		
Male	0.60	0.41-0.87	
Age(years)			0.004
< 50	1		
50-59	1.99	1.25-3.18	
≥ 60	1.78	1.17-2.72	
Stage of disease			<0.001
Stage I+II	1		
Stage III+IV	3.32	2.09-5.27	
Histological type			0.08
Adenocarcinoma	1		
Mucinous adenocarcinoma	2.01	0.62-6.52	
Signet-ring carcinoma	2.55	1.12-5.80	
Histological grading			0.024
Well differentiated Grade	1		
Moderately differentiated	1.41	0.91-2.17	
Poorly differentiated	1.86	1.16-2.98	
XRCC1 G399A genotype			0.253
Arg/Arg	1		
Gln/Arg	0.85	0.59-1.24	
Gln/Gln	0.60	0.32-1.14	

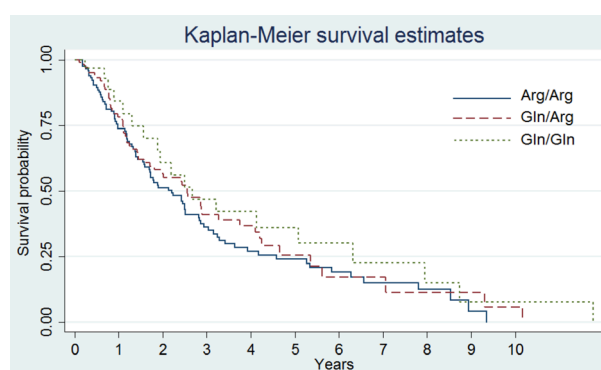*p-value from partial likelihood ratio test

Figure 4. Survival Curve of Colorectal Cancer by *XRCC1* Gene

Gln polymorphisms were 2.20, 2.55, and 2.67 years, respectively.

Factors associated with survival

The results of the initial model which included type of treatment (surgical vs. non-surgical) are shown in Table 3. In the multivariate analysis, male gender was found to have a statistically significant association with better survival (HRadj=0.58; 95%CI= 0.40-0.85), and three factors were found to have a statistically significant

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association with poorer survival: age 50-59 years (HRadj=1.91; 95%CI=1.19-3.06), age 60 years or more (HRadj=1.59; 95%CI=1.01-2.51), and late stage of disease (stages III and IV) (HRadj=3.17; 95%CI=1.99-5.05). In the final model the treatment variable was excluded from the multivariate analysis, and the results are shown in Table 4. Male gender remained significantly associated with better survival (HRadj=0.60; 95%CI=0.41-0.87) and the two older age groups were still significantly associated with poorer survival (for age 50-59 years: HRadj=1.99; 95%CI=1.25-3.18. and for age 60 years or more: HRadj=1.78; 95%CI=1.17-2.72). Late stage also remained significantly associated with poorer survival (HRadj=3.32; 95%CI=2.09-5.27). However, there were now two additional factors associated with a worse prognosis: the presence of signet ring cells ((HRadj=2.55; 95%CI=1.12-5.80) and poor differentiation (HRadj=1.86; 95%CI=1.16-2.98). The *XRCC1* polymorphisms were not associated with survival in either the initial or final multivariate analyses.

Discussion

In Asia, including Thailand, the incidence of CRC has dramatically increased in recent years. The main objective of this study was to investigate the association between *XRCC1* gene polymorphism and CRC survival in Thailand, and this is the first analytic study to explore features of *XRCC1* gene polymorphisms as possible death factors in a Thai population of CRC patients.

Our findings indicate that the *XRCC1* polymorphisms of Arg/Arg, Gln/Arg and Gln/Gln have no association with survival of CRC patients. This is consistent with the conclusions of studies in Germany and Korea (Grimminger et al., 2010; Kim et al., 2010). It also in line with another study in Thailand which found that the genetic variant Gln339Arg in *XRCC1* made no statistically significant contribution to risk of death among Thai patients with stomach cancer (Putthanachote et al., 2014). However, there are differences in physiology and anatomy, environmental carcinogens, genetic mechanisms, and prognosis between the three segments of the bowel: the proximal and distal colon and the rectum (Li & Lai, 2009). For example, a study in Taiwan, explored differences in survival between colon and rectal cancers in terms of associations with *XRCC1* polymorphisms. Rectal cancer patients with *XRCC1* Arg/Gln + Gln/Gln appeared to be at less risk of rectal cancer death when compared with patients who had Arg/Arg. In contrast, colon cancer patients with *XRCC1* Arg/Gln + Gln/Gln appeared to be at greater risk of colon cancer death when compared with patients who have Arg/Arg. These findings were not statistically significant, but they raise important issues about potential differences due to CRC site (Lai et al., 2013).

Normally, it is male gender which is associated with an increased risk of CRC death (for example, the Japanese study by Watanabe et al., 2001). However, in our study, female patients were at higher risk of CRC death than males; one possible explanation for this is that more of the female patients (77.06%) were at late stages of the disease (stages III+IV) than were the males (61.74%). This finding was supported by a Saudi Arabian study, but only for rectal cancer (Al-Ahwal et al., 2013). Not surprisingly, we found ages 50-59 and ≥60 years, tumor stage III+IV, a signet-ring cell carcinoma, and poor differentiation had a significant association with increased risk of CRC death. Similar findings have been previously reported worldwide (Halvorsen and Seim, 1989; Jen et al., 1994; Takebayashi, Aklyama, Yamada, Akiba, & Aikou, 1996; Dignam et al., 2003; Koo et al., 2008; Schetter, Leung S, Sohn et al,, 2008; Laohavinij, Maneechavakajorn & Techatanol, 2010; Nitsche et al., 2013). It is noted that the finding regarding the signet ring cell carcinoma arose despite the fact that this histological type is less common than adenocarcinoma (O'Connell et al., 2004).

The 5-year survival rate of CRC patients in our study was 26.50%. This rate was lower than that found in previous studies reported in Thailand. In 1995 and 2010, (Sriamporn et al., 1995; Laohavinij et al., 2010) the reported 5-year survival rates for CRC patients were 36.8% and 38.6%, respectively, and another study (Berberoglu U, 2004) reported that the 5-year survival was even higher (62%). Our 5-year survival rate is probably low because we obtained data from a tertiary hospital where most of patients were at late stages. Moreover, all the CRC cases in our study were confirmed histologically which means that other conditions with better prognoses were excluded.

Our study did have some limitations. Due to budget and time constraints, we studied only the effect of *XRCC1* Arg399Gln on survival of CRC patients, and this gene is only one type of the various components in the DNA repair process.

In conclusion, while gender, age, stages of disease, histological type (signet-ring cell) and histological grading (poorly differentiated) were factors affecting survival of CRC in a Thai population, no significant differences were founded in the effect of *XRCC1* Arg399Gln polymorphisms on CRC survival. There is, however, a need for further research to confirm our findings, investigate related issues and explore differences and possible interactions in the way which *XRCC1* polymorphisms affect CRC survival between the three different segments of the bowel.

Acknowledgements

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100.0

6.3

75.0

56.3

50.0

25.0

31.3

0

Newly diagnosed without treatment