RESEARCH ARTICLE

Variant Alleles in *XRCC1* Arg194Trp and Arg399Gln Polymorphisms Increase Risk of Gastrointestinal Cancer in Sabah, North Borneo

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Abstract

Background: The *XRCC1* protein facilitates various DNA repair pathways; single-nucleotide polymorphisms (SNPs) in this gene are associated with a risk of gastrointestinal cancer (GIC) with inconsistent results, but no data have been previously reported for the Sabah, North Borneo, population. We accordingly investigated the *XRCC1* Arg194Trp and Arg399Gln SNPs in terms of GIC risk in Sabah. Materials and Methods: We performed genotyping for both SNPs for 250 GIC patients and 572 healthy volunteers using a polymerase chain reaction-restriction fragment length polymorphism approach. We validated heterozygosity and homozygosity for both SNPs using direct sequencing. Results: The presence of a variant 194Trp allele in the Arg194Trp SNP was significantly associated with a higher risk of GIC, especially with gastric and colorectal cancers. We additionally found that the variant 399Gln allele in Arg399Gln SNP was associated with a greater risk of developing gastric cancer. Our combined analysis revealed that inheritance of variant alleles in both SNPs increased the GIC risk in Sabah population. Based on our etiological analysis, we found that subjects ≥50 years and males who carrying the variant 194Trp allele, and Bajau subjects carrying the 399Gln allele had a significantly increased risk of GIC. Conclusions: Our findings suggest that inheritance of variant alleles in *XRCC1* Arg194Trp and Arg399Gln SNPs may act as biomarkers for the early detection of GIC, especially for gastric and colorectal cancers in the Sabah population.

Keywords: Gastrointestinal cancer - Sabah population - *XRCC1* polymorphisms

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Introduction

Cancer is a disease of major impact in world health of which gastrointestinal cancer (GIC) is the most common cancer causing high mortality. According to a report by National Cancer Registry in 2011, a total of 18 219 new cancer incidences were diagnosed among Malaysian population in 2007. Colorectal cancer was recorded as second highest percentage of cancer that occurred in Malaysians after breast cancer with the percentage of 12.3%. Among Malay, Chinese and Indian males, colon cancer was the most common followed by other cancers such as lung cancer, prostate cancer and stomach cancer (Zainal Ariffin and Nor Saleha, 2011).

There are 130 known DNA repair genes in human body (Wood et al., 2001). *XRCC1* gene is the first mammalian gene isolated that affects cellular sensitivity to ionizing radiation (Thompson et al., 1990). Human *XRCC1* gene has been proved in correcting the repair defects in the Chinese hamster ovary cell mutant EM9 (Thompson et al., 1990). *XRCC1* gene is mapped to human chromosome 19q13.2-13.3 (Mohrenweiser et al., 1989; Thompson et al., 1989) and consists of 17 exons (Wood et al., 2001). It encodes a protein of 633 amino acids (Mohamadynejad and Saadat, 2008) that functions in base excision repair (BER) (Caldecott et al., 1996) and in single-strand breaks (SSB) of damaged bases caused by endogenous and exogenous oxidants (Skjelbred et al., 2006). Proteins that associated to *XRCC1* in facilitating the BER and SSB repair processes are polymerase beta, DNA ligase III and poly (ADP-ribose) polymerase (PARP) (Caldecott et al., 1996; Wood et al., 2001; Horton et al., 2008). A study demonstrated by Caldecott et al. revealed that *XRCC1* protein formed complex with DNA ligase III, suggested that *XRCC1* was required for the normal function of DNA ligase III although it has unknown catalytic activity function (Caldecott et al., 1994).

Even though the *XRCC1* does not directly function in repairing the DNA damages, the changes of *XRCC1* native sequence and structure due to single nucleotide

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polymorphisms (SNPs) in this gene might disrupt the function in repairing the DNA damages. The *XRCC1* gene exhibits polymorphic variations including three common SNPs that result in amino acid substitutions in exon 6 (Arg194Trp, base C to T), exon 9 (Arg280His, base G to A) and exon 10 (Arg399Gln, base G to A) (Shen et al., 2000; Stern et al., 2001). Of these, the Arg194Trp and Arg399Gln SNPs have been extensively studied and were associated to GIC risk with inconclusive results, but remain unclear in Sabah (North Borneo) population. Therefore, we accordingly performed this case-control study to examine the association of Arg194Trp and Arg399Gln SNPs in *XRCC1* gene to GIC risk in the population.

Materials and Methods

Subjects and DNA extraction

Peripheral venous blood from a total of 250 GIC patients (134 males and 116 females) from Queen Elizabeth Hospital, Sabah and 572 healthy volunteers (403 males and 169 females) without family cancer history were obtained with consent from January 2010 to December 2014 for this case-control study, regardless the matching of age, gender, and ethnicity. Out of 250 GIC samples, 48 samples were gastric cancer, followed by 175 colorectal, 6 esophageal, 12 liver and 9 pancreas. All subjects were ranged from 15 to 78 years old with mean age ± S.D. of 35.64 ± 0.63. The clinical data for GIC patients were not available as this pilot study solely focused the association of genetic variation to GIC for early screening of the disease in Sabah population. DNA was extracted from all blood samples using QIAamp DNA Blood Mini Kit (QIAGEN, USA) following the manufacturer's instructions. The principle and methodology of this study were reviewed by Sabah State Health Department, Ministry of Health Malaysia, and the ethical approval for this study was obtained from University Malaya Medical Centre Ethical Board Committee with Ref. 654.1.

XRCC1 genotyping and direct sequencing

The *XRCC1* genotyping for codon 194 and codon 399 polymorphic sites was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). DNA samples were amplified using two different primer pairs specific for the two polymorphic regions of *XRCC1* gene. Primer sequences were 5'-GCC AGG GCC CCT CCT TCA A-3' (forward) and 5'-TAC CCT CAG ACC CAC GAG T-3' (reverse) for polymorphic site at exon 6 (codon 194) whereas primers used for polymorphic site at exon 10 (codon 399) were 5'-TCC TCC ACC TTG TGC TTT CT-3' (forward) and 5'-AGT AGT CTG CTG GCT CTG GG-3' (reverse). PCR was performed in a 25 µl reaction mixture containing 100 ng of DNA, 0.3 µM of each primer, 0.2 mM of dNTP mixtures, 2.0 mM of $MgCl_2$ solution, 1.0 unit of *Go Taq*® Flexi DNA polymerase

Table 1. Risk Association of *XRCC1* Arg194Trp and Arg399Gln SNPs to GIC in Sabah Population

	Cases, N	Controls, N	OR (95% CI)	p-value
Arg194Trp SNP				
Allele				
194Arg	371	938	1.00 (Reference)	-
194Trp	129	206	1.58 (1.23 – 2.03)	<0.001*
Genotype				
194Arg/Arg	129	374	1.00 (Reference)	-
194Arg/Trp	113	190	1.72 (1.27 – 2.34)	<0.001*
194Trp/Trp	8	8	2.90 (1.07 – 7.88)	0.037*
194Arg/Trp + 194Trp/Trp	121	198	1.77 (1.31 – 2.40)	<0.001*
Arg399Gln SNP				
Allele				
399Arg	314	721	1.00 (Reference)	-
399Gln	186	423	1.01 (0.81 – 1.26)	0.931
Genotype				
399Arg/Arg	96	231	1.00 (Reference)	-
399Arg/Gln	122	259	1.13 (0.82 – 1.56)	0.444
399Gln/Gln	32	82	0.94 (0.59 – 1.51)	0.794
399Arg/Gln + 399Gln/Gln	154	341	1.09 (0.80 – 1.47)	0.593
Arg194Trp + Arg399Gln SNPs				
Allele				
194Arg + 399Arg	685	1659	1.00 (Reference)	-
194Trp + 399Gln	315	629	1.21 (1.03 – 1.43)	0.020*
Genotype				
194Arg/Arg + 399Arg/Arg	225	605	1.00 (Reference)	-
194Arg/Trp + 399Arg/Gln	235	449	1.41 (1.13 – 1.75)	0.002*
194Arg/Trp + 399Gln/Gln	145	272	1.43 (1.11 – 1.85)	0.005*
194Trp/Trp + 399Arg/Gln	130	267	1.31 (1.01 – 1.70)	0.042*
194Trp/Trp + 399Gln/Gln	40	90	1.20 (0.80 – 1.79)	0.386

*Statistical significant ($p < 0.05$); SNP = single nucleotide polymorphism, N = number of samples, OR = odd ratio, CI = confidence interval, Arg = arginine, Trp = tryptophan, Gln = glutamine

(Promega, USA) and 1X of reaction buffer with conditions set at: 94°C for 4 min, followed by 35 cycles of 94°C for 30 s, 65°C for 30 s and 72°C for 45 s, and a final elongation of 7 min at 72°C. For RFLP analysis, PCR products were digested at 37°C overnight (~16 hr) with 4 units of *Pvu*II (New England Biolabs, England) and 2 units of *Nci*I (New England Biolabs, England) to distinguish the Arg194Trp and Arg399Gln SNPs, respectively. The resulted fragments were electrophoresized on 2% agarose gel stained with ethidium bromide to determine the genotypes of the subjects for both polymorphic sites. Around 5% of the samples containing all genotypes for both SNPs were repeated for PCR-RFLP and all were matched to their genotype, which further confirmed using direct-sequencing.

Statistical analysis

The association between *XRCC1* polymorphisms to risk of GIC was tested using odd ratio (OR) at 95% confidence interval (95% CI) by taking the common genotype (Arg/Arg for both SNPs) as reference group. The significance of association was determined by Fisher's exact test where the association is considered as statistical significant when the *p*-value is less than 0.05. Significant level for sub-group analysis was accordingly adjusted for the Bonferroni correction. SPSS software V17.0 (SPSS Inc., Chicago, Illinois, USA) was used for all of the data analyses.

Results

Overall, the variant allele frequencies for 194Trp and 399Gln in this study were 20.4% and 37.0%, respectively. In Arg194Trp SNP risk association analysis, the presence of 194Trp allele significantly increased the risk to GIC, especially in gastric and colorectal cancers after the Bonferroni correction (Tables 1 and 2). In addition, subjects with variant 399Gln allele were in higher risk for gastric cancer in Sabah population. The combined analysis revealed that the presence of variant allele in both SNPs had a greater risk towards GIC.

In etiological analysis, subjects with age ≥50 years old and males carrying the variant 194Trp allele had significant higher risk to GIC (Table 3). Besides, Bajau subjects with at least one variant 399Gln also showed an increase risk to GIC in this study (Table 4).

Table 2. Risk Association of *XRCC1* Arg194Trp and Arg399Gln SNPs to Different Types of GIC in Sabah Population

	Cases, N	Controls, N	OR (95% CI)	*p*-value
Arg194Trp SNP				
Gastric				
194Arg/Arg	24	374	1.00 (Reference)	-
194Arg/Trp	21	190	1.72 (0.93 – 3.17)	0.081
194Trp/Trp	3	8	5.84 (1.46 – 23.45)	0.013*
194Arg/Trp + 194Trp/Trp	24	198	1.89 (1.05 – 3.41)	0.035
Colorectal				
194Arg/Arg	90	374	1.00 (Reference)	-
194Arg/Trp	81	190	1.77 (1.25 – 2.51)	0.001*
194Trp/Trp	4	8	2.08 (0.61 – 7.05)	0.241
194Arg/Trp + 194Trp/Trp	85	198	1.78 (1.27 – 2.51)	0.001*
Others§				
194Arg/Arg	15	374	1.00 (Reference)	-
194Arg/Trp	11	190	1.44 (0.65 – 3.20)	0.367
194Trp/Trp	1	8	3.12 (0.37 – 26.54)	0.298
194Arg/Trp + 194Trp/Trp	12	198	1.51 (0.69 – 3.29)	0.299
Arg399Gln SNP				
Gastric				
399Arg/Arg	9	231	1.00 (Reference)	-
399Arg/Gln	29	259	2.87 (1.33 – 6.20)	0.007*
399Gln/Gln	10	82	3.13 (1.23 – 7.97)	0.017
399Arg/Gln + 399Gln/Gln	39	341	2.94 (1.40 – 6.18)	0.005*
Colorectal				
399Arg/Arg	74	231	1.00 (Reference)	-
399Arg/Gln	82	259	0.99 (0.69 – 1.42)	0.949
399Gln/Gln	19	82	0.72 (0.41 – 1.27)	0.26
399Arg/Gln + 399Gln/Gln	101	341	0.92 (0.66 – 1.30)	0.654
Others§				
399Arg/Arg	13	231	1.00 (Reference)	-
399Arg/Gln	11	259	0.75 (0.33 – 1.72)	0.502
399Gln/Gln	3	82	0.65 (0.18 – 2.34)	0.51
399Arg/Gln + 399Gln/Gln	14	341	0.73 (0.34 – 1.58)	0.424

*Statistical significant with Bonferroni correction ($p < 0.017$); §Including esophageal (N = 6), pancreas (N = 9) and liver (N = 12); SNP = single nucleotide polymorphism, N = number of samples, OR = odd ratio, CI = confidence interval, Arg = arginine, Trp = tryptophan, Gln = glutamine

Table 3. Association of Age, Gender and Ethnicity in *XRCC1* Arg194Trp SNP to GIC in Sabah Population

	Cases, N	Controls, N	OR (95% CI)	p-value
Age				
<50 years				
194Arg/Arg	36	355	1.00 (Reference)	-
194Arg/Trp	26	186	1.38 (0.81 – 2.35)	0.239
194Trp/Trp	3	7	4.23 (1.05 – 17.06)	0.043
194Arg/Trp + 194Trp/Trp	29	193	1.48 (0.88 – 2.49)	0.138
≥50 years				
194Arg/Arg	93	19	1.00 (Reference)	-
194Arg/Trp	87	4	4.44 (1.45 – 13.58)	0.009*
194Trp/Trp	5	1	1.02 (0.11 – 9.25)	0.985
194Arg/Trp + 194Trp/Trp	92	5	3.76 (1.35 – 10.49)	0.012*
Gender				
Male				
194Arg/Arg	70	266	1.00 (Reference)	-
194Arg/Trp	57	129	1.68 (1.12 – 2.53)	0.013*
194Trp/Trp	7	8	3.33 (1.17 – 9.48)	0.025
194Arg/Trp + 194Trp/Trp	64	137	1.78 (1.19 – 2.64)	0.005*
Female				
194Arg/Arg	59	108	1.00 (Reference)	-
194Arg/Trp	56	61	1.68 (1.04 – 2.72)	0.035
194Trp/Trp	1	0	-	-
194Arg/Trp + 194Trp/Trp	57	61	1.71 (1.06 – 2.77)	0.029
Ethnicity				
Bajau				
194Arg/Arg	22	44	1.00 (Reference)	-
194Arg/Trp	14	20	1.40 (0.60 – 3.29)	0.44
194Trp/Trp	1	2	1.00 (0.09 – 11.64)	1
194Arg/Trp + 194Trp/Trp	15	22	1.36 (0.59 – 3.13)	0.465
Chinese				
194Arg/Arg	27	41	1.00 (Reference)	-
194Arg/Trp	39	33	1.79 (0.92 – 3.51)	0.088
194Trp/Trp	3	0	-	-
194Arg/Trp + 194Trp/Trp	42	33	1.93 (0.99 – 3.76)	0.053
KadazanDusun				
194Arg/Arg	46	163	1.00 (Reference)	-
194Arg/Trp	28	63	1.57 (0.91 – 2.74)	0.107
194Trp/Trp	2	2	3.54 (0.49 – 25.85)	0.212
194Arg/Trp + 194Trp/Trp	30	65	1.64 (0.95 – 2.81)	0.076
Others§				
194Arg/Arg	34	126	1.00 (Reference)	-
194Arg/Trp	32	74	1.60 (0.91 – 2.81)	0.1
194Trp/Trp	2	4	1.85 (0.33 – 10.55)	0.487
194Arg/Trp + 194Trp/Trp	34	78	1.62 (0.93 – 2.81)	0.089

*Statistical significant with Bonferroni correction ($p < 0.025$); §Including other indigenous groups (i.e. Rungus, Murut, etc.) and cross-married ethnicities in Sabah; N = number of samples, OR = odd ratio, CI = confidence interval, Arg = arginine, Trp = tryptophan

Discussion

This study investigated whether the Arg194Trp and Arg399Gln polymorphic sites in *XRCC1* gene could have an impact on GIC risk in Sabah population. *XRCC1* Arg194Trp is located in the linker region that separates DNA polymerase-β interacting domain from the PARP interacting domain (Kubota et al., 1996) whereas *XRCC1* Arg399Gln is located on the COOH-terminal side of the PARP interacting domain within the BRCA1 C-terminal domain (Masson et al., 1998; Zhang et al., 1998) that are thought to mediate several protein-protein interactions (Masson et al., 1998). Amino acid substitutions that occur at these important regions might cause DNA repair deficiency in human (Lunn et al., 1999) as it was previously reported in hamster due to functionality disrupted of *XRCC1* gene (Shen et al., 1998).

Allele frequency of the variant 194Trp in Arg194Trp SNP was higher in GIC patients (25.8%) when compared to controls (18.0%), suggesting that this allele might be an increase risk factor for GIC in Sabah population. Frequency of 194Trp allele in our study was higher than GIC cases reported in Egypt and Mexico (Abdel-Rahman et al., 2000; Muñiz-Mendoza et al., 2012) but was lower than those reported in Eastern Asia including Han Chinese, Japanese and Korean populations (Hong et al., 2005; Wen

Table 4. Association of Age, Gender and Ethnicity in *XRCC1* Arg399Gln SNP to GIC in Sabah Population

	Cases, N	Controls, N	OR (95% CI)	p-value
Age				
<50 years				
399Arg/Arg	31	222	1.00 (Reference)	-
399Arg/Gln	27	248	0.78 (0.45 – 1.35)	0.372
399Gln/Gln	7	78	0.64 (0.27 – 1.52)	0.314
399Arg/Gln + 399Gln/Gln	34	326	0.75 (0.45 – 1.25)	0.267
≥50 years				
399Arg/Arg	65	9	1.00 (Reference)	-
399Arg/Gln	95	11	1.20 (0.47 – 3.05)	0.708
399Gln/Gln	25	4	0.87 (0.24 – 3.07)	0.823
399Arg/Gln + 399Gln/Gln	120	15	1.11 (0.46 – 2.67)	0.82
Gender				
Male				
399Arg/Arg	51	171	1.00 (Reference)	-
399Arg/Gln	68	178	1.28 (0.84 – 1.95)	0.247
399Gln/Gln	15	54	0.93 (0.49 – 1.79)	0.831
399Arg/Gln + 399Gln/Gln	83	232	1.20 (0.80 – 1.79)	0.374
Female				
399Arg/Arg	45	60	1.00 (Reference)	-
399Arg/Gln	54	81	0.89 (0.53 – 1.49)	0.656
399Gln/Gln	17	28	0.81 (0.40 – 1.66)	0.563
399Arg/Gln + 399Gln/Gln	71	109	0.87 (0.53 – 1.42)	0.572
Ethnicity				
Bajau				
399Arg/Arg	13	43	1.00 (Reference)	-
399Arg/Gln	21	14	4.96 (1.98 – 12.42)	0.001*
399Gln/Gln	3	9	1.10 (0.26 – 4.68)	0.895
399Arg/Gln + 399Gln/Gln	24	23	3.45 (1.48 – 8.03)	0.004*
Chinese				
399Arg/Arg	40	41	1.00 (Reference)	-
399Arg/Gln	25	26	0.99 (0.49 – 1.99)	0.968
399Gln/Gln	4	7	0.59 (0.16 – 2.16)	0.421
399Arg/Gln + 399Gln/Gln	29	33	0.90 (0.46 – 1.75)	0.757
KadazanDusun				
399Arg/Arg	17	74	1.00 (Reference)	-
399Arg/Gln	40	113	1.54 (0.81 – 2.92)	0.185
399Gln/Gln	19	41	2.02 (0.95 – 4.30)	0.069
399Arg/Gln + 399Gln/Gln	59	154	1.67 (0.91 – 3.06)	0.098
Others[§]				
399Arg/Arg	26	73	1.00 (Reference)	-
399Arg/Gln	36	106	0.95 (0.53 – 1.71)	0.874
399Gln/Gln	6	25	0.67 (0.25 – 1.83)	0.438
399Arg/Gln + 399Gln/Gln	42	131	0.90 (0.51 – 1.59)	0.716

*Statistical significant with Bonferroni correction ($p < 0.013$); [§]Including other indigenous groups (i.e. Rungus, Murut, etc.) and cross-married ethnicities in Sabah; N = number of samples, OR = odd ratio, CI = confidence interval, Arg = arginine, Gln = glutamine

et al., 2012; Yin et al., 2012; Gao et al., 2014; Huang et al., 2015; Yun et al., 2015). In Arg399Gln SNP analysis, the variant 399Gln allele frequency was slightly higher in GIC (37.2%) when compared to controls (37.0%) in the present study. Interestingly, the 399Gln allele frequency was found higher when compared to those GIC cases reported in Egyptian, Han Chinese, Japanese, Korean and Western Mexican populations (Abdel-Rahman et al., 2000; Hong et al., 2005; Muñiz-Mendoza et al., 2012; Yin et al., 2012; Gao et al., 2014; Yun et al., 2015) but was lower to Thai population (Putthanachote et al., 2015). Difference in distribution of variant allele in both SNPs among studies indicates that there is a need to clarify the allele distribution of different populations for more precise risk estimation of *XRCC1* SNPs towards GIC.

Our study revealed that the presence of variant 194Trp allele in *XRCC1* Arg194Trp SNP was associated with an increase risk of GIC in Sabah population, especially in gastric and colorectal cancers. In agreement with our results, association between the inheritance of 194Trp allele and risk of GIC cancer was also reported in Egyptian, Kashmiri and Korean populations where this allele increased the risk of colorectal cancer (Abdel-Rahman et al., 2000; Hong et al., 2005; Nissar et al., 2015). A recent meta-analysis also claimed that the presence of the 194Trp allele had a higher risk for gastric

cancer in Asian (Zhao et al., 2014). However, the variant 194Trp/Trp genotype was previously been reported as a protective factor for gastric cancer in Chinese (Shen et al., 2000) and pancreatic cancer in US Caucasians (Jiao et al., 2006). In addition to GIC, *XRCC1* Arg194Trp SNP was also associated with other cancers such as breast, lung, glioma and thyroid (Chen et al., 2002; Pachouri et al., 2007; Rodrigues et al., 2011; Du et al., 2013; Feng et al., 2014; Xu et al., 2014). This suggests that 194Trp allele in *XRCC1* gene might be a core factor in altering the DNA repair mechanism and leads to several cancers development, and further investigation will be needed for this aspect.

Besides, the presence of 399Gln allele in the Arg399Gln SNP was significantly associated with higher risk of gastric cancer. Previous studies reported that the heterozygous (399Arg/Gln) and variant (399Gln/Gln) genotypes of this SNP were significant risk factor for GIC in different populations including in Han Chinese for liver, gastric and colorectal cancers (Shen et al., 2000; Pan et al., 2011; Li et al., 2012; Zhao et al., 2012), US Caucasian for pancreatic cancer (Jiao et al., 2006) as well as Egyptian, Kashmiri, Korean and Japanese for colorectal cancer (Abdel-Rahman et al., 2000; Hong et al., 2005; Yin et al., 2012; Nissar et al., 2013). A recent meta-analysis also suggested that subjects with at least one 399Gln allele elevated the risk of hepatocellular cancer in Asian population (Liu et al., 2013) but other claimed that no direct association of this allele to colorectal cancer (Qin et al., 2015). Nevertheless, a study in Han Chinese revealed that these genotypes were reduced risk factor for esophageal squamous-cell carcinoma (ESCC) in the population (Xing et al., 2002). The inconclusive findings of this SNP towards different types of GIC should be further validated for different populations with larger sample size.

Since SNPs within the same gene may interfere with each other in their molecular mechanism, we investigated the combined effect of both SNPs to risk of GIC in this study. Our results suggested that subjects carrying both variant alleles significantly increased the risk of GIC in Sabah population. This finding was in contrast to a study conducted in Han Chinese where individuals with 194Arg/Trp + 399Gln/Gln and 194Trp/Trp + 399Gln/Gln genotypes had a reduced risk to colorectal cancer, but higher risk towards colorectal cancer was observed in individuals with high alcohol intake (Gao et al., 2014), suggesting that lifestyle and environmental factors could alter the risk towards different type of cancers for subjects with similar heredity. As one of the limitations in this study was no description regarding lifestyle of the subjects, therefore interaction between SNPs and lifestyle should be included in future study for better understanding and estimation on risk association of SNPs to GIC.

Sabah is a multi-ethnicities state in Malaysia with majority of Bajau, Chinese and KadazanDusun. More than 30% of our total samples were categorized as others because cross-ethnic married has commonly being practiced in Sabah population. Etiological analysis including all ethnics in Sabah population showed that subjects who were ≥50 years and males carrying the variant 194Trp allele had an increase risk for GIC. When the subjects were stratified to ethnicity, Bajau subjects with 399Gln allele were at higher risk for GIC. This is the first significant study to report the association between *XRCC1* SNPs and etiological factors to GIC risk among Sabah population. Since the molecular mechanism between *XRCC1* gene polymorphisms and etiological factors in GIC development is still unknown, this aspect should be addressed in the future for more effectual in GIC prevention especially in states or countries with multiracial populations such as in Sabah population.

In summary, our study suggested the presence of 194Trp allele significantly exposed higher risk to GIC, especially in gastric and colorectal cancers. Besides, variant 399Gln allele also revealed greater risk for gastric cancer. The presence of variant allele in both SNPs could be act as biomarkers for early detection of GIC among Sabah population as they were significantly increased the risk of the disease. This study also pinpointed a significant gene-etiological interaction towards GIC risk. Future study should include the lifestyle of the subjects and gene-environmental interaction with larger sample size to provide a greater view for GIC risk estimation in different ethnicities among Sabah population.

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