XRCC1 genetic polymorphism and breast cancer risk

Sook-Un Kim[a], Sue Kyung Park[b], Keun-Young Yoo[a], Kyung-Sik Yoon[c], Ji Yeob Choi[a], Jeong-Sun Seo[d], Woong-Yong Park[d], Ju-Han Kim[a], Dong-Young Noh[e], Se-Hyun Ahn[f], Kuk-Jin Choe[e],Paul T. Strickland[g], Ari Hirvonen[h] and Daehee Kang[a]

Pharmacogenetics 2002, 12:335–338

Keywords: XRCC1, genetic polymorphism, breast cancer

[a]Department of Preventive Medicine and [b]Department of Preventive Medicine, Konkuk University College of Medicine, Chungju, Korea, [c]Department of Biochemistry, Eulji Medical College, Taejon, Korea, [d]Department of Biochemistry, Seoul National University, Korea, [e]General Surgery, Seoul National University College of Medicine, Seoul, Korea, [f]Department of General Surgery, Ulsan University College of Medicine, Seoul, Korea, [g]Department of Environmental Health Sciences, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA and [h]Department of Industrial Hygiene and Toxicology, Finnish Institute of Occupational Health, Helsinki, Finland

Correspondence to Daehee Kang, MD, PhD, Department of Preventive Medicine, Seoul National University College of Medicine, 28 Yongon-Dong Chongno-Gu, Seoul 110-799, Korea
Tel: +82 2740 8326; fax: +82 2747 4830; e-mail dhkang@snu.ac.kr

Received 30 August 2001
Accepted 9 March 2002

Breast cancer is the second most frequent cancer in Korean women and the incidence is increasing in both Western countries and Korea [1,2]. Although a substantial proportion of breast cancer cases are explained by well-established risk factors (i.e. later age at first birth, nulliparity and first-degree family history of breast cancer) [3], the reason for the observed worldwide increase in breast cancer incidence is still largely unknown. Recently, inherited differences in the DNA repair capacity were proposed to modify individual susceptibility to cancer.

XRCC1 is thought to play a role in the multistep base excision repair pathway where 'non-bulky' base adducts produced by methylation, oxidation, reduction or fragmentation of bases by ionizing radiation or oxidative damage are removed [4]. It is a multidomain protein that interacts with the nicked DNA and participates with at least three different enzymes, poly ADP-ribose polymerase (PARP), DNA ligase III and DNA polymerase [5].

Three polymorphisms in XRCC1 gene have been described resulting in $Arg^{194}Trp$, $Arg^{280}His$ and $Arg^{399}Gln$ amino acid changes in the XRCC1 protein [5]. The codon 194 and codon 280 polymorphic sites are located in a linker region that separates the DNA polymerase β interacting domain from the PARP-interacting domain. The codon 399 polymorphic site is located in the COOH-terminal side of the PARP-interacting domain, within the BRCT domain, which is homologous to the COOH-terminal region of the breast cancer susceptibility gene BRCA1 [5,6]. Recently, the XRCC1 codon 399 polymorphism was found to be associated with significant alterations in the DNA repair capacity [7], whereas no such data exists for the codon 194 and 280 polymorphisms.

Previous epidemiology studies on the association between genetic polymorphisms of XRCC1 and different types of cancers have given inconsistent results [8–10]. In the sole study on the role of genetic polymorphisms of XRCC1 in breast cancer risk reported to date [11], a significant association was observed between the ^{399}Gln allele and breast cancer risk among African-American women but not among White women. We examined this issue further by conducting a hospital based case–control study of women in South Korea.

The present study population comprised a consecutive series of breast cancer patients ($n = 205$) and age-matched controls ($n = 205$) with no other known cancer or systemic disease, who were admitted to three teaching hospitals located in Seoul, Korea (Seoul National University Hospital, Borame Hospital, and Asan Medical Center) between March 1994 and December 2000. Details of the selection of study subjects and collection of information have been described previously [12,13]. Women with amenorrhea, a previous history of hysterectomy, oophorectomy, hormone replacement therapy and hormone-related diseases, such as thyroid problems, were excluded from both groups. Benign breast tumour, other breast diseases (mastitis, benign calcification, etc.) and other systemic problems such as chronic liver diseases were also excluded from the controls. Approximately 21% of cases and 6% of controls approached were not included in the final study groups because of refusal to participate in the study, failure to interview or lack of a blood sample. According to the above criteria, 306 cases and 234 controls were eligible

for the study. Each case was frequency-matched to one control according to the following age groups: <29, 30–34, 35–39, 40–54, 55–69 and >70 years. Consequently, the final study population comprised 205 cases and 205 controls.

Informed consent was obtained at the time of blood withdrawal. Information on demographic characteristics, education, marital status, family history of breast cancer in first and second relatives, reproductive and menstruation, life style habits (including alcohol consumption, duration of alcohol drinking and diet) were collected using a questionnaire administered by trained interviewers. Information on alcohol consumption was addressed by three questions: (i) How frequently do you drink alcohol (i.e. per week, month, year)? (ii) How long have you been drinking? (iii) Have you ever stopped drinking?

The XRCC1 genotypes were determined by a polymerase chain reaction-restriction fragment length polymorphism method as previously described [7]. To test the reliability of the assay, 50 randomly selected samples were re-tested with identical results.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression. The ORs were adjusted in the multiple logistic model for alcohol consumption, tobacco smoking, education, body mass index, age at menarche, age at first pregnancy, age at menopause, duration of breast feeding and family history of breast cancer. The variables in the final multiple logistic model were selected on the following criteria: significant variables from the bivariate analysis, known risk factors from previous studies and potential confounders.

Those subjects who had smoked more than 400 cigarettes in their lifetime were defined as 'ever' smokers. The frequency of alcohol intake was categorized as follows: (i) non-drinker, never and less than once per month; (ii) light drinker, 1–3 times per month; (iii) heavy drinker, at least once per week. A linear increase in risk with exposure or genotype was evaluated by likelihood ratio test. The product variable between genotype and alcohol consumption [XRCC1 genotype] × [alcohol] was added to the logistic model when evaluating the interactive effect of XRCC1 genotypes and alcohol on breast cancer risk.

The selected characteristics of the study subjects (Table 1) were similar to those reported in previous Western [3] and Korean studies [12,13]. Education, age at first full-term pregnancy, family history of breast cancer and alcohol consumption were among the significantly different variables between cases and controls.

The distributions of XRCC1 genotypes in the control subjects were consistent with those predicted under the conditions of Hardy–Weinberg equilibrium (Table 2). The frequency of XRCC1 codon 194 Trp/Trp genotype (13%) was similar to that previously reported in Asians (10%) [9] but much higher than that found in Caucasians (0–2%) and African-Americans (0%) [10,11]. The frequency of XRCC1 codon 399 Gln/Gln genotype (7%) was also similar to that previously found in Asians (5%) [9] but much higher than that in African-Americans (0–1%) [10,11], whereas it was approximately two-fold lower than that found in Caucasians (13–16%) [8,10,11].

The XRCC1 codon 194 polymorphism had no influence on breast cancer risk, whereas homozygosity for the ^{399}Gln allele placed women at 2.4-fold risk (95% CI 1.20–4.72) for this malignancy; the risk increased to

Table 1 Selected characteristics for matched breast cancer cases and controls

	All women		Premenopausal women		Postmenopausal women	
Factors	Cases (n = 205)	Controls (n = 205)	Cases (n = 124)	Controls (n = 115)[a]	Cases (n = 81)	Controls (n = 85)[a]
Age (years) (SD)	48.2 (12.3)	48.5 (12.3)	40.4 (6.2)	40.4 (6.8)	60.1 (9.3)	58.9 (9.5)
% Education (over college)	29†	20	39	31	15	7
Age at menarche (years) (SD)	15.3 (1.7)	15.4 (1.8)	14.8 (1.5)	14.9 (1.8)	16.0 (1.7)	15.9 (1.7)
Age at menopause (years) (SD)	48.4 (5.4)	47.7 (6.1)	–	–	48.4 (5.4)	47.7 (6.1)
Age at FFTP in parous women (years) (SD)	26 (3.8)†	24 (3.4)	27 (3.4)†	25 (3.2)	25 (4.0)†	23 (3.2)
% Family history	9	4	7	5	12	2
% Use of oral contraceptives	7	8	4	10	11	6
% Smoking (≥ 400 cigarettes lifetime)	5	6	4		6	11
% Drinking (≥ 1 per month)	25*	18	31	25	16	9
Drinking (%)						
Never	75	82	68	75	84	91
Light (1–3 per month)	22	13	28	16	13	8
Heavy (> 1 per week)	3	5	3	9	3	1

*0.05 ≤ P < 0.1 (marginally significant), †P < 0.05 (significant). [a]Five controls were missing in menopausal status. FFTP, First full-term pregnancy.

Table 2 Association between the XRCC1 genotypes and breast cancer risk

	All women			Premenopausal women			Postmenopausal women		
	Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Controls, n (%)	OR (95% CI)	Cases, n (%)	Controls, n (%)	OR (95% CI)
XRCC1 codon 194									
Arg/Arg	88 (42.9)	92 (44.9)	1.0 (reference)	54 (43.6)	57 (49.6)	1.0 (reference)	34 (42.0)	32 (37.6)	1.0 (reference)
Arg/Trp	94 (45.9)	86 (41.9)	1.1 (0.76–1.73)	54 (43.6)	45 (39.1)	1.3 (0.74–2.18)	40 (49.4)	39 (45.9)	1.0 (0.50–1.86)
Trp/Trp	23 (11.2)	27 (13.2)	0.9 (0.48–1.67)	16 (12.8)	13 (11.3)	1.3 (0.57–2.95)	7 (8.6)	14 (16.5)	0.5 (0.17–1.32)
			P for trend = 1.0			P for trend = 0.4			P for trend = 0.2
XRCC1 codon 399									
Arg/Arg	92 (44.9)	90 (43.9)	1.0 (reference)	52 (41.9)	60 (52.2)	1.0 (reference)	40 (49.4)	28 (33.0)	1.0 (reference)
Arg/Gln	79 (38.5)	101 (49.3)	0.8 (0.51–1.16)	52 (41.9)	49 (42.6)	1.2 (0.72–2.10)	27 (33.3)	50 (58.8)	0.4 (0.19–0.74)
Gln/Gln	34 (16.6)	14 (6.8)	2.4 (1.20–4.72)	20 (16.2)	6 (5.2)	3.8 (1.44–10.30)	14 (17.3)	7 (8.2)	1.4 (0.50–3.91)
			P for trend = 0.2			P for trend = 0.02			P for trend = 0.5

The ORs were adjusted for age, education, body mass index, age at menarche, age at first pregnancy, age at menopause, smoking, alcohol consumption, duration of breast feeding, family history of breast cancer and menopausal status at baseline.

3.8-fold (95% CI 1.44–10.30) in premenopausal women. The risk of breast cancer increased with the number of Gln alleles (P for trend = 0.02). Moreover, a synergistic interaction in breast cancer development was observed between the codon 399 polymorphism and alcohol-consumption (P for interaction = 0.08); ever-drinking women with the Gln/Gln genotype had a 3.3-fold risk of breast cancer (95% CI 1.0–10.74) compared to never-drinking women with the other genotypes.

A similar association between the ^{399}Gln allele and individual susceptibility to breast cancer, as found in this study among Asians, was recently observed among African-Americans, but not among Whites [11].

The mechanistic basis for the present findings remains somewhat unclear. However, although the specific function of the XRCC1 protein is unknown, it is believed that the XRCC1 protein is an important component of base excision repair, serving as a scaffold for two other proteins, DNA ligase III and DNA polymerase β, and also serving as a single-strand break sensor by its interaction with poly ADP-ribose polymerase. Moreover, functional studies have suggested that the XRCC1 ^{399}Gln allele is associated with increased levels of DNA damage, possibly due to reduced DNA repair function [7]. Thus, this variant allele may lack proper repair capacity for DNA damage caused by spontaneous replicative errors in proliferation of breast epithelial cells or by free radicals generated by active oestrogen species [14]. This could also offer an explanation for the borderline significant interaction between the polymorphism of XRCC1 codon 399 and alcohol drinking in breast cancer development. There are several putative mechanisms through which alcohol may induce breast cancer: (i) the increase of total oestrogen and free oestradiol; (ii) the formation of free radicals and a rise of lipid peroxidation leading to DNA damage; and (iii) production of cytotoxic compounds. Therefore, the ^{399}Gln variant allele could interact synergistically with alcohol consumption in the development of breast cancer via a reduced capacity to repair DNA damage caused by lipid peroxidation products, cytotoxic compounds and free radicals generated by alcohol consumption [15].

This study has several limitations, such as moderate sample size, hospital controls, potential selection bias (21% of cases and 6% of controls contacted did not participate in the study) and possible changes in diagnostic criteria or independent variables due to the long period required to collect the informations. However, these limitations are not thought to have significantly affected the outcome of the present study. For example, although the questionnaire for diet only changed once during the study period, almost all suspicious breast cancers were confirmed by biopsies.

In addition, potential selection bias due to a higher participation rate in cases than in controls might have affected the true association if there was a disproportionate distribution of genotype frequency between participants and non-participants. However, we were unable to address this issue further as no information was available for non-participants regarding their genotype frequency and other characteristics.

In conclusion, the result of this study, which is the first epidemiological study to evaluate the relationship between two newly discovered polymorphisms of XRCC1 and breast cancer risk in Asian women, suggest that XRCC1 codon 399 polymorphisms may influence individual susceptibility to breast cancer, and that this effect may be influenced by alcohol consumption. Due to several limitations of the study the results should be considered as preliminary and need to be confirmed in larger studies in various ethnic groups.

Acknowledgements

This research was supported in part by a grant (HMP-00-B-21900-0066) of the 2000 Good Health R&D Project, Ministry of Health mp; Welfare, R.O.K., in part by 1999 BK21 Project for Medicine, Dentistry and Pharmacy, in part by the Finnish Academy and in part by the Center for Functional Analysis of Human Genome FG-2-3.

References

1 Farbers JF. The incidence of breast cancer: the global burden, public health considerations. Semin Oncol 1997; 24 (Suppl 1):S1–S20.
2 Yoo KY, Park SK, Sung JH, Kang DH, Kim YC, Kang HS, et al. High risk groups for female breast cancer in Korea. J Korean Cancer Ass 1998; 30:435–439.
3 Madigan MO, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst 1995; 87:1681–1685.
4 Yu Z, Chen J, Ford BN, Brackley ME, Glickman BW. Human DNA repair systems: an overview. Environ Mol Mut 1999; 33:3–20.
5 Shen MR, Jones IM, Mohrenweiser H. Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA genes in healthy humans. Cancer Res 1998; 58:604–608.
6 Callebaut I, Mornon JP. From BRCA1 to RAP1: a widespread BRCT module closely associated with DNA repair. FEBS Lett 1997; 400: 25–30.
7 Lunn RM, Langlois RG, Hsieh LL, Thompson CL, Bell DA. XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res 1999; 59:2557–2561.
8 Nelson HH, Kelsey KT, Mott LA, Karagas MR. The XRCC1 Arg399Gln polymorphism, sunburn, and non-melanoma skin cancer: evidence of gene–environment interaction. Cancer Res 2002; 62:152–155.
9 Ratnasinghe D, Yao S, Tangrea JA., Qiao Y, Andersen MR, Barrett MJ, et al. Polymorphisms of the DNA repair gene XRCC1 and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2001; 10:119–123.
10 Stern MC, Umbach DM, van Gils CH, Lunn RM, Taylor JA. DNA repair gene XRCC1 polymorphisms, smoking, and bladder cancer risk. Cancer Epidemiol Biomarkers Prev 2001; 10:125–131.
11 Duell EJ, Millikan RC, Pittman GS, Winkel S, Lunn RM, Tse CK, et al. Polymorphisms in the DNA repair gene XRCC1 and breast cancer. Cancer Epidemiol Biomarkers Prev 2001; 10:217–222.
12 Park SK, Yoo KY, Lee SJ, Kim SU, Ahn SH, Noh DY, et al. Alcohol consumption, glutathione S-transferase M1 and T1 genetic polymorphisms and breast cancer risk. Pharmacogenetics 2000; 10:1–9.
13 Yim DS, Park SK, Yoo K-Y, Yoon KS, Chung HH, Ahn SH, et al. Relationship between the Val^{158}Met polymorphism of catechol O-methyl transferase and breast cancer. Pharmacogenetics 2001; 11:279–286.
14 Feigelson HS, Henderson B. Estrogen and breast cancer. Carcinogenesis 1996; 17:2279–2284.
15 Brooks PJ. DNA damage, DNA repair, and alcohol toxicity a review. Alcohol Clin Exp Res 1997; 21:1073–1082.