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 Arg194Trp, Arg280His and Arg399Gln 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 399Gln 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.
Those subjects who had smoked more than 400 cigarettes lifetime 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.

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 menstrual, 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. 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 399Gln 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 |
|---------|-----------------------------|-----------------------------|-----------------------------|
| Factors | All women (n = 205) | Controls (n = 205) | All women (n = 124) | Controls (n = 115) | All women (n = 81) | Controls (n = 85) |
| 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) |
| % Family history | 26 (3.8) | 24 (3.4) | 27 (3.4) | 25 (3.2) | 25 (4.0) | 23 (3.2) |
| % Use of oral contraceptives | 9 | 7 | 5 | 7 | 12 | 2 |
| % S mokeing (≥ 400 cigarettes lifetime) | 5 | 6 | 4 | 5 | 6 | 11 |
| % Drinking (> 1 per month) | 25 | 18 | 31 | 25 | 18 | 9 |
| Drinking (%) | 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). aFive controls were missing in menopausal status. FFTP, First full-term pregnancy.
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 399Gln 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 399Gln 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 399Gln 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.

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