Single nucleotide polymorphisms in breast cancer susceptibility gene 1 are associated with susceptibility to lung cancer

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Abstract. BRCA1 is a tumor suppressor that has been found to be involved DNA synthesis during cell replication. In a recent study, the single nucleotide polymorphism (SNP), rs799917, in BRCA1 was found to be associated with the development and progression of various types of tumor. In the present study, the association between rs799917 and susceptibility to lung cancer was evaluated in a Han Chinese population in the Liaoning Province of China. The BRCA1 rs799917 genotypes (C/C, C/T and T/T) were analyzed using TaqMan quantitative PCR in 682 patients with lung cancer and 694 healthy controls, and the results were analyzed using a Student's t-test, a χ^2 test and logistic regression analysis. Individuals carrying the C/T or T/T genotype had a lower risk of lung cancer compared with those carrying the C/C genotype [odds ratio (OR), 0.741; P=0.021; and OR, 0.610; P=0.011, respectively). The C/T + T/T genotype group had an even lower risk (OR, 0.709; P=0.005) compared with that in the C/C genotype group. In the stratified analyses of non-smokers, individuals with the C/T or T/T genotype had a lower risk of developing lung cancer compared with that in those carrying the C/C genotype (OR, 0.681; P=0.013; and OR, 0.569; P=0.021, respectively). The stratified analyses of the BRCA1 rs799917 polymorphism based on pathological type, chemotherapy and radiotherapy, showed that in the squamous cell carcinoma, non-chemotherapy and non-radiotherapy subgroups, individuals with the T/T genotype had a lower risk of lung cancer compared with that in those carrying the C/C genotype (OR, 0.454; P=0.007; OR, 0.485; P=0.002; and OR, 0.599; P=0.020, respectively). In conclusion, the T allele of the rs799917 SNP in BRCA1 was associated with a lower risk of lung cancer in the ethnic Han Chinese population in Liaoning Province and may represent a protective factor against lung cancer.

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Introduction

Global cancer statistics 2020 show that among malignant tumors, lung cancer has high incidence (11.4%) and mortality rates (18%) (1). Smoking and air pollution are important factors contributing to lung cancer based on epidemiological study results (2,3). Due to individual differences, susceptibility to tobacco and carcinogens differs; therefore, predisposition to lung cancer varies. Susceptibility to this disease may be partly genetic and associated with single nucleotide polymorphisms (SNPs). This is particularly apparent with respect to the relationship between lung cancer genetic susceptibility genes and gene-related repair of DNA damage, such as ERCC1, ERCC2, XPA and XRCC1 (4).

BRCA1 is located on the long arm of chromosome 17 and encodes an 1,863-amino-acid protein involved in DNA repair and maintenance integrity of the human genome (5). The human BRCA1 gene (Gene ID, 672) is 81.2 kb in length and located on chromosome 17. The gene consists of 22 coding exons and transcriptionally forms a 5.7-kb mRNA, including the differentially methylated regions and the promoter region (6). The 1,000 Genomes Project has established the most detailed catalogue of mutations in the human genome, with a frequency of BRCA1 mutations of >1% in the population based on DNA sequence variation (7). BRCA1 is a nuclear phosphoprotein, consisting of three major domains, including ubiquitin ligase, nuclear localization signal and BRCA1 Carboxy-terminal

domains; as a tumor suppressor, it has been associated with cell migration (8-10). In human cells, this protein can interact with DNA damage-sensing proteins, DNA damage response effectors, proteins involved in centrosome replication, cell cycle regulators and other proteins, such as 53BP1, Rad50, c-Myc, nuclear localization sequences and PALB2 (11-15). Taken together, this information not only establishes a critical biological role for BRCA1 as a custodian of chromosome integrity during the cell cycle, but also implies the possibility that pathogenic mutations inactivating the BRCA genes could be linked to cancer susceptibility by inducing chromosomal instability and mutagenesis (16,17).

Therefore, the aim of the present study was to determine whether SNPs within BRCA1 might be associated with lung cancer susceptibility. In previous reports, the BRCA1 rs799917 SNP was associated with breast cancer susceptibility (18). However, the rs799917 SNP has not been investigated in patients with lung cancer in China. Thus, a case-control study was conducted in a Han Chinese cohort from the Liaoning Province in China in order to investigate the association between the BRCA1 rs799917 SNP and susceptibility to lung cancer, thus identifying potential genetic causes and providing a scientific basis for primary prevention.

Materials and methods

Study participants. At the start of the study, a total of 2,100 patients were enrolled, including patients with pathological diagnosis of lung cancer (case group) and healthy controls (control group). The following exclusion criteria were used in the case group: i) A history of lung cancer, ii) a history of other concomitant tumors, iii) any cancer-related metastasis, iv) previous chemotherapy or radiotherapy and v) non-autologous transfusion. All patients with lung cancer were histopathologically diagnosed using the TNM staging system (19) with either squamous cell carcinoma (SCC), adenocarcinoma (AD) or small cell lung cancer (SCLC), and were from the Han population in Liaoning Province (China), without any kinship to each other. All clinical data used in the study had to be complete; therefore, 1,376 samples were excluded, due to incomplete clinical data and deficient DNA samples. Thus, a total of 682 patients with lung cancer were recruited from three hospitals: The Department of Radiotherapy from the First Affiliated Hospital of China Medical University (Liaoning, China), The General Hospital of Shenyang Military Region of Liaoning Province (Liaoning, China) and The Liaoning Cancer Hospital (Liaoning, China), between March 2010 and December 2012. A total of 694 healthy controls were randomly selected from the health examination center of The General Hospital of Shenyang Military Region during the same period. The inclusion criteria included: i) Non-basic diseases; ii) no history of tumor; and iii) voluntary participation. The exclusion criteria included: i) Family history of tumors; and ii) non-autologous transfusion. Relevant information was collected using structured questionnaires. Smoking was defined as ≥1 cigarette/day for 6 months continuously or cumulatively over a lifetime (20).

SNP selection and genotyping. The NCBI database (https://www.ncbi.nlm.nih.gov/) was searched for the association between rs799917 SNP and lung cancer, and no relevant data was found. Therefore, the rs799917 SNP was selected, since it had not been previously investigated in patients with lung cancer.

A blood sample (~5 ml) was collected from each participant, then DNA was extracted using standardized protease K digestion, phenol-chloroform extraction and ethanol precipitation. The genotypes of the BRCA1 rs799917 SNP were determined using TaqMan quantitative PCR (Applied Biosystems; Thermo Fisher Scientific, Inc.). The TaqMan universal PCR master mix and predesigned SNP genotyping assay mix, containing PCR primers and probes, were purchased from Applied Biosystems (Thermo Fisher Scientific, Inc.). Genotyping was performed using pre-designed TaqMan probes. The specific amplicon context sequence was TTCTGCATTTCCTGGATTTGAAAAC [A/G] GAGCAA ATGACTGGCGCTTTGAAAC. The PCR reaction mixture (5 μl) consisted of 1 μl DNA sample (>20 ng/μl), 2.5 μl master mix, 0.125 μl probe and 1.375 μl sterile water. The PCR conditions included initial denaturation at 95˚C for 10 min, followed by 47 cycles at 92˚C for 30 sec, 60˚C for 60 sec and final extension at 60˚C for 60 sec. The PCR plates were read on a PRISM 7900 instrument (Applied Biosystems; Thermo Fisher Scientific, Inc.). Deionized water was used as a negative control and the rs3219073/GG SNP of poly(ADP-ribose)polymerase 1 (PARP-1) was used as a positive control, since it has been previously detected in numerous lung cancer samples (21). The $2^{-\Delta\Delta Cq}$ method was used for quantification (22). A double-blind repeat test was performed on randomly selected samples (10%) to verify the results.

Statistical analysis. SPSS version 17.0 (SPSS, Inc.) was used for statistical analysis. Parametric continuous variables are presented as the mean ± SD and compared using an unpaired Student's t-test. The clinicopathological differences between patients with lung cancer and healthy controls were assessed using a χ^2 test, while the goodness-of-fit χ^2 test was performed to determine if the number of alleles for the SNP were significantly different from the expectations of Hardy-Weinberg equilibrium (HWE). Logistic regression analysis, with adjustment for sex and/or smoking status using SPSS Binary Logistic Covariates, was used to determine the association between the genotypes and the risk of lung cancer by calculating the odds ratios (ORs) and 95% confidence intervals (CIs). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of the study population. A total of 682 patients with lung cancer and 694 healthy subjects were recruited into the present study. The characteristics of the participants are listed in Table I. Among the 682 cases, 254 (37.3%) patients were diagnosed with SCC, 226 (33.1%) with AD and 202 (29.6%) with SCLC. A similar number of patients received treatment (chemotherapy, n=267; radiotherapy, n=269). The mean age was 58.96 years for patients and 58.54 years for the controls. The age of the participants was not statistically significantly different between the two groups ($P=0.462$). However, there were more smokers and males in the patient group compared with that in the control group (both $P<0.001$).

Table I. Characteristics of patients with lung cancer (n=682) and heathy controls (n=694).

Characteristics	Patients	Controls	P-value
Average age, years	58.96	58.54	0.462[a]
Sex, n (%)			<0.001[b]
Male	490 (71.8)	375 (54.0)	
Female	192 (28.2)	319 (46.0)	
Smoking status, n (%)			<0.001[b]
Smoker	398 (58.4)	106 (15.3)	
Never smoked	284 (41.6)	588 (84.7)	
Histology, n (%)			NA
Squamous carcinoma	254 (37.3)		
Adenocarcinoma	226 (33.1)		
Small cell lung cancer	202 (29.6)		
Chemotherapy, n (%)			NA
Yes	267 (39.1)		
No	415 (60.9)		
Radiotherapy, n (%)			NA
Yes	269 (39.4)		
No	413 (60.6)		

[a]Analyzed using an unpaired Student's t-test. [b]Analyzed using χ^2 test. NA, not applicable.

Frequency of the BRCA1 rs799917 SNP. There were three BRCA1 rs799917 genotypes in the patients and healthy controls (wild-type homozygous C/C, mutant homozygous T/T and mutant heterozygous C/T; Fig. S1). The genotypes between the cases and the controls were in accordance with HWE (χ^2=3.090; P=0.078 and χ^2=0.194; P=0.66, respectively; Table II). The distribution frequencies of the BRCA1 rs799917 genotypes are presented in Table III. Logistic regression analysis showed that the genotype frequencies of C/C vs. C/T and T/T in the cases were significantly different from that in the controls (OR, 0.745; P=0.011 and OR, 0.699; P=0.036, respectively). As shown in Table I, sex was a significant factor.

In addition, BRCA may affect the mismatch repair complex by reducing its activity (23). Theoretically, toxicity derived from agents (such as tobacco), that promote double-strand DNA damage, emphasizes the role of BRCA in promoting DNA repair (24); therefore, a SNP may negatively influence BRCA. Thus, the differences remained statistically significant after adjusting for sex (OR, 0.730 and P=0.008 for C/T; OR, 0.667 and P=0.020 for T/T), smoking status (OR, 0.737 and P=0.019 for C/T; OR, 0.609 and P=0.010 for T/T) or both (OR, 0.741 and P=0.021 for C/T; OR, 0.610 and P=0.011 for T/T). The C/T + T/T genotype group was associated with a lower risk of developing lung cancer compared with that in the C/C genotype group (OR, 0.734; P=0.005). The differences were also significant after adjusting for sex (OR, 0.714; P=0.002), smoking status (OR, 0.706; P=0.004) or both (OR, 0.709; P=0.005). The results showed the T allele of the BRCA1 rs799917 SNP was associated with a lower risk of developing lung cancer and could be a protective factor against lung cancer.

The risk of developing lung cancer with the three genotypes for the BRCA1 rs799917 SNP was further evaluated based on stratification due to smoking status, pathological types and chemotherapy or radiotherapy for the patients with lung cancer (Table IV). In the stratified analyses for non-smokers, individuals with the C/T or T/T genotype had a lower risk of developing lung cancer compared with those with the C/C genotype (OR, 0.681; P=0.013 and OR, 0.569; P=0.021, respectively). However, a significantly lower risk was not observed for smokers with either the C/T or T/T genotype compared with that in those that smoke with the C/C genotype. When the BRCA1 rs799917 SNP was stratified based on pathological type, individuals with the T/T genotype still had a lower risk of developing lung cancer compared with those with the C/C genotype in the SCC subgroup (OR, 0.454; P=0.007). In addition, those with the C/T genotype appeared to have a lower risk of developing lung cancer compared with those with the C/C genotype; however, the difference was not significant (P=0.055). Significant differences were not identified between the different genotypes among the other pathological subtypes. Individuals with either the C/T or T/T genotype had a lower risk of developing lung cancer compared with those with the C/C genotype in the stratified analysis for those who did not

Table II. Hardy-Weinberg equilibrium.

Groups	Number, n	χ^2	P-value[a]
Patients	682	3.090	0.078
Controls	694	0.194	0.660

[a]Analyzed using the goodness-of-fit χ^2 test.

Table III. Association between the BRCA1 rs799917 polymorphism and the risk of lung cancer.

			Lung cancer risk		Adjusted lung cancer risk for sex and smoking status		Adjusted lung cancer risk for sex		Adjusted lung cancer risk for smoking status	
Genotype	Patients, n (%)	Controls, n (%)	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
C/C	323 (47.4)	276 (39.8)	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
C/T	278 (40.7)	319 (46.0)	0.745 (0.593-0.935)	0.011	0.741 (0.575-0.956)	0.021	0.730 (0.579-0.920)	0.008	0.737 (0.572-0.950)	0.019
T/T	81 (11.9)	99 (14.2)	0.699 (0.500-0.977)	0.036	0.610 (0.418-0.892)	0.011	0.667 (0.474-0.937)	0.020	0.609 (0.417-0.889)	0.010
C/T+T/T	359 (52.6)	418 (60.2)	0.734 (0.593-0.909)	0.005	0.709 (0.558-0.901)	0.005	0.714 (0.575-0.888)	0.002	0.706 (0.556-0.897)	0.004

The data were analyzed using logistic regression. OR, odds ratio; CI, confidence interval.

Table IV. Stratified analyses of the BRCA1 rs799917 polymorphism and the risk of developing lung cancer.

				Lung cancer risk, C/T vs. C/C[b]		Lung cancer risk, T/T vs. C/C[c]	
Clinicopathological variables	C/C[a]	C/T[a]	T/T[a]	OR (95% CI)	P-value	OR (95% CI)	P-value
Smoking status							
Smoker	181/44	164/44	53/18	0.907 (0.568-1.450)	0.684	0.718 (0.383-1.345)	0.300
Non-smoker	142/232	114/275	28/81	0.681 (0.503-0.922)	0.013	0.569 (0.353-0.918)	0.021
Pathological type							
Squamous carcinoma	125/276	105/319	24/99	0.704 (0.492-1.008)	0.055	0.454 (0.257-0.803)	0.007
Adenocarcinoma	104/276	91/319	31/99	0.811 (0.577-1.141)	0.229	0.800 (0.492-1.303)	0.371
Small cell lung cancer	94/276	82/319	26/99	0.764 (0.524-1.116)	0.164	0.641 (0.369-1.112)	0.113
Chemotherapy							
Yes	119/276	109/319	39/99	0.816 (0.584-1.141)	0.235	0.847 (0.528-1.357)	0.489
No	204/276	169/319	42/99	0.721 (0.527-0.968)	0.030	0.485 (0.306-0.767)	0.002
Radiotherapy							
Yes	120/276	119/319	30/99	0.921 (0.659-1.286)	0.628	0.652 (0.390-1.087)	0.101
No	203/276	159/319	51/99	0.659 (0.490-0.884)	0.005	0.599 (0.388-0.923)	0.020

The data were analyzed using logistic regression and results were adjusted for sex or sex and smoking status. [a]Number of patients/number of controls. [b]Adjusted for sex. [c]Adjusted for sex and smoking status.

receive chemotherapy (OR, 0.721 and P=0.030 for C/T; OR, 0.485 and P=0.002 for T/T) or radiotherapy treatment (OR, 0.659 and P=0.005 for C/T; OR, 0.599 and P=0.020 for T/T). However, significant differences were not observed in those that did receive chemotherapy or radiotherapy treatment among the different genotypes.

Discussion

Lung cancer is globally the leading cause of cancer death, particularly in men (25). The incidence rate and developing trend vary significantly based on sex, age, race or ethnicity, socioeconomic status and geographical location, depending on the history of smoking in the individual (25). In a survey, the increase in the incidence rate of lung cancer was shown to rise equally with smoking dose in a clear dose-response relationship (25). Typically, it increased the risk of developing lung cancer by 5 to 10-fold (25). Exposure to an environment filled with tobacco smoke also increases the risk of developing lung cancer among non-smokers by ~20% (25). In the present study, there were more males and smokers in the case group than in the control group.

BRCA1 is a tumor suppressor gene located on chromosome 17q21, that contains 24 exons and encodes a functional macromolecule protein, containing 1,863 amino acids (26). In numerous studies (5,27,28), BRCA1 was shown to participate in several important biological functions, including the cell cycle, apoptosis, gene and protein stability, centrosome replication, DNA damage repair and transcriptional regulation. Furthermore, BRCA1 can affect tumor development, cell migration and response to chemoradiotherapy (5,27,28). DNA damage repair includes homologous recombination repair (HRR), non-homologous end-joining (NHEJ), nucleotide excision repair (NER), base excision repair (BER) and mismatch repair (MMR) (29). In previous studies, BRCA1 was shown to play a significant role in HRR, NHEJ and NER (30,31).

The BRCA1 rs799917 SNP leads to an amino acid change from proline to leucine at position 871 in the BRCA1 protein (32). This mutation may cause a corresponding change in its physiological function; however, the mechanism is unclear. Nicoloso *et al* (18) found that microRNA(miR)-638 could negatively regulate mRNA and protein BRCA1 expression in breast cancer cells and might target the coding sequence (CDS), but not a conserved target site inside the 3'-untranslated region. After miR-638 overexpression, cells expressing the C/C genotype displayed a stronger reduction of BRCA1 protein levels. In addition, the rs799917 T>C SNP located in the BRCA1 CDS could affect the interaction between BRCA1 mRNA and miR-638. The rs799917 T allele was associated with a weaker miR-638-dependent BRCA1 reduction (18). Hypothetically, individuals with the rs799917 T allele express higher mRNA and protein BRCA1 levels compared with those carrying the C allele. In other words, the T allele might indirectly play a protective role in the development of breast cancer. This observation has been validated in human bronchial epithelial cells using chemical carcinogens to induce cell transformation (33), highlighting the essential involvement of both miR-638 and BRCA1 in the tumorigenesis of epithelial cells.

Sirisena *et al* (34) found the G allele of rs799917 SNP (β, -1.069; standard error, 0.537; P=0.047) was associated with age of onset, between 50 and 59 years in patients with sporadic breast cancer from Sri Lanka. In previous studies, the BRCA1 rs799917 SNP was not significantly associated with breast cancer risk (35-38); however, the results have not been consistent. Previous research investigating rs799917 has involved multiple tumors. Zhou *et al* (39) showed that individuals with the T/T genotype had a significantly decreased risk of developing cervical cancer compared with those with the C/T and C/C genotypes. In addition, Chang *et al* (32) investigated the rs799917 SNP with glioblastoma multiforme susceptibility in American Caucasians and found that individuals with the T/T genotype had a reduced risk of developing glioblastoma compared with that in individuals with the C/C genotype. Furthermore, Zhang *et al* (40) found that the risk of developing esophageal SCC (ESCC) was significantly increased in carriers of the C/T or C/C genotype compared with that in those with the T/T genotype, in the Chinese population. Lee *et al* (41) investigated the association between the BRCA1 rs799917 SNP and clinical outcomes in patients with non-small cell lung cancer treated with first-line paclitaxel-cisplatin chemotherapy and found that patients carrying the T allele had a significantly improved chemotherapeutic response and overall survival time. Furthermore, individuals with the rs799917 T/T genotype had a significantly decreased risk of developing gastric cancer compared with those with the C/T and C/C genotypes, in a Chinese Han population (42). Xu *et al* (43) showed the rs799917 T/T genotype could decrease the risk of developing cervical cancer, ESCC, gastric cancer and non-Hodgkin lymphoma among Asian populations in one or more genetic models. Taken together, the results of these studies indicated that the BRCA1 rs799917 SNP, particularly the T allele, could serve as a potential clinical biomarker in patients with cancer.

In the present study, the association between the BRCA1 rs799917 SNP and susceptibility to lung cancer was examined in patients with lung cancer in the Han Chinese population from Liaoning Province (China). The data showed the T allele was associated with a lower risk of developing lung cancer and could be a protective factor against this disease. However, there were limitations to the current study. It is important to validate the results using a larger sample size, and to confirm the result in the Han Chinese population from different geographical regions and in other ethnic groups. In addition, it is important to identify and understand the mechanism by which the rs799917 SNP affects the mRNA and protein BRCA1 expression levels in lung cancer. Therefore, in future experiments, multiple SNPs will be selected (including BRCA1 rs799917) to investigate their association with lung cancer, and MMR protein activity would also be determined by comparing healthy donors and patients with lung cancer to verify the association between SNPs and the development of tumors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DL, YG, BZ, YY and YZ made substantial contributions to conception and design of the study. HC, LB and YQ made substantial contributions to acquisition of data. DL, YG, LL, HC, YY and YZ were involved in drafting the manuscript. DL and LL contributed to analysis and interpretation of data, and were involved in revising the manuscript critically for important intellectual content. DL, YG, YY and YZ agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have given final approval of the version to be published.

Ethics approval and consent to participate

All individual participants voluntarily joined the study and provided written informed consent. The Ethics Committee of the China Medical University (Shenyang, China) approved the investigation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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