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Interaction Between Environmental Risk Factors and Catechol-O-Methyltransferase (COMT) and X-Ray Repair Cross-Complementing Protein 1 (XRCC1) Gene Polymorphisms in Risk of Lung Cancer Among Non-Smoking Chinese Women: A Case-Control Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Backgrpound: Various studies have highlighted the link between polymorphisms in the XRCC1 gene (encoding X-ray repair cross-complementing group 1) with the incidence of decreased DNA repair capacity and an increased predisposition to cancer. Catechol-O-methyltransferase (COMT) plays a crucial role in estrogen-induced cancers. In the present study was analyzed the potential influence of XRCC1 and COMT gene polymorphisms as predisposing factors from a lung cancer perspective, in addition to conducting an investigation into their interaction with environmental risk factors in relation to lung cancer among non-smoking Chinese women.

Material/Methods: The XRCC1 gene T-77C, Arg194Trp, Arg280His, Arg399Gln, COMT gene 186C>T, and Val158Met mutations were evaluated in peripheral blood collected from 261 non-smoking female patients diagnosed with primary lung cancer and 265 female patients with benign lung disease.

Result: The results obtained from this study demonstrated that XRCC1–77TC + CC, XRCC1 399Gln/Gln, COMT 186CT + TT, COMT 158Val/Met genotypes, type of occupation, cooking-oil fumes, and soot exposures were all independent risk factors involved with the occurrence of lung cancer among non-smoking women. Moreover, interactions between environmental exposure factors as well as XRCC1 and COMT gene polymorphisms were determined to play significant contributory roles regarding susceptibility of non-smoking females to lung cancer.

Conclusions: Taken together, T-77C and Arg399Gln polymorphisms of the XRCC1 gene, as well as the 186C>T and Val158Met polymorphisms of the COMT gene, increased the risk of lung cancer in non-smoking women, with the factors of occupation type, cooking-oil fumes, and soot exposures representing key contributing factors.

MeSH Keywords: Amplified Fragment Length Polymorphism Analysis • Genes, abl • Lung Neoplasms

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3081 6 — 32

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Background

Primary lung cancer represents a malignancy with a particularly poor prognosis and is the leading cause of cancer-related deaths worldwide. Although progress has been made from a clinical and research perspective, primary lung cancer is still largely associated with increased rates of prevalence and mortality worldwide [1,2]. Statistics have revealed a worrying trend regarding the disease demographics, highlighting a 2-fold increase in the incidence of lung cancer over the past 30 years [3]. Among all cancer types, an average survival rate of 5-years is reported to be reflective of the poorest prognosis, which is a common circumstance experienced by many lung cancer patients diagnosed with distant and regional diseases [4]. Lung cancer is the foremost cause of smoking-related mortality, which more recently has even exceeded that of coronary artery disease, with reports indicating a rising incidence of lung cancer is associated with genetic factors as well as other nonspecific contributory factors over the last few decades [5,6]. At present, there ares various applicable tumor treatment approaches, including surgery, radiotherapy, ultrasound elastography, and chemotherapy, depending on the patient's condition and clinical staging [7,8]. Studies have revealed that the 5-year survival rate of patients with lung cancer at early stage is 58–73%, while that of patients with lung cancer at a later stage is an abysmal 3.5% [9]. Therefore, an early diagnosis, timely intervention, and close antenatal surveillance play an absolutely vital role in the prognosis of lung cancer [6]. New and more accurate lung cancer predictors are required to provide a better diagnosis and prognosis for patients with lung cancer.

The X-ray repair cross-complementing group 1 (XRCC1) protein, the amount of which shares a significant correlation with resistance to the chemotherapy drug cisplatin in the treatment of lung cancer, has been reported to have a distinct effect on base excision repair (BER) in addition to acting as a scaffold protein for single-strand break repair and BER activities [10]. A previous study indicated the involvement of the estrogen-metabolizing enzyme, catechol-O-methyl transferase (COMT), in the inactivation of catechol estrogens through its transformation into non-genotoxic metabolites, as well as highlighting an association between COMT gene polymorphism and lung cancer, particularly among non-smoking women of Chinese descent [11]. A study performed by Guo et al. demonstrated that XRCC1 gene polymorphisms can influence an individual's susceptibility to lung cancer [12]. A significant finding of a previous study suggested exposure to cooking-oil fumes is a risk factor associated with the incidence of lung cancer among smoking women [13]. Studies have shown that exposure to cooking-oil fumes (mainly composed of 2 types of chemical compounds: aldehydes and polycyclic aromatic hydrocarbons) and environmental factors (especially involving occupational exposure) increase risk of lung cancer [14,15]. Based on the aforementioned literature, we hypothesized that a relationship between COMT, XRCC1, and lung cancer exists. Few studies have investigating the underlying mechanism of COMT and XRCC1 gene polymorphisms, as well as that of environmental risk factors in relation to the susceptibility of lung cancer occurrence, among non-smoking Chinese women. Hence, the central objective of the present study was to provide clinical evidence of a compelling nature that could aid in the prevention of lung cancer occurrence, by further investigating the combined direct and indirect effects of COMT and XRCC1 gene polymorphisms as well as that of environmental risk factors influencing the susceptibility of lung cancer among non-smoking Chinese women.

Material and Methods

Ethical statement

This study was conducted with the approval of the Ethics Committee of Heze Municipal Hospital of Shandong Province. All participating patients signed informed consent documentation prior to enrollment into the study. All procedures of the study were performed in strict accordance with the principles of the Declaration of Helsinki.

Study subjects

We enrolled A total of 261 non-smoking female patients aged between 24–71 years, with an average age of 54.4±10.0 years, with primary lung cancer and who had previously received treatment at the Heze Municipal Hospital of Shandong Province between January 2014 and January 2016. Based on pathological or cytological typing, there were 167 cases of squamous cell carcinoma, 45 cases of adenocarcinoma, 110 cases of large cell carcinoma, 13 cases of adenosquamous carcinoma, and 25 cases of small cell carcinoma. The inclusion criteria were: 1. Non-smoking females aged 24 to 71 years. 2. Primary lung cancer confirmed by bronchoscopy and aspiration biopsy. 3. Patients presented with no other tumors. 4. Patients had complete general information and specimen collection. The exclusion criteria were: Patients with severe heart, liver, kidney, or other dysfunctions combined with any other immune and endocrine system diseases. The control group consisted of 265 female patients aged 25–70 years (with an average age of 54.7±9.5 years), with benign lung diseases (including pneumonia, pulmonary fibrosis, and pulmonary tuberculosis) who had previously received treatment at the Heze Municipal Hospital of Shandong Province between January 2014 and January 2016. The control group inclusion criteria were: 1. Non-smoking women ages 25–70 years. 2. Patients free of any other malignancies and genetic diseases. 3. No blood relations among enrolled patients in the case group. 4. Patients had complete general

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information and specimen collection. The exclusion criteria set for the control group were the same as those in the case group.

Epidemiological data

A unified questionnaire was prepared to gather the basic characteristics of each individual patient among the case and control groups, including name, age, nationality, occupational exposure history, education level, body mass index (BMI) [BMI=body weight (kg)/height^2 (m^2)], income, family history of cancer, passive smoking, cooking fume exposure history, and soot exposure history. The definitions of the related questions were clarified as follows [16]: 1. Smoking: Persons consuming 1 or more cigarettes per day for more than 1 month or if the cumulative amount reaches this level during a short period of time were excluded from the study; 2. Passive smoking history: Subjects exposed to 1 or more cigarettes per day for a period of more than 1 year; 3. Family history of cancer: The immediate family (parents, children, siblings) or second-degree relatives (grandparents, uncle, aunt) who had previously suffered from cancer; 4. Cooking fume exposure history: People engaged in cooking for more than 15 years, during which they would fry food at least twice a week or more, suffering from frequent eye and throat irritation during the cooking process; 5. Soot exposure history: Occurs during the heating and cooking process, the duration of which lasted for more than 3 years, and a minimum of twice a week, accompanied by nose and throat irritation during the process; 6. Occupational exposure history: Persons engaging or previously engaged in work involving exposure of asbestos, coal tar, smoke, heavy metals, or rubber for a period greater than 2 years.

Genomic DNA extraction and genotyping

DNA was extracted using a genomic DNA Extraction Kit (Tiangen Biotech Co., Ltd., Beijing, China) from the peripheral blood collected from patients participating in the study. Polymerase chain reaction (PCR) amplification of XRCC1 and COMT genes was performed: the primer sequences synthesized by the Shanghai Biotechnology Engineering Co., Ltd., Shanghai, China are depicted in Table 1. After the PCR products had been sequenced, the sites of T-77C, Arg399Gln, Arg280His, and Arg194Trp in XRCC1 gene and 186C>T and Val158Met in COMT gene were genotyped using the Sanger terminal termination method. The PCR reaction procedure was performed based on the following steps: pre-denaturation at 95°C for 3 min; 34 cycles of denaturation at 95°C for 30 s, annealing at 55°C for 30 s, at 72°C for 1 min, and at 72°C for 5 min.

Statistical analysis

SPSS 21.0 statistical software (IBM Corp. Armonk, NY, USA) was used for data analysis purposes. Measurement data was presented as mean ± standard deviation and were compared by *t* test. The enumeration data are expressed as percentage or rate and were compared using the χ^2 test. The Hardy-Weinberg equilibrium genetic site assessments were evaluated by χ^2 test. The effects of the environmental risk factors (including age, nationality, education level, BMI, economic income, family history of cancer, passive smoking, occupational exposure history, cooking fume exposure history, and soot exposure history) in regard to lung cancer susceptibility among non-smoking women were identified in accordance with non-conditional logistic regression analysis.

Table 1. Primer sequences for PCR.

Genetic locus	Primer sequence (5'-3')	PCR product length (bp)
XRCC1		
T-77C	F: GAGGAA ACGCTCGTTGCTAAG	336
	R: TCCTCATTAATTCCCTCACGTC	
Arg194Trp	F: GCCAGGGCCCCTCCTTCAA	485
	R: TACCCTCAGACCCACGAGT	
Arg280His	F: CCA GTGGTGCTAACCTAATC	303
	R: CCTACATGAGGTGCGTGCTGT	
Arg399Gln	F: TTGTGCTTTCTCTGTGTCCA	615
	R: TCCTCCAGCCTTTTCTGATA	
COMT		
186C>T	F: GTGCCTTATCGGCTGGAACG	250
	R: TTGATGCCTGGTCCTGGGTC	
Val158Met	F: TCGTGGACGCCGTGATTCAGG	217
	R: AGGTCTGACAACGGGTCAGGC	

PCR – polymerase chain reaction; F – forward primer; R – reverse primer; XRCC1 – X-ray repair cross complementing group 1; COMT – catechol-O-methyltransferase.

Results

Occupation, cooking-oil fume, and soot exposures are linked with the occurrence of lung cancer among non-smoking women

During the current study, 261 female patients with lung cancer served as the case group, while 265 female patients with benign lung diseases represented the control group. As illustrated in Table 2, no significant change was observed in relation to the factors of age, nationality, education level, BMI, economic income, family history of cancer, and passive smoking history

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Table 2. Basic characteristics of study subjects between the case and control groups.

Basic characteristic	Case group (n = 261)	Control group (n = 265)	P value
Age (mean ±SD, years old)	54.4±10.0	54.7±9.5	0.724
Nationality (No.)			
Han	182	168	0.124
Minority	79	97	
Education level (No.)			
Uneducated	26	23	
Primary school	54	60	0.889
Middle school	63	67	
High school and above	118	115	
BMI (mean ±SD)	24.02±3.43	23.53±3.13	0.088
Average monthly income (mean ±SD, CNY)	635.7±357.2	632.5±350.3	0.917
Passive smoking history (No.)			
Yes	156	149	0.410
No	105	116	
Family history of cancer (No.)			
Yes	35	27	0.252
No	226	238	
History of cooking fume exposure (No.)			
Yes	98	76	0.031
No	163	189	
History of soot exposure (No.)			
Yes	82	61	0.030
No	179	204	
History of occupational exposure (No.)			
Yes	69	24	<0.001
No	192	241	

BMI – body mass index; SD – standard deviation.

between patients in the case and control groups (all $p>0.05$). The effects of cooking fume, occupation, and soot exposures were higher among patients in the case group, with lower levels detected in the control group (both $p<0.05$).

XRCC1 gene -77 TC + CC and 399Gln/Gln, COMT gene 186CT+TT, and 158Val/Met are associated with the risk of lung cancer in non-smoking women

DNA was extracted from the peripheral blood collected from the patients to detect XRCC1 and COMT gene polymorphisms. As depicted in Table 3, based on the results of the Hardy-Weinberg genetic equilibrium test, the allele frequencies and genotypes of T-77C, Arg399Gln, Arg280His, Arg194Trpof XRCC1 gene, and Val158Met and Ala72Ser of COMT gene had reached equilibrium in the control group, while the frequency of XRCC1–77CC, XRCC1 194Arg/Arg, XRCC1 194Arg/Trp, XRCC1 194Trp/Trp, XRCC1 280Arg/Arg, XRCC1 280Arg/His, XRCC1 280His/His, XRCC1 399Arg/Gln or COMT 158Met/Met exhibited no notable statistical difference between the case and control groups (all $p>0.05$). The gene frequency of XRCC1–77TC, XRCC1–77TC + CC, XRCC1 399Gln/Gln, COMT 186CT, COMT 186TT, COMT 186CT + TT and COMT 158Val/Met were elevated in the case group, while lower levels were recorded in the control group (all $p<0.05$).

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Table 3. Genotype distribution and allele frequency of XRCC1 and COMT in the case and control groups.

Genotype	Control group n (%)		Case group n (%)		OR (95% CI)		P value
XRCC1 T-77C							
TT	153	(57.74)	125	(47.89)	1.00	(reference)	–
TC	44	(16.61)	67	(25.67)	1.864	(1.191–2.917)	0.006
CC	68	(25.66)	69	(26.44)	1.242	(0.824–1.871)	0.299
TC+CC	112	(42.26)	136	(52.11)	1.486	(1.054–2.097)	0.024
XRCC1 Arg194Trp							
Arg/Arg	203	(76.61)	189	(72.41)	1.00	(reference)	–
Arg/Trp	60	(22.64)	66	(25.29)	1.181	(0.790–1.766)	0.416
Trp/Trp	2	(0.75)	6	(2.29)	3.222	(0.642–16.17)	0.134
XRCC1 Arg280His							
Arg/Arg	222	(83.77)	208	(79.69)	1.00	(reference)	–
Arg/His	41	(15.47)	49	(18.77)	1.26	(0.808–2.013)	0.295
His/His	2	(0.75)	4	(1.53)	2.135	(0.387–11.78)	0.373
XRCC1 Arg399Gln							
Arg/Arg	144	(54.34)	123	(47.13)	1.00	(reference)	–
Arg/Gln	98	(36.98)	99	(37.93)	1.183	(0.818–1.710)	0.372
Gln/Gln	23	(8.68)	39	(14.94)	1.985	(1.124–3.506)	0.017
COMT: 186C>T							
CC	109	(41.13)	79	(30.27)	1.00	(reference)	–
CT	106	(40.00)	121	(46.36)	1.575	(1.067–2.326)	0.022
TT	50	(18.87)	61	(23.37)	1.683	(1.049–2.702)	0.031
CT+TT	156	(58.87)	182	(69.73)	1.610	(1.123–2.307)	0.009
COMT Val158Met							
Val/Val	81	(30.57)	69	(26.44)	1.00	(reference)	–
Val/Met	85	(32.08)	115	(44.06)	1.588	(1.037–2.433)	0.033
Met/Met	99	(37.36)	77	(29.51)	0.913	(0.589–1.415)	0.684

P<0.05 compared with the control group; Odds ratio (OR) value was corrected by age, history of cooking fume exposure, occupational exposure and soot exposure; CI – confidence interval; XRCC1 – X-ray repair cross complementing group 1; COMT – catechol-O-methyltransferase.

Table 4. Unconditional logistic regression analysis of the lung cancer susceptibility among non-smoking women.

Risk factors	Regression coefficient	P value	OR (95% CI)
XRCC1–77TC+CC	0.450	0.016	1.568 (1.086–2.265)
XRCC1 399Gln/Gln	0.672	0.028	1.958 (1.074–3.570)
COMT 186CT+TT	0.595	0.003	1.813 (1.227–2.679)
COMT 158Val/Met	0.653	0.001	1.922 (1.305–2.830)
History of cooking fume exposure	0.403	0.041	1.496 (1.016–2.202)
History of soot exposure	0.500	0.018	1.649 (1.089–2.498)
History of occupational exposure	1.262	< 0.001	3.531 (2.086–5.976)

OR – odds ratio; CI – confidence interval; XRCC1 – X-ray repair cross complementing group 1; COMT – catechol-O-methyltransferase.

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The gene frequency of XRCC1–77TT, XRCC1 399Arg/Arg, COMT 186CC and COMT 158 Val/Val was decreased in the case group and ascended in the control group (all $p<0.05$). The XRCC1–77 TT, XRCC1 399Arg/Arg, COMT 186CC, and COMT 158 Val/Met genotypes were used as references. The results show that XRCC1–77 TC + CC, XRCC1 399Gln/Gln, COMT 186CT + TT, and COMT 158Val/Met were risk genes linked to the occurrence of lung cancer among non-smoking women (OR=1.468, 95% CI=1.054–2.097; OR=1.985, 95% CI=1.124–3.056; OR=1.610, 95% CI=1.123–2.307, OR=1.588, 95% CI=1.037–2.433).

The independent risk factors for lung cancer risk in non-smoking women

Non-conditional logistic regression model was used to analyze the multivariate analysis regarding the relationship between XRCC1 T-77C, XRCC1 Arg399Gln, COMT Val158Met, and COMT 186C>T polymorphisms and the histories of exposure in the form of occupational exposure, cooking fume exposure, and soot exposure in relation to the risk of lung cancer among non-smoking women. As shown in Table 4, the obtained results revealed that XRCC1–77TC + CC, XRCC1 399Gln/Gln, COMT 186CT + TT, and COMT 158Val/Met genotypes, and the histories of occupational exposure, cooking fume exposure, and soot exposure were all correlated with the occurrence of lung cancer among non-smoking women and were considered as independent risk factors for lung cancer susceptibility among non-smoking women ($p<0.05$).

The interaction between XRCC1 and COMT gene polymorphisms and environmental exposure for lung cancer risk in non-smoking women

The roles of XRCC1 T-77C, Arg399Gln, Arg280His, and Arg194Trp, COMT 186C>T, and Val158Met polymorphisms and the histories of cooking fume exposure, occupational exposure, and soot exposure on lung cancer susceptibility among non-smoking women were further analyzed by using a non-conditional logistic regression model, the results of which are illustrated in Table 5. Non-smoking women with COMT 186CT + TT or COMT 158Met/Met genotypes were determined to have an elevated risk of lung cancer occurrence with a history of cooking fume exposure (both $p<0.05$). Non-smoking women with XRCC1 399Arg/Gln, XRCC1 399Gln/Gln, COMT 186CT + TT, or COMT 158Met/Met genotypes exhibited an increased risk of lung cancer among those who had a history of soot exposure and occupational exposure (all $p<0.05$). No detection was made in regard to XRCC1 T-77C, Arg194Trp, and Arg280His polymorphisms and lung cancer susceptibility in non-smoking women with a history of cooking fume exposure, occupational exposure, or soot exposure (all $p>0.05$). These finding indicate that the interaction of environmental risk factors, as well as that of XRCC1 and COMT gene polymorphisms, have adverse effects on lung cancer susceptibility in non-smoking women.

Haplotype frequencies of XRCC1 and COMT genes are associated with the risk of lung cancer among non-smoking women

A correlation between haplotype frequencies of XRCC1 and COMT genes and lung cancer in non-smoking women was detected. Haplotype frequencies of XRCC1 and COMT genes are shown in Table 6. Haplotypes that failed to meet statistical requirements were eliminated in a few patients. In regard to the XRCC1 gene, 5 kinds of haplotypes that met the statistical requirements were included, and the results indicated that non-smoking women with XRCC1C-Arg-Arg-Gln and C-Trp-His-Gln had lower risks of lung cancer occurrence ($p>0.05$), while the risks were greater among those with XRCC1 C-Trp-Arg-Arg, C-Trp-His-Arg, and T-Arg-Arg-Arg ($p>0.05$). Regarding the COMT gene, non-smoking women with COMT C-Met exhibited a remarkably higher susceptibility to lung cancer, while those with COMT T-Met had a reduced susceptibility to lung cancer (both $p<0.05$). There was a very low and insignificant decrease in lung cancer susceptibility among non-smoking women with COMT C-Val ($p>0.05$). The results obtained demonstrated that the haplotype frequencies of XRCC1 and COMT genes are associated with the occurrence of lung cancer in non-smoking women.

Discussion

Lung cancer remains one of the deadliest malignancies known to mankind, resulting in deaths of more than one million people annually. Lung cancer among women (usually nonsmokers) has becomes one of the most prevalent cancers around the world [17]. Females have the highest mortality rate among all types of cancers, with more lung cancer deaths recorded per year than that of other cancer deaths, and higher than breast, colorectal, prostate, and pancreatic cancers combined [6,18]. Chinese women have very high rates of lung cancer [19]. Lung carcinogenesis is a complicated, long, multi-stage process characterized by the interplay of predisposed cancer genes, as well as specific environmental exposures [20]. XRCC1 and COMT gene polymorphisms and cooking-oil fume exposure are central risk factors in the progression of lung cancer [11,21]. In the present study we investigated the potential effects of environmental risk factors and XRCC1 and COMT gene polymorphisms in relation to lung cancer susceptibility among non-smoking Chinese women. We found a distinct correlation of XRCC1 and COMT gene polymorphisms and environmental risk factors with lung cancer susceptibility.

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Table 5. Effect of XRCC1 T-77C, Arg194Trp, Arg280His and Arg399Gln, COMT Val158Met and 186C>T gene polymorphisms and histories of cooking fume exposure and soot exposure on lung cancer susceptibility among non-smoking women.

Genotype	With history of cooking fume exposure		OR	*P* value	With history of soot exposure		OR	*P* value	With history of occupational exposure		OR	*P* value
	Control group n (%)	Case group n (%)	(95% CI)		Control group n (%)	Case group n (%)	(95% CI)		Control group n (%)	Case group n (%)	(95% CI)	
TT	43 (56.58)	49 (50.00)	1.00 (reference)		37 (60.66)	43 (52.44)	1.00 (reference)		12 (50.00)	30 (43.38)	1.00 (reference)	
TC+CC	33 (43.42)	49 (50.00)	1.303 (0.714–2.380)	0.389	24 (39.34)	39 (47.56)	1.398 (0.714–2.739)	0.328	12 (50.00)	39 (56.52)	1.300 (0.512–3.29)	0.581
XRCC1 Arg194Trp												
Arg/Arg	60 (78.95)	73 (74.49)	1.00 (reference)		47 (77.05)	60 (73.17)	1.00 (reference)		16 (66.67)	35 (50.72)	1.00 (reference)	
Arg/Trp	15 (19.74)	23 (23.47)	1.260 (0.604–2.628)	0.537	13 (21.31)	21 (25.61)	1.265 (0.574–2.789)	0.559	8 (33.33)	30 (43.48)	1.714 (0.644–4.563)	0.278
Trp/Trp	1 (1.32)	2 (2.04)	1.644 (0.145–18.58)	0.685	1 (1.64)	1 (1.22)	0.783 (0.048–12.86)	0.864	0 (0.00)	4 (5.80)	4.183 (0.212–82.38)	0.183
XRCC1 Arg280His												
Arg/Arg	64 (84.21)	79 (80.61)	1.00 (reference)		53 (83.61)	63 (76.83)	1.00 (reference)		18 (75.00)	42 (60.87)	1.00 (reference)	
Arg/His	11 (14.47)	17 (17.35)	1.252(0.547–2.863)	0.594	9 (14.75)	18 (21.95)	1.619 (0.671–3.909)	0.281	6 (25.00)	24 (34.78)	1.714 (0.599–4.906)	0.312
His/His	1 (1.32)	2 (2.04)	1.620(0.144–18.29)	0.694	1 (1.64)	1 (1.22)	0.809 (0.049–13.27)	0.882	0 (0.00)	3 (4.35)	3.047 (0.149–62.05)	0.262
XRCC1 Arg399Gln												
Arg/Arg	40 (52.63)	38 (38.78)	1.00 (reference)		43 (70.49)	36 (43.91)	1.00 (reference)		11 (45.83)	8 (11.59)	1.00 (reference)	
Arg/Gln	29 (38.16)	46 (46.94)	1.670 (0.878–3.176)	0.117	16 (26.23)	35 (42.68)	2.613 (1.248–5.471)	0.009	11 (45.83)	42 (60.87)	5.250 (1.701–16.21)	0.003
Gln/Gln	7 (9.21)	14 (14.29)	2.105 (0.766–5.782)	0.144	2 (3.27)	11 (13.41)	6.569 (1.366–31.60)	0.009	2 (8.33)	19 (27.54)	6.569 (1.366–31.60)	0.001
COMT 186C>T*												
CC	31(40.79)	24(24.49)	1.00 (reference)		27 (44.26)	21 (25.61)	1.00 (reference)		18 (75.00)	28 (40.58)	1.00 (reference)	
CT+ TT	45(59.21)	74(75.51)	2.124 (1.110–4.066)	0.022	34 (55.74)	61 (74.39)	2.307 (1.136–4.683)	0.019	6 (25.00)	41 (59.42)	4.393 (1.550–12.45)	0.004
COMT Val158Met												
Val/Val	26 (34.21)	22 (22.45)	1.00 (reference)		25 (40.98)	20 (24.39)	1.00 (reference)		5 (20.83)	4 (5.80)	1.00 (reference)	
Val/Met	32 (42.11)	40 (40.82)	1.477 (0.709–3.078)	0.296	18 (29.51)	29 (35.36)	2.014 (0.877–4.627)	0.097	9 (37.50)	25 (36.23)	3.472 (0.759–15.88)	0.098
Met/Met	18 (23.68)	36 (36.73)	2.364 (1.060–5.270)	0.034	18 (29.51)	33 (40.24)	2.292 (1.007–5.214)	0.046	10 (41.67)	40 (57.97)	5.000 (1.131–22.11)	0.024

OR – odds ratio; CI – confidence interval; XRCC1 – X-ray repair cross complementing group 1; COMT – catechol-O-methyltransferase.

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Table 6. Haplotype frequencies of XRCC1 and COMT genes in the case and control groups.

Haplotype	Control group n (%)	Case group n (%)	OR (95% CI)	*P* value
XRCC1 (-77-194-280-399)				
C-Arg-Arg-Gln	108 (20.4)	127 (24.3)	1.229 (0.917–1.645)	0.167
C-Trp-Arg-Arg	19 (3.6)	16 (3.1)	0.837 (0.426–1.645)	0.605
C-Trp-His-Arg	18 (3.4)	14 (2.7)	0.770 (0.378–1.565)	0.468
C-Trp-His-Gln	27 (5.1)	43 (8.2)	1.030 (0.724–1.463)	0.05
T-Arg-Arg-Arg	341 (64.3)	315 (60.3)	0.794 (0.615–1.024)	0.075
COMT (186-158)				
C-Met	77 (14.5)	26 (5.0)	0.308 (0.194–0.490)	<0.001
C-Val	247 (46.6)	253 (48.5)	1.078 (0.846–1.373)	0.545
T-Met	206 (38.9)	243 (46.6)	1.370 (1.072–1.750)	0.012

Odds ratio (OR) was corrected by age, occupational exposure, cooking fume exposure, and soot exposure; CI – confidence interval; XRCC1 – X-ray repair cross complementing group 1; COMT – catechol-O-methyltransferase.

Based on our observations and Hardy-Weinberg equilibrium assessment, XRCC1–77 TC + CC, XRCC1 399Gln/Gln, COMT 62CT + TT, and COMT 158Val/Met were all determined to be risk factors in the occurrence of lung cancer. HWE placed emphasis on 2 genotypes of an autosomal gene locus randomly genotyped in a discrete population [22]. Li et al. revealed that XRCC1 (a DNA repair protein) is related to the single-strand break repair and base excision repair pathway, while individuals with homozygous XRCC1 399Gln/Gln genotype and XRCC1–77 combined TC and CC genotypes presented with a slightly elevated risk of lung cancer [16]. A series of previous studies also suggested that polymorphisms and haplotype of XRCC1 have an effect on the occurrence and survival of lung cancer [23,24]. Reports have shown that smoking and the genetic polymorphisms of XRCC1-399 and XRCC1-194 were related to the risk of lung cancer [25]. As a key modulator in the extraneural dopamine catabolism, COMT plays a vital role in the mechanisms of drug reward [26]. Tan et al. reported that the COMT l58Val/Met polymorphism can confer a genetic susceptibility among females with lung cancer [20], which agrees with our findings, which are also consistent with a previous study that highlighted a link between COMT polymorphisms and the risks lung cancer, particularly among non-smoking Chinese women [11]. Reports have suggested an association between COMT genetic variations and several other conditions, including pain sensitivity, various neurobehavioral disorders, and an array of human cancers [27].

Our study also revealed that non-smoking women with COMT 62CT + TT or COMT 158Met/Met genotypes possess a greater susceptibility to lung cancer, particularly among patients with a history of cooking fume exposure, while non-smoking women with XRCC1 399Arg/Gln, XRCC1 399Gln/Gln, COMT 62CT+ TT, or COMT 158Met/Met genotypes were found to possess a greater risk of lung cancer occurrence, including patients with histories of occupational exposure and soot exposure. Based on a study conducted by Beveridge et al., occupational exposure to nickel and cadmium was identified as a factor increasing the risk of lung cancer [28]. The outcomes of a previous study have also suggested that exposure to cooking-oil fumes was associated with elevated risk of lung cancer among Chinese non-smoking females [29]. Furthermore, the risk factor of cooking-oil fume exposure continues to be associated with a significant increase in risk of lung cancer [13,30]. Moreover, another study indicated that COMT haplotypes, such as the Val108/158Met polymorphism, play a notable role in nicotine dependence, as well as conferring protection among females but not in their male counterparts [31]. Our study indicates that non-smoking women with COMT C-Met haplotype possess a higher susceptibility to lung cancer, while those with COMT T-Met haplotypes have a lower susceptibility. A previous study demonstrated that 3 common haplotypes of the human COMT gene, which are divergent in 1 nonsynonymous and 2 synonymous positions, code for the difference in COMT enzymatic activity and are involved in pain sensitivity [32].

Conclusions

We found that T-77C and Arg399Gln polymorphisms of XRCC1 gene and 186C>T and Val158Met polymorphisms of COMT gene confer a greater risk for lung cancer among non-smoking women, brought about by contributory factors, including occupation, cooking-oil fume exposure, and soot exposure. A notable strength of our findings is the evaluation of primary

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environmental risk factors and our evaluation of the proposed genetic host factors and their involvement in lung carcinogenesis in a specific population. To the best of our knowledge, this is the first study of its kind investigating the interplay between XRCC1 and COMT gene polymorphisms as well as environmental factors in lung cancer among non-smoking Chinese women. This study provides further insights into the pathogenesis of lung cancer and presents a new target in the clinical diagnosis and treatment of lung cancer. However, our study is limited by the small sample size and lack of ethnic diversity. Therefore, to improve lung cancer prevention and treatment, future studies are needed to expand the sample size and include other ethnic populations to investigate the specific mechanisms involved.

Conflicts of interest

None.

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