Technology in Cancer Research & Treatment
2017, Vol. 16(6) 1150–1159

DOI: 10.1177/1533034617736162
journals.sagepub.com/home/tct
SAGE

DNA Repair Mechanism Gene, *XRCC1A* (*Arg194Trp*) but not *XRCC3* (*Thr241Met*) Polymorphism Increased the Risk of Breast Cancer in Premenopausal Females: A Case–Control Study in Northeastern Region of India

K. Rekha Devi, PhD[1], Jishan Ahmed, MS[2], Kanwar Narain, PhD[1], Kaustab Mukherjee, MSc[1], Gautam Majumdar, MD[3], Saia Chenkual, MS[4], and Jason C. Zonunmawia, MBBS[4]

Abstract

X-ray repair cross complementary group gene is one of the most studied candidate gene involved in different types of cancers. Studies have shown that X-ray repair cross complementary genes are significantly associated with increased risk of breast cancer in females. Moreover, studies have revealed that X-ray repair cross complementary gene polymorphism significantly varies between and within different ethnic groups globally. The present case–control study was aimed to investigate the association of X-ray repair cross complementary 1A (Arg194Trp) and X-ray repair cross complementary 3 (Thr241Met) polymorphism with the risk of breast cancer in females from northeastern region of India. The present case–control study includes histopathologically confirmed and newly diagnosed 464 cases with breast cancer and 534 apparently healthy neighborhood community controls. Information on sociodemographic factors and putative risk factors were collected from each study participant by conducting face-to-face interviews. Genotyping of X-ray repair cross complementary 1A (Arg194Trp) and X-ray repair cross complementary 3 (Thr241Met) was carried out by polymerase chain reaction-restriction fragment length polymorphism. For statistical analysis, both univariate and multivariate logistic regression analyses were performed. We also performed stratified analysis to find out the association of X-ray repair cross complementary genes with the risk of breast cancer stratified based on menstrual status. This study revealed that tryptophan allele (R/W-W/W genotype) in X-ray repair cross complementary 1A (Arg194Trp) gene significantly increased the risk of breast cancer (adjusted odds ratio = 1.44, 95% confidence interval = 1.06-1.97, $P < .05$ for R/W-W/W genotype). Moreover, it was found that tryptophan allele (W/W genotype) at codon 194 of X-ray repair cross complementary 1A (Arg194Trp) gene significantly increased the risk of breast cancer in premenopausal females (crude odds ratio = 1.66, 95% confidence interval = 1.11-2.46, $P < .05$ for R/W-W/W genotype). The present study did not reveal any significant association of X-ray repair cross complementary 3 (Thr241Met) polymorphism with the risk of breast cancer. The present study has explored that X-ray repair cross complementary 1A (Arg194Trp) gene polymorphism is significantly associated with the increased risk of breast cancer in premenopausal females from northeastern region of India which may be beneficial for prognostic purposes.

Keywords

breast cancer, polymorphism, antigen, hypoxia, meta-analysis, ethnicity, reproductive factors, food habits

[1] Regional Medical Research Centre, NE Region, Indian Council of Medical Research, Dibrugarh, Assam, India
[2] Assam Medical College and Hospital, Dibrugarh, Assam, India
[3] Regional Cancer Centre, Agartala, Tripura, India
[4] Civil Hospital, Aizawl, Mizoram, India

Corresponding Author:
K. Rekha Devi, PhD, Regional Medical Research Centre, NE Region, Indian Council of Medical Research, Dibrugarh, Assam 786001, India.
Email: krekha75@yahoo.co.in

Abbreviations

BC, breast cancer; BER, base excision repair; 95% CI, 95% confidence interval; HWE, Hardy-Weinberg Equilibrium; NE, northeast; OR, odds ratio; PCBR, Population Based Cancer Registry data; PCR-RFLP, polymerase chain reaction–based restriction fragment length polymorphism; XRCC, *X-ray repair cross complementary*

Received: June 09, 2017; Revised: August 23, 2017; Accepted: September 15, 2017.

Introduction

X-ray repair cross complementary group (*XRCC*) gene is one of the most studied candidate gene involved in different types of cancers.[1-4] *XRCC* genes are involved in base excision repair (BER) and single-strand break in damaged DNA in human genome.[1-5] Molecular epidemiological studies have shown that *XRCC* genes are significantly associated with lung cancer,[6-9] oral cancer,[10] bladder cancer,[11-13] ovarian cancer,[14,15] esophageal cancer,[16] and gastric cancer.[17-23] Moreover, studies have revealed that *XRCC* gene polymorphism is highly variable in different ethnic populations.[24-28]

Studies have shown that defect in DNA repair mechanism is significantly associated with the increased risk of breast cancer (BC) in females.[29] Molecular epidemiological studies have been carried out globally to investigate the association of DNA repair mechanism genes with the risk of BC in females from different ethnicity.[30] Studies have revealed that polymorphisms in *XRCC1A* (*Arg194Trp*) and *XRCC 3* (*Thr241Met*) genes are significantly associated with the increased risk of BC in different ethnic populations, though the results are inconsistent which may be due to environmental factors, ethnocultural variations, and/or variations in linkage disequilibrium of these 2 genes, namely, *XRCC1A* and *XRCC3*.[24,29,31-41]

In India, BC is an emerging public health concern.[42] Thus, identification of epidemiological and genetic factors significantly associated with the increased or decreased risk of BC in females from different ethnic groups of India is at utmost need to combat this disease at the earliest.[43] In recent years, Population Based Cancer Registry (PBCR) data of India have reported high number of BC cases in females from northeast (NE) region of India.[43,44] The PBCR data have shown incidence of BC in females of NE region varies from 7.2 per 100 000 populations in Tripura to 30 per 100 000 populations in Aizawl and Kamrup districts.[43] Molecular epidemiological studies have revealed that mutations and/or polymorphisms in tumor suppressor genes, DNA repair mechanism genes, and innate immune pathway genes are significantly associated with the increased risk of BC in females from NE region of India.[45,46] Our earlier study has found that 22-base pair deletion in promoter region of *TLR2* gene significantly increased the risk of BC in females from NE region of India carrying proline allele at codon 72 of their *TP53* gene.[47] Thus, to elucidate the association of DNA repair mechanism genes with the risk of BC in females from this region, the present case–control study was carried out in 4 different states of NE region, India, namely, Assam, Meghalaya, Tripura, and Mizoram. The present molecular epidemiological study was aimed to investigate the association of *XRCC1A* (*Arg194Trp*) and *XRCC3* (*Thr241Met*) polymorphism with the risk of BC in females from NE region which may be beneficial for prognostic purposes.

Materials and Methods

Ethics Statement

This study has been approved by the institutional ethics committee of Regional Medical Research Centre, Indian Council of Medical Research–NE Region, Dibrugarh, Assam (RMRC/Dib/IEC(Human)/2008-09/3243 dated February 19, 2009). All the participants, both cases and controls, provided their written informed consent to be included in this study.

Study Participants and Specimen Collection

This case–control study, conducted from 2010 to 2014, included females from 4 states of NE region of India, namely, Assam, Meghalaya, Mizoram, and Tripura. All 464 BC cases were confirmed by histopathological analysis and all were newly diagnosed. Patients with severe clinical symptoms, patients with recurrent cancer, patients too old to be interviewed, and patients refused to be interviewed were excluded from this study. Five hundred thirty-four neighborhood controls, that is, apparently healthy female participants, were selected by organizing community surveys from the neighborhood of cases. Exclusion criteria for selecting controls were females not willing to participate in the study or having any other type of disease or have undergone blood transfusion in the last 1 year. Information on sociodemographic factors, anthropogenic measurements, and other putative risk factors was collected from the cases and controls by face-to-face interviews, and information gathered was recorded in a predesigned questionnaire. Peripheral whole blood was collected from each study participant in EDTA-containing vials and stored at −80C until analyzed. Breast tissue biopsy samples were immediately fixed in neutral-buffered formalin and kept for 48 hours. Subsequently, the fixed breast tissue samples were thoroughly washed in 70% ethanol, dehydrated in graded series of ethanol, cleaned in xylene, and embedded in paraplast (Sigma St. Louis, MO, USA) for further histological and immunohistochemical analyses.

Genotyping of XRCC1A (Arg194Trp) and XRCC3 (Thr241Met) Polymorphisms

Isolation of DNA for genotyping was carried out by using Qiagen DNeasy(R) Blood kit, and amplification and identification of *XRCC1A* (*Arg194Trp*) *and XRCC3* (*Thr241Met*) genes were performed using the following primer sequences: 5′-GCC CCG TCC CAG GTA-3′ (forward), 5′-AGC CCC AAG ACC CTT CAC T-3′ (reverse) for *XRCC1A* (*Arg194Trp*) and 5′-GGT CGA GTG ACA GTC CAA AC-3′ (forward), and 5′-TGC AAC GGC TGA GGG TCT T-3′ (reverse) for *XRCC3* (*Thr241Met*) gene, respectively. Genotyping of *XRCC1A* and *XRCC3* was carried out by polymerase chain reaction–based restriction fragment length polymorphism (PCR-RFLP) as described by Zhang *et al*.[48] In brief, PCR was performed with 100 ng of genomic DNA using 12.50 μL GoTaq Hot Start master mix (2x; Promega, Madison, WI, USA) with 9.0 μL nuclease-free water (Promega), 0.50 μL 25 mmol/L magnesium chloride (Promega), and 10 pmol 0.5 μL of each forward and reverse primers. Polymerase chain reaction was carried out using GeneAmp PCR system 9700 (Applied Biosystem, USA). The PCR conditions were initial denaturation at 95°C for 2 minutes followed by 32 cycles at 95°C for 0.5 seconds, 63°C for 0.5 seconds, and 72°C for 60 seconds for *XRCC1A* (*Arg194Trp*) and 95°C for 0.5 seconds, 65°C for 0.5 seconds, and 72°C for 60 seconds for *XRCC3* (*Thr241Met*) gene followed by at 72°C for 10 minutes for both the primers. The amplified products were subjected to *MspI* (New England Biolabs, Beverly, Massachusetts) and *NlaIII* (New England Biolabs) restriction enzyme digestion for *XRCC1A* (*Arg194Trp*) *and XRCC3* (*Thr241Met*) genes, respectively, in a 7.50 μL reaction mixture containing restriction endonuclease and reaction buffer following the manufacturer's protocol. The reaction mixture was incubated at 37°C for 16 hours. The restriction-digested products were then resolved on polyacrylamide gel electrophoresis for *XRCC1A* (*Arg194Trp*) and on 3% agarose gel for *XRCC3* (*Thr241Met*) genotyping, respectively. Gels were stained with ethidium bromide and visualized in ultraviolet light. The PCR-RFLP products were further confirmed by Lab Chip (Caliper Life Sciences Inc, Waltham, Massachusetts).

Statistical Analysis

Univariate and multivariate logistic regression analyses were performed by using SPSS version 17.0 (SPSS Inc, Chicago, Illinois). A P value <.05 was taken as statistically significant. Initially, we carried out univariate logistic regression analysis where a single putative risk factor was analyzed to determine the crude odds ratio (OR) and 95% confidence interval (CI). The multiple logistic regression analysis was performed adjusted for age, region, menstrual status, marital status, betel nut chewing, tobacco smoking or chewing, alcohol consumption, dry fish and dry meat, and bamboo shoots consumption. We also carried out stratified analysis where the study population was stratified into 2 groups, based on their menopausal status: group 1 participants were premenopausal females, whereas group 2 consisted of postmenopausal females from NE region of India. Before performing association study, the Hardy-Weinberg equilibrium (HWE) for any deviation from expected allele frequencies was tested by using $\chi 2$ test.

Table 1. Demographic Features of Study Population.

S. No.	Demographic Features	Cases With Breast Cancer	Apparently Healthy Controls
1	Mean age (SD)	47.31 (10.96), n = 454	41.89 (11.02), n = 484
2	Menstrual status	n = 454	n = 484
	Premenopausal	237	366
	Postmenopausal	217	118
3	Marital status	n = 459	n = 518
	Married	430	471
	Unmarried	29	47
4	Family history of BC	n = 464	n = 534
	Yes	7	8
	No	457	526

Abbreviations: BC, breast cancer; SD, standard deviation.

Results

Patient Characteristics

The study comprised of 464 histopathologically confirmed newly diagnosed BC cases and 534 apparently healthy neighborhood community control samples collected from adjacent regions from where cases were obtained. Demographic features of both cases and controls are presented in Table 1.

Test for HWE

Before carrying out association studies with genotypic data, control results were tested for HWE. Both *XRCC1A* (*Arg194-Tryp*) and *XRCC3* (*Thr241Met*) polymorphisms in control samples did not deviate from HWE (P = .114 for *XRCC1A* [*Arg194Trp*] gene and P = .250 for *XRCC3* [*Thr241Met*] gene).

Association of XRCC1A (Arg194Trp) Polymorphisms With the Risk of BC in Females From NE Region of India

To investigate the association of *XRCC1A* (*Arg194Tryp*) polymorphism with the increased risks of BC, both univariate and multivariate logistic regression analyses were carried out. Multivariate logistic regression analysis was performed after adjustment of age, region, menstrual status, marital status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat, and bamboo shoots consumption habit. Univariate logistic regression analysis has revealed that tryptophan allele (*R/W-W/W* genotype) in *XRCC1A* (*Arg194Trp*) gene significantly increased the risk of BC in females from NE region of India (crude OR = 1.31, 95% CI = 1.02-1.70, P < .05; Table 2), whereas multivariate logistic regression analysis after

Table 2. Association of *XRCC1A* (*Arg194Trp*) Polymorphism With the Risk of Breast Cancer in Females From NE Region of India.

Genotypes	Cases	Controls	Crude OR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
Codominant model	n = 464	n = 534				
R/R	263	338	Ref		Ref	
R/W	178	166	1.37 (1.05-1.79)	.018[a]	1.42 (1.03-1.95)	.031[a]
W/W	23	30	0.98 (0.55 -1.73)	.959	1.69 (0.82-3.46)	.152
Dominant model	n = 464	n = 534				
R/R	263	338	Ref		Ref	
R/W-W/W	201	196	1.31 (1.02-1.70)	.033[a]	1.44 (1.06-1.97)	.019[a]
Recessive model	n = 464	n = 534				
R/R-R/W	441	504	Ref		Ref	
W/W	23	30	0.87 (0.50 -1.53)	.642	1.45 (0.72-2.95)	.294

Abbreviations: AOR, adjusted OR, adjusted for age, region, marital status, menopausal status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat, and bamboo shoots consumption habit; CI, confidence interval; NE, northeast; OR, odds ratio; R, arginine; W, tryptophan; XRCC, *X-ray repair cross complementary*.
[a]Statistically significant at $P < .05$.

Table 3. Association of *XRCC1A* (*Arg194Trp*) Polymorphism With Risk of Breast Cancer in Females From NE Region of India Stratified on the Basis of Menopausal Status.

	Group 1: Premenopausal Females						Group 2: Postmenopausal Females					
Genotypes	Cases	Controls	Crude OR (95% CI)	*P* value	AOR (95% CI)	*P* value	Cases	Controls	Crude OR (95% CI)	*P* value	AOR (95% CI)	*P* value
Codominant model	n = 237	n = 366					n = 217	n = 118				
R/R	136	234	Ref		Ref		121	77	Ref		Ref	
R/W	84	108	1.33 (0.93-1.90)	0.1	1.56 (1.03-2.35)	0.03[a]	90	39	1.46 (0.91-2.35)	0.11	1.32 (0.74-2.35)	0.34
W/W	17	24	1.21 (0.63-2.34)	0.55	2.48 (1.08-5.69)	0.03[a]	6	2	1.90 (0.37-9.70)	0.43	2.21 (0.29-16.8)	0.44
Dominant model	n = 237	n = 366					n = 217	n = 118				
R/R	136	234	Ref		Ref		121	77	Ref		Ref	
R/W-W/W	101	132	1.31 (0.94-1.83)	0.1	1.66 (1.11-2.46)	0.012[a]	96	41	1.49 (0.93-2.37)	0.09	1.35 (0.76-2.38)	0.3
Recessive model	n = 237	n = 366					n = 217	n = 118				
R/R-R/W	220	342	Ref		Ref		211	116	Ref		Ref	
W/W	17	24	1.10 (0.57-2.09)	0.76	2.02 (0.90-4.54)	0.08	6	2	1.64 (0.32-8.30)	0.54	1.94 (0.26-14.5)	0.51

Abbreviations: AOR, adjusted OR, adjusted for age, region, marital status, menopausal status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat, and bamboo shoots consumption habit; CI, confidence interval; NE, northeast; OR, odds ratio; R, arginine; W, tryptophan; XRCC, *X-ray repair cross complementary*.
[a]Statistically significant at $P < .05$.

adjustment of age, region, menstrual status, marital status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat, and bamboo shoots consumption habit has revealed that tryptophan allele in *XRCC1A* genotype increased the risk of BC 1.44-fold (adjusted OR = 1.44, 95% CI = 1.06-1.97, $P <$ .05 for *R/W-W/W* genotype; Table 2).

Moreover, to find out the association of *XRCC1A* (*Arg194Trp*) genotype with the risk of BC, we carried out stratified logistic regression analysis. For stratified analysis, the study population was divided into 2 strata: strata 1 comprised of premenopausal females, whereas strata 2 comprised of postmenopausal females. After stratification based on menopausal status of study population, univariate logistic regression analysis and multivariate logistic regression analysis adjusted for age, region, menstrual status, marital status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat, and bamboo shoots consumption habit were carried out. Multivariate logistic regression analysis of stratified data set has shown that tryptophan allele (*R/W-W/W* genotype) in *XRCC1A* (*Arg194Trp*) gene significantly increased the risk of BC in premenopausal females (crude OR = 1.66, 95% CI = 1.11-2.46, $p<0.05$ for *R/W-W/W* genotype) from NE region of India (Table 3).

Association of XRCC3 (Thr241Met) Polymorphism With Risk of BC in Females From NE Region, India

To investigate the association of *XRCC3* (*Thr241Met*) genotype with the risk of BC in females from NE region of India, both univariate and multivariate logistic regression analyses after adjusting for age, region, menstrual status, marital status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat, and bamboo shoots consumption habit were carried out. Both univariate and multivariate logistic regression analyses have revealed no significant association of *XRCC3* (*Thr241Met*) genotype with the risk of BC (Table 4).

Moreover, to find out the association of *XRCC3* (*Thr241Met*) gene polymorphism with risk of BC in premenopausal and postmenopausal females in NE region of India, we carried out stratified logistic regression analysis by stratifying the study

Table 4. Association of *XRCC3* (*Thr241Met*) Polymorphism With Risk of Breast Cancer in Females From NE Region of India.[a]

Genotypes	Cases	Controls	Crude OR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
Co-dominant model	n = 464	n = 534				
T/T	350	426	Ref		Ref	
T/M	100	99	1.22 (0.90-1.67)	.194	1.11 (0.76-1.60)	.578
M/M	14	9	1.89 (0.81-4.42)	.141	1.90 (0.71-5.08)	.195
Dominant model	n = 464	n = 534				
T/T	350	426	Ref		Ref	
T/M-M/M	114	108	1.28 (0.95-1.73)	.100	1.17 (0.82-1.67)	.364
Recessive model	n = 464	n = 534				
T/T-T/M	450	525	Ref		Ref	
M/M	14	9	1.81 (0.77-4.23)	.168	1.86 (0.70-4.96)	.209

Abbreviations: AOR, adjusted OR, adjusted for age, region, marital status, menopausal status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat and bamboo shoots consumption habit; CI, confidence interval; M, methionine; NE, northeast; OR, odds ratio; T, threonine; XRCC, *X-ray repair cross complementary*.
[a]Statistically significant at $P < .05$.

Table 5. Association of *XRCC3* (*Thr241Met*) Polymorphism With Risk of Breast Cancer in Females From NE Region of India Stratified on the Basis of Menopausal Status.[a]

			Group 1: Premenopausal Females				Group: 2 Postmenopausal Females					
Genotypes	Cases	Controls	Crude OR (95% CI)	*P* Value	AOR (95% CI)	*P* Value	Cases	Controls	Crude OR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
Codominant model	n = 237	n = 366					n = 217	n = 118				
T/T	183	292	Ref		Ref		162	93	Ref		Ref	
T/M	46	68	1.07 (0.71-1.63)	.72	1.01 (0.63-1.61)	.95	49	22	1.27 (0.72-2.24)	.34	1.37 (0.70-2.70)	.35
M/M	8	6	2.12 (0.72-6.23)	.16	2.14 (0.60-7.56)	.23	6	3	1.14 (0.28-4.69)	.84	0.91 (0.16-5.12)	.92
Dominant model	n = 237	n = 366					n = 217	n = 118				
T/T	183	292	Ref		Ref		162	93	Ref		Ref	
T/M-M/M	54	74	1.16 (0.78-1.73)	.45	1.09 (0.70-1.71)	.69	55	25	1.26 (0.73-2.16)	.39	1.31 (0.69-2.50)	.4
Recessive model	n = 237	n = 366					n = 217	n = 118				
T/T-T/M	229	360	Ref		Ref		211	115	Ref		Ref	
M/M	8	6	2.09 (0.71-6.11)	.17	2.13 (0.60-7.51)	.23	6	3	1.09 (0.26-4.44)	.9	0.86 (0.15-4.81)	.87

Abbreviations: AOR, adjusted OR, adjusted for age, region, marital status, menopausal status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat and bamboo shoots consumption habit; CI, confidence interval; M, methionine; NE, northeast; OR, odds ratio; T, threonine; XRCC, *X-ray repair cross complementary*.
[a]Statistically significant at $P < .05$.

population into 2 groups, namely, group 1 for premenopausal females and group 2 for postmenopausal females. After stratification, both univariate logistic regression analysis and multivariate logistic regression analysis adjusted for age, region, menstrual status, marital status, betel nut chewing, tobacco smoking, alcohol consumption, dry fish, dry meat, and bamboo shoots consumption habit were carried out. Both univariate and adjusted multivariate logistic regression analyses of stratified data set revealed no significant association of *XRCC3* (*Thr241Met*) gene with the risk of BC (Table 5).

Discussion

XRCC genes are commonly known for their involvement in BER mechanisms in small DNA lesions generally induced by oxidative stress.[25] Defects in DNA repair mechanisms have been found to be significantly associated with increased risk of BC.[29] Molecular epidemiological studies have revealed that polymorphisms in DNA repair mechanism genes are significantly associated with the increased or decreased risk of BC in different ethnic populations.[49,50] The present study was carried out to investigate the association of 2 most studied candidate genes of DNA repair mechanism, namely, *XRCC1A* (*Arg194Trp*) and *XRCC3* (*Thr241Met*), with the risk of BC in females from NE region of India.

Epidemiological studies have shown that reproductive status of females is significantly associated with the risk of BC.[51] Endocrinological studies have revealed that alternations from male to female sex hormone ratio, that is, from androgen to estrogen conversion, high rate of androgen biosynthesis, and low circulatory estrogen level, are significantly associated with the increased risk of BC in females at different menstrual phase.[52] It has been found that high concentration of circulating estradiol is significantly protective in the onset of BC.[53] However, both clinical and epidemiological studies did not reveal yet how low estrogen synthesis promotes early onset of BC in premenopausal females.[54] It is postulated that genetic alternation in metabolic and/or inflammatory genes, tumor suppressor genes, and DNA repair mechanism genes in tumor

microenvironment of breast may be important determinant to develop BC in females.[51,54]

Studies have shown that reproductive factors and food habit significantly increased the risk of BC in females by modulating cellular oxidative stress.[55] Molecular epidemiological studies have shown that polymorphisms in DNA repair pathway-associated genes may produce altered protein product which can modulate tumorigenesis and its transformation toward carcinogenesis in breast tissue.[56] Studies from NE region of India have shown that reproductive status and food habits are significantly associated with the increased risk of BC in females in this region.[57] Moreover, epidemiological studies have shown that betel nut chewing significantly increase the risk of BC in females from NE region.[46] Biochemical studies have revealed that betel nuts are mainly composed of different types of alkaloids, such as arecoline, arecaidine, guvacine, and guvacoline, which effectively bind with the DNA after being nitrated and may produce DNA adducts[58] and thus significantly associated with the increased risk of BC in females.[59,60] Molecular epidemiological studies have postulated that tobacco smoke–derived carcinogens can modulate the expression of DNA repair mechanism pathway genes.[30] Experimental studies have suggested that tobacco smoke contain polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and nitrosamines which cross the alveolar membrane in the lung tissue and after conjugation with lipoproteins carried to the breast epithelium via circulation,[61] where these carcinogenic chemicals induce DNA adducts.[62] Epidemiological studies have shown significant association between smoking and the increased risk of BC among postmenopausal females.[33] Similarly, studies have shown that ethanol consumption significantly stimulates the cell proliferation by altering the expression of transcription factors associated with the ER signaling pathway in females.[63,64] Biochemical studies have shown that heterocyclic amines present in dried fish and fried meat act as strong carcinogens.[65] In NE region of India, people from different ethnic groups consume dry fish and dry meat either regularly or occasionally.[66] Studies have shown that dry fish and dry meat consumption significantly associated with the increased risk of cancers in NE region.[67] Keeping these in view, it is hypothesized that betel nut chewing, tobacco smoking and/or chewing, alcohol, dry fish, and dry meat consumption act as putative risk factors for tumorigenesis in females from NE region of India.[68] In the present study, to investigate the association of *XRCC1A* (*Arg194Trp*) and *XRCC3* (*Thr241Met*) polymorphisms with the increased risk of BC in females from NE region of India, we performed multivariate logistic regression analysis making adjustment of age, region, menstrual status, marital status, betel nut chewing, tobacco chewing and/or smoking, alcohol, dry fish, and dry meat consumption habits.

Molecular epidemiological studies have shown that *Arg/Trp* (*R/W*) allele in *XRCC1A* (*Arg194Trp*) gene is significantly associated with the increased risk of BC in perimenopausal females, aged between 45 and 54 years.[69] Moreover, studies have revealed that protein product of *XRCC1A* (*Arg194Trp*) gene is associated with the regulation of protein–protein interactions in ADPRT and DNA polymerase β.[3,25] It has been found that sequence alternation in *XRCC1A* (*Arg194Trp*) gene encodes a twisted gene product capable to modulate cellular innate DNA repair mechanism and thus increase the risk of oncogenesis.[70-73] Molecular epidemiological studies have revealed significant association of *XRCC1* polymorphism with the increased risk of BC in females, although the results are inconsistent in different ethnic populations globally[38,39,41,74] (Figure 1). Our present case–control study has shown that tryptophan allele (*R/W-W/W* genotype) in *XRCC1A* (*Arg194Trp*) gene significantly increased the risk of BC 1.44-fold (adjusted OR = 1.44, 95% CI 1.06-1.97, $P < .05$). This study has also revealed that *W/W* genotype in *XRCC1A* (*Arg194Trp*) gene significantly increased the risk of BC 2.48-fold (OR = 2.48, 95% CI 1.08-5.69, $P < .05$) in premenopausal females from NE region of India (Table 3).

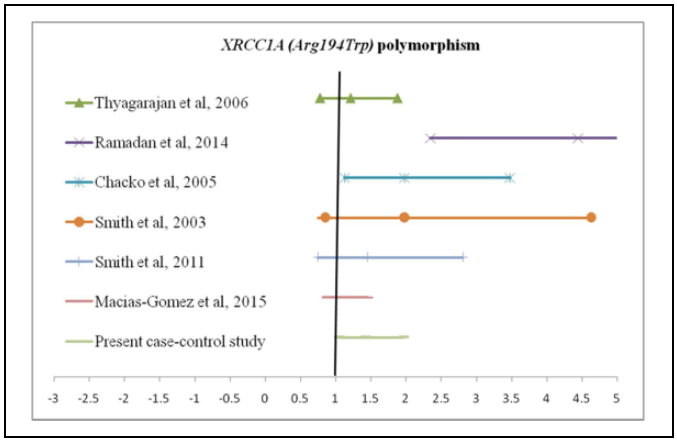

Figure 1. Association of XRCC1A (Arg194Trp) polymorphism with the increased risk of breast cancer (BC) and its comparison with our present case–control study. Comparative analysis of association between XRCC1A (Arg194Trp) polymorphism and the risk of BC in different ethnic populations globally.

XRCC3 gene encodes a protein, related to the member of *Rad 51* family, responsible for homologous recombination repair of DNA double-strand break.[75,76] Studies have shown that single base pair substitution in the exon number 7 of the *XRCC3* gene, commonly known as codon 241, may influence the enzyme function of DNA repair mechanism and thus causes DNA damage. *In vitro* studies have shown that *XRCC3* gene knockout cells are highly sensitive to DNA damaging agents.[77] Molecular epidemiological studies have revealed that *XRCC3 Thr241Met* polymorphism may alter DNA repair capacity and significantly influence the susceptibility to carcinogens (Figure 2). Studies have found significant association between *XRCC3* polymorphism and increased risk of colon cancer,[78,79] gastric cancer,[22,23] bladder cancer,[13] thyroid cancer,[80] renal cell carcinoma,[81] and lung cancer.[82,83] Moreover, studies have shown that methionine allele (*M/M* genotype) in *XRCC3* (*Thr241Met*) gene significantly increased the risk of BC.[72,73,84-87] However, studies also have found no association of *XRCC3* (*Thr241Met*) gene with the risk of BC and thus compelled to hypothesize that ethnic variation also persists between *XRCC3* (*Thr241Met*)

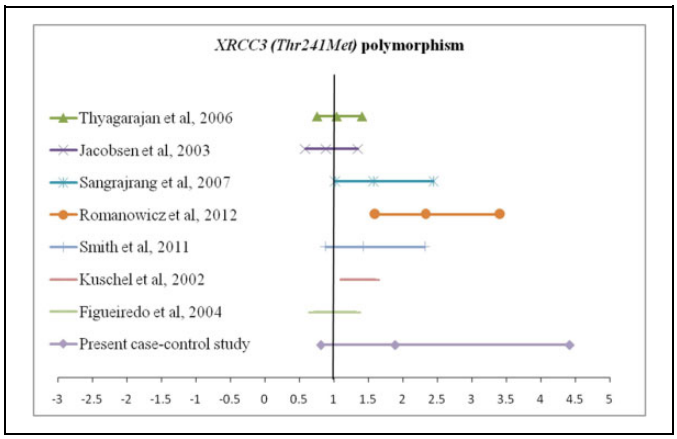

Figure 2. Association of XRCC3 (Thr241Met) polymorphism with the increased risk of breast cancer (BC) and its comparison with our present case–control study. Comparative analysis of association between XRCC3 (Thr241Met) polymorphism and the risk of BC in different ethnic populations globally.

polymorphism and the risk of BC in females.[38,40,88-90] However, It has been assumed that *XRCC3* (*Thr241Met*) is an important candidate gene in tumorigenesis.[91] Thus, to investigate the association of *XRCC3* (*Thr241Met*) polymorphism with the increased risk of BC in females from NE region of India, we carried out both univariate and multivariate logistic regression analyses after adjustment for reproductive factors and food habits. Moreover, to find out the association between *XRCC3* polymorphism and the risk of BC in females, we stratified our study population into premenopausal and postmenopausal strata. However, the present case–control study did not reveal any significant association of *XRCC3* (*Thr241Met*) polymorphism with the risk of BC in females from NE region of India (Table 5).

In the present case–control study, we did not perform follow-up study of patients with BC to investigate the association of *XRCC1A* (*Arg194Trp*) and *XRCC3* (*Thr241Met*) polymorphisms with the anticancer treatment regime due to logistic issues. Moreover, we were also unable to explore the expressional profiling of these 2 genes due to limited resources. Thus, the primary limitations of this study are cross-sectional design instead of longitudinal design and unavailability of expressional profiling data of *XRCC1A* and *XRCC3* genes, respectively.

Conclusion

The present study has revealed that *XRCC1A* (*Arg194Trp*) polymorphism is significantly associated with the increased risk of BC in females from NE region of India. Moreover, this study has shown that tryptophan allele in *XRCC1A* (*Arg194Trp*) gene significantly increased the risk of BC 2.48-fold in premenopausal females. However, the present study did not reveal any significant association of *XRCC3* (*Thr241Met*) polymorphism with the risk of BC. Future studies with larger sample size and with more single-nucleotide polymorphisms related to DNA repair mechanism of human genome are required to elucidate the association of DNA repair mechanism genes with the risk of BC in females from NE region of India.

Acknowledgments

The authors would like to thank all study participants for their cooperation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Indian Council of Medical Research (ICMR), India.

References

1. Figueiredo JC, Knight JA, Briollais L, Andrulis IL, Ozcelik H. Polymorphisms XRCC1-R399Q and XRCC3-T241 M and the risk of breast cancer at the Ontario site of the Breast Cancer Family Registry. *Cancer Epidemiol Biomarkers Prev*. 2004; 13(4):583-591.
2. Webb PM, Hopper JL, Newman B, et al. Double-strand break repair gene polymorphisms and risk of breast or ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):319-323. doi:10.1158/1055-9965.EPI-04-0335.
3. Duell EJ, Millikan RC, Pittman GS, et al. Polymorphisms in the DNA repair gene XRCC1 and breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2001;10(3):217-222.
4. Khlifi R, Kallel I, Hammami B, Hamza-Chaffai A, Rebai A. DNA repair gene polymorphisms and risk of head and neck cancer in the Tunisian population. *J Oral Pathol Med*. 2014;43(3):217-224. doi:10.1111/jop.12114.
5. Thacker J, Zdzienicka MZ. The XRCC genes: expanding roles in DNA double-strand break repair. *DNA Repair (Amst)*. 2004;3(8-9):1081-1090. doi:10.1016/j.dnarep.2004.04.012.
6. Liu D, Wu J, Shi GY, Zhou HF, Yu Y. Role of XRCC1 and ERCC5 polymorphisms on clinical outcomes in advanced non-small cell lung cancer. *Genet Mol Res*. 2014;13(2):3100-3107. doi:10.4238/2014.April.17.6.
7. Du Y, He Y, Mei Z, Qian L, Shi J, Jie Z. Association between genetic polymorphisms in XPD and XRCC1 genes and risks of non-small cell lung cancer in East Chinese Han population. *Clin Respir J*. 2016;10(3):311-317. doi:10.1111/crj.12218.
8. Peng Y, Li Z, Zhang S, et al. Association of DNA base excision repair genes (OGG1, APE1 and XRCC1) polymorphisms with outcome to platinum-based chemotherapy in advanced nonsmall-cell lung cancer patients. *Int J Cancer*. 2014;135(11): 2687-2696. doi:10.1002/ijc.28892.
9. Li L, Wan C, Wen FQ. Polymorphisms in the XRCC1 gene are associated with treatment response to platinum chemotherapy in advanced non-small cell lung cancer patients based on meta-analysis. *Genet Mol Res*. 2014;13(2):3772-3786. doi:10.4238/2014.May.16.1.
10. Santana T, Sa MC, de Moura Santos E, Galvao HC, Coletta RD, Freitas RA. DNA base excision repair proteins APE-1 and XRCC-

1 are overexpressed in oral tongue squamous cell carcinoma. *J Oral Pathol Med*. 2017;46(7):496-503. doi:10.1111/jop.12529.
11. Dong LM, Zhang XY, Teng H, Li MS, Wang P. Meta-analysis demonstrates no association between XRCC1 Arg399Gln polymorphism and bladder cancer risk. *Genet Mol Res*. 2014;13(4): 9976-9985. doi:10.4238/2014.November.28.2.
12. Ramaniuk VP, Nikitchenko NV, Savina NV, et al. Polymorphism of DNA repair genes OGG1, XRCC1, XPD and ERCC6 in bladder cancer in Belarus. *Biomarkers*. 2014;19(6):509-516. doi:10.3109/1354750X.2014.943291.
13. Zhang M, Li W, Hao Z, Zhou J, Zhang L, Liang C. Association between twelve polymorphisms in five x-ray repair cross-complementing genes and the risk of urological neoplasms: a systematic review and meta-analysis. *EBioMedicine*. 2017;18: 94-108. doi:10.1016/j.ebiom.2017.03.009.
14. Monteiro MS, Vilas Boas DB, Gigliotti CB, Salvadori DM. Association among XRCC1, XRCC3, and BLHX gene polymorphisms and chromosome instability in lymphocytes from patients with endometriosis and ovarian cancer. *Genet Mol Res*. 2014;13(1): 636-648. doi:10.4238/2014.January.28.9.
15. Wang L, Lu H, Li J, et al. The association between XRCC1 genetic polymorphisms and the risk of endometrial carcinoma in Chinese. *Gene*. 2015;554(2):155-159. doi:10.1016/j.gene.2014.10.041.
16. Zhou Q, Zou BW, Xu Y, et al. DNA repair gene polymorphisms and clinical outcome of patients with primary small cell carcinoma of the esophagus. Tumour Biol. 2015;36(3):1539-1548. doi: 10.1007/s13277-014-2718-y.
17. Zhao ZM, Li CG, Hu MG, Gao YX, Liu R. Influence of the c. 1517G>C genetic variant in the XRCC1 gene on pancreatic cancer susceptibility in a Chinese population. *Genet Mol Res*. 2014; 13(2):4466-4472. doi:10.4238/2014.June.16.5.
18. Meng H, Lu S, Zhang Z, et al. Association of XRCC1 gene polymorphisms with susceptibility to gastric cancer in Chinese Han population. *J Pharm Pharmacol*. 2014;66(10):1463-1468. doi:10.1111/jphp.12264.
19. Li W, Yang F, Gui Y, Bian J. DNA repair gene XRCC1 Arg194Trp polymorphism and susceptibility to hepatocellular carcinoma: a meta-analysis. *Oncol Lett*. 2014;8(4):1725-1730. doi:10.3892/ol.2014.2351.
20. Wu H, Xu C, Chen G, Wang J. X-ray repair cross-complementing 1 polymorphism and prognosis of platinum-based chemotherapy in gastric and colorectal cancer: a meta-analysis. *J Gastroenterol Hepatol*. 2014;29(5):926-933. doi:10.1111/jgh.12444.
21. Srivastava A, Srivastava K, Pandey SN, Choudhuri G, Mittal B. Single-nucleotide polymorphisms of DNA repair genes OGG1 and XRCC1: association with gallbladder cancer in North Indian population. *Ann Surg Oncol*. 2009;16(6):1695-1703. doi:10.1245/s10434-009-0354-3.
22. Carrera-Lasfuentes P, Lanas A, Bujanda L, et al. Relevance of DNA repair gene polymorphisms to gastric cancer risk and phenotype. *Oncotarget*. 2017;8(22):35848-35862. doi:10.18632/oncotarget.16261.
23. Gong H, Li H, Zou J, et al. The relationship between five non-synonymous polymorphisms within three XRCC genes and gastric cancer risk in a Han Chinese population. *Tumour Biol*. 2016; 37(5):5905-5910. doi:10.1007/s13277-015-3502-3.
24. Popanda O, Tan XL, Ambrosone CB, et al. Genetic polymorphisms in the DNA double-strand break repair genes XRCC3, XRCC2, and NBS1 are not associated with acute side effects of radiotherapy in breast cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(5):1048-1050. doi:10.1158/1055-9965.EPI-06-0046.
25. Kuschel B, Auranen A, McBride S, et al. Variants in DNA double-strand break repair genes and breast cancer susceptibility. *Hum Mol genet*. 2002;11(12):1399-1407.
26. Rao KS, Paul A, Kumar AS, et al. Allele and genotype distributions of DNA repair gene polymorphisms in South Indian healthy population. *Biomark Cancer*. 2014;6:29-35. doi:10.4137/BIC.S19681.
27. Takeshita H, Fujihara J, Yasuda T, Kimura-Kataoka K. Worldwide distribution of four SNPs in X-ray and repair and cross-complementing group 1 (XRCC1). *Clin Transl Sci*. 2015;8(4): 347-350. doi:10.1111/cts.12237.
28. Goricar K, Kovac V, Dolzan V. Clinical-pharmacogenetic models for personalized cancer treatment: application to malignant mesothelioma. *Sci Rep*. 2017;7:46537. doi:10.1038/srep46537.
29. Smolarz B, Makowska M, Samulak D, et al. Single nucleotide polymorphisms (SNPs) of ERCC2, hOGG1, and XRCC1 DNA repair genes and the risk of triple-negative breast cancer in Polish women. *Tumour Biol*. 2014;35(4):3495-3502. doi:10.1007/s13277-013-1461-0.
30. Shen J, Gammon MD, Terry MB, et al. Polymorphisms in XRCC1 modify the association between polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, dietary antioxidants, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2): 336-342. doi:10.1158/1055-9965.EPI-04-0414.
31. Huang Y, Li L, Yu L. XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms in breast cancer risk: a meta-analysis. *Mutagenesis*. 2009;24(4):331-339. doi:10.1093/mutage/gep013.
32. Bewick MA, Conlon MS, Lafrenie RM. Polymorphisms in XRCC1, XRCC3, and CCND1 and survival after treatment for metastatic breast cancer. *J Clin Oncol*. 2006;24(36):5645-5651. doi:10.1200/JCO.2006.05.9923.
33. Metsola K, Kataja V, Sillanpaa P, et al. XRCC1 and XPD genetic polymorphisms, smoking and breast cancer risk in a Finnish case-control study. *Breast Cancer Res*. 2005;7(6):R987-R997. doi:10.1186/bcr1333.
34. Patel AV, Calle EE, Pavluck AL, Feigelson HS, Thun MJ, Rodriguez C. A prospective study of XRCC1 (X-ray cross-complementing group 1) polymorphisms and breast cancer risk. *Breast Cancer Res*. 2005;7(6):R1168-R1173. doi:10.1186/bcr1355.
35. Millikan RC, Player JS, Decotret AR, Tse CK, Keku T. Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(10):2326-2334. doi:10.1158/1055-9965.EPI-05-0186.
36. Macias-Gomez NM, Peralta-Leal V, Meza-Espinoza JP, et al. Polymorphisms of the XRCC1 gene and breast cancer risk in the Mexican population. *Fam Cancer*. 2015;14(3):349-354. doi:10.1007/s10689-015-9787-y.
37. Loizidou MA, Michael T, Neuhausen SL, et al. Genetic polymorphisms in the DNA repair genes XRCC1, XRCC2 and XRCC3 and risk of breast cancer in Cyprus. *Breast Cancer Res Treat*. 2008;112(3):575-579. doi:10.1007/s10549-007-9881-4.

38. Al Zoubi MS, Zavaglia K, Mazanti C, et al. Polymorphisms and mutations in GSTP1, RAD51, XRCC1 and XRCC3 genes in breast cancer patients. *Int J Biol Markers*. 2017;32(3): e337-e343. doi:10.5301/ijbm.5000258.
39. Jalali C, Ghaderi B, Amini S, Abdi M, Roshani D. Association of XRCC1 Trp194 allele with risk of breast cancer, and Ki67 protein status in breast tumor tissues. *Saudi Med J*. 2016;37(6):624-630. doi:10.15537/Smj.2016.6.13540.
40. Romanowicz H, Pyziak L, Jablonski F, Brys M, Forma E, Smolarz B. Analysis of DNA repair genes polymorphisms in breast cancer. *Pathol Oncol Res*. 2017;23(1):117-123. doi:10.1007/s12253-016-0110-5.
41. Sanjari Moghaddam A, Nazarzadeh M, Noroozi R, Darvish H, Mosavi Jarrahi A. XRCC1 and OGG1 gene polymorphisms and breast cancer: a systematic review of literature. *Iran J Cancer Prev*. 2016;9(1):e3467. doi:10.17795/ijcp-3467.
42. Murthy NS, Chaudhry K, Rath GK. Burden of cancer and projections for 2016, Indian scenario: gaps in the availability of radiotherapy treatment facilities. *Asian Pac J Cancer Prev*. 2008;9(4):671-677.
43. Sharma JD, Kataki AC, Vijay CR. Population-based incidence and patterns of cancer in Kamrup Urban Cancer Registry, India. *Natl Med J India*. 2013;26(3):133-141.
44. Krishnatreya M, Kataki AC, Sharma JD, et al. Descriptive epidemiology of common female cancers in the north east India—a hospital based study. *Asian Pac J Cancer Prev*. 2014;15(24): 10735-10738.
45. Ghatak S, Lallawmzuali D, Lalmawia, et al. Mitochondrial D-loop and cytochrome oxidase C subunit I polymorphisms among the breast cancer patients of Mizoram, Northeast India. *Curr Genet*. 2014;60(3):201-212. doi:10.1007/s00294-014-0425-2.
46. Kaushal M, Mishra AK, Raju BS, et al. Betel quid chewing as an environmental risk factor for breast cancer. *Mutat Res*. 2010; 703(2):143-148. doi:10.1016/j.mrgentox.2010.08.011.
47. Devi KR, Chenkual S, Majumdar G, et al. TLR222 (-196-174) significantly increases the risk of breast cancer in females carrying proline allele at codon 72 of TP53 gene: a case-control study from four ethnic groups of North Eastern region of India. *Tumour Biol*. 2015;36(12):9995-10002. doi:10.1007/s13277-015-3795-2.
48. Zhang Z, Wan J, Jin X, et al. Genetic polymorphisms in XRCC1, APE1, ADPRT, XRCC2, and XRCC3 and risk of chronic benzene poisoning in a Chinese occupational population. *Cancer Epidemiol Biomarkers Prev*. 2005;14(11 Pt 1):2614-2619. doi:10.1158/1055-9965.EPI-05-0143.
49. Chang-Claude J, Popanda O, Tan XL, et al. Association between polymorphisms in the DNA repair genes, XRCC1, APE1, and XPD and acute side effects of radiotherapy in breast cancer patients. *Clin Cancer Res*. 2005;11(13):4802-4809. doi:10.1158/1078-0432.CCR-04-2657.
50. Smith TR, Liu-Mares W, Van Emburgh BO, et al. Genetic polymorphisms of multiple DNA repair pathways impact age at diagnosis and TP53 mutations in breast cancer. *Carcinogenesis*. 2011; 32(9):1354-1360. doi:10.1093/carcin/bgr117.
51. Suba Z. Triple-negative breast cancer risk in women is defined by the defect of estrogen signaling: preventive and therapeutic implications. *Onco Targets Ther*. 2014;7:147-164. doi:10.2147/OTT.S52600.
52. Stoll BA. Teenage obesity in relation to breast cancer risk. International journal of obesity and related metabolic disorders. *Int J Obes Relat Metab Disord*. 1998;22(11):1035-1040.
53. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*. 2008;109(1): 123-139. doi:10.1007/s10549-007-9632-6.
54. Suba Z. Circulatory estrogen level protects against breast cancer in obese women. *Recent Pat Anticancer Drug Discov*. 2013;8(2): 154-167.
55. Aitken RJ, Smith TB, Jobling MS, Baker MA, De Iuliis GN. Oxidative stress and male reproductive health. *Asian J Androl*. 2014;16(1):31-38. doi:10.4103/1008-682X.122203.
56. Liu L, Chen C, Gong W, et al. Epoxyeicosatrienoic acids attenuate reactive oxygen species level, mitochondrial dysfunction, caspase activation, and apoptosis in carcinoma cells treated with arsenic trioxide. *J Pharmacol Exp Ther*. 2011;339(2):451-463. doi:10.1124/jpet.111.180505.
57. Kaushal M, Mishra AK, Sharma J, et al. Genomic alterations in breast cancer patients in betel quid and non betel quid chewers. *PloS One*. 2012;7(8):e43789. doi:10.1371/journal.pone.0043789.
58. Bhattacharjee C, Sharan RN. Aqueous extract of betel nut-induced adducts on pMTa4 DNA acquires stability in the presence of Na+ and K+ ions. *Mol Med Rep*. 2008;1(3):435-441.
59. Synowiec E, Stefanska J, Morawiec Z, Blasiak J, Wozniak K. Association between DNA damage, DNA repair genes variability and clinical characteristics in breast cancer patients. *Mutat Res*. 2008;648(1-2):65-72. doi:10.1016/j.mrfmmm.2008.09.014.
60. Wasson MK, Chauhan PS, Singh LC, et al. Association of DNA repair and cell cycle gene variations with breast cancer risk in Northeast Indian population: a multiple interaction analysis. *Tumour Biol*. 2014;35(6):5885-5894. doi:10.1007/s13277-014-1779-2.
61. Kotnis A, Namkung J, Kannan S, et al. Multiple pathway-based genetic variations associated with tobacco related multiple primary neoplasms. *PloS One*. 2012;7(1):e30013. doi:10.1371/journal.pone.0030013.
62. Rundle A, Tang D, Hibshoosh H, et al. Molecular epidemiologic studies of polycyclic aromatic hydrocarbon-DNA adducts and breast cancer. *Environ Mol Mutagen*. 2002;39(2-3):201-207.
63. Frydenberg H, Flote VG, Larsson IM, et al. Alcohol consumption, endogenous estrogen and mammographic density among premenopausal women. *Breast Cancer Res*. 2015;17:103. doi:10.1186/s13058-015-0620-1.
64. Slattery ML, Lundgreen A, John EM, et al. MAPK genes interact with diet and lifestyle factors to alter risk of breast cancer: the Breast Cancer Health Disparities Study. *Nutr Cancer*. 2015;67(2): 292-304. doi:10.1080/01635581.2015.990568.
65. Pais P, Salmon CP, Knize MG, Felton JS. Formation of mutagenic/carcinogenic heterocyclic amines in dry-heated model systems, meats, and meat drippings. *J Agric Food Chem*. 1999;47(3): 1098-1108.
66. Saha S, Gupta K, Kumar S. Cardiovascular health among healthy population of Northeast region of India: a cross-sectional study comparing urban-tribal difference. *J Indian Med Assoc*. 2013; 111(12):810-814, 816.
67. Malakar M, Devi KR, Phukan RK, et al. p53 codon 72 polymorphism interactions with dietary and tobacco related habits and

risk of stomach cancer in Mizoram, *India.* Asian Pac J Cancer Prev. 2014;15(2):717-723.
68. Chandirasekar R, Kumar BL, Sasikala K, et al. Assessment of genotoxic and molecular mechanisms of cancer risk in smoking and smokeless tobacco users. *Mutat Res Genet Toxicol Environ Mutagen*. 2014;767:21-27. doi:10.1016/j.mrgentox.2014.04.007.
69. Silva SN, Moita R, Azevedo AP, et al. Menopausal age and XRCC1 gene polymorphisms: role in breast cancer risk. *Cancer Detect Prev*. 2007;31(4):303-309. doi:10.1016/j.cdp.2007.07.001
70. Smith TR, Miller MS, Lohman K, et al. Polymorphisms of XRCC1 and XRCC3 genes and susceptibility to breast cancer. *Cancer Lett*. 2003;190(2):183-190.
71. Chacko P, Rajan B, Joseph T, Mathew BS, Pillai MR. Polymorphisms in DNA repair gene XRCC1 and increased genetic susceptibility to breast cancer. *Breast Cancer Res Treat*. 2005;89(1): 15-21. doi:10.1007/s10549-004-1004-x.
72. Przybylowska-Sygut K, Stanczyk M, Kusinska R, Kordek R, Majsterek I. Association of the Arg194Trp and the Arg399Gln polymorphisms of the XRCC1 gene with risk occurrence and the response to adjuvant therapy among Polish women with breast cancer. *Clin Breast Cancer*. 2013;13(1):61-68. doi:10.1016/j.clbc.2012.09.019.
73. Ramadan RA, Desouky LM, Elnaggar MA, Moaaz M, Elsherif AM. Association of DNA repair genes XRCC1 (Arg399Gln), (Arg194Trp) and XRCC3 (Thr241Met) polymorphisms with the risk of breast cancer: a case-control study in Egypt. *Genet Test Mol Biomarkers*. 2014;18(11):754-760. doi:10.1089/gtmb.2014.0191.
74. Batar B, Guven G, Eroz S, Bese NS, Guven M. Decreased DNA repair gene XRCC1 expression is associated with radiotherapy-induced acute side effects in breast cancer patients. *Gene*. 2016; 582(1):33-37. doi:10.1016/j.gene.2016.01.040.
75. Shu XO, Cai Q, Gao YT, Wen W, Jin F, Zheng W. A population-based case-control study of the Arg399Gln polymorphism in DNA repair gene XRCC1 and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2003;12(12):1462-1467.
76. Silva SN, Tomar M, Paulo C, et al. Breast cancer risk and common single nucleotide polymorphisms in homologous recombination DNA repair pathway genes XRCC2, XRCC3, NBS1 and RAD51. *Cancer Epidemiol*. 2010;34(1):85-92. doi:10.1016/j.canep.2009.11.002.
77. Singleton BK, Griffin CS, Thacker J. Clustered DNA damage leads to complex genetic changes in irradiated human cells. *Cancer Res*. 2002;62(21):6263-6269.
78. Agostini M, Zangrando A, Pastrello C, et al. A functional biological network centered on XRCC3: a new possible marker of chemoradiotherapy resistance in rectal cancer patients. *Cancer Biol Ther*. 2015;16(8):1160-1171. doi:10.1080/15384047.2015.1046652.
79. Krupa R, Sliwinski T, Wisniewska-Jarosinska M, et al. Polymorphisms in RAD51, XRCC2 and XRCC3 genes of the homologous recombination repair in colorectal cancer—a case control study. *Molecular Biol Rep*. 2011;38(4):2849-2854. doi:10.1007/s11033-010-0430-6.
80. Sarwar R, Mahjabeen I, Bashir K, Saeed S, Kayani MA. Haplotype based analysis of XRCC3 gene polymorphisms in thyroid cancer. *Cell Physiol Biochem*. 2017;42(1):22-33. doi:10.1159/000477109.
81. Loghin A, Banescu C, Nechifor-Boila A, et al. XRCC3 Thr241Met and XPD Lys751Gln gene polymorphisms and risk of clear cell renal cell carcinoma. *Cancer Biomark*. 2016;16(2): 211-217. doi:10.3233/CBM-150558.
82. Catana A, Pop M, Marginean DH, et al. XRCC3 Thr241Met polymorphism is not associated with lung cancer risk in a Romanian population. *Clujul Med*. 2016;89(1):89-93. doi:10.15386/cjmed-523.
83. Liu HX, Li J, Ye BG. Correlation between gene polymorphisms of CYP1A1, GSTP1, ERCC2, XRCC1, and XRCC3 and susceptibility to lung cancer. *Genet Mol Res*. 2016;15(4). doi:10.4238/gmr15048813.
84. Mao CF, Qian WY, Wu JZ, Sun DW, Tang JH. Association between the XRCC3 Thr241Met polymorphism and breast cancer risk: an updated meta-analysis of 36 case-control studies. *Asian Pac J Cancer Prev*. 2014;15(16):6613-6618.
85. Pramanik S, Devi S, Chowdhary S, Surendran ST, Krishnamurthi K, Chakrabarti T. DNA repair gene polymorphisms at XRCC1, XRCC3, XPD, and OGG1 loci in Maharashtrian population of central India. *Chemosphere*. 2011;82(7):941-946. doi:10.1016/j.chemosphere.2010.10.100.
86. Romanowicz-Makowska H, Smolarz B, et al. The association between polymorphisms of the RAD51-G135C, XRCC2-Arg188His and XRCC3-Thr241Met genes and clinicopathologic features in breast cancer in Poland. *Eur J Gynaecol Oncol*. 2012;33(2):145-150.
87. Sangrajrang S, Schmezer P, Burkholder I, et al. The XRCC3 Thr241Met polymorphism and breast cancer risk: a case-control study in a Thai population. *Biomarkers*. 2007;12(5):523-532. doi:10.1080/13547500701395602.
88. Jacobsen NR, Nexo BA, Olsen A, et al. No association between the DNA repair gene XRCC3 T241 M polymorphism and risk of skin cancer and breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2003;12(6):584-585.
89. Saadat M, Ansari-Lari M. Polymorphism of XRCC1 (at codon 399) and susceptibility to breast cancer, a meta-analysis of the literatures. *Breast Cancer Res Treat*. 2009;115(1):137-144. doi:10.1007/s10549-008-0051-0.
90. Thyagarajan B, Anderson KE, Folsom AR, et al. No association between XRCC1 and XRCC3 gene polymorphisms and breast cancer risk: Iowa Women's Health Study. *Cancer Detect Prev*. 2006;30(4):313-321. doi:10.1016/j.cdp.2006.07.002.
91. Su H, Cheng Z, Huang J, et al. Arabidopsis RAD51, RAD51C and XRCC3 proteins form a complex and facilitate RAD51 localization on chromosomes for meiotic recombination. *PLoS Genet*. 2017;13(5):e1006827. doi:10.1371/journal.pgen.1006827.