Biomarkers, September–October 2007; 12(5): 523–532

informa
healthcare

The *XRCC3* Thr241Met polymorphism and breast cancer risk: a case–control study in a Thai population

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Abstract

The X-ray repair cross-complementing group 3 gene (*XRCC3*) belongs to a family of genes responsible for repairing DNA double-strand breaks caused by normal metabolic processes and exposure to ionizing radiation. Polymorphisms in DNA repair genes may alter an individual's capacity to repair damaged DNA and may lead to genetic instability and contribute to malignant transformation. We examined the role of a polymorphism in the *XRCC3* gene (rs861529; codon 241: threonine to methionine change) in determining breast cancer risk in Thai women. The study population consisted of 507 breast cancer cases and 425 healthy women. The polymorphism was analysed by fluorescence-based melting curve analysis. The *XRCC3* 241Met allele was found to be uncommon in the Thai population (frequency 0.07 among cases and 0.05 among controls). Odds ratios (OR) adjusted for age, body mass index, age at menarche, family history of breast cancer, menopausal status, reproduction parameters, use of contraceptives, tobacco smoking, involuntary tobacco smoking, alcohol drinking, and education were calculated for the entire population as well as for pre- and postmenopausal women. There was a significant association between 241Met carrier status and breast cancer risk (OR 1.58, 95% confidence interval (CI) 1.02–2.44). Among postmenopausal women, a slightly higher OR (1.82, 95% CI 0.95–3.51) was found than among premenopausal women (OR 1.48, 95% CI 0.82–2.69). Our findings suggest that the *XRCC3* Thr241Met polymorphism is likely to play a modifying role in the individual susceptibility to breast cancer among Thai women as already shown for women of European ancestry.

Keywords: *Breast cancer, DNA repair, genetic polymorphism, XRCC3*

(Received 28 November 2006; accepted 12 April 2007)

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ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.1080/13547500701395602

Introduction

In Thailand, breast cancer is the second most common cancer among women and the incidence is still increasing (Sriplung et al. 2005). To date, the aetiology of breast cancer is only partially known: among the established risk factors are nulliparity, high age at first child's birth, and family history of breast cancer (Dumitrescu & Cotarla 2005). In addition, insufficient repair of DNA damage is supposed to contribute to the development of breast cancer (Dumitrescu & Cotarla 2005, Garcia-Closas et al. 2006). Among the most important lesions are DNA double-strand breaks (DSB) caused by endogenous exposure to free radicals produced during normal cellular metabolism and exogenous exposure to chemicals and ionizing radiation (van Gent et al. 2001). Genetic variants of DNA repair genes may lead to interindividual variation in DNA repair activity and may, thus, modify breast cancer risk. The repair of DSB in human cells is controlled by homologous recombination (HR) and non-homologous end-joining (NHEJ). Numerous genes are involved in these pathways, but here, we focus on the *XRCC3* gene as the XRCC3 protein plays a central role in HR where it interacts with the Rad51 protein, enabling Rad51 protein multimers to assemble at the site of damage (Bishop et al. 1998). The Thr241Met amino acid substitution due to a C18607T transition at exon 7 in the *XRCC3* gene has been found to be functionally active as it is associated with an increased number of micronuclei in lymphocytes of humans exposed to ionizing radiation (Aka et al. 2004, Angelini et al. 2005). In addition, the variant allele was associated with increased risk of squamous cell carcinoma of the head and neck (Shen et al. 2002), whereas no association was previously shown with lung cancer (Misra et al. 2003), colon cancer (Mort et al. 2003) or non-melanoma skin cancer (Jacobsen et al. 2003). Conflicting results have been published on the association with bladder cancer (Matullo et al. 2001a, Shen et al. 2003) and malignant melanoma (Winsey et al. 2000, Duan et al. 2002).

Regarding breast cancer risk, a meta-analysis was performed recently using data of women from Europe (six studies), USA (four) and Australia (one) (Garcia-Closas et al. 2006). This analysis reported a small increase in risk for the Met/Met genotype compared with the Thr/Thr genotype (odds ratio (OR) = 1.16, 95% confidence interval (CI) 1.04–1.30). The meta-analysis concentrated on women of European ancestry as, for this polymorphism, allele frequencies are different in various ethnicities. Among Asians, the Met allele is considerably less prevalent (ranging from 0.02–0.07) (Shen et al. 2004, Jin et al. 2005, Yeh et al. 2005) than among European women (ranging from 0.32–0.41) (Jacobsen et al. 2003, Smith et al. 2003, Forsti et al. 2004, Millikan et al. 2005, Popanda et al. 2006). In Asians, therefore, the genetic background might be different from that of Europeans leading to different risk estimates in both populations. For Asian populations, only one recent study with a small number of study participants found an association between the *XRCC3* Thr241Met polymorphism and breast cancer risk (Zhang et al. 2005). For a more detailed evaluation of the impact of this polymorphism on breast cancer risk in different ethnicities, further data about Asian populations are needed. Here, we present data on the association between the polymorphism *XRCC3* Thr241Met and the risk of breast cancer in a case–control study of Thai women.

Material and methods

Study population

Cases were all new incident breast cancer patients histologically diagnosed in the National Cancer Institute in Bangkok and in the hospital in Khon Kaen province of North Eastern Thailand during the period May 2002 to March 2004, with a participation rate of 99.6% (554/556). Controls were randomly selected from healthy women who visited patients admitted to the same hospitals for diseases other than breast or ovarian cancer. The participation rate among visitors who were asked to participate was 98.7% (572/579). Informed consent was obtained from all participants and a structured questionnaire was administered by trained interviewers to collect information on demographic and anthropometric data, reproductive and medical history, residential history, physical activity and occupation as well as diet (see Table I). Lifestyle exposure parameters were reported as follows: tobacco smoking – less than or equal to (non-smoker) vs. more than 50 cigarettes over a 6-month period (smoker); involuntary tobacco smoking – less vs. more than or equal to 1 h of exposure per day during the last 2 years (sum of three sources: from the spouse, at the workplace or in public settings); alcohol consumption – less vs. more than or equal to once a week for at least 6 months. The prevalence of smoking among Thai women is very low in our study, but data from other studies on Thai women also show that the smoking prevalence is below 5% (see also the InterASIA Collaborative Group 2003, Sriamporn et al. 2005).

Approximately 7 ml of blood were collected from participants, but 45 cases and 149 controls refused to give blood samples. In total, blood samples from 507 cases and 425 controls were included in the genotype analysis, resulting in a participation rate of 91.2% (cases) and 73.4% (controls). Genomic DNA was isolated from buffy coats using a QIAmp DNA blood kit (Qiagen, Hilden, Germany). The study was approved by the ethical review committee for research in human subjects, Ministry of Public Health, Thailand.

Genotype analysis

Genotypes were determined by PCR (primers: 5′-AGCCCCATTCCGCTGTGAA-3′ and 5′-CTTGGTGCTCACCTGGTTGAT-3′) followed by melting point analysis (LightCycler, Roche Diagnostics, Mannheim, Germany; probes: 5′-GGGGCCACG CTGCGTGA-FITC-3′ and 5′-LCRed640-CTGAGCAGTGCCTTCCAGAGCCC TGTGCp-3′; TibMolbiol, Berlin, Germany) in analogy to previously published protocols (Popanda et al. 2006). Analysis was performed in 10-μl volumes using Qiagen reagents (1 × PCR buffer, 2.5 mM total $MgCl_2$, 0.2 mM dNTPs, 0.1% BSA in DMSO, 1 × Q-solution, 0.5 U Taq DNA polymerase, 0.5 μM of each primer, 0.15 μM of each probe and 10 ng DNA) and the following reaction conditions: initial denaturation at 95°C for 3 min, 40 cycles of denaturation at 95°C for 15 s, annealing at 62°C for 10 s and elongation at 72°C for 12 s. Melting curve analysis was performed with a ramping rate of 0.2°C per s and continuous fluorescence detection. Measurements for quality control included a control containing water instead of the DNA template, evaluation of melting curves by two independent observers blinded to the case–controls status of samples, automatic comparison of melting points with reference samples for which identity was proven by restriction fragment length

Table I. Selected characteristics of the study population.

Characteristics	Cases	Controls	*p*-Value
Age (years), *n* (mean ± SD)	507 (48.0 ± 10.0)	425 (45.3 ± 12.2)	<0.01
Age at menarche	501 (14.9 ± 1.9)	425 (14.8 ± 1.8)	0.41
Age at menopause	235 (47.1 ± 5.3)	177 (46.8 ± 5.1)	0.49
Age at first pregnancy	391 (23.0 ± 5.4)	295 (22.8 ± 5.0)	0.67
Pregnancy ($n = 932$), *n* (%)			
No	116 (22.9%)	130 (30.6%)	<0.01
Yes	391 (77.1%)	295 (69.4%)	
Breastfeeding ($n = 686$), *n* (%)			
No	45 (11.5%)	20 (6.8%)	0.04
Yes	346 (88.5%)	275 (93.2%)	
Oral contraceptive use ($n = 932$), *n* (%)			
No	283 (55.8%)	256 (60.2%)	0.17
Yes	224 (44.2%)	169 (39.8%)	
Menopausal status ($n = 932$), *n* (%)			
Premenopausal	268 (52.9%)	245 (57.6%)	0.14
Postmenopausal	239 (47.1%)	180 (42.4%)	
Body mass index (kg m^{-2}), *n* (mean ± SD)	506 (24.2 ± 4.0)	425 (23.1 ± 4.0)	<0.01
Tobacco smoking ($n = 932$), *n* (%)			
No	493 (97.2%)	419 (98.7%)	0.18
Yes	14 (2.8%)	6 (1.4%)	
Involuntary smoking ($n = 912$), *n* (%)			
No	440 (89.3%)	395 (94.3%)	<0.01
Yes	53 (10.7%)	24 (5.7%)	
Alcohol consumption ($n = 932$), *n* (%)			
No	471 (92.9%)	403 (94.8%)	0.28
Yes	36 (7.1%)	22 (5.2%)	
Family history of breast cancer in first-degree relatives ($n = 932$), *n* (%)			
No	488 (96.3%)	419 (98.6%)	0.03
Yes	19 (3.7%)	6 (1.4%)	
Education ($n = 931$), *n* (%)			
≤9 years	374 (73.9%)	238 (56.0%)	<0.01
>9 years	132 (26.1%)	187 (44.0%)	
Study area ($n = 932$), *n* (%)			
Bangkok	292 (57.6%)	251 (59.1%)	0.65
Khon Kaen	215 (42.2%)	174 (40.9%)	

polymorphisms or sequence analysis, and repetition of 15% of randomly selected samples. Here, 100% concordance was found.

Statistical analysis

Breast cancer patients were compared with controls for basic demographic and lifestyle characteristics (Table I). Genotypes of both cases and controls were tested as to whether they were in Hardy–Weinberg equilibrium using the χ^2 test of goodness of fit with one degree of freedom, with respect to the distribution of the two considered allele groups. Because the *XRCC3* 241Met allele is uncommon in this population,

individuals with genotypes Thr/Met and Met/Met were combined in one group as 241Met allele carriers and compared with Thr/Thr homozygotes as the reference.

For analysing the association of breast cancer risk with the *XRCC3* polymorphism, ORs and their 95% CIs were calculated and assessed for statistical significance according to Breslow and Day (1980), both as crude ORs and as adjusted ORs. In addition, multivariate unconditional logistic regression analysis was performed to assess the association between occurrence of breast cancer and prevalence of the polymorphism and to adjust for potential confounders. Covariates were selected when either significant in the univariate analysis at the level of 5% (age, body mass index (BMI), reproduction parameters, hazardous lifestyle, education) or when considered as a relevant factor for the occurrence of breast cancer in general (family history of breast cancer (FH), age at menarche, menopausal status, use of contraceptives). FH, menopausal status, use of contraceptives and education (≤ 9 years, >9 years) were incorporated in the model as binary predictors. Alcohol consumption, active and involuntary smoking were combined into one binary variable 'hazardous lifestyle' (0 = no regular alcohol consumption and no active or involuntary smoking, 1 = other). In the analysis of all subjects, reproduction was a combination of pregnancy and breastfeeding in five categories: non-pregnant, age at first pregnancy ≤ 22 years and non-breastfeeding, age at first pregnancy ≤ 22 years and breastfeeding, age at first pregnancy >22 years and non-breastfeeding, age at first pregnancy >22 years and breastfeeding. To deal with possible non-linearity, continuous predictors (age, BMI and age at menarche) were modelled by using fractional polynomials (Royston & Sauerbrei 1999). Finally, ORs resulted from multivariate logistic regression model including age (non-linear), BMI, FH, age at menarche, reproduction parameters (five classes), menopausal status, use of contraceptives, hazardous lifestyle and education.

Possible interaction effects for age × BMI, polymorphism × hazardous lifestyle, polymorphism × BMI and polymorphism × reproduction were tested by introducing an interaction term into the logistic regression model using the standard Wald test. The significance level was set to 0.1 in accounting for the lower power to test for interaction compared to testing for single covariate's effects.

In addition, subgroups based on menopausal status were analysed. Here, reproduction was categorized as non-pregnant, age at first pregnancy ≤ 22 years and age at first pregnancy >22 years. Thus, ORs in subgroups were adjusted by age (linear), BMI, FH, age at menarche, reproduction parameters (three classes), use of contraceptives, hazardous lifestyle and education. Statistical analyses were performed using the statistical packages SAS (SAS Institute, Cary, NC) for Windows Version 9.

Results

Characteristics of the study population were compared by case–control status, as shown in Table I. The mean age of controls (45.3 ± 12.2 years) was significantly lower than that of breast cancer patients (48.0 ± 10.0 years) ($p < 0.01$). Pregnancy, breastfeeding, BMI, involuntary tobacco smoking, FH and education were different between cases and controls. However, no significant differences were found between cases and controls for oral contraceptive use, menopausal status, smoking and alcohol consumption.

Table II. Association between *XRCC3* Thr241Met polymorphisms and breast cancer risk.

	Cases *n* (%)	Control[a] *n* (%)	Crude OR[e] (95% CI)	Adjusted OR[b] (95% CI)
All subjects	507 (100)	424 (100)		
Thr/Thr	437 (86.2)	384 (90.6)	1.00 (reference)	1.00 (reference)
Thr/Met	69 (13.6)	38 (9.0)	n.c.	n.c.
Met/Met	1 (0.2)	2 (0.5)	n.c.	n.c.
Thr/Met, Met/Met	70 (13.8)	40 (9.4)	1.54 (1.02–2.32)	1.58 (1.02–2.44)[c]
Met allele frequency	0.07	0.05	$p=0.05$	$p=0.04$
Premenopausal women	268 (100)	245 (100)		
Thr/Thr	232 (86.7)	221 (90.2)	1.00 (reference)	1.00 (reference)
Thr/Met, Met/Met	36 (13.3)	24 (9.8)	1.40 (0.81–2.42) $p=0.23$	1.48 (0.82–2.69)[d] $p=0.19$
Postmenopausal women	239 (100)	179 (100)		
Thr/Thr	205 (86.0)	163 (91.1)	1.00 (reference)	1.00 (reference)
Thr/Met, Met/Met	34 (14.0)	16 (8.9)	1.66 (0.89–3.13) $p=0.11$	1.82 (0.95–3.51) [d] $p=0.07$

[a]Only 424 control samples were analysed because no polymerase chain reaction product was obtained for one sample.
[b]Only patients with complete information were used for unconditional logistic regression analysis ($n=922$).
[c]Adjusted for age (non-linear using fractional polynomial functions), body mass index (BMI), family history of breast cancer, age at menarche, reproduction parameters (five classes), menopausal status, use of contraceptives, hazardous lifestyle, education.
[d]Adjusted for age (linear), BMI, family history of breast cancer, age at menarche, reproduction parameters (three classes), use of contraceptives, hazardous lifestyle, education.
[e]When adjusted for age: for all subjects (non-linear age adjustment using the fractional polynomial: $age^{-0.5}+age^{-0.5}\log(age)$) odds ratio (OR) = 1.56 (1.03–2.37), $p=0.04$; for premenopausal women (linear age adjustment): OR = 1.41 (0.80–2.48), $p=0.24$; for postmenopausal women (linear age adjustment): OR = 1.69 (0.90–3.17), $p=0.10$.
CI, confidence interval; n.c., not calculated.

Genotype frequencies for *XRCC3* Thr241Met polymorphism in cases and controls were in Hardy–Weinberg equilibrium. Met allele frequency was 0.07 for cases and 0.05 for controls (p-values of χ^2 test: 0.31 and 0.32, respectively).

The results of both univariate and multivariate logistic regression analysis are shown in Table II with the crude and the adjusted ORs, respectively, for all subjects and pre- and postmenopausal women, separately for age only or for all covariates. A significant association ($p=0.04$) between 241Met carrier status and breast cancer risk was observed, OR 1.58, 95% CI 1.02–2.44, adjusted for age, BMI, FH of breast cancer, age at menarche, reproduction parameters (five classes), menopausal status, use of contraceptives, hazardous lifestyle and education. Interaction effects between age and BMI as well as polymorphism and hazardous lifestyle, BMI or reproduction were not observed ($p>0.85$). In the subgroup analysis, *XRCC3* 241Met allele carriers showed a slightly higher risk in postmenopausal (OR 1.82, 95% CI 0.95–3.51) than in premenopausal women (OR 1.48, 95% CI 0.82–2.69).

Discussion

In our breast cancer case–control study among Thai women, allele frequencies measured for the *XRCC3* Thr241Met polymorphism in cases and controls were

similar to those determined in other Asian populations (Shen et al. 2004, Jin et al. 2005, Yeh et al. 2005, Zhang et al. 2005). A separate evaluation of allele frequencies according to the two study areas yielded identical results for both regions (data not shown) indicating that our risk estimates are based on an ethnically homogenous Asian population.

The *XRCC3* Thr241Met polymorphism was associated with breast cancer risk (OR 1.58, 95% CI 1.02–2.44). This result determined in a Thai population is higher than that evaluated by two meta-analyses including breast cancer studies in women of European ancestry (OR 1.16, 95% CI 1.04–1.30 (Garcia-Closas et al. 2006) and 1.14, 95% CI 1.06–1.23 (Han et al. 2006)). A further meta-analysis form the Breast Cancer Association Consortium (2006) also included samples from not yet published studies, but could not confirm the association between breast cancer and the *XRCC3* polymorphism. In the two latter analyses, data from a study with individuals of Asian origin were included (Zhang et al. 2005). However, the number of cases in this study was small (220 cases, 310 controls) and the Met allele frequency (0.27) did not correspond to that published for Chinese populations (0.02–0.07) (Shen et al. 2004, Jin et al. 2005, Yeh et al. 2005, Zhang et al. 2005). Therefore, our data support the finding that *XRCC3* Thr241Met polymorphism is weakly associated with breast cancer risk.

Our risk estimate took into consideration several risk factors known from literature to affect the gene–risk association including age, reproductive parameters, hormonal use and hazardous lifestyle (Dumitrescu & Cotarla 2005). Some of these risk factors were considerably different between cases and controls in our study (Table I). This is in accordance with previous studies of breast cancer (Dumitrescu & Cotarla 2005), with the exception of pregnancy and education. More cases had children than controls, but pregnancy is estimated as being protective, and controls were more highly educated than cases. As neither criteria were used in patient recruitment as inclusion criteria, these differences might have happened by chance. They were, however, considered in our multivariate regression analysis as adjustment factors together with other covariates differing in our population or being especially important risk factors. One example is age that was different among cases and controls in our study. Therefore, we adjusted for this difference by modelling age as an exponential variable in the logistic regression model. The multivariate regression analysis for age only and for the complete model including all covariates and the interaction analysis revealed that they had only a minor effect on the risk estimate for the *XRCC3* polymorphism. Thus, our results were robust to different model adjustments. This indicates that the risk contribution of the genetic variant is moderate but not affected by the known strong breast cancer risk factors such as pregnancy, breastfeeding and family history of breast cancer.

We also separated our evaluation in pre- and postmenopausal women. There is strong evidence that risk factors differ in these two groups of breast cancer and it is plausible that factors interacting with this polymorphism in determining breast cancer risk also have a different role in pre- vs. postmenopausal cancers (Dumitrescu & Cotarla 2005). Since the observed effect is likely due to the interaction of the genetic variant with endogenous or exogenous risk factors (e.g. ionizing radiation), one might expect an effect modification by menopausal status. This is, however, not supported by our data which show no strong evidence of heterogeneity in risk estimates by menopausal status.

To study the relevance of the *XRCC3* Thr241Met polymorphism for breast cancer risk further, a more detailed analysis of *XRCC3* should include more polymorphisms of this gene which could contribute to breast cancer risk and which would allow haplotype reconstruction. In a lung cancer study, mainly two polymorphisms have been found to co-segregate together with the Thr241Met (C to T change at nucleotide position 18067) polymorphism, a polymorphism in the 5'-untranslated region (A to G at nucleotide position 4541) and a non-coding polymorphism at IVS5-14 (A to G at nucleotide position 17893) (Jacobsen et al. 2004). The relatively rare GAT haplotype including the Met241 coding variant was found to be associated with a more than 4-fold increase in breast cancer risk (Kuschel et al. 2002). This supports our results that the Met241 allele could influence breast cancer risk. Considering the fact that this breast cancer study was performed in Europeans, it would be highly relevant to study the haplotype pattern in an Asian population with very different allele frequencies.

The association of the variant allele of *XRCC3* The241Met with breast cancer risk is further supported by several associations of this polymorphism with functional markers for DNA repair activity. Relatively high bulky DNA adduct levels in lymphocyte DNA (Matullo et al. 2001b) and an increased number of micronuclei in peripheral lymphocytes of humans exposed to ionizing radiation were described for Met allele carriers (Aka et al. 2004, Angelini et al. 2005), which is consistent with the notion that the polymorphism is associated with lower DNA repair capacity. No differences in homology-directed repair of DSB have, however, been found between the wild-type and the variant XRCC3 protein (Araujo et al. 2002). Thus, we are aware that the *XRCC3* polymorphism, although apparently functional, cannot give the complete information about variability in gene function. A more comprehensive analysis of *XRCC3* including variants in genes of other DNA repair pathways, mainly the DSB repair pathways (HR and NHEJ) are required.

Conclusion

Our results suggest that *XRCC3* Thr241Met polymorphism is likely to play a modifying role in the individual susceptibility to breast cancer among Thai women. In addition, large population-based studies also including Asian populations are warranted to confirm the genetic role of *XRCC3* Thr241Met in breast cancer susceptibility.

Acknowledgements

The authors wish to thank S. Pummai and P. Waas for their excellent technical assistance. We also acknowledge the contributions of all participants of this study. This work was supported by National Center for Genetic Engineering and Biotechnology (Thailand) and a Guest Scientist Fellowship of the German Cancer Research Center (DKFZ).

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