Contribution of X-Ray Repair Complementing Defective Repair in Chinese Hamster Cells 3 (*XRCC3*) Genotype to Leiomyoma Risk

WEN-SHIN CHANG[1,2*], CHIA-WEN TSAI[1*], JU-YU WANG[3*], TSUNG-HO YING[4], TSAN-SENG HSIAO[5], CHIN-LIANG CHUANG[5], TE-CHENG YUEH[5], CHENG-HSI LIAO[5], CHIN-MU HSU[1], SHIH-PING LIU[1], CHI-LI GONG[1], CHANG-HAI TSAI[1] and DA-TIAN BAU[1,2,6]

[1]*Terry Fox Cancer Research Laboratory, Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[2]*Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan, R.O.C.;*
[3]*Basic Medical Science, Department of Nursing, Hung-Kuang University, Taichung, Taiwan, R.O.C.;*
[4]*Department of Obstetrics and Gynecology, Chung Shan Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[5]*Taichung Armed Forces General Hospital, Taichung, Taiwan, R.O.C.;*
[6]*Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan, R.O.C.*

Abstract. *Aim: The present study aimed at investigating whether X-ray repair cross complementing protein 3 (XRCC3) genotype may serve as a useful marker for detecting leiomyoma and predicting risk. Materials and Methods: A total of 640 women (166 patients with leiomyoma and 474 healthy controls) were examined for their XRCC3 rs1799794, rs45603942, rs861530, rs3212057, rs1799796, rs861539, rs28903081 genotype. The distributions of genotypic and allelic frequencies between the two groups were compared. Results: The results showed that the CT and TT genotypes of XRCC3 rs861539 were associated with increased leiomyoma risk (odds ratio=2.19, 95% confidence interval=1.23-3.90; odds ratio=3.72, 95% confidence interval=1.23-11.26, respectively). On allelic frequency analysis, we found a significant difference in the distribution of the T allelic frequency of the XRCC3 rs861539 ($p=5.88\times10^{-5}$). None of the other six single nucleotide polymorphisms were associated with altered leiomyoma susceptibility. Conclusion: The T allele (CT and TT genotypes) of XRCC3 rs861539 contributes to increased risk of leiomyoma among Taiwanese women and may serve as a early detection and predictive marker.*

Worldwide, uterine leiomyoma is the most commonly diagnosed benign uterine neoplasm, and almost one fourth of women were affected by leiomyoma during their lifetime (1). Early during the 1970s, uterine leiomyoma was found to be monoclonal, and its tumorigenesis may be derived from growth and proliferation of a single smooth muscle cell (2). Uterine leiomyoma is estimated to be present in 30-70% of clinically reproductive women, and has become a common health threat (3-5). Statistically, it was estimated that about seven out of every ten Caucasian women and eight out of every ten African American women eventually develop uterine leiomyoma (3). In addition, some factors such as ethnicity, nulliparity, obesity, diet and age, especially those of early menarche, were revealed to be predisposing factors for uterine leiomyoma (6). Although clear heredity or genetic involvement has not yet been well-described for uterine leiomyoma, it has been shown that individual differences in susceptibility may be inherited in genes encoding DNA repair proteins, which may be closely associated with personal uterine leiomyoma risk (7). Furthermore, Hakverdi and colleagues found novel chromosomal aberrations in the tissues from patients with uterine leiomyoma (8).

The X-ray repair cross-complementing group 3 (*XRCC3*) gene located on human chromosomes 14q32.3, encodes for the DNA repair protein XRCC3. In 1998, XRCC3 was shown to play a role in homologous recombination (HR) to repair double-strand breaks *via* interacting with RAD51 recombinase (*RAD51*) (9). In 2002, *XRCC3*-mutant cells

*These Authors contributed equally to this study.

Correspondence to: Da-Tian Bau, Terry Fox Cancer Research Laboratory, Department of Medical Research, China Medical University Hospital, 2 Yuh-Der Road, Taichung, 404 Taiwan, R.O.C. Tel: +886 422052121 Ext. 7534, e-mail: datian@mail.cmuh.org.tw; artbau2@gmail.com

Key Words: Genotype, leiomyoma, polymorphism, Taiwan, *XRCC3*.

Table I. *Distributions of selected demographic data of the 166 patients with leiomyoma and the 474 non-leiomyoma controls.*

Characteristic	Patients (n=166)			Controls (n=474)			*p*-Value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			49.6 (8.9)			50.3 (9.2)	0.6133
<40	80	48.2%		239	50.4%		
≥40	86	51.8%		235	49.6%		0.6525
Height, cm							
<155	66	40.0%		215	45.4%		
≥155	100	60.0%		259	54.6%		0.2376
Weight status, kg							
<45	84	50.6%		242	51.1%		
≥45	82	49.4%		232	48.9%		0.9284
No. of children							
0	108	65.1%		237	50.0%		
1	33	19.9%		166	35.0%		
2	22	13.2%		47	9.9%		
>2	3	1.8%		24	5.1%		**0.0003**

[a]Based on Student's *t*-test (mean age) or Chi-square test. Statistically significant results are shown in bold.

were found to have increased gene conversion tract lengths, increased frequencies of discontinuous tracts, and frequent local rearrangements. The results indicated that XRCC3 is involved not only in HR initiation, but also in formation and stabilizing of HR intermediates (10). In recent years, mounting evidence has shown the association between the genotypes of *XRCC3*, such as the rs861539 C/T (also named Thr241Met, T241M, C18067T and C722T) single nucleotide polymorphism (SNP) and risk of cancer, including of the lung (11-13), oral cavity (14), stomach (15), bladder (16), breast (17, 18), colorectum (19) and nasopharynx (20). In addition, variants of this polymorphism may affect the function of XRCC3, with decreased DNA repair capacity and elevated level of bulky DNA adducts in leukocytes of healthy individuals (11). Thus, the rs861539 polymorphism and others of *XRCC3* may also contribute to the pathogenesis and development of uterine leiomyoma.

In the present study, we aimed to examine the contribution of *XRCC3* genotype to uterine leiomyoma risk. The distributions of the genotypic and allelic frequencies for *XRCC3* at promoter A-315G (rs1799794), promoter C-280T (rs45603942), intron5 (rs861530), exon6 (rs3212057), intron7 (rs1799796), exon8 (rs861539) and exon10 (rs28903081) were examined among women with and without uterine leiomyoma in Taiwan.

Materials and Methods

Investigated population. Six hundred and forty pre-menopausal women with and without uterine leiomyoma were recruited in this study. Among them, 166 were surgically- and histologically-diagnosed with leiomyoma. The other 474 women were confirmed as not having leiomyoma after detailed ultrasonography. Patients with previous malignancy, metastasized cancer from other or unknown origin, and any genetic or familial diseases were excluded. The clinical characteristics of patients, including histological details, were all graded and defined by expert surgeons. All participants voluntarily completed a self-administered questionnaire and provided their peripheral blood samples. Approval from the Institutional Review Board and written-informed consent was obtained from all participants. We also sincerely followed the principles outlined in the Declaration of Helsinki for human investigations. The demographic information for the leiomyoma cases and healthy controls are listed in Table I.

Genotyping conditions. Genomic DNA was extracted from peripheral blood leucocytes using the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan). In this study, a total of seven polymorphic sites were analyzed in both the control and case groups. Briefly, all of the seven polymorphic sites were genotyped by means of a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Each PCR reaction consisted of an initial cycle at 94˚C for 5 min; 40 cycles at 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension at 72˚C for 10 min. After the PCR process, the SNP-containing DNA amplicons were subjected to individual overnight digestion by the restriction endonucleases listed in Table II for genotyping of each SNP. Following digestion, each sample was immediately analyzed by 3% agarose gel electrophoresis. Details such as the primer sequences, and enzymatic digestion conditions for genotyping of each SNP are summarized in Table II.

Statistical analyses. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *XRCC3* SNPs in the controls from those expected under the Hardy–Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's chi-square test was used to compare

Table II. *Summary of the rs numbers, primers, amplicon length before and after enzyme digestion, restriction enzymes for all the X-ray repair cross complementing protein 3 (XRCC3) single nucleotide polymorphisms.*

rs Number	Primer sequence	Restriction enzyme	Amplicon length	Allele and enzymatic fragment sizes
rs1799794	F: 5'-CACACTGCGGTCTTGCAGTG-3'	*Bts*CI	505 bp	G: 505 bp
	R: 5'-CAGGCTGGGTCTGGATACAA-3'			A: 289 + 216 bp
rs45603942	F: 5'-GGGATGCAGGTTCAACTGAC-3'	*Alu*I	352 bp	C: 352 bp
	R: 5'-AACTTGGACTGTGTCAAGCA-3'			T: 187 + 165 bp
rs861530	F: 5'-CCGAGGAACGTGCTGAACTT-3'	*Fat*I	497 bp	G: 497 bp
	R: 5'-CTCCCTAACAGCCTCCATGT-3'			A: 293 + 204 bp
rs3212057	F: 5'-CCATGACCGCAGGCACTTGT-3'	*HpyCH4*III	455 bp	G: 455 bp
	R: 5'-AGAACGCGACAAGGATGGTA-3'			A: 235 + 220 bp
rs1799796	F: 5'-GG AACCAGTTGT GTGAGCCT-3'	*Alu*I	430 bp	G: 430 bp
	R: 5'-CCTGGTTGATGCACAGCACA-3'			A: 226 + 204 bp
rs861539	F: 5'-GACACCTTGT TGGAGTGTGT-3'	*Fat*I	358 bp	C: 358 bp
	R: 5'-GTCTTCTCGATGGTTAGGCA-3'			T: 200 + 158 bp
rs28903081	F: 5'-CTGCTTCCTGTTTCTCAGGT-3'	*BstU*I	198 bp	A: 198 bp
	R: 5'-GCACTGATCGTGTAGGAACA-3'			G: 102 + 96 bp

the distribution of the *XRCC3* genotypes between leiomyoma cases and healthy controls. Student's *t*-test was used to compare the difference between case and control groups by age. The leiomyoma risk associated with the genotypes was estimated as odds ratio (OR) with 95% confidence intervals (CIs) using unconditional logistic regression. Data were recognized as significant when the statistical *p*-value outcome was less than 0.05.

Results

The frequency distributions of demographic characteristics for the 166 patients with leiomyoma and 474 non-leiomyoma controls are summarized in Table I. There was no difference in the distributions of age, height and weight between the patient and control groups (Table I). Overall, women in the control group had significantly more children than those in the patient group (p=0.0003) (Table I).

The distributions of the *XRCC3* genotypic frequencies for rs1799794, rs45603942, rs861530, rs3212057, rs1799796, rs861539 and rs28903081 among the patients with leiomyoma and controls are presented and analyzed in Table III. The data show that the genotypes of *XRCC3* rs861539 were differently distributed between leiomyoma and non-leiomyoma groups (p=0.0018) (Table III). *XRCC3* rs861539 heterozygous variant CT and homozygous variant TT genotypes were significantly associated with higher risk of leiomyoma (p=0.0018) compared with the wild-type CC genotype (Table III). The distributions of the *XRCC3* genotypes of rs1799794, rs45603942, rs861530 and rs1799796 were not different among the patients and controls (Table III). In this study, we found that our Taiwanese population had only one genotype at *XRCC3* rs3212057 (GG) and rs28903081 (GG) (Table III).

We also examined the distributions of the *XRCC3* allelic frequencies for rs1799794, rs45603942, rs861530, rs1799796 and rs861539 among the controls and the patients, and the results are presented in Table IV. Consistent with the findings that the CT and TT genotypes of XRCC3 rs861539 were associated with an increased risk of leiomyoma (Table III), the T allele was found at a significantly higher percentage (10.8%) among the patients than the controls (4.6%) ($p=5.88\times10^{-5}$) (Table IV). For the other polymorphic sites of XRCC3 examined, the distributions of the allelic frequencies were not different between the control and patient groups (Table IV).

Discussion

Uterine leiomyomas are the most common female genital tumors (21, 22). In Taiwan, the prevalence of uterine leiomyoma has been increasing in recent years. However, despite its high incidence, its etiology and pathogenesis remain obscure. Clinically, uterine leiomyoma has many features similar to those of solid tumors. Loss of maintenance of genome integrity is closely associated with tumorigenesis, and cancer may occur more frequently among those who carry inherited defects in their DNA repair genes such as *XRCC3*. XRCC3 protein has been reported to play a role in DNA repair (23), and mutations of *XRCC3* gene have been related to severe chromosomal instability (10). From the viewpoint of proteomics, the altered quality (activity) and quantity (expression level) of XRCC3 protein have been reported to be associated with a more aggressive tumor phenotype, higher recurrence rate, and poorer prognosis of several types of cancers, such as of the breast and colorectum, and in non-small cell lung cancer (24-26).

We surveyed the MEDLINE database, finding no literature investigating the association of *XRCC3* genotypes with leiomyoma susceptibility. In this case–control study in

Table III. *Distribution of X-ray repair cross complementing protein 3 (XRCC3) genotypes among patients with leiomyoma and non-leiomyoma controls.*

Genotype	Patients (n=166)	%	Controls (n=474)	%	*p*-Value[a]	Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)[b]
rs1799794					0.9048		
GG	40	24.1%	113	23.8%		1.00 (Reference)	1.00 (Reference)
AG	91	54.8%	268	56.6%		0.96 (0.62-1.48)	0.99 (0.65-1.52)
AA	35	21.1%	93	19.6%		1.06 (0.63-1.81)	1.07 (0.66-1.84)
rs45603942					0.8906		
CC	153	92.2%	441	93.0%		1.00 (Reference)	1.00 (Reference)
CT	11	6.6%	29	6.1%		1.09 (0.53-2.24)	1.11 (0.61-1.88)
TT	2	1.2%	4	0.9%		1.44 (0.26-7.95)	1.36 (0.37-5.86)
rs861530					0.7817		
AA	53	31.9%	140	29.5%		1.00 (Reference)	1.00 (Reference)
AG	90	54.2%	260	54.9%		0.91 (0.62-1.36)	0.94 (0.65-1.41)
GG	23	13.9%	74	15.6%		0.82 (0.47-1.44)	0.85 (0.52-1.38)
rs3212057					1.0000		
GG	116	100.0%	474	100.0%		1.00 (Reference)	1.00 (Reference)
AG	0	0.0%	0	0.0%		1.00	1.00
AA	0	0.0%	0	0.0%		1.00	1.00
rs1799796					0.5999		
AA	83	50.0%	227	47.9%		1.00 (Reference)	1.00 (Reference)
AG	72	43.4%	223	47.0%		0.88 (0.61-1.27)	0.91 (0.64-1.33)
GG	11	6.6%	24	5.1%		1.25 (0.58-2.67)	1.19 (0.62-2.36)
rs861539					**0.0018**		
CC	137	82.5%	437	92.0%		1.00 (Reference)	1.00 (Reference)
CT	22	13.3%	32	6.7%		**2.19 (1.23-3.90)**	**2.26 (1.15-4.24)**
TT	7	4.2%	6	1.3%		**3.72 (1.23-11.26)**	**4.21 (1.28-10.89)**
rs28903081					1.0000		
GG	716	100.0%	358	100.0%		1.00 (Reference)	1.00 (Reference)
AG	0	0.0%	0	0.0%		1.00	1.00
AA	0	0.0%	0	0.0%		1.00	1.00

CI: Confidence interval. [a]*p*-Value based on chi-square test. Statistically significant results are shown in bold. [b]Adjusted for age, height, weight and number of children.

Taiwan, we are the first to examine seven polymorphic genotypes of *XRCC3*, and their contribution to determine individual susceptibility to leiomyoma. We found that *XRCC3* rs861539 variant CT and TT genotypes were associated with an increased leiomyoma risk (Tables III and IV). There was also a significant trend that carrying two variant T alleles was associated with higher risk than carrying one (OR=3.72 *vs*. 2.19, p=0.0018) or none (Table III). The T allele can serve as a biomarker for early detection of and predictive for leiomyoma.

Regarding factors, we found that age, height and weight were not risk factors for leiomyoma in Taiwan (Table I). In 2001, it was reported that individuals carrying a T allele at *XRCC3* rs861539 have a significantly higher level of bulky DNA adducts in their lymphocyte DNA than those carrying the C allele (11, 27). Although we did not measure the levels of bulky DNA adducts in white blood cells in our study, our findings support previous data showing that people with *XRCC3* rs861539 CT and TT genotypes had a more instable genome than those with wild-type CC genotype, leading to a higher risk for leiomyoma (14, 20).

Table IV. *Distribution of X-ray repair cross complementing protein 3 (XRCC3) alleles among patients with leiomyoma and non-leiomyoma controls.*

Allele	Patients	%	Controls	%	*p*-Value[a]
rs1799794					
G	171	51.5%	494	52.1%	0.8497
A	161	48.5%	454	47.9%	
rs45603942					
C	317	95.5%	911	96.1%	0.6251
T	15	4.5%	37	3.9%	
rs861530					
A	196	59.0%	540	57.0%	0.5106
G	136	41.0%	408	43.0%	
rs1799796					
A	238	71.7%	677	71.4%	0.9244
G	94	28.3%	271	28.6%	
rs861539					
C	296	89.2%	904	95.4%	**5.88×10^{-5}**
T	36	10.8%	44	4.6%	

[a]Based on Chi-square test. Statistically significant results are shown in bold.

Elevated lifetime estrogen exposure is a major risk factor for breast cancer and estrogen-induced reactive oxygen species (ROS) and ROS-mediated signaling pathways contribute to breast cancer development. ROS was found to activate mitogenic growth factor signaling pathway in primarily cultured human leiomyoma smooth muscle cells (28). At the same time, ROS may cause DNA double-strand breaks which should be removed by XRCC3 and other DNA repair proteins. The etiology of leiomyoma is complex, and one possible mechanism is that women exposed to estrogen for longer due to their earlier menarche or later menopause may be at higher risk of leiomyoma as a result of exposure to ROS for a longer period during their lifetime. Therefore, age- and hormone-related factors are risk factors for leiomyoma (4, 5). Regarding genetic factors of leiomyoma, women with variant genotypes at *XRCC3* rs861539 may be at even higher risk since their genomes are more unstable than those with wild-type genotype. In the future, it is very important to investigate the gene interaction with other factors to reveal the etiology of leiomyoma.

In conclusion, our findings suggest for the first time that the T allele of *XRCC3* rs861539 may be associated with higher risk of leiomyoma, and can serve as a marker for early detection and prediction of leiomyoma.

Acknowledgements

We appreciate Chia-En Miao, Lin-Lin Hou, Tzu-Chia Wang, Yun-Ru Syu for their excellent technical assistance. This study was supported by research grants from Taichung Armed Forces General Hospital (104-A11, 104-A13, 104-A23) and Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002). The authors declare no conflict of interest.

References

1 Cramer DW: Epidemiology of myomas. Semi Reprod Endocrinol *10*: 320-324, 1992.
2 Townsend DE, Sparkes RS, Baluda MC and McClelland G: Unicellular histogenesis of uterine leiomyomas as determined by electrophoresis by glucose-6-phosphate dehydrogenase. Am J Obstet Gynecol *107*: 1168-1173, 1970.
3 Baird DD, Dunson DB, Hill MC, Cousins D and Schectman JM: High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol *188*: 100-107, 2003.
4 Ekin M, Cengiz H, Ozturk E, Kaya C, Yasar L and Savan K: Genitourinary symptoms and their effects on quality of life in women with uterine myomas. Int Urogynecol J *25*: 807-810, 2014.
5 Tal R and Segars JH: The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update *20*: 194-216, 2014.
6 Verit FF and Yucel O: Endometriosis, leiomyoma and adenomyosis: the risk of gynecologic malignancy. Asian Pac J Cancer Prev *14*: 5589-5597, 2013.
7 Hsieh YY, Chang CC, Bau DT, Yeh LS, Tsai FJ and Tsai CH: X-ray repair cross-complementing group 4 (XRCC4) promoter -1394(*)T-related genotype, but not XRCC4 codon 247/intron 3 or xeroderma pigmentosum group D codon 312, 751/promoter -114, polymorphisms are correlated with higher susceptibility to myoma. Fertil Steril *90*: 1417-1423, 2008.
8 Hakverdi S, Demirhan O, Tunc E, Inandiklioglu N, Uslu IN, Gungoren A, Erdem D and Hakverdi AU: Chromosome imbalances and alterations in the p53 gene in uterine myomas from the same family members: familial leiomyomatosis in Turkey. Asian Pac J Cancer Prev *14*: 651-658, 2013.
9 Liu N, Lamerdin JE, Tebbs RS, Schild D, Tucker JD, Shen MR, Brookman KW, Siciliano MJ, Walter CA, Fan W, Narayana LS, Zhou ZQ, Adamson AW, Sorensen KJ, Chen DJ, Jones NJ and Thompson LH: XRCC2 and XRCC3, new human RAD51-family members, promote chromosome stability and protect against DNA cross-links and other damages. Mol Cell *1*: 783-793, 1998.
10 Brenneman MA, Wagener BM, Miller CA, Allen C and Nickoloff JA: XRCC3 controls the fidelity of homologous recombination: roles for XRCC3 in late stages of recombination. Mol Cell *10*: 387-395, 2002.
11 Matullo G, Palli D, Peluso M, Guarrera S, Carturan S, Celentano E, Krogh V, Munnia A, Tumino R, Polidoro S, Piazza A and Vineis P: XRCC1, XRCC3, XPD gene polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. Carcinogenesis *22*: 1437-1445, 2001.
12 Qian B, Zhang H, Zhang L, Zhou X, Yu H and Chen K: Association of genetic polymorphisms in DNA repair pathway genes with non-small cell lung cancer risk. Lung Cancer *73*: 138-146, 2011.
13 Guo S, Li X, Gao M, Li Y, Song B and Niu W: The relationship between XRCC1 and XRCC3 gene polymorphisms and lung cancer risk in northeastern Chinese. PLoS One *8*: e56213, 2013.
14 Tsai CW, Chang WS, Liu JC, Tsai MH, Lin CC and Bau DT: Contribution of DNA double-strand break repair gene XRCC3 genotypes to oral cancer susceptibility in Taiwan. Anticancer Res *34*: 2951-2956, 2014.
15 Bashir H, Majid S, Hamid R, Farooq R, Wani HA, Shoib S and Bhat AA: Polymorphism of the XRCC3 gene and risk of gastric cancer in a Kashmiri population: a case–control study. Eur J Cancer Prev *24*: 167-175, 2015.
16 Zhu X, Zhong Z, Zhang X, Zhao X, Xu R, Ren W and Li S: DNA repair gene XRCC3 T241M polymorphism and bladder cancer risk in a Chinese population. Genet Test Mol Biomarkers *16*: 640-643, 2012.
17 Sangrajrang S, Schmezer P, Burkholder I, Boffetta P, Brennan P, Woelfelschneider A, Bartsch H, Wiangnon S, Cheisilpa A and Popanda O: The XRCC3 Thr241Met polymorphism and breast cancer risk: a case–control study in a Thai population. Biomarkers *12*: 523-532, 2007.
18 Krupa R, Synowiec E, Pawlowska E, Morawiec Z, Sobczuk A, Zadrozny M, Wozniak K and Blasiak J: Polymorphism of the homologous recombination repair genes RAD51 and XRCC3 in breast cancer. Exp Mol Pathol *87*: 32-35, 2009.
19 Jin MJ, Chen K, Song L, Fan CH, Chen Q, Zhu YM, Ma XY and Yao KY: The association of the DNA repair gene XRCC3 Thr241Met polymorphism with susceptibility to colorectal cancer in a Chinese population. Cancer Genet Cytogenet *163*: 38-43, 2005.

20 Liu JC, Tsai CW, Hsu CM, Chang WS, Li CY, Liu SP, Shen WC and Bau DT: Contribution of double-strand break repair gene XRCC3 genotypes to nasopharyngeal carcinoma risk in Taiwan. Chin J Physiol *58*: 64-71, 2015.
21 Cramer SF and Patel A: The frequency of uterine leiomyomas. Am J Clin Pathol *94*: 435-438, 1990.
22 Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC and Hunter DJ: Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol *90*: 967-973, 1997.
23 Brenneman MA, Weiss AE, Nickoloff JA and Chen DJ: XRCC3 is required for efficient repair of chromosome breaks by homologous recombination. Mutat Res *459*: 89-97, 2000.
24 Bewick MA, Conlon MS and Lafrenie RM: Polymorphisms in *XRCC1, XRCC3*, and *CCND1* and survival after treatment for metastatic breast cancer. J Clin Oncol *24*: 5645-5651, 2006.
25 Zhan P, Wang Q, Qian Q and Yu LK: *XRCC3* Thr241Met gene polymorphisms and lung cancer risk: a meta-analysis. J Exp Clin Cancer Res *32*: 1, 2013.
26 Liu Y, Chen H, Chen L and Hu C: Prediction of genetic polymorphisms of DNA repair genes *XRCC1* and *XRCC3* in the survival of colorectal cancer receiving chemotherapy in the Chinese population. Hepatogastroenterology *59*: 977-980, 2012.
27 Matullo G, Guarrera S, Carturan S, Peluso M, Malaveille C, Davico L, Piazza A and Vineis P: DNA repair gene polymorphisms, bulky DNA adducts in white blood cells and bladder cancer in a case–control study. Int J Cancer *92*: 562-567, 2001.
28 Mesquita FS, Dyer SN, Heinrich DA, Bulun SE, Marsh EE and Nowak RA: Reactive oxygen species mediate mitogenic growth factor signaling pathways in human leiomyoma smooth muscle cells. Biol Reprod *82*: 341-351, 2010.

Received May 11, 2015
Revised June 16, 2015
Accepted June 18, 2015