

*Null Results in Brief*Genetic Variations in *XRCC2* and *XRCC3* Are Not Associated with Endometrial Cancer Risk

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Introduction

Endometrial cancer is a component of hereditary nonpolyposis colorectal carcinoma, primarily the consequence of mutations in genes involved in mismatch repair (MMR; *MSH2*, *MLH1*, *PMS1*, and *PMS2*). In addition to the repair of DNA replication errors, MMR genes have been implicated in homologous recombination repair (HRR) in yeast and in mammalian cells (1, 2). The involvement of the MMR genes in the DNA HRR pathway implies that defects in the HRR pathway may contribute to the development of hereditary nonpolyposis colorectal carcinoma tumorigenesis. Recently, Mohindra *et al.* (3) reported that human tumor cell lines (colon, uterine, ovarian, and endometrial) deficient in MMR also had defects in HRR induced by DNA double-strand breaks, and these tumor cell lines were hypersensitive to thymidine, which was not due to MMR deficiency or deoxynucleoside triphosphate pool imbalance. A *XRCC2* frameshift mutation identified in the MMR-deficient uterine tumor cell line SKUT-1 conferred hypersensitivity to thymidine or mitomycin C in a MMR-proficient line, suggesting that HRR defects may lead to the thymidine sensitivity of MMR-deficient tumor cell lines (3). These findings additionally support the hypothesis that HRR deficiency may confer susceptibility to hereditary nonpolyposis colorectal carcinoma tumorigenesis. *XRCC2* and *XRCC3*, as two *RAD51* paralogues, facilitate the formation of RAD51 foci formation in HRR. We assessed whether candidate polymorphisms in *XRCC2* and *XRCC3* genes in HRR pathway are associated with endometrial cancer risk in a nested case-control study within the Nurses' Health Study.

Materials and Methods

This nested case-control study (cases, $n = 220$; controls, $n = 666$) included both prevalent and incident pathologically confirmed endometrial cancer cases diagnosed up to June 1, 1998, from the blood subcohort of the Nurses' Health Study. Controls were matched to cases (3:1) on year of birth,

menopausal status at blood draw, and hormone replacement therapy status at blood draw. The characteristics of cases and controls have been described previously (4). Genotyping assays were performed by the 5'-nuclease assay (TaqMan) using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Genotyping was performed by laboratory personnel blinded to case-control status, and blinded quality control samples were inserted to validate genotyping procedures; concordance for the blinded samples was 100%. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression. We inferred haplotypes using the ARLEQUIN 2.0 software package (5).

Results

We observed no overall associations of the four genotypes with endometrial cancer risk (Tables 1 and 2). We observed that, compared with the *XRCC2* 31479 G/G genotype, the multivariate ORs for the G/A and A/A genotypes were 0.95 (95% CI, 0.58–1.54) and 2.05 (95% CI, 0.24–17.82), respectively. Three common haplotypes in *XRCC3* accounted for 99% of chromosomes in the present study population. As compared with women who were homozygous for *XRCC3* 4541A, women who were heterozygous for 4541G allele had a multivariate risk of 1.00 (95% CI, 0.69–1.43), and women who were homozygous for 4541G allele had a multivariate risk of 0.75 (95% CI, 0.30–1.87). As compared with non-carriers, the multivariate ORs for women with one *XRCC3* 17893G allele and two alleles were 0.95 (95% CI, 0.66–1.36) and 0.69 (95% CI, 0.39–1.21), respectively, with an OR of 0.89 (95% CI, 0.63–1.25) for carriage of at least one G allele. As compared with women with 18067 C/C genotype, women with C/T and T/T genotypes had multivariate OR of 1.03 (95% CI, 0.72–1.47) and 1.15 (95% CI, 0.67–1.98), respectively. No significant interactions were observed between these polymorphisms and risk factors such as body mass index, weight gain, and smoking (pack-years).

Discussion

We observed neither associations of *XRCC2* and *XRCC3* polymorphisms with endometrial cancer risk, nor significant differences in *XRCC3* haplotype distribution in cases and controls. The fairly large number of cases, the prospective collection of covariate information, and the high follow-up rates strengthen the validity of this study. Given the sample size and the allele frequencies among controls, we had 95% power for the *XRCC2* G31479A and 99% for the three *XRCC3* polymorphisms of detecting the OR of 2.0 for the variant allele carriers *versus* noncarriers. The functional effects of the two polymorphisms *XRCC2* G31479A (R188H) and *XRCC3* C18067T (T241M) on cell survival

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after mitomycin C-induced DNA interstrand cross-linking have been studied in *in vitro* experiments (6, 7). Neither of the two variants displayed a significant effect on damage sensitivity. Genetic variations in *XRCC2* and *XRCC3* genes have recently been evaluated in relation to breast cancer risk. This is the first article of polymorphisms in HRR and endometrial cancer risk. In summary, we did not provide evidence that women with the polymorphisms in *XRCC2* and *XRCC3* genes had an altered risk of endometrial cancer.

Table 1 Associations between *XRCC2* and *XRCC3* genotypes and endometrial cancer risk

	Cases	Controls	Matched odds ratio ^a	Multivariate odds ratio ^b
<i>XRCC2</i> G31479A (Arg ¹⁸⁸ His)				
G/G	183	557	1.00	1.00
G/A	32	99	1.03 (0.67–1.60)	0.95 (0.58–1.54)
A/A	2	3	2.02 (0.34–12.08)	2.05 (0.24–17.82)
<i>P</i> _{trend}			0.68	0.97
G/A + A/A	34	102	1.06 (0.69–1.63)	0.98 (0.61–1.57)
<i>XRCC3</i> A4541G (5'-UTR)				
A/A	140	438	1.00	1.00
A/G	73	200	1.13 (0.82–1.58)	1.00 (0.69–1.43)
G/G	7	25	0.85 (0.37–1.98)	0.75 (0.30–1.87)
<i>P</i> _{trend}			0.74	0.71
A/G + G/G	80	225	1.10 (0.80–1.51)	0.97 (0.68–1.37)
<i>XRCC3</i> A17893G (IVS5–14)				
A/A	100	274	1.00	1.00
A/G	97	296	0.90 (0.65–1.25)	0.95 (0.66–1.36)
G/G	23	89	0.71 (0.42–1.18)	0.69 (0.39–1.21)
<i>P</i> _{trend}			0.19	0.26
A/G + G/G	120	385	0.86 (0.63–1.16)	0.89 (0.63–1.25)
<i>XRCC3</i> C18067T (Thr ²⁴¹ Met)				
C/C	94	280	1.00	1.00
C/T	97	306	0.96 (0.70–1.33)	1.03 (0.72–1.47)
T/T	29	79	1.12 (0.69–1.82)	1.15 (0.67–1.98)
<i>P</i> _{trend}			0.80	0.64
C/T + T/T	126	385	0.99 (0.73–1.35)	1.05 (0.75–1.48)

Table 2 *XRCC3*-inferred haplotypes in cases and controls

A4541G	Haplotypes A17893G	C18067T	Allele frequency (%)		<i>P</i>
			Cases (<i>n</i> = 440)	Controls (<i>n</i> = 1314)	
0	0	0	0.13	0.10	0.24
0	0	1	0.35	0.35	0.94
0	1	0	0.33	0.36	0.32
1	0	0	0.20	0.19	0.76

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