Null Results in Brief

XRCC2 and XRCC3 Polymorphisms Are Not Associated with Risk of Colorectal Adenoma

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Introduction

The XRCC2 and XRCC3 proteins participate in homologous recombination and DNA double-strand break repair to maintain chromosomal stability. Coding-region variants in XRCC2 (Arg188His) and XRCC3 (Thr241Met) have been associated with cancers at several sites (1-3). The XRCC3 241Met homozygous variant has also been associated with increased DNA adduct levels, suggesting a role for this protein in repairing DNA adducts (2).

We assessed the association between XRCC2 R188H, XRCC3 T241M, and two intronic XRCC3 polymorphisms and risk of colorectal adenoma in two case-control studies nested in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) cohorts. We hypothesize that XRCC2 and XRCC3 polymorphisms modify risk of colorectal adenoma associated with smoking and alcohol intake; both established risk factors for colorectal adenoma (4). In addition, we examine the XRCC2 and XRCC3 polymorphisms and their potential interaction with plasma and dietary folate in relation to risk of colorectal adenoma.

Materials and Methods

Detailed information about the design of the NHS (cases, n = 556; controls, n = 557) and HPFS (cases, n = 376; controls, n = 725) nested case-control studies has been published previously (4). Genotyping of coding region XRCC2 R188H (rs3218536) and XRCC3 T241M (rs861539), and intronic XRCC3 A>G 4541 (rs1799794) and XRCC3 A>G 17893 (rs1799796) single nucleotide polymorphisms was carried out using the *TaqMan* allelic discrimination system (Applied Biosystems, Foster City, CA). Plasma folate was measured for some of the NHS nested case-control participants (cases, n = 345; controls, n = 333) (5). Odds ratios and 95% confidence intervals were calculated using conditional and unconditional logistic regression and were adjusted for established colorectal cancer risk factors (4). Interactions between genotype and exposure to smoking, dietary folate, plasma folate, and alcohol intake were tested by the likelihood ratio test.

Results

The distribution of the XRCC2 and XRCC3 genotypes conformed to Hardy-Weinberg expectations and these polymorphisms were not in linkage disequilibrium. We observed no association between XRCC2 and XRCC3 genotype and risk of colorectal adenoma in separate and combined analyses of women and men from the NHS and HPFS cohorts, respectively (Table 1). In addition, no difference in risk was found between early (tubular histology and <1 cm in diameter) and advanced (villous or tubulovillous histology and ≥1 cm in diameter) lesions in men and women (data not shown). No statistically significant interactions were observed between genotype and smoking, alcohol intake, dietary folate, or plasma folate (data available from www.channing.harvard.edu/nhs/pub.html#xrcc2004). Cigarette smoking increased risk of colorectal adenoma in our study for both men and women, regardless of XRCC2 or XRCC3 genotype. In addition, alcohol intake increased risk of colorectal adenoma in men for all genotypes. There was no evidence that the effect of XRCC2 or XRCC3 genotype varied by plasma or dietary folate in NHS.

Discussion

In the present study, we observed no association between XRCC2 and XRCC3 and risk of colorectal adenoma. We had >80% power to detect risk ratios of 1.6 (XRCC2 R188H), 1.7 (XRCC3 T241M), 1.7 (XRCC3 A>G 17893), and 2.4 (XRCC3 A>G 4541) for homozygous carriers of the variant alleles in both groups. XRCC2 and XRCC3 are required for the formation of the protein complex necessary for homologous recombination repair of DNA double-strand breaks, which, if not repaired, can lead to chromosome rearrangement and genomic instability.

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Table 1. Associations between XRCC genotypes and colorectal adenoma risk in the NHS and the HPFS

Genotype	HPFS			NHS			HPFS + NHS		
	Cases (%)	Controls (%)	OR (95% CI)*	Cases (%)	Controls (%)	OR (95% CI)*	Cases (%)	Controls (%)	OR (95% CI)†
N	376 (34.2)	725 (65.8)		556 (50.0)	557 (50.0)		932 (42.1)	1282 (57.9)	
XRCC2 R188H									
Arg/Arg	302 (85.3)	582 (84.6)	1.00 (ref.)	450 (86.9)	441 (84.5)	1.00 (ref.)	751 (86.2)	1021 (84.5)	1.00 (ref.)
Arg/His + His/His	52 (14.7)	106 (15.4)	0.96 (0.65-1.42)	68 (13.1)	81 (15.5)	0.81 (0.56-1.18)	120 (13.8)	187 (15.5)	0.88 (0.68-1.13)
XRCC3 A>G 4541									
A/A	229 (62.9)	467 (65.8)	1.00 (ref.)	365 (66.6)	342 (62.6)	1.00 (ref.)	593 (65.1)	808 (64.4)	1.00 (ref.)
A/G	119 (32.7)	223 (31.4)	1.06 (0.79-1.43)	167 (30.5)	180 (33.0)	0.87 (0.66-1.16)	286 (31.4)	402 (32.1)	0.98 (0.81-1.18)
G/G	16 (4.4)	20 (2.8)	1.73 (0.84-3.56)	16 (2.9)	24 (4.4)	0.65 (0.31-1.34)	32 (3.5)	44 (3.5)	0.97 (0.61-1.57)
XRCC3 A>G 17893									
A/A	180 (49.2)	329 (46.7)	1.00 (ref.)	256 (48.7)	250 (47.5)	1.00 (ref.)	436 (48.9)	578 (47.0)	1.00 (ref.)
A/G	155 (42.4)	303 (43.0)	0.89 (0.66-1.20)	212 (40.3)	222 (42.2)	0.87 (0.65-1.17)	366 (41.1)	524 (42.6)	0.93 (0.77-1.12)
G/G	31 (8.5)	73 (10.4)	0.87 (0.52-1.48)	58 (11.0)	54 (10.3)	1.00 (0.65-1.54)	89 (10.0)	127 (10.4)	0.90 (0.67-1.22)
XRCC3 T241M									
Thr/Thr	140 (39.6)	257 (37.4)	1.00 (ref.)	191 (39.6)	187 (39.4)	1.00 (ref.)	331 (39.6)	442 (38.1)	1.00 (ref.)
Thr/Met	164 (46.3)	322 (46.8)	0.90 (0.66-1.22)	222 (46.1)	218 (45.9)	1.11 (0.82-1.52)	385 (46.1)	540 (46.5)	0.95 (0.78-1.16)
Met/Met	50 (14.1)	109 (15.8)	0.87 (0.57-1.33)	69 (14.3)	70 (14.8)	1.03 (0.66-1.63)	119 (14.3)	179 (15.4)	0.89 (0.68-1.17)

Abbreviations: OR, odds ratio; CI, confidence interval.
*Conditional logistic regression adjusted for matching factors and family history of colorectal cancer, pack-years smoking, aspirin use, body mass index, postmenopausal hormone use (NHS), and intake of folic acid and alcohol.
†Unconditional logistic regression adjusted for age, sex, and family history of colorectal cancer.

DNA double-strand breaks can arise during DNA replication and are also induced by some carcinogens. High alcohol consumption has been related to higher risk of colorectal neoplasia through an antifolate effect, which may lead to uracil misincorporation into DNA and result in chromosomal breaks (4). DNA in human colon cells can also be damaged by adduct forming carcinogens derived from tobacco smoke (6). The XRCC2 and XRCC3 polymorphisms analyzed here did not modify the association between smoking, plasma folate, dietary folate, alcohol consumption, and adenoma risk. Our results suggest that cigarette smoking and high alcohol intake increase the risk of colorectal adenoma in men and women regardless of XRCC2 and XRCC3 genotypes.

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