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Polymorphisms of the NER pathway genes, *ERCC1* and *XPD* are associated with esophageal adenocarcinoma risk

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Abstract

Purpose—Functional variation in DNA repair capacity through single nucleotide polymorphisms (SNPs) of key repair genes is associated with a higher risk of developing various types of cancer. Studies have focused on the nucleotide excision repair (NER) and base excision repair (BER) pathways. We investigated whether variant alleles in seven SNPs within these pathways increased the risk of esophageal adenocarcinoma.

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Methods—DNA was extracted from prospectively collected blood specimens. The samples were genotyped for SNPs in NER genes (*XPD Lys751Gln*, *XPD Asp312Asn*, *ERCC1 8092C/A*, and *ERCC1 118C/T)*, and BER genes (*XRCC1 Arg399Gln*, *APE1 Asp148Glu*, and *hOGG1 Ser326Cys*). The presence of variant alleles was correlated with risk of esophageal adenocarcinoma both individually and jointly.

Results—Variant alleles in NER SNPs *XPD Lys751Gln* (AOR = 1.50, 95% CI 1.1–2.0), *ERCC1 8092 C/A* (AOR = 1.44, 95% CI 1.1–1.9), and *ERCC1 118C/T* (AOR = 1.42, 95% CI 1.0–1.9) were individually associated with esophageal adenocarcinoma risk. An increasing number of variant alleles in NER SNPs showed a significant trend with esophageal adenocarcinoma risk (p = 0.007).

Conclusions—The presence of variant alleles in NER genes increases risk of esophageal adenocarcinoma. There is evidence of an additive role for SNPs along a common DNA repair pathway. Future larger studies of esophageal adenocarcinoma etiology should evaluate entire biological pathways.

Keywords

DNA repair; Esophageal cancer; Adenocarcinoma; Polymorphism; Nucleotide excision pathway

Introduction

In North America, the most common histologic form of esophageal cancer is adenocarcinoma which develops from the columnar epithelium of the distal esophagus. The overall incidence of esophageal adenocarcinoma in North America rose over 350% from 1974 to 1994, a trend most pronounced in Caucasian males [1, 2]. This rise in incidence is among the most rapid of any malignant solid tumor [3]. Contrastingly, the incidence of squamous cell carcinoma of the esophagus has been declining; this trend is most significant among blacks in the United States, although incidence in this group remains higher than any others [4, 5]. Whereas squamous cell carcinoma has been definitively linked to smoking and alcohol abuse [5], the increasing incidence of esophageal adenocarcinoma may be explained partly by the impact of environmental risk factors for esophageal adenocarcinoma, including chronic gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), smoking, alcohol, obesity, and possibly dietary factors [6–11]. However, if 15 million North Americans suffer from GERD, only 0.1% of this at risk population develop esophageal adenocarcinoma annually [9] and unknown genetic or environmental factors likely exist. A better understanding of this genetic susceptibility is needed.

Efficient repair of this damage through DNA repair enzymes helps to maintain DNA stability [12]. Functional variation in DNA repair capacity (DRC) through genetic variation such as single nucleotide polymorphisms (SNPs) of key repair genes is associated with a higher risk of developing various types of cancer [13–22]. Two DNA repair pathways have been particularly well studied for genetic variation: NER and BER. Key proteins in the transcription-coupled nucleotide excision repair (NER) pathway (involved in correcting UV-induced lesions, chemical adducts, and crosslinks) include xeroderma pigmentosum group D (*XPD*), and excision repair cross-complementing group 1 (*ERCC1*) [23]. Base excision repair (BER) is involved in repair of single-strand breaks resulting from exposure to endogenously produced reactive oxygen species, ionizing radiation, and alkylating agents [24]. Key proteins in this pathway include X-ray repair cross-complementing group 1 (*XRCC1*), AP endonuclease 1 (*APE1*), and 8-oxoguanine DNA glycosylase (*hOGG1*). In addition to individual SNPs modulating risk of esophageal adenocarcinoma, the joint effect of multiple polymorphisms across a single pathway may also exert a combined effect in modifying risk [25].

There have been few reports of the association between DNA repair pathways and esophageal adenocarcinoma risk. A study by Casson et al. in a Canadian population (n = 56) showed a protective effect of the variant of both the *XPD Lys751Gln* and *XRCC1 Arg399Gln* polymorphisms [7]. Conversely, a study by Ye et al. on a Swedish population (n = 96) found a positive association between the *XPD Lys751Gln* variant and risk of esophageal adenocarcinoma [26]. In our own study on a North American population (n = 183), we confirmed the Ye et al. findings. We also showed a combined effect with *XPD Lys751Gln* and *XRCC1 Arg399Gln* (in those with three or four variant alleles) [27].

Spurred by our initial results, in the present study we examined a more comprehensive list of NER and BER SNPs. The SNPs were *XPD Lys751Gln*, *XPD Asp312Asn*, *ERCC1 8092C/A*, and *ERCC1 118C/T* in the NER pathway, and *XRCC1 Arg399Gln*, *APE1 Asp148Glu* and *hOGG1 Ser326Cys* in the BER pathway. Although a number of studies have examined a selection of these polymorphisms in relation to other cancers, including esophageal squamous cell carcinoma [28–32], an evaluation of these two pathways has not been reported comprehensively for esophageal adenocarcinoma.

Methods

Case and control populations

The study was approved by the Human Subjects Committees of Massachusetts General Hospital (MGH), Harvard School of Public Health, and Princess Margaret Hospital. A total of 183 cases and 336 controls were utilized from our previous study, representing patients recruited at MGH from 1999 to 2003. The details of their recruitment, secondary screening, and interview are published [27]. To this total, another 143 cases were added following continued recruitment from 2003 to 2005, also at MGH. These were also histologically confirmed, incident esophageal adenocarcinoma patients. All were reviewed in a similar fashion to that previously published to ensure that we excluded gastric cardia cases [27]. The total number of cases was 326.

Additional controls were selected using identical methods to our previous study [27]. These were healthy friends and healthy nonblood-related family members of hospital patients who never received a diagnosis of cancer. To maintain comparability with our previous paper and that of Casson et al. [7], we only selected controls without GERD symptoms. After a similar frequency-matching process (for race, gender, and age) and secondary screening, 118 controls remained. The total number of controls were thus 454 (118 + 336). From 1999 to 2005, only rudimentary lifetime GERD information was obtained (Yes/No). Starting in 2006, study definitions changed to include controls with detailed cumulative GERD information as part of a future validation cohort. Thus, we limited this present analysis to a dataset that had a uniform control definition (1999–2005).

Interview

A trained interviewer administered a questionnaire to cases, gathering clinical and demographical information. The questions included demographic variables (age, race, gender, adult height, adult BMI, healthy weight 6 months prior to start of disease symptoms), a detailed past medical history (in particular previous exposure to radiation), family history, and a comprehensive smoking and alcohol intake profile. Adult BMI was defined as healthy weight in their twenties. Smoking habits, and alcohol status were all defined at 1 year prior to diagnosis for cases, or 1 year prior to interview for controls. Smoking was classified into patients who were never-smokers, ex-smokers (quit >1 year previously), and current smokers (smoking currently or quit<1 year previously). Alcohol use

was defined as patients who never used alcohol versus those who had used alcohol at any time in the past.

Genotyping

DNA was extracted from peripheral blood samples using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN). Four NER (*XPD Lys751Gln*, *XPD Asp312Asn*, *ERCC1 8092C/A*, *ERCC1 118C/T*) and three BER (*XRCC1 Arg399Gln*, *APE1 Asp148Glu*, *hOGG1 Ser326Cys*) SNPs were detected using Taqman® assays. Details of primers and conditions are available upon request and described in Assays-On-Demand™ (http://www.assays-on-demand.com). Two individuals checked all genotyping results blindly and independently with >99% concordance for each SNP. A random 15% of samples and all equivocal results were regenotyped. Less than 0.5–0.6% of samples failed repeated genotyping.

Statistical analysis

All cases and controls were compared for age and sex to ensure frequency matching. All subjects with complete information on age, sex, smoking status (never, ex-, and current), and adult BMI, were included in analysis. After excluding patients with incomplete data, the total number of cases analyzed was 312, with 454 controls. Adult weight of individuals while in their 20s was chosen as the most representative measure of normal adult weight for calculating healthy adult BMI, as most patients with esophageal adenocarcinoma lost weight within the 1 year prior to diagnosis. Demographic and genotype information was compared across the various genotypes using chi-squared tests and Wilcoxon rank tests. Odds ratios (ORs) (and 95% CI) were derived using unconditional logistic regression models for the seven SNPs and their variants. Each analysis was also adjusted for confounding factors (age, sex, smoking status, adult BMI).

In the planned pathway analysis, we tabulated the number of NER SNPs with at-risk alleles, and similarly did the same for the BER SNPs. We evaluated dominant, additive, and recessive genetic models. A test of trend was used to look for risk association trends for each of these models. All statistical analyses were performed using SAS statistical package (SAS 9.1, SAS Institute, Cary, NC).

Results

A total of 312 cases and 454 controls were included in the analysis. Table 1 shows demographic information for both cases and controls. There was a significantly greater number of cases with high adult BMIs (BMI > 30, $p < 0.0001$). There were a greater proportion of never-smokers and ex-smokers in the controls than in the cases ($p = 0.0004$). The percentage of ever alcohol users in the cases was higher than in the controls ($p = 0.01$). Among the cases, there were 22 Stage 1 (7%), 124 Stage 2 (41%), 77 Stage 3 (25%), and 83 Stage 4 (27%) cancers. Staging was incomplete in six cases.

Table 2 shows the genotype frequency of each polymorphism among cases and controls. In some cases, the total number analyzed did not match the number of cases/controls due to failed genotyping. All SNPs were in Hardy–Weinberg Equilibrium. Crude ORs and ORs adjusted for age, sex, smoking status, and adult BMI (adjusted odds ratios, AORs) are shown in Table 2. After adjustment, three individual NER polymorphisms were associated with esophageal adenocarcinoma risk. Carrying at least one variant allele resulted in an increased risk of esophageal adenocarcinoma for the *XPD Lys751Gln* (AOR = 1.50 (95% CI 1.1–2.0)), *ERCC1 8092C/A* (AOR = 1.44 (95% CI 1.1–1.9)), and *ERCC1 118C/T* (AOR =

1.42 (95% CI 1.0–1.9)) polymorphisms. Results for *XPD Asp312Asn* and all three BER polymorphisms were not significantly associated with esophageal adenocarcinoma risk.

For combined effects of all four NER SNPs (Table 3), we evaluated first a dominant model (i.e., the presence of one dominant variant allele is enough to alter phenotype), and so stratified the population into five groups, based on number of SNPs with variant alleles using a reference group of individuals with no variant alleles. There was a significant trend for greater number of alleles in cases compared to controls ($p = 0.007$, trend test). AOR for the group with four SNPs with variant alleles was 1.79 (95% CI 1.1–2.8) when compared to the reference group. Similar analyses performed for the three BER SNPs (Table 3) found trends but were not statistically significant. Then, we carried out all our combined SNP analyses using an additive model (each allele contributes the same weight in altering risk) (Table 4). The AOR for the NER group with 7–8 at risk alleles was 2.39 (95% CI 1.1–5.2), and overall there was a strongly significant trend ($p = 0.007$, test of trend). There were no significant results in the combined BER analysis. None of the recessive models were statistically significant.

We also performed exploratory analyses. Analyses restricted to Caucasian patients resulted in virtually identical results (data not shown). We evaluated combinations of NER and BER polymorphic variants (including analyzing individuals with identical number of variant alleles but with different proportions of heterozygous versus homozygous variants) and found that the strongest associations were with the three NER SNPs that were independently associated with esophageal adenocarcinoma risk. The sample sizes were too small to evaluate females separately, but the main associations were similar between all individuals and for males alone. Associations in current, ex-, and never-smokers subgroups were in the same direction and of similar magnitude to the main effects of the entire population. Alcohol data were not uniformly collected on all controls. However, when we analyzed the subset of individuals with alcohol data (261 cases, 290 controls), direction and magnitude of associations were similar (data not shown). Analysis that excluded non-Caucasians was virtually identical to results reported above (data not presented).

Discussion

Our study found that the presence of variant alleles in three NER SNPs (*XPD Lys751Gln*, *ERCC1 8092C/A*, and *ERCC1 118C/T*) was individually associated with esophageal adenocarcinoma risk. Associations with the two *ERCC1* SNPs are novel findings and not previously described. Individual BER SNPs were not significantly associated with esophageal adenocarcinoma risk.

We also found that when combined, an increasing number of variant alleles in NER SNPs showed a significant trend with esophageal adenocarcinoma risk in both additive and dominant inheritance models. There is no commonly acceptable method for combining at-risk alleles in a pathway analysis. Some researchers have studied associations between DNA repair polymorphisms and lung cancer risk using combined analysis of at-risk alleles [24, 33–35], and this method has also been used in breast cancer [36]. We took a similar approach in the present study. Because the primary analysis was decided *a priori*, we modeled all four NER SNPs even though only three were statistically significant individually. We are the first to report a NER pathway analysis of multiple SNPs altering risk of esophageal adenocarcinoma.

A limitation of our study may be missing covariate data. There have been many studies of individual environmental risk factors for esophageal adenocarcinoma [6–11]. We did not collect information on dietary factors and occupational history and so we were unable to

study gene-environmental interactions in the etiology of esophageal adenocarcinoma. Gene-smoking and gene-alcohol interactions cannot be accurately measured due to sample size considerations. However, an improved understanding of the main effects of genes and environment separately will allow detailed gene-environmental interactions to be examined in future larger studies. Our population size, although expanded from our previous study, is still too small to avoid spurious results. Rather, our results are suggestive, and the need for further larger validation studies is clear. Our decision to select only non-GERD controls limits our ability to analyze GERD-polymorphism interactions but we are also less apt to include controls with occult Barrett's esophagus thus providing us with a comparison group with less potential confounding factors. Our analyses suggest both dominant and additive models of NER can explain our results, but are unable to allow us to determine which is the actual genetic inheritance model. Finally, we had some missing alcohol data (though alcohol is still only a putative risk factor for esophageal adenocarcinoma).

The association between adult BMI, smoking and alcohol habits and esophageal adenocarcinoma risk in our study confirms results in prior studies [6–11]. Our previous study on a North American Caucasian population showed an association between *XPD Lys751Gln* and increased esophageal adenocarcinoma risk [27]. In this study, we confirm the role of *XPD Lys751Gln* in increasing the risk of esophageal adenocarcinoma. We also extend our findings to include novel positive associations with two other NER SNPs (*ERCC1 8092C/A* and *ERCC1 118C/T*). These findings are in keeping with the known association between NER pathway polymorphisms and alterations in DNA repair capacity [15, 16, 20, 37], and in turn, the increased risk of various cancers associated with diminished repair capacity (e.g., squamous cell carcinoma of the esophagus [12, 29, 31], lung cancer [18, 20, 21], breast cancer [17, 19], prostate cancer [14], and malignant melanoma [15]). *ERCC1 8092C/A* has been found to have positive associations in breast cancer risk [38, 39], glioma risk [40], and a gene-smoking interaction in lung cancer risk [41]. The *ERCC1 118C/T* was mostly found to be associated with predicting outcome in treated patients with various types of cancer, including colon cancer [42, 43]. Other studies in lung cancer found *ERCC1 118C/T* to be nonsignificant in predicting outcome in treated lung cancer patients [44, 45]. The findings of three statistically significant SNPs in the NER pathway where joint results are of greater magnitude than each individual SNP suggests, but does not prove, a pathway effect, an intriguing concept that warrants additional testing.

There have been studies showing an increased risk of esophageal squamous cell carcinoma in the presence of certain BER SNPs [12, 29, 31, 32]. However, in our population of patients, we found no significant increase in risk for several individual BER SNPs or in a joint analysis under any model of inheritance.

Our study reports novel associations with the *ERCC1 8092C/A* and *ERCC1 118C/T* SNPs and confirms earlier results with *XPD Lys751Gln.* We also found a joint effect for SNPs along NER, a common DNA repair pathway. Our analyses also highlights the difficulties posed with studying rare diseases and small sample sizes as our previously reported finding of an association with *XRCC1* was not confirmed in the current larger dataset. We cannot conclude lack of association with all BER SNPs as we only evaluated a small handful of polymorphisms. Future larger validation studies into the genetic etiology of esophageal adenocarcinoma should consider comprehensively evaluating entire biological pathways.

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Table 1

Demographic characteristics of esophageal adenocarcinoma cases and controls

	Case (n = 312)[a]	Control (n = 454)	p-value
Gender			
Male	279 (89%)[b]	397 (87%)	
Female	33 (11%)	57 (13%)	0.40[c]
Median age (range), years	64 (21–91)	64 (19–96)	0.64[e]
Race			
Caucasian	302 (98%)	446 (98%)	
Other	7 (2%)	8 (2%)	0.62[c]
Median Adult BMI (range)	23 (15–39)	22 (14–36)	0.002[d]
≤25	216 (69%)	374 (82%)	
> 25–30	76 (24%)	68 (15%)	
> 30	20 (6%)	12 (3%)	< 0.0001[c]
Smoking status			
Non-smokers	62 (20%)	144 (32%)	
Ex-smokers	171 (55%)	233 (51%)	
Current smokers	77 (25%)	77 (17%)	0.0004[c]
Alcohol use[e]			
Never	28 (11%)	53 (18%)	
Ever	233 (89%)	237 (82%)	0.01[c]
Stage			
Stage 1	22 (7%)		
Stage 2a	69 (23%)	N/A	
Stage 2b	55 (18%)		
Stage 3	77 (25%)		
Stage 4a	27 (9%)		
Stage 4b	56 (18%)		

[a] Number of cases/controls may not add up to same total for each variable due to missing data

[b] Percentages may not add up to 100 due to rounding

[c] Pearson's Chi square test

[d] Wilcoxon Rank test

[e] Alcohol data was missing in 51 cases and 114 controls

Table 2

Frequencies, crude and adjusted odds ratios (OR) for polymorphisms in risk of esophageal adenocarcinoma cases and controls

	Case (%)	Control (%)	*p*-value[a]	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
XPD Lys751Gln					
Lys/Lys	104 (33)	193 (43)		1	1
Lys/Gln	159 (51)	208 (46)		1.40 (1.0–1.9)	1.45 (1.1–2.0)
Gln/Gln	49 (16)	52 (11)	0.02	1.75 (1.1–2.8)	1.68 (1.0–2.7)
Gln/−				1.49 (1.1–2.0)	1.50 (1.1–2.0)
XPD Asp312Asn					
Asp/Asp	117 (38)	199 (44)		1	1
Asp/Asn	150 (48)	206 (45)		1.24 (0.9–1.7)	1.27 (0.9–1.7)
Asn/Asn	43 (14)	49 (11)	0.18	1.49 (0.9–2.4)	1.46 (0.9–2.4)
Asn/−				1.29 (0.9–1.7)	1.30 (0.9–1.8)
ERCC1 8092C/A					
C/C	157 (50)	259 (57)		1	1
A/C	127 (41)	167 (37)		1.26 (0.9–1.7)	1.38 (1.0–1.9)
A/A	28 (9)	28 (6)	0.12	1.65 (0.9–2.9)	1.81 (1.0–3.2)
A/−				1.31 (1.0–1.8)	1.44 (1.1–1.9)
ERCC1 118C/T					
C/C	59 (19)	73 (16)		1	1
T/C	147 (47)	197 (43)		1.29 (0.9–1.8)	1.39 (1.0–1.9)
T/T	106 (34)	183 (40)	0.18	1.40 (0.9–2.1)	1.52 (1.0–2.3)
T/−				1.32 (1.0–1.8)	1.42 (1.0–1.9)
XRCC1 Arg399Gln					
Arg/Arg	136 (44)	216 (48)		1	1
Arg/Gln	133 (43)	182 (40)		1.16 (0.9–1.6)	1.15 (0.8–1.6)
Gln/Gln	42 (14)	54 (12)	0.52	1.24 (0.8–2.0)	1.32 (0.8–2.1)
Gln/−				1.18 (0.9–1.6)	1.19 (0.9–1.6)
APE1 Asp148Glu					
Asp/Asp	75 (24)	123 (27)		1	1
Asp/Glu	162 (52)	228 (50)		1.06 (0.8–1.5)	1.08 (0.8–1.5)

	Case (%)	Control (%)	*p*-value[a]	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Glu/Glu	74 (24)	103 (23)	0.65	0.97 (0.5–1.8)	0.87 (0.4–1.7)
Glu/−				1.05 (0.8–1.4)	1.05 (0.8–1.4)
hOGG1 Ser326Cys					
Ser/Ser	198 (64)	294 (65)		1	1
Ser/Cys	95 (31)	133 (29)		1.17 (0.8–1.7)	1.25 (0.9–1.8)
Cys/Cys	17 (5)	26 (6)	0.93	1.18 (0.8–1.8)	1.20 (0.8–1.8)
Cys/−				1.17 (0.8–1.6)	1.23 (0.9–1.7)

[a] Pearson's Chi square test

[b] Adjusted for age, sex, smoking status, and adult BMI

Table 3

A joint pathway analysis of NER & BER polymorphisms in esophageal adenocarcinoma risk using an additive genetic model

# at-risk alleles	Case (%)	Control (%)	Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
NER				
0	49 (16)	95 (21)	1	1
1–2	94 (30)	148 (33)	1.23 (0.8–1.9)	1.24 (0.8–1.9)
3–4	97 (31)	132 (29)	1.43 (0.9–2.2)	1.53 (1.0–2.4)
5–6	50 (16)	61 (13)	1.59 (1.0–2.6)	1.76 (1.0–3.0)
7–8	20 (6)	16 (4)	2.42 (1.2–5.1)	2.39 (1.1–5.2)
BER				
0	16 (5)	30 (6)	1	1
1	95 (31)	135 (28)	1.32 (0.7–2.6)	1.58 (0.8–3.2)
2	82 (27)	180 (37)	1.03 (0.5–2.0)	1.19 (0.6–2.4)
3	78 (25)	81 (17)	1.81 (0.9–3.6)	2.07 (1.0–4.2)
4–6	37 (12)	55 (11)	1.26 (0.6–2.6)	1.48 (0.7–3.2)

[a] Adjusted for age, sex, smoking status, and adult BMI

Table 4

A joint pathway analysis of either NER & BER polymorphisms in esophageal adenocarcinoma risk using a dominant genetic model

No. of SNPs with variant alleles	Case (%)	Control (%)	Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Combined NER				
0	49 (16)	95 (21)	1	1
1	27 (9)	60 (13)	0.87 (0.5–1.5)	0.91 (0.5–1.6)
2	79 (25)	106 (23)	1.45 (0.9–2.3)	1.44 (0.9–2.3)
3	45 (15)	61 (14)	1.43 (0.9–2.4)	1.50 (0.9–2.6)
4	110 (35)	130 (29)	1.64 (1.1–2.5)	1.79 (1.1–2.8)
Combined BER				
0	16 (5)	30 (7)	1	1
1	115 (37)	185 (41)	1.17 (0.6–2.2)	1.38 (0.7–2.7)
2	127 (41)	170 (38)	1.40 (0.7–2.7)	1.58 (0.8–3.1)
3	50 (16)	66 (15)	1.42 (0.7–2.9)	1.72 (0.8–3.6)

[a] Adjusted for age, sex, smoking status, and adult BMI