

# DNA Repair Polymorphisms and Risk of Colorectal Adenomatous or Hyperplastic Polyps

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## Abstract

Genetic variability in DNA repair genes may contribute to differences in DNA repair capacity and susceptibility to cancer, especially in the presence of exposures such as smoking. In a Minnesota-based case-control study of cases with only adenomatous polyps ( $n = 384$ ), only hyperplastic polyps ( $n = 191$ ), or both types of polyps ( $n = 119$ ) versus polyp-free controls ( $n = 601$ ), we investigated the role of polymorphisms in the DNA repair genes *O*<sup>6</sup>-methylguanine methyltransferase (*MGMT*; p.L84F and p.I143V), *XPB* (p.D312N and p.K751Q), and *XPG* (p.D1104H). *MGMT* polymorphisms were not associated with polyp risk. Overall, a homozygous variant *XPB*-combined genotype was associated with an increased risk of adenomatous polyps [odds ratio (OR), 1.57; 95% confidence interval (95% CI), 1.04-2.38] and an *XPG* genotype with a decreased risk of hyperplastic polyps (OR, 0.36; 95% CI, 0.13-0.98). However, age stratification showed that the *XPB* association was present only in subjects  $\geq 60$  years old

(OR, 3.77; 95% CI, 1.94-7.35), whereas the *XPG* association was observed largely in subjects  $< 60$  years old (OR, 0.20; 95% CI, 0.05-0.91). Smokers did not have a significantly increased risk of adenomatous polyps in the absence of synchronous hyperplastic polyps, except for subjects with a homozygous variant *XPB* genotype or a homozygous wild-type *XPG* genotype (OR, 3.93; 95% CI, 1.68-9.21 and OR, 1.59; 95% CI, 1.01-2.50, respectively). Smoking was associated with a statistically significant 2.5- to 6-fold increased risk of hyperplastic polyps for individuals with most of the DNA repair genotypes. However, no substantial increase was observed among individuals who were homozygous variant for *XPG* (*1104HH*; OR, 1.38; 95% CI, 0.25-7.65). Our data suggest that polymorphisms in DNA repair genes may be risk factors for colorectal neoplasia and that they may exacerbate the effects of exposures to carcinogens. (Cancer Epidemiol Biomarkers Prev 2005; 14(11):2501-8)

## Introduction

Carcinogens can interact with DNA to form bulky adducts that can lead to incorrect base pairing in the next replication cycle and eventually to cancer. Possible sources of carcinogens include dietary, lifestyle, and occupational exposures (1); endogenous alkylating agents; and *in situ* carcinogen formation mediated by the bacterial or chemical nitrosation of amines (2). However, an extensive system of DNA repair enzymes can reverse damage to DNA. Nucleotide excision repair (NER) is a major pathway that removes bulky DNA adducts and helix-distorting lesions. Included among the NER genes are the *Xeroderma pigmentosum* (*XP*) genes. *XPB* (also known as *ERCC2*) encodes an ATP-dependent helicase that is a component of the transcription factor complex TFIIH, which participates in both NER and basal transcription (3). *XPB* plays an important role in DNA repair by eliminating bulky DNA adducts produced by environmental toxins and xenobiotics through the NER pathway (3). *XPG* (also known as *ERCC5*) is a structure-specific endonuclease that cleaves damaged DNA approximately five nucleotides 3' to the site of the lesion and is also required nonenzymatically for subsequent 5' incision by the *XPB*/*ERCC1* heterodimer during the NER process (4-6).

*O*<sup>6</sup>-methylguanine methyltransferase (*MGMT*) is a ubiquitous repair protein that plays a vital role in minimizing the mutagenic effects of alkylating agents. Unlike the NER genes, which excise damaged DNA, *MGMT* is able to act as a single

protein that reverses alkylation damage (7). It catalyzes the transfer of a variety of alkyl groups from guanine to an active site cysteine. *MGMT* seems to lack the ability to dealkylate itself and participates in a single reaction and is thereby irreversibly inactivated (8, 9). Point mutations induced by alkylating agents originate principally from *O*<sup>6</sup>-alkylguanine and *O*<sup>4</sup>-alkylthymine (10). Alkylated adenine derivatives have been found in the urine of smokers (11) and procarcinogenic DNA adducts that arise from exposure to methylating agents have been detected in human colorectal DNA at levels comparable with those that cause adverse effects in model systems (2).

Genetic alterations in the DNA repair genes can impair their function and lead to an altered neoplasia risk. Defective NER is associated with rare, autosomal recessive inherited disorders (12). *XP* patients are extremely susceptible to sunlight and have a high incidence of skin cancers (12) as well as an increased risk of internal cancers (13). However, several amino acid changes in NER genes occur at polymorphic frequencies in healthy individuals (14-16). Two polymorphic amino acid changes were identified in *XPB*, *p.D312N*, and *p.K751Q*, which have allele frequencies between 0.35 and 0.44 (for review, see ref. 17). The functional effect of the *XPB* polymorphisms is unclear. Whereas some researchers have reported impaired repair of UV-induced DNA damage or of aromatic DNA adducts in the presence of *XPB* variant alleles (18-24), others found no association of *XPB* polymorphisms and the capacity to repair benzo(a)pyrene diol epoxide DNA adducts or chromatid aberrations (25-28). The cause of these apparently contradictory results may be the different assay systems used and the different types of DNA damage investigated.

The *XPG p.D1104H* polymorphism has an allele frequency of ~0.25 in Caucasians (14, 29) and 0.5 in Koreans (30). *XPG p.D1104H* homozygous variant individuals seemed to have a somewhat higher thymidine-dimer repair rate than homozygous wild-type individuals, whereas no difference was observed in the repair of thymidine-cytidine dimers (29).

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**Table 1. Genotyping assay conditions**

| Polymorphism        | Primers and probes              | [MgCl], mmol/L       | Cycling                            |
|---------------------|---------------------------------|----------------------|------------------------------------|
| <i>MGMT</i> p.L84F  |                                 |                      |                                    |
| FP                  | 5'-CCCGAGGCTATCGAAGAGTTC-3'     | 4                    | 95°C, 15 s; 60°C, 60 s             |
| RP                  | 5'-GTTACCGACCTTGCTGGAAAAC-3'    |                      |                                    |
| L84                 | 5'VIC-CCGGCTCTTCACCA-NFQ3'      |                      |                                    |
| F84                 | 5'6FAM-CCGGCTTTCACCA-NFQ3'      |                      |                                    |
| <i>MGMT</i> p.I143V |                                 |                      |                                    |
| FP                  | 5'-TTGACCCCAAAGACCTCGTT-3'      | 3                    | 95°C, 15 s; 60°C, 60 s             |
| RP                  | 5'-CGCTGCTGCAGACCACTCT-3'       |                      |                                    |
| I143                | 5'VIC-CCATCTCAATCCCGT-NFQ3'     |                      |                                    |
| V143                | 5'6FAM-CCATCTCTGTCCTCCCGT-NFQ3' |                      |                                    |
| <i>XPD</i> p.D312N  |                                 |                      |                                    |
| FP                  | 5'-AGCTCATCTCTCCGCAGGATCAA-3'   | Universal master mix | 94°C, 30 s; 64°C, 45 s; 72°C, 60 s |
| RP                  | 5'-CCTCTGCGAGGAGACGCTATCAG-3'   |                      |                                    |
| D312                | 5'VIC-CTTCGTCCGGGAGCA-NFQ3'     |                      |                                    |
| N312                | 5'6FAM-CTTCGTTCGGGAGCA-NFQ3'    |                      |                                    |
| <i>XPD</i> p.K751Q  |                                 |                      |                                    |
| FP                  | 5'-CCCTCTCCCTTTCTCTGTCT-3'      | 3                    | 95°C, 15 s; 60°C, 60 s             |
| RP                  | 5'-CACTCAGAGCTGCTGAGCAATC-3'    |                      |                                    |
| K751                | 5'VIC-ATCCTCTTCAGCGTCT-NFQ3'    |                      |                                    |
| Q751                | 5'6FAM-TCCTCTGCAGCGTC-NFQ3'     |                      |                                    |
| <i>XPG</i> p.D1104H |                                 |                      |                                    |
| FP                  | 5'-ATACATGCGGTGGATTTTGG-3'      | 4                    | 95°C, 15 s; 60°C, 60 s             |
| RP                  | 5'-CGCAGCTGTTCCTTTGTACA-3'      |                      |                                    |
| D1104               | 5'VIC-TCAAGTGAAGATGCTGAA-NFQ3'  |                      |                                    |
| H1104               | 5'6FAM-CAAGTGAATCATGCTGAA-NFQ3' |                      |                                    |

Three polymorphisms leading to amino acid changes have been identified in *MGMT* (p.L84F, p.I143V, and p.K178R; refs. 31-33). The p.I143V and the K178R polymorphisms seem to be in linkage disequilibrium (32, 34). The frequencies of *MGMT* variant alleles in Caucasians are around 0.12 (32-35). Because the p.I143V polymorphism is close to the alkyl acceptor Cys<sup>145</sup> of the *MGMT* active site and this amino acid is conserved among mammalian *MGMT*s, this mutation may affect the function of *MGMT*.

The association of *XPD* polymorphisms and risk of neoplasia has been explored for a number of cancers (for review, see ref. 17). The data on DNA repair gene polymorphisms are not consistent by specific gene or by cancer site—at least in part because of underpowered studies. However, given different exposures and doses for different cancers, heterogeneity is expected (23, 29, 30, 34-50).

Adenomatous and hyperplastic colorectal polyps have several similar risk factors. Male sex, smoking, and alcohol consumption have been associated with an increased risk; on the other hand, nonsteroidal anti-inflammatory drugs (NSAID) use, postmenopausal hormone therapy, and calcium intake tend to be associated with a reduced risk (51). However, age seems to be a risk factor for adenomatous but not hyperplastic polyps. Smoking, on the other hand, is associated with a higher risk of hyperplastic than of adenomatous polyps (51). In the present study, we investigated whether altered DNA repair capacity due to genetic polymorphisms influenced the risk of adenomatous or hyperplastic polyps in the presence of a number of environmental exposures.

## Materials and Methods

**Study Participants.** This case-control study was conducted between April 1991 and April 1994 as part of the Minnesota Cancer Prevention Research Unit, a National Cancer Institute-funded program project that combined several units within the University of Minnesota and Digestive Healthcare, a large multiclinic private gastroenterology practice. Participant recruitment for this case-control study has been described previously (52). Briefly, patients ages 30 to 74 years who were

scheduled for a colonoscopy were recruited before colonoscopy so as to blind patients and recruiters to the final diagnosis. Patients with colorectal adenomatous and/or hyperplastic polyps and polyp-free controls without individual history of ulcerative colitis, Crohn's disease, adenomatous polyps, and cancer (except nonmelanoma skin cancer), and who were free of known genetic syndromes associated with a predisposition to colonic neoplasia, were recruited into the study. The study was approved by the internal review boards of the University of Minnesota and each endoscopy site. Written informed consent was obtained.

Based on colonoscopic and pathologic findings, participants were assigned to groups of colorectal adenomatous polyps only ( $n = 395$ ), hyperplastic polyps only ( $n = 196$ ), or both types of polyps ( $n = 122$ ). Controls ( $n = 621$ ) were polyp-free at colonoscopy. Patients for whom the colonoscopy did not reach the cecum were ineligible; removed polyps were examined histologically using standard diagnostic criteria (53).

Information on use of aspirin and NSAID, lifestyle factors and diet, anthropometry, demographics, and medical information, including family history of cancer and polyps, was obtained by questionnaire. The participation rate for all colonoscoped patients was 68%.

**Table 2. *MGMT* and *XPD* haplotypes**

| <i>MGMT</i> | p.L84F<br>(c.250C>T)  | p.I143V<br>(c.427A>G)  | Frequency | SE    |
|-------------|-----------------------|------------------------|-----------|-------|
| L-I         | C                     | A                      | 0.774     | 0.003 |
| F-I         | T                     | A                      | 0.106     | 0.017 |
| L-V         | C                     | G                      | 0.102     | 0.017 |
| F-V         | T                     | G                      | 0.018     | 0.036 |
| <i>XPD</i>  | p.D312N<br>(c.934G>A) | p.K751Q<br>(c.2231A>C) | Frequency | SE    |
| D-K         | G                     | A                      | 0.551     | 0.010 |
| N-Q         | A                     | C                      | 0.311     | 0.009 |
| D-Q         | G                     | C                      | 0.081     | 0.005 |
| N-K         | A                     | A                      | 0.057     | 0.006 |

**Table 3. Associations between polymorphisms in *MGMT*, *XPD*, and *XPG* and risk of colorectal polyps**

| Gene                            | Genotypes                       | Controls, <i>n</i> | Adenomatous polyps only |                   | Hyperplastic polyps only |                   | Adenomatous and hyperplastic polyps |                   |
|---------------------------------|---------------------------------|--------------------|-------------------------|-------------------|--------------------------|-------------------|-------------------------------------|-------------------|
|                                 |                                 |                    | <i>n</i>                | OR* (95% CI)      | <i>n</i>                 | OR* (95% CI)      | <i>n</i>                            | OR* (95% CI)      |
| <i>MGMT</i>                     | L-I/L-I (wt/wt)                 | 358                | 250                     | 1.00 (Reference)  | 114                      | 1.00 (Reference)  | 71                                  | 1.00 (Reference)  |
|                                 | L-I/F-I                         | 101                | 54                      | 0.71 (0.47-1.07)  | 41                       | 1.35 (0.85-2.15)  | 21                                  | 0.96 (0.51-1.80)  |
|                                 | L-I/L-V                         | 102                | 63                      | 0.90 (0.60-1.33)  | 32                       | 1.00 (0.61-1.63)  | 14                                  | 0.81 (0.41-1.60)  |
|                                 | F-I/F-I                         | 10                 | 2                       | 0.27 (0.05-1.38)  | 2                        | 0.81 (0.16-4.06)  | 3                                   | 2.20 (0.49-9.86)  |
|                                 | F-I/L-V or L-I/F-V              | 33                 | 21                      | 0.90 (0.48-1.68)  | 3                        | 0.31 (0.09-1.07)  | 11                                  | 1.88 (0.80-4.39)  |
|                                 | F-I/F-V                         | 3                  | 0                       | —                 | 0                        | —                 | 0                                   | —                 |
|                                 | L-V/L-V                         | 6                  | 3                       | 0.83 (0.19-3.67)  | 2                        | 1.05 (0.19-5.89)  | 2                                   | 2.69 (0.45-16.21) |
|                                 | L-V/F-V                         | 2                  | 1                       | 0.45 (0.03-5.92)  | 0                        | —                 | 0                                   | —                 |
|                                 | F-V/F-V                         | 0                  | 1                       | —                 | 0                        | —                 | 0                                   | —                 |
|                                 | Homozygous wt                   | 358                | 250                     | 1.00 (Reference)  | 114                      | 1.00 (Reference)  | 71                                  | 1.00 (Reference)  |
|                                 | Heterozygous <sup>†</sup>       | 203                | 117                     | 0.80 (0.59-1.09)  | 73                       | 1.17 (0.81-1.70)  | 35                                  | 0.89 (0.54-1.47)  |
| Homozygous variant <sup>‡</sup> | 54                              | 28                 | 0.74 (0.44-1.26)        | 7                 | 0.45 (0.19-1.05)         | 16                | 1.79 (0.88-3.64)                    |                   |
| <i>XPD</i>                      | D-K/D-K (wt/wt)                 | 187                | 109                     | 1.00 (Reference)  | 58                       | 1.00 (Reference)  | 44                                  | 1.00 (Reference)  |
|                                 | D-K/N-K                         | 39                 | 23                      | 1.01 (0.57-1.78)  | 10                       | 0.83 (0.39-1.76)  | 10                                  | 1.09 (0.51-2.35)  |
|                                 | D-K/D-Q                         | 52                 | 38                      | 1.25 (0.78-2.03)  | 21                       | 1.30 (0.72-2.34)  | 9                                   | 0.74 (0.34-1.60)  |
|                                 | D-K/N-Q or N-K/D-Q              | 230                | 140                     | 1.04 (0.76-1.43)  | 67                       | 0.94 (0.63-1.40)  | 40                                  | 0.74 (0.46-1.18)  |
|                                 | N-K/N-K                         | 1                  | 2                       | 3.43 (0.31-38.28) | 1                        | 3.22 (0.20-52.36) | 0                                   | —                 |
|                                 | N-K/N-Q                         | 26                 | 13                      | 0.86 (0.42-1.74)  | 7                        | 0.87 (0.36-2.10)  | 3                                   | 0.49 (0.14-1.69)  |
|                                 | D-Q/D-Q                         | 1                  | 4                       | 6.86 (0.76-62.18) | 1                        | 3.22 (0.20-52.36) | 1                                   | 4.25 (0.26-69.28) |
|                                 | D-Q/N-Q                         | 28                 | 23                      | 1.41 (0.77-2.57)  | 9                        | 1.04 (0.46-2.32)  | 4                                   | 0.61 (0.20-1.82)  |
|                                 | N-Q/N-Q                         | 50                 | 43                      | 1.48 (0.92-2.36)  | 21                       | 1.35 (0.75-2.44)  | 10                                  | 0.85 (0.40-1.81)  |
|                                 | Homozygous wt                   | 187                | 109                     | 1.00 (Reference)  | 58                       | 1.00 (Reference)  | 44                                  | 1.00 (Reference)  |
|                                 | Heterozygous <sup>†</sup>       | 321                | 201                     | 1.10 (0.80-1.53)  | 98                       | 0.94 (0.62-1.40)  | 59                                  | 0.92 (0.56-1.50)  |
|                                 | Homozygous variant <sup>‡</sup> | 106                | 85                      | 1.57 (1.04-2.38)  | 39                       | 1.29 (0.77-2.15)  | 18                                  | 1.01 (0.51-2.01)  |
|                                 | <i>XPG</i>                      | D1104/D1104        | 353                     | 247               | 1.00 (Reference)         | 122               | 1.00 (Reference)                    | 71                |
| D1104/H1104                     |                                 | 226                | 125                     | 0.86 (0.64-1.16)  | 68                       | 0.93 (0.64-1.34)  | 44                                  | 1.12 (0.70-1.79)  |
| H1104/H1104                     |                                 | 37                 | 23                      | 0.94 (0.52-1.72)  | 6                        | 0.36 (0.13-0.98)  | 7                                   | 1.11 (0.44-2.82)  |

\*Multivariate adjusted for age, sex, BMI, kcal, alcohol intake, dietary fiber, regular NSAIDs use, hormone replacement therapy, and pack-years of smoking.

<sup>†</sup>Heterozygotes: L-I/F-I and L-I/L-V; homozygous variants: F-I/F-I, F-I/L-V or L-I/F-V, F-I/F-V, L-V/L-V, L-V/F-V, and F-V/F-V.

<sup>‡</sup>Heterozygotes: D-K/N-K, D-K/D-Q, D-K/N-Q, or N-K/D-Q; homozygous variant: N-K/N-K, N-K/N-Q, D-Q/D-Q, D-Q/N-Q, and N-Q/N-Q.

The activities associated with the present study were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

**Genotyping.** Genomic DNA was extracted from peripheral WBC using the Puregene kit (Gentra Systems, Minneapolis, MN). DNA was available for genotyping for 601 controls, 384 adenoma cases, 191 hyperplastic polyp cases, and 119 cases with both adenomatous and hyperplastic polyps. Missing genotyping data were due to lack of amplification or ambiguous results (<0.5%). Polymorphisms in *XPD* (p.D312N, p.K751Q), *MGMT* (p.L84F, p.I143V), and *XPG* (p.D1104H) were detected by allelic discrimination using a 5' nuclease assay on a 7900HT sequence detection system (Applied Biosystems, Foster City, CA). The 5' nuclease genotyping assays were validated by genotyping 100 individuals by both 5' nuclease assay and RFLP or sequencing. There were no discrepancies between assays. Primers and minor-groove-binding probes with nonfluorescent quenchers were obtained from Applied Biosystems. Genotyping assays were done in 20  $\mu$ L reactions containing 200 nmol/L of each amplification primer, 100 nmol/L of each probe, 1 $\times$  Taqman core reagents (Applied Biosystems) or universal master mix (Applied Biosystems), MgCl<sub>2</sub>, and 4 ng genomic DNA. The 40 amplification cycles were preceded by incubations at 50°C for 2 minutes and denaturation at 94°C for 10 minutes. Primer and probe sequences, MgCl<sub>2</sub> concentrations, and amplification variables for each polymorphism are listed in Table 1. Positive controls for all the genotypes as well as four negative controls were included in each plate. For quality control purposes, genotyping for 94 randomly selected samples was repeated. There were no discrepancies. All genotypes were in Hardy-Weinberg equilibrium.

**Statistical Analysis.** Haplotype frequencies were estimated using the expectation maximization algorithm as implemented

in the program Hplus (54). Based on the results (see Table 2), the *MGMT* and *XPD* combined genotypes were collapsed into homozygous wild type, heterozygous, and homozygous variant. For both genes, homozygous wild type consisted of individuals who were homozygous wild type at both polymorphisms. *MGMT* heterozygotes carried one mutation, either p.L84F or p.I143V, and homozygous variants had at least two mutations. Because the *XPD* variant allele carrying both mutations (p.D312N and p.K751Q; see Table 2) was the most frequent one, heterozygotes consisted of individuals who were heterozygous for one or both polymorphisms, and homozygous variants were homozygous variant for at least one of the polymorphisms.

Unconditional logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (95% CI) based on the profile likelihood function comparing cases (with adenomatous or hyperplastic polyps) with polyp-free controls in association with *MGMT*, *XPD*, and *XPG* genotypes. The multivariate analysis was controlled by previously identified risk factors (age, sex, smoking, alcohol use, body mass index, dietary fiber intake, total caloric intake, NSAIDs use, and, among women, ever use of postmenopausal hormone therapy). These variables either had been shown previously to be modulators of risk of colorectal polyps in this population (31) or altered some risk estimates by at least 10%. All data were analyzed with SAS 9.1 and statistical tests were two-sided (SAS Institute, Cary, NC).

## Results

**DNA Repair Polymorphisms.** Characteristics of the study population and risk factors for colorectal polyps have been described previously (51, 52, 55, 56). Briefly, adenoma cases

**Table 4. Associations between polymorphisms in *MGMT*, *XPD*, and *XPG* and risk of colorectal polyps stratified by age**

| Diagnostic group                  | Enzyme | Genotype                  | Age (y) |          |                  |       |          |                   | <i>P</i> <sub>interaction</sub><br>(age × genotype) |
|-----------------------------------|--------|---------------------------|---------|----------|------------------|-------|----------|-------------------|---|
|                                   |        |                           | <60     |          |                  | ≥60   |          |                   |   |
|                                   |        |                           | Cases   | Controls | OR*<br>(95% CI)  | Cases | Controls | OR*<br>(95% CI)   |   |
| Adenomatous polyps only           | MGMT   | Homozygous wt             | 133     | 249      | 1.00 (Reference) | 117   | 109      | 2.38 (1.65-3.44)  | 0.09  |
|                                   |        | Heterozygous <sup>†</sup> | 65      | 141      | 0.96 (0.65-1.43) | 52    | 62       | 1.43 (0.90-2.26)  |   |
|                                   |        | Homozygous variant        | 11      | 42       | 0.54 (0.26-1.11) | 17    | 12       | 2.78 (1.18-6.52)  |   |
|                                   | XPD    | Homozygous wt             | 57      | 128      | 1.00 (Reference) | 52    | 59       | 1.92 (1.14-3.25)  |   |
|                                   |        | Heterozygous <sup>‡</sup> | 101     | 222      | 1.05 (0.69-1.60) | 100   | 99       | 2.37 (1.50-3.75)  |   |
|                                   |        | Homozygous variant        | 51      | 82       | 1.39 (0.83-2.32) | 34    | 24       | 3.77 (1.94-7.35)  |   |
|                                   | XPG    | Homozygous wt             | 127     | 247      | 1.00 (Reference) | 120   | 106      | 2.34 (1.62-3.38)  |   |
|                                   |        | Heterozygous              | 66      | 156      | 0.94 (0.64-1.38) | 59    | 70       | 1.80 (1.16-2.79)  |   |
|                                   |        | Homozygous variant        | 16      | 30       | 0.99 (0.49-2.00) | 7     | 7        | 2.13 (0.69-6.56)  |   |
| Hyperplastic polyps only          | MGMT   | Homozygous wt             | 78      | 249      | 1.00 (Reference) | 36    | 109      | 1.29 (0.78-2.14)  | 0.64  |
|                                   |        | Heterozygous <sup>†</sup> | 50      | 141      | 1.32 (0.84-2.09) | 23    | 62       | 1.18 (0.66-2.11)  |   |
|                                   |        | Homozygous variant        | 6       | 42       | 0.51 (0.20-1.27) | 1     | 12       | 0.37 (0.04-3.11)  |   |
|                                   | XPD    | Homozygous wt             | 37      | 128      | 1.00 (Reference) | 21    | 59       | 1.16 (0.59-2.27)  |   |
|                                   |        | Heterozygous <sup>‡</sup> | 73      | 222      | 1.03 (0.63-1.68) | 25    | 99       | 0.86 (0.46-1.61)  |   |
|                                   |        | Homozygous variant        | 25      | 82       | 1.04 (0.56-1.96) | 14    | 24       | 2.54 (1.10-5.83)  |   |
|                                   | XPG    | Homozygous wt             | 80      | 247      | 1.00 (Reference) | 42    | 106      | 1.34 (0.83-2.16)  |   |
|                                   |        | Heterozygous              | 53      | 156      | 1.13 (0.73-1.75) | 15    | 70       | 0.76 (0.39-1.47)  |   |
|                                   |        | Homozygous variant        | 3       | 30       | 0.20 (0.05-0.91) | 3     | 7        | 1.09 (0.26-4.63)  |   |
| Adenomatous + hyperplastic polyps | MGMT   | Homozygous wt             | 34      | 249      | 1.00 (Reference) | 37    | 109      | 3.07 (1.73-5.44)  | 0.99  |
|                                   |        | Heterozygous <sup>†</sup> | 13      | 141      | 0.87 (0.42-1.80) | 22    | 62       | 2.43 (1.25-4.75)  |   |
|                                   |        | Homozygous variant        | 10      | 42       | 1.71 (0.72-4.05) | 6     | 12       | 4.55 (1.39-14.87) |   |
|                                   | XPD    | Homozygous wt             | 16      | 128      | 1.00 (Reference) | 28    | 59       | 3.46 (1.60-7.50)  |   |
|                                   |        | Heterozygous <sup>‡</sup> | 33      | 222      | 1.24 (0.61-2.49) | 26    | 99       | 2.51 (1.19-5.32)  |   |
|                                   |        | Homozygous variant        | 8       | 82       | 0.86 (0.33-2.22) | 10    | 24       | 4.84 (1.72-13.68) |   |
|                                   | XPG    | Homozygous wt             | 34      | 247      | 1.00 (Reference) | 37    | 106      | 2.85 (1.60-5.08)  |   |
|                                   |        | Heterozygous              | 22      | 156      | 1.35 (0.73-2.51) | 22    | 70       | 2.67 (1.34-5.30)  |   |
|                                   |        | Homozygous variant        | 1       | 30       | 0.25 (0.03-1.98) | 6     | 7        | 8.38 (2.33-30.13) |   |

\*Multivariate adjusted for sex, BMI, kcal, alcohol intake, dietary fiber, regular NSAIDs use, hormone replacement therapy and pack-years of smoking.

<sup>†</sup>Heterozygotes: L-I/F-I and L-I/L-V; homozygous variants: F-I/F-I, F-I/L-V or L-I/F-V, F-I/F-V, L-V/L-V, L-V/F-V, and F-V/F-V.

<sup>‡</sup>Heterozygotes: D-K/N-K, D-K/D-Q, D-K/N-Q, or N-K/D-Q; homozygous variant: N-K/N-K, N-K/N-Q, D-Q/D-Q, D-Q/N-Q, and N-Q/N-Q.

were older than individuals with hyperplastic polyps or polyp-free controls, and are more likely to be male.

We genotyped the study participants for two polymorphisms in *MGMT* (p.L84F and p.I143V) and *XPD* (p.D312N and p.K751Q) and the p.D1104H polymorphism in *XPG*. Allele frequencies of 0.12 and 0.12 for *MGMT* p.L84F and p.I143V, 0.37 and 0.39 for *XPD*p.D312N and p.K751Q, and 0.23 for *XPG*p.D1104H are comparable with those for Caucasians in other studies (14, 25, 29, 33, 35, 57-59). There was partial linkage disequilibrium between the two polymorphisms in *MGMT*, with the haplotype carrying both variants being the least frequent haplotype (see Table 2). Partial linkage disequilibrium was also present between the polymorphisms in *XPD*, where the haplotype with both variants was the most frequent non-wild-type haplotype.

**Main Associations of DNA Repair Polymorphisms.** Because of their different risk profiles, cases were stratified by diagnosis (i.e., whether they were diagnosed with only adenomatous polyps, only hyperplastic polyps, or both types of polyps). Table 3 shows the main associations of individual genotypes for each gene. No association was observed between *MGMT* genotypes and risk of any phenotype. There was a statistically significantly increased adenoma risk for individuals with two *XPD* variant alleles. *XPG* homozygous variant individuals had a significantly decreased risk of developing hyperplastic polyps.

Because the homozygous variant *MGMT* and *XPD* genotypes were relatively rare and—within a gene—showed similar associations with polyp risk, the genotypes were collapsed into homozygous wild-type, heterozygous, and homozygous variant in all subsequent analyses (see Materials and Methods). Using the collapsed genotypes, a

homozygous variant *XPD* genotype was associated with an increased risk for adenomatous polyps only (OR, 1.57; 95%CI, 1.04-2.38) but not for hyperplastic polyps only (OR, 1.29; 95% CI, 0.77-2.15) or for carrying both types of polyps (OR, 1.01; 95% CI, 0.51-2.01; see Table 3).

**Effect of DNA Repair Polymorphisms as a Factor of Age.** In this study population, we showed earlier that age was a strong risk factor for developing adenomatous polyps only or both types of polyps, but not hyperplastic polyps (51). Women were at lower risk of hyperplastic as well as adenomatous polyps. We, therefore, tested whether DNA repair polymorphisms affected these relationships.

In keeping with earlier analyses of this study population (51), we dichotomized the age groups at 60 years of age, which represents an approximate median split of the age distribution. None of the polymorphisms modified the increased risk of adenomatous polyps in the older subjects (Table 4). However, the inverse association between hyperplastic polyp risk and a homozygous variant *XPG* genotype was observed only in the <60-year-old participant group (OR, 0.20; 95% CI, 0.05-0.91, *P*<sub>interaction</sub> = 0.07). In contrast, a homozygous variant *XPD* combined genotype was associated with an increased risk of the hyperplastic polyps phenotype in the ≥60-year-old participants (OR, 2.54; 95% CI, 1.10-5.83). Among *XPG* homozygous variant individuals, the risk of developing both types of polyps was higher in the ≥60-year age group than in the <60-year age group (OR, 8.38; 95% CI, 2.33-30.13 versus OR, 0.25; 95% CI, 0.03-1.98; see Table 4). Among *XPG* homozygous wild-type individuals, those age ≥60 years had an ~3-fold higher risk of both types of polyps than study subjects who were <60 years old. However, these risk ratios were based on small numbers and, thus, the *P* value testing for gene-age

interaction was not statistically significant. There were no significant gene-age interactions for adenomatous polyps only.

**Interactions between Smoking, DNA Repair Polymorphisms, and Polyp Risk.** Smoking was a risk factor for the development of hyperplastic polyps only and of both types of polyps, increasing the risk 4- to 5-fold (51), but not for the development of adenomatous polyps only. The risk of adenomatous polyps in smokers was not modified by *MGMT* combined genotypes (Table 5). Heavy smokers who were homozygous variant for *XPD* or wild-type for *XPG* had a significantly increased risk of adenomatous polyps (OR, 3.93; 95% CI, 1.68-9.21 and OR, 1.59; 95% CI, 1.01-2.5 respectively) compared with nonsmokers who were homozygous wild-type.

DNA repair polymorphisms modified the increased risk of hyperplastic polyps due to smoking. Heavy smokers who were homozygous wild-type for *XPD* or homozygous variant for *MGMT* or *XPG* did not have a significantly increased risk of hyperplastic polyps, whereas heavy smokers carrying all other combined genotypes did (Table 5). Furthermore, there was a significant *MGMT* genotype-smoking interaction for hyperplastic polyp risk ( $P_{\text{interaction}} = 0.02$ ). However, heavy smokers were at increased risk of developing the phenotype showing both types of polyps, regardless of genotype, with the exception of those with *XPG* homozygous variant genotypes.

**Other Risk Factors.** Other exposures that can alter risk of polyps or can potentially affect DNA repair include alcohol and vitamin intake (folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub>), as well as meat consumption. None of these exposures, in conjunction with DNA repair polymorphisms, resulted in a significantly increased or decreased risk for any of the polyps (data not shown). Furthermore, there were no sex-specific differences in the associations of DNA repair polymorphisms and polyp risk. Because polymorphisms in individual DNA repair genes were risk factors for colorectal polyps, we examined whether an increasing number of variant DNA repair alleles had an additive effect. The observed main associations for *XPD* and adenomatous polyps and *XPG* and hyperplastic polyps persisted but were not modified by the presence of polymorphisms in another gene (data not shown).

## Discussion

DNA repair genes have been studied in the context of risk factors for developing cancer and as predictors of response of patients to chemotherapy and survival. Associations between *XPD*, *XPG*, and *MGMT* polymorphisms and colorectal neoplasia have not been explored extensively. The only study exploring colorectal cancer risk and NER polymorphisms found no associations (42). In our study population, *XPD* homozygous variant individuals were at increased risk of adenomatous polyps. The difference between the two studies may in part be due to the study size and the type of analysis done. The study of Mort et al. (42) was small (45 cases and 44-71 controls) and allele frequencies in cases and controls were used to calculate ORs. Unlike the analyses presented here (based on genotype frequencies), this approach reduces the sensitivity of the analyses.

An increased risk of colorectal adenomas among *XPD* homozygous variants is consistent with the decreased DNA repair capacity of variant enzymes, which has been observed in some (18-24), but not all (25, 27, 28), functional studies. Heavy smokers have a higher carcinogen exposure and are, therefore, more likely to have a higher level of DNA adducts

(60-62). The approximately 4-fold increased risk of an adenomatous polyp in homozygous variant *XPD* smokers compared with wild-type nonsmokers also suggests impaired DNA repair capacity in these individuals.

The polymorphisms in *XPD* do not seem to alter gene function dramatically. However, even a slight impairment in function may eventually be detrimental, especially in the presence of steady and high exposure to DNA-damaging agents. The inverse association between *XPG* genotype and hyperplastic polyp risk is observed only among younger individuals, suggesting perhaps that a longer exposure to DNA-damaging agents may overcome a possible genetic advantage. It remains to be established what degree, if any, of functional improvement is associated with the *XPG* variant allele.

In this study, *MGMT* genotype was not associated with altered polyp risk. There are no studies that clearly show a functional effect of the polymorphisms. However, the p.I143V polymorphism is close to the *MGMT* active site and the wild-type allele is generally conserved among mammalian *MGMT*s, which suggests that this mutation may affect function. It is possible that *in vivo*, *MGMT* genotype effects are less obvious because the function of this gene can also be impaired by methylation. Whereas a number of studies showed that *MGMT* can be hypermethylated in tumors, including colorectal tumors (63), methylated alleles can be found in normal tissue as well.<sup>1</sup>

Folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> intake did not modulate the associations of DNA repair genotypes and polyp risk. Folate metabolites provide methyl groups for a number of pathways, including purine and pyrimidine synthesis, and high folate intake has been associated with decreased colorectal neoplasia risk (64, 65). The lack of association of NER polymorphisms, folate, and vitamin B<sub>6</sub>/B<sub>12</sub> intake, and colorectal polyp risk suggests that nucleotide synthesis is not a limiting factor in the repair of DNA damage in this population.

In this study, the *XPD* homozygous variant individuals were at an increased risk of adenomatous polyps but *XPG* homozygous variant individuals were at a decreased risk of hyperplastic polyps. This observation suggests that the polymorphisms affect function in a different manner. These genotype associations persisted in the stratified analyses and further support the observation that adenomatous and hyperplastic polyps have different risk profiles as we have reported earlier (51).

The study population in this case-control study was not necessarily representative of the population, because only individuals who underwent colonoscopy were eligible. Individuals in the control group were more likely to have a family history as an indication for colonoscopy and probably underwent screening for this reason. On the other hand, the major advantage of this clinic-based approach was that the presence of polyps was clearly established and that the control group was free of any polyps. Studies that use a population-based unscreened control group include a substantial proportion of individuals with undetected polyps, which will attenuate any study findings. Furthermore, considering the large number of tests done to evaluate gene-environment interactions, results should be interpreted with caution.

Another aspect of carcinogen exposure, DNA damage, DNA repair, and colorectal neoplasia risk is the role of biotransformation enzymes, which show substantial genetic variability. The efficiency with which a carcinogen is

<sup>1</sup>J. Bigler et al., unpublished data.

**Table 5. Associations between polymorphisms in *MGMT*, *XPD*, and *XPG* and risk of colorectal polyps stratified by smoking**

| Diagnostic group                  | Enzyme | Genotype                  | Smoking (pack-years) |       |                   |
|-----------------------------------|--------|---------------------------|----------------------|-------|-------------------|
|                                   |        |                           | 0                    | Cases | Controls          |
| Adenomatous polyps only           | MGMT   | Homozygous wt             | 92                   | 175   | 1.00 (Reference)  |
|                                   |        | Heterozygous <sup>†</sup> | 41                   | 98    | 0.79 (0.49-1.28)  |
|                                   |        | Homozygous variant        | 13                   | 24    | 1.08 (0.50-2.33)  |
|                                   | XPD    | Homozygous wt             | 37                   | 94    | 1.00 (Reference)  |
|                                   |        | Heterozygous <sup>†</sup> | 77                   | 156   | 1.17 (0.71-1.93)  |
|                                   |        | Homozygous variant        | 32                   | 46    | 1.83 (0.96-3.47)  |
|                                   | XPG    | Homozygous wt             | 87                   | 166   | 1.00 (Reference)  |
|                                   |        | Heterozygous              | 49                   | 116   | 0.82 (0.52-1.29)  |
|                                   |        | Homozygous variant        | 10                   | 16    | 1.20 (0.49-2.92)  |
| Hyperplastic polyps only          | MGMT   | Homozygous wt             | 28                   | 175   | 1.00 (Reference)  |
|                                   |        | Heterozygous <sup>†</sup> | 15                   | 98    | 1.03 (0.52-2.05)  |
|                                   |        | Homozygous variant        | 1                    | 24    | 0.30 (0.04-2.31)  |
|                                   | XPD    | Homozygous wt             | 20                   | 94    | 1.00 (Reference)  |
|                                   |        | Heterozygous <sup>†</sup> | 16                   | 156   | 0.46 (0.22-0.95)  |
|                                   |        | Homozygous variant        | 9                    | 46    | 0.99 (0.41-2.37)  |
|                                   | XPG    | Homozygous wt             | 30                   | 166   | 1.00 (Reference)  |
|                                   |        | Heterozygous              | 14                   | 116   | 0.61 (0.30-1.23)  |
|                                   |        | Homozygous variant        | 0                    | 16    | —                 |
| Adenomatous + hyperplastic polyps | MGMT   | Homozygous wt             | 15                   | 175   | 1.00 (Reference)  |
|                                   |        | Heterozygous <sup>†</sup> | 8                    | 98    | 1.19 (0.45-3.09)  |
|                                   |        | Homozygous variant        | 5                    | 24    | 3.86 (1.17-12.71) |
|                                   | XPD    | Homozygous wt             | 8                    | 94    | 1.00 (Reference)  |
|                                   |        | Heterozygous <sup>†</sup> | 11                   | 156   | 1.02 (0.36-2.82)  |
|                                   |        | Homozygous variant        | 9                    | 46    | 2.62 (0.83-8.27)  |
|                                   | XPG    | Homozygous wt             | 14                   | 166   | 1.00 (Reference)  |
|                                   |        | Heterozygous              | 10                   | 116   | 1.06 (0.42-2.66)  |
|                                   |        | Homozygous variant        | 4                    | 16    | 3.34 (0.88-12.71) |

\*Multivariate adjusted for age, sex, BMI, kcal, alcohol intake, dietary fiber, regular NSAIDs use, and hormone replacement therapy.

<sup>†</sup>Heterozygotes: L-I/F-I and L-I/L-V; homozygous variants: F-I/F-I, F-I/L-V or L-I/F-V, F-I/FV, L-V/L-V, L-V/F-V, and F-V/F-V.

<sup>‡</sup>Heterozygotes: D-K/N-K, D-K/D-Q, D-K/N-Q, or N-K/D-Q; homozygous variant: N-K/N-K, N-K/N-Q, D-Q/D-Q, D-Q/N-Q, and N-Q/N-Q.

inactivated and eliminated from the body may influence the amount of DNA damage that occurs. The interplay between genetic variants in biotransformation enzymes and in DNA repair capacity will need to be explored in future studies.

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**Table 5. Associations between polymorphisms in *MGMT*, *XPD*, and *XPG* and risk of colorectal polyps stratified by smoking (Cont'd)**

|       |          |                  |       |          |                   | <i>P</i> <sub>interaction</sub> (smoking × genotype) |
|-------|----------|------------------|-------|----------|-------------------|--|
| 1-25  |          |                  | >25   |          |                   |  |
| Cases | Controls | OR* (95% CI)     | Cases | Controls | OR* (95% CI)      |  |
| 74    | 97       | 1.48 (0.97-2.27) | 77    | 78       | 1.50 (0.97-2.33)  |  |
| 43    | 65       | 1.24 (0.75-2.04) | 29    | 34       | 1.14 (0.62-2.08)  |  |
| 3     | 20       | 0.30 (0.08-1.07) | 12    | 9        | 1.84 (0.67-5.07)  | 0.20   |
| 35    | 46       | 1.70 (0.90-3.19) | 33    | 42       | 1.45 (0.76-2.75)  |  |
| 56    | 93       | 1.60 (0.94-2.74) | 62    | 67       | 1.70 (0.98-2.96)  |  |
| 29    | 43       | 1.60 (0.83-3.09) | 23    | 12       | 3.93 (1.68-9.21)  | 0.42   |
| 74    | 108      | 1.28 (0.83-1.95) | 78    | 72       | 1.59 (1.01-2.50)  |  |
| 40    | 61       | 1.36 (0.81-2.28) | 34    | 44       | 1.17 (0.67-2.05)  |  |
| 6     | 13       | 0.91 (0.32-2.58) | 6     | 5        | 1.46 (0.41-5.15)  | 0.79   |
| 50    | 97       | 3.04 (1.76-5.25) | 33    | 78       | 2.32 (1.28-4.21)  |  |
| 19    | 65       | 1.77 (0.89-3.51) | 37    | 34       | 6.23 (3.25-11.97) |  |
| 3     | 20       | 0.93 (0.25-3.39) | 3     | 9        | 2.27 (0.55-9.37)  | 0.02   |
| 16    | 46       | 1.56 (0.72-3.38) | 20    | 42       | 1.77 (0.83-3.76)  |  |
| 40    | 93       | 1.85 (0.99-3.48) | 39    | 67       | 2.44 (1.27-4.69)  |  |
| 16    | 43       | 1.59 (0.73-3.48) | 14    | 12       | 5.09 (1.96-13.25) | 0.09   |
| 40    | 108      | 1.84 (1.06-3.19) | 48    | 72       | 3.09 (1.76-5.43)  |  |
| 30    | 61       | 2.54 (1.38-4.59) | 23    | 44       | 2.64 (1.36-5.13)  |  |
| 3     | 13       | 1.03 (0.27-3.92) | 3     | 5        | 1.38 (0.25-7.65)  | 0.54   |
| 27    | 97       | 3.83 (1.79-8.16) | 28    | 78       | 3.22 (1.50-6.89)  |  |
| 8     | 65       | 1.72 (0.65-4.61) | 17    | 34       | 4.19 (1.74-10.13) |  |
| 3     | 20       | 2.26 (0.55-9.24) | 8     | 9        | 8.06 (2.30-28.18) | 0.16   |
| 11    | 46       | 2.65 (0.90-7.80) | 24    | 42       | 4.74 (1.77-12.72) |  |
| 24    | 93       | 3.79 (1.48-9.71) | 23    | 67       | 2.76 (1.06-7.34)  |  |
| 3     | 43       | 0.90 (0.20-3.97) | 6     | 12       | 5.52 (1.46-20.86) | 0.04   |
| 25    | 108      | 2.78 (1.29-5.96) | 31    | 72       | 3.32 (1.53-7.19)  |  |
| 13    | 61       | 3.11 (1.28-7.57) | 19    | 44       | 3.88 (1.68-8.96)  |  |
| 0     | 13       | —                | 3     | 5        | 3.73 (0.76-18.35) | 0.86   |

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