***Review***

# Polymorphisms in DNA Repair Genes and Associations with Cancer Risk[1]

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## Abstract

**Common polymorphisms in DNA repair genes may alter protein function and an individual's capacity to repair damaged DNA; deficits in repair capacity may lead to genetic instability and carcinogenesis. To establish our overall understanding of possible *in vivo* relationships between DNA repair polymorphisms and the development of cancer, we performed a literature review of epidemiological studies that assessed associations between such polymorphisms and risk of cancer. Thirty studies of polymorphisms in *OGG1*, *XRCC1*, *ERCC1*, *XPC*, *XPD*, *XPF*, *BRCA2*, and *XRCC3* were identified in the April 30, 2002 MEDLINE database (National Center for Biotechnology Information. PubMed Database: http://www.ncbi.nlm.nih.gov/entrez). These studies focused on adult glioma, bladder cancer, breast cancer, esophageal cancer, lung cancer, prostate cancer, skin cancer (melanoma and nonmelanoma), squamous cell carcinoma of the head and neck, and stomach cancer. We found that a small proportion of the published studies were large and population-based. Nonetheless, published data were consistent with associations between: (*a*) the *OGG1* S326C variant and increased risk of various types of cancer; (*b*) the *XRCC1* R194W variant and reduced risk of various types of cancer; and (*c*) the *BRCA2* N372H variant and increased risk of breast cancer. Suggestive results were seen for polymorphisms in other genes; however, small sample sizes may have contributed to false-positive or false-negative findings. We conclude that large, well-designed studies of common polymorphisms in DNA repair genes are needed. Such studies may benefit from analysis of multiple genes or polymorphisms and from the consideration of relevant exposures that may influence the likelihood of cancer in the presence of reduced DNA repair capacity.**

## Introduction

DNA in most cells is regularly damaged by endogenous and exogenous mutagens. Unrepaired damage can result in apoptosis or may lead to unregulated cell growth and cancer. If DNA damage is recognized by cell machinery, several responses may occur to prevent replication in the presence of genetic errors. At the cellular level, checkpoints can be activated to arrest the cell cycle, transcription can be up-regulated to compensate for the damage, or the cell can apoptose (1). Alternatively, the damage can be repaired at the DNA level enabling the cell to replicate as planned. Complex pathways involving numerous molecules have evolved to perform such repair. Because of the importance of maintaining genomic integrity in the general and specialized functions of cells as well as in the prevention of carcinogenesis, genes coding for DNA repair molecules have been proposed as candidate cancer-susceptibility genes (2–4).

At least four pathways of DNA repair operate on specific types of damaged DNA, and each pathway involves numerous molecules (illustrated in Fig. 1). BER[3] operates on small lesions such as oxidized or reduced bases, fragmented or nonbulky adducts, or those produced by methylating agents. The single damaged base is removed by base-specific DNA glycosylases; *e.g.,* the oxidized base 8-oxoguanine is excised by 8-oxoguanine DNA glycosylase. The abasic site is then restored by endonuclease action, removal of the sugar residue, DNA synthesis using the other strand as a template, and ligation (Ref. 5; Fig. 1). Molecules involved with the restoration phase of BER include apurinic/apyrimidinic endonuclease (APEX or APE), polynucleotide kinase, DNA polymerase-$\beta$, and XRCC1. Additional information on BER can be found in Lu *et al.* (6).

The NER pathway (Fig. 1) repairs bulky lesions such as pyrimidine dimers, other photo-products, larger chemical adducts, and cross-links (5). The NER pathway involves at least four steps: (*a*) damage recognition by a complex of bound proteins including XPC; (*b*) unwinding of the DNA by the TFIIH complex that includes XPD; (*c*) removal of the damaged single-stranded fragment (usually about 27–30 bp) by molecules including an ERCC1 and XPF complex; and (*d*) synthesis by DNA polymerases (Ref. 7; Fig. 1). For more details on the NER pathway of DNA repair, see a review by Friedberg (7).

Double-strand breaks can be produced by replication errors and by exogenous agents such as ionizing radiation; repair of double-strand breaks is intrinsically more difficult than other types of DNA damage because no undamaged template is available (8). At least two pathways of double-strand-break repair exist. In the homologous recombination pathway, DNA ends are resected, the newly exposed 3′ single-stranded tails

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[3] The abbreviations used are: BER, base-excision repair; APEX, apurinic/apyrimidinic endonuclease; XRCC1, X-ray repair complementing defective in Chinese hamster 1; NER, nucleotide-excision repair; XPC, xeroderma pigmentosum complementation group C; TFIIH, transcription factor IIH; XPD, xeroderma pigmentosum complementation group D; ERCC1, excision-repair cross-complementing 1; XPF, xeroderma pigmentosum complementation group F; *XRCC3*, X-ray repair complementing defective in Chinese hamster 3; LIG4, ligase IV; MMR, mismatch repair; SCCHN, squamous cell carcinoma of the head and neck; OR, odds ratio; CI, confidence interval; UTR, untranslated region; *NAT-2*, *N*-acetyltransferase type 2.

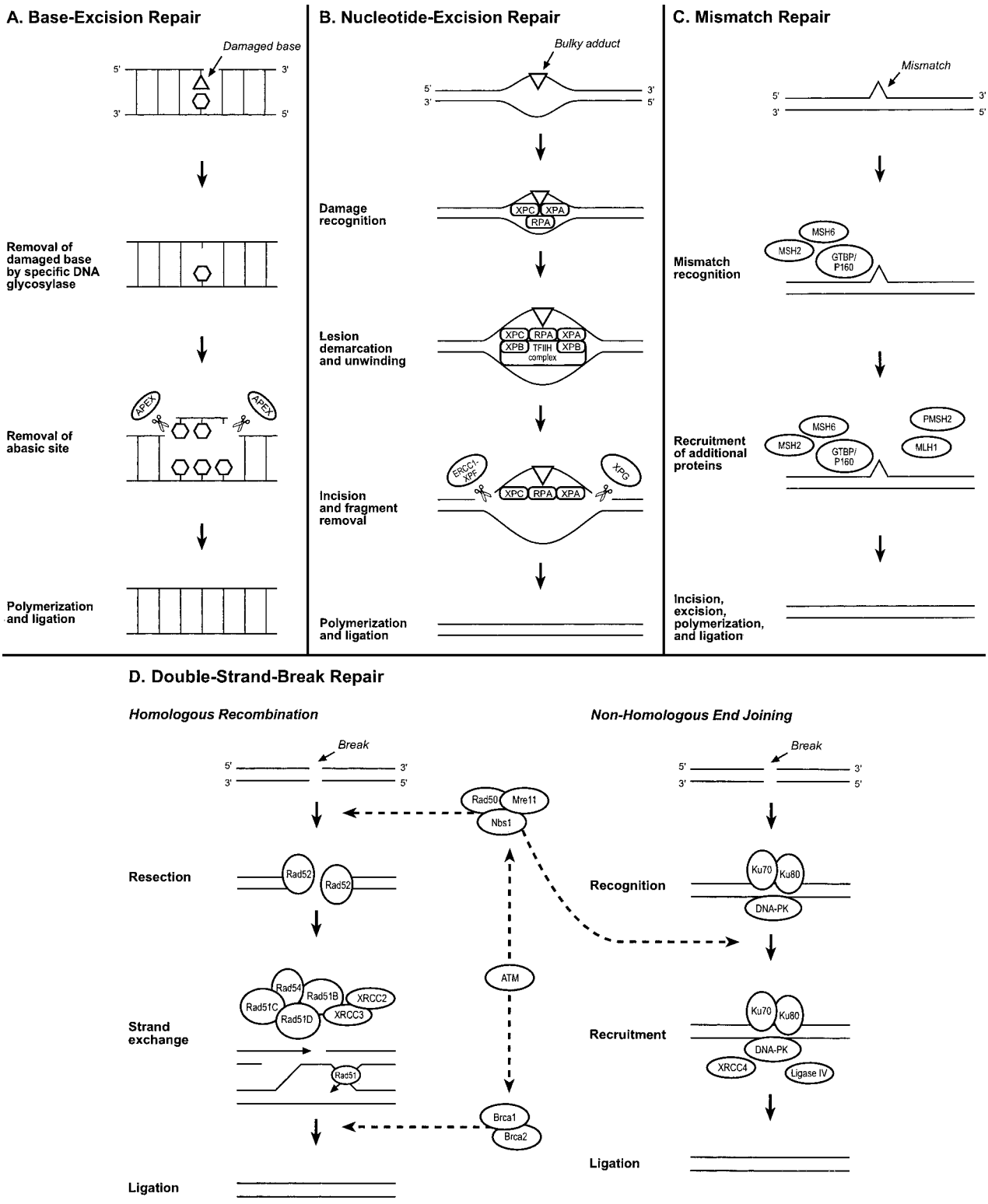


*Fig. 1.* *A*, BER acts on small lesions and involves release of the damaged base and removal of up to a few neighboring nucleotides. *B*, NER acts on larger lesions or adducts and involves lesion recognition, formation of the TFIIH complex, unwinding, incision and removal of 25–30 nucleotides. *C*, MMR is thought to involve *MLH1*, *MSH2*, *PMS2*, and *MSH6* in damage recognition, followed by excision, polymerization, and ligation. *D*, double-strand-break repair consists of two pathways. Homologous recombination in mitotic cells is thought to consist of strand exchange catalyzed by *Rad52* and *Rad51* and involving *XRCC2* and *XRCC3* and, indirectly, *BRCA1* and *BRCA2*. In nonhomologous end-joining, Ku-heterodimers recruit *DNA-PK*; *XRCC4* and *LIG4* are phosphorylated; and the DNA ends are joined. (Figure is adapted from Refs. 5, 7, 8, and 93, and from the NIH DNA Repair Interest Group Website: http://www.nih.gov/sigs/dna-rep.html. and the Molecular Biology Web Book: http://www.web-books.com/MoBio/Free/Ch7G.htm).

then invade the double helix of the homologous, undamaged partner molecule, strands are extended by DNA polymerase, then cross-overs yield two intact DNA molecules (Ref. 8; Fig. 1). This pathway is thought to involve more than 16 molecules including products of the breast cancer genes *BRCA1* and *BRCA2* and *XRCC3* (8). The nonhomologous end-joining repair pathway involves direct ligation of the two double-strand-break ends and also involves numerous molecules, including LIG4. Khanna and Jackson (8) have reviewed additional details of double-strand-break repair.

An additional category of DNA repair is MMR, which corrects replication errors (base-base or insertion-deletion mismatched) caused by DNA polymerase errors (9). Genes involved with MMR include *MLH1*, *MSH2*, *PMS2*, and *MSH6* (Fig. 1). In colorectal cancers, MMR deficiency leads to the instability of short sequence repeats (microsatellite instability) because these repeats, such as $(ca)_n$, are particularly prone to slippage during replication (10, 11). For more details on MMR, see Kolodner *et al.* (12) or Aquilina and Bignami (9).

At least three cancer syndromes exist where the disease-causing mutations occur in DNA repair genes. First, individuals with particular inherited defects in the NER pathway have xeroderma pigmentosum, which confers a greatly increased risk of basal-cell carcinoma with sunlight exposure (13). Second, mutations in MMR genes are known to segregate in families with hereditary nonpolyposis colorectal cancer (14). Finally, mutations in *BRCA1* and *BRCA2* have been shown to confer substantially increased risk of breast cancer (15). Additional rare diseases related to defects in DNA repair genes have been reviewed by Moses (16).

Novel, common nontruncating polymorphisms in DNA repair genes are being identified continuously[4] (17), and these polymorphisms may also play a role in carcinogenesis. A growing body of literature, including observations of inter-individual differences in measures of DNA damage, suggests that these polymorphisms may alter the functional properties of DNA repair enzymes (18–20). Here, we systematically review published epidemiological studies of DNA-repair polymorphisms and the risk of cancer at various sites. DNA repair genes and polymorphisms that have not yet been examined in epidemiological studies are not discussed further here, although other types of studies (*e.g., in vitro* studies) may implicate them in carcinogenesis. Our hope is that a consolidation and analysis of current epidemiological results, combined with advances in our understanding of molecular mechanisms, may help elucidate connections between cancer risk and DNA repair.

## Methods

Relevant studies were identified in the April 30, 2002 MEDLINE database[5] using the search phrases "DNA repair AND polymorph*" and using names of individual DNA repair genes (*e.g., XRCC1*). Abstracts from scientific meetings were not reviewed. Because DNA repair is universal to all tissues, cancers at any site were considered. Studies of *p53* and genes particularly involved with cell-cycle control (*e.g., CCND1*, *CHK2*) were not included. Eligible epidemiological studies were those that assessed DNA repair polymorphisms in relation to risk of carcinoma using peripheral blood or buccal tissue samples from at least 50 cases and 50 controls; six studies with sample size of less than 50 each of cases and controls were excluded (21–26). Epidemiological analyses were compiled and reviewed, and three Tables were created: (*a*) Table 1, a description of DNA-repair polymorphisms assessed in epidemiological studies of cancer; (*b*) Table 2, a description of each epidemiological study (sorted by cancer site); and (*c*) Table 3, results of epidemiological studies for each polymorphism. The following notation is used throughout to describe polymorphisms: uppercase letters represent amino acids with numbers representing the codon position, whereas lowercase letters represent nucleotides with numbers representing the nucleotide position.

## Results

By the end of April 2002, associations between DNA repair polymorphisms and risk of several types of cancers had been examined in a total of 30 published studies of adult glioma bladder cancer, breast cancer, esophageal cancer, lung cancer, prostate cancer, skin cancer (melanoma and nonmelanoma), SCCHN, skin cancer, and stomach cancer (27–56). Variants of the following genes were examined in epidemiological studies: BER genes *OGG1* and *XRCC1*; NER genes *ERCC1*, *XPC*, *XPD*, and *XPF*; and double-strand-break repair genes *BRCA2* and *XRCC3* (no studies examining polymorphisms in MMR genes were identified). Investigated polymorphisms are listed in Table 1. Although additional polymorphisms exist in these and other DNA repair genes,[6] we focus here only on polymorphisms that were investigated in epidemiological studies with the goal of summarizing relevant *in vivo* evidence for involvement with cancer risk.

Table 2 describes characteristics of the 30 epidemiological studies sorted by cancer site and year of publication. Most studies were conducted in the United States, Asia (Taiwan, China, Japan, Korea), or Europe (Italy, United Kingdom, Finland, Germany, Poland, Sweden); one Australian and one South American (Brazilian) study were published. Twenty-nine were case-control studies (27–37, 39–56), and one study of lung cancer used a nested case-control design (38). All but six of the studies included 450 or fewer cases: the median number of cases studied was 203 (range, 71–1667), considering a large multicenter study of breast cancer as five separate studies (30). Most of the studies were hospital-based, although population-based studies of adult glioma (27), breast cancer (30, 31), lung cancer (39, 46), skin cancer (55), and stomach cancer (55) were published. Results of each study are given in Table 3 (sorted by gene, polymorphism, and cancer site) and discussed below.

**BER Genes.** The product of the *OGG1* gene catalyzes the excision of a modified base, 8-oxoguanine, from DNA that has been damaged by exposure to reactive oxygen species; reduced ability to excise 8-oxoguanine may lead to an accumulation of oxidation-induced mutations. Association of a common S326C polymorphism in *OGG1* with cancer was assessed in six epidemiological studies; as shown in Table 3, fairly consistent increased risks were observed (34–36, 46, 47, 56). The largest study was a United States population-based multiethnic study of lung cancer that identified a significantly increased risk associated with the *CC* genotype (*CC versus SS*: adjusted OR, 2.1; 95% CI, 1.2–3.7; Ref. 46). A smaller, Japanese hospital-

[4] National Center for Biotechnology Information. DbSNP: http://www.ncbi.nlm.nih.gov/SNP/.

[5] National Center for Biotechnology Information. PubMed Database: http://www.ncbi.nlm.nih.gov/entrez.

[6] Mohrenweiser, H. W., Xi, T., Vazquez-Matas, J., and Jones, J. M. Identification of 127 Amino Acid Substitution Variants in Screening 37 DNA Repair Genes in Humans. Cancer Epidemiol. Biomark Prev. *11:* 1054–1064, 2002.

*Table 1* Polymorphisms in DNA repair genes examined in epidemiological studies of cancer risk

| Repair pathway and genes | Chromosomal location/MIM number[e] | Polymorphism (Ref.)[a] | Rare allele frequency in controls[b] |
|---|---|---|---|
| Base excision repair | | | |
| *OGG1* | 3p26.2/601982 | S326C 1245*c*→*g* (66) | 0.22–0.45 |
| | | 3402*g*→*a*[c] | 0.35 |
| | | 3574*g*→*a*[c] | 0.23 |
| | | 6170*g*→*c*[c] | 0.25 |
| | | 7143*a*→*g*[c] | 0.15 |
| | | 9110*a*→*g*[c] | 0.23 |
| | | 10629*c*→*g*[c] | 0.50 |
| | | 10660*a*→*t*[c] | 0.23 |
| | | 11657*a*→*g*[c] | 0.13 |
| | | 11826*a*→*t*[c] | 0.23 |
| *XRCC1* | 19q13.2/194360 | R194W 26304*c*→*t* (90) | 0.06–0.35 |
| | | R280H 27466*g*→*a* (91) | 0.00–0.10 |
| | | R399Q 28152*g*→*a* (90) | 0.14–0.39 |
| Nucleotide excision repair | | | |
| *ERCC1* | 19q13.2–13.3/126380 | 19007*g*→*a* (90) | 0.45 |
| | | 3′ UTR 8092*c*→*a* (90) | 0.27 |
| *XPC* | 3p25/278720 | 1457-1461 delins $(at)_n$ (91) | 0.33 |
| *XPD* | 19q13.2–13.3/278730 | 22541*c*→*a* (91) | 0.40–0.45 |
| | | D312N 23591*g*→*a* (90) | 0.33–0.44 |
| | | L751Q 35931*a*→*c* (90) | 0.06–0.42 |
| *XPF* | 16p13.3–13.13/278760 | 5′ UTR 2063*t*→*a* (90) | 0.31 |
| | | 30028*t*→*c* (91) | 0.33 |
| Double-strand-break repair | | | |
| *BRCA2* | 13q12.3/600185 | 5′ UTR −26*a*→*g*[d] | 0.28 |
| | | N289H 1093*a*→*c*[d] | 0.03 |
| | | N372H 1342*a*→*c*[d] | 0.22–0.29 |
| | | T1915M 5972*c*→*t*[d] | 0.05 |
| | | R2034C 6328*c*→*t*[d] | 0.01 |
| | | K3326X 10204*a*→*t* (92) | 0.01 |
| *XRCC3* | 14q32.3/600675 | 5′region 4541*a*→*g* (90) | 0.23 |
| | | T214M 18067*c*→*t* (90) | 0.23–0.38 |

[a] Published description of polymorphism. Amino acids are represented by uppercase letters and nucleotides are represented by lowercase letters.
[b] Frequency of rare allele among controls in epidemiological studies cited here.
[c] Celera Genomics. Celera Human Reference SNP Database: http://www.celera.com/genomics/academic/home.cfm?ppage=cds&cpage=snps.
[d] National Human Genome Research Institute. Breast cancer information core database: http://research.nhgri.nih.gov/bic/.
[e] Mendelian Inheritance in Man.

based lung-cancer study supported these results (35). A third lung-cancer study also suggested an increased risk when comparing the two homozygote groups (*CC versus SS* with OR, 2.2 and 95% CI, 0.4–11.8); however, a decreased risk was suggested when heterozygotes were included (*SC/CC versus SS*: OR, 0.7; 95% CI, 0.4–1.3; Ref. 36). This inconsistency highlights the difficulties associated with combining genotype groups. An increased risk associated with the *CC* genotype were also seen in analyses of prostate cancer (*CC versus SS* nonfamilial cases: adjusted OR, 3.3; 95% CI, 1.2–8.8; familial cases: adjusted OR, 2.1; 95% CI, 0.7–6.6; Ref. 47) and of esophageal cancer (*CC versus SS/SC*: OR, 1.9; 95% CI, 1.3–2.6; Ref. 34). A Brazilian stomach-cancer study, on the other hand, observed no association (56).

Nine additional *OGG1* polymorphisms were assessed in a study of prostate cancer, and significantly increased ORs comparing rare-allele homozygotes with common-allele homozygotes were seen with two of these polymorphisms: 7143*a*→*g* (*gg versus aa*: adjusted OR, 5.1; 95% CI, 1.1–23.3) and 11657*a*→*g* (*gg versus aa*: adjusted OR, 9.8; 95% CI, 1.3–17.6; Ref. 47). Comparison of familial prostate-cancer cases with screening controls also yielded increased ORs associated with the *gg* genotype of each of these polymorphisms (7143*a*→*g gg versus aa*: adjusted OR, 8.2; 95% CI, 1.5–45.5; and 11657*a*→*g gg versus aa*: adjusted OR, 13.9; 95% CI, 1.6–125.0); and family-based association tests suggested an increased risk of transmission of the *g* allele to affected sons (significant for 11657*a*→*g*, $P = 0.02$; not significant for 7143*a*→*g*, $P = 0.17$; Ref. 47). The consistency of results across polymorphisms and analytical techniques in this study suggests that *OGG1* may have a role in prostate carcinogenesis.

The XRCC1 protein plays an important role in BER; after excision of a damaged base, it stimulates endonuclease action and acts as a scaffold in the subsequent restoration of the site (57). Three polymorphisms in *XRCC1* (R194W, R399Q, and R280H) have been examined in epidemiological studies with fairly consistent results (28, 29, 31, 33, 37–39, 41, 44, 48, 51–53, 55). As shown in Table 3, most of the published R194W studies reported a reduced risk of cancer associated with the *W* allele (29, 31, 38, 41, 48, 55). The largest study was a breast-cancer study of African Americans ($n = 253$ cases) and Caucasians ($n = 386$ cases) that showed age-adjusted ORs of 0.7 (*RW/WW versus RR*; Caucasians: 95% CI, 0.3–1.5; African Americans: 95% CI, 0.4–1.3) and no evidence of interactions with smoking, menopausal status, or occupational exposure (31). Two lung-cancer studies and a bladder-cancer study also observed inverse associations with the *W* allele; adjusted ORs and 95% CIs (*RW/WW versus RR*) were 0.7 (0.4–1.2), 0.4 (0.2–0.9), and 0.6 (0.3–1.0), respectively (29, 38, 41). Possible interactions with smoking and drinking status were seen in

*Table 2* Epidemiological studies of DNA repair polymorphisms and risk of various cancers

| Cancer | Reference | Location | Population | Cases (n) | Controls (n) | Matching variables | Genes studied |
|---|---|---|---|---|---|---|---|
| Adult glioma | Chen *et al.* 2000 (27) | USA[a] | Population-based | 159 | 122 | Age, sex, ethnicity | *ERCC1* |
| Bladder cancer | Matullo *et al.* 2001b (28) | Italy | Hospital, males | 124 | 37 urology<br>47 non-urology | None | *XRCC1, XPD, XRCC3* |
| | Stern *et al.* 2001 (29) | USA | Hospital, Af Amer, Cauc | 235 | 213 | Age, sex, race | *XRCC1* |
| Breast cancer | Healey *et al.* 2000 (30), Series 1 | UK | Hospital cases, population controls | 234 | 266 | None | *BRCA2* |
| | Healey *et al.* 2000 (30), Series 2 | UK | Population-based | 1667 | 1201 | None | *BRCA2* |
| | Healey *et al.* 2000 (30), Series 3 | UK | Population-based | 450 | 228 | Age, family doctor | *BRCA2* |
| | Healey *et al.* 2000 (30), Series 4 | Germany | Population-based | 659 | 659 | Age, sex, residence | *BRCA2* |
| | Healey *et al.* 2000 (30), Series 5 | Finland | Population-based | 449 | 449 | Age, sex, residence | *BRCA2* |
| | Duell *et al.* 2001 (31) | USA | Population-based, Af Amer, Cauc | 253 Af-Amer<br>386 Cauc | 266 Af-Amer<br>381 Cauc | Age, race | *XRCC1* |
| | Spurdle *et al.* 2002 (32) | Australia | Population-based, <60 yr | 1397 | 775 | Age | *BRCA2* |
| Esophageal cancer, squamous cell | Lee *et al.* 2001 (33) | Taiwan | Hospital | 105 | 264 | Age, sex, race | *XRCC1* |
| | Xing *et al.* 2001 (34) | China | Hospital, cancer screening | 196 | 201 | Age, sex | *OGG1* |
| Lung cancer | Sugimura *et al.* 1999 (35) | Japan | Hospital, males | 241 | 197 | None | *OGG1* |
| | Wikman *et al.* 2000 (36) | German | Hospital, heavy-smoking population | 105 | 105 | Age, race, smoking | *OGG1* |
| | Butkiewicz *et al.* 2001 (37) | Poland | Hospital, males | 96 | 96 | Age, sex, smoking, occupational exposures | *XRCC1, XPD, XRCC3* |
| | Ratnasinghe *et al.* 2001 (38) | China | Nested case-control mining cohort | 108 | 216 | Age, sex | *XRCC1* |
| | Divine *et al.* 2001 (39) | USA | Population-based Cauc (Hisp and non-Hisp) | 172 | 143 | None | *XRCC1* |
| | David-Beabes *et al.* 2001 (40) | USA | Hospital, Cauc, Af Amer | 331 | 687 | Age, sex, ethnicity | *XPD, XRCC3* |
| | David-Beabes and London 2001 (41) | USA | Hospital cases, population controls Cauc, Af Amer | 154 Af-Amer<br>180 Cauc | 243 Af-Amer<br>461 Cauc | Age, sex, ethnicity | *XRCC1* |
| | Zhou *et al.* 2002 (42) | USA | Hospital, friend/non-blood relative controls, Cauc | 1092 | 1240 | None | *XPD* |
| | Park *et al.* 2002a (43) | Korea | Hospital, males | 250 | 163 | Age | *XPD* |
| | Park *et al.* 2002b (44) | Korea | Hospital, males | 192 (111 squamous cell) | 135 | Age | *XRCC1* |
| | Hou *et al.* 2002 (45) | Sweden | Hospital cases, population controls | 185 | 162 | Age, sex, hospital catchment area, smoking | *XPD* |
| | Le Marchand *et al.* 2002 (46) | USA | Population-based, Cauc, Japanese, Hawaiian | 298 | 405 | Age, sex, ethnicity | *OGG1* |
| Prostate cancer | Xu *et al.* 2002 (47) | USA | Hospital, Cauc | 245 nonfamilial cases<br>159 familial cases | 222 unrelated controls | None | *OGG1* |
| SCCHN | Sturgis *et al.* 1999 (48) | USA | Hospital, HMO controls | 203 | 424 | Age, sex, ethnicity | *XRCC1* |
| | Sturgis *et al.* 2000 (49) | USA | Hospital, HMO controls, Non-Hisp Cauc | 189 | 496 | Age, sex, ethnicity, smoking | *XPD* |
| | Shen *et al.* 2001 (50) | USA | Hospital, HMO controls | 287 | 311 | Age, sex, smoking | *XPC* |
| | Olshan *et al.* 2002 (51) | USA | Hospital | 98 | 161 | Age, sex | *XRCC1* |
| Skin cancer, melanoma | Winsey *et al.* 2000 (52) | UK | Hospital, Cauc | 125 with high risk of relapse or metastasis | 211 cadaver renal transplant donors | None | *XRCC1, XPD, XPF, ERCC1, XRCC3* |
| Skin cancer, non-melanoma | Nelson *et al.* 2002 (53) | USA | Population-based, Cauc | 499 basal cell carcinoma<br>246 squamous cell carcinoma | 431 | Age, sex | *XRCC1* |
| | Vogel *et al.* 2001 (54) | USA | Hospital, Cauc | 71 basal cell carcinoma | 118 w/mild skin disorder | Age, sex | *XPD* |
| Stomach cancer | Shen *et al.* 2000 (55) | China | Population-based | 188 | 166 | Age, sex | *XPC, XRCC1* |
| | Hanaoka *et al.* 2001 (56) | Brazil | Hospital, Japanese, and non-Japanese living in Brazil | 96 Japanese<br>236 non-Japanese Brazilian | 192 Japanese<br>236 non-Japanese Brazilian | Age, sex, ethnicity, trimester of hospital admission | *OGG1* |

[a] USA, United States; UK, United Kingdom; Af Amer, African American; Cauc, Caucasian; Hisp, Hispanic; w/, with; HMO, health maintenance organization.

*Table 3* Results of epidemiological studies of DNA repair polymorphisms and risk of various cancers

| Gene and polymorphism | Cancer | Reference | Cases (*n*), study type[a] | Allele frequency[b] | Case/Control genotype frequencies[c] | Comparison groups[d] | OR (95% CI)[e] | Adjustment variables | Interactions studied |
|---|---|---|---|---|---|---|---|---|---|
| Base excision repair | | | | | | | | | |
| *OGG1* | | | | | | | | | |
| S326C | Esophageal cancer | Xing *et al.* 2001 (34) | 101–250, H | 0.40 | Ca: 40,39,21%<br>Co: 34,53,13% | CC *vs.* SS/SC | **1.9 (1.3–2.6)** | Age, sex, smoking | No interaction w/smoking[f] |
| | Lung cancer | Sugimura *et al.* 1999 (35) | 101–250, H | 0.41 | Ca: 35,48,17%<br>Co: 32,54,14% | CC *vs.* SS/SC | 1.7 (0.9–3.2) squamous-cell only<br>**3.0 (1.3–6.8)** | Age, smoking | hi-smokers 2.3 (0.8–7.1); lo-smokers 1.2 (0.6–2.5) |
| | | Wikman *et al.* 2000 (36) | 101–250, H | 0.22 | Ca: 65,30,5%<br>Co: 57,41,2% | CC *vs.* SS | 2.2 (0.4–11.8) | None | No joint effect w/*GSTM1*, *GSTP1*, tumor type or smoking status |
| | | Le Marchand *et al.* 2002 (46) | 251–500, P | 0.45 Hawaiian<br>0.42 Japanese<br>0.22 Caucasian | Ca: 41,37,22%<br>Co: 44,43,13% | CC *vs.* SS | **2.1 (1.2–3.7)** | Age, sex, ethnicity, smoking, saturated fat and vegetable intakes | Largest increase in risk for Hawaiians **3.6 (1.0–11.9)**. Suggested interaction with total vegetable intake: protective association among *CC*s with > median intake ($P = 0.24$). No smoking interaction suggested, no difference by subtype. |
| | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.27 | Non-familial<br>Ca: 61,36,3%<br>Co: 55,36,9% | CC *vs.* SS | **3.3 (1.2–8.8)** | Age | None |
| | | | 101–250, H | 0.27 | Familial<br>Ca: 61,35,4%<br>Co: 55,36,9% | CC *vs.* SS | 2.1 (0.7–6.6) | Age | None |
| | Stomach cancer | Hanaoka *et al.* 2001 (56) | 51–100, H | JB 0.43 | JB<br>Ca: 34,50,16%<br>Co: 35,44,21% | CC/SC *vs.* SS | JB 1.0 (0.5–1.9) | Age, sex | No difference by subtype. No evidence of interactions with smoking or vegetable or beef intake. |
| | | | 101–250, H | NJB 0.22 | NJB<br>Ca: 64,32,4%<br>Co: 60,36,4% | CC/SC *vs.* SS | NJB 0.8 (0.6–1.3) | Age, sex | Possible interactions with smoking and beef intake, but not with vegetable intake. No difference by subtype. |
| 7143*a*→*g* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.15 | Non-familial<br>Ca: 68,26,5%<br>Co: 71,28,1% | *gg vs. aa* | **5.1 (1.1–23.3)** | Age | None |
| | | | 101–250, H | 0.15 | Familial<br>Ca: 64,32,5%<br>Co: 71,28,1% | *gg vs. aa* | **8.2 (1.5–45.5)** | Age | None |
| 11657*a*→*g* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.13 | Non-familial<br>Ca: 70,25,5%<br>Co: 74,25,1% | *gg vs. aa* | **9.8 (1.3–76.9)** | Age | None |
| | | | 101–250, H | 0.13 | Familial<br>Ca: 67,29,5%<br>Co: 74,25,1% | *gg vs. aa* | **13.9 (1.6–125.0)** | Age | None |

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|---|---|---|---|---|---|---|---|---|---|
| 3402*g*→*a* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.35 | Non-familial<br>Ca: 40,44,16%<br>Co: 43,45,12% | *aa vs. gg* | Not given; n.s. | Age | None |
| 3574*g*→*a* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.23 | Non-familial<br>Ca: 67,28,5%<br>Co: 60,34,6% | *aa vs. gg* | Not given; n.s. | Age | None |
| 6170*g*→*c* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.25 | Non-familial<br>Ca: 63,33,4%<br>Co: 58,34,7% | *cc vs. gg* | Not given; n.s. | Age | None |
| 9110*a*→*g* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.23 | Non-familial<br>Ca: 66,31,3%<br>Co: 60,34,7% | *gg vs. aa* | Not given; n.s. | Age | None |
| 10629*c*→*g* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.50 | Non-familial<br>Ca: 28,44,27%<br>Co: 30,41,30% | *gg vs. cc* | Not given; n.s. | Age | None |
| 10660*a*→*t* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.23 | Non-familial<br>Ca: 65,32,4%<br>Co: 61,32,7% | *tt vs. aa* | Not given; n.s. | Age | None |
| 11826*a*→*t* | Prostate | Xu *et al.* 2002 (47) | 101–250, H | 0.23 | Non-familial<br>Ca: 66,31,3%<br>Co: 60,33,7% | *tt vs. aa* | Not given; n.s. | Age | None |
| *XRCC1* | | | | | | | | | |
| R194W | Bladder cancer | Stern *et al.* 2001 (29) | 101–250, H | Af Amer 0.16<br>Cauc 0.09 | Af Amer:<br>Ca: 95,5,0%<br>Co: 72,23,0%<br>Cauc:<br>Ca: 88,12,0%<br>Co: 83,17,0% | RW/WW *vs.* RR | 0.6 (0.3–1.0) | Age, sex, race | Smoking interaction suggested (n.s.; increased protection among less-smokers) |
| | Breast cancer | Duell *et al.* 2001 (31) | 251–500, P | Af Amer 0.06 | Af Amer:<br>Ca: 91,8,1%<br>Co: 88,12,0% | RW/WW *vs.* RR | Af Amer: 0.7 (0.3–1.5) | Age | Smoking, menopausal status, occupational exposures—n.s. |
| | | | 251–500, P | Cauc 0.07 | Cauc:<br>Ca: 90,10,0%<br>Co: 86,14,1% | RW/WW *vs.* RR | Cauc: 0.7 (0.4–1.3) | Age | Smoking, menopausal status, occupational exposures—n.s. |
| | Esophageal cancer | Lee *et al.* 2001 (33) | 101–250, H | 0.30 | Ca: 51,45,4%<br>Co: 47,46,7% | RR *vs.* RW/WW | Not given; n.s. | Age, sex, smoking, alcohol, areca | Stratified by drinking, n.s. |
| | Lung cancer | Butkiewicz *et al.* 2001 (37) | 51–100, H | 0.05 | Not given | Not given | Not given; n.s. | Age and pack-year | None |
| | | Ratnasinghe *et al.* 2001 (38) | 101–250, N | 0.34 | Ca: 48,44,8%<br>Co: 40,50,10% | RW/WW *vs.* RR | 0.7 (0.4–1.2) | Radon, smoking | Smoking $P = 0.05$, alcohol $P = 0.04$ |
| | | David-Beabes and London 2001 (41) | 101–250, H | Af Amer 0.08 | Af Amer:<br>Ca: 92,6,1%<br>Co: 84,15,1% | RW/WW *vs.* RR | Af Am: **0.4 (0.2–0.9)** | Age, sex, smoking | Among smokers (>20 cigs/day) Af Amer: **0.2 (0.1–0.9)** |
| | | | 101–250, H | Cauc 0.06 | Cauc:<br>Ca: 87,12,0%<br>Co: 88,12,0% | RW/WW *vs.* RR | Cauc: 1.0 (0.5–1.8) | Age, sex, smoking | Among smokers (>20 cigs/day) Cauc: 0.5 (0.2–1.1) |

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| | SCCHN | Sturgis *et al.* 1999 (48) | 101–250, H | 0.07 | Ca: 89,11,1%<br>Co: 86,14,0% | RW/WW *vs.* RR | 0.7 (0.4–1.3)[g]<br>Oral/pharyngeal cancers: **0.4 (0.2–0.8)**[g] | Age, sex, race, smoking, alcohol | Combining risk genotypes further increase risk 0.3 (0.1–0.7)[g] |
| | | Olshan *et al.* 2002 (51) | 51–100, H | 0.08 | Ca: 84,16,0%<br>Co: 84,16,0% | RW/WW *vs.* RR | 1.3 (0.6–2.9) | Age, sex | Nonsignificant smoking interaction; further increase in risk if ever-smoker |
| | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.09 | Ca: 86,14,0%<br>Co: 83,17,0% | Not given | Not given; n.s. | None | None |
| | Stomach cancer | Shen *et al.* 2000 (55) | 101–250, P | 0.35 | Ca: 51,41,8%<br>Co: 42,46,11% | RW/WW *vs.* RR | 0.7 (0.4–1.1)[g]<br>gastric cardia: **0.5 (0.3–0.9)**[g] | Age, sex, family history, smoking, alcohol, *H. pylori* | Possible strengthened effect with combined R399Q genotype |
| R280H | Bladder cancer | Stern *et al.* 2001 (29) | 101–250, H | Af Amer 0, Cauc 0.05 | Af Amer:<br>Ca: 89,11,0%<br>Co: 100,0,0%<br>Cauc:<br>Ca: 92,8,0%<br>Co: 72,7,1% | RH/HH *vs.* RR | 1.1 (0.5–2.2) | Age, sex, race | Smoking, no interaction |
| | Esophageal cancer | Lee *et al.* 2001 (33) | 101–250, H | 0.10 | Ca: 74,26,0%<br>Co: 80,19,1% | RR *vs.* RH/HH | Not given; n.s. | Age, sex, smoking, alcohol, areca | Stratified by drinking, n.s. |
| | Lung cancer | Butkiewicz *et al.* 2001 (37) | 51–100, H | 0.05 | Not given | Not given | Not given; n.s. | Age and pack-year | None |
| | | Ratnasinghe *et al.* 2001 (38) | 101–250, N | 0.07 | Ca: 78,19,3%<br>Co: 85,15,0% | RH/HH *vs.* RR | 1.8 (1.0–3.4) | Radon, smoking | Alcohol $P = 0.02$ |
| R399Q | Bladder cancer | Stern *et al.* 2001 (29) | 101–250, H | Af Amer 0.15<br>Cauc 0.36 | Af Amer:<br>Ca: 47,53,0%<br>Co: 69,31,0%<br>Cauc:<br>Ca: 40,50,10%<br>Co: 40,37,13% | RQ/QQ *vs.* RR | 0.7 (0.4–1.3) | Age, sex, race | Smoking interaction suggested (n.s.; increased protection among less-smokers) |
| | | Matullo *et al.* 2001b (28) | 101–250, H | 0.39 | Ca: 43,47,10%<br>Urological co: 33,51,16%<br>Non-urological co: 40,46,14% | RQ/QQ *vs.* RR | Urological controls: 0.6 (0.2–1.7)<br>Non-urological controls: 0.8 (0.3–2.3) | None | OR further decreased for ex-smokers, 0.3 (0.1–1.0), still n.s. |
| | Breast cancer | Duell *et al.* 2001 (31) | 251–500, P | Af Amer 0.14 | Af Amer:<br>Ca: 65,32,3%<br>Co: 74,24,2% | RQ/QQ *vs.* RR | Af Amer:<br>**1.7 (1.1–2.4)** | Age | Possible interactions with smoking and occupation exposure to ionizing radiation |
| | | | 251–500, P | Cauc 0.36 | Cauc:<br>Ca: 42,45,13%<br>Co: 43,41,16% | RQ/QQ *vs.* RR | Cauc: 1.0 (0.8–1.4) | Age | Possible interactions with smoking and occupation exposure to ionizing radiation |
| | Esophageal cancer | Lee *et al.* 2001 (33) | 101–250, H | 0.30 | Ca: 61,31,8%<br>Co: 50,41,9% | RR *vs.* RQ/QQ | Not given; n.s. | Age-, sex, smoking, alcohol, areca-adjusted | Suggested interactions of drinking, smoking, and areca chewing. Drinkers, **0.4 (0.1–0.9)**[g]; non-drinkers, 1.3 (0.5–3.4)[g] |
| | Lung cancer | Butkiewicz *et al.* 2001 (37) | 51–100, H | 0.35 | Not given | Not given | Not given; n.s. | Age and pack-year | None |
| | | Ratnasinghe *et al.* 2001 (38) | 101–250, N | 0.24 | Ca: 55,37,7%<br>Co: 54,37,5% | RQ/QQ *vs.* RR | 1.0 (0.6–1.6) | Radon, smoking | Alcohol, smoking, radon, arsenic, n.s. |

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| | | Divine *et al.* 2001 (39) | 101–250, P | 0.32 | Ca: 48,36,17%<br>Co: 46,45,10% | QQ *vs.* RQ/RR | **2.5 (1.1–5.8)** | Age, smoking, race | Restricted to non-Hispanic, risk increases to age, smoking, race adjusted, 3.3 (1.2–10.7) |
| | | David-Beabes and London 2001 (41) | 101–250, H | Af Amer 0.18 | Af Amer:<br>Ca: 68,30,2%<br>Co: 67,29,4% | QQ *vs.* RR | Af Amer: 0.6 (0.2–2.3) | Age, sex, smoking | Among smokers (>20 cigs/day), Af Amer, 0.3 (0.1–0.9) |
| | | | 101–250, H | Cauc 0.36 | Cauc:<br>Ca: 48,42,9%<br>Co: 40,47,13% | QQ *vs.* RR | Cauc: 0.6 (0.3–1.3) | Age, sex, smoking | Among smokers (>20 cigs/day) Cauc, 0.4 (0.2–1.0) |
| | | Park *et al.* 2002b (44) | 101–250, H | 0.22 | Ca: 52,39,9%<br>Co: 60,36,4% | QQ *vs.* RR | 2.1 (0.8–5.4) | Age, pack-years | |
| | | | 101–250, H | | Squamous cell<br>Ca: 46,41,13%<br>Co: 60,36,4% | QQ *vs.* RR | **3.3 (1.2–9.2)** | Age, pack-years | Smoking interaction suggested: ≤40 pack-years **5.8 (1.5–22.7)**; <40 pack-years 1.4 (0.3–6.8) |
| | Skin cancer, nonmelanoma | Nelson *et al.* 2002 (53) | 251–500, P | 0.38 | Basal cell carcinoma<br>Ca: 43,46,12%<br>Co: 41,43,17% | QQ *vs.* RR | 0.7 (0.4–1.0) | Age, sex, tendency to burn | Suggested interaction with number of lifetime sunburns suggested protection if <3 lifetime sunburns; suggested increased risk if 3+ |
| | | | 101–250, P | 0.38 | Squamous cell carcinoma<br>Ca: 44,46,10%<br>Co: 41,43,17% | QQ *vs.* RR | **0.6 (0.3–0.9)** | Age, sex, tendency to burn | Significant interaction with number of lifetime sunburns ($P < 0.02$): suggested protection if <3 lifetime sunburns; suggested increased risk if 3+. Among *QQ*, OR (3+ burns *vs.* <3) **6.8 (2.4–19.2)**; among RR this OR 1.5 (0.9–2.5) |
| | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.36 | Ca: 47,15,12%<br>Co: 55,36,9% | Not given | Not given; n.s. | None | None |
| | SCCHN | Sturgis *et al.* 1999 (48) | 101–250, H | 0.34 | Ca: 46,38,16%<br>Co: 43,47,11% | QQ *vs.* RR/RQ | 1.6 (1.0–2.6) | Age, sex, race, smoking, alcohol | Current smokers **3.2 (1.3–7.9)** and drinkers **2.2 (1.1–4.6)**. Combining risk genotypes of R194H increase risk **3.2 (1.3–7.8)** for oral/pharangeal cancers |
| | | Olshan *et al.* 2002 (51) | 51–100, H | 0.36 | Ca: 46,51,3%<br>Co: 39,51,11% | QR *vs.* RR<br>QQ *vs.* RR | 0.8 (0.4–1.1)<br>**0.1 (0.04–0.6)** | Age, sex | Suggestion of nonsignificant smoking interaction (increased risk with *Q* allele and smoking) |
| | Stomach cancer | Shen *et al.* 2000 (55) | 101–250, P | 0.26 | Ca: 49,44,7%<br>Co: 57,36,8% | RQ/QQ *vs.* RR | 1.5 (1.0–2.4) | Age, sex, family history, smoking, alcohol, *H. pylori* | Possible combined genotype effect w/R194H |
| Nucleotide excision repair | | | | | | | | | |
| *ERCC1* | | | | | | | | | |
| 19007*g*→*a* | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.45 | Ca: 35,50,15%<br>Co: 27,55,18% | Not given | n.s. | None | None |
| 3′ UTR 8092 *c*→*a* | Adult glioma | Chen *et al.* 2000 (27) | 101–250, P | 0.27 | Ca: 60,35,5%<br>Co: 51,44,5% | ac/aa *vs.* cc | 0.7 (0.4–1.1)<br>Oligoastrocytoma only ($n = 28$)<br>**0.2 (0.1–0.6)**[g] | Age | None |

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| *XPC* | | | | | | | | | |
| 1457-1461 delins $(at)_n$ | SCCHN | Shen *et al.* 2001 (50) | 251–500, H | 0.33 | Ca: 36,47,17%<br>Co: 45,43,12% | ++ *vs.* −− | **1.9 (1.1–3.1)** | Age, sex, smoking, alcohol, cancer site | Age > 66 **5.6 (2.2–14.0)** |
| *XPD* | | | | | | | | | |
| 22541*c*→*a* | SCCHN | Sturgis *et al.* 2000 (49) | 101–250, H | 0.45 | Ca: 33,51,16%<br>Co: 31,49,20% | aa *vs.* cc | 0.9 (0.5–1.6) | Age, sex, smoking, alcohol | No interactions with age, sex, smoking or alcohol |
| | Skin cancer, BCC | Vogel *et al.* 2001 (54) | 51–100, H | 0.41 | Ca: 24,54,21%<br>Co: 38,42,20% | ca/aa *vs.* cc | 1.9 (1.0–3.8)<br>no BCC fam hist: **3.3 (1.4–8.2)** | None | Possible difference in risk by family history. No interaction w/number of lifetime sunburns |
| | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.40 | Ca: 35,53,12%<br>Co: 33,54,13% | Not given | Not given; n.s. | None | None |
| D312N | Lung cancer | Butkiewicz *et al.* 2001 (37) | 51–100, H | 0.44 | Ca: 45,36,19%<br>Co: 31,51,18% | DN/NN *vs.* DD | **0.5 (0.3–1.0)**[g] | Age and pack-year | Largest D312N effect among light smokers (> protection than non- and heavy smokers) |
| | | Zhou *et al.* 2002 (42) | 1001–1500, H | 0.33 | Ca: 42,44,14%<br>Co: 44,46,10% | NN *vs.* DD | **1.5 (1.1–2.0)** | Age, sex, pack-years, smoking status, time since cessation | Significant interaction with smoking ($P < 0.01$); nonsmokers **3.4 (1.9–6.0)**, heavy smokers 0.8 (0.5–1.2) |
| | | Hou *et al.* 2002 (45) | 101–250, H | 0.37 | Ca: 37,51,12%<br>Co: 41,44,15% | DN/NN *vs.* DD | Not given; n.s. | Age, sex, smoking (pack-years or environmental tobacco smoke) | Suggested interactions with smoking and age. Ever-smokers: 0.8 (0.4–1.5), never-smokers: 1.8 (0.9–3.3). Never-smokers < 70 yr: **2.6 (1.1–6.5)**. |
| | Skin cancer, BCC | Vogel *et al.* 2001 (54) | 51–100, H | 0.38 | Ca: 43,37,20%<br>Co: 44,37,19% | DN/NN *vs.* DD | 1.1 (0.6–1.9)<br>BCC fam hist: **5.3 (1.2–23.9)** | None | Possible difference in risk by family history. No interaction w/number of lifetime sunburns. |
| | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.36 | Ca: 39,43,18%<br>Co: 42,45,13% | Not given | Not given; n.s. | None | None |
| L751Q | Bladder cancer | Matullo *et al.* 2001b (28) | 101–250, H | 0.42 | Ca: 32,53,15%<br>Urological co: 32,60,8%<br>Nonurological co: 26,57,17% | LQ/QQ *vs.* LL | Urologic controls: 0.9 (0.4–2.1); Non-urologic controls: 0.7 (0.3–1.9) | None | In each smoking group, L751Q is n.s.; however, ORs are <1 in non- and ex-smokers and current smokers: *LQ/QQ vs.* LL, 2.5 (0.9–7.0) |
| | Lung cancer | Butkiewicz *et al.* 2001 (37) | 51–100, H | 0.42 | Not given | Not given | Not given; n.s. | Age and pack-year | None |
| | | David-Beabes *et al.* 2001 (40) | 251–500, H | Cauc 0.35, Af Amer 0.25 | Ca: 44,42,14%<br>Co: 48,42,10% | LQ/QQ *vs.* LL | 1.1 (0.8–1.5)<br>Results similar stratified by race | Ethnicity, age, sex, smoking | None |
| | | Zhou *et al.* 2002 (42) | 1001–1500, H | 0.37 | Ca: 39,46,15%<br>Co: 40,46,13% | QQ *vs.* LL | 1.2 (0.9–1.5) | Age, sex, pack-years, smoking status, time since cessation | Significant interaction with smoking ($P = 0.01$): non-smokers **2.0 (1.1–3.4)**, heavy smokers 0.7 (0.4–1.1) |

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|---|---|---|---|---|---|---|---|---|---|
| | | Park *et al.* 2002a (43) | 101–250, H | 0.06 | Ca: 88,12,0%<br>Co: 89,11,0% | LQ/QQ *vs.* LL | Not given; n.s. | Age, pack-years | No interactions with age, smoking status, or pack-years. No difference by subtype. |
| | | Hou *et al.* 2002 (45) | 101–250, H | 0.37 | Ca: 38,44,17%<br>Co: 43,40,17% | LQ/QQ *vs.* LL | Not given; n.s. | Age, sex, smoking (pack-years or environmental tobacco smoke) | Suggested interactions with smoking and age. Ever-smokers: 0.8 (0.4–1.5), never-smokers: **2.0 (1.1–3.8)**. Never-smokers < 70 years: **3.2 (1.3–8.0)**. |
| | SCCHN | Sturgis *et al.* 2000 (49) | 101–250, H | 0.11 | Ca: 40,44,16%<br>Co: 44,45,11% | QQ *vs.* LL | 1.7 (1.0–2.8) | Age, sex, smoking, alcohol | n.s., but effect of 751Q increased among older, current smokers and current drinkers. |
| | Skin cancer, BCC | Vogel *et al.* 2001 (54) | 51–100, H | 0.36 | Ca: 34,49,17%<br>Co: 38,52,10% | LQ/QQ *vs.* LL | 1.2 (0.6–2.2) | None | No interaction w/number of lifetime sunburns |
| | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.40 | Ca: 38,43,19%<br>Co: 34,51,15% | | Not given; n.s. | | None |
| *XPF* | | | | | | | | | |
| 5′ UTR 2063 *t→a* | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.31 | Ca: 62,30,8%<br>Co: 49,40,11% | ta/aa *vs.* tt | **0.6 (0.4–1.0)**[g] n.s. when Bonferronni adjusted | None | Suggestion of interaction w/*XRCC3* |
| 30028 *t→c* | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.33 | Ca: 58,32,10%<br>Co: 47,41,12% | tc/cc *vs.* tt | **0.6 (0.4–1.0)**[g] n.s. when Bonferronni adjusted | None | Suggestion of interaction w/*XRCC3* |
| Double-strand break repair | | | | | | | | | |
| *BRCA2* | | | | | | | | | |
| N372H | Breast cancer | Healey *et al.* 2000 (30), Series 1 | 101–250, H | 0.27 | Ca: not given<br>Co: 51,43,4% | HH *vs.* NN | 1.7 (0.8–3.5) | None | None |
| | | Healey *et al.* 2000 (30), Series 2 | 1501–2000, P | 0.27 | Ca: not given<br>Co: 53,41,6% | HH *vs.* NN | **1.4 (1.1–1.8)** | None | None |
| | | Healey *et al.* 2000 (30), Series 3 | 251–500, P | 0.25 | Ca: not given<br>Co: 54,41,4% | HH *vs.* NN | 1.8 (0.9–3.6) | None | None |
| | | Healey *et al.* 2000 (30), Series 4 | 501–750, P | 0.29 | Ca: not given<br>Co: 50,43,7% | HH *vs.* NN | 1.1 (0.7–1.6) | None | None |
| | | Healey *et al.* 2000 (30), Series 5 | 251–500, P | 0.22 | Ca: not given<br>Co: 61,33,5% | HH *vs.* NN | 1.1 (0.6–1.9) | None | None |
| | | Healey *et al.* 2000 (30), Series 2–5 | >3000, P | 0.22–0.29 | Ca: not given<br>Co: 53,40,7% | HH *vs.* NN | **1.3 (1.0–1.6)** | None | None |
| | | Healey *et al.* 2000 (30), Series 1–5 | >3000, H/P | 0.22–0.29 | Ca: not given<br>Co: 53,41,6% | HH *vs.* NN | **1.3 (1.1–1.6)** | None | None |

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| | | Spurdle *et al.* 2002 (32) | 1501–1500, P | 0.26 | Ca: 52,39,9%<br>Co: 54,40,6% | HH *vs.* NN/NH | **1.4 (1.0–2.0)** | Age, country of birth, state, education, marital status, number of live births, height, weight, age at menarche, oral contraceptive use, family history | Similar results when stratified by family history or restricted to non-mutation carriers or to Caucs. |
| 5′UTR-26*a*→*g* | Breast cancer | Healey *et al.* 2000 (30), Series 1 | 101–250, H | 0.28 | Not given | ag *vs.* aa | **0.6 (0.5–0.8)** | None | None |
| | | Healey *et al.* 2000 (30), Series 1–5 | >3000, H/P | Not given | Not given | ag *vs.* aa | **Not given, n.s.** | None | None |
| N289H | Breast cancer | Healey *et al.* 2000 (30), Series 1 | 101–250, H | 0.03 | Not given | NH *vs.* NN | 1.2 (0.6–2.7) | None | None |
| T1915M | Breast cancer | Healey *et al.* 2000 (30), Series 1 | 101–250, H | 0.05 | Not given | TM *vs.* TT | 0.4 (0.1–1.2) | None | None |
| R2034C | Breast cancer | Healey *et al.* 2000 (30), Series 1 | 101–250, H | 0.01 | Not given | RC *vs.* RR | 0.7 (0.2–2.3) | None | None |
| K3326X | Breast cancer | Healey *et al.* 2000 (30), Series 1 | 101–250, H | 0.01 | Not given | KX *vs.* KK | 1.7 (0.4–6.9) | None | None |
| *XRCC3* | | | | | | | | | |
| T241M | Bladder cancer | Matullo *et al.* 2001b (28) | 101–250, H | 0.35 | Ca: 26,52,22%<br>Urological co: 50,37,13%<br>Nonurological co: 49,28,23% | TM/MM *vs.* TT | Urological controls: 2.8 (1.3–6.0)<br>Non-urological controls: 2.7 (1.4–5.4) | None | Significant interaction with *NAT-2*, controlling for age |
| | Lung cancer | Butkiewicz *et al.* 2001 (37) | 51–100, H | 0.33 | Not given | Not given | Not significant | Age and pack-year | None |
| | | David-Beabes *et al.* 2001 (40) | 251–500, H | Cauc 0.38, Af Amer 0.23 | Ca: 50,40,10%<br>Co: 45,43,11% | TM/MM *vs.* TT | 1.0 (0.7–1.3)<br>Results similar stratified by race | Ethnicity, age, sex, smoking | None |
| | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.30 | Ca: 31,52,17%<br>Co: 52,37,11% | TM/MM *vs.* TT | **2.4 (1.4–3.9)**[h] | None | Suggestion of interaction w/*XPF* |
| 5′ region 4541*a*→*g* | Skin cancer, melanoma | Winsey *et al.* 2000 (52) | 101–250, H | 0.23 | Ca: unclear<br>Co: unclear | Not given | Not given; n.s. | None | None |

[a] Study types: H, hospital; P, population-based; N, nested case-control.
[b] Rare-allele frequency in controls: Af Amer, African American; Cauc, Caucasian; JB, Japanese Brazilian; NJB, non-Japanese Brazilian.
[c] Frequencies of individuals homozygous for the common allele, heterozygous, and homozygous for the rare allele respectively. Ca, case; Co, control.
[d] Genotypes represent amino acids in uppercase letters and nucleotides in lowercase letters.
[e] Bold signifies exclusion of 1.0 from 95% CI.
[f] w/, with; n.s., not significant; cig, cigarette; BCC, basal cell carcinoma.
[g] For consistency across studies, ORs and 95% CIs are inverted from those presented in the paper so that to individuals homozygous for the common allele are part of the referent group.
[h] Calculation of OR unclear.

these studies (29, 38, 41); such stratification by relevant exposures may provide information regarding the underlying biological mechanisms. Studies of SCCHN and stomach cancer also suggest decreased risks when individuals with *RW* or *WW* genotype are compared with those with *WW* genotype (Table 3; Refs. 48 and 55); in each of these studies, this inverse association was statistically significant only when restricted to subtypes of disease (oral/pharyngeal cancers: OR, 0.4; 95% CI, 0.2–0.8; gastric cardia: OR, 0.5; 95% CI, 0.3–0.9; Refs. 48, 55). Because different subsets of a cancer may result from different molecular pathways, this strategy of refining the phenotype may improve power to detect genetic associations, although subset analyses can be misleading in the absence of a clear biological rationale. Only one small study of SCCHN (98 cases, 161 controls) estimated an increase in risk associated with the *W* allele, but the 95% CI was not inconsistent with a reduced risk of the magnitude discussed above (Table 3; Ref. 51). No associations with R194W were seen in small studies (≤125 cases) of esophageal cancer (33), non-small cell lung cancer (37), or melanoma (52).

A second *XRCC1* polymorphism (R399Q) has also been well studied; however, the results suggested associations in different directions for different cancers: decreased risk for nonmelanoma skin carcinoma (53), esophageal cancer (33), and bladder cancer (28, 29); increased risk for breast cancer (31) and stomach cancer (55). There were inconsistent results for SCCHN (48, 51) and lung cancer (37–39, 41, 44), and no association was seen with melanoma (52), although the melanoma study was plagued by the use of cadaver controls. A relatively large population-based study of nonmelanoma skin cancer revealed inverse associations with the *QQ* genotype (*QQ versus RR*: basal cell carcinoma adjusted OR, 0.7; 95% CI, 0.4–1.0; squamous cell carcinoma adjusted OR, 0.6; 95% CI, 0.3–0.9; Ref. 53). Putative interactions with the number of lifetime sunburns were seen: the inverse association was limited to those with fewer than three sunburns, and an increased risk with *QQ* genotype was seen among those with three or more sunburns (53). Inverse associations with the 399*Q* allele were also suggested in studies of esophageal cancer (Ref. 33; among drinkers only) and bladder cancer (Refs. 28, 29; particularly among former or light-smokers), similar to the R194W results in these studies. An increased risk of breast cancer was seen among African-American carriers of the 399*Q* allele in one study (*RQ/QQ versus RR*; age-adjusted OR, 1.7; 95% CI, 1.1–2.4); data were also consistent with interactions with smoking and occupational exposure to ionizing radiation (31). A stomach-cancer study found an increased risk associated with the 399*Q* allele (*RQ/QQ versus RR* adjusted OR, 1.5; 95% CI, 1.0–2.4; Ref. 55). This study combined risk genotypes at R194H and R399Q and the association with risk was stronger (194*RR* +399*RQ*/399*QQ versus* 194*WW*/194*RW* +399*RR* adjusted OR, 1.7; 95% CI, 1.1–2.7; Ref. 55), however, it is not clear that the combined associations were greater than expected given the individual associations. Two hospital-based SCCHN studies yielded inconsistent results at *XRCC1* R399Q (48, 51). The larger study observed an increase in risk associated with the *QQ* genotype (Q*Q versus RR/RQ* adjusted OR, 1.6; 95% CI, 1.0–2.6; Ref. 48), and the smaller study observed a decrease in risk (*QQ versus RR* adjusted OR, 0.1; 95% CI, 0.04–0.6; Ref. 51). Lung-cancer studies of *XRCC1* R399Q have also shown inconsistent results. One population-based analysis suggested increased risk for lung cancer among individuals with *QQ* genotype (OR, 2.5; 95% CI, 1.1–5.8; Ref. 39), as did a second hospital-based study that found a further increase in risk among squamous cell cases only (OR, 3.3; 95% CI, 1.2–9.2; Ref. 44). However, another larger lung-cancer study suggested decreased risk (African Americans: OR, 0.6; 95% CI, 0.2–2.3; Caucasians: OR, 0.6; 95% CI, 0.3–1.3; Ref. 41), and two lung-cancer studies showed no differences (37, 38). Inconsistent *XRCC1* R399Q results in these lung-cancer studies may be attributable to population sample differences or other study-design issues; the relationship between XRCC1 and lung cancer risk is yet to be clearly elucidated.

Only four relatively small studies assessed the less common *XRCC1* R280H polymorphism (29, 33, 37, 38). One small nested case-control study of lung cancer reported an OR of 1.8 (95% CI, 1.0–3.4) for carriers of one or two *H* alleles and a statistically significant interaction with alcohol consumption ($P = 0.02$; Ref. 38). Three small studies of bladder, esophageal, and non-small cell lung cancer did not suggest any association, although small sample size and low frequency of the *H* allele limited power (29, 33, 37).

**NER Genes.** The *XPD* gene product is a subunit of TFIIH and is necessary for NER and transcription. Whereas *XPD* mutations are clearly deleterious (13), effects of common polymorphisms [L751Q, *D*312*N*, and a silent *c→a* change at nucleotide 22541 (codon 156)] on risk of carcinoma remain unclear. The most commonly studied polymorphism was the *XPD* L751Q polymorphism; although no statistically significant findings have been reported, suggestive results were observed in some studies. The largest study of L751Q was a United States hospital-based lung cancer study (1092 cases, 1240 controls) that found essentially no increase in risk in the dataset overall but did observe evidence of an interaction with smoking status ($P = 0.01$) with an increased risk among nonsmokers (*QQ versus LL* adjusted OR, 2.0; 95% CI, 1.1–3.4; Ref. 42). A similar relationship between L751Q and smoking status was seen in a smaller Swedish study of lung cancer (45), although two other lung-cancer studies found no suggestions of association or interactions with smoking (40, 43). One study of SCCHN among United States Caucasians reported a multivariate-adjusted OR of 1.7 (*QQ versus LL*; 95% CI, 1.0–2.8); ORs in this study were higher among older individuals and among those who smoked or drank at the time of the study (49). Small, possibly under-powered, studies of bladder-cancer (28), basal-cell-carcinoma (54), non-small cell lung cancer (37), and melanoma (52) did not observe any associations.

Five of the above mentioned *XPD* studies also examined associations with the *XPD* D312N polymorphism. A large lung-cancer study (1092 cases, 1240 controls) reported an elevated risk (*NN versus DD* adjusted OR, 1.5; 95% CI, 1.1–2.0) and an interaction with smoking ($P < 0.01$), again with the increased risk limited to nonsmokers (*NN versus DD* adjusted OR, 3.4; 95% CI, 1.9–6.0; Ref. 42). This interaction was also seen in a smaller lung cancer study (45). An inverse association was seen between the rare allele and risk of non-small cell lung cancer (*DN/NN versus NN* OR, 0.5; 95% CI, 0.3–1.0; Ref. 37). A further decreased risk was observed among light smokers but not among non- and heavy-smokers; the small number of subjects in the study precludes interpretation of smoking interactions (37). A small basal-cell-carcinoma study found no association with D312N except when restricted to individuals with a family history of nonmelanoma skin cancer (*DN/NN versus NN* OR, 5.3; 95% CI, 1.2–23.9; Ref. 54); however, reasons for this stratification are unclear. No association with this polymorphism was seen in a British study of melanoma (52).

Finally, three studies also examined associations with *XPD*'s silent codon 156 polymorphism (*c→a* at nucleotide 22541). A small basal-cell-carcinoma study suggested an in-

creased risk (*ca*/*aa versus cc* OR, 1.9; 95% CI, 1.0–3.8) that was even higher among individuals without a family history of basal-cell-carcinoma (54). Other studies of this polymorphism failed to find any association with SCCHN (49) or with melanoma (52).

Other NER genes examined in a small number of epidemiological studies were *XPC*, *XPF*, and *ERCC1*. *XPC* encodes part of the XPC-HR23B complex, which is thought to play an early role in NER by initially detecting the DNA damage (58). In *XPC*, a poly (at) insertion/deletion polymorphism (PAT) was shown to confer a statistically significantly increased risk for SCCHN in one hospital-based study (++ *versus* −− multivariate-adjusted OR, 1.9; 95% CI, 1.1–3.1; Ref. 50). Among individuals over 65 years old, risk was further increased with an OR of 5.6 (95% CI 2.2–14.0; 50). Other studies have not yet examined this polymorphism or another one with which it is in linkage disequilibrium (K939Q; Ref. 50). The gene products of *XPF* and *ERCC1* together form a complex that incises DNA at the 5′ side of a bulky-adduct lesion (59). A British melanoma study examined two polymorphisms in *XPF* and observed an inverse association with both; these were a *t* to *a* change at position 2063 in the 5′ UTR (*ta*/*aa versus tt* unadjusted OR, 0.6; 95% CI, 0.4–1.0) and a *t* to *c* change at position 30028 in exon 11 (*tc*/*cc versus tt* unadjusted OR, 0.6; 95% CI, 0.4–1.0; Ref. 52). *XPF* genotypes appeared to have an additive affect in combination with specific *XRCC3* genotypes on the risk of melanoma in this study (see below in Double-Strand-Break Repair Genes), suggesting hypotheses for future examination (52). This study of melanoma also examined an exon 4 polymorphism in *ERCC1* and found no association (52). In a United States population-based study, a 3′ UTR polymorphism (*c*→*a* 8092) in *ERCC1* was shown to have a nonsignificant inverse association with risk of adult glioma (*ca*/*aa versus cc* age-adjusted OR, 0.7; 95% CI, 0.4–1.1; Ref. 27). When restricted to 28 cases of oligoastrocytoma, this inverse association was stronger (*ca*/*aa versus cc* age-adjusted OR, 0.2; 95% CI, 0.1–0.6). Although this result may be evidence of the importance of this polymorphism in this subset of tumors, it may be a spurious result from analysis of a small number of cases (27).

**Double-Strand-Break Repair Genes.** Numerous genes are involved in the repair of DNA double-strand breaks; however, only two contain common polymorphisms that have been examined in epidemiological studies of cancer risk; these are *BRCA2* and *XRCC3*. The gene product of *BRCA2* promotes and regulates the homologous recombination pathway of DNA double-strand-break repair (60–63). Healey *et al.* examined six common *BRCA2* polymorphisms (see Table 1) in a collection of 234 British hospital-based breast cancer cases and 266 population-based controls (Series 1; Ref. 30). An *a* to *g* change at position −26 in the 5′ UTR was associated with reduced risk (*ga versus aa* unadjusted OR, 0.6; 95% CI, 0.5–0.8), and the N372H polymorphism was associated with increased risk of breast cancer (*HH versus NN* unadjusted OR, 1.7; 95% CI, 0.9–3.5; Ref. 30). Associations with these 2 polymorphisms were subsequently assessed in four other European population-based case-control series, and the association with the 5′ UTR polymorphism was not confirmed (30). For the N372H polymorphism, however, OR estimates for individuals with the *HH* genotype were more consistently elevated (Table 3; 30). Combined, the association was statistically significant (*HH versus NN* unadjusted OR, 1.3; 95% CI, 1.1–1.6), even when the first hypothesis-generating series was excluded (*HH versus NN* unadjusted OR, 1.3; 95% CI, 1.0–1.6; Ref. 30). Results from a large Australian population-based study supported these findings for the N372H polymorphism (1397 cases, 775 controls; *HH versus NN/NH* adjusted OR, 1.4; 95% CI, 1.0–2.0; Ref. 32).

*XRCC3* is also involved in the homologous recombinational pathway of DNA double-strand-break repair (its gene product interacts directly with Rad51; Refs. 64, 65). Four reports have been published that assessed the association between cancer risk and the T241M polymorphism of *XRCC3*: one suggested an association with bladder cancer (28), one with melanoma (52), and two showed no association with lung cancer (37, 40). The largest analysis of T241M was a United States lung-cancer study (331 cases, 667 controls) which found no association after adjustment for ethnicity, age, sex, and smoking status (Table 3; 40). This was consistent with a smaller study of non-small cell lung cancer that found no association after adjustment for age and smoking (37). A statistically significant increased risk of bladder cancer was seen among individuals with one or two copies of the rare allele in a small Italian study (*TM/MM versus TT* age-adjusted OR, 2.8; 95% CI, 1.3–6.0 using urologic controls; Ref. 28). Interactions with the *N*-acetyltransferase type 2 (*NAT-2*) genotype were suggested, such that the *XRCC3* association was statistically significant only among those with *NAT-2* slow genotype (*TM/MM versus TT* age-adjusted OR, 3.4; 95% CI, 1.5–7.9; Ref. 28). In a small British study of T241M, a statistically significantly increased risk of melanoma persisted after adjustment for multiple comparisons (*TM/MM versus TT* unadjusted OR, 2.4; 95% CI, 1.4–3.9). However, the use of cadaveric controls may not be appropriate, and the methods used for OR estimation were unclear (52). It was additionally suggested that the risk conferred by the *XRCC3 241M* allele is additive and that melanoma risk is determined by the combined number of rare alleles at *XRCC3* T241M, *XPF* 5′ UTR 2063*t*→*a*, and *XPF* exon 11 30028*t*→*c* (52). This study found no association with an *A* to *G* polymorphism in the 5′ region of *XRCC3* (52).

In summary, there were only a few DNA repair polymorphisms that were consistently associated with cancer risk across epidemiological studies: the *OGG1* S326C variant with increased risk of cancer at various sites; the *XRCC1* R194W variant with reduced risk of cancer at various sites; and the *BRCA2* N372H variant with increased risk of breast cancer in a plausible site-specific manner.

## Discussion

Epidemiological studies of common polymorphisms in DNA repair genes, if large and unbiased, can provide insight into the *in vivo* relationships between DNA repair genes and cancer risk. Such studies may identify empirical associations indicating that a polymorphism in a gene of interest has an impact on disease, independent of metabolic regulatory mechanisms and other genetic and environmental variability. Findings from epidemiological studies can complement *in vitro* analyses of the various polymorphisms, genes, and pathways. In addition, epidemiological studies of common polymorphisms can lead to increased understanding of the public health dimension of DNA-repair variation.

At least 30 epidemiological studies have attempted to assess associations between DNA repair polymorphisms and cancer risk. Only a small proportion of studies were large and population-based, however, some consistencies in results are apparent. Primarily, the *C* allele at codon 326 in *OGG1* (S326C) appeared to be associated with an increased risk in five case-control studies of esophageal cancer, lung cancer, and prostate cancer (34–36, 46, 47); one study of stomach cancer

found no association (56). Secondly, the *W* allele at codon 194 in *XRCC1* (R194W) appeared consistently associated with decreased cancer risk in case-control studies of bladder cancer, breast cancer, lung cancer, SCCHN and stomach cancer (29, 31, 41, 48, 55) and in a nested case-control study of lung cancer (38). Four other studies found no association with the *W* allele (33, 37, 51, 52). Finally, the *H* allele at *BRCA2*'s codon 372 (N372H) seemed consistently associated with breast-cancer risk. OR estimates from five European case-control studies ranged from 1.1 to 1.8, and the combined analysis yielded an OR of 1.3 (30). An Australian study of 1092 cases and 775 controls is consistent with these results (32). *BRCA2* polymorphisms have not been examined in published studies of other cancers.

This review of the epidemiological literature thus suggests that *OGG1* S236C, *XRCC1* R194W, and *BRCA2* N372H may be involved in carcinogenesis; functional studies of these polymorphisms can provide additional insight. *Escherichia coli* assays of *OGG1* S236C suggested that the *236C* allele may lead to reduced repair of 8-oxoguanine or reduced substrate specificity (66, 67); however, human cell-line studies suggested no association with functional activity as measured by 8-oxoguanine levels, or 8-oxoguanine glycosylase activity (68–71). Human studies of *XRCC1* R194W have reported no associations with indicators of DNA-repair capacity such as DNA-adduct levels, frequency of mutations in glycophorin A, or sensitivity to ionizing radiation (18–20, 72). A comparison of *BRCA2* N372H genotypes among spontaneous abortions and live births suggested an *in utero* selection against female fetuses with an *HH* genotype (30). Additional work on the functional relevance of these and other polymorphisms may shed light on whether it is the polymorphism itself, a variant that is in linkage disequilibrium, or another unknown factor that may play a causal role in carcinogenesis or development.

Assessment of effect modification may be particularly beneficial in studies of DNA-repair polymorphisms, because effects of polymorphisms may be apparent only in the presence of DNA-damaging agents such as tobacco smoke or ionizing radiation (73–76). For example, two studies of *XPD* and lung cancer observed consistent patterns of interaction between smoking behavior and genotype at D312N or L751Q: risk of lung cancer associated with either variant allele was higher among nonsmokers (or lighter-smokers) than among smokers (or heavier-smokers; Refs. 42, 45). Although other studies found no evidence of such interactions, these results are consistent with the hypothesis that the effect of *XPD* genotype on risk of lung cancer may be apparent only in the presence of lower levels of DNA damage than those caused by smoking (42). Another gene-environment interaction was suggested by a study of squamous cell carcinoma: the etiology of sunburn-related squamous cell carcinoma may differ by *XRCC1* R399Q genotype: among individuals with *QQ* genotype ($n = 97$), three or more sunburns conferred a 6.8-fold increased risk (95% CI, 2.4–19.2), whereas among individuals with *RR* genotype ($n = 283$), only a 1.5-fold increased risk was seen (95% CI, 0.9–2.5; Ref. 53). Although stratification by relevant exposure imparts smaller sample sizes and is restricted by the limitations of exposure measurement, examination of particular gene-by-exposure effects may be particularly useful in the context of an *a priori* biological hypothesis.

It is essential that epidemiological investigations of DNA repair polymorphisms are adequately designed. Unfortunately 83% of the reviewed reports studied fewer than 500 cases and 56% of the studies reviewed here analyzed fewer than 250 cases (even after exclusion of studies with less than 50 cases). Large and combined analyses such as those by Healey *et al.* (30) and Spurdle *et al.* (32) are preferred to minimize the likelihood of both false-positive and false-negative results. In addition, controls should be chosen in such a way that, if they were cases, they would be included in the case group; when controls are matched to cases, it is essential to account for matching in the analysis. When appropriate, confounding should be controlled for with particular consideration for race and ethnic group. An additional major concern is the grouping of genotypes for calculation of ORs; without functional data to dictate genotype groupings, it seems prudent to present two ORs per polymorphism (one for heterozygotes *versus* common-allele homozygotes and one for rare-allele homozygotes *versus* common-allele homozygotes) so that dominant, codominant, or recessive patterns may be elucidated.

Continued advances in single nucleotide polymorphism maps and in high-throughput genotyping methods will facilitate the analysis of multiple polymorphisms within genes and analysis of multiple genes within pathways. Data from multiple polymorphisms within a gene can be combined to create haplotypes, the set of multiple alleles on a single chromosome. None of the studies reviewed here reported haplotype associations, although several studies analyzed multiple polymorphisms within a gene, sometimes with inconsistent results. The analysis of haplotypes can increase power to detect disease associations because of higher heterozygosity and tighter linkage disequilibrium with disease-causing mutations (77–79). In addition, analysis of haplotypes offers the advantage of not assuming that any of the genotyped polymorphisms is functional; rather, it allows for the possibility of an ungenotyped functional variant to be in linkage disequilibrium with the genotyped polymorphisms (80). Analysis of data from multiple genes within the same DNA-repair pathway (particularly those known to form complexes) can provide more comprehensive insight into the studied associations. One study reviewed here examined multiple genes in multiple DNA-repair pathways and observed a possible additive effect of *XPF* and *XRCC3* alleles on the risk of melanoma (52), shedding light on the complexities of the many pathways involved with DNA repair and neoplasia development, and providing hypotheses for future functional studies. Because of concerns over inflated type I error rates in pathway-wide or genome-wide association studies, methods of statistical analysis seeking to obviate this problem are under development (81). The ability to include haplotype information and data from multiple genes, and to model their interactions, will provide more powerful and more comprehensive assessments of the DNA repair pathways.

In addition to possible associations with cancer risk, DNA repair polymorphisms are candidates for modifiers of highly penetrant genes (82, 83) and for association with response to treatment or survival time after cancer diagnosis (84–88). Common polymorphisms of the DSB repair genes *Rad51* and *ATM* have been implicated as possible modifiers of *BRCA1/2*-associated breast-cancer risk (82, 83). In addition, DNA repair polymorphisms may prove relevant in pharmacogenetics by modifying the repair capacity in response to cytotoxic or radiation therapy (84). Numerous DNA repair polymorphisms were recently assessed in two survival analysis: one found that a polymorphism in the DSB repair gene *LIG4* was associated with poorer survival time after breast cancer diagnosis (85), and another found that combined genotype at the MMR gene *MLH1* and cytochrome P450 1A1 (involved in xenobiotic metabolism) predicted event-free survival time after an acute lymphocytic leukemia diagnosis (86). Other studies of colorectal cancer have suggested associations between *XRCC1* R399Q and *XPD*

L751Q and poorer response to platinum-based treatment (87, 88). Because cancer-treatment regimens are often based on the induction of DNA damage, polymorphisms in repair pathways may be important for treatment response, toxicity, and survival.

In summary, 30 studies of DNA repair polymorphisms and risk of adult glioma, bladder cancer, breast cancer, esophageal cancer, lung cancer, prostate cancer, SCCHN, skin cancer (melanoma and nonmelanoma), and stomach cancer were reviewed here. This review, which is limited by the bias against publication of null findings (89), highlights the complexities inherent in epidemiological research and, particularly, in molecular epidemiological research. Only a small proportion of studies reviewed here were large and population based. Despite these challenges, there is evidence that some polymorphisms in DNA repair genes play a role in carcinogenesis, notably *OGG1* S326C, *XRCC1* R194W, and *BRCA2* N372H. Additional epidemiological analyses of these and other DNA repair-polymorphisms will provide essential information about the *in vivo* relationships between the DNA-repair mechanisms and carcinogenesis and can complement *in vitro* analysis. Large, well-designed epidemiological studies are needed to help further illuminate the complex landscape of DNA repair and cancer risk.

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