

Breast cancer risk is not associated with polymorphic forms of xeroderma pigmentosum genes in a cohort of women from Washington County, Maryland

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Abstract

Background: The genes mutated in the cancer-prone syndrome, xeroderma pigmentosum (XP genes), have been well studied both biochemically and mechanistically. These genes are important components of the DNA nucleotide excision repair (NER) pathway, which protects against environmentally-induced cancers. XP genes are also downstream of the hereditary breast cancer syndrome gene, BRCA1, suggesting that XP genes may be important to hereditary forms of breast cancer as well. Although mutated XP genes are rare, polymorphic forms with potential functional deficiencies are common, and could pose a significant cancer risk in the general population.

Hypothesis: This study tested the hypothesis that common polymorphic variants of XP genes were asso-

ciated with the risk of breast cancer among a population of women in Washington County, Maryland.

Methods: Five single nucleotide polymorphisms (SNPs) among four XP genes (XPC, XPD, XPF and XPG) were genotyped from DNA samples collected at baseline, and then analyzed by conditional logistic regression for association with the incidence of breast cancer. 321 cases were individually matched to 321 controls, by age and menopausal status.

Results: No significant associations were found between breast cancer risk and any of the XP genotypes. Odds ratios for all genotypes ranged from 0.61 to 1.14, and none were statistically significant. Adjustment and stratification for family history of breast cancer did not alter the findings.

Conclusion: These results suggest that polymorphisms of XP genes are not likely to be significant risk factors for women within the general population. This study did not address, however, risks for subpopulations of women with high exposures to DNA damaging agents.

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Introduction

Evidence suggests that DNA damage and repair is important to both environmental and hereditary forms of breast cancer. Environmental carcinogens can produce DNA lesions that are repaired by several well-characterized repair pathways, including nucleotide excision repair (NER). NER removes the bulky

DNA adducts that are produced by various physical and chemical environmental agents [1]. Xeroderma pigmentosum (XP) patients can have mutations in one of several genes involved for NER, and are known to be at very high risk for environmentally-induced cutaneous cancers, and probably internal cancers as well [2, 3]. Also, recent evidence shows that BRCA1, one of the genes mutated in the most common type of hereditary breast cancer, is responsible for transcriptional control of multiple XP genes [4, 5], suggesting that hereditary breast cancer susceptibility may also be mediated through NER. Given that XP genes seem to be potentially important to both environmental and hereditary breast cancer, we examined whether common allelic variations among a panel of XP genes was associated with breast cancer risk in the general population. We hypothesized that inheriting allelic variants of XP genes, with potentially altered enzymatic activity, may affect the risk of somatic mutation and cancer.

We report here on the findings of a case-control study of XP genes and primary breast cancer risk, nested within a large well-characterized cohort study population in Washington County, Maryland—a semi-rural community of predominantly Caucasians.

Five non-synonymous single nucleotide polymorphisms (SNPs) among four XP genes were genotyped from blood DNA collected at baseline (1989). These genes—XPC, XPD (ERCC2), XPF (ERCC4), and XPG (ERCC5)—are the genes mutated in XP complementation groups C, D, F, and G, respectively. They are all central players in the NER pathway. XPC and XPD are thought to have DNA damage recognition functions. XPF and XPG are involved in incision 5' and 3', respectively, to the DNA lesion [6]. A potential association between specific heterozygous and homozygous genotypes of these genes and subsequent development of primary breast cancer was assessed.

Methods

Study population

A nested case-control study was conducted using the population-based CLUE II cohort. The CLUE II cohort was established in 1989. Individuals residing in Washington County, Maryland, and surrounding regions were invited to donate blood for cancer and heart disease research (campaign slogan “Give us a clue to cancer and heart disease”). The CLUE II cohort consists of 32,892 individuals including approximately 30% of county residents [7]. Collected blood specimens were centrifuged, separated as buffy coat, red blood

cells, and plasma, and then stored at -70°C . Cancers that develop among cohort participants were ascertained through linkage to both the Washington County and, since 1992, the Maryland State Cancer Registries. In 1996, and about every 2 years afterwards, participants were asked to complete a follow-up questionnaire asking about health events, medication use, and cancer risk factors.

For this study, 321 incident cases of breast cancer that occurred after blood donation to CLUE II in 1989 were identified. Incident cases were defined as women with a first-time diagnosis of breast cancer (International Classification of Disease-8 174 and ICD-9 174). Cases were excluded if they had a diagnosis of any other cancer except for non-melanoma skin cancer and cervical cancer in situ, or were under 18 at the time of blood donation. Controls were individually matched to cases (1:1) by gender (female sex), age at blood donation (within 1 year), and menopausal status at blood donation. Selected controls were cancer-free, except possibly for non-melanoma skin cancer and cervical cancer in situ, and were not known to be deceased up to the date of diagnosis of the case.

Information on breast cancer risk factors was obtained from several sources, including a questionnaire that was sent in 1995 to a portion of the CLUE II breast cancer cases and controls who were part of a case-control study on organochlorine compounds and a 1996 follow-up questionnaire that was sent to all CLUE II participants. The overall response rate to the 1996 questionnaire was 79%, with an 81% response rate among CLUE II female participants. The 1995 questionnaire response rates were 89% for breast cancer cases and 79% for controls [7]. The questionnaires contained detailed information on family history of breast cancer, reproductive history, medication history and selective dietary intake. The study was approved by the Committee on Human Research of the Johns Hopkins Bloomberg School of Public Health.

Genotyping

Among the four XP genes studied here, five validated non-synonymous SNPs (rs2228001; rs17655; rs1799793; rs2228000; rs1800067) were identified from public databases (NIH dbSNP, NCI SNP:500, and NIEHS GeneSNPs). These SNPs were chosen because they involved amino acid changes that could alter protein function (i.e., non-synonymous), and they had minor allelic frequencies of at least 5% among Caucasians, which would make them prevalent enough within our study population to demonstrate statistically significant associations with disease.

Genomic DNA was extracted from peripheral buffy coat using the alkaline lysis method [8]. Extracted DNA samples were resuspended in 10 mM Tris-HCl/1 mM EDTA (TE) and the DNA concentration quantified by absorbance at 260 nm (A_{260}). DNA concentration was set at 100 $\mu\text{g/ml}$. The genotypes were assessed using the patented fluorogenic method for nucleic acid analysis commonly known as the Taqman® or 5′nuclease assay (Applied Biosystems Division, Perkin-Elmer, Foster City, CA). Hardy-Weinberg equilibrium of the observed frequency of the genotypes among controls was confirmed by the goodness of fit chi-square (Table 1). The success rate for genotyping was 85%.

Statistical analysis

Differences in the distribution of breast cancer risk factors between breast cancer cases and controls were compared using chi square tests. These included: education (<12, ≥ 12 years), history of first or second degree relative with breast cancer (no, yes), age at menarche (<12, 12–13, >13), age at first birth (<20, 20–24, 25–29 and ≥ 30), history of oral contraceptive use (never, former, current), history of other hormone use (never, current estrogen, current progesterone, former estrogen or progesterone) and smoking exposure (never, former and current).

Conditional logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the association between the genotypes and breast cancer. The breast cancer risk factors considered as possible confounders were age at menarche, age at first birth, family history of breast cancer, hormone use, duration of breastfeeding, and smoking history. With the exception of family history, none of these risk factors was statistically significantly associated with breast cancer and none changed the parameter estimates by greater than 10% when entered in the multivariate conditional logistic model. Therefore, only family history of breast cancer was adjusted for in the multivariate conditional logistic model.

Because there was some missing information on family history (16.8% for cases, 20.2% for controls) and genotypes (15.8%), we approached the conditional logistic analysis in two different ways. First, the analysis was carried out omitting paired observations that had missing data for any model parameter. Second, the data analysis was carried out using complete data sets generated by multiple imputation [9, 10]. We generated probability distributions for the missing values, given the observed data, using decision trees. Independent samples from those probability distributions

were used to generate 10 replicates of imputed complete data sets. Parameter estimates and standard errors were then combined from the analyses of the individual complete data sets, taking the variability between the parameter estimates from the 10 data sets as well as the standard error in each parameter estimate into account [9, 10]. Adjusting with imputed data was done to reduce the possibility that the missing data introduced some type of information bias. Imputation has the advantage in that it requires fewer assumptions than simply dropping observations with missing data and, therefore, can support the validity of a finding where some observations have missing data [11].

Results

Cases and controls were nearly identical for age at blood donation (mean age 56.8 vs. 56.6 years, respectively) and menopausal status in 1989 (70.7% and 70.4% postmenopausal, respectively) due to individual matching on these factors. Cases were slightly more likely than controls to be nulliparous (12.1% vs. 7.8%), to have a history of current or former oral contraceptive use (26.5% vs. 23.7%) and current or former estrogen and/or progesterone use (20.2% vs. 19.6%), but none of these differences were statistically significant. However, cases were much more likely than controls to have a family history of breast cancer (20.6% vs. 9.0%; $P = <0.001$). In univariate analysis, family history was associated with a statistically significant increased risk of breast cancer of approximately 2.4-fold (OR 2.43, 95% CI 1.54–3.84). (Distribution of these and other selected characteristics and risk factors in breast cancer cases and matched population controls has been previously reported [12]).

Genotypes frequency distributions for cases and controls are shown in Table 1. Chi-square tests showed none of the genotype distributions were significantly different between cases and controls, and the Hardy-Weinberg equilibrium test showed that distributions of the alleles among the genotypes was not significantly different from equilibrium for any of the genes, with the possible exception of XPD Asp312Asn, which showed borderline significance in both cases ($P = 0.07$) and controls ($P = 0.05$).

Odds ratios and 95% confidence interval for each genotype's association with breast cancer were calculated by conditional logistic regression, as appropriate to the matched study design, using the most common homozygous genotype as the reference group. Results from univariate analysis are shown in Table 2. There were no statistically significant associations between

Table 1 SNP genotype frequencies among cases and controls*

Gene/SNP codon	Genotype	Cases <i>n</i> = 321	Controls <i>n</i> = 321	χ^2 <i>P</i> value
XPC Ala499Val	GG	153	157	0.12
	AG	87	104	
	AA	13	14	
	Missing	68	46	
	HW <i>P</i> value	0.89	0.54	
XPC Lys939Gln	TT	98	105	0.86
	GT	136	136	
	GG	47	46	
	Missing	40	34	
	HW <i>P</i> value	0.99	0.86	
XPD (ERCC2) Asp312Asn	GG	110	102	0.32
	GA	128	142	
	AA	22	29	
	Missing	61	48	
	HW <i>P</i> value	0.07	0.05	
XPF (ERCC4) Arg415Gln	GG	221	231	0.38
	AG	37	43	
	AA	1	1	
	Missing	62	46	
	HW <i>P</i> value	0.68	0.50	
XPG (ERCC5) Asp1104His	GG	159	165	0.65
	CG	93	95	
	CC	12	15	
	Missing	57	46	
	HW <i>P</i> value	0.73	0.79	

*The *P* value for the Hardy-Weinberg equilibrium test is shown for cases and controls, for each SNP. Differences in genotype frequency distribution between breast cancer cases and controls were compared using chi square tests and the *P* values are shown

any of the genotypes and risk of breast cancer. However, there appeared to be a potentially protective association for the variant XPD Asn312 allele, with an apparent allelic dose response (heterozygote OR = 0.83; homozygote OR = 0.61), but the test for trend was not statistically significant ($P = 0.19$). Since a family history of breast cancer was potentially a phenotypic marker for the genotypic associations of interest here, and because a valid association between a highly prevalent genotype and breast cancer might be expected to account for some proportion of family history risk, the analysis was repeated with either adjustment for family history (Table 2) or stratification by family history (data not shown). Neither approach revealed any genotype associations with breast cancer. Also, models with and without imputed data observations did not change the negative genotype findings (Table 2). Family history, however, remained a significant risk factor in all of the models tested.

Discussion

The “common allele, common disease” hypothesis is the central paradigm for most all SNP association studies of cancer [13]. It proposes that allelic variation among normal genes can account for some portion of the variation in cancer risk seen within normal

populations. Major candidate genes for allelic effects are typically those responsible for genetic diseases with high cancer risk phenotypes. In this regard, DNA repair genes, or more specifically NER pathway genes, have received the most attention, and for good reason. The autosomal recessive DNA repair diseases, xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy (TTD), account for mutations in at least 13 separate genes in the NER pathway, and most of these are associated with increased risk of cancer among affected individuals [14]. Additionally, human cellular studies [15] and knockout mouse models [16] indicate that intermediate phenotypes exist for heterozygotes, suggesting that carriers of these relatively rare mutated alleles may be at higher than normal cancer risk.

The question of whether more common allelic variants of NER genes can also modify risk, however, is more difficult to answer. The fundamental hypothesis has been that allelic variants, with potential functional deficiencies, may be responsible for significant cancer risk. Determining whether common alleles can modify cancer risks at or near normal baseline risk levels is a more challenging to ascertain, but potentially more significant from a public health perspective, because allelic variants could be important even at low penetrance since they have high prevalence within the general population. For breast cancer in particular,

Table 2 Conditional logistic regression analysis of breast cancer risk associated with SNP genotypes and family history of breast cancer*

Gene/SNP codon	Odds ratio (95% Confidence interval)			
	Variable	Univariate (unadjusted)	Multivariate Model I (family history-adjusted)	Multivariate Model II (family history-adjusted)
XPC Ala499Val	No. of pairs	214	n/a	n/a
	Family Hist	2.32 (1.35–3.97)	n/a	n/a
	No. of pairs	228	142	321
	GG	1.00	1.00	1.00
	AG	0.99 (0.66–1.48)	1.14 (0.69–1.90)	0.83 (0.56–1.24)
XPC Lys939Gln	AA	1.11 (0.44–2.75)	1.09 (0.36–3.32)	0.92 (0.41–2.08)
	Family Hist	n/a	2.11 (1.08–4.09)	2.41 (1.44–4.02)
	No. of pairs	259	168	321
	TT	1.00	1.00	1.00
	GT	1.05 (0.72–1.54)	1.08 (0.66–1.77)	1.08 (0.75–1.57)
XPD (ERCC2) Asp312Asn	GG	1.07 (0.61–1.88)	1.05 (0.51–2.17)	1.09 (0.60–1.99)
	Family Hist	n/a	2.65 (1.43–4.90)	2.37 (1.44–3.89)
	No. of pairs	233	147	321
	GG	1.00	1.00	1.00
	GA	0.83 (0.57–1.20)	1.03 (0.63–1.68)	0.84 (0.58–1.20)
XPF (ERCC4) Arg415Gln	AA	0.61 (0.32–1.13)	0.87 (0.38–1.98)	0.82 (0.45–1.48)
	Family Hist	n/a	1.98 (1.04–3.78)	2.36 (1.42–3.91)
	No. of pairs	233	143	321
	GG	1.00	1.00	1.00
	AG/AA	1.04 (0.61–1.78)	0.89 (0.47–1.71)	0.88 (0.55–1.39)
XPG (ERCC5) Asp1104His	Family Hist	n/a	2.09 (1.10–3.96)	2.38 (1.45–3.92)
	No. of pairs	239	152	321
	GG	1.00	1.00	1.00
	CG	0.96 (0.65–1.41)	1.14 (0.69–1.86)	0.96 (0.66–1.40)
	CC	0.98 (0.38–2.52)	0.68 (0.16–2.91)	0.85 (0.35–2.07)
	Family Hist	n/a	2.01 (1.06–3.83)	2.38 (1.44–3.93)

*Odds ratios for univariate models of SNP genotypes or family history alone (unadjusted odds ratios) are shown, along with odds ratios for SNP genotypes adjusted for family history (Models I and II). In Model I, observations with missing data were omitted from the regression calculation (actual number of case/control pairs used in analysis is shown). In Model II, all observations were retained and the missing data were imputed, using a multiple imputation approach. (Confidence intervals for Model II incorporate variability introduced by the use of imputed data)

segregation analysis of residual family clustering in among non-carriers of BRCA1/2 mutations suggests that family clustering is best explained by a number of low-penetrance sequence variants [17, 18].

In this study, we tested the hypothesis that common variant alleles of the genes involved in XP contributed to breast cancer risk in the general population. We chose five SNPs among four XP genes, based on their potential functional role (i.e., non-synonymous) and frequency in the population (> 5% allele frequency). We found no significant associations between any of the tested XP genotypes and breast cancer incidence, regardless of family history, and reanalysis with imputation of missing data did not alter the findings. In addition, the findings for these five XP gene SNPs are consistent with our earlier negative finding for another non-synonymous SNP of XPD (Lys751Gln; rs13181) [12].

The identification of SNPs of candidate DNA repair genes that contribute to cancer susceptibility is an area of intense investigation [19], and several previous case–

control studies have explored XP genes and breast cancer. Recently, Zhang and coworkers, in a study of Chinese women, have reported a marginally significant breast cancer risk associated with XPC Lys939Gln (AC genotype, OR 1.46 95%CI 1.00–2.16), and protection associated with XPD Asp312Asn (AA genotype referenced to GG; OR 0.51, 95% CI 0.27–0.94) [20]. With regard to XPD Asp312Asn, an earlier study of German women also suggested a protective effect of the AA genotype for breast cancer. Using the AA genotype as a reference group, they reported GG as a risk genotype (GG genotype referenced to AA, OR: 2.06; 95%CI: 1.39–3.07), which translates into a reciprocal protective association for the AA genotype (OR = 0.48) that is very similar to the one reported for the Chinese women. Our study also suggested a protective trend for the variant A allele in univariate analysis (Table 2). Taken together, these epidemiological studies of breast cancer risk and cellular studies of apoptosis support a protective role for the variant A allele (i.e., Asn312).

In terms of DNA repair function, there are some reasons to doubt the validity of a protective role for the A allele. First, an adverse effect of the variant A allele on DNA repair would be more likely, since the non-variant Asp312 amino acid, coded by the common G allele, is evolutionarily highly conserved, suggesting an important role for this residue in the protein's DNA repair function. Second, the Asn coded by the variant A allele is neutral, while the common G allele's Asp is negatively charged, suggesting a potentially substantial disruption to DNA repair function of the protein. Taken together, these factors suggest that a protective role for the A allele in terms of DNA repair is suspect. Nevertheless, XPD has an additional functional role in apoptosis [21], and there has been a report that cells homozygous for the variant A allele have more apoptotic cells than those either heterozygous or homozygous for the common allele [22]. Since it has been proposed that apoptosis of DNA-damaged cells may preclude their transformation [23], the enhanced apoptosis by Asn312 may afford some protection against cancer by eliminating cells with mutagenic DNA damage, and this may supercede any DNA repair role for this gene in breast cancer risk.

Other case-control studies have reported positive associations between various XP gene SNPs and breast cancer incidence. Terry and coworkers found breast cancer risk associated with the Gln/Gln genotype of XPD751 specifically among women who currently smoked, suggesting an interaction between smoking and DNA repair [24]. We did not find any associations for any of our XP genotypes, when we stratified by smoking. Smith and coworkers reported a statistically significant difference in the XPF Arg415Gln genotype distributions between breast cancer cases and controls ($P = 0.02$), but the rarity of the homozygous variant precluded calculation of odds ratios [25]. We also found the homozygous variant genotype to be too rare for reliable measures of association. We, therefore, collapsed the homozygous and heterozygous variants, but still found no significant difference between our cases and controls ($P = 0.38$). Kumar and coworkers reported a marginally significant increase in breast cancer risk associated with the variant allele of XPG Asp1104His (combined heterozygote and homozygote OR = 1.50, 95%CI 1.04–2.16) [26]. We saw no association for XPG Asp1104His.

One limitation with the epidemiological evidence has been that most reported associations fail to be confirmed by subsequent studies in other populations [13]. For example, Forsti and coworkers studied XPC

and XPD SNPs among Finish and Polish breast cancer case-control groups and found some marginal associations for both genes in the Finns, but these associations could not be reproduced in the Poles [27]. This problem is often most apparent with hospital-based retrospective studies with community controls that could have had biases, since hospital admissions are often selective and their catchment populations are complex. The strength of this current study is its design. Being that this case-control study is nested within a large prospective cohort study that had DNA collected before disease and is under continuous longitudinal follow-up with a comprehensive cancer registry, it is less likely to suffer from selection, recall, or information biases that can influence retrospective case-control studies. Also, the environmental exposure experience of women in this study population is typical of many other communities in the United States, suggesting that the findings are generalizable to those communities as well.

In conclusion, our findings suggest that common polymorphisms in these XP genes are not significant determinants of breast cancer risk in this population. Nevertheless, it is possible that an association exists for these genes, but the particular SNPs chosen did not pick up the association. We believe, however, that this is unlikely. Sequence variations of these particular genes are well-described and validated in public databases, and the non-synonymous high-prevalence SNPs we chose would have the greatest potential to alter protein function and impact on breast cancer incidence within our population. Also, there is high linkage disequilibrium within these four genes (<http://www.hapmap.org>), so that the findings for our specific SNPs are likely to be informative for linked polymorphic variants that were not directly assessed. Nevertheless, it is possible that rarer SNPs might confer susceptibility to breast cancer, but their low frequencies in the general population would require a very high relative risk in order for them to have significant population attributable risks for breast cancer.

Although little evidence for breast cancer association was found for these XP genes, it could be that increased breast cancer risk would only be apparent under exposures to specific environmental carcinogens. Since little information was available about individual exposures to DNA damaging agents, we cannot rule out the possibility that subpopulations of women with high exposures to DNA damaging agents might be at significantly greater risk of breast cancer due to their XP genotype. In fact, it is highly likely that DNA repair genes would interact with their exposure environment. The possibility of gene-environment

interactions for XP and other NER genes warrants further study.

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References

- Lindahl T, Wood RD (1999) Quality control by DNA repair. *Science* 286:1897–1905
- Kraemer KH, Levy DD, Parris CN, Gozukara EM, Moriwaki S, Adelberg S, Seidman MM (1994) Xeroderma pigmentosum and related disorders: examining the linkage between defective DNA repair and cancer. *J Invest Dermatol* 103 Suppl. 5:96S–101S
- Kraemer KH, Lee M-M, Andrews AD, Lambert WC (1994) The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer: The xeroderma pigmentosum paradigm. *Arch Dermatol* 130:1018–1021
- Somasundaram K (2003) Breast cancer gene 1 (BRCA1): role in cell cycle regulation and DNA repair—perhaps through transcription. *J Cell Biochem* 88(6):1084–1091
- El-Deiry WS (2002) Transactivation of repair genes by BRCA1. *Cancer Biol Ther* 1(5):490–491
- Reardon JT, Sancar A (2005) Nucleotide excision repair. *Prog Nucleic Acid Res Mol Biol* 79:183–235
- Helzlsouer KJ, Alberg AJ, Huang HY, Hoffman SC, Strickland PT, Brock JW, Burse VW, Needham LL, Bell DA, Lavigne JA, et al (1999) Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. *Cancer Epidemiol Biomarkers Prev* 8(6):525–532
- Klitsch M, Neuhuber F (2000) Evaluation of an alkaline lysis method for the extraction of DNA from whole blood and forensic stains for STR analysis. *J Forensic Sci* 45(3):669–673
- Rubin DB (1996) Multiple imputation after 18+ years. *J Am Stat Assoc* 91(434):473–489
- Schafer JL (1997) Analysis of incomplete multivariate data. vol. 72. Chapman & Hall, New York
- Greenland S, Finkle WD (1995) A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 142(12):1255–1264
- Brewster AM, Jorgensen TJ, Ruczinski I, Huang HY, Hoffman S, Thuita L, Newschaffer C, Lunn RM, Bell D, Helzlsouer KJ (2006) Polymorphisms of the DNA repair genes XPD (Lys751Gln) and XRCC1 (Arg399Gln and Arg194Trp): relationship to breast cancer risk and familial predisposition to breast cancer. *Breast Cancer Res Treat* 95(1):73–80
- Pharoah PD, Dunning AM, Ponder BA, Easton DF (2004) Association studies for finding cancer-susceptibility genetic variants. *Nat Rev Cancer* 4(11):850–860
- Lehmann AR (2003) DNA repair-deficient diseases, xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. *Biochimie* 85(11):1101–1111
- Amiel A, Peretz G, Slor H, Weinstein G, Fejgin MD (2004) Molecular cytogenetic parameters in fibroblasts from patients and carriers of xeroderma pigmentosum. *Cancer Genet Cytogenet* 149(2):154–160
- Cheo DL, Meira LB, Burns DK, Reis AM, Issac T, Friedberg EC (2000) Ultraviolet B radiation-induced skin cancer in mice defective in the Xpc, Trp53, and Apex (HAP1) genes: genotype-specific effects on cancer predisposition and pathology of tumors. *Cancer Res* 60(6):1580–1584
- Antoniou AC, Pharoah PD, McMullan G, Day NE, Ponder BA, Easton D (2001) Evidence for further breast cancer susceptibility genes in addition to BRCA1 and BRCA2 in a population-based study. *Genet Epidemiol* 21(1):1–18
- Antoniou AC, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, Ponder BJ, Easton DF (2002) A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *Br J Cancer* 86(1):76–83
- Goode EL, Ulrich CM, Potter JD (2002) Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol Biomarkers Prev* 11(12):1513–1530
- Zhang L, Zhang Z, Yan W (2005) Single nucleotide polymorphisms for DNA repair genes in breast cancer patients. *Clin Chim Acta* 359(1–2):150–155
- Spillare EA, Wang XW, von Kobbe C, Bohr VA, Hickson ID, Harris CC (2005) Redundancy of DNA helicases in p53-mediated apoptosis. *Oncogene* 25(14):2119–2123
- Seker H, Butkiewicz D, Bowman ED, Rusin M, Hedayati M, Grossman L, Harris CC (2001) Functional significance of XPD polymorphic variants: attenuated apoptosis in human lymphoblastoid cells with the XPD 312 Asp/Asp genotype. *Cancer Res* 61(20):7430–7434
- Rothkamm K, Lobrich M (2003) Evidence for a lack of DNA double-strand break repair in human cells exposed to very low X-ray doses. *Proc Natl Acad Sci USA* 100(9):5057–5062
- Terry MB, Gammon MD, Zhang FF, Eng SM, Sagiv SK, Paykin AB, Wang Q, Hayes S, Teitelbaum SL, Neugut AI, et al (2004) Polymorphism in the DNA repair gene XPD, polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 13(12):2053–2058
- Smith TR, Levine EA, Perrier ND, Miller MS, Freimanis RI, Lohman K, Case LD, Xu J, Mohrenweiser HW, Hu JJ (2003) DNA-repair genetic polymorphisms and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 12(11 Pt 1):1200–1204
- Kumar R, Høglund L, Zhao C, Forsti A, Snellman E, Hemminki K (2003) Single nucleotide polymorphisms in the XPG gene: determination of role in DNA repair and breast cancer risk. *Int J Cancer* 103(5):671–675
- Forsti A, Angelini S, Festa F, Sanyal S, Zhang Z, Grzybowska E, Pamula J, Pekala W, Zientek H, Hemminki K, et al (2004) Single nucleotide polymorphisms in breast cancer. *Oncol Rep* 11(4):917–922