

# XPD Polymorphism and Risk of Subsequent Cancer in Individuals with Nonmelanoma Skin Cancer

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## Abstract

**Background:** Individuals with nonmelanoma skin cancer (NMSC) are at increased risk of developing subsequent cancers. Genetic predisposition to reduced DNA repair capacity may be an underlying susceptibility factor explaining the excess risk of malignancies. To test this hypothesis, a cohort study was conducted to examine the association between XPD *Lys751Gln* polymorphism and risk of a second primary cancer in individuals with NMSC. **Methods:** A subgroup of 481 individuals with a history of NMSC who participated in the CLUE II community-based cohort was followed for the development of a second primary cancer. Blood specimens donated in 1989 were genotyped for the XPD *Lys751Gln* polymorphism using the 5' nuclease assay. Cox proportional regression with delayed entry was used to calculate the incidence rate ratio (IRR) and 95% confidence interval (95% CI) for risk of developing a second primary cancer according to XPD genotype. All

statistical tests were two sided. **Results:** Eighty individuals developed a second primary cancer. The most frequent occurring cancers were of the prostate (18%), lung (15%), and breast (15%). Persons with at least one *Gln* allele had an increased risk of a second primary cancer compared with the reference *Lys/Lys* genotype (adjusted IRR 2.22, 95% CI 1.30-3.76). When the reference category was limited to never smokers with the *Lys/Lys* genotype, the risk of developing a second primary cancer associated with having at least one *Gln* allele was increased >3-fold in both never smokers (IRR 3.93, 95% CI 1.36-11.36) and ever smokers (IRR 6.14, 95% CI 2.17-17.37). **Conclusion:** These findings suggest that individuals with NMSC who have the variant XPD *Gln* allele are at increased risk of developing a second primary cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(8):1271-5)

## Background

Nonmelanoma skin cancers (NMSC) are the most common cancers diagnosed in the United States. Over 1 million new cases of basal and squamous cell carcinomas of the skin occur annually, and exposure to UV radiation is the leading risk factor (1, 2). UV radiation causes skin carcinogenesis by inducing cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts that form between adjacent pyrimidine bases (3). Suboptimal repair of these DNA lesions by the nucleotide excision repair (NER) pathway leads to the accumulation of mutations in important cell cycle regulatory genes that may eventually result in tumor development (4, 5).

The overall prognosis of NMSC is excellent, but several studies have shown that affected individuals are at increased risk of developing subsequent cutaneous and noncutaneous malignancies (6-19) and have a higher overall cancer mortality rate (20, 21) compared with the general population. The excess incidence of noncutaneous malignancies in individuals with a prior NMSC is unexplained. One hypothesis is that genetic predisposition to reduced DNA repair capacity may be an underlying susceptibility factor, increasing the risk of a subsequent malignancy (19, 22).

Polymorphisms of genes involved in the major NER pathway are of particular interest as candidate genes that may contribute to interindividual variations in DNA repair capacity and cancer susceptibility. In addition to the removal of mutagenic UV-induced photoproducts, the NER pathway is responsible for the removal of bulky and helical distorting DNA adducts induced by chemical carcinogens and cellular metabolites (3, 23).

Given the involvement of the NER pathway in the removal and repair of a wide variety of carcinogenic DNA lesions, defects in this pathway may predispose an individual to both cutaneous and noncutaneous malignancies. Within this pathway, a plausible candidate susceptibility gene is the common XPD polymorphism in exon 23 that causes an amino acid substitution of lysine for glutamine (24). The normal functioning XPD protein

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plays an essential role in NER and participates in the unwinding of DNA at the site of a deleterious DNA lesion (25, 26). Rare recessively inherited mutations in XPD as seen in individuals with xeroderma pigmentosum syndrome are associated with defects in NER and an elevated risk of skin cancers and internal cancers (27). Functional studies, although not entirely consistent (28), tend to show that the XPD *Lys751Gln* polymorphism is associated with reduced DNA repair capacity (29-31).

To test the hypothesis that reduced DNA repair capacity may explain the association between NMSC and subsequent cancers, we followed a cohort of individuals with a history of NMSC to examine the association between XPD *Lys751Gln* genotype status and risk of developing a second primary cancer.

## Subjects and Methods

Study participants were residents of Washington County, Maryland, who took part in a cohort study called CLUE II based on the slogan "Give us a clue to cancer and heart disease" (32). The CLUE II cohort was established in 1989 when 25,080 Washington County adult residents donated a blood specimen and completed a brief questionnaire, which included a history of previous cancer, smoking habits, and demographic information. In the questionnaire, participants were asked if they ever had cancer, the organ of involvement, where it was diagnosed, and the date of diagnosis. Compared with the Washington County's population, participation in the CLUE II cohort was greater among women, the better educated, and individuals in the 45 to 74 age range. Blood specimens were centrifuged, separated as buffy coat, RBC, and plasma, and stored at  $-70^{\circ}\text{C}$ . Cancers diagnosed among cohort participants are identified by computerized record linkage to the Washington County cancer registry. This registry was established in 1958, and cases of cancer that occur in county residents are identified from discharge records and pathologic specimens from the Washington County Hospital as well as from death records.

The present study was limited to 509 CLUE II participants who self-reported a cancer history that consisted only of basal and squamous carcinoma of the skin prior to entry into the study. The XPD *Lys751Gln* genotype status was not available for 17 participants. Reasons for missing data included no available blood specimen (1 individual) and inadequate DNA extracts (16 individuals). An additional 11 individuals did not provide date at NMSC diagnosis. This left 481 individuals in the analytic cohort for the present study.

A second primary cancer was defined as the first incident cancer (excluding basal or squamous cell skin cancer) that occurred after the date of entry into CLUE II. Information was collected on the cancer histology, primary site, and date of diagnosis. The following *International Classification of Diseases, Ninth Edition* codes were grouped: 162 (lung and bronchus) and 163 (pleura), 154 (rectal) and 153 (colon) and 151 (stomach), 161 (larynx) and 146 (tonsil), and 174 (breast) and 233 (breast *in situ*). The six cancer diagnoses (uterus, vagina, testes, and unknown primary) were grouped as "other epithelial." The vital status of CLUE II cohort participants are

determined using several methods including review of death certificates issued by the State of Maryland and the social security index, national death index, review of Washington County obituary reports, and responses from biannual questionnaire mailings to the CLUE II cohort. Follow-up of the cohort is estimated to be 98% complete for vital status. The study was approved by the Human Research Committee of the Johns Hopkins Bloomberg School of Public Health.

## Laboratory Assay

Genomic DNA was extracted from peripheral buffy coat using the alkaline lysis method (33). Extracted DNA samples were resuspended in Tris-EDTA, and DNA concentration was quantified by fluorometry. DNA concentration was set at 100  $\mu\text{g}/\text{mL}$ . The XPD *Lys751Gln* genotype was assessed using the patented fluorogenic method for nucleic acid analysis commonly known as the Taqman or 5' nuclease assay (Celera Genomics, Rockville, Maryland). As a quality control check, repeat genotyping was done on a sample of specimens.

## Statistical Analysis

Cox proportional hazard modeling with delayed entry (left truncation) was used to calculate the incidence rate ratio (IRR) and 95% confidence interval (95% CI) of developing a second primary cancer for participants with the XPD genotypes *Gln/Gln* and *Lys/Gln* using as the reference group the *Lys/Lys* genotype (34). Person-year at risk for developing a second primary cancer was calculated from age at diagnoses of NMSC to age at diagnosis of second primary cancer, accounting for left truncated data with age at entry into the CLUE II study determining when end points can begin to be observed. This type of adjustment known as "delayed entry" or "left truncation" was necessary, because participants did not come under observation for a second primary cancer or death until after entry into the CLUE II cohort. Individuals who did not develop a second primary cancer were censored at their age of death or age at study end (March 2002), whichever came first.

IRRs were calculated from age-adjusted Cox regression models and fully adjusted models that included age at NMSC diagnosis, education level ( $<12$  or  $\geq 12$  years), sex, and cigarette smoking (never, former, or current). The mean age at NMSC diagnosis and mean time from diagnosis of NMSC to CLUE II entry of participants who developed a second primary cancer (cases) and those who did not were compared using the Student's *t* test.  $\chi^2$  test was used to evaluate for differences in race, sex, education level, cigarette smoking status, and XPD *Lys751Gln* polymorphism status between the two groups of participants.

The association between genotype and subsequent cancer risk was examined stratifying by smoking status at baseline. For stratified analyses, individuals heterozygous and homozygous for the variant *Gln* allele were combined, because functional studies have shown a decreased repair capacity associated with at least one *Gln* allele (31). Proportionality of hazards over time for

the *Lys/Lys* group compared with the *Lys/Gln* and *Gln/Gln* combined group was assessed quantitatively by a test of Schoenfeld residuals and was not shown to be violated.

Analyses were done using Stata Statistical Software version 7.0 (Stata Corporation, College Station, TX).

## Results

The baseline characteristics of study participants are shown in Table 1. There were 233 (48%) women and 248 (52%) men. The majority of participants were White, reflecting the racial composition of the county. At entry into the CLUE II study, 52% of participants were current or former smokers. During the follow-up period, 80 participants developed a second primary cancer. The cancer types were prostate (17.5%), lung and pleura (15.0%), breast (15.0%), bladder (8.7%), colorectal and stomach (8.7%), melanoma (7.5%), lymphoma (7.5%), liver (7.5%), larynx and tonsil (2.5%), leukemia (2.5%), and other epithelial (7.5%). The mean time from diagnosis of NMSC skin cancer to CLUE II study entry was 8 years. There were 113 deaths among the 481 participants. In this cohort of persons with a history of NMSC, the age-adjusted risk of developing a second primary cancer was statistically significantly higher in former smokers (IRR 1.84, 95% CI 1.13-2.99) and current smokers (IRR 2.44, 95% CI 1.22-4.88) compared with never smokers. Men were at higher risk of a second primary cancer compared with women (IRR 1.35, 95% CI 0.86-2.11), and participants with <12 years of education

compared with  $\geq 12$  years (IRR 1.36, 95% CI 0.85-2.16) had slightly elevated risks that were not statistically significant (data not shown).

The frequency of the variant *Gln* allele was 38%, which was consistent with the frequency observed in previous studies of Caucasian populations (35-38), and the distribution of genotypes in the study population was in Hardy-Weinberg equilibrium (Table 2). In the fully adjusted model, individuals who had a variant *Gln* allele were 2.22 times more likely (95% CI 1.30-3.76) to develop a second primary cancer compared with individuals homozygous for the *Lys/Lys* genotype (Table 2). Risk was similar for individuals heterozygous or homozygous for the *Gln* allele but was statistically significant only in the heterozygotes.

The fully adjusted risk of developing a smoking-related second primary cancer such as lung and pleura cancer ( $n = 12$ ), bladder ( $n = 7$ ), larynx and tonsil ( $n = 2$ ), and colorectal ( $n = 6$ ) was also evaluated by XPD genotype. Individuals with the variant *Gln* allele were at higher risk of developing a smoking-related cancer (*Lys/Gln* versus *Lys/Lys* IRR 1.62, 95% CI 0.68-3.84; *Gln/Gln* versus *Lys/Lys* IRR 1.72, 95% CI 0.50-5.87), but the finding was not statistically significant. For the non-smoking-related cancers, the association observed was *Lys/Gln* versus *Lys/Lys* IRR 3.06, 95% CI 1.51-6.18 and *Gln/Gln* versus *Lys/Lys* IRR 2.29, 95% CI 0.87-6.05 (data not shown).

The joint effect of ever smoking and carrying the *Gln* allele on risk of developing a second primary cancer was assessed (Table 3). The results showed that, compared with never smokers with the *Lys* allele, the variant *Gln* allele was associated with a statistically significant increased risk of a second primary cancer in never smokers (IRR 3.93, 95% CI 1.36-11.36) and was even more pronounced in ever smokers (IRR 6.14, 95% CI 2.17-17.37). The test for interaction was not statistically significant ( $P = 0.1$ ).

**Table 1. Baseline characteristics of a cohort of individuals with a history of NMSC, Washington County, Maryland, 1989 to 2002**

Characteristic	Developed second primary cancer		P
	Yes ( $n = 80$ , $n$ (%))	No ( $n = 401$ , $n$ (%))	
Mean $\pm$ SD age at NMSC diagnosis	58 $\pm$ 11.7	54 $\pm$ 13.8	0.00
Mean $\pm$ SD time from diagnosis of NMSC to CLUE II entry	8.3 $\pm$ 8.4	8.8 $\pm$ 9.0	0.6
Race			
White	80 (100)	400 (99.8)	0.65
Other	0	1 (0.2)	
Sex			
Female	33 (41.3)	200 (49.9)	0.16
Male	47 (58.7)	201 (50.1)	
Years of education in 1989			
<12	50 (62.5)	108 (26.9)	0.056
$\geq 12$	30 (37.5)	293 (73.1)	
History of cigarette smoking in 1989			
Never	28 (35.0)	202 (50.4)	0.084
Former	40 (50.0)	154 (38.4)	
Current	12 (15.0)	44 (11.0)	
Missing	0	1 (0.2)	
XPD genotypes			
<i>Lys/Lys</i>	18 (22.5)	160 (39.9)	0.007
<i>Lys/Gln</i>	51 (63.8)	184 (45.9)	
<i>Gln/Gln</i>	11 (13.7)	57 (14.2)	

## Conclusion

In a cohort with a history of NMSC, the risk of developing a second primary cancer was approximately doubled in those with the variant *Gln* allele compared with those homozygous for the *Lys* allele. These data suggest that reduced DNA repair capacity at least partly explains the higher risk of cancer among individuals with a diagnosis of NMSC.

Ten population-based registry studies have observed that, after adjusting for age, overall cancer incidence is greater in persons with a history of NMSC compared with the general population (6-8, 10-15, 18). The preponderance of evidence from these studies indicates that the increased cancer risk in those with a history of NMSC not only is due to the incidence of malignancies with shared risk factors such as recurrent NMSC, incident melanoma, or lip cancer (6, 7, 12-15) but also includes an increased risk of numerous other primary cancer sites. Furthermore, not only cancer incidence but also cancer mortality is higher in those with a personal history of NMSC (21). The increased cancer mortality is due to poorer prognosis in addition to the increased risk of cancer. Among patients diagnosed with cancers of the

**Table 2. IRRs of second primary cancer by XPD genotype in a cohort of individuals with a history of NMSC, Washington County, Maryland, 1989 to 2002**

XPD genotypes	Developed second primary cancer		Incident cases per 100 person-years	Age-adjusted IRR (95% CI)	Multivariate adjusted IRR* (95% CI)
	No, n (%)	Yes, n (%)			
<i>Lys/Lys</i>	160 (39.9)	18 (22.5)	0.92	1.00 (reference)	1.00 (reference)
<i>Lys/Gln</i>	184 (45.9)	51 (63.8)	2.10	2.27 (1.32-3.89)	2.27 (1.32-3.91)
<i>Gln/Gln</i>	57 (14.2)	11 (13.7)	1.50	1.87 (0.88-3.98)	1.98 (0.93-4.21)
<i>Lys/Gln</i> and <i>Gln/Gln</i>			1.96	2.19 (1.29-3.70)	2.22 (1.30-3.76)

\*Adjusted for age at NMSC diagnosis, sex, years of education in 1989, and cigarette smoking status in 1989 (never, former, or current).

colon, breast, lung, prostate, and non-Hodgkin's lymphoma, survival is significantly worse in those with prior history of NMSC than those with no previous NMSC (20).

Immune suppression induced by UV light (10, 13), infection with the human papilloma virus (15), Epstein-Barr virus (8), cigarette smoking (6, 7), and poor DNA repair capacity (19, 21) have all been postulated as possible etiologic links to multiple cancers in individuals with a history of NMSC. There have been no studies to date, however, that provide empirical evidence that any of these factors contribute to the increased risk of a second primary cancer. The results of this study suggest that the elevated risk of second cancer in persons with a history of NMSC is at least partly due to genetic susceptibility mediated by reduced DNA repair capacity.

There is evidence to support the hypothesis that reduced repair of DNA damage from exogenous and endogenous insults is an important determinant of susceptibility to cancers of several sites (23). Polymorphisms of important genes in DNA repair pathways that decrease DNA repair capacity may contribute to the interindividual variation in DNA repair capacity that has been observed in skin cancer development and other malignancies. The XPD *Gln* allele has been associated with increased DNA adduct levels (35-37) and reduced DNA repair capacity either on its own (31) or in combination with other DNA repair gene variant alleles including the variant *Asn* allele of XPD *Asp312Asn* (29, 30). Alternatively, suboptimal repair of X-ray DNA damage has been shown with *Lys* allele (28). The *Lys751Gln* variant has been associated with increased risk of lung cancer (29, 36, 38) and the head and neck cancers (39) with some reported inconsistencies (40).

Although the test of interaction was not statistically significant, the risk of developing a second primary

cancer was observed to be highest in ever smokers with the *Gln* allele compared with never smokers with the *Lys/Lys* genotype. The risk was similar among never smokers with the *Gln* allele and ever smokers homozygous for the *Lys/Lys* allele. This finding suggests that the variant *Gln* allele may be as significant as a smoking history in increasing the risk of a second primary cancer among individuals with a history of NMSC skin cancer. The subset analysis did not suggest a stronger association between XPD *Gln* allele and smoking-related cancers compared with the non-smoking-related cancers. In fact, the three most frequent cancers that developed among the study participants were prostate, lung, and breast. This was not unexpected as they are also the most frequent occurring malignancies in the U.S. population (1). It is of interest, however, that reduced DNA repair capacity and presence of DNA adducts have been associated with both lung and breast cancer (41, 42).

The strengths of our study include its community-based setting and our ability to ascertain cancer outcomes through record linkage of study participants to the Washington County cancer registry. We were able to adjust for potential confounders of subsequent cancer risk such as age, gender, cigarette smoking, and education level as a surrogate of socioeconomic status. Data on sunlight exposure were lacking; however, it may be assumed that the whole cohort was exposed to substantial doses of UV radiation given that UV radiation is the major risk factor for NMSC (2). Nevertheless, our inferences would be more certain if the study had incorporated individual data on sunlight exposure. Because similar excess risks of developing a second primary cancer have been found in individuals with a history of squamous and basal cell skin cancer (10, 11), these histologic subtypes have a shared susceptibility factor responsible for the increased risk of subsequent

**Table 3. IRRs of second primary cancer according to XPD genotype and cigarette smoking status in a cohort of individuals with a history of NMSC, Washington County, Maryland, 1989 to 2002**

Smoking status*	XPD genotypes	Developed second primary cancer		Incident cases per 100 person-years	Multivariate adjusted IRR (95% CI) <sup>†</sup>
		Yes, n (%)	No, n (%)		
Never	<i>Lys/Lys</i>	4 (5.0)	83 (20.7)	0.40	1.00 (reference)
	<i>Lys/Gln</i> and <i>Gln/Gln</i>	24 (30.0)	119 (29.7)	1.52	3.93 (1.36-11.36)
Ever	<i>Lys/Lys</i>	14 (17.5)	77 (19.3)	1.42	3.51 (1.14-10.80)
	<i>Lys/Gln</i> and <i>Gln/Gln</i>	38 (47.5)	121 (30.3)	2.30	6.14 (2.17-17.37)

\*Data missing for one participant for cigarette smoking status.

<sup>†</sup>Adjusted for age at diagnosis of NMSC, sex, and years of education in 1989.

cancers. To test this hypothesis, we would have analyzed the data stratified by histologic subtype of NMSC. Unfortunately, information on NMSC histologic subtype was not known; therefore, future studies would be needed to address this issue.

In summary, the results of this study suggest that reduced DNA repair capacity may be an underlying risk factor responsible for the observed increased incidence of secondary cancers in individual with a history of NMSC. Additional relevant polymorphisms of the XPD gene such as XPD *Asn312Asp* and genes in other DNA repair pathways should also be examined as a logical next step as well as replication of the findings in other larger populations.

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