



Polymorphisms in the DNA repair genes *XPD*, *XRCC1*, *XRCC3*, and *APE/ref-1*, and the risk of lung cancer among male smokers in Finland

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Abstract

Associations between lung cancer risk and common polymorphisms in the DNA repair genes xeroderma pigmentosum complementation group D (*XPD*), X-ray repair cross-complementing group 1 (*XRCC1*), *XRCC3* and apurinic/apyrimidinic endonuclease/redox factor 1 were examined within a randomized clinical trial designed to determine whether alpha-tocopherol, beta-carotene, or both would reduce cancer incidence among male smokers in Finland. We found no direct association between lung cancer risk and any of the DNA repair genotypes studied, however, the association between *XPD* codon 751 genotype and lung cancer was modified by alpha-tocopherol supplementation, and the association between *XRCC1* codon 399 genotype and lung cancer was modified by the amount of smoking. Our results suggest that common alterations in single DNA repair genes are not major determinants of lung cancer susceptibility among smokers.

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1. Introduction

Despite an overwhelming amount of evidence indicating that cigarette smoking is the major cause of lung cancer today, only a small fraction of smokers get lung cancer during their lifetime. This observation suggests that genetic and other environmental factors are important determinants of risk.

Inherited deficiencies in DNA repair have been

Abbreviations: *XPD*, xeroderma pigmentosum complementation group D; *XRCC1*, X-ray repair cross-complementing group 1; *XRCC3*, X-ray repair cross-complementing group 3; *APE/ref-1*, apurinic/apyrimidinic endonuclease/redox factor 1.

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associated with a predisposition to cancer. This fact, along with experimental evidence identifying various repair proteins involved in the removal of tobacco-induced DNA damage, supports the theory that repair genotype may mediate lung cancer risk. In order to examine further the association between DNA repair genotype and lung cancer incidence, we conducted a case-control study nested within the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study.

The ATBC study was a randomized trial designed to determine whether alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung, prostate and other cancers among male smokers. The trial showed a 16% increase in lung cancer incidence with beta-carotene supplementation and no overall effect for alpha-tocopherol [1]. In addition, there was no evidence of an interaction between the two supplements, or between either supplement and smoking, in the effect on lung cancer incidence [2]. The size of this study, along with the availability of data on the general characteristics of the study population (including detailed dietary, smoking, and medical histories), a fasting blood sample for each individual obtained at baseline, and an active prospective follow-up to ascertain all cancer end-points, make this an ideal cohort for studying whether particular genetic polymorphisms are associated with cancer incidence.

Specific polymorphisms in xeroderma pigmentosum complementation group D (*XPD*) (Asp312Asn and Lys751Gln), X-ray repair cross-complementing group 1 (*XRCC1*) (Arg280His and Arg399Gln), *XRCC3* (Thr241Met) and apurinic/apyrimidinic endonuclease/redox factor 1 (*APE/ref-1*) (Asp148Glu) were selected for investigation because the product of each of these genes may be involved in the repair of tobacco-induced DNA damage [3,4], and the prevalence of each variant allele was reasonably high in our study population.

2. Materials and methods

2.1. Study population

The original study population consisted of participants in the ATBC Study. During the period from 1985 through 1988, a total of 29 133 men in

southwestern Finland, who were 50–69 years of age and who smoked at least five cigarettes/day, were randomly assigned to receive vitamin supplements or placebo. The overall design, rationale, and objectives of this prospective study have been published, as have the main trial results [1,2]. The ATBC study was approved by the institutional review boards of the US National Cancer Institute and the National Public Health Institute of Finland.

2.2. Selection of cases and controls

A nested case-control sample set was constructed based on the availability of a whole blood sample collected between April 1992 and March 1993 from 20 305 men. The cases consisted of 315 men, diagnosed with primary lung cancer during the years 1986–1994. Using incidence density sampling, controls were selected from cohort participants who were alive and free of cancer at the time the matched case was diagnosed. Controls were matched to cases on age (± 5 years), intervention group, study clinic, and date of blood draw (± 45 days) in a 1:1 ratio.

2.3. DNA isolation and genotype analyzes

DNA was isolated from whole blood samples as described previously [5]. Repair genotypes were determined using a previously described Taqman technique [6] and an ABI Prism 7700 sequence detector (PE Biosystems, Foster City, CA). Polymerase chain reaction (PCR) primers and dual-labeled allele discrimination probes were designed using PrimerExpress, version 1.0 (PE Biosystems). Oligonucleotide sequences for primers and probes to detect the polymorphisms were:

XPD codon 312: PCR forward: GTACCGGCGTCTGGTGA, PCR reverse: GGATGGAGCCAGGCACTG, G allele probe: ^{VIC}CTGCCCGACGAAGTGCTGCAG^{TAMRA}, A allele probe: ^{FAM}CTGCCCAACGAAGTGCTGCAGG^{TAMRA};

XPD codon 751: PCR forward: AGGATCAGCTG GGCCTGTC, PCR reverse: GAACCGTTTATGGC CCCAC, T allele probe: ^{VIC}CTCTATCCTCTT-CAGCGTCTCCT^{TAMRA}, Y allele probe: ^{FAM}CTC-TATCCTCTGCAGCGTCTCCT^{TAMRA};

XRCC1 codon 280: PCR forward: GACCCCCAG TGGTGCTAACC, PCR reverse: GCCTTCTCCTC GGGGTTTG, A allele probe: ^{VIC}AGCTCCAAC TATACCCCAGCCACA^{TAMRA}, G allele probe: ^{FAM}AGCTCCAAC TCGTACCCCAGCCAC^{TAMRA};

XRCC1 codon 399: PCR forward: GTAAG-GAGTGGGTGCTGGACTGT, PCR reverse: GTCT GACTCCCCTCCAGATTCC, A allele probe: ^{VIC}CTGCCCTCCCAGAGGTAAGGCCCTC^{TAMRA}, G allele probe: ^{FAM}CTGCCCTCCC GGAGG-TAAGGCC^{TAMRA};

XRCC3 codon 241: PCR forward: GGGCCAGG-CATCTGCAGT, PCR reverse: GGTGCTCACCTG GTTGATGC, T allele probe: ^{VIC}TGGGGGC-CATGCTGCGTG^{TAMRA}, C allele probe: ^{FAM}TGG GGGCCACGCTGCGT^{TAMRA};

APE/ref-1 codon 148: PCR forward: TCTATC TCTGCCCCACCTCTTG, PCR reverse: ACG AGTCAAATTCAGCCACAATC, A allele probe: ^{VIC}TCATGCTCCTCATCGCCTATAGA^{TAMRA}, Y allele probe: ^{FAM}TCATGCTCCTCCTCGCCTA-TAGA^{TAMRA}.

Genotyping reactions (10 μ l) contained ~20 ng of genomic DNA, 1 \times TaqMan Master Mix, dual-labeled probes (100 nM each), and PCR primers (900 nM each). Reactions were performed in 96-well MicroAmp Optical reaction plates (PE Biosystems). Plates were incubated at 50°C for 2 min and 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 62°C for 1 min. Reaction data were analyzed with Sequence Detection System, version 1.6.3 (PE Biosystems). All laboratory personnel were blind to the case-control status of the samples. Amplified DNA from several individuals exhibiting each genotype was electrophoresed on an agarose gel to confirm amplicon size and sequenced to confirm each genotype. A random sample of 10% of the specimens was assayed a second time and showed 100% concordance. Less than 3% of all the samples could not be genotyped; these samples were dropped from subsequent statistical analyses.

2.4. Statistical analyzes

The Chi-square test was used to test the null hypothesis that the distribution of genotypes was the same for cases and controls. Conditional logistic

regression was used to evaluate the association between genotype and lung cancer incidence. Baseline covariates were identified as potential confounders by examining their distribution by case-control status and genotype (Wilcoxon signed-rank test for continuous variables; Chi-square test for categorical variables). Covariates were included in the model if they changed the odds ratio (OR) by more than 20% or caused a significant change in the likelihood ratio statistic ($P \leq 0.05$). Selected covariates (age, intervention group, smoking duration, and smoking amount) were evaluated as effect modifiers by examining the change in the likelihood ratio statistic after including the covariate and the genotype-covariate cross-product term in the conditional logistic regression model. If a cross-product term was found to be statistically significant, an unmatched analysis was conducted using unconditional logistic regression adjusted for the original matching criteria and stratified by the putative effect modifier. Continuous covariates evaluated as effect modifiers were categorized into percentiles based upon their distribution among control subjects. All statistical analyzes were performed using STATA 6.0 (Stata Corporation, College Station, TX).

3. Results and discussion

Univariate analyses of baseline data that might be related to lung cancer risk in this population revealed only a few differences between cases and controls (Table 1). Because of the study matching, there were no case-control differences in age or intervention group distributions. Compared to controls, however, cases smoked more cigarettes per day, smoked for a greater number of years ($P < 0.001$), and had a lower body mass index ($P = 0.03$).

We found no evidence of a direct association between any of the repair genotypes and lung cancer risk (Table 2). Given the sample size of our study and the prevalence of the various genotypes in our control population, we had $\geq 80\%$ power (two-sided test of significance, $\alpha = 0.05$) to detect an OR of 1.6 for carriers of at least one variant allele (versus no variant alleles) for *XPD* codon 312, *XRCC1* codon 399, or *XRCC3* codon 241; we had $\geq 80\%$ power to detect an OR of 1.7, 1.8, and 1.9 for carriers of at least one variant allele for *XPD* codon 751, *XRCC1* codon 280,

Table 1
Selected baseline characteristics^a

| Characteristic | Cases (<i>n</i> = 315) | Controls (<i>n</i> = 315) |
|--------------------------------------|--------------------------------|----------------------------|
| Age at randomization (years) | 60 (55–63) | 59 (55–63) |
| Years smoked | 40 (37–45) ^b | 40 (34–44) |
| Cigarettes/day | 20 (16–25) ^b | 20 (15–25) |
| Alcohol (g ethanol/day) | 8.9 (2.0–22.8) | 10.2 (2.0–23.8) |
| Body Mass Index (kg/m ²) | 25.3 (23.2–28.0) ^c | 26.1 (23.8–28.4) |
| Energy intake (kcal/day) | 2649 (2141–3191) | 2651 (2236–3167) |
| Fat (kcal/day) | 114.6 (89.5–149.0) | 110.8 (92.0–137.7) |
| Fiber (g/day) | 23.0 (17.4–30.8) | 24.5 (18.1–32.2) |
| Vitamin C (mg/day) | 79.5 (58.8–113.1) ^c | 86.6 (65.6–113.3) |
| Serum cholesterol (mmol/l) | 6.2 (5.3–6.9) | 6.1 (5.4–6.9) |
| Serum α-tocopherol (mg/l) | 11.3 (9.4–13.2) | 11.4 (9.9–13.4) |
| Serum β-carotene (μg/l) | 169 (105–246) | 166 (118–257) |
| Serum retinol (μg/l) | 563 (483–642) | 571 (500–652) |

^a Data are median (interquartile range).

^b *P* < 0.02, Wilcoxon signed-rank test.

^c *P* < 0.05, Wilcoxon signed-rank test.

or *APE/ref-1* codon 148, respectively. The frequencies of these variant alleles in our control population (Table 2) were similar to those reported previously [4, 7–10], and Chi-square analysis of the distribution of repair genotypes in our control population indicated that all of the alleles were in Hardy–Weinberg equilibrium.

When we evaluated potential gene-environment interactions we found that the association between *XPD* codon 751 genotype and lung cancer risk was modified by alpha-tocopherol intervention (*P* = 0.003 for the interaction term). Stratified analysis, (adjusted for beta-carotene intervention, age, number of cigarettes per day, and years of smoking), revealed that among men who received alpha-tocopherol, those with the Lys/Gln or Gln/Gln genotype were 50% less likely to develop lung cancer than those with the Lys/Lys genotype (Table 3).

XPD is an ATP-dependent, 5′-3′ helicase subunit of transcription factor IIIH which is believed to play an important role in both messenger RNA transcription and nucleotide excision repair (reviewed in ref. [11]). Most attempts to prevent cancer by alpha-tocopherol supplementation have been based on the hypothesis that this vitamin supplement acts by scavenging reactive oxygen species in cell membranes, thereby

reducing the formation of mutagenic lipid peroxidation products in cells (reviewed in ref. [12]). While it is conceivable that the anti-mutagenic effects of alpha-tocopherol may be obscured in individuals with adequate capacities for DNA repair, (for example, those who are homozygous wild-type at *XPD* codon 751), our finding of an interaction between alpha-tocopherol supplementation and *XPD* codon 751 genotype on lung cancer risk should be interpreted with caution since the functional significance of the codon 751 polymorphism of *XPD* has not yet been determined, and neither the *XPD* polymorphism nor the alpha-tocopherol intervention had a direct effect on lung cancer risk in our study population [1]. Furthermore, previous studies have failed to establish a direct relationship between alpha-tocopherol treatment and an individual's ability to carry out nucleotide excision repair [13].

We also found that the association between *XRCC1* codon 399 genotype and lung cancer risk was modified by the amount of smoking (*P* = 0.03 for the interaction term). Analysis of *XRCC1* codon 399 genotype stratified by number of cigarettes per day (and adjusted for age, intervention group, and years of smoking), however, revealed contradictory results: among men who smoked 20–24 cigarettes per day,

Table 2
Association between lung cancer risk and *XPD*, *XRCC1*, *XRCC3* or *APE/ref-1* polymorphisms in male smokers

| Genotype | Cases (%) | Controls (%) | OR (95% CI) ^a |
|----------------------------|-----------|--------------|--------------------------|
| <i>XPD</i> codon 312 | | | |
| Asp/Asp | 143 (46) | 125 (40) | 1.00 |
| Asp/Asn | 127 (40) | 147 (47) | 0.72 (0.50–1.04) |
| Asn/Asn | 43 (14) | 40 (13) | 0.93 (0.55–1.58) |
| Asp/Asn + Asn/Asn | 170 (54) | 187 (60) | 0.77 (0.56–1.07) |
| <i>XPD</i> codon 751 | | | |
| Lys/Lys | 112 (36) | 103 (34) | 1.00 |
| Lys/Gln | 145 (47) | 153 (51) | 0.82 (0.56–1.19) |
| Gln/Gln | 53 (17) | 46 (15) | 1.02 (0.61–1.70) |
| Lys/Gln + Gln/Gln | 198 (64) | 199 (66) | 0.87 (0.61–1.23) |
| <i>XRCC1</i> codon 280 | | | |
| Arg/Arg | 260 (84) | 260 (86) | 1.00 |
| Arg/His | 47 (15) | 42 (14) | 1.03 (0.67–1.58) |
| His/His | 2 (1) | 0 (0) | |
| Arg/His + His/His | 49 (16) | 42 (14) | 1.17 (0.73–1.88) |
| <i>XRCC1</i> codon 399 | | | |
| Arg/Arg | 151 (48) | 154 (49) | 1.00 |
| Arg/Gln | 140 (44) | 130 (42) | 1.07 (0.78–1.48) |
| Gln/Gln | 24 (8) | 29 (9) | 0.77 (0.42–1.43) |
| Arg/Gln + Gln/Gln | 164 (52) | 159 (51) | 1.01 (0.72–1.40) |
| <i>XRCC3</i> codon 241 | | | |
| Thr/Thr | 160 (51) | 149 (49) | 1.00 |
| Thr/Met | 124 (40) | 134 (44) | 0.96 (0.69–1.34) |
| Met/Met | 29 (9) | 23 (7) | 1.12 (0.59–2.12) |
| Thr/Met + Met/Met | 153 (49) | 157 (51) | 1.14 (0.62–2.12) |
| <i>APE/ref-1</i> codon 148 | | | |
| Asp/Asp | 64 (21) | 65 (22) | 1.00 |
| Asp/Glu | 167 (54) | 160 (53) | 1.05 (0.67–1.66) |
| Glu/Glu | 79 (25) | 77 (25) | 0.92 (0.56–1.51) |
| Asp/Glu + Glu/Glu | 246 (79) | 237 (78) | 1.00 (0.66–1.52) |

^a ORs and 95% CIs are adjusted for years of smoking and number of cigarettes per day.

Table 3
The effect of *XPD* codon 751 genotype on lung cancer risk, stratified by alpha-tocopherol intervention

| Alpha-tocopherol | Lys/Lys | | Lys/Gln + Gln/Gln | |
|------------------|----------------|-------|-------------------------------|--------|
| | OR (reference) | ca/co | OR (95% CI) ^a | ca/co |
| + | 1.00 | 55/33 | 0.50 (0.30–0.84) ^b | 89/104 |
| – | 1.00 | 57/70 | 1.39 (0.86–2.26) | 109/95 |

^a ORs and 95% CIs are adjusted for beta-carotene intervention, age, years of smoking, and number of cigarettes per day.

^b $P = 0.009$.

Table 4
The effect of *XRCC1* codon 399 genotype on lung cancer risk, stratified by amount of smoking

| Number of cigarettes per day | Arg/Arg | | Arg/Gln + Gln/Gln | |
|------------------------------|----------------|-------|-------------------------------|-------|
| | OR (reference) | ca/co | OR (95% CI) ^a | ca/co |
| < 15 | 1.00 | 24/39 | 0.96 (0.43–2.14) | 18/32 |
| 15–19 | 1.00 | 19/26 | 1.16 (0.49–2.75) | 23/27 |
| 20–24 | 1.00 | 39/45 | 1.64 (0.91–2.95) ^b | 70/49 |
| ≥ 25 | 1.00 | 69/44 | 0.59 (0.34–1.04) ^c | 53/51 |

^a ORs and 95% CIs are adjusted for alpha-tocopherol and/or beta-carotene intervention, age, and years of smoking.

^b $P = 0.099$.

^c $P = 0.069$.

those with Arg/Gln or Gln/Gln genotypes were 60% more likely to develop lung cancer compared to those with the Arg/Arg genotype; in contrast, among men who smoked ≥ 25 cigarettes per day, those with Arg/Gln or Gln/Gln genotypes were 40% less likely to develop lung cancer compared to those with the Arg/Arg genotype (Table 4).

XRCC1 is a multi-domain protein which interacts with at least three other proteins (poly-ADP-ribose polymerase, DNA ligase III, and DNA polymerase β) to repair single-strand breaks in DNA [14,15]. The *XRCC1* codon 399 polymorphism occurs in the coding region of the poly (ADP-ribose) polymerase binding domain of the *XRCC1* protein and was therefore postulated to have an affect on DNA-protein complex assembly, and ultimately, the efficiency of DNA single-strand break repair [16]. Experimental evidence indicating that this polymorphism may have little or no biological relevance [17], along with equivocal results from epidemiologic studies, suggest that previously reported associations between the *XRCC1* codon 399 polymorphism and cancer, may be due to chance. Recently, Stern et al. reported that the homozygous variant *XRCC1* codon 399 genotype may be associated with a decreased risk of bladder cancer and that this protective effect may be more pronounced in lower-dose smokers [9]; in contrast, Duell et al. reported that possessing at least one variant *XRCC1* codon 399 allele was associated with an increased risk of breast cancer among African American (but

not white) women, but that breast cancer risk was modified by duration of smoking only among African American women with the Arg/Arg *XRCC1* codon 399 genotype [18]. Sturgis et al have also reported an association between homozygous variant *XRCC1* codon 399 genotype and head and neck cancer; this association was most pronounced in current (versus former or never) smokers and was not modified by sex, ethnicity or age [19].

Furthermore, Park et al. recently reported an association between the *XRCC1* codon 399 Gln allele and increased risk of squamous cell carcinoma (but not all cancer) of the lung [7], while Divine et al. recently reported an association between the *XRCC1* codon 399 Gln/Gln genotype and increased risk of adenocarcinoma of the lung [20]. In our study, 140 (44%) lung cancer cases were squamous cell carcinomas, and 56 (18%) lung cancer cases were adenocarcinomas. We found no evidence of a direct association between *XRCC1* genotype and the risk of either tumor subtype (data not shown), although, the relatively small samples defined by tumor subtype would have limited our ability to detect such associations.

In the study conducted by Park et al. the association between the *XRCC1* codon 399 Gln allele and increased risk of squamous cell carcinoma of the lung was most pronounced among smokers who had less tobacco exposure (those who had ≤ 40 pack years of smoking) [7]. It is conceivable that such an association might have been obscured in our study

population of predominantly heavy smokers if high levels of tobacco-induced DNA damage in the pulmonary cells of heavy smokers were to direct such cells toward apoptosis (rather than mutagenesis), or induce an alternative DNA damage processing response. Although the difference in risk was not statistically significant ($P = 0.099$), in our study, the OR associated with having one or more Gln alleles, was 1.64 among men who smoked 20–24 cigarettes per day.

Finally, our results are in agreement with those of others who have failed to demonstrate direct associations between lung cancer risk and common polymorphisms in DNA repair genes in smokers [8, 21–23]. Perhaps such results are not surprising, given the overlapping substrate specificity of various DNA repair pathways and the complex relationship between DNA damage, DNA repair, cell transformation, and cell death.

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