Research article

**Association between polymorphisms in DNA repair genes and survival of non-smoking female patients with lung adenocarcinoma**

Zhihua Yin1,2, Baosen Zhou*1,2, Qincheng He1, Mingchuan Li1, Peng Guan1,2, Xuelian Li1,2, Zeshi Cui3, Xiaoxia Xue3, Meng Su1,4, Rui Ma4, Weijun Bai4, Shuyue Xia5, Yanduo Jiang6, Shun Xu7, Yi Lv8 and Xun Li8

Address: 1Department of Epidemiology, School of Public Health, China Medical University, Shenyang 110001, PR China, 2Key Laboratory of Cancer Etiology and Intervention, University of Liaoning Province, Shenyang 110001, PR China, 3The Third Center for Laboratory Technology and Experimental Medicine, China Medical University, Shenyang 110001, PR China, 4Department of Internal Medicine, Liaoning Cancer Hospital & Institute, Shenyang 110042, PR China, 5Department of Respiratory Medicine, Fengtian Hospital Affiliated to Shenyang Medical College, Shenyang 110024, PR China, 6Department of Pathology, 202 Hospital of Chinese PLA, Shenyang 110003, PR China, 7Department of Thoracic Surgery, The First Affiliated Hospital of China Medical University, Shenyang 110010, PR China and 8Shenyang Center for Disease Control and Prevention, Shenyang 110031, PR China

Email: Zhihua Yin - zhyin@mail.cmu.edu.cn; Baosen Zhou* - bszhou@mail.cmu.edu.cn; Qincheng He - qche@mail.cmu.edu.cn; Mingchuan Li - lmingchuan@hotmail.com; Peng Guan - pguan@mail.cmu.edu.cn; Xuelian Li - zimu0124@yahoo.com.cn; Zeshi Cui - labczs@mail.cmu.edu.cn; Xiaoxia Xue - xxxue@mail.cmu.edu.cn; Meng Su - sumeng_1980@126.com; Rui Ma - Marui0000@yahoo.com.cn; Weijun Bai - BWJ815@TOM.COM; Shuyue Xia - SYX262@yahoo.com.cn; Yanduo Jiang - ydjiang202@yahoo.com.cn; Shun Xu - xushun2005@sina.com; Yi Lv - sycdcly@163.com; Xun Li - lixunsy@hotmail.com

* Corresponding author

**Abstract**

**Background:** Excision repair cross-complementing group 1 (ERCC1) and group 2 (ERCC2), and X-ray repair cross-complementing group 1 (XRCC1) proteins play important roles in the repair of DNA damage and adducts. Single nucleotide polymorphisms (SNPs) of DNA repair genes are suspected to influence treatment effect and survival of cancer patients. This study aimed to investigate the relationship between polymorphisms in ERCC2, ERCC1 and XRCC1 genes and survival of non-smoking female patients with lung adenocarcinoma.

**Methods:** We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method to evaluate SNPs in ERCC2, ERCC1 and XRCC1 genes among 257 patients.

**Results:** The overall median survival time (MST) was 13.07 months. Increasing numbers of either ERCC1 118 or XRCC1 399 variant alleles were associated with shorter survival of non-smoking female lung adenocarcinoma patients (Log-rank P < 0.001). The adjusted hazard ratios (HRs) for individuals with CT or TT genotype at ERCC1 Asn118Asn were 1.48 and 2.67 compared with those with CC genotype. For polymorphism of XRCC1 399, the HRs were 1.28 and 2.68 for GA and AA genotype. When variant alleles across both polymorphisms were combined to analysis, the increasing number of variant alleles was associated with decreasing overall survival. Using the stepwise Cox regression analysis, we found that the polymorphisms in ERCC1 and XRCC1, tumor stage and chemotherapy or radiotherapy status independently predicted overall survival of non-smoking female patients with lung adenocarcinoma.

**Conclusions:** Genetic polymorphisms in ERCC1 and XRCC1 genes might be prognostic factors in non-smoking female patients with lung adenocarcinoma.
Background
Lung cancer is a major cause of cancer mortality worldwide, and more than a million people in the world die from the disease each year [1]. Adenocarcinoma accounts for about 25% to 40% of all lung cancers, and is now the most common form of lung cancer in women [2]. It is the most frequent subtype occurring in those who have never smoked. Five-year survival rate of lung cancer is at only 15% in the United States and even lower in China [3]. Genetic factors are considered to influence the treatment effectiveness of lung cancer [4], and thus affect the prognosis of patients. There are some molecular markers showing potential as therapeutic and prognostic indicators, but none could be used into clinical practice [5,6]. Of these factors, DNA repair capacity (DRC) is an important one. Several studies have shown associations between inefficient DNA repair and lung cancer risk [7,8]. It is also possible that individual DRC can affect the survival of lung cancer patients. It has been speculated that single nucleotide polymorphisms (SNPs) in DNA repair genes may change gene expression and activity, hence influence the effectiveness of cancer treatment and survival of patients [9]. To test above possibility, we assess the relationship between survival of lung adenocarcinoma patients and SNPs in three DNA repair genes, including excision repair cross-complementing group 1 (ERCC1) and group 2 (ERCC2), and X-ray repair cross-complementing group 1 (XRCC1). ERCC2 is located in chromosome 19q13.2-13.3 and codes for an evolutionarily conserved helicase, a subunit of TFIIH complex which is essential for transcription and nucleotide excision repair (NER). The common SNPs of ERCC2 gene is at exon 4, without amino acid change—Asn/Asn, rs11615. The study showed that ERCC1 and ERCC2 mRNA levels were correlated with DRC [10]. XRCC1 protein plays a central role in base excision repair (BER) pathway by interacting with other DNA repair proteins. The most extensively studied SNP of XRCC1 gene is at exon 399 (G > A substitution at position 39931, exon 23, Lys>Gln, rs13181) and codon 312 (G >A substitution at position 23951, exon 10, Asp>Asn, rs1799793). ERCC1 is also located in chromosome 19q13.2-13.3 and codes for a leading protein in NER, responsible for recognition of DNA damage and removal of the damaged nucleotides. The common SNP of ERCC1 gene is at exon 118 (C > T substitution at exon 4, without amino acid change—Asn/Asn, rs11615).}

Methods
Patient recruitment and follow-up
All patients were from the ongoing study of lung cancer in non-smoking females, which started from July, 1999 in Shenyang city, China. The human investigations were approved by the Institutional Review Board of China Medical University, and informed consent was obtained from each participant or their representatives if direct consent could not be obtained. All patients were unrelated ethnic Han Chinese. Individual with a total of 100 cigarettes in his lifetime was defined as a smoker, otherwise he was considered as a non-smoker. Each participant donated 10 ml venous blood and was interviewed to collect demographic data and clinical information. For this study, we identified 285 patients who were diagnosed with histologically confirmed lung adenocarcinoma (stage I-IV) between the years 1999 and 2004. The year 2004 was chosen as the last year of eligibility in order that all participants have adequate follow-up. About the histological subtype of 285 patients, 228 were diagnosed using surgical specimen and 57 using exfoliated cells of lung adenocarcinoma patients whose tumor stages were determined by thoracic imageology.

DNA extraction and genotyping
Genomic DNA samples were extracted by guanidine hydrochloride (GuHCl) method. SNP was analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method as described previously [13]. The PCR primers (Takara Biotechnology Dalian Co., Ltd., China) for amplifying DNA fragment containing the ERCC2 751, ERCC2 312, ERCC1 118 and XRCC1 399 sites were 751 F5'-GCC CGC TCT GGA TTA TAC G-3' and R5'-TAA TAT CGG GGC TCA CCC TGC AGC ACT TCC T-3', 312 F5'-TG TGT GTG GCT GCC CCG ATC TGT TGG TCT-3' and R5'-TAA TAT CCG GCC TCA CCC TGC AGC ACT TCC T-3', 118 F5'-AGG ACC ACA GGA CAC GCA GA-3' and R5'-CAT AGA ACA GTG CAG AAC AC-3', 399 F5'-TTC TGG TCG TTT CTC TGT GTC CA-3' and R5'-TCC TCC AGC CTT TTC TGA TA-3', respectively. The PCR products were
digested with restriction enzyme (New England Biolabs, Beverly, MA) PstI (for \textit{ERCC2} 751), StyI (for \textit{ERCC2} 312), BsrDI (for \textit{ERCC1} 118) and MspI (for \textit{XRCC1} 399) to determine the genotypes. A 10% masked and random sample of patients was tested twice by different persons, and the results were found to be concordant for all of the masked duplicate sets.

**Statistical analysis**

The associations between overall survival and demographic characteristics, clinical features, and genetic SNPs were estimated using the Kaplan-Meier method and Log-rank test. Survival time was calculated from the date of cancer diagnosis to the date of death or last follow-up. In some analyses, we combined the heterozygous genotype with the homozygous rare genotype as the particular group in order to increase sample size. Univariate and multivariable Cox proportional hazards regression models were performed to estimate crude hazard ratio (HR) or adjusted HR and their 95% confidence intervals (CIs). The stepwise Cox regression model was also used to determine factors predictive of cancer prognosis, with a significant level of P < 0.05 for entering and P > 0.10 for removal of the variables. All the statistical analyses were performed using Statistical Product and Service Solutions (SPSS) v13.0.

| Table 1: Patient characteristics and clinical features |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Patients (%)    | MST (mon)       | Log-rank P value| HR (95% CI)     |
| Age (years)     |                 |                 |                 |                 |
| ≤50             | 105 (40.9)      | 14.93           | 0.493           | 1.00            |
| >50             | 152 (59.1)      | 12.47           | 1.10 (0.84-1.45)|                 |
| Tumor stage     |                 |                 |                 |                 |
| I               | 44 (17.1)       | 45.80           | < 0.001         | 1.00            |
| II              | 34 (13.2)       | 18.57           | 2.48 (1.36-4.53)|                 |
| III             | 149 (58.0)      | 11.07           | 3.46 (2.14-5.61)|                 |
| IV              | 30 (11.7)       | 9.07            | 4.66 (2.59-8.37)|                 |
| Surgical operation |             |                 |                 |                 |
| No              | 53 (20.6)       | 6.20            | 0.005           | 1.00            |
| Yes             | 204 (79.4)      | 15.50           | 0.61 (0.44-0.86)|                 |
| Chemotherapy or radiotherapy | |                 |                 |                 |
| No              | 31 (12.1)       | 9.00            | 0.803           | 1.00            |
| Yes             | 226 (87.9)      | 13.30           | 0.94 (0.59-1.51)|                 |

Abbreviation: MST, median survival time; HR, hazard ratio; CI, confidence interval.

AHR adjusted for age, stage, surgical operation and chemotherapy or radiotherapy.

BLog-rank P and HR were calculated compared with wild genotype (AA) of \textit{ERCC2} 751 polymorphism.

CLog-rank P and HR were calculated compared with wild genotype (GG) of \textit{ERCC2} 312 polymorphism.

| Table 2: Genetic polymorphisms in DNA repair genes and survival of patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Genotype        | Patients (%)    | MST (mon)       | Log-rank P       | HR (95% CI)     | Adjusted HR (95% CI) |
| \textit{ERCC2} Lys751Gln | | | | |
| AA              | 194 (75.5)      | 14.50           | 1.00             | 1.00            |
| AC              | 59 (23.0)       | 10.40           | 0.40 (1.01-1.94) | 1.32 (0.95-1.84)|                 |
| CC              | 4 (1.5)         | 12.27           | 0.73 (0.23-2.28) | 0.79 (0.25-2.48)|                 |
| AC/CC           | 63 (24.5)       | 10.97           | 1.33 (0.97-1.82) | 1.27 (0.92-1.75)|                 |
| \textit{ERCC2} Asp312Asn | | | | |
| GG              | 229 (89.1)      | 13.23           | 1.00             | 1.00            |
| GA              | 27 (10.5)       | 12.40           | 0.95 (0.60-1.49) | 0.95 (0.60-1.49)|                 |
| AA              | 1 (0.4)         | 4.40            | 8.25 (1.12-60.60)| 8.55 (1.14-64.25)|                 |
| GA/AA           | 28 (10.9)       | 9.83            | 0.99 (0.63-1.54) | 0.99 (0.63-1.54)|                 |
| \textit{ERCC1} Asn118Asn | | | | |
| CC              | 140 (54.5)      | 17.23           | 1.00             | 1.00            |
| CT              | 94 (36.6)       | 11.07           | < 0.001          | 1.58 (1.18-2.12)| 1.48 (1.10-1.99)|                 |
| TT              | 23 (8.9)        | 6.20            | 2.82 (1.72-4.62) | 2.67 (1.62-4.40)|                 |
| \textit{XRCC1} Arg399Gln | | | | |
| GG              | 117 (45.5)      | 19.10           | 1.00             | 1.00            |
| GA              | 102 (39.7)      | 10.40           | < 0.001          | 1.41 (1.05-1.91)| 1.28 (0.95-1.74)|                 |
| AA              | 38 (14.8)       | 9.23            | 2.33 (1.56-3.47) | 2.68 (1.79-4.02)|                 |

Abbreviation: MST, median survival time; HR, hazard ratio; CI, confidence interval.

AHadjusted for age, stage, surgical operation and chemotherapy or radiotherapy.

BLog-rank P and HR were calculated compared with wild genotype (AA) of \textit{ERCC2} 751 polymorphism.

CLog-rank P and HR were calculated compared with wild genotype (GG) of \textit{ERCC2} 312 polymorphism.
Results

Patient characteristics
The mean age of patients was 51.16 ± 9.48 years (range 18-75 years). The distribution of characteristics and clinical features of 257 lung adenocarcinoma patients were shown in Table 1. There were 206 deaths. The overall median survival time (MST) was 13.07 months. As Table 1 showed, patients with advanced cancer or without surgical operation had significantly shorter MSTs (Log-rank P < 0.05). Univariate Cox regression analysis suggested that the risks of death of lung adenocarcinoma were increased in patients with stage II, III and IV compared with those with stage I (HRs were 2.48, 3.46 and 4.66, respectively). The result also showed that the patients undergoing surgical operation had a decreased risk of death (HR = 0.61).

Genotype frequencies of genetic polymorphisms
Table 2 showed the genotype frequencies of four SNPs in 257 patients. All genotype frequencies of these four polymorphisms were found to be in Hardy-Weinberg equilibrium. The variant allele frequencies were 13.0% for ERCC2 751, 5.6% for ERCC2 312, 27.2% for ERCC1 118 and 34.6% for XRCC1 399 polymorphism. No associations were found between genotypes and age, tumor stage, surgical operation, chemotherapy or radiotherapy (data not shown).

Genetic polymorphisms and survival of patients
The associations between genotypes of four SNPs and survival of non-smoking female patients with lung adenocarcinoma were suggested in Table 2. Patients with CT or TT genotype at ERCC1 Asn118Asn showed significantly shorter survival time than those with CC genotype (11.07, 6.20 months versus 17.23 months) (Log-rank test, P < 0.001). In terms of XRCC1 399 polymorphism, the difference in the MSTs among patients with GG (19.10 months), GA (10.40 months) and AA (9.23 months) was statistically significant (Log-rank test, P < 0.001). However no associations were found between two SNPs of ERCC2 gene and the overall survival of patients.

In the further analysis, lung adenocarcinoma patients were stratified by stage. There were no significant differences in survival times of stage I-II patients with variant genotypes of four SNPs. For patients with stage III or IV, Kaplan-Meier analyses proved that individuals with heterozygous variant or homozygous variant genotype at ERCC1 Asn118Asn or XRCC1 Arg399Gln had shorter MSTs than those with wild genotype (Figure 1). The MSTs of patients with CC, CT and TT genotype at ERCC1 Asn118Asn were 14.53, 9.57 and 5.03 months and the difference was significant (Log-rank P < 0.001). For XRCC1 399 polymorphism, patients with GA or AA genotype lived shorter than those with GG genotype and corresponding MSTs were 9.57, 4.27 and 14.20 months (Log-rank P < 0.001). There were no differences in MSTs according to genotypes of ERCC2 751 or 312 polymorphism.

In the Cox regression model, after adjusting for age, tumor stage, surgical operation and chemotherapy or radiotherapy, variant genotypes of ERCC1 118 or XRCC1 399 polymorphism were associated with higher risks of death for non-smoking female patients with lung adenocarcinoma (Table 2). With the CC genotype at ERCC1 Asn118Asn being the reference, the HR for CT genotype was 1.48 (P = 0.009) compared to 2.67 (P < 0.001) in the TT genotype. In terms of XRCC1 399 polymorphism, we found that compared with those carrying GG genotype, the HRs were 1.28 (P = 0.109) and 2.68 (P < 0.001) for individuals with GA and AA genotype, respectively.

In addition to evaluating the genetic polymorphisms separately, we studied the association between patients’ survival and the total number of variant alleles of ERCC1 and...
XRCC1 polymorphisms (Table 3). In the double homozygous group (0 variant allele), the overall MST was 25.10 months. As the number of variant alleles increased, the MSTs decreased to 13.07, 9.27, 6.30 and 3.87 months. The Log-rank test was statistically significant (P < 0.001). The HRs for individuals with 1, 2, 3, 4 variant allele(s) were 1.52, 2.33, 2.98 and 9.24 compared with those carrying 0 variant allele. Besides, the effect was also conspicuous for the patients with stage III-IV (Log-rank P < 0.001) but not significant for those with stage I-II (P = 0.145).

Furthermore we evaluated an interaction effect of the two SNPs on the survival of non-smoking female patients with lung adenocarcinoma. We found that individuals carrying both ERCC1 Asn118Asn or XRCC1 Arg399Gln variant alleles were at a higher death risk of lung adenocarcinoma than those with only one of them (adjusted HRs were 2.44, 1.79 and 1.64, respectively) (Table 4).

Stepwise Cox proportional hazard analysis was used to study the relationship between factors including demographic characteristics, clinical features and genetic SNPs and survival of non-smoking female patients with lung adenocarcinoma. Four variables (stage, chemotherapy or radiotherapy, ERCC1 118 and XRCC1 399 polymorphisms) were included in the Cox regression model (Table 5).

**Discussion**

In this study, we explored the relationship between SNPs of three DNA repair genes and survival of non-smoking female patients with lung adenocarcinoma in China. In WHO Western Pacific Region, lung cancer was the commonest cancer cause of death in women and the proportion of adenocarcinoma in lung cancer has increased quickly in both genders over the last few decades [14]. So we focused our study on lung adenocarcinoma in females who were requested to be non-smokers in order to control the confounding influence of smoking. This study showed that being advanced stage, without chemotherapy or radiotherapy, ERCC1 Asn118Asn or XRCC1 Arg399Gln polymorphism were proved to be unfavorable prognostic factors for lung adenocarcinoma in Chinese non-smoking women. However, the associations have not been found between ERCC2 751 or 312 polymorphism and survival of lung adenocarcinoma.

The XRCC1 protein is considered to play an important role in both base excision repair and single-strand break repair. XRCC1 Arg399Gln polymorphism was the commonest one among more than 60 validated SNPs in XRCC1 gene and showed no major variations by ethnicity [15]. This polymorphism has been suggested to be a risk
factor for the development of lung cancer [16-20]. In our previous study, a significant association between XRCC1 399Gln/Gln genotype and risk of lung cancer in Chinese non-smoking women was found [21]. In the present study, we found that non-smoking female lung adenocarcinoma patients with AA genotype at XRCC1 Arg399Gln had a shorter survival time (9.23 months vs. 19.10 months) and higher risk of death (adjusted HR = 2.68, 95%CI = 1.79-4.02) than those with GG genotype. It is consistent with other studies, although those results were obtained from the subjects of all genders, smoking status and histopathologic subtypes [22-24].

As for ERCC1 Asn118Asn polymorphism, we observed that the patients with CT or TT genotype showed a significantly shorter survival time than those with CC genotype (11.07 and 6.20 versus 17.23 months). In the multivariable Cox regression, ERCC1 118 variant genotype (CT/TT) remained prognostic factors of lung adenocarcinoma (HR = 1.60, P value = 0.001). To date, only a few studies have examined the relationship between ERCC1 polymorphism and survival of lung cancer, and they didn’t control the influence of gender, smoking status and histopathologic subtypes [25-27]. In terms of chemotherapy response, a few studies suggested an association between ERCC1 Asn118Asn polymorphism and response to platinum-based treatment of lung cancer [25,27,28]. Although these studies have shown possible relationship between ERCC1 polymorphism and effectiveness of cancer treatment or survival of cancer patients, the biological effect of this synonymous SNP is unclear.

In our study, no associations were found between the overall survival and two SNPs of ERCC2 gene. This is consistent with other studies [22,25,29], but there are studies showing an opposite effect [24]. The explanation for these discordant results remains to be elucidated.

Many clinical features may play important roles in the survival of cancer patients. The multivariable Cox regression in this study showed that being advanced stage (III+IV) and without chemotherapy or radiotherapy treatment were independent unfavorable prognostic factor for lung adenocarcinoma in non-smoking female population. Surgical status wasn’t included in the stepwise Cox model maybe because the surgical treatment is decided by the patients’ conditions such as tumor stage and histopathologic subtypes, so the surgical status may be a dependent variable but not an independent prognostic factor.

Genetic polymorphisms as either prognostic or predictive biomarkers have many advantages, especially in the advanced cancer setting. First of all, the biological specimen for detecting SNP is easily to obtain. Second, the detecting method is simple, precise and practical. Finally, in the advanced cancer setting, diagnoses are made using specialized and mostly body-harmed method; otherwise SNP detecting can avoid these problems.

In conclusion, this study analyzed four SNPs in three DNA repair genes in relation to survival of non-smoking female patients with lung adenocarcinoma in China. The results suggested that besides clinical features such as tumor stage and chemotherapy or radiotherapy treatment, polymorphisms of ERCC1 Asn118Asn and XRCC1 Arg399Gln were associated with survival of patients. Because DNA repair is a complex system including many pathways and genes, larger studies with more genetic polymorphisms, even haplotypes, in different ethnic populations and the functional or biological relevance of these polymorphisms are needed to confirm our conclusions.

**Conclusions**

Genetic polymorphisms in ERCC1 and XRCC1 genes might be prognostic factors in non-smoking female patients with lung adenocarcinoma.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

ZY, BZ, ML, and PG performed the analysis, interpreted the data and drafted the manuscript. BZ, QH, and ZC contributed to the design and coordination of the study and helped to draft the manuscript. XLL, RM, WB, SX, YJ, SX, YL, and XL participated in data collection, DNA isolation and interpreted the data. XX, XLL, ZY and MS participated in SNP genotyping and revised the manuscript. All authors read and approved the final manuscript.

**Table 5: Stepwise Cox regression analysis on survival of lung adenocarcinoma**

| Variable | β       | SEM       | HR   | 95%CI      | P value |
|----------|---------|-----------|------|------------|---------|
| stage (III+IV vs. I+II) | 0.661   | 0.102     | 1.94 | 1.59-2.36  | < 0.001 |
| chemotherapy or radiotherapy | -1.095  | 0.307     | 0.34 | 0.18-0.61  | < 0.001 |
| ERCC1 118 (CT/TT vs. CC) | 0.473   | 0.142     | 1.60 | 1.22-2.12  | 0.001   |
| XRCC1 399 (GA/AA vs. GG) | 0.405   | 0.143     | 1.50 | 1.13-1.98  | 0.005   |

Abbreviation: SEM, Standard error of difference; HR, hazard ratio; CI, confidence interval. β, regression coefficient.
Acknowledgements

We are grateful to patients for their participation. We would like to thank all the personnel at the hospitals and Shenyang CDC in our study. This study was supported by National Natural Science Foundation of China (No. 30471493), Natural Science Foundation of Liaoning Province (No. 20072103), Provincial Education Department of Liaoning (No. 2008232) and China Medical Board (No. 00726).

References

1. Guilbert JJ: The world health report 2002—reducing risks, promoting healthy life. Educ Health (Abingdon) 2003, 16:230.
2. Tamboli P, Ro JY: Pathologic evaluation of lung cancer. In lung cancer Edited by: Fossella FV, Komaki R, Potosnak JB. New York: Springer-Verlag; 2002:73-74. [Buzdar AU and Freedman RS (Series Editor): The M. D. Anderson Cancer Care Series.]
3. Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 2002, 55:74-108.
4. Viktorsson K, De Petris L, Lewensohn R: The role of p53 in treatment responses of lung cancer. Biochem Biophys Res Commun 2005, 331:868-880.
5. Moradi LR, Misso NL, Dlamini Z, Bhoola KD: Molecular genetics and mechanisms of apoptosis in carcinomas of the lung and pleura: therapeutic targets. Int Immunopharmacol 2007, 7:1934-1947.
6. Sato M, Shames DS, Gazdar AF, Minna JD: A translational view of the molecular pathogenesis of lung cancer. J Thorac Oncol 2007, 2:327-343.
7. Wei Q, Cheng L, Amos CI, Wang LE, Guo Z, Hong WK, Spitz MR: Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J Natl Cancer Inst 2000, 92:1764-1772.
8. Chen L, Spitz MR, Hong WK, Wei Q: Reduced expression levels of nucleotide excision repair genes in lung cancer: a case-control analysis. Carcinogenesis 2000, 21:1527-1530.
9. Bernig T, Chanock SJ: Challenges of SNP genotyping and genetic variation: its future role in diagnosis and treatment of cancer. Expert Rev Mol Diagn 2006, 6:319-331.
10. Vogel U, Dybdahl M, Fretz G, Nexø BA: DNA repair capacity: inconsistency between effect of over-expression of five NER genes and the correlation to mRNA levels in primary lymphocytes. Mutat Res 2000, 461:147-150.
11. Abdel-Rahman SZ, El-Zein RA: The 399Gln polymorphism in the DNA repair gene XRCC1 modulates the genotoxic response induced in human lymphocytes by the tobacco-specific nitrosamine NNK. Cancer Lett 2000, 159:63-71.
12. Dimou L, Pali D, Pefkos M, Guerrera S, Carturan S, Celentano E, Krogg V, Munna A, Tumino R, Polidoro S, Piazza A, Vines P: XRCC1, XRCC3, XPD genes, polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. Carcinogenesis 2001, 22:1437-1445.
13. Yin Z, Li M, Cui Z, He Q, Zhou B: Relationship between ERCC2 polymorphism and risk of lung cancer in Chinese non-smoker. Chinese Journal of Cancer Research 2007, 19:184-188.
14. Boyle P, Levin B: World Cancer Report 2008 WHO: WHO press; 2008.
15. Hung RJ, Hall J, Brennan P, Boffetta P: Genetic polymorphisms in the base excision repair pathway and cancer risk: a huge review. Am J Epidemiol 2005, 162:925-942.
16. Zienoldiny S, Campa D, Lind H, Ryberg D, Skaug V, Stangeland L, Phillips DH, Czaniz F, Haugan A: Polymorphisms of DNA repair genes and risk of non-small cell lung cancer. Carcinogenesis 2008, 27:560-567.
17. Shera M, Berndt SI, Rothman N, Mumford JL, He X, Yeager M, Welch R, Chanock S, Keohavong P, Donahue M, Zheng T, Caporaso N, Lan Q: Polymorphisms in the DNA base excision repair genes APE1 and XRCC1 and lung cancer risk in Xuan Wei, China. Anticancer Res 2005, 25:537-542.
18. De Ruyck K, Szumkessel M, De Rudder I, Dehoeore A, Vral A, Claes K, Velghe A, Van Meerbeeck J, Thierens H: Polymorphisms in base-excision repair and nucleotide-excision repair genes in relation to lung cancer risk. Mutat Res 2007, 631:101-110.
19. Zhou W, Liu Q, Miller D, Thorun SW, Xu LL, Wain JC, Lynch TJ, Su L, Christiani DC: Polymorphisms in the DNA repair genes XRCC1 and ERCC2, smoking, and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2003, 12:359-365.
20. Park JY, Lee SY, Jeon HS, Bae NC, Chae SC, Joo S, Kim CH, Park JH, Kam S, Kim IS, Jung TH: Polymorphism of the DNA repair gene XRCC1 and risk of primary lung cancer. Cancer Epidemiol Biomarkers Prev 2002, 11:23-27.
21. Li M, Yin Z, Guan P, Li X, Cui Z, Zhang J, Bai W, He Q, Zhou B: XRCC1 polymorphisms, cooking oil fume and lung cancer in Chinese women nonsmokers. Lung cancer 2008, 62:145-151.
22. Sreeja L, Symalwa VS, Symalva V, Harharian S, Raveendran PB, Viyaparakshina RV, Madhavan J, Anilkhalil R: Prognostic importance of DNA repair gene polymorphisms of XRCC1 Arg399Gln and XPD Lys749Gln in lung cancer patients from India. J Cancer Res Clin Oncol 2008, 134:645-652.
23. Wu X, Gu J, Wu TT, Swisher SG, Liao Z, Correa AM, Liu J, Etzel CJ, Amos CI, Huang M, Chiang SS, Milas L, Hittelman WN, Ajani JA: Genetic variations in radiation and chemotherapy drug action pathways predict clinical outcomes in esophageal cancer. J Clin Oncol 2006, 24:3789-3798.
24. Gurubhagavatula S, Liu G, Park S, Zhou W, Su L, Wain JC, Lynch TJ, Neuberg DS, Christiani DC: XPD and XRCC1 genetic polymorphisms are prognostic factors in advanced non-small-cell lung cancer patients treated with platinum chemotherapy. J Clin Oncol 2004, 22:2594-2601.
25. Ryu JS, Hong YC, Han HS, Lee JE, Kim S, Park YM, Kim YC, Hwang TS: Association between polymorphisms of ERCC1 and XPD and survival in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy. Lung Cancer 2004, 44:311-316.
26. Zhou W, Gurubhagavatula S, Liu G, Park S, Neuberg DS, Wain JC, Lynch TJ, Su L, Christiani DC: Excision repair cross-complementation group I polymorphisms predict overall survival in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. Clin Cancer Res 2004, 10:4939-4943.
27. Islas D, Sarrias C, Rosell R, Alonso G, Domene M, Taron M, Lopez-Vivanco A, Camps C, Botia M, Nuñez L, Sanchez-Ronco M, Sanchez JJ, Lopez-Brea P, Barneto I, Paredes A, Medina B, Artal A, Lianes P: Single nucleotide polymorphisms and outcome in docetaxel-cisplatin-treated advanced non-small-cell lung cancer. Ann Oncol 2004, 15:1194-1203.
28. Su D, Ma S, Liu P, Jiang Z, Lv W, Zhang, Y, Deng Q, Smith S, Yu H: Genetic polymorphisms and treatment response in advanced non-small cell lung cancer. Lung Cancer 2007, 56:281-288.
29. Giachino DF, Ghio P, Regazzoni S, Mandrile G, Novello S, Selvaggi G, Gregori D, DeMarchi M, Scagliotti GV: Prospective assessment of XPD Lys749Gln and XRCC1 Arg399Gln single nucleotide polymorphisms in lung cancer. Clin Cancer Res 2007, 13:2876-2881.

Pre-publication history

The pre-publication history for this paper can be accessed here:
http://www.biomedcentral.com/1471-2407/9/439/prepub

Publish with BioMed Central and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."
Sir Paul Nurse, Cancer Research UK

Your research papers will be:
- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright