Allelic polymorphisms as biomarkers of risk and outcome in colorectal and head and neck cancer

PhD thesis

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INTRODUCTION:

Malignancies of the gastrointestinal tract are among the most frequent malignant diseases in Hungary . Cancer of the colorectal region is the second most frequent cause of death from malignant diseases. Traditional gastronomical habits which include fatty and dietary fiber deficient foods and the popularity of meats preserved by smoke explain the high prevalence of these diseases .

Head and neck cancer is a malignant disease of the upper aerodigestive tract (oral, pharyngeal, and laryngeal regions); histologically it is commonly squamous cell carcinoma. In 2006, 70,200 cases were registered in the European Union, which is 3.1% of the total number of cancer cases. The number of fatalites caused by this type of cancer was 25,300 in the same year. All together, cancer of the head and neck region is the third most common cause of cancer death among men in Hungary. Unfortunately the incidence and mortality of head and neck cancer shows an increasing tendency. In 1975, only 462 patients died from head and neck cancer. This means that the mortality of this cancer has increased by 387 % in the last thirty-two years in Hungary.

Metabolizing enzymes:

In our present study we aim to examine the relationship between certain allelic polymorphisms and related cancer risk, and its influence on the survival of the patients. Our area of interest is in two allelic polymorphisms of glutathione-*S*-transferases, the GSTM1 and GSTT1 metabolizing enzymes. Glutathione-*S*-transferases (GSTs) are involved in the metabolism of endogenous and exogenous carcinogenic substances, such as environmental carcinogens, reactive oxygen species and chemotherapeutic agents, by catalyzing reactions between glutathione and electrophilic compounds and is an important means of cellular protection against mutagenic factors. In humans, GST enzymes are divided into five subclasses: alpha (α), mu (μ), pi (π), theta (θ) and zeta (ζ). GSTM1, belonging to the μ class is located on chromosome 1, while GSTT1, belonging to the θ class, is located on chromosome 22. GSTM1 products catalyze the conjugation of glutathione to epoxide derivatives of polycyclic aromatic hydrocarbons, which are found in tobacco smoke and in smoked meats in high concentration. GSTT1 products are involved in activation and

detoxification reactions and catalyze the conjugation of industrial chemicals with glutathione.

The null genotype of these genes (deletions of both paternal and maternal alleles) causes the lack of GSTM1 and GSTT1 proteins which results in an increased risk of development of certain types of cancers. Polymorphisms in GSTM1 and GSTT1 may modify the risk of colorectal cancer, and may be important in determining an individual's susceptibility to colorectal cancer.

P53 tumor suppressor gene:

Another target of our study was to investigate the influence of p53 on colon cancer. P53 is a tumor-supressor gene that plays an important role in controlling cell cycle regulation and inhibiting clonal expansion. P53 is one of most frequently mutated genes in malignant diseases. Several polymorphisms have been registered in the p53 gene locus. One of the most important polymorphisms of this area is in codon 72 of exon 4 coding for the Arg (72Arg: CGC), or Pro (72Pro: CCC) variant. The Arg variant has been shown to induce apoptosis with higher efficacy than the Pro variant. Several studies found a relationship between p53 aberration and malignancies, including colon carcinoma.

XRCC1 (X-ray repair cross complementing) gene:

Carcinogenic metabolites of tobacco and alcohol cause direct DNA damage and, in addition, produce oxidative stress which also contributes to the carcinogenic process. Naturally, genetic susceptibility plays an important role in the development of malignant disease. A multiplex mechanism protects against DNA lesions inside cells. Base damage and single-strand breaks (SSBs) of DNA are the most frequent DNA lesions and they are repaired through base excision repair (BER) mechanisms.

X-ray repair cross complementing 1 (XRCC1) protein plays an important role in the BER pathway. The observation that XRCC1 deficiency in mice is lethal in the embryonic stage supports the theory that the function of XRCC1 is a key factor in DNA repair. Mutations in the XRCC1 gene are known to contribute to the development of human

tumours. Based on data from the literature, two SNPs might be associated with the development of malignant diseases: Arg194Trp in exon 6 and Arg399Gln in exon 10.

In our study, we tested the effect of allelic polymorphisms GSTM1, GSTT1 and p53 in colorectal cancer, and XRCC1 polymorphisms in head and neck cancer in the Hungarian population.

These polymorphisms may be able to modify the risk of cancer development in humans and might also have an effect on the clinical outcome of malignant diseases.

OBJECTIVES:

- To determine the distribution of GSTM1 and GSTT1 0/+ alleles among colorectal cancer patients and healthy control individuals. (Effect of GSTM1 and T1 polymorphisms on the risk of development of colorectal cancer.)
- To determine the distribution of Arg/Pro alleles in codon 72 of p53 suppressor gene among colorectal cancer patients and healthy control individuals. (Effect of Arg/Pro in codon 72 of p53 gene on the risk of development of colorectal cancer.)
- Is there any difference among the overall survivals of colorectal patients with different allels of GSTM1, GSTT1 and p53 genes? (Do the examined polymorphisms have any influence on the prognosis of colorectal tumors?) Is there any difference in the effect of these polymorphisms on the survival according to the stage of disease?
- To determine the distribution of different allels of codons 194 and 399 in XRCC1 gene among head and neck cancer patients and healthy control individuals. (Effect of XRCC1 polymorphisms on the risk of development of head and neck cancer.)
- Is there any difference among the overall survivals of head and neck cancer patients with different alleles of XRCC1 gene? (Do the above mentioned polymorphisms have any influence on the prognosis of head and neck tumors?) Is there any difference in the effect of these polymorphisms on the survival according to the stage of disease?

MATERIAL AND METHODS:

Formalin-fixed, paraffin-embedded tissue samples were used for the first part of the study. Samples were collected in the Markusovszky Hospital (Szombathely, Hungary). All colorectal cancer cases were diagnosed as adenocarcinomas. 182 patients were enrolled in our study (127males and 55 females; mean age 63.4 ± 6.4 years). For tumor staging, Dukes' classification was used: 50 tumor cases were Dukes' A, 50 were Dukes' B, 50 were Dukes' C, and 32 Dukes' D. All patients were followed up. Survival data were taken from the oncological departments' database.

A 2 μl DNA solution separated from paraffin embedded tissue blocks was used for PCR. For amplification the following primers were used:

GSTT1: forward 5'-TT CC T TAC TGG TCC TCA CAT CTC-3',
reverse 5'-TCA CCG GAT CAT GGC CAG CA-3';
and GSTM1: forward 5'-GAA CTC CCT GAA AAG CTA AAG C-3',
reverse 5'-GTT GGG CTC AAA TAT ACG GTG G-3'.

P53 genotyping (codon 72, Arg/Pro polymorphism) was performed using 3' primer: GCAACTGACCGTGCAAGTCA and 5' primers for Arg variant ATGCCAGAGGCTGCTCCCCG and for the Pro variant ATGCCAGAGGCTGCTCCCCC. For the PCR reaction, PCR Master Mix (Promega, Woods Hollow, USA) was used, according to the manufacturer's instructions.

The results were compared with those obtained from age-and sex-matched healthy controls.

189 patients participated in the head and neck cancer study. Sample collection, pathological identification and collection of clinical variables were carried out at the Markusowszky County Hospital Szombathely, Hungary. Men were overrepresented in the population: samples originated from 163 men and only 26 women. The mean age±SD of patients was 57.6± 8.1 years. All patients had a history of smoking and all patients had a histological diagnosis of squamous cell carcinoma. The samples were taken from intraoperatively removed, formalin-fixed and paraffin-embedded blocks of tissue.

For staging of the patients, the American Joint Committee on Cancer (AJCC) criteria were used. According to these criteria, 14 SI, 12 SII, 37 SIII, 32 SIVA and 13 SIVB stage

patients were identified. Patients with head and neck cancer were followed up, with the endpoint being either an interval of 60 months after diagnosis or on the death of the patient.

An age- and sex-matched healthy control group of 102 individuals was used to compare the frequency of polymorphic variants in patients with those of a cancer-free population.

For PCR reaction, 5 µl of DNA solution was used. For genotyping of XRCC1 a PCR - based restriction fragment length polymorphism (RFLP) analysis was used.

Primer sequences for exon 6, Arg194Trp were:

5'- GCC AGG GCC CCT CCT TCA A -3' and

5'- TAC CCT CAG ACC CAC GAG T -3'.

The primers for Arg399Gln on exon 10 were:

5'- TGC TTT CTC TGT GTC CA -3' and

5'- TCC AGC CTT TTC TGA TA -3'.

The amplification was performed in a 25 µl reaction volume, with Platinum PCR Supermix (Invitrogen, Carlsbad, USA), according to the manufacturer's instructions.

The restriction enyzyme *Pvu*II was used to distinguish the Arg194Trp polymorphism and *Msp*I enzyme to distinguish the Arg399Gln polymorphism. The restriction products were analyzed by electrophoresis on a 3% agarose gel containing ethidium bromide.

Additionally, we determined whether a subset of these polymorphisms was related to the overall survival of the patients in the hope that genotypes could be used to predict survival of patients with head and neck cancer. Kaplan-Meier survival analyses were performed after the samples were divided into groups according to gene status. A probability of $P<0.05$ was considered as statistically significant.

Epi Info for Windows program was used for all statistical and graphical purposes.

NEW RESULTS ACCORDING TO THE SCIENTIFIC OBJECTIVES:

- Individuals with GSTM1 0 genotype had a significantly higher risk of development of colorectal cancer (OR: 2.00, 95% CI: 1.29-3.10) In case of GSTT1 the difference has not proved to be statistically significant.

- Individuals bearing a Pro allel of p53 gene had a significantly higher risk of develpoment of colorectal cancer than the Arg/Arg homozygotes (OR: 1.83, 95% CI: 1.14-2.92).
- -The Pro allel of p53 gene proved to be an unfavourable prognostical marker in colorectal cancer petients. Patients bearing the Arg/Arg allel have a significantly longer survival than those with Pro allel (log-rank:12.98, d.f.: 1, p: 0.0003). GSTM1+ and GSTT1+ allels proved to be also favourable prognostic markers, (comparing survivals: GSTM1 log-rank: 8.03, d.f.: 1, p: 0.0046, GSTT1 log-rank: 6.29, d.f.:1, p: 0.0122). In case of all three genotypes, their prognostic values seemed to be most significant in Dukes B stage.
- In case of head and neck cancer, the polymorphism of codon 194 of XRCC1 gene was not proved to be a significant risk factor, but the presence of Gln allel of codon 399 resulted in a higher risk for development of cancer (OR: 1.70, 95% CI: 1.11-2.61).
- The prognosis of the head and neck cancer was more unfavourable – the overall survival was shorter – by patients bearing the Arg/Arg allel on codon 194 of XRCC1 gene (log-rank: 6.37, d.f.: 1, p:0.0116). In case of codon 399, there was no statistically significant association. Both Arg194Trp (p:0.0477) and Arg399Gln (p: 0.0355) polymorphisms resulted in statistically significant overall survival differences at stage III. patients. In other stages there was no significant difference.

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