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The impact of genetic factors on the incidence of multiple primary tumors (MPT) of the head and neck

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Abstract

One of the most troublesome failures in head and neck tumors treatment is the incidence of multiple primary tumors (MPT). The aim of the study was to identity the genetic factors associated with the predisposition of second cancer occurrence. The polymorphisms of genes involved in carcinogen metabolic activation (*CYP1A1, CYP2E1*), detoxication (*GSTM1, GSTT1, GSTM3, NAT2,*) and DNA repair (*XPD* /A35931C-exon 23 and C22541A-exon 6/, *XRCC1* /G28152A-exon 10 and C26304T-exon 6/, *XRCC3*/C18067T/) were studied by PCR-based techniques to analyze genotypes and allele distribution in 84 patients with MPT correlated with 182 subjects with a single tumor of head and neck and 143 cancer-free male volunteers recruited from healthy smokers. Out of 11 polymorphisms examined significant differences between studied groups in *CYP1A1, GSTM1, NAT2* genes, but not at the *CYP2E1, GSTT1, GSTM3, XPD* (exon 23 and 6), *XRCC1* (exon 10 and 6) and *XRCC3* were established. Further, the coexistence of some genotypes/alleles associated with a higher cancer risk, so called 'risk genotypes' was established as an added genetic factor to MPT development. The interpretation of our data indicates that the same group of low-penetration genes is involved in the development of single and multiple primary head and neck cancer but their association with MPT is significantly stronger.

Keywords: Head and neck cancer; Multiple primary tumors; Genetic factor; Genotyping

1. Introduction

Despite recent advances in the diagnostics and treatment of head and neck squamous cell carcinoma (HNSCC) survival rates still remain at unchanged low levels (40–50%). One of the reasons for failure is the development of multiple primary tumors (MPT) with an occurrence assessed of 10–30% or even more [1–3]. The increasing number of MPT in recent decades has become an important therapeutic concern. Patients with multiple cancers are the group characterized by a poor prognosis connected to low cure and survival rates. 5-year survival rates are estimated at between 8–12%; the second cancer

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constitutes approximately 71% of failures, whereas the first tumor is responsible for 15% [2,4]. Aetiology of HNSCC is strongly associated with tobacco smoking and alcohol drinking [5–9], these environmental factors are important but not crucial in the cases, when further independent tumors occur [10–13]. Although tobacco/alcohol abuse plays an important role in cancer risk, only every 10th individual develops cancer and every 100th suffers from MPT. Thus, a contribution of genetic factors seems to be substantial to determine the risk of single and even more of multiple primary cancer. According to current knowledge, a primary target to identify the genetic risk of HNSCC cancer is associated strongly with individual variations in the metabolism of tobacco smoke carcinogens and DNA repair efficacy. Tobacco smoke is a complex mixture of carcinogenic compounds [14], requiring metabolic activation by phase I enzymes followed by detoxification involving phase II enzymes [15]. The activated compounds can exert their carcinogenic effect via DNA adduct formation [16] or generate other DNA lesions. When DNA lesions are located in crucial genes (oncogenes, tumor suppressor genes), not subsequently repaired by DNA repair enzymes, the whole cascade of events may lead to cancer initiation starting from the conversion of DNA lesions to mutations. Polymorphism in genes encoding enzymes involved in activation, detoxification of tobacco smoke carcinogens as well as DNA repair may alter their expression and function, and thereby it becomes an important host factor in determining the variation in the risk of cancer [17–22].

The present study was undertaken to assess the possible association of polymorphisms in genes coding activation (*CYP1A1, CYP2E1*), detoxication (G*STM1, GSTT1, GSTM3, NAT2,*) and DNA repair enzymes (*XPD, XRCC1* and XRCC3) in the risk of multiple cancers of the head and neck.

2. Material and methods

2.1. Subjects

The examined group consisted of 84 patients with multiple primary malignancies. There were two control groups: first completed from patients with a single malignancy and second recruited from healthy smokers (Table 1). The single cancer group included 182 patients with cancers of the larynx, palatine tonsil, tongue, hypopharynx and paranasal

Table 1
Characteristics of studied groups

Characteristics	Multiple tumors *n* (%)		Single cancer *n* (%)	Healthy *n* (%)
Total	84		182	143
Gender				
Men	75 (89.3)		178 (97.8)	143 (100)
Women	9 (10.7)		4 (2.2)	–
Age				
Range	23–84		40–80	50–66
Mean age±SD	62.5±9.2		61.2±9.2	53.1±2.8
Tumor localization	*I cancer focus*	*II cancer focus*		
Larynx	39 (46.3)	27 (32.1)	150 (82.4)	–
Parotid gland	8 (9.5)	11 (13.1)	4 (2.2)	–
Lung	8 (9.5)	5 (6.0)	–	–
Tonsil, soft palate	4 (4.8)	8 (9.5)	14 (7.7)	–
Tongue	4 (4.8)	7 (8.3)	8 (4.4)	–
Paranasal sinuses	3 (3.6)	–	–	–
Nose	2 (2.4)	3 (3.6)	2 (1.1)	–
Skin of the face	2 (2.4)	5 (6.0)	–	–
Auricle	1 (1.2)	3 (3.6)	–	–
Upper lip	1 (1.2)	–	4 (2.2)	–
Esophagus	–	2 (2.4)	–	–
Other localizations	12 (14.3)	13 (15.5)	–	–