Translational Oncology
www.transonc.com
Volume 2 Number 2 June 2009 pp. 84–88 84

Polymorphisms of Metabolizing Enzymes and Susceptibility to Ethmoid Intestinal-type Adenocarcinoma in Professionally Exposed Patients[1]

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Abstract

Intestinal-type adenocarcinoma (ITAC) of ethmoid is a rare tumor associated with occupational exposure to wood and leather dusts. Polymorphisms in xenobiotic metabolizing enzymes play an important role in gene-environment interactions and may contribute to a high degree of variance in individual susceptibility to cancer risk. The aim of this study was to investigate by polymerase chain reaction the role of polymorphisms at *CYP1A1* and *GSTM1* genes in 30 ethmoid ITAC patients and 79 healthy donors. The distribution of Thr/Asn genotype at *CYP1A1* codon 461 was significantly overrepresented among the patients (23.3%; $P = .0422$), whereas the Ile/Val genotype at *CYP1A1* codon 462 was not significantly different between cases and controls ($P = .76$). The *GSTM1* null genotype was not significantly different between cases and control ($P = 1$), but we observed that the combined codon 461 Thr/Asn and *GSTM1* null genotype was overrepresented in the patient group ($P = .0019$). The results reveal that patients with *CYP1A1* codon 461 polymorphism may be at high genetic risk of ITAC and that the risk increases in the presence of combined polymorphism of *CYP1A1* and *GSTM1* null genotype. This strongly suggests that *CYP1A1* codon 461 and *GSTM1* null genotype may be useful in selecting exposed individuals at risk for ethmoid ITAC.

Translational Oncology (2009) 2, 84–88

Introduction

Intestinal-type adenocarcinoma (ITAC) of the ethmoid is a rare tumor characterized by high local aggressiveness, predominance among males, and association with occupational exposure in particular to wood and leather dust [1–3]. Intestinal-type adenocarcinoma is the most common histotype in all European series of patients treated with anterior craniofacial resection [4–6], whereas it is very rare in American series [7–9]. A widespread use of masks and aspiration devices in American furniture industries may probably explain this difference. The standard treatment of this tumor remains surgery and radiotherapy [10], even if recently complemented by chemotherapy [11].

Given the close correlation between ethmoid ITAC and exposure to wood and leather dust, the relationship between polymorphisms of genes involved in the metabolism of xenobiotics and cancer susceptibility is of significant interest because they are thought to predispose the risk of an individual if exposed to a chemical.

Most carcinogens are processed by metabolizing enzymes in two broad steps. The phase I enzymes (CYP450 superfamily) mediate

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[1]This work was supported by grants from the Italian Ministry of Health (Ricerca Finalizzata 2004) and Associazione Italiana per la Ricerca sul Cancro.
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Received 15 December 2008; Revised 30 January 2009; Accepted 20 February 2009

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DOI 10.1593/tlo.08226

the metabolic "activation" of environmental carcinogens that is required for their interactions with DNA and their genotoxic effect. The phase II enzymes (glutathione *S*-transferase, or GST family) are responsible for biotransforming and detoxifying carcinogens. Competition and interplay between phase I and II metabolic pathways modulate the levels of DNA adducts, and so the genetic variability in metabolic activities related to these enzymes may influence the risk of cancer development.

Two polymorphisms of the *CYP1A1* gene, belonging to CYP450 superfamily, have been related to cancer susceptibility: a C → A transition leading to a substitution of threonine for asparagine at codon 461 (Thr461Asn) [12] and an A → G transition leading to a substitution of isoleucine for valine at codon 462 (Ile462Val) [13]. Moreover, GST gene polymorphisms consisting of a structural deletion that confers a null genotype have been associated with a higher risk of cancer [14,15].

A number of groups have investigated the possible association between the polymorphic variants of metabolizing enzymes such as *CYP1A1* and *GSTM1* in oral squamous cell carcinoma (SCC), sometimes with conflicting results. One study of a Japanese patient cohort found that patients with specific polymorphisms in these genes have a genetically higher risk of tumor development [16], whereas no such association was observed in a German population [17]. Considering other tumor types and the smoking habit, it has been reported that the *CYP1A1* Ile462Val variant is associated with a three-fold increased risk of lung carcinoma in Japan [18], although this was not confirmed by a similar study in Finland [19]. It has also been reported that *CYP1A1-GSTM1* polymorphisms are associated with a grater risk of colorectal cancer [20].

The aim of this case-control study was to investigate ethmoid ITACs for polymorphisms of the *CYP1A1* and *GSTM1* metabolizing enzymes. We found (and reported for the first time to the best of our knowledge) that *CYP1A1* codon 461 polymorphism is overrepresented in ITAC patients in comparison with controls, and often associated with the *GSTM1* null genotype, thus suggesting that these polymorphisms may be associated with a high degree of susceptibility to this type of tumor.

Materials and Methods

Study Group

The patients' cohort consisted of a total of 30 patients with histologically documented ITAC of ethmoid, surgically resected at the Fondazione IRCSS Istituto Nazionale Tumori, Milan, between 1988 and 2007.

All patients were male and presented a disease onset mean age of 60 years (range, 41-78 years). Nineteen patients were occupationally exposed to wood dust, and 10 to leather dust; the one remaining showed a nonspecific exposure (Table 1).

The first 15 cases were previously investigated for alterations in the *TP53*, $p14^{ARF}$, $p16^{INK\alpha}$, and *HRAS* genes [21] and for deregulation of the *APC-βcatenin* and *KRAS-BRAF* pathways, along with loss of heterozygosity at 18q [22]. In this study, we applied the same case numeration as that used in our previous studies.

The control group consisted of 79 consecutive blood donors with no history of cancer (a patient/control ratio of approximately 1:2) who were firstly surveyed by means of a questionnaire to determine their suitability to be blood donor and to obtain information about demographic factors. This control group including 79 men (mean age, 53 years; range, 31-70 years) was homogeneous in terms of race (whites) and residence (Italy) without any documented exposure history.

DNA Extraction

For the first 15 patients, the analyses were made using formalin-fixed paraffin-embedded specimens, whereas fixed and/or whole blood samples were available for the remaining patients.

DNA was isolated from formalin-fixed paraffin-embedded tumor sections and peripheral blood following the instructions of DNA purification kit (Qiagen, Chatsworth, CA).

CYP1A1 *Analysis*

The Thr461Asn and Ile462Val polymorphisms were detected by means of polymerase chain reaction (PCR) using primer sequences 5′-AACGGTTTCTCACCCCTGAT-3′ and 5′-GGTCATGTC-CACCTTCACG-3′. The PCR was carried out with 100 ng of genomic DNA in 25 μl of a mixture containing 25 mM $MgCl_2$, 2.5 μl of 1× PCR Buffer (Bionova, Cambridge, United Kingdom), 0.4 μM of each primer, 0.2 mM deoxyribonucleotide triphosphates, and 2.5 U of *Taq* Gold (Applied Biosystems, Foster City, CA). After initial denaturation at 95°C for 8 minutes, amplification was performed for 35 cycles at 95°C (30 seconds), 59°C (30 seconds), 72°C (1 minute), followed by final elongation at 72°C (7 minutes). The PCR products were resolved by means of agarose gel electrophoresis, and DNA fragments were sequenced using an automated DNA sequencer (ABI PRISM, 3100, Genetic Analyzer, Applied Biosystems, Foster City, CA).

Table 1. Gender, Age, Histotype, and Professional Exposure of the Patients Involved in the Study.

N	Age/Gender	Histotype	Professional Exposure
T1	58/M	PTCC II	Leather dust
T2	56/M	PTCC II	Wood dust
T3	75/M	PTCC II	Wood dust
T4	67/M	PTCC II	Wood dust
T5	63/M	AGE	Leather dust
T10	50/M	PTCC II	Wood dust
T11	55/M	AGE	Leather dust
T12	51/M	PTCC II	Wood dust
T13	43/M	PTCC II	Wood dust
T14	78/M	PTCC II + AGE	Leather dust
T16	63/M	PTCC II	Wood dust
T17	49/M	PTCC II	Leather dust
T18	63/M	PTCC II	Wood dust
T19	64/M	SRC	Aspecific
T21	77/M	PTCC II	Wood dust
T22	41/M	PTCC II	Wood dust
T23	64/M	PTCC II	Wood dust
T24	63/M	PTCC II	Leather dust
T26	68/M	AGE	Wood dust
T27	67/M	PTCC II	Wood dust
T28	58/M	PTCC II	Wood dust
T29	69/M	AGE	Leather dust
T30	63/M	PTCC II	Wood dust
T31	68/M	PTCC II	Leather dust
T32	64/M	PTCC II	Wood dust
T33	50/M	PTCC II	Wood dust
T34	72/M	AGE	Leather dust
T35	60/M	PTCC II	Leather dust
T36	51/M	PTCC II	Wood dust
T37	43/M	PTCC II	Wood dust

AGE indicates alveolar-globet cell; *M*, male; *PTCC*, papillary-tubular cylinder cell; *SRC*, signet-ring cell.

Table 2. Distribution of *CYP1A1* and *GSTM1* Polymorphisms among ITAC Patients and Control Subjects, OR Estimates with 95% CL, and Fisher's Exact *P* Values for Testing the Difference in Genotype Distribution between Cases and Controls.

Genotype	Cases		Controls		OR (95% CL)*	*P*
	N	%	*N*	%		
Overall series: 30 cases						
CYP1A1 Thr461Asn						
Thr/Thr	23	76.7	73	92.4	1.00	
Thr/Asn	7	23.3	6	7.6	3.70 (1.13, 12.1)	0.0422
Asn/Asn	0	–	0	–	–	
CYP1A1 Ile462Val						
Ile/Ile	29	96.7	70	92.1	1.00	
Ile/Val	1	3.3	5	6.6	0.48 (0.01, 4.62)	0.7644
Val/Val	0	—	1	1.3	—	
GSTM1						
Positive	11	45.8	34	44.7	1.00	1.000
Null	13	54.2	42	55.3	0.96 (0.35, 2.69)	

*The reference distribution for ORs computation is that of controls.

GSTM1 *Analysis*

The null genotype assay was carried out by a comparative duplex PCR. The primers used to amplify a 230-bp fragment of *GSTM1* gene were 5′-GAACTCCCTGAAAAGCTAAAGC-3′ and 5′-GTTGGGCTCAAATATACGGTGG-3′ [23].

β-Globin gene was amplified in the same reaction as an internal positive control with primers 5′-ACACAACTGTGTTCACTAGC-3′ and 5′-GCAAGACTTCTCCTCAGGAG-3′. Amplification was performed for 35 cycles under the following conditions: 30-second denaturation at 97.5°C, 1-minute primer annealing at 50°C, and 30-second primer extension at 72°C.

Statistical Analysis

The *CYP1A1* and *GSTM1* polymorphisms were described by reporting the absolute frequencies and corresponding percentages of *CYP1A1* codon 461 and 462 and *GSTM1* genotypes in ITAC patients and controls as a whole or in subgroups defined by age (≤60 years or >60 years). *CYP1A1* codon 461 was also analyzed according to the *GSTM1* genotype because it was possible to anticipate an interaction between them.

The observed and expected genotype frequencies in the controls were compared using the Hardy-Weinberg equilibrium theory. The differences in the frequencies of genotypes and the individual alleles between cases and controls, as well as between the subgroups, were assessed using Fisher's exact tests. Exact odds ratios (ORs) and the corresponding 95% confidence limits (CL) were also calculated as a measure of association, with ORs of 1 denoting the absence of association and those more than or less than 1 indicating an overrepresented or underrepresented genotype, respectively, in the cases compared with controls. The possible interaction between *CYP1A1* codon 461 and *GSTM1* genotypes was checked using the Breslow-Day test. All *P* values reported are two-sided, and the threshold used for statistical significance was 5%.

Results

CYP1A1 *Polymorphisms: Thr461Asn and Ile462Val*

Firstly, the analyses were performed on 15 formalin-fixed paraffin-embedded ITAC samples (T1-T21) of which blood samples were not available. Subsequently, we analyzed both fixed tumor and the corresponding blood samples available in four new patients (T22-T26). The genotypes Thr/Thr and Thr/Asn at codon 461 of *CYP1A1* were found in three and one fixed ITACs, as well as in the corresponding blood samples. Thus, we exclusively analyzed the blood samples of 11 additional new ITAC patients (T27-T37).

The distribution of *CYP1A1* codon 461 and 462 polymorphisms in ethmoid ITAC cases and controls is shown in Table 2.

The frequencies of the Thr/Thr, Thr/Asn, and Asn/Asn genotypes at codon 461 in the control group were 92.4%, 7.6%, and 0%, respectively, in agreement with the Hardy-Weinberg equilibrium (exact *P* = 1.00); the corresponding frequencies in the ITAC one were of 76.7%, 23.3%, and 0%, respectively. The overall difference between cases and controls for *CYP1A1* polymorphism at codon 461 was statistically significant (*P* = .0422) and corresponded to a more frequent Asn allele (from 3.8% in controls to 11.7% in the cases). The Thr/Asn genotype was significantly overrepresented among the cases (OR = 3.70; 95% CL, 1.13, 12.1; Figure 1).

The frequencies of Ile/Ile, Ile/Val, and Val/Val genotypes at codon 462 among the controls were 92.1%, 6.6%, and 1.3%, respectively, again in agreement with the Hardy-Weinberg equilibrium (exact *P* = .13), whereas the corresponding figures among the cases were 96.7%, 3.3%, and 0%, respectively. The genotype distribution was not significantly different between cases and controls (*P* = .76).

GSTM1 *Null Genotype Assay*

The analysis was performed in 24 ethmoid ITAC cases owing to an unsuccessful PCR amplification of the other six specimens.

Thirteen ethmoid ITAC patients (54%) carried the *GSTM1* null genotype and 11 (46%) revealed the *GSTM1*-positive genotype (Table 2 and Figure 2). In the control group, 42 (55.3%) of 76 people showed a *GSTM1* null genotype and 34 (44.7%) carried a *GSTM1*-positive genotype (Table 2).

The *GSTM1* null genotype was not significantly different between cases and control (*P* = 1).

CYP1A1 *Codon 461 and* GSTM1 *Interaction*

The distribution of *CYP1A1* codon 461 polymorphism in the cases and controls in relation to *GSTM1* genotype is shown in the Table 3.

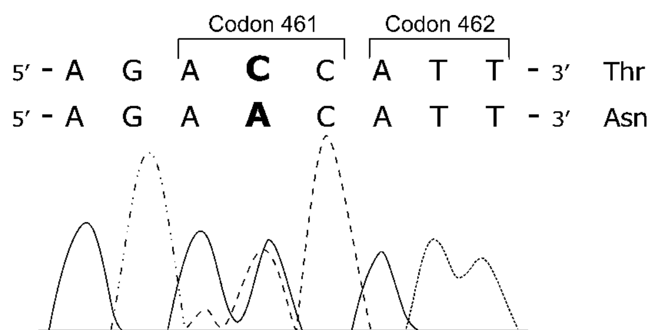

Figure 1. *CYP1A1* polymorphism analysis. The assay was carried out by DNA amplification through PCR and automatic sequencing. The *CYP1A1* nucleotide sequence analysis shows a C → A transition at codon 461 leading to the Thr/Asn genotype in a ITAC sample. The genotype Ile/Ile was present at codon 462.

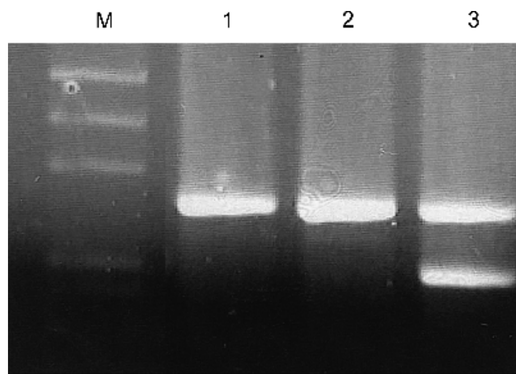

Figure 2. *GSTM1* null genotype analysis. The assay was carried out by a comparative duplex PCR. The *GSTM* gene (lower band) was coamplified with a *β-globin* fragment gene (upper band). A visible specific *GSTM* PCR product in lane 3 indicates the retention of *GSTM*, whereas the absence of the PCR product in lanes 1 and 2 indicates the *GSTM* null genotype. The presence of the housekeeping *β-globin* PCR product in all lanes indicates a good DNA integrity. *M* indicates marker (1-kb ladder).

Among the subjects with *GSTM1*-positive genotype, the distribution of codon 461 polymorphism was similar between cases and controls, whereas the number of people carrying both *CYP1A1* codon 461 polymorphism and *GSTM1* null genotype was significantly higher among the ethmoid ITAC patients than controls ($P = .0019$, OR = 25.6).

The test for interaction between *CYP1A1* codon 461 and *GSTM1* polymorphisms was also significant ($P = .0107$).

Discussion

Ethmoid ITACs are uncommon tumors associated with occupational exposure to wood and other industrial dusts. In a previous study of *TP53*, $p16^{INKa}$, and $p14^{ARF}$ deregulation in a series of ITAC, we observed a high occurrence of gene alterations, in particular, a high rate of $p16^{INKa}$ and $p14^{ARF}$ methylation and *TP53* mutations consisting of a G:C → A:T transition [21], which is a type of mutation that is typically related to carcinogen exposure [24].

Starting from these findings suggesting a causal relationship between the presence of genotoxic agents and gene alterations, we decided to compare the genotypes of the metabolizing enzymes *CYP1A1* and *GSTM1* in these patients with those found in a group of healthy donors to verify whether it is possible to identify subjects with tumor risk.

To the best of our knowledge, this is the first time that the association between *CYP1A1* and *GSTM1* polymorphisms has been evaluated in ITAC.

The results showed that Thr/Asn genotype at *CYP1A1* codon 461 was significantly overrepresented among these patients, suggesting that Thr/Asn genotype could lead to greater susceptibility to ethmoid ITAC. On the contrary, no significant difference was found in the distribution of the *CYP1A1* codon 462 and *GSTM1* null genotype between cases and controls. Little is known about the biological significance of *CYP1A1* codon 461 polymorphism, but, on the basis of the current preclinical evidence [25–27], it is possible that the 461 variant may lead to greater catalytic activity, thus favoring an accumulation of activated carcinogens, which, coupled with a less-efficient detoxification by *GSTM1*, could increase the risk of ethmoid ITAC.

We therefore assessed the relative risks for the combinations of the *CYP1A1* and *GSTM1* genotypes and observed that a combined codon 461 Thr/Asn and *GSTM1* null genotype segregated among ethmoid ITAC patients with an odds ratio of 25.6. This value was higher than that observed for the *CYP1A1* Thr/Asn polymorphism alone (OR = 3.70). Similar results have been reported by Sato et al. [16], whose study revealed an higher occurrence of oral SCC in patients with both polymorphisms, although the *CYP1A1* gene polymorphism was at codon 462 instead of codon 461. These findings indicate that the loss of metabolic balance between the activation of carcinogens by the Thr/Asn genotype of *CYP1A1* and their detoxification by *GSTM1* is synergistic, perhaps involving *CYP1A1* different codons depending on the tumor type.

Polymorphisms of *CYP1A1* and *GSTM1* genes have also been described in colorectal cancer [20], a tumor with histopathological resemblance to ITAC despite a different etiology. Interestingly, we have previously reported genetic alterations in ethmoid ITAC patients that are similar to those observed in colorectal cancer, including *TP53*, *APC*, and *KRAS* mutations and loss of heterozygosity of chromosome 18q [21,22]. In this context, our findings of *CYP1A1* and *GSTM1* polymorphisms in ethmoid ITAC provide further evidence that the morphologic similarities between ITAC and CRC mirror resemblance at a genetic level. However, recent results showed in ITAC absence of microsatellite instability, occurring in 10% to 15% of colorectal cancer [28], and a pattern of gains and losses only partially similar to colorectal cancer [29].

No information of genotype distribution is expected from age because of the small number of patients and from gender because of the preponderance of males among subjects with ITAC of ethmoid due to occupational exposure.

In conclusion, starting from the overrepresentation of the deregulation of the two metabolizing enzymes here investigated in ethmoid ITAC patients, we can assume that individuals with *CYP1A1* codon 461 polymorphism are genetically at high risk of developing ITAC of ethmoid and that the risk increases in the presence of combined genotyping of *CYP1A1* and *GSTM1* genes. Nevertheless, to draw definitive conclusions, these preliminary results need to be confirmed in a larger number of ITAC cases and extended to a control group represented by a cohort of professionally exposed individuals who did not develop the disease. If these future analyses will confirm the role of these two polymorphisms in the ITAC susceptibility, *CYP1A1* codon 461 and *GSTM1* null genotype characterization may be useful in selecting

Table 3. Distribution of *CYP1A1* Codon 461 Polymorphism among ITAC Patients and Control Subjects, OR Estimates with 95% CL, and Fisher's Exact *P* Values for Testing the Difference in Genotype Distribution between Cases and Controls.

GSTM1 Genotype: 24 Cases	Cases		Controls		OR (95% CL)*	$P^{\dagger}$
	N	%	*N*	%		
Positive: 11 cases						
CYP1A1 Thr461Asn						
Thr/Thr	10	90.9	29	85.3	1.00	1.000
Thr/Asn	1	9.1	5	14.7	0.58 (0.01, 6.24)	
Null: 13 cases						
CYP1A1 Thr461Asn						
Thr/Thr	8	61.5	41	97.6	1.00	
Thr/Asn	5	38.5	1	2.4	25.6 (2.23, >50.0)	0.0019

Figures are shown according to the *GSTM1* genotype.
*The reference distribution for ORs computation is that of controls.
$^{\dagger}P = .0107$ for the interaction.

and monitoring individuals at risk for developing ethmoid ITAC due to occupational exposure to carcinogens. Furthermore, as different populations with other tumor types, such as HNSCC and lung carcinoma [15–17], show variations in the distribution of *CYP1A1* and *GSTM1* polymorphisms, it is necessary to verify whether such epidemiological and geographical differences can also be observed in ethmoid ITAC patients.

Acknowledgments

The authors thank Gianni Roncato for photographic assistance. All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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