Larynx Cancer Risk in Relation to Glutathione S-Transferase $M1$ and $Tl$ Genotypes and Tobacco Smoking

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Abstract

Glutathione S-transferase (GST) isoenzymes are involved in the detoxification of several tobacco smoke-derived carcinogens. It is thus conceivable that deficiency in GST activity due to homozygous deletion of the GSTM1 and GSTT1 genes (null genotypes) may modulate susceptibility to smoking-induced cancers. The effects of the GSTM1 and GSTT1 null genotypes on laryngeal cancer risk were evaluated using peripheral blood DNA from 129 larynx cancer patients and 172 noncancer controls, all of whom were regular smokers. Increased larynx cancer risk was related to the GSTM1 null genotype [odds ratio (OR) = 1.6, 95% confidence interval (CI) = 1.0-2.8]. The OR associated with the GSTT1 null genotype was increased, although not significantly (OR = 1.4, 95% CI = 0.7-2.9). Individuals with concurrent lack of GSTM1 and GSTT1 genes had a doubled, although not significant, risk for larynx cancer when compared with those having at least one of these genes (OR = 2.0, 95% CI = 0.8-5.2) and had almost a 3-fold risk (OR = 2.7, 95% CI = 1.0-7.4) when compared with those with both genes. Moreover, a significant interaction between the GSTM1 genotype and levels of tobacco consumption (P < 0.05) was found; the GSTM1 null genotype was associated with an increased risk of larynx cancer among smokers of 20 g/day or less (OR = 2.9, 95% CI = 1.3-6.3) but not among heavier smokers (OR = 1.0; 95% CI = 0.5-2.0). In contrast, the GSTT1 null genotype posed an increased, although not significant, risk among long-term smokers (OR = 2.3, 95% CI = 0.9-5.4).

Introduction

France is among the countries with the highest incidence rates of laryngeal cancer in men (1). Tobacco smoking and alcohol consumption are the major established risk factors for this malignancy (2, 3).

Most environmental carcinogens are metabolized via complex enzymatic mechanisms involving both activation (phase I) and inactivation (phase II) reactions. Some of these reactions are genetically determined, and it is thus conceivable that individual variations in responses to carcinogens may modulate cancer risk.

GSTs detoxify many electrophilic substrates by conjugation with reduced glutathione. Absence of GSTM1 activity, a $\mu$-class enzyme, which detoxifies the reactive metabolites of benzo(a)pyrene and other polycyclic aromatic hydrocarbons (4), is due to homozygous inherited deletion of the gene (5). A similar polymorphism of the GSTT1 gene, encoding a $\theta$-class enzyme, was recently discovered (6). GSTT1 metabolizes various potential carcinogens such as monohalomethanes and ethylene oxide, which are present in cigarette smoke and are ubiquitously used as methylating agents, pesticides, and solvents (7).

Epidemiological data on the role of GSTs in mediating laryngeal cancer risk are very limited; the few studies addressing associations between GSTM1 phenotype/genotype have given inconclusive results (8-10). To date, the effect of the GSTT1 polymorphism in relation to this neoplasm has been investigated in only one study; the frequency of the GSTT1 null genotype in larynx cancer patients was almost twice that in the control group (10). Moreover, interactive effects of GST genotypes and tobacco smoking on larynx cancer risk have been poorly assessed.

In this study, we investigated the effect of the GSTM1 and GSTT1 polymorphisms on the risk of laryngeal cancer among Caucasian smokers, in relation to their smoking habits.

Materials and Methods

Subjects. The study population was from a hospital-based case-control study performed in France (11, 12). Cases were all eligible Caucasian patients with histologically confirmed primary squamous cell carcinoma of the larynx. A control group, frequency matched on age, sex, and hospital, consisted of all eligible Caucasian patients without previous or actual malignant disease. The main diagnoses in the control population were rheumatological (33%), infectious and parasitic diseases (10%), respiratory (9%), cardiovascular (8%), digestive (6%) and traumatological (6%) diseases. The main admission motive was related to general symptoms (7.0%) for the other categories.

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The abbreviations used are: GST, glutathione S-transferase; ICD-O, International Classification of Diseases for Oncology; OR, odds ratio; CI, confidence interval; df, degree of freedom.
Only regular smokers, defined as people having smoked at least 5 cigarettes (or cigars or pipes) per day for at least 5 years, were included. Patients were recruited by one of the seven trained study interviewers who determined eligibility through a short questionnaire. Each interviewer had to include both cases and controls. Detailed information on recent and past tobacco use, alcohol consumption, and occupational exposures was recorded during a personal interview.

**Genotyping.** Blood samples were available from 129 larynx cancer patients and 172 controls fulfilling the criteria described above. They were collected into EDTA tubes and stored at −20°C until total WBC DNA extraction was performed using standard protocols. A multiplex PCR method was used to detect the presence or absence of GSTM1 and GSTTI genes as described previously (13, 14). This PCR method had both GST-specific primer pairs in the same amplification mixture and included a third primer pair for β-globin. The absence of the GSTM1- or GSTTI-specific fragment indicated the corresponding null genotype, whereas the β-globin-specific fragment indicated the presence of amplifiable DNA in the reaction mixture.

**Statistical Analysis.** Primary sites of larynx tumor were coded according to the ICD-O (15) and were subdivided into supraglottic, and glottic/subglottic (ICD-O codes 161.1, 161.0, and 161.2, respectively), because of possible differences in carcinogenic effect of tobacco and alcohol on these parts of larynx (16).

The consumption of each type of tobacco in grams per day and the consumption of alcoholic beverages in grams of pure ethanol per day were expressed as described previously (12). The average daily consumption of tobacco (or alcohol) was calculated by dividing the cumulative lifetime tobacco (or alcohol) consumption by the overall duration of smoking (or drinking). Ex-smokers (or ex-drinkers) were defined as people who had stopped smoking (or drinking) at least 1 year before the diagnosis.

ORs and 95% CIs associated with GST null genotypes were calculated by unconditional logistic regression using Statistical Analysis Software version 6.11 (SAS Institute, 1995). ORs were adjusted for sex, age, and variables related to smoking and alcohol consumption as confounding factors. Because there were no women among glottic/subglottic larynx cancer patients, analyses in this subpopulation were restricted to men.

The extent to which each putative high-risk genotype could modify the effect of tobacco or the extent to which tobacco exposure could modulate the effect of genotype was evaluated by likelihood ratio test to compare the goodness of fit of the model with and without interaction term (17). For that purpose, the average daily consumption of tobacco and the duration of smoking were expressed as continuous or categorical variables (17); the latter was defined by two levels of smoking exposure according to the approximate median distribution in the control group.

**Results**
From the 129 larynx cancer patients, 55 (43%) were classified as supraglottic, 47 (36%) were classified as glottic/subglottic, and 27 (21%) were classified as unspecified or unclassifiable cancers (i.e., tumor that overlaps the boundaries of two or more subcategories and whose point of origin cannot be determined or is not otherwise specified). The main characteristics of the study population are presented in Table 1. The age distributions were quite similar in cases (55.0 years) and controls (54.9 years). The study subjects were almost all men. Cases had a higher average daily tobacco consumption than controls (30.4 versus 25.1 g/day) and a longer duration of smoking (34.6 versus 32.2 years). Ninety-one percent of cases and 72% of controls were current smokers; the remainder were almost entirely smokers of cigarettes associated with another tobacco product. Seventy percent of cases and 67% of controls were current smokers. The mean daily consumption of alcohol was higher in larynx cancer cases than in controls (98.1 versus 77.1 g/day). A significantly higher proportion of cases consumed 80 g of ethanol/day or more (60 versus 37%; P < 0.001). The mean duration of alcohol drinking was similar among cancer cases and controls (30.1 versus 29.0 years).

Frequencies of genotypes by cancer subsites are shown in Table 2. The frequencies of the GSTM1 null and GSTTI null genotypes were slightly higher in larynx cancer cases (60.5 and 19.4%, respectively) compared with the controls (52.3 and 15.7%, respectively). Frequency of the GSTTI null genotype in glottic/subglottic cancer cases (27.7%) was nearly twice that observed in the controls. Among larynx cancer patients, the frequency of the GSTM1 and GSTTI genotypes did not differ significantly between supraglottic and glottic/subglottic cases. In the control group, the frequencies of the genotypes were similar within the main medical diagnoses (data not shown).

Multivariate analysis (Table 2) revealed a borderline significant relationship between laryngeal cancer and the GSTM1 null genotype (OR = 1.6, 95% CI = 1.0–2.8). A nonsignificant association was observed with the GSTTI null genotype (OR = 1.4, 95% CI = 0.7–2.9) or with concurrent lack of the GSTM1 and GSTTI genes compared with the other genotype combinations (OR = 2.0, 95% CI = 0.8–5.2). Similar results were found for supraglottic and glottic/subglottic larynx cancers, separately.

Results of the analysis of the interaction between the GSTM1 and GSTTI genotypes on larynx cancer risk are shown in Table 3. Although the interaction was not significant (χ² = 0.094, 1 df; P = 0.76), the risk related to the combined GSTM1 and GSTTI null genotype was 2.7-fold higher (95% CI = 1.0–7.4) than it was in the putatively lowest risk group with both of the genes.

A significant interaction between the GSTM1 genotype and the two levels of daily tobacco consumption (≤20 and 20+ g/day) was found (χ² = 4.0, 1 df; P < 0.05). The GSTM1 null genotype was associated with an increased risk of larynx cancer among smokers of 20 g tobacco/day or less (OR = 2.9, 95% CI = 1.3–6.3) but not among smokers with a greater average daily tobacco consumption (OR = 1.0, 95% CI = 0.5–2.0; Table 4). The interactive effect was close to significance when
AORs were adjusted for sex, age (<50, 50-54, 55-59, 60-64, and 65+ years), duration of smoking in years (≤25, 26–34, and 35+), smoking status (former/current smokers), inhalation (no/yes), daily consumption of tobacco in g/day (≤20, 21–30, and 31+), daily consumption of alcohol in g/day (≤40, 41–80, 81–120, and 121+), exclusive cigarette smokers (no/yes), and drinking status (never drinkers/ex-drinkers/current drinkers).

Subjects with the positive genotype serve as the reference category.

Positive, presence of the gene at least at one allele; null, absence of the gene.

Table 2 Number of cases/controls and ORs* (95% CI) of larynx cancer in relation to the GSTM1 and GSTT1 genotypes

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>All larynx cancers (n = 129)*</th>
<th>Supraglottic cancers (n = 55)*</th>
<th>Glottic/subglottic cancers (n = 47)*</th>
<th>Controls (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GSTM1 genotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (%)</td>
<td>51 (39.5)</td>
<td>23 (41.8)</td>
<td>19 (40.4)</td>
<td>82 (47.7)</td>
</tr>
<tr>
<td>Null (%)</td>
<td>78 (60.5)</td>
<td>32 (58.2)</td>
<td>28 (59.6)</td>
<td>90 (52.3)</td>
</tr>
<tr>
<td>OR (95% CI)**</td>
<td>1.6 (1.0–2.8)</td>
<td>1.6 (0.8–3.3)</td>
<td>1.5 (0.7–3.3)</td>
<td></td>
</tr>
<tr>
<td><strong>GSTT1 genotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (%)</td>
<td>104 (80.6)</td>
<td>46 (83.6)</td>
<td>34 (72.3)</td>
<td>145 (84.3)</td>
</tr>
<tr>
<td>Null (%)</td>
<td>25 (19.4)</td>
<td>9 (16.4)</td>
<td>13 (27.7)</td>
<td>27 (15.7)</td>
</tr>
<tr>
<td>OR (95% CI)**</td>
<td>1.4 (0.7–2.9)</td>
<td>1.6 (0.6–4.1)</td>
<td>2.2 (0.9–5.3)</td>
<td></td>
</tr>
<tr>
<td><strong>GSTM1 and GSTT1 genotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one positive (%)</td>
<td>115 (89.1)</td>
<td>50 (90.9)</td>
<td>40 (85.1)</td>
<td>160 (93.0)</td>
</tr>
<tr>
<td>Both null (%)</td>
<td>14 (10.9)</td>
<td>5 (9.1)</td>
<td>7 (14.9)</td>
<td>12 (7.0)</td>
</tr>
<tr>
<td>OR (95% CI)**</td>
<td>2.0 (0.8–5.2)</td>
<td>2.5 (0.6–10.3)</td>
<td>2.5 (0.7–8.6)</td>
<td></td>
</tr>
</tbody>
</table>

* ORs were adjusted for sex, age (≤50, 50–54, 55–59, 60–64, and 65+ years), duration of smoking in years (≤25, 26–34, and 35+), smoking status (former/current smokers), inhalation (no/yes), daily consumption of tobacco in g/day (≤20, 21–30, and 31+), daily consumption of alcohol in g/day (≤40, 41–80, 81–120, and 121+), exclusive cigarette smokers (no/yes), and drinking status (never drinkers/ex-drinkers/current drinkers).

Also including 26 unspecified or unclassifiable larynx cancers; data on smoking and/or alcohol drinking were missing for 6 cases and 8 controls.

ICD-O code 161.0 and 161.2; ORs were calculated for men only; data on smoking and/or alcohol drinking were missing for three cases and seven controls.

Subjects with at least one positive genotype serve as the reference category.

Discussion

Genetic polymorphism of the GSTM1 isoenzyme, involved in the detoxification of a number of tobacco carcinogens, has seemed to be a good candidate as a modulator of individual susceptibility to smoking-induced cancers. To date, however, little is known on the effect of the GSTM1 null genotype and the levels of smoking were not significant. However, contrary to GSTM1, the effect of the GSTT1 null genotype was limited to long-term smokers (OR = 2.3 and 95% CI = 0.9–5.4 among smokers for more than 30 years and OR = 0.8 and 95% CI = 0.2–2.5 among smokers for 30 years or less; Table 4). The ORs associated with the GSTT1 null genotype were not modified when the duration of smoking was considered as a continuous variable.

Daily tobacco consumption was expressed as a continuous variable (χ² = 2.0, 1 df; P = 0.15). In contrast, no interaction was found between the GSTM1 genotype and duration of smoking (P = 0.79). The interactions between the GSTT1 genotype and the levels of smoking were not significant. However, contrary to GSTM1, the effect of the GSTT1 null genotype was limited to long-term smokers (OR = 2.3 and 95% CI = 0.9–5.4 among smokers for more than 30 years and OR = 0.8 and 95% CI = 0.2–2.5 among smokers for 30 years or less; Table 4). The ORs associated with the GSTT1 null genotype were not modified when the duration of smoking was considered as a continuous variable.

These divergent results. In the present study, the risk associated with the GSTM1 null genotype is unlikely to be explained by differences in tobacco or alcohol exposures between cases and controls, because these confounders were taken into account in the analyses.

This study failed to reveal a significant relationship between larynx cancer risk and the GSTT1 null genotype, in agreement with the sole previous investigation on this topic (10). Interestingly, in both studies, a slightly higher frequency of the GSTT1 null genotype was found for glottic rather than supraglottic larynx cancer. However, the limited power to detect significant risks attributable to the GSTT1 deletion in these studies precludes definitive conclusions from being drawn.

Because GSTM1 and GSTT1 genes are involved in the detoxification of tobacco smoke-derived carcinogens, individuals with concurrent lack of these genes are expected to be at particular risk of developing smoking-related cancers. Our results are in agreement with this hypothesis; smokers lacking both GST genes had a doubled, although not significant, risk for larynx cancer when compared with those having at least one of these genes and had a 2.7-fold risk of borderline significance when compared to those with both genes. Similar results were previously reported; in one study on head and neck cancer, a more than 3-fold increase in risk was observed (21, 22), whereas in another study on lung cancer, a significant interaction between GSTM1 and GSTT1 genotypes was found in a non-Caucasian population (23). Moreover, these results are supported by recent findings among smokers; the highest frequency of chromatide aberrations was observed in lymphocytes of subjects lacking the GSTM1 gene when the GSTT1 gene was concurrently missing (24).

In most of the previous studies on interactions between metabolic genotypes and tobacco smoking (18), smoking exposure was expressed as pack-years (the number of packs of 20 cigarettes smoked per day multiplied by the number of years of smoking). This assumes equivalent effects of daily tobacco consumption and duration of smoking in carcinogenesis. However, it is well known that a moderate intake for a long period carries a higher risk of smoking-related cancers than a high
intake for a shorter period (16, 25, 26). Accordingly, the cumulative tobacco consumption alone may not serve as a suitable measure of smoking exposure. In this study, the effect of the GSTM1 null genotype was similar across two levels of pack-years (data not shown). In contrast, our data suggest that the association between larynx cancer and the GSTM1 genotype could depend on daily tobacco consumption. The GSTM1 null genotype was associated with a significantly increased risk of larynx cancer only among smokers of 20 g tobacco/day or less. This is in contrast to the previous observation of a higher proportion of subjects with a deficiency in GSTM1 activity being heavy smokers (8). However, lack of adjustment for the main confounding factors renders the results difficult to compare to ours. Interaction between the GSTM1 polymorphism and tobacco exposure has been subject to several studies on lung cancer with discrepant results (reviewed in Ref. 27). Our findings are in agreement with those from a previous study on lung cancer, in which confounding factors were appropriately controlled (28). In addition, the GSTM1 null genotype was more markedly associated among lighter smokers with squamous cell carcinoma of the lung in a Japanese population (29) and with small cell carcinoma in a European population (30). This gives additional support to the hypothesis that genetic variation in the ability to metabolize a particular carcinogen may be irrelevant at very high exposure levels (28, 30). On the other hand, although no significant interaction with smoking was observed, a clear tendency of an increase in risk was seen for the GSTT1 null genotype among long-term smokers. This finding remains, however, to be confirmed in future studies. Different effects of the GSTM1 and GSTT1 genotypes were found according to levels of tobacco exposure (Table 4). Because GSTM1 and GSTT1 are implicated in the metabolism of different carcinogens in tobacco smoke (5, 7) present in different concentrations (2), their carcinogenic potential may be of different importance and could explain the observed patterns of risk.

Because alcohol is also recognized as a strong causative factor in larynx carcinogenesis, in particular for supraglottic cancer (16), polymorphisms in genes involved in the metabolism of ethanol, i.e., CYP2E1 (31) and alcohol dehydrogenase 3 (9), could also play an important role in the occurrence of larynx cancer and should also be of interest in future studies on this topic.

In conclusion, the GSTM1 null genotype conferred an increased risk of larynx cancer, mainly among lighter smokers.

Table 1  Number of cases/controlsa and ORs (95% CI) of larynx cancer in relation to the GSTM1/GSTM1 genotype combinations

<table>
<thead>
<tr>
<th>GSTM1 genotypeb</th>
<th>Positive</th>
<th>Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1</td>
<td>1.6  (0.9-2.9)</td>
</tr>
<tr>
<td>38/64</td>
<td>1</td>
<td>61/77</td>
</tr>
<tr>
<td>Null</td>
<td>1.3</td>
<td>2.7  (1.0-7.4)</td>
</tr>
<tr>
<td>11/12</td>
<td>11/11</td>
<td></td>
</tr>
</tbody>
</table>

a Data on smoking and/or alcohol drinking were missing for six cases and eight controls.
b ORs were adjusted for sex, age (<50, 50–54, 55–59, 60–64, and 65+ years), duration of smoking in years (<25, 26–34, and 35+), smoking status (former/current smokers), inhalation (no/yes), daily consumption of tobacco in g/day (<20, 21–30, and 31+), daily consumption of alcohol in g/day (<40, 41–80, 81–120, and 121+), exclusive cigarettes smokers (no/yes), and drinking status (never drinkers/ex-drinkers/current drinkers). Subjects with both positive genotypes serve as the reference category.

Table 4  Number of cases/controlsa and ORs (95% CI) of larynx cancer in relation to GST genotypes and different measures of tobacco exposureb

<table>
<thead>
<tr>
<th>GSTM1 genotypec</th>
<th>Positive</th>
<th>Null</th>
<th>Positive</th>
<th>Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1</td>
<td>2.9  (1.3-6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17/38</td>
<td>1</td>
<td>47/69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21+</td>
<td>1</td>
<td>1.0  (0.5-2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32/38</td>
<td>1</td>
<td>52/72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51/11</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>GSTT1 genotyped</th>
<th>Positive</th>
<th>Null</th>
<th>Positive</th>
<th>Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1</td>
<td>1.6  (0.7-3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/33</td>
<td>1</td>
<td>34/66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31+</td>
<td>1</td>
<td>1.4  (0.7-2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37/43</td>
<td>1</td>
<td>65/75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19/12</td>
<td></td>
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</table>

a Data on smoking and/or alcohol drinking were missing for six cases and eight controls.
b Cutoff points were defined according to approximate median distribution in the control group.
c Positive, presence of the gene at least at one allele; null, absence of the gene. ORs were adjusted for sex, age (<50, 50–54, 55–59, 60–64, and 65+ years), duration of smoking in years (<25, 26–34, and 35+), smoking status (former/current smokers), inhalation (no/yes), daily consumption of alcohol in g/day (<40, 41–80, 81–120, and 121+), exclusive cigarette smokers (no/yes), and drinking status (never drinkers/ex-drinkers/current drinkers). Subjects with the positive genotype serve as the reference category.
d ORs adjusted for all variables in the previous model (except duration of smoking) and daily consumption of tobacco in g/day (<20, 21–30, and 31+).
P = 0.07.

The effect of the GSTT1 genotype, if any, appears only after long duration of smoking, but this needs to be confirmed in larger studies. These findings underline the complex nature of relationships between GST polymorphisms and components of tobacco smoke. Well-designed studies on such complex gene-environment interactions should provide the most interesting evidence in molecular epidemiology.

Acknowledgments


References

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