Glutathione S-transferase M1, T1, and P1 Polymorphisms and Survival among Lung Cancer Patients

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Abstract

Glutathione S-transferase (GST) enzymes detoxify therapeutic drugs and reactive oxidants, so GST polymorphisms may influence survival after diagnosis of cancer. We evaluated survival according to GST polymorphisms in a population-based series of lung cancer patients. The study subjects (n = 274) were men diagnosed with lung cancer from 1993 through 1996 who participated in a case control study and provided a blood sample for genotyping. The presence of the GSTM1 and GSTT1 genes were assayed by multiplex PCR. Genotype at the GSTP1 Ile105Val substitution was determined by PCR and oligonucleotide ligation assay. The study subjects were followed for vital status through 2000, and overall survival was evaluated in Kaplan-Meier survival functions and Cox proportional hazards models. Subjects with the GSTM1 null genotype had shorter survival; the proportion of GSTM1 null subjects surviving at 5 years was 0.20 [95% confidence interval (CI) 0.14–0.27], compared with 0.29 (95% CI 0.22–0.37) for GSTM1 present subjects. The relative risk of death associated with GSTM1 null genotype, adjusted for stage at diagnosis and histology, was 1.36, 95% CI 1.04–1.80. There was no association between GSTT1 or GSTP1 genotype and survival in the overall study population, nor in a subgroup of patients treated with chemotherapy (n = 130). For GSTM1, our results are consistent with a previous study, which also observed that the GSTM1-null genotype, which confers susceptibility to lung cancer, was associated with shorter survival. Future studies of lung cancer survival should take into account GSTM1 genotype as well as investigate underlying mechanisms.

Introduction

Inherited GST variants that alter GST-mediated detoxification of carcinogenic chemicals have been extensively investigated as candidate genes for lung cancer susceptibility (1–4). GST polymorphisms may also affect cancer survival, but fewer molecular epidemiology investigations to date have considered the role of genetic variation in these enzymes in determining survival. Hypotheses about GST polymorphisms and survival have been developed through two lines of reasoning: (a) several chemotherapy agents are substrates for GST-catalyzed glutathione conjugation (1, 5–9), as are cellular by-products of reactive oxygen damage (10, 11); therefore, patients may differ in response to chemo and radiation therapy depending on GST activity; and (b) susceptible GST genotypes have been reported to be associated with characteristic patterns of somatic changes in tumor tissue (e.g., p53 or K-ras mutations; Refs. 12–15); if patients with low-activity GST genotypes are more likely to have certain somatic changes, and if the somatic changes represent more aggressive tumor phenotypes (16), GST genotype may be observed to associate with survival differences.

Three studies have reported on survival of lung cancer patients in relation to common polymorphisms affecting GST activity, with inconsistent results. Goto et al. (17) observed a hospital-based series of 232 NSCLC patients for ≤5 years and reported that patients who were homozygous for deletion of the GSTM1 gene (GSTM1-null genotype) had shorter survival than patients with one or two GSTM1 alleles (GSTM1 present genotype, which represents normal GSTM1 activity). In contrast, no association between mean disease-free survival time and GSTM1 genotype was reported in a series of 105 surgically treated NSCLC patients observed for 5 years (18). In a third study of 250 lung cancer cases (all histologies were included), GSTM1 genotype, the GSTT1 gene deletion, and the GSTP1 Ile105Val single nucleotide polymorphism were studied in relation to survival, and the overall proportion surviving at 1 year was similar across categories of each GST genotype (19). These investigations differed in several aspects of study design, including size of the study populations, observation of NSCLC patients only or of all lung cancers, length of follow-up, and choice of different end points, death versus disease-free interval. The discordant results may be related to these differences in approach.

Thus, there are plausible mechanisms through which a cancer patient’s inherited genotype for GST enzymes may...
influence his or her survival, but evidence for a role of these genetic differences in lung cancer survival is limited. Characterization of associations between drug metabolizing enzyme polymorphisms and patient prognosis could contribute to identifying individual differences in potential to benefit from particular types of therapy. We have investigated survival in relation to genotype for three common GST polymorphisms in a population-based cohort of men with lung cancer.

Subjects and Methods
The study subjects were men aged 18–74 with a first diagnosis of primary lung cancer (all histologies) in 1993 through 1996 in six nonurban counties of western Washington state. Men meeting these eligibility criteria were ascertained through the Western Washington CSS, a population-based SEER program cancer registry (20). Eligible subjects were contacted and asked to complete a structured telephone interview for a case control study. We requested that subjects who participated in the interview also provide a blood sample for genotyping. The case control study methods and participation rates have been described previously (21). Although we used a rapid reporting mechanism to identify subjects as quickly as possible after diagnosis, we found that many of the men diagnosed with lung cancer were deceased, too ill to be interviewed, or too ill to provide a blood sample by the time we attempted to contact them for the study. Blood samples were obtained from 42% of the 661 eligible lung cancer case subjects. These 274 patients form the study cohort and were followed for survival for the present analysis.

The age range among the participants was 28–74 years, with a median of 62 years. The majority (263) of the men (96%) were Caucasian, 4 were Native-American, 2 were Asian, 1 was African-American, and race was unknown for 4 men. We obtained information on stage at diagnosis (categorized according to SEER program criteria as local, regional, or distant), tumor site, histology, and type of primary therapy from the CSS. Patients with distant stage of disease at diagnosis were less likely to participate in the blood draw and, therefore, were underrepresented in the group with blood samples (31%) compared with the overall group of eligible lung cancer patients (58%). Participants with blood samples available also differed from eligible patients with no sample with regard to several other characteristics that were correlated with less advanced disease at diagnosis and/or good prognosis, so that lung cancer patients with a blood sample were less likely to be current smokers, were more likely to have a body mass index (calculated as weight in kilograms divided by height in meters, squared) above the median, were more likely to have a tumor location in the upper lobe, and were more likely to have been treated by surgery, compared with all eligible patients.

GST genotypes were determined from DNA extracted from lymphocytes. The presence of GSTM1 and GSTT1 genes was assayed by multiplex PCR (22), and genotype at the GSTP1 Ile105Val substitution was determined by PCR and the oligonucleotide ligation assay method (23), with primers and probes for GSTP1 as described previously (24).

Subjects were followed for vital status through 2000 by the CSS by active follow-up and matching to electronic death certificate records from the state of Washington and the National Center for Health Statistics. Survival analysis methods were used to consider the influence of GST genotypes on patient survival. We calculated survival time as the time from diagnosis to death or to the end of follow-up for each patient. Death from any cause was treated as a failure in the survival analysis, and living subjects were censored at the time of last contact. We calculated person-years at risk within each genotype category as the sum of survival times of all subjects in that category. Overall survival in relation to GST genotype was evaluated by Kaplan-Meier survival function and log-rank tests, stratified by stage at diagnosis. RR of death was estimated by the hazard ratio from a multivariate Cox proportional hazards model, with adjustment for categories of stage at diagnosis as strata in the model and other prognostic characteristics as covariates. RRs within subgroups according to type of therapy, and by tumor histology, were calculated by including a multiplicative interaction term in the Cox model. The likelihood ratio test comparing models with and without the interaction term was used to evaluate the statistical significance of effect modification. Stata software (Stata Corp., College Station, TX) was used for statistical analysis.

Results
The distributions of GST genotypes according to patient characteristics are shown in Table 1. Genotypes for GSTM1 and GSTT1 were available for all 274 subjects, GSTP1 genotype assay results were not interpretable for 21 subjects, so the GSTP1 analysis is based on 253 subjects. Generally, the distribution of genotypes was not related to stage at diagnosis, tumor histology, or site of the tumor. An association between GSTM1 null genotype and increased risk of lung cancer was present in this study population and most apparent for NSCLC; accordingly, the cohort of cases followed for survival contained an excess of GSTM1 null genotypes among subjects with non-small cell type cancers (56%) compared with the total case group (52%). GSTT1 null genotypes were somewhat less frequent (12%) among patients with distant disease at diagnosis than in the overall case group (19%), but this difference was consistent with chance.

The Kaplan-Meier survival functions for overall survival among 274 men with lung cancer by GST genotypes are presented in Fig. 1. A total of 214 deaths was observed during the follow-up period. Median follow-up among men who were alive at the time of observation from diagnosis. Follow-up was essentially complete to 5 years, with only 1 living subject censored (lost to follow-up) before 4 years and 7 subjects censored between years 4 and 5. On the basis of the difference in the survival curves by GSTM1 genotype shown in Fig. 1A, and on the log-rank test (χ² = 3.36, 1 df; P = 0.07), there was an indication that GSTM1 null individuals had poor survival compared with GSTM1 present subjects. The Kaplan-Meier estimates of overall survival at 1, 3, and 5 years were 0.77 (95% CI 0.69–0.84), 0.39 (96% CI 0.30–0.47), and 0.29 (95% CI 0.22–0.37) for GSTM1 present subjects and 0.77 (95% CI 0.69–0.83), 0.34 (95% CI 0.26–0.41), and 0.2 (95% CI 0.14–0.27) for GSTM1 null subjects. There was no evidence of a survival difference by GSTT1 genotype (χ² = 0.77, 1 df; P = 0.38), nor by GSTP1 genotype (χ² = 0.12, 2 df; P = 0.94).

The RRs of death associated with GSTM1, GSTT1, and GSTP1 genotypes are shown in Table 2. After adjustment for stage and histology, which were strong predictors of survival, GSTM1 null genotype was associated with shorter survival among lung cancer patients, with an adjusted death RR of 1.36, compared with GSTM1 present. Additional adjustment for age, race, education, current smoking, total

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1 Nazar-Stewart et al., submitted for publication.
Effect on the RR. The RR of death associated with history of a previous primary malignancy had essentially no pack-years of smoking, body mass index, tumor site, or tumor type and survival according to type of therapy. The increased hazard of death associated with GSTM1 null genotype among patients with small cell lung cancer (RR \( \approx 1.15 \)) was similar to that for patients with NSCLC (RR \( \approx 1.34 \)). For GSTT1 genotype, an adjusted Cox model indicated slightly worse survival associated with the GSTT1-null genotype (RR \( \approx 1.17 \)), but this difference is likely to be attributable to chance. Receiving radiation treatment was related to stage at diagnosis; radiation was noted for 69% of patients who were current smokers within a year of diagnosis (RR \( \approx 1.15 \)). For patients who received both chemotherapy and radiation therapy (n = 97, 84 deaths), the RR associated with GSTM1 null genotype was 1.56 (95% CI 1.01–2.41). Among patients who received neither chemotherapy nor radiation therapy (n = 83, 45 deaths), the RR associated with GSTM1 null genotype was 0.88 (95% CI 0.48–1.6). Consistent with the results from the overall study population, analysis of subgroups by type of therapy did not reveal evidence of associations between GSTT1 or GSTP1 and lung cancer survival.

Previous studies have assessed GST survival association separately for smokers versus never-smokers. In our study population, only 11 subjects reported being lifetime never-smokers, so an analysis limited to nonsmokers was not possible. When we considered RR of death associated with GSTM1 null genotype by current smoking status, an increased risk for GSTM1 null was seen in both the subjects who were current smokers within a year of diagnosis (n = 155, RR of death associated with GSTM1 null genotype = 1.52, 95% CI 1.06–2.19) and those who were former or never-smokers (n = 119, RR = 1.23, 95% CI 0.80–1.89). Current smokers had slightly poorer survival compared with a reference group that included former smokers and never-smokers (RR = 1.15, 95% CI 0.86–1.53, adjusted for histology and SEER stage). Poor prognosis for smokers was more marked (RR = 1.7, 95% CI 1.14–2.52) in the subgroup of patients who received radiation therapy. Within the sub-

<table>
<thead>
<tr>
<th>Histology</th>
<th>Total Present</th>
<th>Null Present</th>
<th>Null</th>
<th>Ile/Ile</th>
<th>Ile/Val</th>
<th>Val/Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma NOS</td>
<td>34 (12.4)</td>
<td>22 (16.8)</td>
<td>12 (8.4)</td>
<td>28 (12.6)</td>
<td>6 (11.5)</td>
<td>9 (8.4)</td>
</tr>
<tr>
<td>Large cell</td>
<td>8 (2.9)</td>
<td>4 (3.1)</td>
<td>4 (2.8)</td>
<td>6 (2.7)</td>
<td>2 (3.8)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Small cell</td>
<td>52 (19.0)</td>
<td>37 (20.6)</td>
<td>25 (17.5)</td>
<td>41 (18.5)</td>
<td>11 (21.2)</td>
<td>17 (15.9)</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>81 (29.6)</td>
<td>37 (28.2)</td>
<td>44 (30.8)</td>
<td>67 (30.2)</td>
<td>14 (26.9)</td>
<td>36 (33.6)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>96 (35.0)</td>
<td>40 (30.5)</td>
<td>56 (39.2)</td>
<td>77 (34.7)</td>
<td>19 (36.5)</td>
<td>40 (35.6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.1)</td>
<td>1 (0.8)</td>
<td>2 (1.4)</td>
<td>3 (1.4)</td>
<td>0 (0.0)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Treated by radiation</td>
<td>Yes 134 (52.8)</td>
<td>63 (53.4)</td>
<td>71 (52.2)</td>
<td>107 (51.9)</td>
<td>27 (56.3)</td>
<td>53 (55.2)</td>
</tr>
<tr>
<td></td>
<td>No 120 (47.2)</td>
<td>55 (46.6)</td>
<td>65 (47.8)</td>
<td>99 (48.1)</td>
<td>21 (43.8)</td>
<td>43 (44.8)</td>
</tr>
<tr>
<td>Treated by chemotherapy</td>
<td>Yes 142 (55.0)</td>
<td>73 (58.9)</td>
<td>69 (51.5)</td>
<td>115 (55.0)</td>
<td>27 (55.1)</td>
<td>50 (51.0)</td>
</tr>
<tr>
<td></td>
<td>No 116 (45.0)</td>
<td>51 (41.1)</td>
<td>65 (48.5)</td>
<td>94 (45.0)</td>
<td>22 (44.9)</td>
<td>48 (49.0)</td>
</tr>
</tbody>
</table>

\( ^a \) The total number of subjects with genotype results for GSTP1 is 253.
groups of patients who were treated by chemotherapy or radiation, the influence of \textit{GSTM1} genotype on survival did not vary according to smoking status ($P$s for interaction 0.68 and 0.97).

\textbf{Discussion}

In summary, we found that men with lung cancer who had \textit{GSTM1} null genotypes had shorter overall survival. When other patient prognostic factors were taken into account in a multivariate model, the \textit{GSTM1}-survival association remained statistically significant, indicating that the association was independent of stage at diagnosis and histology. \textit{GSTM1} null genotype was associated with shorter survival for lung cancer patients with both non-small cell and small cell histologies. However, because of the small number of patients with small cell lung cancer in our study, the CIs were somewhat wide for that group.

The study population that we followed for survival was a population-based sample, and, through the CSS registry, we were able to observe almost all of the participating lung cancer patients from time of diagnosis to \textit{H}11350 5 years or until death. The number of deaths observed during the follow-up period (214) was large enough to provide reasonable power to assess the main effects of the genotypes of interest and rule out any strong associations of \textit{GSTT1} or \textit{GSTP1} with survival. The \textit{GSTM1}-survival association was significant; however, the lower 95% confidence limit approached 1. Because the study population was limited to men, and the source population was largely Caucasian, results may not be generalizable to female lung cancer patients or members of other ethnic or racial groups.

The cohort of patients for whom we obtained blood for genotyping represented 42\% of the overall eligible population, and participants tended to have lower stage at diagnosis and somewhat better survival than nonparticipants. Poor participation can introduce selection bias in a cohort study when two conditions are met: (a) participation is related to survival; and (b) participation differs according to exposure status, independent of the exposure’s influence on survival. In the present study, participation was related to survival, so one condition that contributes to bias is present. \textit{GST} genotypes of nonparticipants are not known, so we are unable to evaluate whether these exposures were related to participation. However, \textit{GST} genotypic variants do not produce any evident phenotype that would be expected to affect an individual’s tendency to participate in a study, so it is unlikely that the second condition was met. Because survival analysis methods rely on comparisons within the cohort of participating patients, differences between participants and nonparticipants should not introduce bias into our estimates of RRs, although generalizability to those who do not survive long after diagnosis may be limited.

Considered in context of previous studies, our result regarding \textit{GSTM1} and lung cancer survival is consistent with the \textit{GSTM1}-survival association described in a study which
was similar in design, having a large study population and several years of follow-up. Goto et al. (17) reported that, among 232 NSCLC patients, those with the GSTM1 null genotype had worse survival, with 44% of GSTM1 null patients surviving at 3 years, compared with 55% of patients with GSTM1 present. These results are quite comparable with our study population, in which, when NSCLC cases only were considered, 42% of patients surviving at 3 years, compared with 55% of patients with GSTM1 present, in our study population, in which, when NSCLC cases only were considered, 42% of patients surviving at 3 years, compared with 55% of patients with GSTM1 present, in our study population, in which, when NSCLC cases only were considered, 42% of patients surviving at 3 years, compared with 55% of patients with GSTM1 present.

Table 3  GST genotypes and lung cancer survival, by chemotherapy treatment

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Chemotherapy</th>
<th>No Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Person-years</td>
</tr>
<tr>
<td>GSTM1 Present</td>
<td>63</td>
<td>152</td>
</tr>
<tr>
<td>GSTM1 Null</td>
<td>66</td>
<td>120</td>
</tr>
<tr>
<td>GSTT1 Present</td>
<td>106</td>
<td>222</td>
</tr>
<tr>
<td>GSTT1 Null</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>GSTP1 Ile/Ile</td>
<td>46</td>
<td>93</td>
</tr>
<tr>
<td>GSTP1 Ile/Val</td>
<td>58</td>
<td>141</td>
</tr>
<tr>
<td>GSTP1 Val/Val</td>
<td>14</td>
<td>19</td>
</tr>
</tbody>
</table>

a RR estimated by the hazard ratio from Cox proportional hazards models, adjusted for stage and histology.

Table 4  GST genotypes and lung cancer survival, by radiation treatment

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Radiation</th>
<th>No radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Person-years</td>
</tr>
<tr>
<td>GSTM1 Present</td>
<td>48</td>
<td>177</td>
</tr>
<tr>
<td>GSTM1 Null</td>
<td>66</td>
<td>139</td>
</tr>
<tr>
<td>GSTT1 Present</td>
<td>93</td>
<td>250</td>
</tr>
<tr>
<td>GSTT1 Null</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td>GSTP1 Ile/Ile</td>
<td>47</td>
<td>122</td>
</tr>
<tr>
<td>GSTP1 Ile/Val</td>
<td>46</td>
<td>134</td>
</tr>
<tr>
<td>GSTP1 Val/Val</td>
<td>16</td>
<td>37</td>
</tr>
</tbody>
</table>

a RR estimated by the hazard ratio from Cox proportional hazards models, adjusted for stage and histology.

b In the test for interaction between GSTM1-null and radiation therapy, P = 0.02.

data, which may not be completely reliable regarding therapies. Multiple subgroup comparisons according to type of therapy were made, so chance should be considered as an explanation for the interaction between GSTM1 genotype and radiation therapy.

Although the GSTP1 allelic variants have been reported to have different activities in glutathione conjugation of both nitrogen mustard and cisplatin chemotherapy agents in vitro (7, 8, 25), we did not find evidence that GSTP1 genotype influences survival among lung cancer patients, either in the overall study population or a subgroup treated with chemotherapy. GSTT1 genotype was also unrelated to survival. For both GSTP1 and GSTT1, the analysis of subgroups by type of therapy (Tables 3 and 4) resulted in some RRs that departed from 1, but these were generally based on small numbers of deaths and not statistically significant. The GSTT1 null or GSTP1 Val/Val genotypes are each present in only ~20% of individuals in the population, so given the size of our study population, we cannot rule out modest associations between GSTT1 and GSTP1 genotypes and survival. The study by Yang et al. (19) presents the only previous data that we are aware of regarding GSTT1 and GSTP1 genotypes and survival. Two possible mechanisms for an association between GSTM1 genotype and survival have been suggested, one involving differences in detoxification of treatment agents or GST-mediated protection against oxidative damage during treatment and the other related to differences in carcinogen damage to DNA. Under the first mechanism, individuals with GSTM1 null genotypes would experience a higher effective dose of chemotherapy and/or more reactive oxidant damage to tumor tissue. Therapy might then be more effective in GSTM1 null patients, in which case we would observe...
longer survival for this group, as has been reported for GSTM1 null breast cancer patients (26, 27). In the present study of lung cancer, the direction of the association was the reverse. Shorter survival for patients with reduced capacity for GST-mediated detoxification might be explained by more severe therapy-related toxicity. An increased number of deaths attributed to therapy-related toxicity was reported among GSTT1 null leukemia patients treated with high-dose therapy (28). The survival difference that we observed among lung cancer patients was evident ≥3 years after diagnosis and so seems unlikely to be explained by therapy-related toxicity. A possible explanation for the association observed in our data is that GSTM1 null patients may have had dose reductions or delays caused by toxicity and, therefore, received less effective treatment. We have no information on toxicity, dose delays, or reductions in our study population. The shorter survival in association with GSTM1 null genotype that we observed is also in keeping with the model proposed by Goto et al. (17), in which smokers with GSTM1 null genotype would have more tendency to form carcinogen-DNA adducts in lung tissue and develop cancers that contain mutations of p53, K-ras, and/or genes involved in tumor development, growth, and metastasis. Because of the presence of these mutations, the GSTM1 null patients would be expected to have more aggressive tumor biology and poorer survival, even after taking into account stage, as was observed in the present study.

If GSTM1 genotype affects lung cancer survival, as has now been described in two large study populations, this raises the possibility that survival bias may influence case control studies of GSTM1 genotype in lung cancer etiology. Shorter survival for GSTM1 null patients could result in lower prevalence of the null genotype in the group of cases who are alive and able to participate in a study. If this occurred, the observed odds ratio would be biased low. However, we observed that the proportions of GSTM1 present and GSTM1 null lung cancer patients surviving to 1 year after diagnosis were essentially identical and that survival differences only became apparent after longer follow-up. Therefore, lung cancer case control studies that have ascertained incident cases within a year after diagnosis should not be affected by survival bias. On the basis of our survival data, bias in a study addressing GSTM1 genotype in lung cancer risk would be a concern only if the case group included substantial numbers of prevalent cases.

The evidence of an association between GSTM1 null genotype and increased risk of lung cancer (2–4), association of the same genotype with somatic changes in lung tumor tissue (12–15), as have been characterized previously, and association between GSTM1 genotype and survival, as described here, presents a complex picture. The implications for patient care, if any, are not clear. The underlying mechanism for the GSTM1-survival association should be further investigated. If the mechanism for the GSTM1-survival association is through the presence of p53 and/or K-ras mutations, as seems plausible, then our results may serve to reinforce the importance of considering GSTM1 genotype in future studies of lung cancer survival.

Acknowledgments

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References


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