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Glutathione S-transferase Gene Polymorphisms and Risk and Survival of Pancreatic Cancer

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Abstract

BACKGROUND—Pancreatic cancer is a multifactorial disease with metastasis-prone and therapy-resistant nature. The authors hypothesized that genetic variants of glutathione S-transferase (GST) affect detoxification of carcinogens and anticancer agents in the human pancreas and, thus, the risk and survival of pancreatic cancer.

METHODS—Genotypes of *GSTM1*, *GSTT1*, and *GSTP1* were determined in 352 patients with pancreatic ductal adenocarcinoma and in a control group of 315 healthy, non-Hispanic whites (frequency-matched by age and sex). Survival analysis was performed in a subset of 290 patients. Epidemiological and clinical information was obtained. A multiple unconditional logistic regression model, a Cox proportional hazards model, and log-rank tests were used for statistical analysis.

RESULTS—No significant main effects of any of 3 *GST* genes on the risk of pancreatic cancer were observed. Subgroup analysis showed that older individuals (aged 62 years) who carried the *GSTP1**C (¹⁰⁵Val-¹¹⁴Val) containing genotype tended to have a reduced risk compared with younger individuals who carried the non-*C genotype (for sex and pack-years of smoking, the adjusted odd ratio was 0.54; 95% confidence interval [95% CI], 0.29-1.02). In a survival analysis of 138 patients who received 5-fluorouracil, patients who carried the *GSTP1**C containing genotype had a significantly longer survival than patients who carried the non-*C genotype (multivariate hazard ratio, 0.45; 95% CI, 0.22-0.94).

CONCLUSIONS—The *GSTP1**C variant conferred a possible protective effect against pancreatic cancer in older individuals and a significant survival advantage in patients who received 5-fluorouracil. The current findings must be confirmed before further inferences can be made.

Keywords

glutathione S-transferase M1 (GSTM1); GSTT1; GSTP1; polymorphism; haplotype; risk; survival; pancreatic cancer

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It is estimated that, in 2006, approximately 33,730 Americans will develop pancreatic cancer, and 32,300 will die from this disease.¹ The mortality rate of pancreatic cancer (10.5 per 100,000 population) is almost equal to its incidence rate (11.0 per 100,000 population) for both sexes and all ethnic groups.² Cigarette smoking is the only established environmental risk factor for pancreatic cancer. Very little is known about how genetic and environmental factors interact to foster the development of this malignancy.³ Clinically, treatment of pancreatic cancer remains a challenge, and there is great heterogeneity in the way patients respond to chemotherapy. Therefore, it is important to understand how genetic factors contribute to both predisposition to and clinical outcome of this disease.

The cytosolic glutathione S-transferases (GSTs) (Enzyme Commission no. 2.5.1.18) are a family of phase II isoenzymes that are important parts of the cell defense against numerous harmful chemicals that are produced endogenously and exogenously. GSTs catalyze the addition of reduced glutathione (GSH) to a variety of electrophilic compounds, including tobacco carcinogens⁴⁻⁶ and anticancer agents.⁷ Eight families of soluble GSTs in humans have been identified,⁸ and they have overlapping substrate specificities. GST- μ , GST- Θ , and GST- π are encoded by the *GSTM1*, *GSTT1*, and *GSTP1* genes, respectively; and these 3 genes have been examined extensively in association with genetic susceptibility^{9,10} and clinical outcomes of several types of human cancer.¹¹⁻¹⁵ Homozygous deletion of the *GSTM1* and *GSTT1* genes (null genotype) has been associated with the loss or lack of enzyme activity and increased vulnerability to cytogenetic damage.^{16,17} It has been shown that the exon 5 A1404G, which encodes an isoleucine (Ile)→valine (Val) exchange at codon 105 (Ile¹⁰⁵Val) (reference single nucleotide polymorphism [rs] no. 947894), and exon 6 C2294T, which encodes an Ala→Val exchange at codon 114 (Ala¹¹⁴Val) (rs no. 1799811) of the *GSTP1* gene, confer lower levels of metabolizing activity toward a variety of carcinogens and anticancer agents.¹⁸⁻²⁰ GST- μ , GST- Θ , and GST- π all are expressed in the human gastrointestinal tract.²¹ In particular, GST- π appears to be one of the constitutive elements of the human pancreas.²²

In the current study, we investigated the association between *GST* gene polymorphisms and the risk of pancreatic cancer as well as the clinical outcome of patients with cancer. We hypothesized that these polymorphisms influence the detoxification of carcinogens, reactive oxygen species, and anticancer drugs, thereby influencing susceptibility to pancreatic cancer as well as the clinical outcome of patients.²³

MATERIALS AND METHODS

Study Population

We investigated the association between polymorphisms and pancreatic cancer risk in a hospital-based, case-control study. Patients and controls were recruited consecutively from January 20, 2000 to December 20, 2004. Patients with pathologically confirmed primary pancreatic ductal adenocarcinoma (International Classification of Diseases for Oncology code C25.3; World Health Organization, 2000) were recruited from the Gastrointestinal Center at The University of Texas M. D. Anderson Cancer Center (M. D. Anderson). Controls were healthy, cancer-free individuals who were recruited from friends and genetically unrelated family members (usually spouses or in-laws) of patients who were diagnosed with cancers other than pancreatic cancer. No study participants had a prior history of cancer (except for nonmelanoma skin cancer). Patients and controls were frequency-matched by age, sex, and race. Informed consent to participate in interviews and to provide a blood sample was obtained from each participant. The study was approved by the M. D. Anderson Institutional Review Board.

During the study period, 561 potential patients were approached, and 442 patients (78.8%) consented to participate in the study. Fifty-one of those 442 patients (11.5%) were excluded because they failed to donate a blood sample after signing their informed consent. In total, 483 potential controls were approached, and 372 individuals (77.0%) consented to participate in the study. Fifteen of those 372 controls (4.0%) were excluded because of incomplete questionnaire data. Consequently, 391 patients and 357 controls met the eligibility criteria. Because of the known ethnic variations in pancreatic cancer risk and genotype distribution, the case-control analysis was focused on non-Hispanic white individuals only, including 352 patients (90.0%) and 315 controls (88.2%). Survival analysis was conducted among 290 non-Hispanic white patients who received chemotherapy or chemoradiation at M. D. Anderson, and their complete medical records were available.

Exposure and Clinical Data Collection

Information on demographics and smoking exposure was collected by personal interview using a structured questionnaire, as described previously.²⁴ The participants were classified as ever-smokers or never-smokers according to whether they had ever smoked >100 cigarettes in their lifetime. Cumulative smoking exposure was estimated in pack-years, which were based on the average number of daily cigarette intake and the number of years smoked.

Clinical information of 290 patients was abstracted from the patients' medical records, as described previously.²⁵ A comprehensive medical record review was performed to obtain information on neoadjuvant and/or adjuvant chemotherapy/chemoradiation for patients with resectable tumors and on first- and second-line definitive treatments for patients with unresectable tumors. None of these patients underwent tumor resection before they came to M. D. Anderson. Treatment regimens during the entire disease process were collapsed into 3 groups: 1) gemcitabine (GEM)-cisplatin (CDDP) (including oxaliplatin)-based therapy, including GEM/CDDP alone or followed by GEM/radiation; 2) GEM-based therapy, including GEM alone, GEM/radiation, and GEM/investigational agents; and 3) 5-fluorouracil (5-FU)-based therapy, including 5-FU/radiation, 5-FU/other agents, and 5-FU/other agents/radiation. The majority of patients who received 5-FU (88%) received concurrent radiotherapy. Capecitabine, 1 of the synthesized 5-FU prodrugs, was the most common agent administered in 5-FU-based therapy (received by approximately 95% of patients). Treatment was started within 1 month of pathologic diagnosis of pancreatic cancer.

Survival Measurement

The subset of 290 patients was followed through December 30, 2005. The primary endpoint was overall survival (OS) duration from the date of pathologic diagnosis of pancreatic cancer to the date of death from any cause. Patients who were alive at the end of the study period were censored on the last date of follow-up. Each patient's vital status was obtained and cross-checked with at least 1 of the following: inpatient medical record, the M. D. Anderson Tumor Registry, and the Social Security Death Index.²⁵

Genotyping

Genomic DNA was extracted from peripheral blood mononuclear cells that were obtained from the participants by using the Qiagen DNA isolation kit (Qiagen, Valencia, CA). The DNA aliquot was stored at 4°C for immediate use. *GSTM1* and *GSTT1* null genotypes were identified by using multiplex polymerase chain reaction, as described previously.²⁶ The experiment reagents were purchased from PGC Scientifics (Frederick, MD). The *GSTP1* polymorphisms were identified by using the Masscode system (BioServe Biotechnologies, Ltd., Laurel, MD). We analyzed a random 10% of samples in duplicate for quality control. Any discrepancy in genotype calls (0.2% of the duplicate) was resolved by using additional genotyping.

Unsuccessful genotyping occurred most often in *GSTP1* assays (<6% of samples) and was caused by inadequate quality or quantity of DNA.

Statistical Analyses

The Intercooled Stata 9.0 software program (Stata Corporation, College Station, TX) and SPSS 12.0 software (SPSS Inc., Chicago, IL) were used for statistical analyses. All of the statistical tests were 2-tailed, and P values $\leq .05$ were considered statistically significant. The Pearson chi-square test was used to examine differences in the distribution of the risk factors and genotypes between patients and controls. The SNPalyze software program (DYNACOM Company, Ltd., Mobara, Japan) was used to test for Hardy-Weinberg equilibrium of *GSTP1* genotypes and linkage disequilibrium of the 2 alleles. The effect of different allele combinations of the *GSTP1* gene was evaluated by using haplotype analysis. Haplotypes were reconstructed from the genotype data by using the PHASE software program (version 2).²⁷ A diplotype (combined genotype) was assigned for each participant.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated by using an unconditional logistic regression model to examine the association between genotype and pancreatic cancer risk. Potential confounding factors were adjusted in the multivariate model when relevant (ie, when their removal from the multivariate model caused the β parameter estimates to change by >10%). Potential multiplicative interactions between gene-gene, gene and age (<62 years vs ≥ 62 years; 62 years was the median age in the control group), smoking (never-smoker vs ever-smoker), and pack-years of smoking (light smoker vs heavy smoker; the median number of pack-years in ever-smokers among controls was used as the cut-off point) were explored by generating a cross-product term in the unconditional logistic regression models. The likelihood-ratio test was used to test the significance of the interaction term in the models.

Survival curves were estimated using the Kaplan-Meier product-limit method. Differences in the survival curves were tested by using the log-rank test. Factors that showed a significant effect on survival in the log-rank test were included in the multivariate Cox proportional hazards model to estimate hazard ratios (HRs) and the 95% CIs. Stratified analyses were performed to evaluate the association between genotypes and OS by age, sex, tumor resection, clinical stage, and treatment modality, as defined beforehand. Bonferroni correction was used to adjust the statistical significance level when multiple testing was performed in which $\alpha = .05/k$, with k equal to the number of independent hypotheses tested.

RESULTS

Characteristics of the Study Participants

There were no significant differences in distribution according to age (10-year intervals) or sex between patients and controls (P .37 and P .40, respectively). The mean age was 61.7 years (range, 37-87 years) for patients and 61.4 years (range, 32-88 years) for controls. Women accounted for 43.8% and 47.0% of patients and controls, respectively. Ever-smokers were more prevalent among patients (62.5%) than among controls (53.3%; $P = .02$), with an unadjusted OR of 1.46 (95% CI, 1.06-2.01). The prevalence of heavy smoking (≥ 22 pack-years) was 38.1% in patients and 27.0% in controls ($P = .01$; data not shown).

Genotype and Haplotype

Table 1 shows the genotype distribution in patients and controls. The prevalence of the genotype or variant allele was within the ranges commonly reported in whites of European ancestry.^{28,29} The *GSTP1* genotype distribution was in Hardy-Weinberg equilibrium in both patients and controls ($P > .30$). Ile¹⁰⁵Val and Ala¹¹⁴Val were in complete linkage

disequilibrium ($P < .0001$; $D' = 1.0$ for both patients and controls). Three haplotypes putatively were inferred— $^{105}\text{Ile-}^{114}\text{Ala}$ (65.9%), $^{105}\text{Val-}^{114}\text{Ala}$ (25.9%), and $^{105}\text{Val-}^{114}\text{Val}$ (8.2%)—which corresponded to the *GSTP1**A, *GSTP1**B, and *GSTP1**C alleles, respectively.^{19,30} The *GSTP1**D allele ($^{105}\text{Ile-P}^{114}\text{Val}$) was not found in our study population. The haplotype distribution did not differ between patients and controls ($P = .64$). Six diplotypes (variant combinations) were reconstructed: *GSTP1* *A/*A, *A/*B, *A/*C, *B/*B, *B/*C, and *C/*C. It is noteworthy that the *GSTP1**A/*C diplotype was related to a lower risk of pancreatic cancer compared with the *GSTP1**A/*A diplotype (OR, 0.62; 95% CI, 0.37-1.03) (Table 1). We defined the genotype as *GSTP1**C-containing if the $^{105}\text{Val-}^{114}\text{Val}$ allele combination was present; we classified all other genotypes as non-*GSTP1**C reference genotypes.²⁹

Potential *GSTP1* Polymorphism and Age Interaction in the Risk-association Study

We observed a potential interaction between age and the *GSTP1* Ile¹⁰⁵Val polymorphism in modifying the risk of pancreatic cancer ($P_{\text{interaction}} = .05$) (Table 2). Furthermore, older individuals (aged ≥ 62 years) who carried the *GSTP1**C ($^{105}\text{Val-}^{114}\text{Val}$)-containing genotype had a nonsignificant reduced risk of pancreatic cancer compared with younger individuals who carried the non-*C genotype (OR adjusted for sex and pack-years of smoking, 0.54; 95% CI, 0.29-1.02). The interaction effect between *GSTP1**C and age also was not statistically significant ($P = .22$).

Clinical Characteristics of the Patients

The characteristics of the subset of 290 patients who were included in the survival analysis (age, sex, and smoking status) were similar to the characteristics of the entire patient group. Of those 290 patients, 84 patients (29.0%) had localized tumors, 51 patients (17.6%) had potentially resectable tumors, 94 patients (32.4%) had locally advanced tumors, and 61 patients (21.0%) had metastatic tumors. During the study period, 69.3% of the patients died, and the median survival duration was 11.8 months. The median follow-up duration for the surviving patients was 24.5 months. The log-rank test showed that female sex, tumor resected, early-stage disease (localized or potentially resectable vs locally advanced or metastatic), low baseline serum CA19-9 level (categorized by quartile distribution), and a good performance status (<3) were significant, positive prognostic factors for OS at an $\alpha = .05$ level of significance. These factors were included in the Cox regression model to estimate the adjusted HR.

Genotype and Survival According to Treatment Modalities

We observed no statistically significant associations between any of the polymorphisms and the clinical characteristics, treatment modalities, or OS of patients (log-rank test; all P values $\geq .40$). Because the association between polymorphisms and OS did not differ according to the first-line or second-line therapy, the analysis was based on whether patients ever received GEM/CDDP-, GEM-, or 5-FU-based therapy (Table 3).

Among the patients who received GEM/CDDP-based treatment, *GSTP1* Val¹⁰⁵Val carriers had a longer median survival time (MST) than patients who carried the other 2 genotypes (log-rank test; $P = .02$). In the patients who received GEM-based treatment, the *GSTP1* ¹¹⁴Val carriers survived significantly shorter than the Ala¹¹⁴Ala carriers (log-rank test; $P = .02$). However, the associations were not statistically significant after other clinical predictors were considered. The *GSTP1* Ile¹⁰⁵Val polymorphism was associated significantly with OS in 138 patients who received 5-FU-based therapy. The MST was 15.8 months (95% CI, 13.1-20.9 months) for patients who carried the Ile/Ile genotype, 22.2 months (95% CI, 16.0-37.9 months) for patients who carried the Ile/Val genotype, and 35.8 months (95% CI, 14.4 months to not achieved) for patients who carried the Val/Val genotype (log-rank test; $P = .02$) (Fig 1A). Compared with the Ile¹⁰⁵Ile genotype, the adjusted HR was 0.64 (95% CI, 0.38-1.09; $P = .06$).

for the Ile¹⁰⁵Val genotype and 0.40 (95% CI, 0.18-0.89; $P = .015$) for the Val¹⁰⁵Val genotype. The *GSTP1* Ile¹⁰⁵Val polymorphism had no effect on OS in patients who did not receive 5-FU (Fig.1B). Furthermore, the *GSTP1**C carriers survived significantly longer than patients who carried the non-*C genotypes (adjusted HR, 0.45; 95% CI, 0.22-0.94; $P = .025$) (Table 3). However, after Bonferroni correction for multiple testing, the different survival function by *GSTP1* genotype (*C vs non-*C) was not statistically significant ($P = .025$) at an α level of .17 ($\alpha = .05/3$, assuming 3 independent hypotheses because of 3 treatment regimens). Tumor resection, tumor stage, the *GSTP1* Ile¹⁰⁵Val polymorphism, and the serum CA19-9 level remained significant independent prognostic factors for survival among the patients who received 5-FU.

There was no significant interactive effect between *GSTP1* polymorphisms and smoking status or pack-years of smoking. In addition, there was no suggestive association between *GSTM1* and *GSTT1* genotypes and the risk or survival of pancreatic cancer, either in combination with other polymorphisms or with other exposure factors (data not shown).

DISCUSSION

To our knowledge, this study is the first to suggest a role of *GSTP1* polymorphisms in pancreatic pathogenesis. We observed that the *GSTP1**C allele potentially was related to a reduced risk of pancreatic cancer in older individuals and was associated significantly with a reduced hazard of dying in patients who received 5-FU-based treatment. It is unlikely that the *GSTM1* and *GSTT1* null genotypes play a major role in pancreatic pathogenesis.

Individuals with reduced GST enzymatic activity may be at a greater risk for cancer because of decreased detoxification of tobacco carcinogens. Results from a previous study on pancreatic cancer indicated an interaction between the *GSTT1* null genotype and heavy smoking in risk modification.³¹ Despite the finding in the current study that smoking is a significant risk factor for pancreatic cancer, we did not detect any gene-smoking interaction effect. Instead, we observed a nonsignificant, negative association between the risk of pancreatic cancer and the presence of the *GSTP1**C allele exclusively in older individuals. The *GSTP1**C variants encode the amino acids ¹⁰⁵Val [in the central part of the hydrophobic substrate binding site (H site)] and ¹¹⁴Val (at the beginning of helix 5 outside the H site). Such amino acid substitutions may limit free access of the substrate to the H site, the efficient conjugation with glutathione, and the thermostability of the enzyme.^{32,33} Several studies have reported an age-specific effect of the *GSTP1* polymorphism on the risk of cancer.^{34,35} The underlining biologic mechanism remains unclear. The possible interaction between age and *GSTP1* genotype should be interpreted with caution. Previous studies of the association between *GSTP1* polymorphisms and cancer risk generated mixed results.³⁶⁻³⁸ The discrepancy may be explained in part by the variations in study size, control selection, and genotyping methods as well as by different levels of metabolizing activity conferred by particular alleles toward the electrophilic compounds that are major etiologic agents in certain organs.

Using various study systems, it has been shown that different *GSTP1* alleles have different degrees of protection against the cytotoxicity of different anticancer agents.³⁹ For example, the *GSTP1**A allele has significantly higher activity against 1-chloro-2,4-dinitrobenzene,¹⁹ thiotepa,^{39,40} and chlorambucil⁴¹; whereas *GSTP1**B and *GSTP1**C have higher conjugation activity toward cisplatin, carboplatin,³⁹ and epoxides of benzo[*a*]pyrene.⁴² Expression of GST- π is up-regulated significantly in pancreatic adenocarcinoma,⁴³ indicating its potential role in acquired resistance to certain anticancer drugs. Among the various anticancer agents involved in pancreatic cancer treatment, CDDP is the only one shown to be the substrate for GST- π . However, we did not observe that *GSTP1* polymorphisms modified the survivorship of patients who received CDDP-based therapy, but we did observe a reduced hazard of dying

associated with the *GSTP1**C variant allele in patients who received 5-FU or 5-FU after CDDP. Although capecitabine is a 5-FU prodrug that undergoes complex metabolic pathways and nuclear transport activity before exerting its cytotoxic activity,⁴⁴ no established data have demonstrated that GSTs are involved in the conjugation of 5-FU and its intermediate metabolites. Nevertheless, results from a previous study indicated an increased survival associated with the *GSTP1*¹⁰⁵Val variant in patients with advanced colorectal cancer who received 5-FU/oxaliplatin.¹² Results from another study⁴⁵ indicated an increase in GST- π expression in human gastrointestinal cancer cells after sequential administration of CDDP and 5-FU. The same study⁴⁵ also showed that resistance of a gastrointestinal cancer cell line to 5-FU was related to the expression of multidrug resistance-associated protein. Multidrug resistance-associated protein and GST- π are common cofactors in drug resistance. Goto et al.⁴⁶ demonstrated that GSH and GST- π are not important to the intracellular metabolism of 5-FU; however, those authors observed nuclear GST- π accumulation in cancer cells in response to treatment with several anticancer drugs, including 5-FU. This evidence lent some indirect support to the association between *GSTP1* polymorphisms and survival in patients who received treatment with 5-FU. We speculated that the *GSTP1**C allele may affect cellular sensitivity to 5-FU through the drug-resistance mechanism. GST- π is a known regulator of the activity of Jun N-terminal kinase (JNK), which is activated transiently in response to oxidative stress.⁴⁷ The *C allelic variant may interfere with the regulatory role of GST- π on JNK activity and, ultimately, in the modulation of apoptosis, depending on the redox status of the cell.³² Another possibility is that the *GSTP1* gene polymorphisms are in linkage disequilibrium with other nearby genes that determine the biologic properties of 5-FU.

In the current study, we failed to demonstrate any effect of GSTM1 and GSTT1 polymorphisms on pancreatic cancer risk and survival either individually or in combination with other factors. The lack of an association with risk was consistent with previous findings.^{48,49} The predominant expression of GST- π in pancreatic cells may explain why polymorphisms of *GSTP1*, but not of GSTM1 or GSTT1, exerted certain effects on risk and survival of pancreatic cancer in this study.^{50,21} Alternatively, deficiency of an individual GST-I and GST- Θ isoenzyme may be compensated by other isoforms. We may have missed weak effects conferred by GSTM1 and GSTT1 polymorphisms, because our genotyping assay could not distinguish between wild-type and heterozygous individuals.⁵¹

Our survival analysis was limited in a number of ways. 1) Although we adjusted significant predictors of clinical outcome of pancreatic cancer in the multivariate models, we do not know whether residual confounding effects of tumor resection or tumor stage or uncontrolled effects of multiple chemotherapy agents or nutritional status would bias the study observations. 2) We were unable to monitor the cytotoxic effects in patients who received chemotherapy. Indeed, clinical outcomes reflect the balance of the drug response of cancer cells and cytotoxic effects on normal cells. 3) It is not feasible to evaluate GST expression at the messenger RNA or protein levels or enzyme activity in the pancreas during the course of treatment. Therefore, genotype and phenotype associations cannot be established. 4) After Bonferroni correction for multiple testing, the association between the *GSTP1**C allele and survival in patients who received treatment with 5-FU was not statistically significant. Therefore, the preliminary finding from this hypothesis-generating study must be replicated in other studies. 5) Our observations were made among non-Hispanic white patients and may not be applicable to other ethnic groups.

In summary, in this report, we have data suggesting that genetic polymorphisms of *GSTP1* may be among the mechanisms that modify the risk of pancreatic cancer in older individuals and affect the survival of patients who receive 5-FU-based treatment. Because our major findings were based on post-hoc hypotheses, they must be confirmed in larger, well-characterized populations. Both risk and survival are phenotypic consequences of the interplay

of multiple genes in different pathways. Further in-depth studies will be required to improve our understanding of the roles of genetic variations and molecular regulatory machineries of GST- π and other players in pancreatic cancer development and clinical management.

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FIGURE 1.

The probability of survival is illustrated according to the presence of the glutathione S-transferase P1 (*GSTP1*) isoleucine (Ile)→valine (Val) exchange at codon 105 (Ile¹⁰⁵Val) polymorphism in patients who received 5-fluorouracil (5-FU)-based chemotherapy/chemoradiation (A) and patients who received therapies other than 5-FU (B). *P* values were determined from log-rank tests.

TABLE 1
Distribution of Glutathione S-transferase Genotypes in Pancreatic Cancer Patients and Controls

Genotype	No. (%)		Unadjusted OR [95% CI]
	Patients (n = 352)	Controls (n = 315)	
GSTM1			
Wild type	187 (54.0)	157 (49.8)	1.00
Null	159 (46.0)	158 (50.2)	0.84 [0.62-1.16]
GSTT1			
Wild type	271 (78.6)	248 (78.7)	1.00
Null	74 (21.4)	67 (21.3)	1.01 [0.68-1.49]
GSTP1 Ile ¹⁰⁵ Val			
Ile/Ile	151 (44.7)	117 (39.3)	1.00
Ile/Val	141 (41.7)	146 (49.0)	0.75 [0.54-1.04]
Val/Val	46 (13.6)	35 (11.7)	1.02 [0.62-1.68]
Ile/Val and Val/Val	187 (55.3)	181 (60.7)	0.80 [0.58-1.10]
Val allele frequency	0.34	0.36	
GSTP1 Ala ¹¹⁴ Val			
Ala/Ala	286 (85.4)	242 (81.2)	1.00
Ala/Val	46 (13.7)	55 (18.5)	0.71 [0.46-1.08]
Val/Val	3 (0.9)	1 (0.3)	2.53 [0.26-24.6]
Ala/Val and Val/Val	49 (14.6)	56 (18.8)	0.74 [0.49-1.13]
Val allele frequency	0.08	0.10	
GSTP1 diplotype*			
*A/*A	161 (45.8)	127 (40.3)	1.00
*A/*B	117 (33.2)	113 (35.9)	0.82 [0.58-1.16]
*A/*C	32 (9.1)	41 (13.0)	0.62 [0.37-1.03]
*B/*B	25 (7.1)	19 (6.0)	1.04 [0.55-1.97]
*B/*C	14 (4.0)	14 (4.5)	0.79 [0.36-1.71]
*C/*C	3 (0.8)	1 (0.3)	2.34 [0.24-23.0]

OR indicates odds ratio; 95% CI, 95% confidence interval; GST, glutathione S-transferase; *GSTM1*, GST M1 polymorphism; *GSTT1*, GST T1 polymorphism; *GSTP1*, GST P1 polymorphism; Ile, isoleucine; Val, valine; Ala, alanine.

* A, 105Ile-114Ala; *B, 105Val-114Ala; *C, 105Val-p114Val.

TABLE 2
Glutathione S-transferase P1 Polymorphisms and Age Interaction in Modifying Pancreatic Cancer Risk

Genotype	Age, y	No. of patients/controls	Adjusted OR [*]	P [†]
<i>GSTP1</i> Ile ¹⁰⁵ Val				
Ile/Ile	<62	57/57	1.00	
Ile/Ile	≥62	89/57	1.61 (0.98-2.65)	
Ile/Val and Val/Val	<62	93/79	1.20 (0.74-1.92)	
Ile/Val and Val/Val	≥62	89/101	0.92 (0.57-1.47)	.05
<i>GSTP1</i> Ala ¹¹⁴ Val				
Ala/Ala	<62	128/109	1.00	
Ala/Ala	≥62	158/133	0.99 (0.70-1.40)	
Ala/Val and Val/Val	<62	29/26	0.94 (0.52-1.70)	
Ala/Val and Val/Val	≥62	20/30	0.52 (0.28-0.98)	.22
<i>GSTP1</i> genotypes				
Non- [*] C	<62	135/119	1.00	
Non- [*] C	≥62	168/140	1.04 (0.74-1.45)	
[*] C	<62	29/26	0.98 (0.54-1.76)	
[*] C	≥62	20/30	0.54 (0.29-1.02)	.22

OR indicates odds ratio; *GSTP1*, glutathione S-transferase P1 polymorphism; Ile, isoleucine; Val, valine; Ala, alanine; ^{*}C, ¹⁰⁵Val¹¹⁴Val.

^{*} ORs were adjusted for sex and for the number of smoking pack-years (continuous).

[†] P value for likelihood ratio test for interaction between age (<62 years vs ≥62 years; 62 years was the median age in the control group) and *GSTP1* polymorphisms.

Glutathione S-transferase P1 Polymorphisms and Overall Survival by Treatment Modality in Patients With Pancreatic Cancer

TABLE 3

Polymorphism	GEM/CDDP-based treatment					GEM-based treatment					5-FU-based treatment				
	No. of patients	No. of deaths	MS, Months	HR (95% CI)	P [†]	No. of patients	No. of deaths	MS, Months	HR (95% CI)	P [†]	No. of patients	No. of deaths	MS, Months	HR (95% CI)	P [†]
Overall	150	105	15.9			146	109	17			138	87	18.6		
<i>GSTP1</i> ¹⁰⁵ Ile/Ile	62	45	16.2	1.00		64	44	18.1	1.00		62	45	15.8	1.00	
Ile/Val	56	42	12.8	1.06 (0.67-1.69)		66	51	14.5	1.03 (0.67-1.57)		49	27	22.2	0.64 (0.38-1.09)	
Val/Val	27	15	24.5	0.74 (0.40-1.37)		13	11	19.6	0.92 (0.46-1.83)		20	9	35.8	0.40 (0.18-0.89)	
Ile/Val and Val/Val	83	57	14.4	0.99 (0.62-1.42)	.02	79	62	16.2	1.00 (0.67-1.51)	.41	69	36	23.3	0.56 (0.34-0.92)	.02
<i>GSTP1</i> ¹¹⁴ Ala/Ala	118	83	15.9	1.00		122	90	18.3	1.00		118	76	18.6	1.00	
Ala/Val and Val/Val	25	16	14.5	1.06 (0.59-1.92)	.46	18	16	8.5	1.58 (0.88-2.82)	.02	18	9	22.3	0.45 (0.24-1.02)	.24
<i>GSTP1</i> genotype Non- ³ C	125	90	15.8	1.00		129	94	18.3	1.00		117	78	16.2	1.00	
*C	25	15	18.2	1.10 (0.60-2.30)	.30	17	15	11.8	1.44 (0.80-2.61)	.02	19	9	22.3	0.45 (0.22-0.94) [‡]	.11

GEM indicates gemcitabine; CDDP, cisplatin; 5-FU, 5-fluorouracil; MS, medial survival; HR, hazard ratio; 95% CI, 95% confidence interval; *GSTP1*, glutathione S-transferase P1 polymorphism; Ile, isoleucine; Val, valine; ALA, alanine; *C, 105Val-114Val.

* HRs were adjusted for sex, tumor resection, tumor stage, CA19-9 value, and performance status.

[†] P value for log-rank test.

[‡] P = .025 (not significant at a Bonferroni-adjusted α level of .017).