Association of *GSTM1*, *GSTT1*, and *GSTP1* Gene Polymorphisms with the Risk of Prostate Cancer: A Meta-analysis

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Abstract

The glutathione *S*-transferase (*GST*) gene superfamily encodes for enzymes involved in conjugation of electrophilic compounds to glutathione. Several polymorphisms in the *GST* genes have been implicated as risk factors for prostate cancer. We did a meta-analysis of 11 studies with *GSTM1* genotyping (2,063 prostate cancer cases and 2,625 controls), 10 studies with *GSTT1* genotyping (1,965 cases and 2,554 controls), and 12 studies with *GSTP1* genotyping (2,528 cases and 3,076 controls). The random effects odds ratio was 1.08 [95% confidence interval (95% CI), 0.93-1.25, no significant between-study heterogeneity] for the *GSTM1* null versus nondeleted genotype and 0.90 (95% CI, 0.73-1.12; $P = 0.03$ for heterogeneity) for the *GSTT1* null versus nondeleted genotype. Overall, the random effects odds ratio was 1.05 (95% CI, 0.90-1.21; $P < 0.01$ for heterogeneity) for the *GSTP1-Val* versus *GSTP1-Ile* allele. For all three polymorphisms, there was a trend for the presence of an association in the earliest published studies, but this did not seem to be validated in subsequent research. For *GSTT1*, larger studies gave different results than smaller ones. The meta-analysis shows that these three polymorphisms are unlikely to be major determinants of susceptibility to prostate cancer on a wide population basis. (Cancer Epidemiol Biomarkers Prev 2005;14(1):176–81)

Introduction

The glutathione *S*-transferase (*GST*) gene superfamily consists of four gene classes (*A*, *M*, *T*, and *P*) encoding for enzymes which catalyze the conjugation of electrophilic compounds to glutathione (1). These enzymes are also believed to play a crucial role in the protection of DNA from oxidative damage (2). GSTM1 and GSTT1 have different substrate specificities in detoxification of carcinogenic polycyclic aromatic hydrocarbons (1). Moreover, GSTT1 may also catalyze the activation of certain xenobiotics to genotoxic metabolites, such as dichloromethane and other halogenated alkanes (3, 4); thus, the net effect (protection or susceptibility) in relationship to carcinogenesis, if any, is difficult to predict. GSTM1 activity is absent in ~40% to 60% of the Caucasian population as a result of the inheritance of two null alleles (5). Similarly, GSTT1 activity is absent (homozygous gene deletion) in ~20% to 30% of Caucasians (5). GSTP1 is a major enzyme involved in the inactivation of cigarette smoke carcinogens, such as benzo [*a*]pyrene diol epoxide, and other toxic constituents, such as acrolein (1). *GSTP1* expression has been studied in preneoplastic and neoplastic prostate lesions (6-9). An A313G transition in exon 5 of the *GSTP1* gene, which replaces isoleucine at codon 105 with valine (*I105V*) within the active site of the enzyme, has been identified (10). This substitution is associated with reduced enzymatic activity for certain substrates and altered thermostability (11, 12).

Molecular epidemiologic studies have presented inconclusive results concerning a potential role of the *GSTM1* (13-23), *GSTT1* (15-24), and *GSTP1* (10, 15-21, 25-28) polymorphisms in prostate cancer susceptibility. Single studies may have been underpowered to detect modest effects. Given the amount of accumulated data, a quantitative synthesis of the evidence and analysis of the between-study heterogeneity was deemed important to perform.

Materials and Methods

Identification and Eligibility of Relevant Studies and Data Extraction. We considered all studies that examined the association of the *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms with prostate cancer. Sources included MEDLINE, EMBASE, and the HuGENet database (last search update 4/2004). The search strategy was based on combinations of ''prostate cancer,'' ''glutathione *S*-transferase,'' ''*GST*,'' ''polymorphism,'' ''allele,'' and ''genetics.'' References of retrieved articles were also screened.

The meta-analysis was designed on the same principles as previous meta-analyses of candidate genetic risk factors for prostate cancer done by our team (29-31). Methodology is given in detail in previous publications (29-31). In brief, studies of unrelated prostate cancer cases and prostate cancer-free controls [with or without benign prostatic hyperplasia (BPH)] were eligible. Cases with prostate cancer were eligible regardless of whether they had a first-degree relative with prostate cancer or not. Among overlapping reports, we retained the one with largest sample size.

Meta-analysis. The analysis for *GSTM1* and *GSTT1* polymorphisms compared cases against controls for the contrast of the null (homozygous deletion of the gene) versus the nondeleted genotype (heterozygous or homozygous presence of the gene), as originally proposed (15). The analysis for the *GSTP1* polymorphism was based on the contrast of alleles.

The odds ratio (OR) was used as the metric of choice. For each genetic contrast, we estimated the between-study heterogeneity across all eligible comparisons using the χ^2-based Q statistic

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(considered significant for $P < 0.10$; ref. 32). Data were combined using both fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird) models (32). Random effects incorporate an estimate of the between-study variance and provide wider 95% confidence intervals (95% CI), when the results of the constituent studies differ among themselves. Random effects are reported unless stated otherwise. Subgroup analyses estimated race-specific ORs.

Table 1. Characteristics of studies included in the meta-analyses

First author, year	Country	Selection/characteristics of cases and controls (age range [mean])		Racial descent	Eligible subjects*	
		Prostate cancer	Controls		Prostate cancer	Controls
Harries, 1997	United Kingdom	Not clarified (62-88 [70.4])	Randomly selected from the Clinical Biochemistry Department at Edinburgh Royal Infirmary	Caucasian	36	155
Murata, 1998	Japan	Histologically documented cancer [73]	Patients with other urological diseases. Serological (PSA, prostatic acid phosphatase), physical and histological examinations [71.2]	Asian	115	204
Wadelius, 1999	Sweden	Not clarified. Family history in 12.4% [71]	Randomly selected from the county population register. Family history in 11.2% [71]	Caucasian	178	160
Autrup, 1999	Denmark	Histologically documented cancer (43-90 [69.4])	Blood donors and healthy men participating in a biomarker study (43-96 [53.2])	Caucasian	153	288
Kelada, 2000	United States	Review of medical records. Men were excluded if they reported exposure to finasteride, were diagnosed more than 12 months before joining the study, or had cancer at any site (41-80 [61.2])	Normal DRE, not elevated serum PSA, no previous cancer diagnosis, no exposure to finasteride at the time of study ascertainment (41-80 [60.2])	Caucasian†	276	499
Steinhoff, 2000	Germany	Histologically documented cancer [65]	Patients undergoing surgery for nonmalignant abdominal diseases. No history of cancer [62]	Caucasian	91	127
Shepard, 2000	United States	Review of medical records and pathology reports (40-84)	Physicians participating in Physicians' Health Study. Cohort with negative clinical history of cancer who returned blood samples (40-84)	Caucasian	590	803
Gsur, 2001	Austria	Histologically documented cancer by TRUS-guided biopsy after a suspicious finding on DRE, elevated serum PSA or both [66]	BPH patients with lower urinary tract symptoms. Prostate cancer was excluded by negative DRE and not elevated serum PSA, by TRUS-guided biopsy, or by transurethral resection of the prostate [65.7]	Caucasian	166	166
Kote-Jarai, 2001	United Kingdom	Histologically documented cancer	Individuals who were spouses of patients enrolled in another cancer study. No previous diagnosis of any cancer	Caucasian	275	280
Murata, 2001	Japan	Histologically documented cancer Serological, physical and biopsy examinations [73]	BPH patients with no previous diagnosis of cancer. Serological, physical and histological examinations [71]	Asian	115	200
Luscombe, 2002	United Kingdom	Histologically documented cancer (n = 190); clinically malignant prostate on DRE, positive bone scan and serum PSA > 20 ng/ml (n = 20) [70.6]	BPH on DRE with serum PSA in the age-related reference range [67]	Caucasian	210	155
Jeronimo, 2002	Portugal	Histologically documented cancer (48-74)	BPH patients (n = 43) and healthy male volunteer blood donors (n = 98 [45-82])	Caucasian	105	141
Kidd, 2003	United States	Review of medical records and pathology reports	Participants of the ATBC Cancer Prevention Study	Caucasian	206	194
Acevedo, 2003	Chile	Histologically documented cancer by TRUS-guided biopsy after a suspicious finding on DRE, elevated serum PSA or both [68.6]	BPH on histological examination after a suspicious finding on DRE, elevated serum PSA or both [63.4]	Caucasian	102	128
Nakazato, 2003	Japan	Histologically documented cancer and prostate cancer in first-degree relatives (40-88 [70.6])	Negative DRE, not elevated serum PSA, without history of cancer (51-88 [71.2])	Asian	81	105

(Continued on the following page)

Table 1. Characteristics of studies included in the meta-analyses (Cont'd)

First author, year	Country	Selection/characteristics of cases and controls (age range [mean])		Racial descent	Eligible subjects*	
		Prostate cancer	Controls		Prostate cancer	Controls
Nam, 2003	Canada	Histologically documented cancer by TRUS-guided biopsy after an abnormal DRE or elevated serum PSA. Family history in 13.7% [66.6]	No invasive cancer in 1 (n = 292), 2 (n = 200), or more (n = 56) biopsy sessions after abnormal DRE or elevated serum PSA. Normal prostate tissue (n = 39), inflammation/BPH (n = 406), and PIN (n = 103) [64.4]	Caucasian ‡	483	548
Medeiros, 2004	Portugal	Histologically documented cancer (45-85)	Not elevated serum PSA (42-84)	Caucasian	150	185

Abbreviations: DRE, digital rectal examination; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
*All eligible subjects were genotyped with the exception of 7 cancer patients and 12 controls (*GSTP1*) in Wadelius et al. (27), 19 cancer patients and 81 controls (*GSTM1*), 20 cancer patients and 30 controls (*GSTT1*) in Kelada et al. (22), 2 cancer patients and 10 controls (*GSTM1*), 2 cancer patients and 2 controls (*GSTT1*), 2 cancer patients and 7 controls (*GSTP1*) in Kote-Jarai et al. (18), 1 cancer patient and 1 control (*GSTP1*) in Luscombe et al. (25), 6 cancer patients and 6 controls (*GSTM1*), 4 cancer patients and 5 controls (*GSTT1*), 36 cancer patients and 26 controls (*GSTP1*) in Kidd et al. (21), and 8 cancer patients and 2 controls (*GSTM1*), 5 cancer patients and one control (*GSTT1*) in Medeiros et al. (23).
† Caucasian (84.0%), African (13.3%), Asian or other (2.7%).
‡ Caucasian (83.9%), African (8.7%), Asian (5.7%), other (1.7%).

Cumulative meta-analysis (33) and recursive cumulative meta-analysis (34, 35) evaluated whether the summary ORs changed over time as data accumulated (36). Inverted funnel plots and the Begg-Mazumdar diagnostic (nonparametric τ correlation coefficient; ref. 37) evaluated whether the magnitude of the observed association was related to each study's variance (38). Finally, we evaluated whether the summary results were different when the analyses were limited to studies that confirmed histologically all prostate cancer cases and specifically screened all controls to rule out prostate cancer.

Analyses were conducted in SPSS 11.0 (SPSS, Inc., Chicago, IL), StatXact (Cytel Inc., Boston, MA), and Meta-Analyst (Joseph Lau, Boston, MA). All *P*s are two tailed.

Results

Eligible Studies

Excluding overlapping data, we identified 17 eligible reports (10, 13-28) with 11, 10, and 12 studies on *GSTM1* (13-23), *GSTT1* (15-24), and *GSTP1* (10, 15-21, 25-28), respectively. There was a considerable diversity of ethnic groups. Twelve reports (13-20, 23-26) selected prostate cancer patients based on a histologic diagnosis from biopsy or prostatectomy, whereas the other five (10, 21, 22, 27, 28) did not clarify the exact diagnostic criteria. Three reports (17, 19, 27) mentioned positive family history of prostate cancer in 12.4%, 13.7%, and 100% of patients, respectively, whereas the remaining did not comment on family history. Controls did not have a clinical diagnosis of prostate cancer at study entry, but the amount of additional screening to exclude prostate cancer differed substantially across studies (Table 1).

With four exceptions (14-16, 25) where the mean age of controls and cases differed by ≥3 years, the reported mean or median age of cases and controls was very similar (difference, ≤2 years) and specific matching for age was described in six studies (20-23, 27, 28). One study also matched for smoking status (28). Only three reports (17, 20, 28) mentioned specifically blinding of the personnel who did the genotyping. All studies used PCR. The distribution of genotypes in control groups was consistent with Hardy-Weinberg equilibrium for the *GSTP1* polymorphism in all studies.

Meta-analyses Databases

GSTM1. The eligible studies included 2,098 patients with prostate cancer and 2,728 controls of whom 2,063 and 2,625, respectively, had genotype data. The null genotype was similarly common among controls of Caucasian descent (48%; 95% CI, 45-51) and Asian descent (45%; 95% CI, 39-51). In controls of Caucasian descent, prevalence was relatively similar in most countries (54% in Denmark, 53% in the United States, 50% in the United Kingdom and Portugal, 49% in Austria, and 45% in Germany), but it was surprisingly low in a Chilean study (23%).

GSTT1. The eligible studies included 1,996 patients with prostate cancer and 2,592 controls of whom 1,965 and 2,554, respectively, had genotype data. The overall prevalence of the null genotype was 19% (95% CI, 17-21) and 49% (95% CI, 43-55) in control subjects of Caucasian and Asian descent, respectively. The prevalence rates of the null genotype across the controls of Caucasian descent were 24% in Portugal and United Kingdom, 20% in Austria, 15% in Denmark and the United States, and 13% in Germany.

GSTP1. The eligible studies included 2,574 patients with prostate cancer and 3,122 controls of whom 2,528 and 3,076, respectively, had genotype data. The prevalence of the *Val* allele was 32% (95% CI, 31-33) and 14% (95% CI, 9-19) in control subjects of Caucasian and Asian descent, respectively. The prevalence rates of the *Val* allele across the control subjects of Caucasian descent were 38% in Austria; 33% in Portugal; 33% in Sweden, Denmark, and the United States; 30% in the United Kingdom; and 27% in Germany. Overall, the prevalence of *Val/Val* homozygosity was 11% and 0% in control subjects of Caucasian and Asian descent, respectively. The respective prevalence rates of *Ile/Val* heterozygosity were 43% and 28%.

Quantitative Synthesis

GSTM1. There was no evidence that the null genotype modified the risk of prostate cancer (Fig. 1A). The summary OR was 1.08 (95% CI, 0.93-1.25, P = 0.34), without statistically significant between-study heterogeneity. No association was observed in subjects of Caucasian (OR, 1.11; P = 0.39, P = 0.04 for between-study heterogeneity) and Asian descent (OR, 1.11; P = 0.61, no significant between-study heterogeneity).

GSTT1. The contrast of genotypes did not suggest any strong genetic effect (Fig. 1B). The summary OR was 0.90 (95% CI, 0.73-1.12; $P = 0.34$) and there was statistically significant between-study heterogeneity ($P = 0.03$ for heterogeneity). We also found no evidence of an association in subjects of Caucasian descent (OR, 1.04; $P = 0.78$, no significant between-study heterogeneity) and Asian descent (OR, 0.91; $P = 0.80$, $P = 0.05$ for between-study heterogeneity).

GSTP1. There was no evidence that the *Val* allele modified the risk of prostate cancer (Fig. 1C). The summary OR was 1.05 (95% CI, 0.90-1.21; $P = 0.54$) and there was highly significant heterogeneity among the 11 study comparisons ($P < 0.01$ for heterogeneity). No association was observed in subjects of Caucasian descent (OR, 1.02; $P = 0.81$, $P < 0.01$ for between-study heterogeneity) and there was only one study with subjects of Asian descent (OR, 1.25; $P = 0.44$).

Bias Diagnostics

GSTM1. The magnitude of the summary OR had not been stable over time and it had changed considerably per year with an apparent continuous dissipation of the postulated effect (by random effects, summary OR for null versus nondeleted genotype was 1.32 at the end of 1998, 1.30 in 1999, 1.15 in 2000, 1.13 in 2001, 1.07 in 2003, and 1.08 in 2004). The effect size was not related to study variance ($P = 0.39$). Analyses limited to studies with rigorous selection of cases and controls yielded similar results [9 comparisons (3,625 subjects); OR, 1.14; 95% CI, 1.00-1.30, no significant between-study heterogeneity].

GSTT1. The magnitude of the summary OR continuously diminished over time (by random effects, summary OR for null versus nondeleted genotype was 1.30 at the end of 1999, 1.15 in 2000, 0.94 in 2001, 0.91 in 2003, and 0.90 in 2004). Moreover, there was evidence that larger studies showed different results than smaller studies ($P = 0.09$ for the tau correlation between the natural logarithm of the OR and the study variance). Analyses limited to studies with rigorous selection of cases and controls excluded any effect [8 comparisons (3,403 subjects); OR, 0.98; 95% CI, 0.77-1.25; $P = 0.05$ for between-study heterogeneity].

GSTP1. The magnitude of the summary OR had not been stable over time and it had changed considerably after the first year (by random effects, summary OR for *Val* versus *Ile* was 1.56 at the end of 1997, 1.11 in 1999, 0.99 in 2000, 1.00 in 2001, 1.02 in 2002, and 1.05 in 2003). The effect size was not related to study variance ($P = 0.31$). Analyses limited to studies with rigorous selection of cases and controls yielded similar results [8 comparisons (6,726 alleles); OR, 1.04; 95% CI, 0.86-1.25; $P < 0.01$ for heterogeneity].

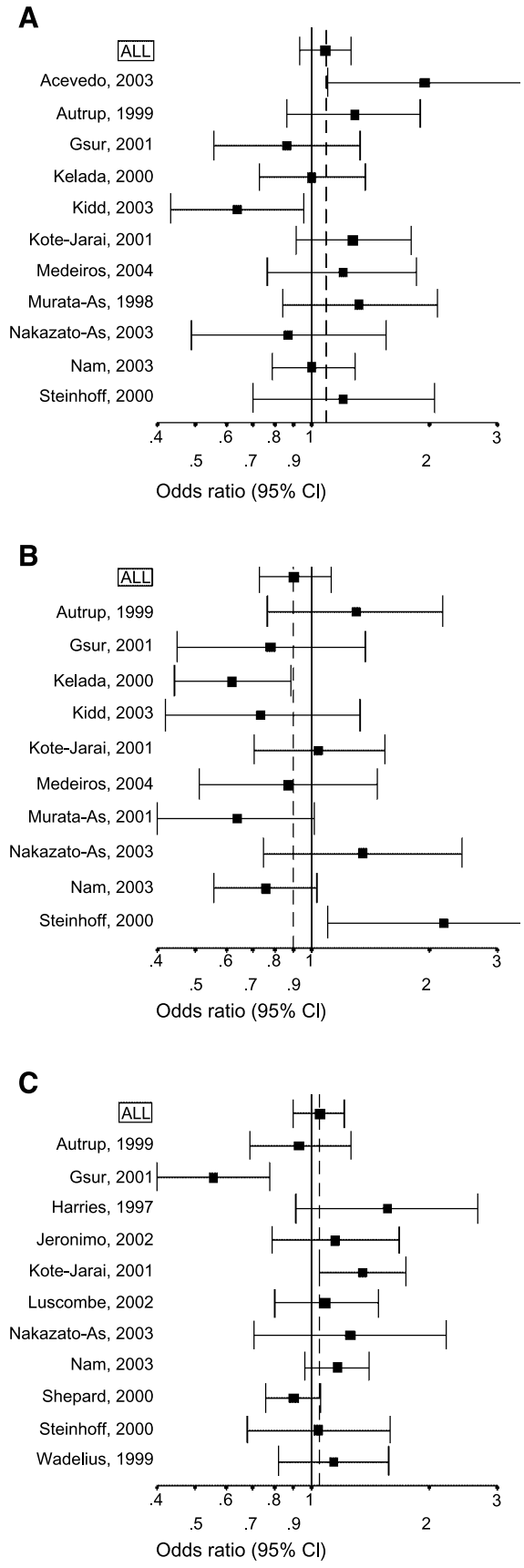

Figure 1. A. Effect of the *GSTM1* null versus nondeleted genotype on the risk of prostate cancer. Each comparison is presented by the name of the first author and the year of publication. *As,* subjects of Asian descent. The point estimate of the OR and the accompanying 95% CI for each comparison are shown. Also shown is the summary random effects estimate for the comparison along with the respective 95% CI. Values >1, an increased risk for prostate cancer with the null genotype. **B.** Effect of the *GSTT1* null versus nondeleted genotype on the risk of prostate cancer. Values >1, an increased risk for prostate cancer with the null genotype. Otherwise, figure set up as per Fig. 1A. **C.** Effect of the *GSTP1-Val* versus *GSTP1-Ile* allele on the risk of prostate cancer. Values >1, an increased risk for prostate cancer with the *Val* allele. Otherwise, figure set up as per Fig. 1A.

Discussion

The current evidence does not show any increased risk for prostate cancer conferred by these three common *GST* polymorphisms and the 95% CIs are narrow enough to exclude a large genetic effect. Whereas a trend for potential genetic effects was suggested in early data for all three polymorphisms, this was not validated with subsequent research. Postulated genetic associations for prostate cancer need to be carefully validated across several studies, because early and small genetic association studies may come up with spurious findings (36, 38-40).

The biochemical evidence for a putative relationship of these *GST* polymorphisms with prostate cancer is also equivocal. These enzymes may regulate pathways that prevent damage from several carcinogens (1-4). However, it is unlikely that specific environmental carcinogens whose effect might also be modifiable by *GST* genotype have a high attributable fraction for prostate cancer. For *GSTT1* in particular, protective and susceptibility effects to cancer may counterbalance each other. In addition to metabolism of chemical carcinogens, GST enzymes metabolize steroid hormones, compounds found in the diet, and other agents potentially involved in prostate carcinogenesis. Furthermore, GST enzymes are involved in the intracellular transport of steroid hormones (41) and the isomerization of androst-5-ene-3,17-dione to androst- 4-ene-3,17-dione, the immediate precursor of testosterone (1). However, the exact role of steroid hormones in the pathogenesis of prostate cancer has been a contentious issue (42, 43). Polymorphisms in genes coding for enzymes of the androgen biosynthesis and metabolism pathway have also been postulated as prostate cancer determinants (44, 45), but meta-analyses have yielded mostly negative results (29, 30).

The *GST* polymorphisms have also been studied extensively in terms of susceptibility for other malignancies. Previous meta-analyses on these polymorphisms yielded negative results for breast (46) and colon cancer (47), whereas others have suggested the possible presence of modest associations for head and neck (48), lung (49), and bladder cancer (50). Nevertheless, even in the latter cases, the summary ORs have been small (in the range of 1.17-1.44).

Some analytic issues should also be considered. First, some nondifferential misclassification bias is possible. Most studies could not exclude latent prostate cancer cases in the control group. Furthermore, control groups included a large, often unknown proportion of subjects with BPH. BPH may be also affected by these same polymorphisms, but susceptibility to prostate enlargement is a different issue than susceptibility to cancer. We could not address whether these *GST* polymorphisms may have an effect on the clinical behavior of prostate cancer or other clinicopathologic attributes. The meta-analysis cannot exclude the possibility that other polymorphisms in *GST* genes may still be useful to pursue. Moreover, we could not address gene-gene and gene-environmental interactions. The latter may be important for genes that code proteins with detoxifying function, but would require detailed information on exposures to various potential carcinogens and individual-level data (51) and would be most meaningful only for common exposures that are found to be strong risk factors for the disease.

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