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**要　　旨**：喫煙は尿路上皮がんの主要な原因の一つであるが,すべての喫煙者ががんに罹患するわけではない．この事象から,尿路上皮がんのリスク要因として,遺伝的背景の存在が示唆されてきた．タバコの煙には多くのがん原性化学物質が含まれており,これらは第Ⅰ相,第Ⅱ相の薬物代謝酵素によって活性化,解毒される．従ってDNAと反応する究極がん原性物質の量は,活性化と解毒の代謝的バランスによって決定されると考えられる．近年,薬物代謝酵素には遺伝子多型の存在が明らかとなり,シトクロームP450,グルタチオンS-トランスフェラーゼ (GST),N-アセチルトランスフェラーゼ(NAT),スルフォトランスフェラーゼの遺伝子多型と尿路上皮がんとの関連性に関する多数の分子疫学研究が実施されている．GSTM1遺伝子欠損型,NAT２遅延型では軽度のリスクの上昇が報告されているが,他の薬物代謝酵素との関連性については一致した結果が得られていない．これらの関連性を明らかにするためには,優れた研究デザインによる大規模研究が必要である．

**キーワード**：分子疫学，膀胱がん，シトクロームP450，グルタチオンS-トランスフェラーゼ，N-アセチルトランスフェラーゼ．

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REVIEW

# Genetic polymorphisms of human cytosol glutathione *S*-transferases and prostate cancer

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Glutathione *S*-transferases (GSTs) are involved in the metabolism of a wide range of carcinogenic chemicals. In humans, cytosol GSTs are divided into eight classes: α (GSTA), μ (GSTM), π (GSTP), θ (GSTT), τ (GSTZ), σ (GSTS), ο (GSTO) and κ (GSTK). The allelic polymorphism of these enzymes is associated with variations in enzyme activity; hence, it may affect the concentration of activated carcinogenic chemicals in the body. In addition to the metabolism of chemical carcinogens, GSTs metabolize steroid hormones, compounds in the diet and other agents potentially involved in prostate carcinogenesis. Three genetic polymorphisms of GSTs, *GSTM1*0* (null), *GSTT1*0* (null) and *GSTP1* A313G, have been well documented. No consistent associations between *GSTM1*, *GSTT1* or *GSTP1* genotypes and prostate cancer have been observed. Recent meta-analysis reports show that these polymorphisms of *GSTM1*, *GSTT1* and *GSTP1* are unlikely to be major determinants of susceptibility to prostate cancer.

Keywords: cancer, glutathione transferase, GST, methylation, polymorphism, prostate, SNP

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It is generally accepted that cancer risk is determined by the interaction of environmental and genetic factors. Except for hereditary tumors, external carcinogenic exposure is involved in human tumorigenesis. Carcinogenic chemicals, however, undergo a complicated process of metabolism in the human body. Typically, these chemicals are activated by the so-called Phase I enzymes, resulting in the formation of electrophilic, reactive compounds [1]. The amount of active carcinogens is in good correlation with the risk of DNA damage and cancer formation. Detoxifying enzymes, Phase II enzymes, help in the removal of carcinogens from the body [2]. Most of these enzymes conjugate the carcinogenic chemical with a small molecule, making it less toxic and more water-soluble. Therefore, it seems logical to assume that the detoxifying capacity determines, to a certain extent, individual susceptibility to cancer. Among the Phase II enzymes, the glutathione *S*-transferase (GST) superfamily is suspected to have an influence on cancer susceptibility [3]. GSTs are likely to contribute to interindividual differences in responses to xenobiotics. This review describes the relationship between genetic polymorphisms of human cytosol GSTs and prostate cancer.

## Prostate cancer

Carcinoma of the prostate is most common in Western countries and second only to lung cancer as a cause of death due to cancer [4]. As well as other malignancies, prostate carcinoma develops through the accumulation of somatic genetic and epigenetic alterations, resulting in the activation of tumor suppressor genes, caretaker genes and oncogenes. The overall lifetime probability of developing clinically evident prostate cancer by the age of 80 years is much lower than its prevalence at autopsy. The estimated lifetime risk for diagnosis of prostate cancer is 16%, and out of that 3–4% die due to this disease [5]. There is a large variation in prostate cancer incidence rates between racial/ethnic groups, being highest among Africans, intermediate among Caucasians and lowest among Asians [6]. This international variation suggests that both genetic and environmental factors play important roles in the etiology of prostate cancer.

Recently, a new hypothesis has been proposed, in which exposure to environmental factors, such as infectious agents and dietary carcinogens, and hormonal imbalances lead to injury of the prostate, resulting in carcinoma of the prostate [7,8]. Approximately 20% of all human malignancies in adults result from chronic inflammation. Although the cause of prostatic inflammation is unclear, there are various potential sources such as direct infection, urine reflux inducing chemical and physical trauma, dietary factors, estrogens and combinations of these. Epidemiological studies show significant associations between infection, inflammation and prostatic carcinoma, however, these are inconclusive. Many noninfectious mechanisms appear to lead to prostatic epithelial cell and stromal damage; for example, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP) induces

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prostate inflammation and atrophy. These phenomena are thought to be related to cellular detoxification. Such environmental factors interact with a variable genetic predisposition related, in part, to differences in the metabolism of carcinogen xenobiotics. Genetic polymorphisms that affect the expression of genes regulating the activity of specific enzymes may modulate susceptibility to prostate cancers. Among the candidate genes to be studied in relation to these interindividual differences, cytosol GST may play a relevant role.

## GST & genetic polymorphism

The glutathione transferases (EC 2.5.1.18) have historically also been called glutathione *S*-transferases, and it is this latter name that gave rise to the widely used abbreviation, GST. GSTs are prominent contributors to the cellular biotransformation of electrophilic compounds. They provide protection against the genotoxic and carcinogenic effects of numerous xenobiotics and compounds of endogenous origins. Originally, GSTs were found in the soluble cell fraction, and the enzymes occurring in the cytoplasm are usually referred to as cytosol GSTs.

The cytosol GST enzymes have a relatively wide range of substrates, for example, polycyclic aromatic hydrocarbon, monohalomethanes, heterocyclic amines, ethylene oxide and different pesticide solvents. In addition to the metabolism of chemical carcinogens, GST enzymes are involved in the intracellular transport of steroid hormones [9] and the isomerization of androst-5-ene-3,17-dione to androst-4-ene-3,17-dione, the immediate precursor of testosterone [10].

In humans, cytosol GSTs are divided into eight classes: α (GSTA), μ (GSTM), π (GSTP), θ (GSTT), τ (GSTZ), σ (GSTS), ο (GSTO) and κ (GSTK), each of which contains one or more of the homodimeric or heterodimeric isoforms [11,12]. There have been many reports of genetic polymorphisms for *GSTM1*, *GSTM3*, *GSTT1*, *GSTP1* and *GSTA1*, resulting in either decreased or altered enzyme activity. Owing to their role in metabolism, these polymorphisms may play an important role in prostate cancer susceptibility.

### *GSTM1*

A total of five μ class genes (*M1–M5*) situated in tandem on chromosome 1p13.3 have been identified. *GSTM1* is expressed in human liver, stomach, brain and other tissues, while *GSTM2–M5* subunits have been detected in extrahepatic tissues. *GSTM1*, located on chromosome 1p13.3, detoxifies a number of electrophillic substances, including carcinogens such as polycyclic aromatic hydrocarbons, ethylene oxide, epoxides and styrene. *GSTM1* expression is hormonally controlled and induced by phenobarbital or by propylthiouracil [13]. Some lipid peroxidation products may be common substrates of both GSTM1 and GSTT1 [14].

Three polymorphisms of the *GSTM1* gene, namely *GSTM1*0*, *GSTM1*A* and *GSTM1*B*, have been identified (Table 1). *GSTM1*0* is a deleted allele, and the homozygous allele (*GSTM1*-null genotype) expresses no GSTM1 protein. Most studies of *GSTM1* polymorphism and cancer have compared the homozygous deletion genotype with the genotypes containing at least one functional allele. *GSTM1A* and *GSTM1B* differ by a C→G substitution at base position 534. This C→G substitution results in the substitution of Lys→Asn at amino acid 172 [35]. The Lys→Asn substitution results in no functional difference between the two alleles [36]. As a result, *GSTM1A* and *GSTM1B* are categorized together as non-null conjugator phenotypes.

Table 2 summarizes the frequency of homozygous deletion polymorphisms in *GSTM1*. The homozygous deletion genotype frequency in *GSTM1* ranges from 22.7 to 54.2% in Caucasians, from 27.1 to 46.7% in African–Americans and from 42.6 to 54.5% in Asians. We have to be cautious when interpreting the results since the frequencies of the polymorphisms were from controls of molecular epidemiological studies concerning prostate cancer. These prostate cancer studies used different study designs; hospital-based (for males with benign prostatic hyperplasia) or population-based.

*GSTM3* is also located on chromosome 1p13.3. Alleles have been identified in *GSTM3*, with *GSTM3*A* and *GSTM3*B* differing in intron 6 by a three base pair (bp) deletion in *GSTM3*B*. Although the difference between *GSTM3*A* and *GSTM3*B* is intronic, its importance is suggested by the presence of a recognition motif for the versatile transcription factor YY1 in *GSTM3*B* but not in *GSTM3*A* [37]. Importantly, *GSTM3*B* and *GSTM3*A* are in linkage disequilibrium with *GSTM1*0* [10]. These results suggest that, in some cases, links between clinical phenotypes and *GSTM1* genotypes may reflect polymorphisms in *GSTM3* or, indeed, other μ class GST genes.

**Table 1. Human soluble glutathione *S*-transferase polymorphisms relevant to prostate cancer.**

| Enzyme designation | Class | Gene | Chromosome location | Known alleles | Nucleotide change |
|---|---|---|---|---|---|
| GSTA1–1 | α | *GSTA1* | 6p12 | *GSTA1*A* | T567, C69 and G52 |
| | | | | *GSTA1*B* | G567, T69 and A52 |
| GSTM1–1 | μ | *GSTM1* | 1p13.3 | *GSTM1*0* | Null |
| | | | | *GSTM1*A* | C534 |
| | | | | *GSTM1*B* | G534 |
| GSTM3–3 | μ | *GSTM3* | 1p13.3 | *GSTM3*A* | Wild-type |
| | | | | *GSTM3*B* | Three base pair deletion intron 6 |
| GSTT1–1 | θ | *GSTT1* | 22q11.2 | *GSTT1*0* | Null |
| | | | | *GSTT1*1* | Present |
| GSTP1–1 | π | *GSTP1* | 11q13 | *GSTP1*A* | A313 and C341 |
| | | | | *GSTP1*B* | G313 and C341 |
| | | | | *GSTP1*C* | G313 and T341 |

### *GSTT1*

*GSTT1* encoding for θ class is located on chromosome 22q11.2, and helps in catalyzing the conjugation of halomethanes in human erythrocytes [36]. Substrates of GSTT1 include industrial chemicals, such as methyl chloride, methyl bromide, dichloromethane, ethylene oxide and diepoxy butane, a reactive metabolite of 1,3-butadiene [39,40]. Two alleles have been identified at the *GSTT1* locus: one functional (*GSTT1*1*) and the other nonfunctional (*GSTT1*0*) [36]. Individuals with a homozygous deletion genotype are categorized as having the negative conjugator phenotype, while those who carry either one or both functional alleles are grouped as having the positive conjugator phenotype. The prevalence rates of the null genotype were 26.7 and 41.9–48.3% of the controls of African–American and Asian descent, respectively (Table 2). Among Caucasians, the frequency ranged from 13–58.7% (Table 2).

### *GSTP1*

*GSTP1*, a member of the π gene family, is located at 11q13, expressed predominantly in the basal layer of the normal prostate epithelium [41]. GSTP1 metabolizes a variety of potential carcinogens, including cigarette smoke-derived chemicals such as benzo[a]pyrene diol epoxides and acrolein [10]. By contrast with most cancers, prostate carcinogenesis is associated with marked downregulation of *GSTP1*. The events leading up to the inactivation of GSTP1 during prostate carcinogenesis remain unclear. Several investigators have speculated that the early loss of GSTP1 function leads to increased vulnerability to oxidant and heterocyclic amine carcinogens, both implicated in prostate carcinogenesis [42,43]. Hence, heritable differences in GSTP1 function may also be associated with prostate cancer development. Two genetic polymorphisms, in exons 5 and 6, both resulting in an amino acid substitution, have been found. However, only the change in exon 5, that is the A→G polymorphism at nucleotide 313, results in an amino acid substitution (Ile105Val) in the substrate-binding site of GSTP1 [44]. The substitution was linked to a change in enzymatic activity [44]. The prevalence rates of the Val/Val homozygosity was 9–12.6% in Caucasian subjects, 13.3–19% in African–Americans and 0–5.4% in Asians, respectively (Table 2).

### *GSTA1*

The α class GSTs, in other words GSTA1–5, are encoded by genes clustered within 6p12. Of all the GSTs, the α class isoenzymes are the most abundant GSTs found in the human liver, and are, notably, responsible for metabolizing the nitrogen mustard group of some anticancer drugs, and for binding endogenous compounds such as bilirubin in the liver [8]. Especially, *GSTA1*, *GSTA2* and *GSTA3* are widely expressed in human tissues, predominantly in the liver, while *GSTA4* is rarely expressed and *GSTA5* is normally undetectable [45,46]. Members of the α class possess high glutathione peroxidise activity, and play an important role in protecting cells against reactive oxygen species and the products of peroxidation. GSTA1 is also active towards several carcinogenic substrates, including polycyclic aromatic hydrocarbon epoxides [10], and the meat-derived carcinogen *N*-acetoxy-2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (*N*-acetoxy-PhIP) [47]. A polymorphism that

**Table 2. Frequency of *GSTM1*, *GSTT1*, *GSTP1* (Ile105Val) and *GSTA2* genotypes in three major ethnic groups**

| First author | Country | Racial descent | *GSTM1*-null (%) | *GSTT1*-null (%) | *GSTP1* (Ile/Val) (%) | | | *GSTA1*B/*B* | | | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Ile/Ile **A/*A* | Ile/Val **A/*B* or **C* | Val/Val **B* or **C/*B* or **C* | **A/*A* | **A/*B* | **B/*B* | |
| Autrup *et al.* (1999) | Denmark | Caucasian | 53.5 | 15.3 | 42 | 58* | | | | | [15] |
| Rebbeck *et al.* (1999) | USA | Caucasian | 47.6 | 31.2 | | | | | | | [16] |
| Shepard *et al.* (2000) | USA | Caucasian | | | 45.4 | 44.1 | 10.5 | | | | [17] |
| Steinhoff *et al.* (2000) | Germany | Caucasian | 45 | 13 | 55 | 36 | 9 | | | | [18] |
| Gsur *et al.* (2001) | Austria | Caucasian | 48.8 | 19.9 | 39.2 | 48.2 | 12.6 | | | | [19] |
| Kote-Jarai *et al.* (2001) | UK | Caucasian | 50.0 | 23.7 | 51.2 | 38.5 | 10.3 | | | | [20] |
| Jeronimo *et al.* (2002) | Portugal | Caucasian | | | 43.3 | 47.5 | 9.2 | | | | [21] |
| Kidd *et al.* (2003) | USA | Caucasian | 53 | 15 | 57 | 43* | | | | | [22] |
| Acevedo *et al.* (2003) | Chile | Caucasian | 22.7 | | | | | | | | [23] |
| Debes *et al.* (2004) | USA | Caucasian | | | 38.2 | 49.0 | 12.9 | | | | [24] |
| Medeiros *et al.* (2004) | Portugal | Caucasian | 54.2 | 58.7 | | | | | | | [25] |
| Shankar *et al.* (2005) | India | Caucasian | 35.4 | 20.1 | 57.6 | 38.9 | 3.5 | | | | [26] |
| Agalliu *et al.* (2006) | USA | Caucasian | 47.5 | 16.9 | 43.2 | 45.7 | 11.1 | | | | [27] |
| Watson *et al.* (1998) | USA | Caucasian | | | 42 | 51 | 7 | | | | [28] |

*GSTP1 *Val allele (Ile/Val and Val/Val)*

**Table 2. Frequency of *GSTM1*, *GSTT1*, *GSTP1* (Ile105Val) and *GSTA2* genotypes in three major ethnic groups**

| First author | Country | Racial descent | *GSTM1*- null (%) | *GSTT1*-null (%) | *GSTP1* (Ile/Val) (%) | | | *GSTA1*B/*B* | | | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Ile/Ile **A/*A* | Ile/Val **A/*B* or **C* | Val/Val **B* or **C/*B* or **C* | **A/*A* | **A/*B* | **B/*B* | |
| Sweeney *et al.* (2003) | USA | Caucasian | | | | | | 35.8 | 47.5 | 16.7 | [29] |
| Ning *et al.* (2004) | USA | Caucasian | | | | | | 29.6 | 54.3 | 16.1 | [30] |
| London *et al.* (1995) | USA | African-American | 27.1 | | | | | | | | [31] |
| Watson *et al.* (1998) | USA | African-American | | | 35 | 46 | 19 | | | | [28] |
| Agalliu *et al.* (2006) | USA | African-American | 46.7 | 26.7 | 6.7 | 80.0 | 13.3 | | | | [27] |
| Sweeney *et al.* (2003) | USA | African-American | | | | | | 29.8 | 57.4 | 12.8 | [29] |
| Ning *et al.* (2004) | USA | African-American | | | | | | 39.7 | 49.2 | 11.1 | [30] |
| Murata *et al.* (1998) | Japan | Asian | 42.6 | | | | | | | | [32] |
| Watson *et al.* (1998) | USA | Asian | | | 67 | 30 | 3 | | | | [28] |
| Nakazato *et al.* (2003) | Japan | Asian | 50.5 | 41.9 | 72.4 | 27.6 | 0 | | | | [33] |
| Komiya *et al.* (2005) | Japan | Asian | 54.5 | 48.3 | 72.9 | 23.7 | 5.4 | 81.0 | 17.0 | 2.0 | [34] |

*GSTP1 *Val allele (Ile/Val and Val/Val)*

influences the hepatic expression of *GSTA1* has recently been described [45,48]. Liver cytosols from individuals who carried the variant *GSTA1*B* allele, which consists of several linked SNPs in the proximal promoter region of *GSTA1*, had reduced levels of GSTA1 enzyme [49]. The gene has a polymorphic SP1-binding site that results in fourfold higher mean hepatic expression of *GSTA1*A* compared with *GSTA1*B* [45,48].

There are a few reports regarding GST α expression in normal and malignant prostate tissues, demonstrating low levels of GST α expression in high-grade prostatic intraepithelial neoplasia and prostate cancers. Increased expression of *GSTA1* was also detected in proliferative inflammatory atrophy (PIA), suggesting the involvement of localized increases in oxidative stress. Recently, using antibodies for Ya, Yc and Yk-type subunits, an immunohistochemical study was conducted in normal and malignant prostate tissues, showing low levels of GST α expression in prostate cancers and heterogeneous staining patterns. These suggest that a lack of detoxification activity plays an important role in carcinogenesis of the prostate.

## Association of GST polymorphism with prostate cancer susceptibility

The genetic polymorphism of GSTs has been investigated in many molecular epidemiological studies as a susceptibility factor for prostate cancer development. For each study, we abstracted the publication date, country where the study was conducted, control source and the numbers of cases and controls (Table 3). Healthy subjects recruited from hospitals as controls were categorized as 'hospital-healthy'.

The 13 available case-control studies investigated the association between *GSTM1* polymorphism and prostate cancer (Table 3). Three case-control studies reported associations between the *GSTM1*-null genotype and prostate cancer risks [23,26,27]. In a large, case-control study (559 cases, 523 controls), Agalliu *et al.* demonstrated that the *GSTM1*-null genotype was associated with an increased risk of prostate cancer (OR: 1.54; 95% CI: 1.19–2.01) [27]. Among *GSTM1*-null individuals, the relative risk increased linearly with increasing pack-years of smoking (p-value for trend = 0.007), with the highest OR observed for heavy smokers (>30 pack-years). Two other studies in Chile [23] and India [26], which are consistent with Agalliu's data, showed a statistically significant OR of 1.94 and 2.24 for prostate cancer among *GSTM1*-null subjects, respectively. However, ten other studies did not recognize an increased risk associated with a lack of *GSTM1* activity. In addition, Kelada *et al.* observed no interaction between smoking and the *GSTM1* genotype [50]. Moreover, the *GSTM1*-null genotype did not have a familial prostate cancer risk [33].

To our knowledge, there are 11 reports investigating the associations between *GSTT1* polymorphism and prostate cancer (Table 3). Eight case-control studies reported no associations between the *GSTT1*-null genotype and prostate cancer risk. However, two studies reported significant associations between the *GSTT1*-null genotype and prostate cancer risk [18,26]. Intriguingly, in one of those reporting American patients with carcinoma of the prostate, a significantly increased frequency of *GSTT1* non-null genotype was found [50]. Furthermore, a Japanese study yielded similar results of a significantly higher frequency of the *GSTT1* non-null genotype among smokers [32].

There are 12 case-control studies that investigated the association between *GSTP1* polymorphisms and prostate cancer. The results of these studies are inconsistent. Three of them reported that *GSTP1* Ile/Val or Val/Val genotypes might be associated with prostate cancer risk [19,20,26]; the Ile/Val or Val/Val genotypes have been associated with a significant increase in the risk of prostate cancer in North Indian populations [26]. Kote-Jarai *et al.* found that patients in the UK with the *GSTP1* Val/Val genotype were at a higher risk of early-onset prostate cancer [20]. On the contrary, Gsur *et al.* reported that there was a significant decrease in the Val allele (Ile/Val and Val/Val) among cases compared with controls [19]. This result suggests that the Val allele is associated with a decreased risk of prostate cancer in Austrians. However, in nine other studies the *GSTP1* Ile105Val polymorphism was not associated with a statistically significant increase in the risk of prostate cancer.

Thus, it is evident that the association of *GSTM1*, *GSTT1* and *GSTP1* polymorphisms with prostate cancer risk differs widely among different populations, suggesting the significance of ethnic differences and environmental factors on prostate cancer susceptibility.

Recently, Ntais *et al.* reported a meta-analysis that included data from 11 studies with *GSTM1* genotyping (2063 prostate cancer cases and 2625 controls), ten studies with *GSTT1* genotyping (1965 cases and 2554 controls) and

**Table 3. Summary of case–control studies on *GSTM1*, *GSTT1*, *GSTP1* (Ile105Val) and *GSTA1* genotypes and prostate cancer incidence**

| Study | Country | Control source | Racial descent | Cases (n) | Controls (n) | *GSTM1*-null, OR (95% CI) | *GSTT1*-null, OR (95% CI) | *GSTP1*(any Val), OR (95% CI) | *GSTA1*B/*B*, OR (95% CI) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| Murata *et al.* (1998) | Japan | Hospital | Asian | 115 | 204 | 1.3 (0.82–2.04) | | | | [32] |
| Autrup *et al.* (1999) | Denmark | Healthy | Caucasian | 153 | 288 | 1.27 (0.85–1.90) | 1.31 (0.77–2.19) | 0.80 (0.54–1.19) | | [15] |
| Kelada *et al.* (2000) | USA | Hospital | Caucasian | 276 | 499 | 1.00 (0.69–1.29) | 1.61 (1.14–2.28) | | | [50] |
| Shepard *et al.* (2000) | USA | Hospital | Caucasian | 590 | 803 | | | 0.81 (0.63–1.06) | | [17] |
| Steinhoff *et al.* (2000) | Germany | Hospital | Caucasian | 91 | 127 | 1.20 (0.71–2.05) | 2.31 (1.17–4.59) | 1.09 (0.66–1.77) | | [18] |
| Gsur *et al.* (2001) | Austria | Hospital (BPH) | Caucasian | 166 | 166 | 0.86 (0.55–1.36) | 0.78 (0.43–1.42) | 0.24 (0.09–0.61) | | [19] |
| Kote-Jarai *et al.* (2001) | UK | Healthy | Caucasian | 275 | 280 | 1.29 (0.92–1.81) | 1.05 (0.71–1.55) | Ile/Val 1.30 (0.99–1.69) Val/Val 1.80 (1.11–2.91) | | [20] |
| Jeronimo *et al.* (2002) | Portugal | Healthy + BPH | Caucasian | 105 | 141 | | | 1.02 (0.59–1.75) | | [21] |
| Kidd *et al.* (2003) | USA | Participants of the ATBC cancer prevention study | Caucasian | 206 | 194 | 0.64 (0.43–0.95) | 0.74 (0.42–1.33) | 1.10 (0.72–1.69) | | [22] |
| Acevedo *et al.* (2003) | Chile | BPH | Caucasian | 102 | 128 | 1.94 (1.04–3.63) | | | | [23] |
| Nakazato *et al.* (2003) | Japan | Hospital | Asian | 81 (familial) | 105 | 0.98 (0.58–1.66) | 0.87 (0.49–1.55) | Ile/Val 0.97 (0.50–1.36) Val/Val 9.31 (0.47–184) | | [33] |

**GSTT1* non-null, *OR (95% CI).*

*§GSTA1*A/*B* or **B/*B, OR: 1.49, 95% CI: 0.96-2.32.*

*ATBC: Finnish male paticpants of the Alpha Tocophenol Beta Carotene (ATBC) cancer prevention study; BPH: Benign prostatic hypertrophy.*

**Table 3. Summary of case–control studies on *GSTM1*, *GSTT1*, *GSTP1* (Ile105Val) and *GSTA1* genotypes and prostate cancer incidence**

| Study | Country | Control source | Racial descent | Cases (n) | Controls (n) | *GSTM1*-null, OR (95% CI) | *GSTT1*-null, OR (95% CI) | *GSTP1*(anyVal), OR (95% CI) | *GSTA1*B/*B*, OR (95% CI) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| Debes *et al.* (2004) | USA | Healthy | Caucasian | 438 (familial) 499 (sporadic) | 510 | | | 1.00 (0.74–1.37) 0.84 (0.65–1.09) | | [24] |
| Medeiros (2004) | Portugal | Healthy | Caucasian | 150 | 185 | 1.20 (0.75–1.90) | 0.87 (0.51–1.51) | | | [25] |
| Ning *et al.* 2004 | USA | Healthy | Caucasian | 254 | 81 | | | | 0.80 (0.36–1.78) | [30] |
| | | | African–American | 93 | 63 | | | 0.81 (0.25–2.61) | | |
| Shankar *et al.* (2005) | India | No information | Caucasian | 127 | 144 | 2.24 (1.37–3.65) | 1.89 (1.09–3.28) | 2.48 (1.51–4.08) | | [26] |
| Komiya *et al.* (2005) | Japan | Healthy | Asian | 190 | 294 | 0.76 (0.52–1.12) | 1.39 (0.95–2.03)* | 0.87 (0.57–1.35) | 1.33 (0.39–4.51)§ | [34] |
| Agalliu *et al.* (2006) | USA | Healthy | Caucasian | 559 | 523 | 1.54 (1.19–2.01) | 1.04 (0.73–1.47) | Ile/Val 0.95 (0.72–1.25), Val/Val 1.10 (0.71–1.69) | | [27] |

**GSTT1* non-null, *OR (95% CI)*.

§*GSTA1*A/*B* or **B/*B, OR: 1.49, 95% CI: 0.96-2.32.*

*ATBC: Finnish male paticpants of the Alpha Tocophenol Beta Carotene (ATBC) cancer prevention study; BPH: Benign prostatic hypertrophy.*

12 studies with *GSTP1* genotyping (2528 cases and 3076 controls) [51]. The random effects OR was 1.08 (95% CI: 0.95–1.25) for the *GSTM1*-null genotype versus the *GSTM1*-nondeleted genotype, and 0.90 (95% CI: 0.73–1.12) for the *GSTT1*-null genotype versus the *GSTT1*-nondeleted genotype. There was no evidence that the *GSTP1* Val allele modified the risk of prostate cancer. The summary of OR was 1.05 (95% CI: 0.90–1.21). No association was observed in subjects of Caucasian descent (OR = 1.02), and there was only one study subject of Asian descent (OR = 1.25).

There have been only two case-control studies of *GSTA1*. Ning *et al.* reported that the OR associated with risk of prostate cancer according to *GSTA1* genotype was not significant within race and after adjustment for age [30]. Komiya *et al.* stated that the frequency of *GSTA1*A/*B* or **B/*B* genotype individuals among cases increased to 26.3% compared with the control groups (19.0%) [34]; however, this difference did not reach statistical significance (OR 1.49; 95% CI: 0.96–2.32) after adjustment for age and smoking status. The apparent lack of interaction between the *GSTA1* genotype and prostate cancer risk suggests a low impact of hepatic GST expression on the risk of the disease. For example, this may be due to the importance of 2-amino-1-methyl-6-phenylimidazo [4,5] PhIP activation locally in the target tissue, activation of *N*-hydroxy-PhIP by paths other than O-acetylation [52], and the low importance of PhIP in the etiology of prostate cancer.

Agalliu *et al.* found evidence suggesting that carriers of the *GSTM3*B/*B* genotype have a fivefold increased risk of onset of prostate cancer (OR: 5.5; 95% CI: 1.2–25.8) [27]. However, their report is only one study that is relevant to prostate cancer, and no other reports regarding the *GSTM3* genotype and prostate cancer have been found.

Although some substrates are metabolized by specific GST isoenzymes [10], they have overlapping substrate specificities; therefore, a combination of unfavorable genotypes could theoretically confer a high risk. In a few studies, an increased risk was observed when a combination of the variant GST genotypes was present [20,26,34]. Kote-Jarai *et al.* [20] and Shanker *et al.* [26] demonstrated that the combination of GST genotypes might define a specific high-risk genotype (*GSTM1*, *GSTT1*-null and *GSTP1* Val allele) in the UK and India. On the other hand, Komiya *et al.* observed that the OR of carrying the combined genotyping of *GSTA1*A/*B* or **B/*B* and *GSTT1* nondeletion was 2.08 (95% CI: 1.14–3.80), with the combined genotyping of *GSTA1*A/*A* and *GSTT1*-null as a reference in Japanese [34].

## Future perspective

A number of independent studies have demonstrated the importance of polymorphisms in xenobiotic metabolism as risk factors in the development of cancer associated with chemical exposure. According to these results, many case-control studies have been undertaken regarding *GST* genes and the risk of prostate cancer. However, the evidence from recent studies has not been consistent. The reasons for this disparity in risk are mostly unclear; however, we can speculate on three possibilities.

The first possible reason for these discrepancies, the biochemical evidence for the putative relationship of GST polymorphisms with prostate cancer, is equivocal. It is unlikely that specific environmental carcinogens whose effect might also be modifiable by GST genotype have a high attributable risk for prostate cancer. The second reason is that, in addition to the metabolism of chemical carcinogens, GSTs are involved in the intracellular transport and the synthesis of steroid hormones [12], and compounds found in the diet are potentially involved in prostate carcinogenesis. Population differences in androgen levels and dietary factors have been implicated as a possible explanation. The third reason for these discrepancies may be insufficient study power or bad study design, or a bias against publishing the absence of correlations. Bartsch *et al.* provided state-of-the-art reviews of the application of biomarkers and the design and analysis of molecular epidemiological studies [53]. The prerequisites for proper study design and conduct include:

- A clear definition of representative study populations and controls
- A sample size adequate to provide enough statistical power
- Proper documentation (or measurement) of exposure
- Avoidance of confounding data because of the use of mixed ethnicity study subjects
- Study of only the gene polymorphisms that have been demonstrated to lead to altered phenotypic expression

The rigor and size of study designs will need to increase, as multiple comparisons and the power issue dictate. In parallel with these studies, a clearer understanding of the genetic bias of the polymorphisms has emerged, together with more accurate and less invasive methods for the screening of populations.

## Expert opinion

Three genetic polymorphisms of GSTs, that is *GSTM1*0* (null), *GSTT1*0* (null) and *GSTP1 A313G*, have been well documented. However, associations between other polymorphisms of GSTs, that is to say *GSTA*, *GSTZ*, *GSTS*, *GSTO* and *GSTK*, and prostate cancer are not well known. It will be interesting to know whether polymorphisms in these genes influence susceptibility to prostate cancer.

Of particular interest are studies of gene–environment interactions and gene–gene–environment interactions. To date, molecular epidemiology studies of prostate cancer have rarely looked at a variety of potential gene–environment interactions or explored associations and interactions with more than one genetic polymorphism. Future studies that examine the association among several genetic polymorphisms should take into account risk factors for prostate cancer, such as diet and other environmental exposures, as well as possible biological pathways. In addition, some studies had limited power to detect more associations between *GST* polymorphisms and prostate cancer risk; further well-designed and large-scale studies are needed to reveal these associations.

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## Executive summary

### *Prostate cancer*

- Carcinoma of the prostate is most common in Western countries, and second only to lung cancer as a cause of death due to cancer.

### *Glutathione S-transferases families*

- In humans, cytosol glutathione *S*-transferases (GSTs) are divided into eight classes: α (GSTA), μ (GSTM), π (GSTP), θ (GSTT), τ (GSTZ), σ (GSTS), ο (GSTO) and κ (GSTK).

### *Glutathione S-transferase substrates*

- GSTs metabolize numerous harmful chemicals produced endogenously and in the environment.

### *Genetic polymorphisms of glutathione S-transferase*

- Cytosol GSTs display polymorphisms in humans, which is likely to contribute to interindividual differences in responses to xenobiotics.

### *Association of glutathione S-transferase polymorphisms with prostate cancer susceptibility*

- Three genetic polymorphisms of GST: *GSTM1*0* (null), *GSTT1*0* (null) and *GSTP1* A313G, have been well documented.
- No consistent associations between *GSTM1*, *GSTT1* or *GSTP1* genotypes and prostate cancer have been observed.

### *Conclusions*

- Further well-designed, large-scale studies are required to detect the precise associations between GST polymorphisms and prostate cancer risk.
- Research is needed on the associations between the polymorphisms of *GSTA*, *GSTZ*, *GSTS*, *GSTO* and *GSTK* and prostate cancer.

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