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Glutathione S-transferase polymorphisms and risk of ovarian cancer: A HuGE review

Steven S. Coughlin, PhD, and Ingrid J. Hall, PhD, MPH

Glutathione S-transferases (GSTs) catalyze the conjugation of glutathione to numerous potentially genotoxic compounds. The *GSTM1* gene codes for the enzyme glutathione S-transferase-mu, the *GSTT1* gene codes for the enzyme glutathione S-transferase-theta, and the *GSTP1* gene codes for the enzyme glutathione S-transferase-pi. *GSTM1* is polymorphically expressed, and three alleles have been identified (*GSTM1-0*, *GSTM1a*, and *GSTM1b*). Two functionally different genotypes at the *GSTT1* locus have been described. Individuals with homozygous deletions of *GSTM* or *GSTT* have reduced or no glutathione S-transferase activity and therefore may be unable to eliminate electrophilic carcinogens as efficiently. However, results of epidemiologic studies do not confirm associations between *GSTM1*, *GSTT1*, and *GSTP1* and epithelial ovarian cancer. **Genet Med 2002:4(4):250–257.**

Key Words: *epidemiology, glutathione* S-*transferases,* GSTM1, GSTP1, GSTT1, *ovarian cancer*

An increasing number of epidemiologic studies have examined associations between *GSTM1*, *GSTT1*, and *GSTP1* and epithelial ovarian cancer. Associations with *GSTM1*, *GSTT1*, and *GSTP1* genotype have not been observed in most studies, many of which have had small sample sizes or other design limitations. However, GSTM1 null genotype was found to be more frequent among cases than controls in a recent study of epithelial ovarian cancer that included more subjects (59% vs. 49%, OR = 1.5, 95% CI 1.1–2.1).[54]

Results from this and one other recent case-control study suggest that deletion of *GSTM1* may increase the risk of specific histological subtypes of ovarian cancer (endometrioid and clear cell).

This Human Genome Epidemiology Network (HUGE Net) review critically evaluates published studies of these associations and offers suggestions for future research.

GENE

Glutathione S-transferases (GSTs) catalyze the conjugation of glutathione to numerous potentially genotoxic compounds, including aliphatic aromatic heterocyclic radicals, epoxides, and arene oxides.[1–3] The enzymes detoxify carcinogenic polycyclic aromatic hydrocarbons and conjugate isothiocyanates. Six families of enzymes have been classified as alpha, mu, pi, theta, zeta, and omega. Glutathione S-transferase-mu (*GSTM1*), glutathione S-transferase-theta (*GSTT1*), and glutathione S-transferase-pi (*GSTP1*) have been studied most.[3] The *GSTM1* gene, which is located on chromosome 1p13.3, codes for the enzyme glutathione S-transferase-mu. The *GSTT1* gene codes for the enzyme glutathione S-transferase-theta; the *GSTT1* gene is located on chromosome 22q11.2. The *GSTP1* gene codes for the enzyme glutathione S-transferase-pi and is located on chromosome 11q13. *GSTA1* and *GSTA2*, the two major glutathione S-transferase-alpha genes, are mentioned less frequently in the literature and are located on chromosome 6p12. The *GSTZ1* gene that encodes glutathione S-transferase-zeta was mapped to chromosome 14q24.3.[4,5] The glutathione S-transferase-omega (*GSTO1*) gene was recently characterized.[6] The GSTs have broad and overlapping substrate specificities that have been previously reviewed.[7]

GENE VARIANTS

GSTM1 is polymorphically expressed, and three alleles have been identified: *GSTM1-0*, *GSTM1a*, and *GSTM1b*.[3] There is no evidence of functional differences between *GSTM1a* and *GSTM1b*, which differ by a substitution in one base pair.[8] The *GSTT1* locus has a single allele that is either present or absent (deleted). Two functionally different genotypes at the *GSTT1* locus have been described. The first, *GSTT1-0*, is a homozygous deletion. The second, *GSTT1-1*, comprises genotypes with one or two functional alleles present. There are also three variant alleles of *GSTP1*. *GSTP1a* and *GSTP1b* differ by an A to G substitution at codon 105 that exchanges isoleucine for valine. *GSTP1c* varies from the "a" allele by the substitution of valine for alanine at codon 114. Individuals with homozygous deletions of *GSTM* or *GSTT* have reduced or no glutathione S-transferase activity and therefore may be unable to eliminate electrophilic carcinogens as efficiently. This may increase the risk of somatic mutations leading to tumor formation. Evidence is lacking on whether heterozygosity in either *GSTM1* or

From the Epidemiology and Health Services Research Branch, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia.

Steven S. Coughlin, PhD, Epidemiology and Health Services Research Branch, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, 4770 Buford Highway NE (K-55), Atlanta, GA 30341.

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GSTT1 affects gene function.[8] An analysis of functional differences in the *GSTP1* variant proteins was performed by evaluating the ability of recombinant *GSTP1* proteins to catalyze the conjugation of glutathione with 1-chloro-2,4-dinitrobenzene, a universal GST substrate. Results showed that catalytic activity was 3- to 4-fold higher for the *GSTP1a* variant than for either *GSTP1b* or *GSTP1c*.[9] This indicates that enzyme activity is significantly reduced in individuals who carry the valine allele.

Cotton et al.[8] summarized information on the frequency of homozygosity and heterozygosity of *GSTM1* and *GSTT1* allelic variants in different populations and ethnic groups; updated information on the frequency of these variants was provided by Geisler and Olshan.[10] Both of these articles are posted on the Centers for Disease Control website on the Internet.[8,10] The frequency of the *GSTM1* null genotype ranges from 23% to 48% in African populations, 33% to 63% in Asian populations, 39% to 62% in European populations, and 23% to 62% in U.S. populations.[8] In selected U.S. populations, the frequency of the *GSTM1* null genotype ranges from 23% to 41% in African-Americans, 35% to 62% in whites, 32% to 53% in Asians, and 40% to 53% in Mexican-Americans.

The frequency of the *GSTT1* null genotype ranges from 15% to 26% in African populations, 16% to 64% in Asian populations, and 10% to 21% in European populations.[8] In U.S. populations, the frequency of the *GSTT1* null genotype ranges from 22% to 29% in African-Americans, 15% to 27% in whites, and 10% to 12% in Mexican-Americans.

To obtain information on the frequency of homozygosity and heterozygosity of *GSTP1* allelic variants in different populations and ethnic groups, we searched MEDLINE by using the MeSH heading "glutathione transferase" and the text word "GSTP1." Reference lists were also reviewed from published articles. Papers written in English and published between January 1993 and March 2001 were reviewed. The majority of the studies reviewed, including studies reporting genotype frequencies among individuals without cancer, had a case-control design.[11–33] The frequencies for polymorphisms in exon 5 and exon 6 of the *GSTP1* gene among control individuals are summarized in Table 1. Studies have been conducted on all continents with the exception of Africa and South America; only two studies have been conducted in the United States. The frequency of the homozygous wildtype genotype at exon 5 ranges from 39% to 59% in whites, 52% to 93% in Asians, and 35% in the single study involving African-Americans. The heterozygous genotype ranged from 30% to 50% among whites, 24% to 44% among Asians, and 46% among African-Americans. The homozygous mutant genotype ranged from 4% to 16% among whites, 4% to 5% among Asians, and 19% for African-Americans. For the exon 6 polymorphism, the frequency of the homozygous wildtype genotype ranged from 75% to 85% among whites, 98% to 100% among Asians, and 95% among African-Americans. Heterozygous genotypes ranged from 15% to 25% among whites, 0% to 2% among Asians, and 5% among African-Americans. The homozygous mutant genotype was only found among persons from India (2%).

DISEASE

Ovarian cancer is the sixth most common cancer among U.S. women.[34] An estimated 23,300 new cases will be diagnosed in 2002 and an estimated 13,900 U.S. women will die from the disease this year. Based upon SEER data for the period 1988 to 1992, ovarian cancer incidence rates among U.S. women were highest among American-Indian women (age-adjusted rate 17.5 per 100,000), followed by non-Hispanic white (age-adjusted rate 15.8 per 100,000), Vietnamese, white Hispanic, and Hawaiian women.[35] Rates were intermediate among African-American women (age-adjusted rate 10.2 per 100,000) and lowest among Korean and Chinese women in the United States over that time period. Worldwide, the highest ovarian cancer incidence rates are found in white women in Europe (especially Scandinavian countries), Israel, and North America. Rates among women in Central and South America and in Asia (including Japan) are relatively low.[36]

The majority of malignant ovarian tumors originate in epithelial cells. More is known about the descriptive epidemiology and etiology of epithelial ovarian cancer than germ cell or sex cord-stromal (follicular) tumors.[36] The most common type of epithelial tumors is serous carcinoma (which comprises about 40% of epithelial ovarian cancers), followed by mucinous carcinomas (6–16%), endometrioid carcinomas (15–25%), and clear cell carcinomas (5–11%).[37]

Established risk factors for epithelial ovarian cancer include age, family history of ovarian cancer, personal history of endometrial or breast cancer, and nulliparity.[36] Other risk factors that have been less consistently associated with ovarian cancer include history of infertility, use of infertility drugs, early age of menarche, late menopause, and use of talc.[36] History of one or more full-term pregnancies, use of oral contraceptives, and possibly tubal ligation and lactation are protective.[38–40] Several studies of ovarian cancer have examined possible associations with endogenous estrogens, hormone replacement therapy, various dietary factors, and other purported risk factors, but results to date have been inconsistent.[36,41] Results from a recent cohort mortality study suggest that hormone replacement therapy of long duration may modestly increase risk.[42]

Although the focus of this review is on glutathione *S*-transferase polymorphisms, we briefly summarize here major genes that have been implicated in some cases of ovarian cancer. Hereditary ovarian cancer due to *BRCA1* or *BRCA2* gene mutations accounts for roughly 5% to 11.7% of all cases of ovarian cancer.[43–45] Women carrying germline mutations in *BRCA1* or *BRCA2* have a high lifetime risk of developing breast and/or ovarian cancer.[43] Other genetic syndromes that may include ovarian cancer as an associated feature include Peutz-Jeghers syndrome, multiple endocrine neoplasia type 1 (*MEN1*), and hereditary nonpolyposis colon cancer (HNPCC).[46,47] Germline mutations in the *LKB1* gene are associated with Peutz-Jeghers syndrome.[46] Mutations of *MLH1* and *MSH2* have been implicated in HNPCC.[47]

Table 1
Population frequency of *GSTP1* polymorphisms among controls

Area of study/ ethnicity	Controls		Exon 5 (codon 105)[a]			Exon 6 (codon 114)[b]			Reference
	Type	*N*	A/A	A/G	G/G	A/A	A/V	V/V	
Australia									
Aboriginal	Convenience sample	52	82	13	4	100	0	0	Harris et al.[14]
Chinese	Convenience sample	50	65	31	4	98	2	0	
European	Convenience sample	199	40	51	9	85	15	0	
Indian	Convenience sample	40	50	45	5	85	13	2	
Australia									
Caucasian	Females with no cancer history age matched to breast cancer cases	129	46	50	4				Curran et al.[12]
Australia	Unrelated females, frequency-matched on age to ovarian cases	292	39	46	15				Spurdle et al.[24]
Estonia	Unrelated volunteers without cataract, glaucoma or uveitis	202	43	45	13	79	21	0	Juronen et al.[16]
Finland	Healthy blood donors	293	53	38	9	82	17	0	Saarikoski et al.[33]
Germany German Austrian Swiss	Nonrelapsed acute lymphoblastic leukemia patients, matched to relapsed cases on sex, age at diagnosis, white blood count at diagnosis, and treatment	64	50	34	16	75	25	0	Stanulla et al.[25]
Italy									
Caucasian	Male coke oven workers	70	56	34	10	91	7	1	Viezzer et al.[27]
Japan	Male smokers free from pulmonary disease with normal function tests	50	52	44	4	100	0	0	Ishii et al.[31]
Japan	Visitors of local medical clinics with no previous diagnosis of cancer	122	93	24	5				Katoh et al.[17]
Japan	Healthy controls	164	69	29	2				Morita et al.[32]
The Netherlands									
Caucasian	Healthy nonpregnant female controls with at least 1 uncomplicated pregnancy and no spontaneous abortion	109	54	41	5				Zusterzeel et al.[30]
The Netherlands									
Caucasian	Healthy volunteers	247	59	36	5				van Lieshout et al.[26]
Norway									
Caucasian	Healthy males matched on age and smoking dose to lung cancer patients	297	52	39	9				Ryberg et al.[23]
Poland	Healthy male volunteers	170	49	44	7				Butkiewicz et al.[11]
Spain									
Caucasian	Healthy volunteers	200	50	44	6				Rodriguez-Frias et al.[21]
UK									
Caucasian	Renal transplant survivors	222	47	39	14	86	14	nd	Marshall et al.[18]
UK									
Caucasian	Controls matched to acute leukemia cases on age, gender, and ethnicity	946	49	37	14				Rollinson et al.[22]
UK									
Caucasian	Community controls, age and sex matched to CRC cases	178	46	42	12	76	21	3	Welfare et al.[29]
UK									
Caucasian	Unrelated patients without neurology problems who attended the North Staffordshire Hospitals	156	47	39	14				Mann et al.[19]

—Continued

Table 1
Continued

Area of study/ethnicity	Controls		Exon 5 (codon 105)[a]			Exon 6 (codon 114)[b]			Reference
	Type	*N*	A/A	A/G	G/G	A/A	A/V	V/V	
UK									
Caucasian	Control individuals	155	51	43	6				Harries et al.[13]
USA, MD									
Caucasian	Matched to breast cancer cases on age, menopausal status, time since last menstrual period, and date of blood donation	113	50	42	8				Helzlsouer et al.[15]
USA, NC									
Caucasian	Convenience sample	287	42	51	7	82	18	0	Watson et al.[28]
African-American	Convenience sample	137	35	46	19	95	5	0	
Taiwanese	Convenience sample	116	67	30	3	nd	nd	nd	
USA, PA, NY									
Caucasian	Hospital controls matched to oral cancer cases on age at diagnosis, race, and sex, with no prior diagnosis of cancer, heart disease, emphysema, or COPD	163	39	53	9	85	14	1	Park et al.[20]
African-American		83	29	53	18	98	2	0	

nd, not determined.
[a]A, isoleucine; G, valine.
[b]A, alanine; V, valine.

DISEASE ASSOCIATIONS

The studies reviewed in this section were identified by searching MEDLINE by using the MeSH headings "ovarian neoplasms" and "glutathione transferase," and the text words "GST" and "glutathione *S*-transferase." Reference lists were also reviewed from published articles. Papers written in English and published between January 1993 and March 2001 were reviewed. Studies that looked at prognosis or chemoresistance were excluded.[48–50]

Lallas et al.[51] examined associations with *GSTM1* genotype in 138 genotyped patients with epithelial ovarian cancer in Iowa and 77 unmatched controls who were paid volunteers (Table 2). Women with a family history of ovarian, breast, or colon cancer were excluded from the control group. Women who had the null *GSTM1* genotype were not at increased risk of ovarian cancer (OR = 0.7, no confidence interval given). No associations were observed between *GSTM1* genotype and age at diagnosis, histological type, or stage of ovarian cancer. This study is limited by the use of volunteer controls and by the small sample size. Associations with *GSTM1a* and *GSTM1b* genotype were examined by Sarhanis et al.[52] in a study involving 84 patients with epithelial ovarian cancer and 312 control patients from the same hospital in North Staffordshire. No associations were observed with the null *GSTM1* genotype in comparisons with homozygosity for either the *GSTM1a* or *GSTM1b* genotypes (Table 2). The study is limited by the use of patient controls and by the small number of cases. Of 23 patients with tumors that produced or expressed p53 protein, 20 (87%) were *GSTM1* null. The frequency distributions of *GSTM1* genotypes in p53-positive and p53-negative tumor samples were significantly different ($P = 0.002$). Hengstler et al.[53] examined associations with *GSTM1* genotype in 103 patients with epithelial ovarian cancer and 115 control patients. The controls included patients from the same hospital in Mainz, Germany, and also nursing home residents. No associations were observed with the null *GSTM1* genotype (OR = 0.8, 95% CI 0.4–1.3). This study is limited by the use of patient controls and by the small sample size. *GSTM1* genotype was unrelated to histological type, grade, or stage of ovarian cancer.

Different results were obtained by Baxter et al.[54] in a study of 219 women with epithelial ovarian cancer who were treated at hospitals in southeast England and 219 healthy female volunteer controls who resided in the same region. The *GSTM1* null genotype was more frequent among the cases than controls (59% vs. 49%, OR = 1.5, 95% CI 1.1–2.1). This study is limited by the use of patient controls and by the small sample size. After stratification by histological subtype, a significantly increased frequency of the *GSTM1* null genotype was only observed for endometrioid (65%, $P = 0.013$) and combined endometrioid/clear cell ovarian cancers (67%, $P = 0.004$). Further evidence that deletion of *GSTM1* may specifically increase the risk of these histological subtypes was observed by Spurdle et al.[24] in a case-control study of epithelial ovarian cancer from Brisbane, Australia (285 hospitalized cases and 295 convenience controls from a twin study who were matched to the cases on age). These investigators observed no associa-

Table 2
Summary of studies of epithelial ovarian cancer and *GSTM1*

Area of study; recruitment period	Cases		Controls		% *GSTM1* null	Variables adjusted for	OR (95% CI) for null versus other genotypes	Subgroup analysis reported	Reference
	Type	*N*	Type	*N*					
Iowa, US; before 1996	Predominately Caucasian patients from hospital/clinic	138	Caucasian volunteers without a family history of cancer	77	58	None	Null versus *GSTM1* positive: 0.7 [CI not provided]	None[a]	Lallas et al.[51]
UK, North Staffordshire; 1993–1994	Caucasian patients from one hospital	84	Unrelated Caucasian patients[b]	312	62	None	Null versus *GSTM1a* homozygote: 0.9 [CI not provided] Null versus *GSTM1b* homozygote: 0.8 [CI not provided]	None[c]	Sarhanis et al.[52]
Southeast UK; 1993–1998	Caucasian patients from hospitals	293	Healthy Caucasian volunteers	219	49	None	Null versus *GSTM1* positive: 1.5 (1.1–2.1)	Histological type[d]	Baxter et al.[54]
Germany, Mainz; 1994–1996	Caucasian patients from one hospital	103	Caucasian patients and nursing home residents	115	38	Age	Null versus *GSTM1* positive: 0.8 (0.4–1.3)	Age categories, positive family history of cancer[e]	Hengstler et al.[53]
Brisbane, Australia; 1985–1996	Predominately Caucasian patients from one hospital[f]	285	Predominately Caucasian women from twin study	297	55	Age	Null versus *GSTM1* positive: 1.0 (0.7–1.5)	Histological type[g]	Spurdle et al.[24]

[a]Age at diagnosis, histological type, and stage of ovarian cancer were unrelated to *GSTM1* genotype.
[b]232 of the patients who served as controls underwent hysterectomy and bilateral oophorectomy for benign disease (menorrhagia and pelvic inflammatory disease); other controls had benign breast disease and mild iron deficiency.
[c]p53 expression was found in 23 tumors; of these, 20 (87%) were *GSTM1* null; the frequency distributions of *GSTM1* genotypes in p53-positive and p53-negative samples were significantly different ($P = 0.002$).
[d]A significantly increased frequency of the *GSTM1* null genotype was observed for endometrioid (65%, $P = 0.013$) and combined endometrioid/clear cell ovarian cancers (67%, $P = 0.004$).
[e]*GSTM1* null genotype was not significantly associated with histologic type, grade, or stage of epithelial ovarian cancer.
[f]Includes 44 cases with low malignant potential and 241 invasive tumors.
[g]The frequency of *GSTM1* variants did not vary with p53 immunohistochemical status. *GSTM1* null genotype was associated with increased risk of endometrioid/clear cell invasive cancer (age-adjusted OR = 2.0, 95% CI 1.0–4.1).

tion with *GSTM1* null genotype overall (age-adjusted OR = 1.0, 95% CI 0.7–1.5). However, *GSTM1* null genotype was associated with increased risk of endometrioid/clear cell invasive cancer (age-adjusted OR = 2.0, 95% CI 1.0–4.1). Because only 32 cases with endometrioid cancer and 15 cases with clear cell carcinoma were included, the study had limited ability to look at associations within histologic subtypes of ovarian cancer. Evidence of (positive or inverse) associations with other histological types was not observed.

Associations with *GSTT1* genotype have also been examined (Table 3). Sarhanis et al.[52] found no association with *GSTT1* genotype in their study of 81 patients and 325 controls. Hengstler et al.[53] examined associations with *GSTT1* genotype in their study of 103 patients with ovarian cancer and 115 con-

Table 3
Summary of studies of epithelial ovarian cancer and *GSTT1*

Area of study; recruitment period	Cases		Controls		% *GSTT1* null	Variables adjusted for	OR (95% CI)for null versus other genotypes	Subgroup analysis reported	Reference
	Type	*N*	Type	*N*					
UK, North Staffordshire; 1993–1994	Caucasian patients from one hospital	81	Unrelated Caucasian patients[a]	325	19	None	Null versus *GSTT1* positive: 0.8 [CI not provided]	None	Sarhanis et al.[52]
Germany, Mainz; 1994–1996	Caucasian patients from one hospital	103	Caucasian patients and nursing home residents	115	14	Age	Null versus *GSTT1* positive: 0.9 (0.4–1.9)	Age categories, positive family history of cancer[b]	Hengstler et al.[53]
Brisbane, Australia; 1985–1996	Predominately Caucasian patients from one hospital	285	Predominately Caucasian women from twin study	295	19	Age	Null versus *GSTT1* positive: 1.1 (0.7–1.6)	Histological type[c]	Spurdle et al.[24]

[a]232 of the patients who served as controls underwent hysterectomy and bilateral oophorectomy for benign disease (menorrhagia and pelvic inflammatory disease); other controls had benign breast disease and mild iron deficiency.
[b]*GSTT1* null genotype was not significantly associated with histologic type, grade, or stage of epithelial ovarian cancer.
[c]The frequency of *GSTT1* variants did not vary with p53 immunohistochemical status. There was a suggestion that ovarian cancers of the endometrioid or clear cell histological subtype had a higher frequency of the *GSTT1* null genotype than other histological subgroups.

trols. No associations were observed with the null *GSTT1* genotype (OR = 0.9, 95% CI 0.4–1.9). *GSTT1* genotype was unrelated to histological type, grade, or stage of ovarian cancer.

Overall, Spurdle et al.[24] found no association with *GSTT1* genotype (age-adjusted OR = 1.1, 95% CI 0.7–1.6) or with *GSTP1* genotype (results not shown) in their case-control study of epithelial ovarian cancer from Brisbane, Australia. However, there was a suggestion that ovarian cancers of the endometrioid or clear cell histological subtype had a higher frequency of the *GSTT1* null genotype than other histological subgroups [$P = 0.04$ for comparison of endometrioid and clear cell subtypes (29% and 33%, respectively) versus serous subtype (17%)], but the differences were not statistically significant overall.

With respect to limitations of existing studies that should be overcome in future research, and gaps in the current epidemiologic knowledge base, only one study has looked for an association with *GSTP1* genotype. In addition, reported studies of *GSTM1*, *GSTT1*, and *GSTP1* and epithelial ovarian cancer have only been carried out among Caucasian populations. Studies that involve other racial and ethnic populations are needed. Furthermore, existing studies have often been based upon patient controls and hospital-based study designs. Studies with a population-based case-control study design are needed, because the latter design is more likely to be scientifically valid. Future studies of *GSTM1*, *GSTT1*, and *GSTP1* and epithelial ovarian cancer should have a larger sample size with adequate numbers of incident cases and population controls, and they should be carried out in diverse populations. Gene-environment interactions, such as possible interactive effects between exogenous hormones and genotype, have not been examined in reported studies. Such interactions should be examined in future studies. A further gap in the existing knowledge base is that few studies have investigated the combined effect of polymorphic alleles in different genes on ovarian cancer risk, as discussed below.

Although results of studies carried out to date do not confirm associations between *GSTM1*, *GSTT1*, and *GSTP1* and epithelial ovarian cancer, the associations are biologically plausible because glutathione *S*-transferases metabolize exogenous and endogenous substances that may have a role in ovarian cancer carcinogenesis.[50,52] Studies that examine associations within specific histologic types of ovarian cancer are a promising area for further research.

INTERACTIONS

Spurdle et al.[24] analyzed the combined effect of the *GSTM1* and *GSTT1* genotypes. The combination of the *GSTM1* null and *GSTT1* null genotypes resulted in an age-adjusted odds ratio of 1.1 (95% CI 0.6–2.0), compared with the *GSTM1* positive and *GSTT1* positive genotypes. Similarly, no association was observed with having all three genotypes hypothesized to increase risk of ovarian cancer (*GSTM1* null, *GSTT1* null, and *GSTP1* GG/AG; age-adjusted OR = 0.8, 95% CI 0.4–1.9). In comparisons of endometrioid/clear cell cases and controls, however, the age-adjusted odds ratio was 3.9 (95% CI 1.4–11.1) for *GSTM1* null combined with *GSTT1* null ($P = 0.01$), compared with the *GSTM1* positive and *GSTT1* positive genotypes.

We did not identify any published studies that evaluated gene-environment interactions and risk of ovarian cancer.

LABORATORY TESTS

Molecular methods for determining *GSTM1* and *GSTT1* null genotype were summarized by Cotton et al.[8] All of the studies reviewed here extracted genomic DNA from blood samples and genotyping methods used in these studies were consistent with standard techniques employed for PCR and PCR-restriction fragment length polymorphisms.

POPULATION TESTING

There is insufficient evidence associating *GSTM1*, *GSTT1*, or *GSTP1* with ovarian cancer for population testing to be considered. More evidence is needed from molecular epidemiology studies to assess the causality of the associations with ovarian cancer.

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APPENDIX

Internet Sites

Data on ovarian cancer frequency

- IARC: http://www-dep.iarc.fr/
- SEER: http://www-seer.ims.nci.nih.gov/
- American Cancer Society: http://www.cancer.org/

General information on ovarian cancer

- National Cancer Institute: http://cancernet.nci.nih.gov/
- American Cancer Society: http://www.cancer.org/

Gene-specific information

GSTM1

- Human Gene Mutation Database: http://archive.uwcm.ac.uk/uwcm/mg/search/120020.html
- OMIM: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?138350#TEXT
- UniGene: http://www.ncbi.nlm.nih.gov/UniGene/clust.cgi?ORG=Hs&CID=5233
- GeneCards: http://bioinfo.weizmann.ac.il/cards-bin/carddisp?GSTM1&search=gstm1&suff=txt

GSTT1

- Human Gene Mutation Database: http://archive.uwcm.ac.uk/uwcm/mg/search/371704.html
- OMIM: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?600436
- UniGene: http://www.ncbi.nlm.nih.gov/UniGene/query.cgi
- GeneCards: http://bioinfo.weizmann.ac.il/cards-bin/carddisp?GSTT1&search=gstt1&suff=txt

GSTP1

- Human Gene Mutation Database http://archive.uwcm.ac.uk/uwcm/mg/search/120024.html
- OMIM http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?134660
- UniGene http://www.ncbi.nlm.nih.gov/UniGene/clust.cgi?ORG=Hs&CID=226795
- GeneCards http://bioinfo.weizmann.ac.il/cards-bin/carddisp?GSTP1&search=gstp1&suff=txt