Case report

Familial adenomatous polyposis complicated by chronic myelogenous leukemia: response to imatinib mesylate

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Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by colonic polyposis and a predisposition for developing colorectal cancer. FAP is frequently complicated by extracolonic disease, but complications of leukemia are rare. We present the first case of FAP complicated by chronic myelogenous leukemia (CML) in a 38-year-old man. The patient had numerous adenomas in the colorectum and a family history compatible with FAP. He was diagnosed as having FAP in February 2000. Two years after the diagnosis, he developed leukocytosis with the Philadelphia chromosome abnormality, indicating complication with CML. Imatinib mesylate was administered for the treatment of CML, and hematologic and cytogenetic remission of CML was achieved in 6 months. Numerous polyps, 2 to 3 mm in diameter, observed in the rectum prior to the administration of imatinib, regressed in size, but not in number, after 1 year of treatment with imatinib. Eighteen months later, however, the polyps were enlarged. In this patient, imatinib administration led to the remission of CML and might also have been responsible for the temporary regression of adenomatous polyps of FAP.

Key words: familial adenomatous polyposis, chronic myelogenous leukemia, imatinib, regression

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder in which precancerous polyps grow in the colorectum. Left untreated, virtually all patients with FAP develop colon cancer in early adulthood.[1] Mutations of the adenomatous polyposis coli (APC) gene are thought to be responsible for the development of FAP.[2] Chronic myeloid leukemia (CML) manifests primarily as an increase in white blood cells (WBC) and is characterized by the Philadelphia chromosome translocation t(9;22)(q34;q11) resulting in the formation of the BCR/ABL fusion gene. Products of the BCR/ABL [2] fusion gene are responsible for the development of CML.[3] Imatinib mesylate was designed to inhibit BCR/ABL tyrosine kinase of CML,[4] and the administration of imatinib effectively induces the remission of CML.[5] Imatinib mesylate is also effective against gastrointestinal stromal tumors (GIST).[6] Recently, imatinib was clinically tested for the treatment of advanced colorectal cancer (http://clinicaltrials.gov/ct/gui/show/NCT00041340?order=16) and adenomatous polyps of FAP (http://www.hereditarycc.org/cgi-bin/read.pl?i=199). We report a case with FAP complicated by CML. We administered imatinib mesylate to treat CML, and observed temporary regression of the adenomatous polyps of FAP during the administration of imatinib.

Case report

A 38-year-old man underwent screening for colon cancer after testing positive for occult blood in the stool in
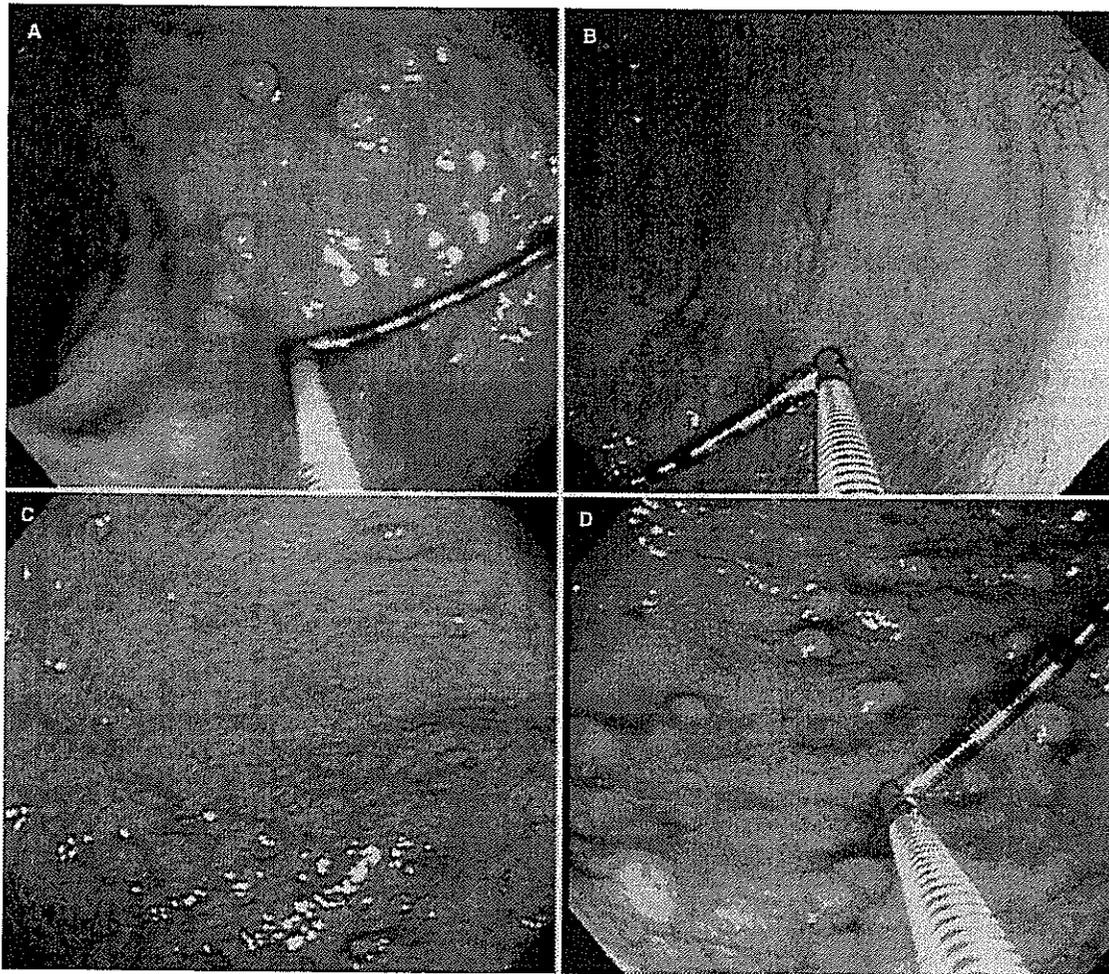
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Fig. 1A–D. Endoscopic examination of the rectum. A polyp was marked to identify the same place in the rectum. *Hatched bar* on the wire indicates 2-mm intervals. **A** July 2002 (prior to the administration of imatinib); **B** and **C** after the administration of imatinib for 1 year (July 2003); **D** after administration of imatinib for 12 to 18 months (January 2004)

April 1999. Double-contrast barium enema and colonoscopy revealed numerous polyps in the colorectum. The patient was referred to the Osaka Medical Center for Cancer and Cardiovascular Disease in February 2000. His father had colorectal polyposis and had died of rectal cancer at the age of 36. Two of his father's brothers and his grandfather also had colorectal cancer. A germline mutation of the *APC* gene was not detected in this patient by a protein truncation test, which detects mutation in approximately 80% of FAP patients.[7] On the basis of the presence of colon polyposis and an autosomal dominant family history, the patient was diag-

nosed with FAP. He underwent prophylactic subtotal colectomy with ileorectal anastomosis in October 2000. He was under intensive colonoscopic surveillance semiannually, and polyps larger than 7 mm in diameter were removed. No colorectal cancer was detected in the removed tissues. In January 2002, his WBC count and serum lactic dehydrogenase levels increased. He was referred to the Division of Hematology-Oncology, Department of Internal Medicine, at the Hyogo College of Medicine in April 2002. Laboratory studies revealed a red blood cell count of 5×10^9/l, hemoglobin 15.7 g/dl, and a WBC count of 48.1×10^6/l, and platelet count of [3]

$222 \times 10^6/l$. Neutrophil alkaline phosphatase (NAP) activity was low (NAP rate 38%, score 82). A myelogram revealed hypercellular (nucleated cell count $987 \times 10^6/l$) and granulocyte-predominant marrow. Chromosomal analysis of bone marrow cells revealed 46XY, t(9;22)(q34;q11) in all 20 metaphases, which is known as the Philadelphia chromosome (Ph) and the critical genetic abnormality of CML. The BCR/ABL fusion transcript, which is generated as the molecular consequence of the Philadelphia chromosome, was present in 56% of bone marrow cells as detected by fluorescent in situ hybridization analysis. The patient was diagnosed with Ph(+) CML in the chronic phase. The patient was given imatinib mesylate 400 mg/day from July 2002. Owing to adverse reactions, including nausea and vomiting, the dose was reduced to 300 mg/day after 1 week. The patient achieved hematologic remission in 2 weeks based on blood count, and attained a complete cytogenetic response after 9 months of imatinib administration based on chromosome and fluorescent in situ hybridization analyses. A colonoscopy in July 2002, prior to the administration of imatinib (Fig. 1A), revealed a number of polyps 2 to 3 mm in diameter in the rectum. After 1 year of administration of imatinib (July 2003) (Fig. 1B and C), the adenomatous polyps showed significant regression in size, but not in number. Eighteen months after the beginning of imatinib administration (January 2004), the adenomatous polyps were again enlarged (Fig. 1D).

Discussion

We report a patient with FAP complicated by CML. Several cases of FAP complicated with leukemia have been reported, but the leukemia is usually the acute type.[5] To our knowledge, this is the first report of a FAP patient complicated by CML. Critical genetic changes of CML in the chronic phase are located on chromosomes 9 and 22,[3] and the *APC* gene of FAP is located on chromosome 5q;[2] thus, there seems no obvious genetic correlation between these diseases. It is possible that these two disorders occurred coincidentally at the same time in this patient.

The product of the *BCR/ABL* gene, which has tyrosine kinase activity, is constitutively produced in patients with Ph(+) CML.[3] Imatinib is a drug designed to interact with the ATP-binding site of the enzyme to inhibit intracellular signal transduction leading to apoptosis of tumor cells.[4] When administered to patients with Ph(+) CML, imatinib decreases the incidence of Ph(+) cells and *BCR/ABL* hybrid genes.[5] Furthermore, imatinib specifically inhibits the signal transduction of tyrosine kinases of c-Kit and platelet-derived growth factor receptors (PDGFR).[9] Recent reports revealed the efficacy of imatinib administration against GIST, which constitutively expresses c-Kit.[6] The present case of FAP was complicated by Ph(+) CML after prophylactic colectomy, while the patient was under careful follow-up. After administration of imatinib, the patient achieved a cytogenetically complete remission and a major molecular response of CML. Spontaneous regression of polyps of FAP is quite rare, and therefore prophylactic colectomy is recommended for the management of FAP.[1] Drugs that induce regression of polyps of FAP are limited to nonsteroidal anti-inflammatory drugs or, in a broad sense, cyclo-oxygenase-2 inhibitors.[10] As the patient did not take such drugs, imatinib mesylate was assumed to be responsible for the polyp regression. Thus, the temporary regression of colorectal adenomatous polyps might have been related to the administration of imatinib mesylate in our patient. Immunohistochemical analysis revealed no c-Kit expression in the adenomatous polyps (data not shown). Preliminary immunohistochemical analysis using currently available anti-PDGFRA antibody did not provide conclusive information on the expression of PDGFRA in adenomatous polyps. This issue and a mutation of the *PDGFR* gene in adenomatous polyps should be further analyzed to clarify the relationship between imatinib administration and polyps regression. Currently, this is the only case in which imatinib was administered to a FAP patient. Studies are currently under way in the United States to test imatinib for the treatment of colorectal cancer or FAP (http://clinicaltrials.gov/ct/gui/show/NCT00041340?order=16, http://www.hereditarycc.org/cgi-bin/read.pl?i=199). The present case might indicate the limited efficacy of imatinib for the regression of adenomatous polyps.

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JG2009

Human Genome Epidemiology (HuGE) Review

Meta- and Pooled Analysis of *GSTT1* and Lung Cancer: A Huge-GSEC Review

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Lung cancer is the most common malignancy in the Western world, and the main risk factor is tobacco smoking. Polymorphisms in metabolic genes may modulate the risk associated with environmental factors. The glutathione S-transferase theta 1 gene (GSTT1) is a particularly attractive candidate for lung cancer susceptibility because of its involvement in the metabolism of polycyclic aromatic hydrocarbons found in tobacco smoke and of other chemicals, pesticides, and industrial solvents. The frequency of the GSTT1 null genotype is lower among Caucasians (10–20%) than among Asians (50–60%). The authors present a meta- and a pooled analysis of case-control, genotype-based studies that examined the association between GSTT1 and lung cancer (34 studies, 7,629 cases and 10,087 controls for the meta-analysis; 34 studies, 7,044 cases and 10,000 controls for the pooled analysis). No association was observed between GSTT1 deletion and lung cancer for Caucasians (odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.87, 1.12); for Asians, a positive association was found (OR = 1.28, 95% CI: 1.10, 1.49). In the pooled analysis, the odds ratios were not significant for either Asians (OR = 0.97, 95% CI: 0.83, 1.13) or Caucasians (OR = 1.09, 95% CI: 0.99, 1.21). No significant interaction was observed between GSTT1 and smoking on lung cancer, whereas GSTT1 appeared to modulate occupational-related lung cancer.

disease susceptibility; epidemiology; genes; genetic predisposition to disease; GSTT1; lung neoplasms; meta-analysis

Abbreviations: CI, confidence interval; GSEC, Genetic Susceptibility to Environmental Carcinogens; GST, glutathione S-transferase; GSTT1, glutathione S-transferase theta 1 gene; OR, odds ratio.

GENE

The glutathione S-transferase (GST) supergene family consists of phase II detoxifying enzymes catalyzing several reduced glutathione-dependent reactions with compounds containing an electrophilic center (1). The GST family comprises at least eight classes of GST isoenzymes: alpha, mu, pi, sigma, theta, kappa, omega, and zeta (2). Genetic polymorphisms have been described in all these classes (3). The soluble GSTs exist as dimeric proteins of approximately 25 kDa; they are highly expressed, constituting up to 4 percent of the total soluble proteins (4).

Two theta-class GSTs, GSTT1 and GSTT2, have been identified in the human liver, and the corresponding genes are localized in the same region on human chromosome 22, specifically in the subband 22q11.2 (5, 6). GSTT1 enzymes show important differences in their catalytic activity compared with other GSTs: they have lower glutathione binding activity, with increased catalytic efficiency (7, 8). Theta is considered the most ancient of the GSTs, and theta-like GSTs are found in almost all organisms investigated (2). The encoded GSTT1 human subunit is about 25,300 Da (9); the gene is 8.1 kb long (10).

Among the GST substrates, there are several environmental carcinogens found in food, air, or medications, such as polycyclic aromatic hydrocarbons, found in combustion products, diet, and tobacco smoke (11). Polycyclic aromatic hydrocarbons are activated by members of the phase 1 cytochrome P-450 supergene family to epoxide-containing metabolites (e.g., benzo[a]pyrene-7,8-diol-9,10-oxide), which are substrates for the mu, alpha, and pi GST classes. GSTT1

is an interesting candidate gene for lung cancer susceptibility because of its involvement in the metabolism of chemicals such as methylating agents, pesticides, and industrial solvents (2). In vitro studies suggest that both GSTT1 and GSTM1 enzymes protect cells from the toxic products of phase 1 detoxification reactions (12, 13).

However, GSTT1-catalyzed reactions can also increase the toxicity of some compounds, such as dichloromethane (2). GSTs also conjugate isothiocyanates, which are potent inducers of enzymes that detoxify environmental mutagens (14). The conjugation process diverts the isothiocyanates from the enzyme induction pathway into excretion (15), leading to elimination of these anticarcinogenic substances (16) and thus decreasing their potential chemopreventive effect (17).

GENE VARIANTS

The most common polymorphism in GSTT1 consists of a deletion of the whole gene, resulting in the lack of active enzyme (18). Complete deletion at the GSTT1 locus (19) was hypothesized by observing the phenotypic variation in glutathione-related detoxification of halomethanes by human erythrocytes, resulting in "conjugator" and "nonconjugator" phenotypes (20). Recently, another less common polymorphism (Thr104Pro) in the GSTT1 gene was described that also results in a nonconjugator phenotype (21).

The frequency of the GSTT1 deletion varies among different populations (22). In particular, the prevalence of the GSTT1 null genotype is lower among Caucasians (10–20 percent) compared with Asians (50–60 percent) (23). The frequency of the GSTT1 null polymorphism in the controls included in the present meta- and pooled analyses is similar to what was previously published (22): 18.7 percent (meta-analysis) and 19.0 percent (pooled analysis) in Caucasians; 53.8 percent and 53.6 percent, respectively, in Asians; and
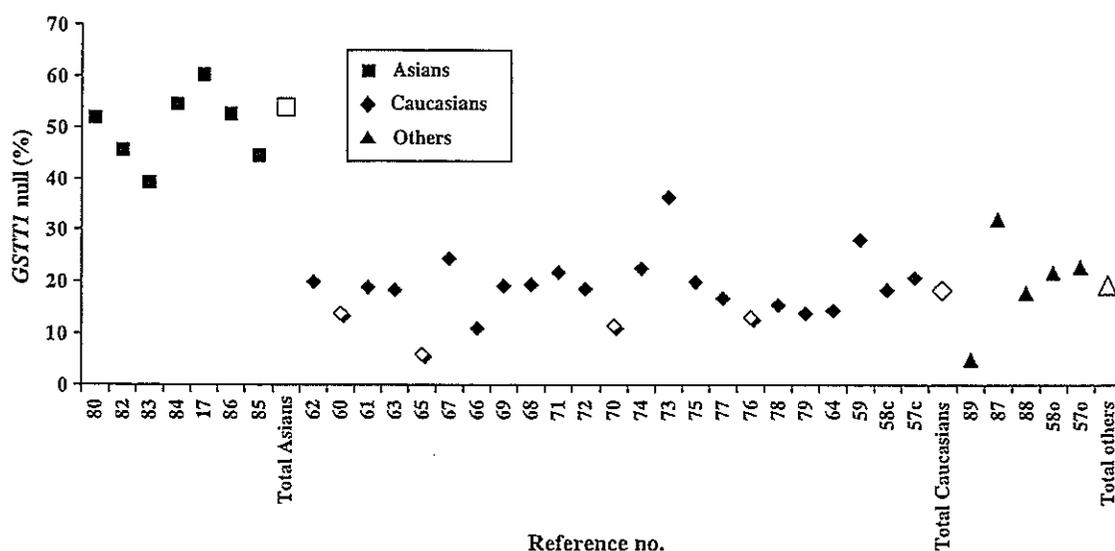
FIGURE 1. Frequency of the glutathione S-transferase gene (*GSTT1*) deletion in controls from the studies included in the meta-analysis according to ethnicity. The larger white square, diamond, and triangle refer to the average frequency of the *GSTT1* deletion in Asians, Caucasians, and others, respectively. The four smaller white and black diamonds correspond to studies performed in the northern European countries (Sweden, Denmark, and Finland), where the frequency of the deletion is significantly lower. 58c/57c and 58o/57o represent, respectively, the frequencies of *GSTT1* null in Caucasians and in African Americans for the studies by Cote et al. (58) and Wenzlaff et al. (57).

19.4 percent (meta-analysis only) for other ethnic groups (Latinos, African Americans, and mixed). The frequency of the *GSTT1* deletion is graphically presented in figure 1 for each study included in the meta-analysis and is stratified according to ethnicity. Among Caucasians, the frequency of the deletion is significantly lower in northern European countries (Sweden, Denmark, and Finland) than elsewhere in Europe, as previously reported (22, 24). The frequency of the *GSTT1* deletion according to geographic area is 52.2 percent (meta-analysis) and 51.2 percent (pooled analysis) in Asians, 17.3 percent (meta-analysis) and 18.0 percent (pooled analysis) in Europeans, and 21.7 percent (meta-analysis) and 27.0 percent (pooled analysis) in North Americans.

Gene function

The main function of the GST enzymes is detoxification of electrophiles by conjugation to glutathione. A wide variety of both endogenous electrophilic substrates, such as by-products of reactive oxygen species activity, and exogenous electrophilic substrates, have been identified (2, 25). *GSTT1* also catalyzes the detoxification of oxidized lipids and DNA (2, 8, 26). Halogenated organic compounds, for example, the ethylene dibromide, *p*-nitrobenzyl chloride (27), *p*-nitrophenetyl bromide (28), methyl chloride, and methyl iodide (29, 30), are known substrates for *GSTT1*. The *GSTT1*+ phenotype catalyzes conjugation of dichloromethane to glutathione, a metabolic pathway that has been shown to be more mutagenic than *GSTT1* null in *Salmonella typhimurium* mutagenicity tester strains (31) and was suggested to be responsible for the carcinogenicity of dichloromethane in the mouse (32). The consequence of the null

genotype is reduced or null conjugation activity and, in most cases, an inability to efficiently eliminate electrophilic carcinogens (19, 33).

DISEASE

Lung cancer is the most common malignancy in the Western world. Although incidence has apparently now peaked in the United States and most of Europe, increasing incidence and mortality is observed in several developing countries. More than a million new cases were diagnosed in 2000, accounting for 12.3 percent of all new cases of cancer, and more than a million subjects died of lung cancer in the same period, accounting for 17.8 percent of all cancer deaths (34). The case fatality (ratio of mortality to incidence), which is an indicator of prognosis, is 0.89, the third worst after that for the pancreas and liver (35).

The main histologic types of lung cancer are squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma. The first three are also referred to as non–small cell lung carcinomas. Squamous cell carcinoma, large cell carcinoma, and small cell carcinoma are more strongly associated with smoking than other histologic types. The histologic characteristics of lung cancer have changed in recent decades: the frequency of adenocarcinoma has risen, while that of squamous cell carcinoma has declined (36–39).

Smoking

The main risk factor for lung cancer is tobacco smoking. Worldwide, the population attributable fraction of lung cancer mortality due to smoking is 79 percent for men and

TABLE 1. Description of the studies included in the meta-analysis

Authors (reference no.), year	No. of cases	No. of controls	Country	Mean age in years (range/SD*)	Male (%)	Histology	Source of controls	Matching criteria	Crude OR*,†	95% CI*
Caucasian studies										
Reszka et al. (59), 2005‡	119	138	Poland	58.9 (range, 30–78)§	74.69§	SqCC* = 36.6%, SCC* = 25.0%, NSCC* = 18.6%, AC* = 8.9%, others = 8.9§	Hospital	Age and gender	0.51	0.28, 0.94
Alexandrie et al. (60), 2004‡	524	530	Sweden	54.9 (range, 19–88)	71.8	SqCC = 31.6%, SCC = 19.5%, AC = 27.5%, LCC* = 3.1%, others = 8.8%, nonclassified = 9.5%	Healthy	None	0.92	0.65, 1.31
Belogubova et al. (61), 2004‡	167	663	Russia	57.6 (range, 18–95; SD, 7.9)	54.3	SqCC = 52.7%, SCC = 12.6%, NSCC = 11.4%, AC = 23.3%	Healthy	None	0.94	0.61, 1.46
Harms et al. (62), 2004	110	119	United States	58.5 (SD, 10.3)	52.4	No information	Healthy	Age, ethnicity, and gender (frequency matching)	1.55	0.84, 2.86
Schneider et al. (63), 2004‡	446	622	Germany	63.9 (range, 20–96; SD, 10.1)	94.0	SqCC = 41.1%, SCC = 15.0%, AC = 25.1%, LCC = 3.6%, others = 15.2%	Hospital	None	0.89	0.65, 1.23
Sobti et al. (64), 2004‡	100	76	India	53.5 (range, 27–80; SD, 9.9)	95.5	SqCC = 71.0%, SCC = 24.0%, AC = 4.0%, LCC = 1.0%	Healthy	Ethnicity	1.30	0.57, 2.94
Sorensen et al. (65), 2004‡	254	265	Denmark	No information	No information	SqCC = 22.0%, SCC = 20.0%, AC = 33.0%, LCC = 6.0%, others = 19.0%	Healthy	Age, gender, and smoking (frequency matching)	2.65	1.44, 4.90
Dialyna et al. (66), 2003‡	122	178	Greece	61.2 (no range or SD)	84.3	SqCC = 18.0%, SCC = 17.2%, NSCC = 38.5%, AC = 24.6%, others = 1.7%	Healthy	None	1.64	0.85, 3.18
Ruano-Ravina et al. (67), 2003‡	125	187	Spain	63.2 (SD, 10.3)	90.4	No information	Hospital	None	0.84	0.49, 1.45
Lewis et al. (68), 2002‡	87	143	United States	62.4 (SD, 12.8)§	59.6	SqCC = 33.3%, SCC = 17.2%, NSCC = 10.3%, AC = 11.5%, nonclassified = 27.6%	Hospital	None	1.15	0.60, 2.21
Stucker et al. (69), 2002‡	251	268	France	59.4 (SD, 9.8)	100	SqCC = 46.0%, SCC = 19.0%, AC = 24.0%, others = 11.0%	Hospital	Age, ethnicity, and gender	0.74	0.47, 1.17
Hou et al. (70), 2001	184	162	Sweden	68.1 (range, 30–92)	<30	SqCC = 22.0%, AC = 51.0%, others = 27.0%	Healthy	Age, gender, and smoking (frequency matching)	1.06	0.60, 1.85
Liu et al. (71), 2001	1,024	1,176	United States	61.4 (SD, 11.5)§	49.7§	SqCC = 25.0%, SCC = 8.3%, AC = 51.0%, LCC = 7.6%, others = 6.3%, not classified = 1.4%§	Healthy	None	0.89	0.72, 1.09
Risch et al. (72), 2001‡	383	346	Germany	58.2 (range, 17–92)§	68.6§	SqCC = 44.0%, SCC = 2.8%, AC = 39.0%, LCC = 4.9%, others = 10.0%§	Hospital	Ethnicity	0.63	0.42, 0.95
Malats et al. (73), 2000‡	122	121	Sweden, Germany, France, Italy, Russia, Rumania, Poland, and Brazil	61.5 (no range or SD)	21.0	SqCC and SCC = 20.7%, AC = 53.7%, others = 25.6%	Hospital	Ethnicity	0.62	0.36, 1.08
Spitz et al. (74), 2000‡	484	458	United States	61.6 (SD, 9.7)§	53.3§	No information	Healthy	Age, ethnicity, gender, and smoking	1.28	0.95, 1.72
To-Figueras et al. (75), 1999‡	164	200	Spain	46.0 (range, 26–87)	88.4 (only cases, no information for controls)	SqCC = 31.7%, SCC = 34.8%, AC = 25.6%, LCC = 7.9%	Healthy	Gender (frequency matching)	1.38	0.84, 2.26

Study	Cases	Controls	Country	Mean age	%	Histology	Source of controls	Matching	OR	95% CI
Saarikoski et al. (76), 1998‡	204	294	Finland	49.7 (SD, 10.2)	91.6	SqCC = 45.2%, AC = 39.4%, others = 15.4%	Healthy	None	0.96	0.56, 1.63
Salagovic et al. (77), 1998‡	117	248	Slovakia	No information	64.1	No information	Healthy	None	0.78	0.42, 1.45
Jourenkova et al. (78), 1997‡	150	172	France	56.6 (no range or SD)	94.1	SqCC = 65.3%, SCC = 34.7%	Hospital	Age and gender (frequency matching)	1.18	0.66, 2.12
Deakin et al. (79), 1996‡	108	509	United Kingdom	69.7 (no range or SD)	52.0	No information	Hospital	None	0.82	0.47, 1.45
Asian studies										
Chan-Yeung et al. (80), 2004	229	197	China	51.7 (SD, 14.9)	63.6	SqCC = 16.6%, NSCC = 19.2%, AC = 55.5%, others = 8.7%	Healthy	Ethnicity	1.55	1.05, 2.28
Liang et al. (81), 2004	152	152	China	No information (Chinese language)	No information (Chinese language)	No information (Chinese language)	Hospital	No information (Chinese language)	2.06	1.30, 3.24
Wang et al. (82), 2003‡	112	119	Japan	55.5 (range, 35–75; SD, 8.2)	65.4	AC = 100%	Healthy	Age and gender	1.08	0.64, 1.81
Sunaga et al. (83), 2002‡	198	152	Japan	63.9 (SD, 11.3)	66.3	AC = 100%	Hospital	None	1.58	1.03, 2.42
Zhao et al. (84), 2001‡	233	187	Singapore	64.7 (SD, 12.4)	0	No information	Hospital	Age (frequency matching)	1.09	0.74, 1.60
Kiyohara et al. (85), 2000‡	86	88	Japan	61.4 (range, 20–86)	100	SqCC = 27.9%, SCC = 14.0%, AC = 46.5%, LCC = 4.7%, others = 7.0%	Healthy	None	1.51	0.83, 2.75
Lan et al. (86), 2000‡	122	122	China	55 (SD, 11.5)	64.8	No information	Healthy	Age and gender (individual matching)	1.35	0.81, 2.24
London et al. (17), 2000‡	232	710	China	58.8 (range, 45–64; SD, 4.8)	100	SqCC = 33.6%, AC = 29.7%, others and nonclassified = 36.6%	Healthy	Age (individual matching)	0.91	0.67, 1.23
Other studies										
Cote et al. (5B), 2005‡	304	398	United States	41.6 (no range or SD)§	44.7§	SqCC = 11.7%, SCC = 13.2%, NSCC = 3.7%, AC = 47.7%, LCC = 9.4%, others = 14.3%§	Healthy	Age, ethnicity, and gender (frequency matching)	1.09	0.76, 1.58
Wenzlaff et al. (57), 2005‡,¶	153	175	United States	58.5 (SD, 13.6)§	45.8§	SqCC = 15.7%, SCC = 6.6%, AC = 54.2%, LCC = 7.2%, others and nonclassified = 16.3%§	Healthy	Age, ethnicity, and gender (frequency matching)	0.84	0.48, 1.44
Yang et al. (87), 2004‡	237	234	United States	54.3 (SD, 4.6) (only cases, no information for controls)§	51.5 (only cases, no information for controls)§	SqCC = 13.5%, SCC = 7.6%, NSCC = 13.1%, AC = 52.3%, LCC = 3.8%, others = 8.9%§	Healthy	None	0.88	0.78, 0.98
Nazar-Stewart et al. (88), 2003	274	500	United States	No mean age (range, 18–74)	100	SqCC = 29.6%, SCC = 19.0%, NSCC = 16.4%, AC = 35.0%	Healthy	Age and gender (frequency matching)	1.07	0.73, 1.56
Gallegos-Arreola et al. (89), 2003–2004	52	178	Mexico	No information	No information	No information	Healthy	None	5.04	1.79, 14.31
Total	7,629	10,087								

* SD, standard deviation; OR, odds ratio; CI, confidence interval; SqCC, squamous cell carcinoma; SCC, small cell carcinoma; NSCC, non–small cell carcinoma; AC, adenocarcinoma; LCC, large cell carcinoma.

† Crude ORs were calculated by using the reported frequencies of the *GSTT1* null genotype in cases and controls. For this reason, they could be slightly different from the adjusted ORs reported in each paper.

‡ Studies included in the pooled analysis.

§ The information concerns all subjects included in the original study and not the subset of subjects with data on *GSTT1*.

¶ Part of the subjects included in this study were also included in the study by Cote et al. (58) (35 cases and 79 controls, personal communication by the authors).

48 percent for women (40). In Western countries, the population attributable fraction due to smoking was estimated to be approximately 90 percent for men and approximately 70 percent for women. Lung cancer risk significantly decreases with smoking cessation; however, the relative risk remains 1.5–2.0 times the risk for never smokers (41). Lung cancer is also associated with environmental tobacco smoke (42). Other risk factors are diet (43), outdoor air pollution, occupational exposures to carcinogens (44), and radon (45).

ASSOCIATIONS AND INTERACTIONS

The association between *GSTT1* and lung cancer was assessed through a meta-analysis of all published papers and a pooled analysis of selected published and unpublished studies. A Medline search was performed from January 1995 (the date when the first case-control studies on *GSTT1* and lung cancer were published) to March 2005 using different combinations of the keywords "glutathione *S*-transferase," "*GSTT1*," and "lung" without restriction on language. The computer search was supplemented by consulting the bibliographies from the articles found through the Medline search and by looking at two review papers (2, 46). An initial screening of all the abstracts provided 50 articles containing information on both *GSTT1* and lung cancer. Eligible were case-control, genotype-based studies that reported the frequency of *GSTT1* or the odds ratio for *GSTT1* and lung cancer. Both hospital- and population-based case-control studies were included in the analysis. Of the 50 articles selected, excluded were two because they were a pooled analysis of existing data (47, 48), three because they reported on studies that included either only cases of lung cancer ($n = 1$) or only controls ($n = 2$), and three because they did not report the frequency of *GSTT1* or the odds ratio of lung cancer for *GSTT1* deletion. We also excluded eight studies (49–56) because the subjects were the same as those in other studies. In case of multiple publications on the same population, the most recent publications, with the largest group of subjects with data on *GSTT1*, were always included in this analysis. Two studies (57, 58) were included in the meta-analysis although they contained a small number (35 cases and 79 controls) of overlapping subjects. Therefore, the final number of articles considered for the present analysis was 34 (17, 57–89), including a total of 7,629 cases and 10,087 controls; table 1 describes the studies.

The pooled analysis was performed by using the Genetic Susceptibility to Environmental Carcinogens (GSEC) database (www.gsec.net). The design of this study is explained in detail elsewhere (90). Briefly, this collaborative project gathers information from both published and unpublished case-control studies on metabolic gene polymorphisms and cancer. The investigators who agreed to participate sent their original data sets, with individual genetic and epidemiologic data for each subject. Quality and logical controls on the data are usually performed by the research assistant when entering the data in the main GSEC database. In addition, a questionnaire was provided to each participant at the time of enrollment in the study; it contained information on the study design, the selection and source of controls, the lab-

oratory methods used for genotyping subjects, the source of DNA for genotype analysis, and the response rates for both cases and controls. Some of this information has been published previously (91).

We selected, from the GSEC database, all studies that had information on *GSTT1* and lung cancer. We also contacted all investigators of studies for which data were not available through the GSEC project and asked them to provide their data for this specific pooled analysis. We were able to obtain data from 27 of the 34 studies included in the meta-analysis (79 percent; refer to table 1 for details). The number of subjects included in some data sets is slightly different from the published data because they may also include some unpublished data. The GSEC database contained seven additional studies with completely unpublished data on *GSTT1* and lung cancer; therefore, the pooled analysis included 34 studies, for a total of 7,044 cases and 10,000 controls.

Statistical analysis

For the meta-analysis, study-specific crude odds ratios and 95 percent confidence intervals for lung cancer for *GSTT1* deletion were estimated on the basis of the reported frequencies of *GSTT1* deletion in cases and controls. The Egger test (92) was performed on the overall data sets and after stratification for ethnicity (Caucasians, Asians, other ethnic groups) and source of the control group (healthy or hospitalized controls). Funnel plots were used for a graphic representation of publication bias.

Other ethnic groups were represented by fewer than three studies each and therefore were grouped together as "others" in the analyses on ethnicity. Such ethnic groups included Latinos (one study), African Americans (two studies), and mixed populations (two studies). The hypothesis of homogeneity among studies was tested by the Q statistic, with p values of <0.05 indicating the presence of heterogeneity among studies. The Q statistic was performed on all of the studies and according to ethnicity and type of controls. When the test for heterogeneity was not statistically significant, a fixed-effects model was performed; a random-effects model was used when heterogeneity across studies was statistically observed (93).

Because the frequency of *GSTT1* null differs according to ethnicity, summary odds ratios were calculated for all studies combined as well as for subgroups of studies performed with different ethnic groups (Caucasians, Asians, others). Further stratification was performed within each of the three ethnic groups according to type of controls (hospital or healthy controls). Use of hospital-based controls can bias the risk estimates if the diseases of the controls are related to the genetic variant under study.

Pooled analysis was performed separately for the two major ethnic groups (Caucasians and Asians) to avoid the confounding effect of ethnicity already observed in the meta-analysis. Study-specific crude odds ratios and 95 percent confidence intervals for lung cancer and *GSTT1* deletion were estimated, and their homogeneity was tested by using both Q and Breslow-Day's tests. Crude and adjusted odds ratios were calculated for each ethnic group and for the total set of the available studies. Separate analyses were
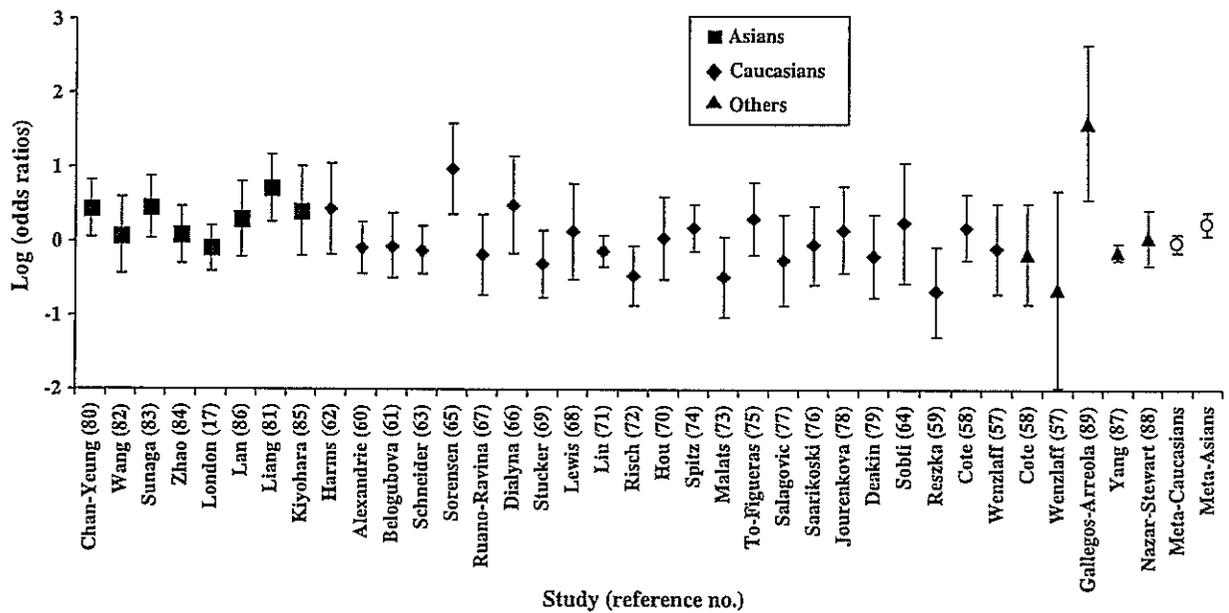
FIGURE 2. Study-specific and meta-log(odds ratios) with 95% confidence intervals for glutathione *S*-transferase gene (*GSTT1*) null and lung cancer according to ethnicity.

conducted on the studies included in both the meta- and pooled analyses and on the studies present in the pooled analysis only, which had not been previously published. When heterogeneity between studies was observed, a sensitivity analysis was performed by restricting the analysis to the studies for which evidence for heterogeneity of effects was not found. Stratified analyses were conducted according to the type of control population, smoking habits, and histologic type (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma). For smoking habits, subjects were divided into four classes by using the information on packs of cigarettes smoked times years of smoking. The baseline class included never smokers; the other three classes were created according to tertiles of the variable pack-years. A further analysis on histologic type was performed to assess whether the *GSTT1* null polymorphism was more frequent in adenocarcinoma than in squamous cell carcinoma cases (the two histologic types present most often in the data set). For this purpose, crude and adjusted odds ratios and 95 percent confidence intervals were calculated.

For studies including Caucasian subjects, the large sample size enabled us to stratify the data according to occupational exposure. Adjusted odds ratios were calculated by using multiple logistic regression models including study number, age (continuous variable), sex, and smoking status (ever/never) as covariates. In the same ethnic group, interactions between *GSTT1* deletion and smoking habits and occupational exposure were formally assessed by adding a product term, respectively, to a model containing the main effect of *GSTT1*, the categories of smoking habits, and the other possible confounding variables (study, age, and sex), and to a model containing the main effect of *GSTT1*, the cat-

egories of occupational exposure (exposed/nonexposed), and the other possible confounding variables (study, age, sex, and smoking habits). Models with or without an interaction term were compared by using the likelihood ratio test. The three studies (65, 74, Dragani (unpublished data)) for which the controls were frequency matched to the cases on smoking were excluded from the analysis of an interaction between *GSTT1* and smoking.

The meta-analysis was performed by using the STATA software package (Stata Corporation, College Station, Texas). The pooled analysis was conducted by using SAS, version 8e software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Meta-analysis

The study-specific odds ratios and the meta-odds ratios for studies including Asian and Caucasian subjects are presented in figure 2. Two studies (57, 58) reported separate analyses for two different ethnic groups (Caucasians and African Americans); therefore, they were included in the analysis of both Caucasians (by calculating the odds ratio for Caucasians only) and the other ethnic groups (by calculating the odds ratio for African Americans only). In the 23 studies on Caucasians, 20 odds ratios were spread around the null effect (nine above the unit and 11 under the unit); only one study (65) reported a significant positive association between lung cancer and *GSTT1* null (odds ratio (OR) = 2.65, 95 percent confidence interval (CI): 1.44, 4.90), whereas two studies (59, 72) reported a significant negative association (OR = 0.63, 95 percent CI: 0.42, 0.95 and

TABLE 2.   Odds ratios and 95% confidence intervals for the association between GSTT1* and lung cancer: meta analysis

	No. of studies†	No. of cases	No. of controls	GSTT1 null cases		GSTT1 null controls		OR*	95% CI*	Q-test p value
				No.	%	No.	%			
All	34	7,629	10,087	1,823‡	24.4‡	2,417‡	24.3‡	1.07	0.96, 1.19	<0.001
Caucasians										
All	23	5,585	7,300	1,017	18.3	1363	18.7	0.99	0.87, 1.12	0.02
Healthy controls	14	3,794	4,794	713	18.8	853	17.8	1.08	0.96, 1.21	0.10
Hospitalized controls	9	1,791	2,506	304	17.0	510	20.4	0.79	0.67, 0.93	0.46
Asians										
All	8	1,364	1,727	669‡	55.3‡	847‡	53.8‡	1.28	1.10, 1.49	0.09
Healthy controls	5	781	1,236	438	56.1	686	55.5	1.18	0.97, 1.42	0.22
Hospitalized controls	3	583	491	231‡	54.0‡	161‡	47.5‡	1.47	1.15, 1.87	0.10
Others: all healthy controls	5	680	1,060	137	20.1	207	19.5	1.08	0.72, 1.59	0.02

* GSTT1, glutathione S-transferase gene; OR, odds ratio; CI, confidence interval.

† Two studies (Cote et al. (58), Wenzlaff et al. (57)) reported separate information on Caucasians and African Americans. We used the OR calculated for both groups together to determine the overall meta-OR and the race-specific ORs for the stratified analysis. For this reason, the data by Cote et al. and Wenzlaff et al. were partially included in the meta-analysis on both Caucasians and other ethnic groups.

‡ No information on the frequency of GSTT1 null from one study (Liang et al. (81), 152 cases and 152 controls).

OR = 0.51, 95 percent CI: 0.28, 0.94, respectively). For Asians, all but one study found odds ratios above 1.00, with three studies (80, 83, 86) reaching statistical significance. The odds ratios in studies including Asian subjects ranged from 0.91 (95 percent CI: 0.67, 1.23) to 2.06 (95 percent CI: 1.30, 3.24). Among the other five studies on different ethnic groups, one (89) reported a very high risk (OR = 5.04, 95 percent CI: 1.79, 14.31) of lung cancer for Latino subjects carrying GSTT1 null; the other four studies, conducted in mixed populations (87, 88) and among African-American subjects (57, 58), reported no association between GSTT1 deletion and lung cancer.

The meta-odds ratios in table 2 refer to the analyses conducted on all studies and on stratified data. The meta-odds ratio for all studies combined was 1.07 (95 percent CI: 0.96, 1.19), with a large heterogeneity (Q-test p < 0.001) and evidence of publication bias (Egger's test p = 0.02). The sensitivity analysis indicated that by excluding five studies (65, 80, 81, 83, 89), the evidence of publication bias was reduced under the significance level (Egger's test p = 0.14), and heterogeneity was no longer present among the studies (Q-test p = 0.23). The meta-odds ratio calculated after exclusion of these five studies was lower (OR = 0.94, 95 percent CI: 0.88, 1.01). Of the five excluded studies, three included Asians, one Latinos, and one Caucasians; therefore, we attributed a large part of the observed heterogeneity to ethnicity.

In the analysis stratified by ethnicity, no association was observed between GSTT1 deletion and lung cancer among Caucasian subjects (OR = 0.99, 95 percent CI: 0.87, 1.12), with heterogeneity between the studies still present (Q-test p = 0.02) but no evidence of publication bias (Egger's test p = 0.42). Heterogeneity was not present after exclusion of the only study that presented a case-cohort design (65).

Among Asians, a significant positive association was found between lung cancer and the GSTT1 null genotype (meta-OR = 1.28, 95 percent CI: 1.10, 1.49). The test for hetero-

geneity was not statistically significant for the eight studies including Asian subjects (Q-test p = 0.09), and no evidence of publication bias was observed (Egger's test p = 0.16).

For all the other studies on different ethnic groups, the meta-odds ratio was 1.08 (95 percent CI: 0.72, 1.59), with heterogeneity (Q-test p = 0.02) but no evidence of publication bias (Egger's test p = 0.28). The heterogeneity was probably due to the different ethnicities included in these studies. Table 2 presents the meta-odds ratios stratified according to type of controls and according to ethnicity. For Caucasians, the association with GSTT1 null was stronger in the analysis conducted of studies including healthy subjects (OR = 1.08, 95 percent CI: 0.96, 1.21) than that for studies including hospital controls (OR = 0.79, 95 percent CI: 0.67, 0.93). Among the studies including Asian subjects, a significant association between GSTT1 deletion and lung cancer was observed only when the analysis was restricted to studies including hospital controls (OR = 1.47, 95 percent CI: 1.15, 1.87), whereas such an association was less evident for studies including healthy controls (OR = 1.18, 95 percent CI: 0.97, 1.42). No heterogeneity or publication bias was found in these stratified analyses (results not shown).

Pooled analysis

Crude study-specific odds ratios and 95 percent confidence intervals are reported in table 3 for Asians and table 4 for Caucasians. No heterogeneity between studies including Asian subjects was observed; for Caucasians, the test for heterogeneity was statistically significant. However, exclusion of one case-cohort study (65) made the sample statistically homogenous (p for Q and Breslow-Day's tests = 0.09).

The summary odds ratios of lung cancer for GSTT1 null and lung cancer are presented in table 5 for Asians and table 6 for Caucasians. The adjusted summary odds ratios for all studies combined were not significant for Asians

TABLE 3.   Description of Asian studies included in the pooled analysis: study-specific crude odds ratios and 95% confidence intervals

Author(s) (reference no.), year	No. of cases	No. of controls	Source of controls	Crude OR*,†	95% CI*
Sugimura (unpublished data)	215	166	Hospital	0.97	0.64, 1.48
Kang (unpublished data)	169	196	Hospital	0.75	0.49, 1.13
Kiyohara et al. (85), 2000‡	86	90	Healthy	1.44	0.80, 2.61
Lan et al. (86), 2000‡	122	122	Healthy	1.35	0.81, 2.24
Wang et al. (82), 2003‡	112	119	Healthy	1.08	0.64, 1.81
Yang et al. (87), 2004	2	7	Healthy	1.33	0.06, 31.12
Zhao et al. (84), 2001‡	233	187	Hospital	1.09	0.74, 1.60
Cote et al. (58), 2005 and Wenzlaff et al. (57), 2005§	2	3	Healthy	2.00	0.05, 78.25
Sunaga et al. (83), 2002‡	198	152	Hospital	1.58	1.03, 2.42
London et al. (17), 2000‡	234	714	Healthy	0.89	0.66, 1.20

* OR, odds ratio; CI, confidence interval.
† *p* value for Breslow-Day's test for homogeneity = 0.3; *p* value for *Q* test for homogeneity = 0.39.
‡ Studies included in the meta-analysis on Asian subjects.
§ The original data set from the two studies did not include overlapping subjects.

(OR = 0.97, 95 percent CI: 0.83, 1.13) or for Caucasians (OR = 1.09, 95 percent CI: 0.99, 1.21). Among Caucasians, when the analysis was restricted to the studies for which the test for heterogeneity was not statistically significant, lower odds ratios were observed. If the analysis was restricted to studies included in both the meta- and pooled analyses, the odds ratios became similar to the summary odds ratios obtained from the meta-analysis. The analysis restricted to studies included in the pooled analysis only, which include unpublished data on *GSTT1* and lung cancer, showed lower odds ratios for both Asian and Caucasian subjects. For both Asians and Caucasians, higher adjusted summary odds ratios were found when the analysis included healthy controls in comparison with hospitalized controls.

A stratified analysis according to smoking status was performed by using the information on packs of cigarettes smoked times years of smoking, available for 2,642 of the 3,129 Asians (84 percent) and for 9,950 of the 13,511 Caucasians (74 percent). The observed association between *GSTT1* and lung cancer was present, although nonsignificant, among never smokers, but it decreased with increasing amount of smoking for both Asians and Caucasians (figure 3).

Small cell carcinoma was associated with *GSTT1* deletion in Asian subjects (crude OR = 1.96, 95 percent CI: 1.15, 3.23), but the odds ratio was not statistically significant after adjusting for study, age, gender, and smoking (adjusted OR = 1.45, 95 percent CI: 0.76, 2.77). No association was found between *GSTT1* and the other histologic types in the two ethnic groups (table 7). The adjusted odds ratio for adenocarcinoma in comparison with squamous cell carcinoma with *GSTT1* deletion was 0.94 (95 percent CI: 0.65, 1.36) for Asian subjects and 1.03 (95 percent CI: 0.83, 1.29) for Caucasian subjects.

The large sample of Caucasians enabled us to perform a stratified analysis according to the presence of occupational exposure. The information was available for 4,719 of 13,511 subjects (35 percent), and the results are reported

in table 8. A significant protective effect of *GSTT1* deletion on lung cancer was observed for subjects occupationally exposed. Because the agents reported in the data set were extremely heterogeneous (chemicals, polycyclic aromatic hydrocarbons, asbestos, metals, radiation, etc.), we restricted the analysis to asbestos exposure and found the same protective effect (table 8).

There was no statistical evidence of multiplicative interaction between *GSTT1* and smoking for Caucasians (*p* for the likelihood ratio test = 0.90). A significant antagonist effect of occupational exposure and *GSTT1* deletion was observed, with an odds ratio for interaction of 0.69 (95 percent CI: 0.51, 0.94, *p* for the likelihood ratio test = 0.02; table 9). However, when we restricted the analysis to asbestos exposure, the interaction with *GSTT1* was nonsignificant (*p* for the likelihood ratio test = 0.08; table 9), although subjects carrying the *GSTT1* deletion and exposed to asbestos had a lower risk of developing cancer in comparison with not occupationally exposed subjects in whom *GSTT1* was present (OR = 0.59, 95 percent CI: 0.41, 0.86).

DISCUSSION

The meta-analysis highlighted a higher risk of developing lung cancer for Asian subjects carrying the *GSTT1* null genotype (OR = 1.28, 95 percent CI: 1.10, 1.49), but the pooled analysis did not confirm this result (adjusted OR = 0.97, 95 percent CI: 0.83, 1.13). The lower odds ratio observed in the pooled analysis was mainly due to two unpublished studies (Sugimura, Kang), which reported a nonsignificant negative association between *GSTT1* and lung cancer. No significant association between lung cancer and *GSTT1* deletion was present in Caucasian subjects in either the meta-analysis or the pooled analysis. Our results were consistent with a previously published pooled analysis on a subset of subjects included in this study that showed no

TABLE 4. Description of Caucasian studies included in the pooled analysis: study-specific crude odds ratios and 95% confidence intervals

Author(s) (reference no.), year	No. of cases	No. of controls	Source of controls	Crude OR*,†	95% CI*
Saarikoski et al. (76), 1998‡	237	347	Healthy	1.15	0.71, 1.87
Dolzan (unpublished data)	201	102	Healthy	0.73	0.41, 1.28
Kremers (unpublished data)	48	71	Healthy	0.64	0.31, 1.33
Alexandrie et al. (60), 2004‡ and unpublished data	596	1,627	Healthy	0.88	0.67, 1.16
Risch et al. (72), 2001‡	399	358	Hospital	0.73	0.49, 1.09
Romkes (unpublished data)	30	43	Healthy	0.38	0.13, 1.13
Deakin et al. (79), 1996‡	163	603	Hospital	0.89	0.56, 1.40
Stucker et al. (69), 2002‡	251	268	Hospital	0.74	0.47, 1.17
Spitz et al. (74), 2000‡	484	458	Healthy	1.28	0.95, 1.72
To-Figueras et al. (75), 1999‡	164	324	Healthy and hospital	1.23	0.79, 1.92
Malats et al. (73), 2000‡	242	157	Hospital	1.05	0.68, 1.60
Jourenkova et al. (78), 1997‡	150	172	Hospital	1.18	0.66, 2.12
Salagovic et al. (77), 1998‡	354	394	Healthy	1.06	0.74, 1.54
Lewis et al. (68), 2002‡	87	143	Hospital	1.15	0.60, 2.21
Ruano-Ravina et al. (67), 2003‡	125	187	Hospital	0.84	0.49, 1.45
Dragani T/Neri (unpublished data)	104	97	Healthy	1.70	0.92, 3.16
Dialyna et al. (66), 2003‡	122	178	Healthy	1.64	0.85, 3.18
Reszka et al. (59), 2005‡	119	138	Hospital	0.51	0.28, 0.94
Schneider et al. (63), 2004‡	499	644	Healthy and hospital	0.87	0.64, 1.19
Yang et al. (87), 2004	216	219	Healthy	0.63	0.41, 0.98
Belogubova et al. (61), 2004‡	167	663	Healthy	0.94	0.61, 1.46
Sobti et al. (64), 2004‡	110	110	Healthy	1.07	0.52, 2.21
Cote et al. (58), 2005 and Wenzlaff et al. (57), 2005§	342	461	Healthy	1.30	0.93, 1.81
Shields (unpublished data)	30	30	Hospital	1.00	0.32, 3.14
Sørensen et al. (65), 2004‡	254	250	Healthy	2.67	1.43, 5.00

* OR, odds ratio; CI, confidence interval.

† p value for Breslow-Day's test for homogeneity = 0.01; excluding the Sørensen et al. study = 0.09. p value for Q test for homogeneity = 0.01; excluding the Sørensen et al. study = 0.09.

‡ Studies included in the meta-analysis on Caucasian subjects.

§ The original data set from the two studies did not include overlapping subjects.

statistically significant effect of *GSTT1* null on lung cancer for Caucasians at younger ages (47). The deletion in the *GSTT1* gene was not associated with lung cancer in two previous reviews (2, 46), even though both authors underlined that *GSTT1* deletion could play a role in lung carcinogenesis when *GSTM1* is concurrently lacking.

Because both smoking and occupational exposure are independent risk factors for lung cancer, we studied their interaction with *GSTT1* by using the pooled data set of individual data. We found no significant interaction between *GSTT1* and lifetime tobacco consumption on lung cancer; however, a negative trend of the odds ratios with increasing amount of lifetime smoking was observed for both Caucasians and Asians. This finding could be explained by the relevant role of genetic factors at low-dose-carcinogen exposures (94–97). The lack of interaction between *GSTT1*

and smoking is consistent with the hypothesis that polycyclic aromatic hydrocarbons, carcinogenic compounds found in tobacco smoke, are minor substrates for *GSTT1* (2).

A significant negative interaction was observed between being occupationally exposed and *GSTT1*: exposed subjects for whom *GSTT1* was present were at higher risk of lung cancer than exposed subjects carrying the *GSTT1* null genotype. It has to be kept in mind that the information on occupational exposure available through the GSEC database is very limited. For example, the data set contains information on only broad categories of agents to which subjects were occupationally exposed; no information on amount or length of exposure is available. Therefore, a more in-depth analysis of this interesting result was not possible. A possible hypothesis is that some compounds present in occupational settings—such as dichloromethane

TABLE 5.   Odds ratios and 95% confidence intervals for the association between *GSTT1** and lung cancer: pooled analysis on Asian subjects

	No. of studies	No. of cases	No. of controls	No. of *GSTT1* null cases	No. of *GSTT1* null controls	OR*	95% CI*	OR†	95% CI
All studies	10	1,373	1,756	695	919	0.93	0.81, 1.08	0.97	0.83, 1.13
Studies included in the meta-analysis on Asian subjects	6	985	1,384	538	749	1.02	0.87, 1.20	1.03	0.86, 1.24
Studies not included in the meta-analysis on Asian subjects	4	388	372	157	170	0.81	0.61, 1.08	0.78	0.58, 1.06
Studies based on healthy controls	6	558	1,055	309	592	0.97	0.79, 1.19	1.01	0.80, 1.27
Studied based on hospitalized controls	4	815	701	386	327	1.03‡	0.84, 1.26	0.97‡	0.78, 1.20

* *GSTT1*, glutathione *S*-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
‡ ORs calculated by excluding controls with other pulmonary diseases—crude: 0.94, 95% CI: 0.76, 1.17; adjusted: 0.78, 95% CI: 0.61, 0.99.

and other halogenated compounds, known substrates of *GSTT1*—are transformed by *GSTT1* into mutagenic intermediates; thus, *GSTT1*-positive subjects might be more prone than *GSTT1*-null subjects to the genotoxic action of halogenated compounds via the *GSTT1* pathway (2). Some translational studies on intermediate biomarkers of exposure and effect suggest that subjects carrying the *GSTT1* deletion may have lower levels of the biomarkers than subjects with the functional *GSTT1*, pointing at a different role of *GSTT1* on cancer causation (98–104).

To our knowledge, this is the first comprehensive meta- and pooled analysis assessing the role of *GSTT1* deletion on lung cancer, and the only one on Asians. The large number of cancer cases included in this analysis ($N = 6,633$) provided 100 percent statistical power to find an odds ratio of 1.5 for both Asians and Caucasians. Because

TABLE 6.   Odds ratios and 95% confidence intervals for the association between *GSTT1** and lung cancer: pooled analysis on Caucasian subjects

	No. of studies	No. of cases	No. of controls	No. of *GSTT1* null cases	No. of *GSTT1* null controls	OR*	95% CI*	OR†	95% CI
All studies	25	5,494	8,044	1,086	1,525	1.05‡	0.97, 1.15	1.09‡	0.99, 1.21
Studies included in the meta-analysis on Caucasian subjects	18	4,523	7,021	837	1,244	1.05§	0.96, 1.16	1.04§	0.93, 1.17
Studies not included in the meta-analysis on Caucasian subjects	7	971	1,023	249	281	0.91	0.75, 1.11	0.96	0.76, 1.22
Studies based on healthy controls	16¶	3,928	5,518	784	1,012	1.11#	1.00, 1.23	1.15#	1.01, 1.30
Studied based on hospitalized controls	11¶	2,229	2,526	427	513	0.93**	0.81, 1.07	0.99**	0.85, 1.16

* *GSTT1*, glutathione *S*-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
‡ ORs calculated by excluding the Sørensen et al. study (65)—crude: 1.04, 95% CI: 0.95, 1.14; adjusted: 1.06, 95% CI: 0.96, 1.17.
§ ORs calculated by excluding the Sørensen et al. study—crude: 1.04, 95% CI: 0.94, 1.15; adjusted: 1.01, 95% CI: 0.90, 1.14.
¶ Two studies (To-Figueras et al. (75), Schneider et al. (63)) contained both healthy and hospital controls. Because it was possible to separate healthy controls from hospital controls, each type of control was included in the correspondent analysis.
# ORs calculated by excluding the Sørensen et al. study—crude: 1.09, 95% CI: 0.98, 1.22; adjusted: 1.07, 95% CI: 0.94, 1.22.
** ORs calculated by excluding controls with other types of cancer or pulmonary diseases—crude: 0.84, 95% CI: 0.72, 0.99; adjusted: 0.88, 95% CI: 0.73, 1.05.
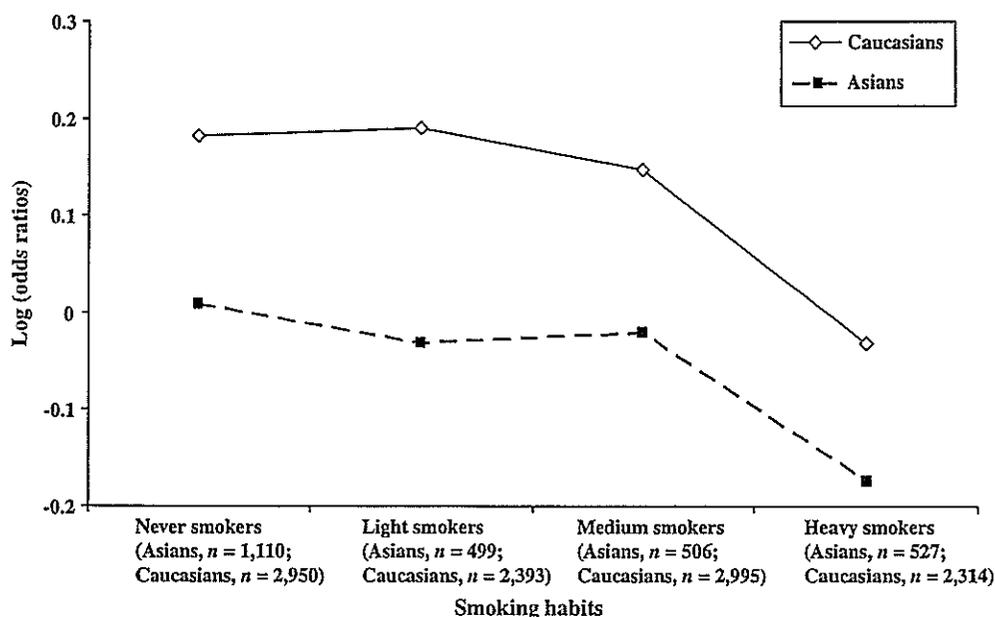
FIGURE 3. Adjusted odds ratios (ORs) for the glutathione S-transferase gene (*GSTT1*) deletion and lung cancer according to smoking habits (tertiles of pack-years): pooled analysis for Asians and Caucasians. ORs were adjusted for study, sex, and age (continuous variable). Asian never smokers: OR = 1.01, 95% confidence interval (CI): 0.77, 1.32; light smokers (0–22 pack-years): OR = 0.97, 95% CI: 0.64, 1.48; medium smokers (23–42 pack-years): OR = 0.98, 95% CI: 0.68, 1.42; heavy smokers (≥43 pack-years): OR = 0.84, 95% CI: 0.59, 1.21. Caucasian never smokers: OR = 1.20, 95% CI: 0.97, 1.48; light smokers (0–22 pack-years): OR = 1.21, 95% CI: 0.97, 1.51; medium smokers (23–43 pack-years): OR = 1.16, 95% CI: 0.93, 1.44; heavy smokers (≥44 pack-years): OR = 0.97, 95% CI: 0.78, 1.20. *p* for Breslow-Day's test for homogeneity = 0.96 for Asians and 0.37 for Caucasians.

the data set includes information on sex and age, it was possible to adjust the odds ratios for the confounding effect of these variables, and we could perform stratified analyses for both smoking status and occupational exposure in Caucasians. The availability of information on potential confounding variables makes the pooled-analyses preferable to the meta-analysis (105). Furthermore, meta-analyses are restricted to published reports and may lead to biased results if publication bias is present; pooled analysis avoids

this problem by also including unpublished studies. In our meta-analysis, no evidence of publication bias was found after stratifying for ethnicity. However, for Asian studies, we observed a lower and no longer statistically significant odds ratio when the pooled analysis including unpublished studies was performed.

A limitation of both meta- and pooled analysis could be the presence of heterogeneity between studies. We verified the hypothesis of homogeneity, and we performed

TABLE 7. Odds ratios and 95% confidence intervals for the association between *GSTT1** deletion and lung cancer, stratified according to histologic type: pooled analysis on Asians and Caucasians

	No. of cases	No. of controls	No. of *GSTT1* null cases	No. of *GSTT1* null controls	OR*	95% CI*	OR†	95% CI
Asians								
Adenocarcinoma	582	913	282	423	1.09	0.88, 1.34	1.06	0.84, 1.34
Squamous cell carcinoma	250	649	108	313	0.82	0.61, 1.10	0.81	0.55, 1.17
Small cell carcinoma	71	549	46	268	1.93	1.15, 3.23	1.45	0.76, 2.77
Caucasians								
Adenocarcinoma	1,106	6,573	209	1,218	1.02	0.87, 1.21	1.12	0.94, 1.34
Squamous cell carcinoma	1,507	6,777	277	1,267	0.98	0.85, 1.13	1.00	0.84, 1.18
Small cell carcinoma	593	6,559	103	1,226	0.91	0.73, 1.14	0.98	0.77, 1.26

* *GSTT1*, glutathione S-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).

TABLE 8. Odds ratios and 95% confidence intervals for the association between *GSTT1** deletion and lung cancer, stratified according to occupational exposure: pooled analysis on Caucasians

	No. of cases	No. of controls	No. of *GSTT1* null cases	No. of *GSTT1* null controls	OR*,†	95% CI*	OR†,‡	95% CI
No occupational exposure	1,192	1,040	251	228	0.95	0.78, 1.16	1.05	0.84, 1.30
Occupational exposure (all chemical agents)	1,349	1,138	225	247	0.72	0.59, 0.88	0.73	0.59, 0.90
Only asbestos exposure	272	323	44	68	0.72	0.48, 1.10	0.56	0.34, 0.94

* *GSTT1*, glutathione *S*-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
‡ *p* for Breslow-Day's test for homogeneity = 0.06.

sensitivity analyses by excluding studies that were a source of heterogeneity. Another possible limitation could be the different method of recruiting controls in the various studies. We considered this possible source of bias by performing a stratified analysis according to the source of controls, in both the meta- and the pooled analysis. Data on hospital controls should provide lower risk estimates if the diseases of the controls were associated with the gene variant under study. We confirmed this hypothesis in the pooled analysis only.

TABLE 9. Adjusted odds ratios and 95% confidence intervals for the main effect and interaction of *GSTT1*,* occupational exposure (all chemicals agents and asbestos only), and lung cancer: pooled analysis on Caucasians

	No. of cases	No. of controls	OR*,†,‡	95% CI†
All chemical agents				
GSTT1 present, no occupational exposure	912	804	1.00	Reference
GSTT1 present, occupational exposure	1,093	888	1.23	1.07, 1.42
GSTT1 null, no occupational exposure	243	227	1.06	0.85, 1.32
GSTT1 null, occupational exposure	221	245	0.90	0.74, 1.11
Asbestos only				
GSTT1 present, no asbestos exposure	912	804	1.00	Reference
GSTT1 present, asbestos exposure	228	255	0.85	0.68, 1.06
GSTT1 null, no asbestos exposure	243	227	1.07	0.86, 1.34
GSTT1 null, asbestos exposure	44	68	0.59	0.41, 0.86

* *GSTT1*, glutathione *S*-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
‡ *p* for interaction (likelihood ratio test) = 0.02 for all chemical agents; 0.08 for asbestos only.

LABORATORY TESTS

The detailed methods used for determining the *GSTT1* genotype are described in each article. Most of the studies included in the present analyses used genomic DNA extracted from blood. One study also used bronchial lavage (68), one study used paraffin-embedded tissues and buccal swabs (58) in addition to blood, and one study used only buccal cells (86). All of the articles reported the use of polymerase chain reaction, with different polymerase chain reaction conditions and different control samples.

POPULATION TESTING

To date, there is insufficient evidence on the role of *GSTT1* in the etiology of lung cancer to make population testing an issue.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

No significant association was found between lung cancer and *GSTT1* deletion either overall or in Caucasians. Among Asians, a positive association was found (OR = 1.28, 95 percent CI: 1.10, 1.49) in the meta-analysis, whereas the association was not confirmed in the pooled analysis (OR = 0.97, 95 percent CI: 0.83, 1.13). *GSTT1* appeared to modulate occupational-related lung cancer, at least for asbestos exposure. Further research on *GSTT1* in occupationally exposed subjects and in lung cancer patients, including the use of intermediate biomarkers of exposure and effect, will be useful to clarify the role of *GSTT1* deletion in the carcinogenic process. Specific studies including subjects exposed to human lung carcinogens could be relevant. Interaction between *GSTT1* and other genetic polymorphisms involved in metabolism of environmental carcinogens would be useful to evaluate the possible combined effect of several genetic variants in relation to specific environmental exposures.

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