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Psychosocial factors, disease status, and quality of life in patients with rheumatoid arthritis☆

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Abstract

Objective: To explore the interrelationships between the psychosocial and illness factors that determine the disease status of patients with rheumatoid arthritis (RA) and to identify how each factor is associated with quality of life (QOL). **Methods:** The study group comprised 120 RA outpatients who completed a series of health examinations and questionnaires. Disease severity, functional disability, counts of swollen and/or tender joints, duration of RA, frequency of arthritis surgery, and C-reactive protein level were assessed by rheumatologists. Self-report inventories completed by the patients were used to assess perceived degree of pain, fatigue (visual analogue scales), depression (Beck Depression Inventory-II), anxiety (Hospital Anxiety and Depression Scale), and social support (Social Support Questionnaire). Mental and physical components of health-related QOL were evaluated using the Short-Form 36 Health Survey. **Results:** After *z*-transformation of the data, a principal axis factor analysis was conducted. A four-factor structure was identified in which the components reflected psychosocial factors, disease activity, current symptoms, and physical functional status, respectively. There was no significant association between psychosocial factors and disease activity, while the other components were moderately correlated with each other. Multiple regression analysis revealed that physical QOL was determined by current symptoms and physical functions. Mental QOL was determined by psychosocial factors, current symptoms, and physical functions. **Conclusion:** Disease activity was independent from psychosocial factors and failed to reflect the perceived physical and mental QOL of RA patients. Clinicians should therefore evaluate psychosocial factors, as well as subjective disease status, to improve the QOL of patients with RA.

Keywords: Disease status; Factor analysis; Psychosocial factors; QOL; Rheumatoid arthritis

Introduction

Several studies, including a recent meta-analysis [1], have reported a higher prevalence of major depressive disorders among patients with rheumatoid arthritis (RA) than among healthy individuals. Patients suffering from severe chronic disorders that are accompanied by pain, disability, and disfigurement are at greater risk of experiencing emotional disturbances [2]. RA is a chronic disease that causes inflammation of the joints and the surrounding tissues.

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Patients with RA are afflicted by pain, stiffness, swelling, and deterioration of the joints. Therefore, it is understandable that RA patients are more likely to have depressive symptoms than healthy individuals [3]. Depression is known to influence perceived disease status and well-being in patients with RA [4]. Psychological factors are also known to cause disparities between the perspectives of RA patients and their clinicians [5,6]. Moreover, affective disturbance can interfere with the long-term prognosis of physical disorders through behavioral and cognitive processes with specific and non-specific biological responses [2]. Thus, it is important for clinicians to consider the psychological status of patients, as well as their physical status, in order to better manage RA. Clinicians feel the significant impact of the psychosocial factors on RA patients through their clinical experiences; however, they rarely examine such aspects in routine clinical practice [7]. Although the American College of Rheumatology Guidelines for the Management of RA do note that psychosocial factors can affect patient outcome and treatment adherence, they do not include psychosocial items in the list of recommendations for the evaluation of disease activity and damage [5]. To expend time on psychological evaluation during the busy clinical practice, they may need evidence more than impression.

The primary purpose of the present study was to determine how psychosocial variables are associated with the clinical variables assessed as part of the routine clinical care of RA patients. We aimed to illustrate the interrelationships between the psychosocial and clinical variables by clarifying the factor structures of their combined data by using factor analysis. We also explored how each factor extracted by the analysis contributed to the physical and mental health-related quality of life (QOL), based on the assumption that improving the perceived QOL was the most important outcome for RA patients. We believe that understanding how each factor influences the perceived QOL will help clinicians to achieve better outcomes for patients with RA.

Materials and methods

Patients

The study group comprised RA patients who met the criteria of the American College of Rheumatology [8] and attended the Outpatient Rheumatology Clinic of the Nagoya University Hospital (Nagoya, Japan). Between 7 March and 18 April 2003, trained research assistants invited 321 patients to participate in the study, giving a brief explanation of the protocol. A total of 303 patients provided written informed consent and completed self-reported questionnaires. Fifty-seven patients were excluded from the study as they did not undergo a blood examination. Of the remaining 246 patients, 120 patients completed all examinations and questionnaires without missing any items and were thus included in the analysis.

Measures

As part of the routine clinical examinations, the rheumatologists assessed the following measures for each of their patients: counts of swollen and/or tender joints, Steinbrocker's functional status [9], and global assessment of disease severity. The rheumatologists also reported on the arthritis surgery experiences of each patient. The C-reactive protein (CRP) level was also measured for each subject. The rheumatologists were blinded to the participation status of their patients.

After these examinations, the participants were asked by the research assistants to complete self-administrative questionnaires that surveyed their socio-demographic characteristics, smoking habits, onset year of RA, and current pain and fatigue using visual analogue scales (VASs). The questionnaires also included a battery of well-validated self-reporting inventories, as described below, for the evaluation of psychological status, social support, and perceived QOL.

The second edition of the Beck Depression Inventory (BDI-II) was used to assess depressive symptoms [10,11]. The BDI is the most popular self-reporting tool for measuring depressive symptoms and has often been used to evaluate psychological distress among RA patients. It was revised to correspond with the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* criteria and published as the BDI-II in 1996. The BDI-II consists of 21

Table 1
Demographic, clinical, and psychosocial characteristics of the patients with RA

Variable	Total N=120	(Min–Max)
Sociodemographic characteristics		
Age	57.7±12.8	(18–85)
Women	81.7%	
Married	75.8%	
Living alone	15.0%	
Current daily smoker	17.5%	
Educational level >12 years	25.8%	
Total income >$60,000/year	25.8%	
Clinical characteristics		
RA disease duration (years)	11.4±10.1	(0.2–45)
Functional disability	2.1±0.7	(1–4)
Rheumatologist global severity	36.6±17.1	(11–91)
Total number of tender joints	4.4±5.5	(0–24)
Total number of swelling joints	2.7±3.0	(0–15)
Laboratory measurements		
CRP (mg/l)	2.3±2.6	(0.1–13.9)
Physical QOL (SF-36)	31.2±18.9	(19.7–60.4)
Mental Health QOL (SF-36)	48.9±10.2	(27.1–74.4)
Pain (VAS)	34.9±23.8	(0–100)
Fatigue (VAS)	33.8±27.1	(0–94)
Psychosocial characteristics		
Depression (BDI-II)	12.7±9.9	(0–48)
Anxiety (HADS-A)	4.4±3.6	(0–19)
Perceived social support		
Available number (SSQ-N)	19.2±9.1	(0–36)
Satisfaction (SSQ-S)	28.1±5.2	(6–36)

Values are shown as mean±S.D. or percentages.

items and the scores range from 0 to 63. A subscale of the Hospital Anxiety and Depression Scale (HADS-A) was used to assess anxiety. This consisted of seven items and yielded a total score ranging from 0 to 21 [12].

The six-item version of the Social Support Questionnaire (SSQ) was used to assess social support [13,14]. The SSQ consists of two subscales that quantify the two basic elements of social support: the number of people that a subject feels he or she can turn to when necessary (i.e., the number score or SSQ-N); and the extent of satisfaction with the available support (i.e., the satisfaction score or SSQ-S). The scores for both subscales range from 0 to 36.

The Short-Form 36 Health Survey (SF-36) was used to evaluate the generic perceived QOL [15–17]. The SF-36 was developed to measure general health status and has been used in various settings worldwide, including with RA patients [18]. It consists of 36 items covering aspects of physical, mental, and biopsychosocial health. In this study, the physical component summary score and the mental component summary score were calculated according to the SF-36 manual [19].

Statistical analysis

Data were analyzed using SPSS for Windows (version 15.0). All statistical tests were two sided, and a P value of $<.05$ was considered significant. All values are reported as the mean±S.D. unless otherwise stated. Because the distribution of the CRP data was skewed and two of the subjects had values of 0, these data were natural log transformed after adding 1 to each value.

A principal axis factor analysis was used to explore the factor structure of the disease status data within the RA patient sample. The following variables were included in the factor analysis: RA disease duration; frequency of surgery for arthritis; rheumatologist's assessments of functional disability and global severity; total counts of swollen and/or tender joints; log-transformed CRP; patient's perceived pain and fatigue; depression; anxiety; and number of, and satisfaction with, available social support. All data were z-transformed for the factor analysis. The correlation matrix for the measured variables was computed initially. The Kaiser–Meyer–Olkin measure of sampling adequacy and the Bartlett's test of sphericity were then used to verify the appropriateness of the factor models [20]. Eigenvalues above 1.0 and scree test criteria [21] were used to determine the number of factors to extract, and a promax rotation was performed. Standardized regression coefficients ≥0.35 were regarded as significant. The factor scores were then calculated by summing the standardized variables weighted by the factor loadings. Pearson's correlation coefficients were used to identify the bivariate relationships between the 13 items, four factor scores, and QOL variables examined. Finally, multivariate regression analyses were then conducted to evaluate the independent association of each factor with physical and mental QOL among the RA patients with adjustment for sociodemographic variables such as age, sex, marital status, and educational levels.

Table 2
Factor loading matrices for the illness components identified among RA patients

	Factor 1	Factor 2	Factor 3	Factor 4
Variables	Psychosocial factors	Disease activity	Current symptoms	Physical status
SSQ-S	*−0.93*	−0.03	0.14	0.10
SSQ-N	*−0.62*	−0.12	0.08	−0.06
HADS-A	*0.61*	−0.10	0.29	0.001
BDI-II	*0.60*	−0.10	*0.43*	0.11
Total number of swelling joints	0.18	*0.87*	−0.24	,0.12
Total number of tender joints	0.12	*0.53*	0.22	−0.24
Rheumatologist global severity	−0.13	*0.58*	*0.38*	−0.11
CRP log	−0.21	*0.46*	0.14	0.11
Pain	−0.03	0.09	*0.81*	−0.02
Fatigue	0.10	0.03	*0.75*	0.10
RA disease duration	0.08	−0.05	−0.18	*0.66*
Frequency of arthritis surgery	−0.07	−0.08	0.21	*0.54*
Functional disability	−0.02	0.24	0.13	*0.53*
Eigenvalues	3.77	2.38	1.62	1.11
Correlation between factors				
Psychosocial factor	1.00			
Disease activity	−0.04	1.00		
Current symptom	0.33	0.40	1.00	
Physical status	0.14	0.15	0.15	1.00

Factor loadings ≥0.35 are printed in italics. The patterns were identified by principal factor analysis with promax rotation.

Results

Background characteristics

The background data for the study participants are shown in Table 1. The mean age of the participants was 57.7 years (S.D.=12.8 years), and the average illness duration was 11.4 years (S.D.=10.1 years). The majority of the subjects were female (81.7 %), married (75.8%), and did not smoke (82.5%).

Factor analysis

The data met the criteria for the Kaiser–Meyer–Olkin test of sample adequacy (value=0.71, minimum accepted level=0.5) and the Bartlett's test of sphericity (χ^2=599, degrees of freedom=78, P<001), indicating their suitability for factor analysis. A principal axis factor analysis was then conducted. The results of the scree test suggested that four factors should be extracted. These first four components accounted for 68.3% of the total variance. After the promax rotation, the eigenvalues of the four components were 3.78, 2.37, 1.62, and 1.11, respectively.

The factor loadings for the 13 items of the four identified factors are shown in Table 2. Depression and the rheumatologist's global assessment both loaded on two factor components: depression loaded on the first and third factor components, while the rheumatologist's global assessment loaded on the second and third factor components.

The first factor comprised satisfaction with social support, number of available supporting individuals, anxiety, and depression, and was considered to reflect psychosocial items. The second factor included total counts of swollen and/or tender joints, rheumatologist's global assessment, and CRP, and was considered to reflect disease activity. The third factor consisted of pain, fatigue, depression, and rheumatologist's global assessment, and was considered to reflect current symptoms. The fourth factor included illness duration, frequency of operation, and functional disability, and was considered to reflect physical functional status.

The psychosocial factor component and the disease activity component showed little correlation, while the current symptom component was moderately correlated with both the psychosocial factors and the disease activity. The physical status component was weakly but significantly correlated with all three other components to similar extents.

Table 3
Correlation coefficients of psychosocial and clinical variables and factor scores with physical and mental QOL

	Physical QOL		Mental QOL	
Variable	*r*	*P*	*r*	*P*
Age	−0.30	<.001	0.12	.18
SSQ-S	0.13	.15	0.49	<.001
SSQ-N	0.18	.05	0.36	<.001
HADS-A	−0.25	.01	−0.51	<.001
BDI-II	−0.47	<.001	−0.60	<.001
Total number of swelling joints	−0.23	.01	−0.13	.17
Total number of tender joints	−0.32	<.001	−0.19	.04
Rheumatologist global severity	−0.37	<.001	−0.15	.10
CRP (log)	−0.34	<.001	−0.09	.35
Pain	−0.47	<.001	−0.45	<.001
Fatigue	−0.44	<.001	−0.47	<.001
RA disease duration	−0.20	.03	0.13	.16
Frequency of arthritis surgery	−0.41	<.001	0.03	.74
Functional disability	−0.49	<.001	0.04	.65
Factor scores[a]				
Psychosocial factor	−0.27	.003	−0.59	<.001
Disease activity	−0.36	<.001	−0.10	.28
Current symptom	−0.56	<.001	−0.52	<.001
Physical status	−0.46	<.001	0.05	.58

[a] Factor scores were derived from principal factor analysis with promax rotation.

Table 4
The multivariate regression analysis for the summary scores of physical and mental QOL[a] adjusted for the sociodemographic variables

	Physical QOL[c]		Mental QOL[d]	
Factor scores[b]	β[e]	*P* value	β[e]	*P* value
Psychosocial factor	−0.05	.52	−0.47	<.001
Disease activity	−0.09	.28	0.03	.69
Current symptom	−0.42	<.001	−0.42	<.001
Physical status	−0.29	<.001	0.19	.009

[a] Physical and mental QOL were measured by using SF-36.
[b] Factor scores were derived from a principal factor analysis including RA disease duration; frequency of surgery for arthritis; rheumatologist's assessments of functional disability and global severity; total counts of swollen and/or tender joints; log-transformed CRP; patient's perceived pain and fatigue; depression; anxiety; and number of, and satisfaction with, available social support.
[c] Adjusted R^2=0.44.
[d] Adjusted R^2=0.49.
[e] Standardized regression coefficients derived from the multivariate regression analysis controlling for age, sex, marital status, and educational levels.

Determinants of physical and mental QOL of RA patients

The correlation coefficients for the two summary QOL scores of the SF-36 and the variables within the four factors extracted from the analysis are presented in Table 3. For the physical QOL, all of the items, except for the number and satisfaction subscales of the SSQ, were significantly negatively correlated with all four factors. The mental QOL was positively correlated with the two subscales of social support and was negatively correlated with anxiety, depression, counts of tender and/or swollen joints, pain, and fatigue. The psychosocial factor score and the current symptom factor score were also significantly correlated with the mental QOL.

Multivariate regression analysis was used to examine which of the four factor scores had greater effects on physical and mental QOL controlling for age, sex, marital status, and educational levels. The standardized regression coefficients shown in Table 4 represent the changes in the QOL variables

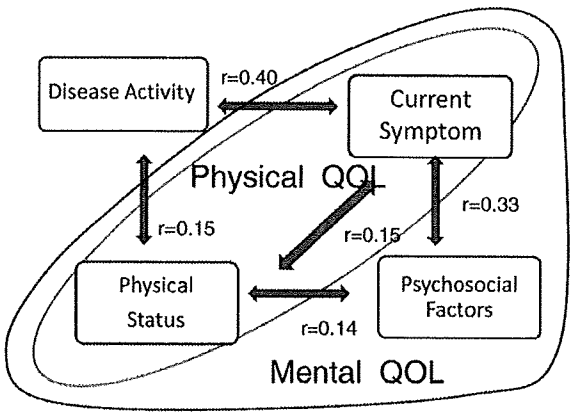

Fig. 1. Interrelationships between psychosocial factors, disease activity, current symptoms, and physical status. Based on the results of the factor analysis derived from the clinical and psychosocial variable data of 120 patients with RA.

that resulted from a change of 1 S.D. in each factor score. Physical QOL was significantly associated with two factor scores, the current symptom score and the physical status score, but not with the psychosocial factor score and the disease activity score. Mental QOL was explained mainly by the psychosocial factor score and the current symptom scores. The physical status score showed a significant positive association with the mental QOL in the multivariate analysis, although the bivariate correlation was not statistically significant (Tables 3 and 4). The disease activity score failed to show significant associations with physical and mental QOL.

Discussion

Factor analysis is a statistical method of multivariate analysis that reduces a large number of intercorrelated variables into a small subset of factors. It originated from psychometrics and is often used to assess the validity of instruments by confirming factor structures to reflect the intended concepts. Recently, factor analysis has been increasingly utilized to understand the nature of complex physical disorders. A number of studies have reported the usefulness of factor analysis to describe metabolic syndrome, which is a cluster of metabolic and anthropometric abnormalities [22–24]. Moreover, the technique of factor analysis has been used to describe the health status of asthma [24]. To our knowledge, this is the first study that applies factor analysis to explore the association between the broad spectrum of variables regarding RA.

Wolfe et al. [4] suggested, from their abundant clinical and research experience as rheumatologists, that illness items could be separated into four categories to evaluate the severity and status of RA: disease activity, current symptoms, patient outcomes, and disease outcomes. They noted that psychosocial factors had a strong influence on symptoms and patient outcomes, but not on disease activity. Interestingly, our current findings and the observed factor structure were in agreement with their theory based on clinical experiences.

We identified four components, which reflected disease activity, current symptoms, physical status, and psychosocial factors (Fig. 1). The psychosocial factor was significantly correlated with both the current symptoms and the physical status, but not with the disease activity. Notably, depression was loaded on both the psychosocial and the current symptom factors, while the rheumatologist's global assessment was loaded on the disease activity and the current symptom factors. These results provided evidence that depression influenced patients' subjective symptoms [7]. Our findings also support a tendency for rheumatologists to evaluate the disease severity of patients based on a combination of objective clinical indices and subjective self-reported symptoms. Rheumatologists take into account complaints of pain and fatigue by patients when making a global assessment. However, our additional analysis revealed that the rheumatologists' global evaluation did not reflect any psychological variables (data not shown). It may imply the difficulty for clinicians to assess the psychological status of patients based upon the variables that are measured at routine clinical examinations.

We examined the impacts of the four extracted factors on the patients' mental and physical QOL measured by the SF-36 [17]. All four-factor scores showed statistically significant associations with the summary score of physical QOL; however, only the current symptom and physical status factors remained significant after adjustment for the influences of the other factors and demographic variables in the multivariate model. Mental QOL was significantly associated with the two factors: the psychosocial factor and the current symptom factor, but not with physical status in the bivariate analysis. In the multivariate model, the association between the mental QOL and the physical status became significant. The observed direction of the association between the physical status and the mental QOL was the opposite of that seen between the physical status and the physical QOL. Patients who had suffered from RA for longer, had experienced more frequent arthritis surgery, and/or had advanced functional disability were more likely to have a poor physical QOL, although they could have a better mental QOL if the psychosocial factors and current symptoms were comparable. This suggests that some patients who had a poor physical status could maintain a good mental QOL despite pain, fatigue, psychological distress, and/or low social support. This corresponds to the general health psychology findings that some patients successfully adjust to their conditions while others do not [25]. Recently, increasing numbers of studies have examined the associations between perceived personal control, self-esteem, coping style, and subjective well-being [3,25,26]. Owing to the limitations of our data, we were unable to further explore this issue. Future research should investigate how patients can maintain their

perceived well-being regardless of their objective and subjective disease status.

We did not find significant associations between disease activity and mental or physical QOL measures even after adjusting for covariates. This was consistent with the findings of a review by Persson et al. [3], which suggested that psychological factors performed better than disease activity as predictors of well-being among RA patients; this again underscored the importance of clinicians evaluating the psychosocial status of patients [7]. As Wolfe [7] and Pincus [27] recommended, clinicians should take into account patients' subjective evaluations, including their psychological status, via brief self-report questionnaires and other similar methods. However, our findings do not deny the importance of disease activity evaluation for RA management. It has been established that disease activity has a great influence on the joint damage and clinical outcomes [28]. Although disease activity fails to associate with the patients' perceived QOL at cross-sectional observation, reducing disease activity is one of the goals of RA therapy definitely [5].

We should note some limitations of our current study. First, more than half of the original subjects did not undergo factor analysis. However, we confirmed the stability of the factor structure of the current data by excluding variables that were missed by most of the subjects (SSQ-N and duration of RA suffering) from the analysis. A total of 209 subjects were included in the analysis, and a comparable pattern matrix was observed. Second, we recruited only those regular visitors to rheumatologists at a university hospital in an urban area of central Japan who were able to complete a battery of questionnaires unaided. We further limited the subjects to those who provided complete data sets without missing values. The sample group was therefore likely to be healthier and to have a higher social economic status than the general RA patient population. Third, because of the cross-sectional design, we were unable to assess the influence of the disease factors on the prognosis. Our ongoing prospective study will clarify the influence of each factor on the RA prognosis. Fourth and finally, we conducted this study under the assumption that the most important outcome for the patients was the perceived QOL; however, it is possible that the importance of each factor might vary according to the outcome.

In conclusion, the disease activity evaluated by routine objective clinical examinations was not associated with psychosocial factors and failed to reflect the perceived physical and mental QOL of RA patients. Clinicians must evaluate the psychosocial status of patients, as well as their subjective disease status, in order to improve the QOL.

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Human Genome Epidemiology (HuGE) Review

Meta- and Pooled Analysis of *GSTP1* Polymorphism and Lung Cancer: A HuGE-GSEC Review

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Lung cancer is the most common cancer worldwide. Polymorphisms in genes associated with carcinogen metabolism may modulate risk of disease. Glutathione *S*-transferase pi (GSTP1) detoxifies polycyclic aromatic hydrocarbons found in cigarette smoke and is the most highly expressed glutathione *S*-transferase in lung tissue. A polymorphism in the *GSTP1* gene, an A-to-G transition in exon 5 (Ile105Val, 313A → 313G), results in lower activity among individuals who carry the valine allele. The authors present a meta- and a pooled analysis of case-control studies that examined the association between this polymorphism in *GSTP1* and lung cancer risk (27 studies, 8,322 cases and 8,844 controls and 15 studies, 4,282 cases and 5,032 controls, respectively). Overall, the meta-analysis found no significant association between lung cancer risk and the *GSTP1* exon 5 polymorphism. In the pooled analysis, there was an overall association (odds ratio = 1.11, 95% confidence interval: 1.03, 1.21) between lung cancer and carriage of the *GSTP1* Val/Val or Ile/Val genotype compared with those carrying the Ile/Ile genotype. Increased risk varied by histologic type in Asians. There appears to be evidence for interaction between amount of smoking, the *GSTP1* exon 5 polymorphism, and risk of lung cancer in whites.

Asian continental ancestry group; epidemiology; glutathione *S*-transferase pi; *GSTP1*; lung neoplasms; smoking

Abbreviations: CI, confidence interval; GSEC, Genetic Susceptibility to Environmental Carcinogens; GSTP1, glutathione *S*-transferase pi; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon.

Editor's note: *This paper is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).*

GENE AND GENE VARIANTS

Glutathione *S*-transferases are a supergene family of phase II enzymes present in many tissues, including lung (1). These enzymes catalyze the detoxification (through conjugation of glutathione) of a variety of reactive electrophilic compounds, including many environmental carcinogens such as benzo[*a*]-pyrene and polycyclic aromatic hydrocarbons (PAHs) (2). The soluble glutathione *S*-transferases comprise 4 main gene classes, alpha (α), mu (μ), pi (π), and theta (θ) (3). Polymorphisms in the glutathione *S*-transferase pi gene, *GSTP1*, located on chromosome 11q13 in humans, have been associated with a reduction in enzymatic activity toward several substrates, including both chemotherapy agents (such as cisplatin, a common agent used in lung cancer treatment) and carcinogens found in tobacco smoke (4–9). Of the several thousand chemicals found in tobacco smoke, at least 50 are known to be carcinogenic, including PAHs, aromatic amines, and nitroso compounds (10).

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GSTP1 detoxifies PAHs and is the most abundant glutathione *S*-transferase isoform in the lungs (1). Two single nucleotide polymorphisms in *GSTP1* that result in a change in amino acids have been identified. A single nucleotide polymorphism in exon 5 (Ile105Val, 313A → 313G), the A-to-G transition that results in an amino acid change from isoleucine to valine, results in significantly lower conjugating activity among individuals who carry one or more copies of the *G* (guanine) allele (Ile/Val or Val/Val) compared with those who have the *A/A* (adenine/adenine; Ile/Ile) genotype (11–13). Having at least one copy of the *G* allele at this locus is also associated with increased levels of hydrophobic adducts in the lung and higher levels of PAH-DNA adducts in human lymphocytes (14). A second single nucleotide polymorphism in exon 6 (Ala114Val, 341C → 341T) results in an amino acid change from alanine to valine, which also appears to confer lower activity (11). Additionally, 3 functional haplotypes have been identified: GSTP1*A (105Ile;114Ala), GSTP1*B (105Val;114Ala), and GSTP1*C (105Val;114Val) (11). A meta-analysis published in 2006 of 5 polymorphisms in glutathione *S*-transferases found no association with *GSTP1* polymorphisms and lung cancer risk in 25 studies published prior to August 2005 (15). The present report includes additional studies published since that time and a pooled analysis examining the association between the *GSTP1* Ile105Val polymorphism and risk of lung cancer.

DISEASE

Lung cancer is the most common cancer worldwide and is responsible for 17.2% of all cancer-related deaths (16). In the United States, overall 5-year survival is about 16% for all stages combined (17). Data from the Surveillance, Epidemiology, and End Results Program indicate that if lung cancer is diagnosed in local stages, survival is significantly better, with overall 5-year survival rates of 49.1%, although fewer than 20% of lung cancers are diagnosed at this stage (17). Along with stage at diagnosis, prognosis also depends on histology type. Because of recent advances in technology that allow a more accurate diagnosis, it is difficult to analyze historic trends in histology types; however, adenocarcinomas of the lung have been increasing in proportion over the last 2–3 decades, especially among women (18). Overall, lung cancer survival rates have not significantly improved with advances in surgical, radiation, or chemotherapy treatments (17).

SMOKING

Cigarette smoking is the greatest risk factor associated with lung cancer development. In the United States and the United Kingdom, approximately 90% of all cases of lung cancer are attributable to current or former cigarette smoking, while the population attributable risks appear to be lower in Japanese populations, especially among women (population attributable risk for men = 67.0%, population attributable risk for women = 14.6%) (19, 20). Other Asian populations report similar risk of lung cancer due to smoking (21, 22). Worldwide, smoking rates have been declining for the past several decades in developed countries and increasing significantly in developing countries. If these trends in smoking rates continue, by 2030, developing countries will account for an estimated 80% of the annual 8 million tobacco-related deaths, many of which will be due to lung cancers (23). Since the induction period for lung cancer appears to be decades, lung cancer will continue to be a major public health issue for generations to come. In addition, the negative health effects of cigarette smoking are not limited to current smokers. In a cohort of former smokers in the United States, 10 years after smoking cessation, the risk of lung cancer is 30%–50% lower than the risk for those who continue to smoke, but lifelong risk remains elevated compared with that for never smokers (24). Furthermore, while cigarette smoking remains the most significant modifiable risk factor, exposure to radon and other occupational and environmental risk factors is associated with development of lung cancer (25, 26).

MATERIALS AND METHODS

Associations and interactions

The association between the exon 5 (Ile105Val, 313A → 313G) polymorphism in *GSTP1* and lung cancer was examined through a meta-analysis of all published papers and a pooled analysis of selected published studies. A MEDLINE search was performed from January 1988 (when the structure of GSTP1 was first described (27)) until March 31, 2007, using different combinations of "glutathione *S*-transferase pi," "GSTP1," "lung," and "lung cancer," restricting the analysis to "human" with no restriction on language. This search was supplemented by examining the reference sections of all selected papers, plus 2 reviews (28, 29) and a pooled analysis of polymorphisms in candidate genes associated with early-onset (<60 years of age at diagnosis) lung cancer (30).

After reviewing all abstracts ascertained from these searches, 34 articles containing information on *GSTP1* polymorphisms and lung cancer were identified. Eligible studies included the frequency of *GSTP1* genotypes or the crude odds ratio for the *GSTP1* exon 5 polymorphism and lung cancer. Both hospital- and population-based case-control studies were included in the analysis. Additionally, 1 study was a nested case-control study from a large cohort of physicians (31). Of the 34 articles selected, 4 were excluded because they were case-only analyses (32–35), 2 because of subject overlap with more recently published studies (36, 37), and 1 because it did not report the genotypes or unadjusted odds ratios (38). Two studies were included in the meta-analysis even though they contained a small number of overlapping subjects (39, 40). Two studies were found in both non-English and, later, English journals; therefore, the data from the English journals were used (41, 42). Only 4 studies reported on the exon 6 (Ala114Val, 341C → 341T) polymorphism, so we restricted the analysis to the exon 5 polymorphism in *GSTP1*. The final number of studies in the meta-analysis was 27, including 8,322 cases and 8,844 controls (31, 39–64) (Table 1).

Table 1. Description of the Studies Included in the Meta-analysis by Ethnicity and Year of Publication

First Author (Reference No.)	Year	No. of Cases	No. of Controls	Country	Mean Age of Cases, Years	Male Cases, %	Histology	Source of Controls	Matching Criteria
Asian studies									
Katoh (47)	1999	47	122	Japan	64.6 (SD, 10.3)	85	SqCC = 51.1%, AC = 25.5%, SCC = 19.1%, LCC = 4.3%	Hospital	None
Kihara (48)	1999	358	257	Japan	62.7 (range, 58–67)	100	SqCC = 33.3%, SCC = 20.4%, AC = 46.3%	Hospital	None
Kiyohara (41)	2000	86	88	Japan	63.8 (range, 35–86)	100	AC = 45.5%, SqCC = 7.9%, SCC = 13.9%, LCC = 4.7%, others = 7.0%	Hospital	None
Lin (51)	2003	198	332	Taiwan	64 (SD, 9)	72.2	AC = 53.0%, SCC = 42.0%, others = 5.0%	Hospital	None
Wang (60)	2003	112	119	China	56.5 (range, 37–75; SD, 8.1)	64.3	AC = 100%	Healthy	Age and gender (frequency matching)
Chan-Yeung (44)	2004	229	197	China	53.8 (SD, 14.3)	67.2	AC = 55.5%, SqCC = 16.6%, NSCLC = 19.2%, others = 8.7%	Healthy	Ethnicity
Chan (43)	2005	75	162	China	63 (no range or SD)	82	AC = 58.7%, SqCC = 41.3%	Hospital	Sex and age
Liang (42)	2005	227	227	China	62.5 (range, 31–86)	74	SqCC = 41.4%, AC = 58.6%	Hospital	Age, gender, and ethnicity (frequency matching)
White studies									
Ryberg (64)	1997	138	297	Norway	62.3 (SD, 10.3)	100	NSCLC = 100%	Healthy	Age, smoking, and ethnicity
Harris (45)	1998	178	199	Australia	66 (range, 38–91; SD, 9.1)	69	SqCC = 43.5%, AC = 18.2%, LCC = 7.7%, SCC = 7.1%, NSCLC = 1.9%, others = 21.6%	Healthy	None
Jourenkova-Mironova (46)	1998	150	172	France	58.4 (no range or SD)	93	SqCC = 65.3%, SCC = 34.7%	Hospital	Age and gender (frequency matching)
Saarikoski (55)	1998	206	293	Finland	62 (SD, 9)	79.8	SqCC = 45.2%, AC = 39.4%, others = 15.4%	Healthy	None
To-Figueras (59)	1999	164	200	Spain	59 (range, 32–87)	88.4	SCC = 34.8%, SqCC = 31.7, AC = 25.6%, LCC = 7.9%	Healthy	Gender
Risch (63)	2001	388	353	Germany	60.9 (range, 28–87)	75.8	SqCC = 44.0%, AC = 39.0%, LCC = 4.9%, SCC = 2.8%, others = 10.8%	Hospital	Ethnicity
Lewis (50)	2002	93	151	United Kingdom	67.4 (SD, 10.4)	63.8	SCC = 16.1%, SqCC = 34.4%, AC = 10.9, others and nonclassified = 38.7%	Hospital	None
Stucker (58)	2002	251	264	France	59.3 (SD, 9.6)	100	SqCC = 46.0%, SCC = 19%, AC = 24.0%, others = 11.0%	Hospital	Age, ethnicity, and gender (frequency matching)
Reszka (54)	2003	138	165	Poland	59.7 (no range or SD)	76.8	SqCC = 44.2%, SCC = 25.4%, NSCLC = 17.4%, AC = 8.7%, others = 4.3%	Hospital	Age and gender (frequency matching)
Wang (61)	2003	362	419	United States	60.9 (SD, 10.1)	52.4		Hospital	Age, gender, ethnicity, and smoking (frequency matching)
Schneider (56)	2004	446	622	Germany	64.4 (SD, 8.7)	90.6	SCC = 15.0%, LCC = 3.6%, AC = 25.1%, SqCC = 41.1%, others = 15.2%	Hospital	None

Larsen (49)	2006	1,095	626	Australia	63.4 (SD, 9.4)	71.9	AC = 45.2%, SqCC = 45.1%, others = 9.7%	Hospital	Age and smoking
Miller (52)	2006	1,921	1,343	United States	66 (no range or SD)	49.7	AC = 43.7%, SqCC = 21.4%, LCC = 7.3%, SCC = 9.2%, others = 18.4%	Healthy	None
Sorensen (57)	2007	429	766	Denmark	No mean age (range, 50–64)	53	SCC = 19%, AC = 32%, SqCC = 23%, others = 26%	Healthy	None
Other studies									
Perera (31)	2002	85	163	United States	61.8 (SD, 7.7)	100	AC = 36.0%, SCC = 16.9%, SqCC = 21.3%, LCC = 9.0%, others = 16.8%	Healthy	Smoking, age, and duration of follow-up
Nazar-Stewart (53)	2003	253	487	United States	No mean age (range, 18–74)	100	SqCC = 29.6%, SCC = 19.0%, NSCLC = 12.0%, LCC = 3.3%, AC = 35.0%, others = 1.1%	Healthy	Age and gender (frequency matching)
Yang (62)	2004	235	233	United States			SqCC = 13.5%, SCC = 7.6%, NSCLC = 13.1%, AC = 52.3%, LCC = 3.8%, others = 9.7%	Hospital	None
Cote (39)	2005	317	407	United States	42.1 (no range or SD)	50	SqCC = 11.7%, SCC = 13.2%, AC = 47.7%, LCC = 9.4%, NSCLC = 3.7%, others = 14.3%	Healthy	Race, sex, 5-year age group, and county of residence
Wenzlaff (40)	2005	141	180	United States	62.4 (range, 40–84; SD, 13.9)	57.8	SqCC = 15.7%, SCC = 6.6%, AC = 54.2%, LCC = 7.2%, others = 16.3%	Healthy	Race, sex, county of residence, and age (frequency matching)

Abbreviations: AC, adenocarcinoma; LCC, large-cell carcinoma; NSCLC, non–small cell lung cancer; SCC, small-cell carcinoma; SD, standard deviation; SqCC, squamous-cell carcinoma.

The pooled analysis was performed by using information collected from researchers who submitted information to the Genetic Susceptibility to Environmental Carcinogens (GSEC) database (www.gsec.net). The design of this study is explained in greater detail elsewhere (65). The primary goal of the GSEC project is to examine the associations between various cancers and genetic polymorphisms by using published and unpublished data solicited from collaborating investigators. These data are then cleaned and entered into a main database that is available to interested investigators for analyses related to the overall goals of the study. Each participating center provided information on the study design, source of controls, laboratory methods used for genotyping, source of DNA for genotyping, and response rates for cases and controls.

From the GSEC database, we selected all studies that included information on *GSTP1* and lung cancer. Only 3 studies (46, 55, 62) provided information on the exon 6 (Ala114Val, 341C → 341T) polymorphism; thus, as in the meta-analysis, all analyses reported on in this paper focus on the polymorphism in exon 5 only. Investigators who had not initially participated in the GSEC project were contacted and asked to provide their data for the pooled analysis. We were able to obtain data from 14 of the 27 studies (51.9%) included in the meta-analysis (Wenzlaff et al. (40) and Cote et al. (39), 2 studies from the same principal investigator, combined their data into a single data set, referred to as Cote et al. in the pooled analyses). An additional study not included in the meta-analysis was used in the pooled analysis (32). The number of subjects included in the published reports may differ somewhat from the numbers in this pooled analysis because the GSEC data set includes some unpublished data. The total number of subjects included in the pooled analysis was 4,282 cases and 5,032 controls.

Statistical analysis

For the meta-analysis, study-specific crude odds ratios and 95% confidence intervals were calculated to estimate the association between the exon 5 (Ile105Val, 313A → 313G) polymorphism in *GSTP1* and lung cancer based on the reported frequencies of *Ile/Ile*, *Ile/Val*, and *Val/Val* genotypes in cases and controls. Odds ratios and 95% confidence intervals were calculated for individuals carrying 1 (*Ile/Val*) or 2 (*Val/Val*) valine alleles compared with individuals carrying 2 isoleucine (*Ile/Ile*) alleles. Homogeneity among studies was tested by using the Breslow-Day test for homogeneity, and, when not statistically significant (based on $P > 0.05$), a fixed-effects model was used for the meta-analysis (66). Heterogeneity was also quantified by using the *I*-squared statistic (67). To test for publication bias, both the Begg and Mazumdar adjusted rank correlation test (68) and the Egger et al. regression asymmetry test (69) were performed. Funnel plots were also created to graphically display evidence of publication bias, and sensitivity analyses to examine the influence of each study on the overall estimate were also performed.

Because the frequency of the polymorphism differs by ethnicity, studies were stratified by the reported ethnicity

of the subject population, with 14 studies in whites, 8 studies in Asians, and 5 studies in populations comprising a mix of other ethnic groups, including whites, African Americans, and Mexican Americans. Crude odds ratios and 95% confidence intervals were also estimated by source of controls (healthy or hospital) and then by both ethnicity and control source.

Summary odds ratios and 95% confidence intervals were calculated for all studies combined, as well as for each ethnic group (white, Asian, other), control source (healthy or hospital), and then by both ethnicity and control source. All analyses were performed by examining risk associated with carrying at least 1 valine allele compared with *Ile/Ile* genotypes at *GSTP1* exon 5 (Ile105Val, 313A → 313G). All meta-analyses were performed with the STATA software package (Stata Corporation, College Station, Texas).

To reduce the potential for confounding associated with ethnicity, the pooled analyses were performed separately for the 2 ethnic groups with the greatest number of studies and participants (whites and Asians). Chi-squared tests were conducted to test for Hardy-Weinberg equilibrium in the reported genotype frequencies among the controls in the pooled analysis, after stratification by ethnicity. Study-specific crude odds ratios and 95% confidence intervals for lung cancer and *GSTP1* genotype were estimated by using unconditional logistic regression models. As with the meta-analysis, odds ratios and 95% confidence intervals were calculated for individuals carrying 1 or 2 *105Val* alleles compared with individuals carrying 2 *Ile* alleles. Heterogeneity between studies was tested by using the Breslow-Day test for homogeneity. Crude and adjusted odds ratios were calculated for each ethnic group, as well as stratified by control source (healthy and hospital), smoking status (nonsmoker/ever smoker), and histologic type (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma). Regarding studies that provided information on pack-years of smoking, this paper presents adjusted odds ratios and 95% confidence intervals for nonsmokers and by tertile of numbers of pack-years of smoking. Regression lines were fitted to test for linear trend between the odds ratios and amount smoked. To formally test for interactions between amount smoked and genotype, cross-product terms were created and tested in the logistic model. The cutpoints for the tertiles of amount smoked were calculated from the controls who smoked. All pooled analyses were performed by using SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The genotype frequencies for the *GSTP1* exon 5 polymorphism varied according to ethnicity. When ethnicity-specific individual data from the controls were used in the pooled analysis, 46.9% of whites carried the *Ile/Ile* genotype, 41.8% carried the *Ile/Val* genotype, and 11.3% carried the *Val/Val* genotype (data not shown). In Asians, the respective percentages were 66.8%, 30.2%, and 3.0%. These frequencies are similar to those for the *GSTP1* exon 5 polymorphism found in other control populations for different cancer sites (70, 71). Among all controls in the pooled analysis, the genotype frequencies were in Hardy-Weinberg equilibrium for both Asians ($P = 0.38$) and whites ($P = 0.17$).

Meta-analysis

For all 27 studies combined, the meta–odds ratio was 1.04 (95% confidence interval (CI): 0.97, 1.10), with no apparent heterogeneity between the studies (P for Q test = 0.27) (data not shown). Thus, a fixed-effects model versus a random-effects model was used. Sensitivity analysis was conducted to examine the influence of each study. Exclusion of the study by Miller et al. (52) resulted in a summary odds ratio of 1.08 (95% CI: 1.00, 1.15) (data not shown).

Two tests were performed to detect publication bias. Publication bias was not identified when Begg's test was performed ($P = 0.10$), but the Egger et al. (69) regression asymmetry test, which tends to suggest the presence of publication bias more frequently than Begg's test, did suggest that publication bias was present ($P = 0.02$). To adjust for this bias, a trim and fill method developed by Duval and Tweedie (72) was implemented. Trimming was based on the fixed-effects model, and the adjusted estimate obtained by using a random-effects model was an odds ratio of 0.99 (95% CI: 0.91, 1.07). Thus, the overall conclusion that there is no association between lung cancer and carrying at least 1 valine allele remained unchanged.

Because of the ethnicity-specific differences in genotype frequency, study-specific crude odds ratios and 95% confidence intervals, stratified by ethnicity, are presented in Figure 1 for individuals carrying at least 1 *105Val* (*Ile/Val* and *Val/Val* vs. *Ile/Ile*) allele. Among studies of whites, only 1 study (64) reported a statistically significant association (odds ratio (OR) = 1.70, 95% CI: 1.13, 2.57). The remaining 13 studies were clustered around the null effect (6 below 1.0 and 7 above 1.0) and were not statistically significant. None reported a negative association. The overall odds ratio for studies in whites was 1.00 (95% CI: 0.93, 1.07). No heterogeneity was identified between the 14 studies included ($P = 0.23$, data not shown). Among the 8 studies in Asian populations, none were statistically significant, with 4 slightly below the null and 4 slightly above the null. The overall odds ratio in Asian studies was 1.09 (95% CI: 0.93, 1.28). No heterogeneity was identified between the 8 studies included ($P = 0.51$, data not shown). In the studies that reported other ethnicities, 4 of the 5 had odds ratio estimates above the null, and 1 was slightly below the null. The overall risk associated with lung cancer and carrying at least 1 valine allele was statistically significant in studies not limited to a single ethnicity, with an odds ratio of 1.19 (95% CI: 1.01, 1.40). No heterogeneity was identified between the 5 studies included ($P = 0.49$, data not shown).

No statistically significant differences were identified when studies were stratified by control source (healthy or hospital, data not shown). Stratifying by both ethnicity and control source resulted in sparse strata for "Asian and healthy" (2 studies) and "other and hospital" (1 study). For other strata, no statistically significant associations between genotype and lung cancer were identified, nor were

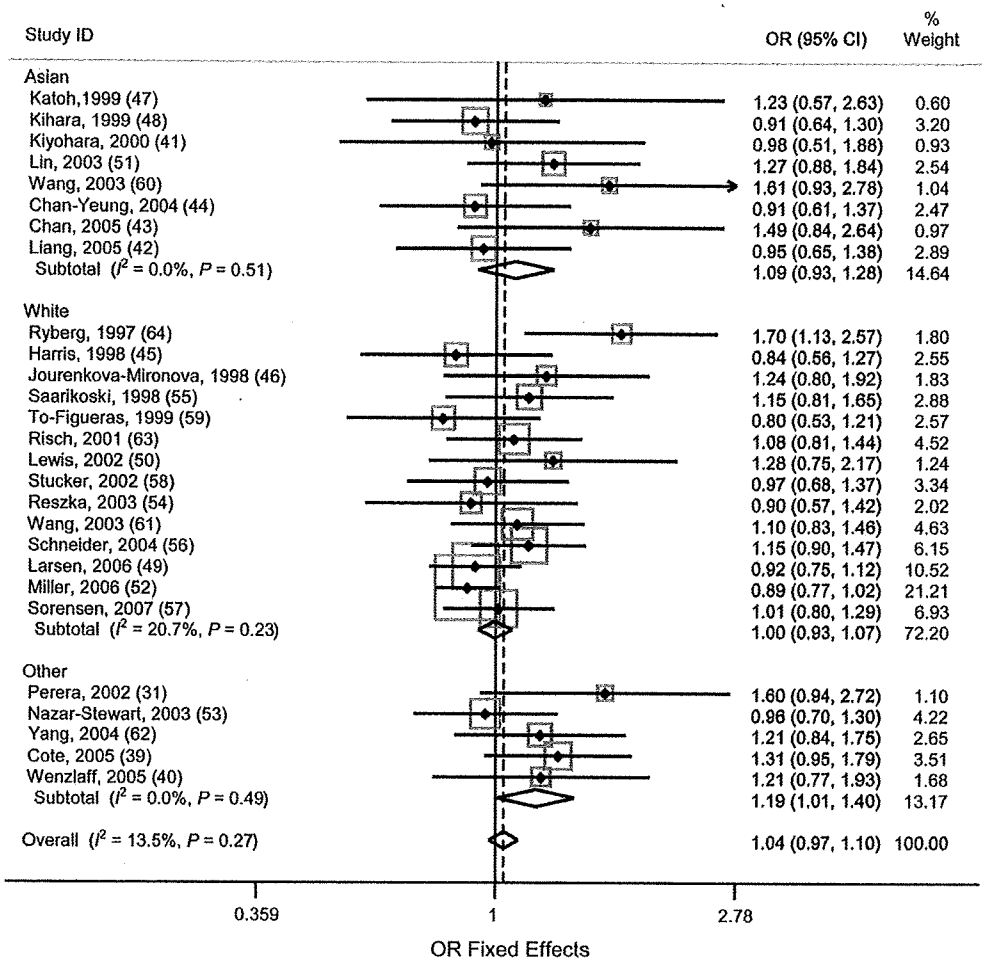

Figure 1. Study-specific (first author, year of publication (reference no.)) and meta-log odds ratios (ORs) with 95% confidence intervals (CIs) for a glutathione *S*-transferase pi gene (*GSTP1*) exon 5 (Ile105Val, 313A → 313G) polymorphism for individuals carrying at least 1 valine allele (*Ile/Val* and *Val/Val* vs. *Ile/Ile*), by ethnicity. The shading around the point estimate reflects the weight of the study in the meta-analysis. The dashed line indicates the overall OR. ID, an assigned study identifier for each study population; Ile, isoleucine.

there any significant differences between strata (data not shown).

Pooled analysis

Table 2 describes the 15 studies included in the pooled analysis. Crude odds ratios and 95% confidence intervals for the association between carrying at least 1 *105Val* allele at *GSTP1* exon 5 are presented. The overall pooled odds ratio associated with carrying at least 1 valine allele is 1.11 (95% CI: 1.03, 1.21) (Table 2).

Table 3 presents ethnicity-specific crude and adjusted odds ratios and 95% confidence intervals for the association between carrying at least 1 *105Val* allele at *GSTP1* exon 5 and lung cancer. In the crude analysis or after adjusting for study ID (an assigned study identifier for each study population), age, sex, or smoking status (ever/never), no increased risk of lung cancer was seen for whites carrying at least 1 valine allele compared with those with the *Ile/Ile* genotype. We found no differences in estimates based on whether the control source was healthy or hospital based. There were also no statistically significant differences in risk when subjects were stratified by ever smoker or nonsmoker status; after adjusting for study ID, age, and sex among nonsmokers; and after adjusting for study ID, age, sex, and number of pack-years of smoking among participants who had ever smoked (Table 3).

Regarding Asian study subjects, those who carried at least 1 *GSTP1 105Val* allele compared with those with the *Ile/Ile* genotype were shown to be at increased risk of lung cancer in both crude analysis (OR = 1.34, 95% CI: 1.07, 1.67) and after adjustment for study ID, age, sex, and smoking status (OR = 1.35, 95% CI: 1.07, 1.70) (Table 3). With the exception of 4 cases and 10 controls, these findings were all based

Table 2. Description of Studies Included in the Pooled Analysis: Study-Specific and Overall Crude Odds Ratios and 95% Confidence Intervals for the Association Between *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphisms and Lung Cancer, by Continent, Country, and Year of Publication

First Author, Year (Reference No.)	No. of Cases	No. of Controls	Country of Study Origin	Source of Controls	Val/Val and Ile/Val vs. Ile/Ile	
					Crude OR	95% CI
Asia						
Wang, 2003 (60)	112	119	China	Hospital	1.61	0.93, 2.78
Liang, 2005 (42)	227	227	China	Hospital	1.22	0.84, 1.78
Kiyohara, 2000 (41)	62	80	Japan	Hospital	1.18	0.58, 2.42
Lin, 2003 (51)	198	332	Taiwan	Hospital	1.27	0.88, 1.84
Australia						
Larsen, 2006 (49)	1,095	626	Australia	Hospital	0.92	0.75, 1.12
Europe						
Sorensen, 2007 (57)	429	765	Denmark	Healthy	1.01	0.80, 1.28
Saarikoski, 1998 (55)	199	293	Finland	Healthy	1.49	1.03, 2.16
Jourenkova-Mironova, 1998 (46)	150	172	France	Hospital	1.24	0.80, 1.92
Schneider, 2004 (56)	480	630	Germany	Hospital	1.09	0.86, 1.39
Butkiewicz, 1999 (32)	165	326	Poland	Healthy	0.94	0.65, 1.37
Reszka, 2003 (54)	217	251	Poland	Hospital	0.93	0.64, 1.33
To-Figueras, 1999 (59)	173	202	Spain	Healthy	1.01	0.67, 1.51
Lewis, 2002 (50)	93	151	United Kingdom	Hospital	1.28	0.75, 2.17
North America						
Yang, 2004 (62)	235	234	United States	Healthy	1.22	0.85, 1.76
Cote, 2005 (39)	447	624	United States	Healthy	1.31	1.02, 1.69
Total	4,282	5,032			1.11	1.03, 1.21

Abbreviations: CI, confidence interval; *GSTP1*, glutathione *S*-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

on studies with hospital-recruited controls; thus, in this paper, these data are not presented for healthy controls. After we stratified by ever/never smoking status, the association between genotype and lung cancer was significant among only Asian nonsmokers (OR = 1.52, 95% CI: 1.09, 2.13) after we adjusted for study ID, age, and sex (Table 3).

Risk of lung cancer and GSTP1 *exon 5 polymorphism by amount smoked.* The large sample of whites for whom we had individual pack-year information (92.3% of the cases and 79.7% of the controls) allowed us to perform an analysis stratified by number of pack-years of cigarette smoking. Table 4 shows the relation among amount smoked, genotype, and lung cancer risk. For nonsmokers, no statistically significant association was seen between carrying at least 1 *105Val* allele and lung cancer risk after we adjusted for study ID, sex, and age (OR = 1.17, 95% CI: 0.92, 1.50). For participants who smoked for 1–28 pack-years, the odds of having lung cancer were 1.23-fold higher among those carrying at least 1 valine allele compared with those with the *Ile/Ile* genotype (95% CI: 1.00, 1.52) after we adjusted for study ID, sex, and age. Among moderate smokers who smoked for 28.01–48 pack-years, risk was not increased (OR = 1.01, 95% CI: 0.82, 1.24), and, among those with the heaviest reported pack-years of smoking (≥48.01), carrying at least 1 *105Val* allele was associated with a decreased risk of lung cancer compared with that for those with *Ile/Ile* genotypes after adjustment for study ID, age, and sex (OR = 0.83, 95% CI: 0.67, 1.03). We found no statistically significant linear trend between risk of lung cancer due to genotype and amount smoked ($P = 0.16$) when nonsmokers were included. There was a statistically significant trend between amount smoked and risk of lung cancer due to genotype ($P = 0.05$) when only ever smokers were examined. The overall effect of interactions between amount of smoking and genotype on lung cancer risk was marginally significant ($P = 0.08$, data not shown). When we used nonsmoking and *Ile/Ile* as the reference group, the group of heavy smokers with *Ile/Val* or *Val/Val* had a significantly increased risk ($P = 0.03$, Table 4).

Risk of lung cancer and GSTP1 *exon 5 polymorphism by histologic type and ethnicity.* Crude and adjusted odds ratios and 95% confidence intervals for the association between carrying at least 1 valine allele and lung cancer risk are presented stratified by histologic type and ethnicity in Table 5. Among whites, there were no statistically

Table 3. Odds Ratios and 95% Confidence Intervals for the Association Between a *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphism (Ile/Val and Val/Val vs. Ile/Ile) and Lung Cancer in the Pooled Analysis, Stratified by Smoking Status and Ethnicity

Ethnic Group	No. of Cases	No. of Controls	OR	95% CI
Asian				
All studies: unadjusted	603	768	1.34	1.07, 1.67
All studies: adjusted[a]	603	768	1.35	1.07, 1.70
Hospital controls: unadjusted	599	758	1.32	1.06, 1.65
Hospital controls: adjusted[a]	599	758	1.32	1.05, 1.68
Smoker: unadjusted	287	298	1.23	0.88, 1.72
Smoker: adjusted[b]	287	298	1.17	0.83, 1.66
Smoker: adjusted[c]	48	49	1.06	0.41, 2.75
Nonsmoker: unadjusted	254	390	1.49	1.08, 2.07
Nonsmoker: adjusted[b]	254	390	1.52	1.09, 2.13
White				
All studies: unadjusted	3,538	4,098	1.07	0.98, 1.17
All studies: adjusted[a]	3,490	4,077	1.05	0.95, 1.16
Healthy controls: unadjusted	1,503	2,268	1.12	0.98, 1.27
Healthy controls: adjusted[a]	1,497	2,254	1.15	0.99, 1.33
Hospital controls: unadjusted	2,035	1,830	1.02	0.90, 1.16
Hospital controls: adjusted[a]	1,993	1,823	1.00	0.87, 1.14
Smoker: unadjusted	3,044	2,737	1.02	0.93, 1.14
Smoker: adjusted[b]	3,035	2,729	1.05	0.95, 1.17
Smoker: adjusted[c]	2,809	2,181	1.00	0.89, 1.13
Nonsmoker: unadjusted	465	1,352	1.18	0.95, 1.45
Nonsmoker: adjusted[b]	455	1,348	1.17	0.92, 1.49

Abbreviations: CI, confidence interval; *GSTP1*, glutathione *S*-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

[a] Adjusted for study ID (an assigned study identifier for each study population), age, sex, and smoking status (ever/never).

[b] Adjusted for study ID, age, and sex.

[c] Adjusted for study ID, age, sex, and pack-years of smoking.

significant differences in risk associated with the *GSTP1* gene polymorphism and adenocarcinoma, squamous cell carcinoma, or small cell carcinoma. In Asian populations, individuals carrying at least 1 valine allele were at increased risk of adenocarcinoma (OR = 1.33, 95% CI: 1.02, 1.74) after adjustment for study ID, age, sex, and smoking status. Risk of squamous cell lung cancer was increased for Asians carrying at least 1 valine allele (OR = 1.44, 95% CI: 1.05, 1.98), but the odds ratio was no longer statistically significant after adjusting for study ID, age, sex, and smoking status (OR = 1.36, 95% CI: 0.95, 1.94).

DISCUSSION

The meta-analysis found no association (OR = 1.04, 95% CI: 0.97, 1.10) between lung cancer risk and carrying 1 or more *GSTP1 105Val* alleles. This finding is similar to that of another meta-analysis of 25 studies with a combined 6,221 cases and 7,602 controls, which reported an unadjusted odds ratio of 1.04 (95% CI: 0.99, 1.09) for the association between lung cancer and carrying the *GSTP1* exon 5 Ile105Val variant (15). After stratifying by the ethnicity of study subjects, studies that included subjects of various ethnic backgrounds (i.e., the study had both African-American and white participants) reported an increase in risk associated with carrying at least 1 *105Val* allele compared with those with *Ile/Ile* genotypes.

The pooled analysis did identify an overall statistically significant increase in lung cancer risk associated with carrying at least 1 valine allele, with an odds ratio of 1.11 (95% CI: 1.03, 1.21). When the studies were stratified by subject ethnicity, this association was seen among Asian subjects but not among white subjects. A pooled analysis of whites diagnosed with early-onset lung cancer (under age 60 years) also reported no association between lung cancer risk and the *GSTP1* exon 5 genotype (30). Unlike the white control populations, who were recruited through either population-based methods or hospitals, almost all Asian controls were recruited by using hospital-based methods. Among Asians, this association between the *Ile/Val* and *Val/Val* genotypes and lung cancer risk was strongest among nonsmokers and those with adenocarcinoma. The higher prevalence of adenocarcinoma of the lung in Asians, particularly among women nonsmokers, was identified decades ago (73) and has received more attention recently with the success of using epidermal growth factor receptor tyrosine kinase inhibitors in these populations (74).

The results from the meta-analyses suggest no association between lung cancer risk and the *GSTP1* exon 5 polymorphism, either overall or stratified by race/ethnicity, whereas the results from the pooled analysis suggest risk of carrying at least 1 *105Val* allele is associated with increased risk of lung cancer overall and also in Asians. Examination of the 95% confidence intervals associated with the risk estimates suggests that these apparently discrepant results are not statistically significant. In addition, the pooled analysis did not contain subjects from all studies included in the meta-analysis, and vice versa, and the pooled analysis allowed for individual adjustment by age, sex, and smoking status. It has been suggested that results from individual subject data that allow for adjustment of confounders, such as the pooled analysis presented here, may best summarize results of multiple studies (75).

We found an interaction between *GSTP1* exon 5 genotype and personal smoking history. Among whites, those classified as "light" smokers (1–28.00 pack-years) were at increased risk of lung cancer if they carried the *Ile/Val* or *Val/Val* genotype compared with those with the *Ile/Ile* genotype. Conversely, heavy-smoking (≥48.01 pack-years) whites carrying the *Ile/Val* or *Val/Val* genotypes were at decreased risk compared with those with the *Ile/Ile* genotype. This interaction may explain some of the variability seen between populations with different recruitment criteria (i.e. early-onset cases who likely do not have as extensive smoking histories) and highlights the need to investigate the gene-environment interactions between genotype and amount smoked (i.e., pack-years).

Table 4. Odds Ratios and 95% Confidence Intervals for the Association Between a *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphism (Ile/Val and Val/Val vs. Ile/Ile) and Lung Cancer in Whites in the Pooled Analysis, Stratified by Pack-years of Smoking

Smoking Status	No. of Cases		No. of Controls		OR[a]	95% CI	*P* Trend	*P* Value[b]
	Ile/Ile	Ile/Val or Val/Val	Ile/Ile	Ile/Val or Val/Val				
Nonsmoker	204	251	656	692	1.17	0.92, 1.50	0.16[c]	Reference
1–28 pack-years	279	386	459	539	1.23	1.00, 1.52		0.09
28.01–48 pack-years	490	557	292	334	1.01	0.82, 1.24		0.57
≥48.01 pack-years	505	592	228	329	0.83	0.67, 1.03	0.05[d]	0.03

Abbreviations: CI, confidence interval; *GSTP1*, glutathione *S*-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

[a] Adjusted for study ID (an assigned study identifier for each study population), age, and sex.

[b] *P* value for nonsmokers and with Ile/Ile as the reference group, adjusted for study ID, age, and sex.

[c] *P*-value test for trend among all 4 categories.

[d] *P*-value test for trend among smokers only.

Laboratory evidence suggests that carrying a *105Val* allele results in reduced GSTP1 enzymatic activity in the cell (11–13). These characterizations, while important for developing a hypothesis about the biologic mechanisms through which carcinogenesis evolves, do not necessarily represent what is occurring in the environment of the human lung. The seemingly protective effect of the *Val/Val* or *Ile/Val* genotype in heavy smokers identified in this pooled analysis does not directly support reduced activity associated with carrying the *Val* allele because it would be expected that those with reduced GSTP1 activity would be at increased risk of malignant transformation after exposure to carcinogens. The continuous assault from heavy smoking may change cellular activity in ways we are currently unable to assess in the human lung. A recent murine model, using GSTP-null mice, found a significantly higher number of adenomas in null mice compared with wild-type mice after exposure to 3 PAHs (76). When adducts in these mice were examined, there were significant differences in the number of adducts formed depending on the PAH they were exposed to, with 1 PAH resulting in no increase in adducts, suggesting that an alternative protective pathway in response to this specific exposure exists. While this study in mice is the first known in vivo model showing the importance of GSTP1 in

Table 5. Odds Ratios and 95% Confidence Intervals for the Association Between a *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphism (Ile/Val and Val/Val vs. Ile/Ile) and Lung Cancer in the Pooled Analysis, Stratified by Histologic Type and Ethnicity

Ethnic Group	Unadjusted				Adjusted[a]			
	No. of Cases	No. of Controls	OR	95% CI	No. of Cases	No. of Controls	OR	95% CI
White								
Adenocarcinoma	1,048	4,098	1.08	0.95, 1.24	1,043	4,077	1.041	0.90, 1.21
Squamous cell carcinoma	1,394	4,098	1.00	0.86, 1.09	1,377	4,077	0.994	0.87, 1.14
Small cell carcinoma	399	4,098	1.11	0.90, 1.36	393	4,077	1.103	0.91, 1.41
Asian								
Adenocarcinoma	384	768	1.32	1.02, 1.70	384	768	1.33	1.02, 1.74
Squamous cell carcinoma	206	768	1.44	1.05, 1.98	206	768	1.36	0.95, 1.94
Small cell carcinoma	5	768	0.50	0.06, 4.52	5	768	0.44	0.04, 4.56
Total								
Adenocarcinoma	1,496	5,032	1.05	0.94, 1.18	1,491	5,009	1.11	0.98, 1.26
Squamous cell carcinoma	1,617	5,032	1.02	0.91, 1.14	1,600	5,009	1.03	0.91, 1.16
Small cell carcinoma	412	5,032	1.22	1.00, 1.49	406	5,009	1.12	0.90, 1.39

Abbreviations: CI, confidence interval; *GSTP1*, glutathione *S*-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

[a] Adjusted for study ID (an assigned study identifier for each study population), sex, smoking (ever/never), and age.

lung carcinogenesis, it is also apparent that the role of glutathione *S*-transferase has yet to be fully elucidated. In this study, we were not able to explore the other major roles that GSTP1 is thought to have in the cell, including resistance to chemotherapy (77), because we did not have information on chemotherapy or other exposures that might help clarify this gene-environment interaction.

The variation in risk associated with lung cancer and *GSTP1* exon 5 genotypes between Asians and whites is likely due to a number of factors, including different exposures in the populations. For example, studies in Asian women nonsmokers suggest that exposure to the carcinogens found in cooking oils increases risk of lung cancer (78, 79). Further studies of gene-environment interactions in lung cancer should also include occupational risk factors such as ionizing radiation (through radon exposure), asbestos, chromium, and arsenic (25, 80). The ability to examine only a small number of potential confounding variables is a limitation to both pooled and meta-analysis studies. It is also possible that publication bias accounts for some of the difference in risk seen between the Asian and white populations. It has been shown that a large proportion of Chinese literature does not reach PubMed and that studies that do are more likely than non-Chinese studies to be statistically significant and report larger measures of effect (i.e., odds ratios) (81). Thus, our findings may be a result of this publication bias, and the inability to include the entire collection of literature is a limitation of this analysis.

Other potential limitations include the presence of heterogeneity between studies. We tested for heterogeneity and performed a sensitivity analysis to determine whether a particular study or studies were a source of heterogeneity. Various amounts of data regarding smoking behaviors were collected, so we were unable to examine number of years of smoking or number of cigarettes smoked per day; therefore, our analyses were restricted to use of the 2 most commonly collected variables: pack-years of use or dichotomous classification as never or ever smokers. Additionally, pack-years of smoking was missing for approximately 20% of individuals identified as ever smokers. There were also differences in how the subjects were identified (hospital based or population), the histologic types of lung cancers included in the studies, the types of tissues used to extract DNA, and genotyping methods. When possible, we stratified by source of controls and histologic type of cancer. It was not feasible to control for the variation in pathologic reports of histology type that may occur by region or country.

LABORATORY TESTS

The methods used for determining *GSTP1* exon 5 genotypes are described in each article. The majority of the studies included in the analyses used genomic DNA extracted from blood, although 3 studies included DNA extracted from blood or lung tissue (32, 43, 49); 2 studies included DNA extracted from blood, lung tissue, or buccal samples (39, 40); and 1 study used blood and bronchial lavage (50). Polymerase chain reaction–based restriction fragment length polymorphism methods were the most frequently cited technique to determine *GSTP1* exon 5 genotypes.

POPULATION TESTING

The evidence to date regarding the polymorphism in *GSTP1* exon 5 and lung cancer risk is insufficient to suggest testing at the population level.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

Overall, the meta-analysis found no significant association between lung cancer and the *GSTP1* exon 5 (Ile105Val) polymorphism for individuals carrying at least 1 *105Val* allele. No association was seen when we stratified by ethnicity in white or Asian populations. In the 5 studies that included more than 1 ethnic group, the meta-analysis suggested that an association between lung cancer and carrying at least 1 valine allele (*Ile/Val* and *Val/Val* vs. *Ile/Ile*) was statistically significant, with an odds ratio of 1.19 (95% CI: 1.01, 1.40), although this finding may be the result of population stratification.

In the pooled analysis, there was a statistically significant, mild overall association (OR = 1.11, 95% CI: 1.03, 1.21) between lung cancer and the *GSTP1* exon 5 (Ile105Val) polymorphism for individuals carrying a *Val/Val* or *Ile/Val* genotype compared with those carrying the *Ile/Ile* genotype. After stratification by ethnicity and adjustment for study ID, age, sex, and smoking status, increased risk associated with the *Val/Val* or *Ile/Val* genotypes and lung cancer was seen in Asian populations only. Among Asians, this risk was highest for nonsmokers and those with adenocarcinoma of the lung.

There is evidence for interaction among amount of smoking (i.e., pack-years), the *GSTP1* exon 5 (Ile105Val) polymorphism, and risk of lung cancer in whites. The odds of lung cancer associated with carrying at least 1 valine allele appear to decrease as the amount of pack-years of smoking increases, with heavy smokers who carry a *Ile/Val* or *Val/Val* genotype at decreased risk of lung cancer compared with their heavy-smoking counterparts with the *Ile/Ile* genotype. This finding highlights the importance of context when studying gene-environment interactions and clearly shows the need to collect detailed exposure information on all study participants, because gene expression, and risk of lung cancer, may differ by the environmental exposure.

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