The association of OGG1 with lung cancer

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1. Objectives

Multiple DNA repair mechanisms exist to avoid the effects of reactive oxygen species (ROS) and maintain genomic integrity. One such pathway of oxidative damage is base-excision repair, and includes the enzyme 8-oxoguanine-DNA glycosylase (OGG1)[1-3]. The product of the OGG1 gene catalyzes the excision of a modified base, 8-oxoguanine, from DNA that has been damaged by exposure to ROS[4-7]. Therefore, a reduced ability to excise 8-oxoguanine may lead to an accumulation of oxidation-induced mutations[4]. The OGG1 gene is located on chromosome 3p26.2, a region that frequently shows loss of heterozygosity in several human cancers[8-10]. Several polymorphisms have been identified in the human OGG1 gene, one of which is a C→G transversion at nucleotide 1245, resulting in the substitution of cysteine for serine at codon 326 (Ser326Cys)[5-8,10]. Genetic polymorphisms in OGG1 may influence oxidative DNA damage and ultimately carcinogenesis[2,3,5,6]. There is currently no convincing evidence that the Ser326Cys polymorphism causes decreased OGG1 activity in humans, although recent *in vitro* studies have suggested that this may be the case[6-10].

The objective of this report is to determine, based on the available literature, whether genetic polymorphisms in OGG1 predict risk of mortality from, or incidence of, lung cancer.

2. Literature searches

Papers that appeared likely from their titles and abstracts to supply relevant information were sought from:

(i) our in-house database, and

(ii) Medline searches

Fourteen papers were identified.

3. Plan

If apparently valid meta-analyses or comprehensive reviews have been published recently that are relevant to the objective of this review, the conclusions reached would be summarized without any attempt to analyse all the individual papers in detail (other than perhaps to look for more recent relevant publications based on larger samples). If no such meta-analysis or reviews are available, the literature would be studied and a formal meta-analysis attempted.

4. Genetic polymorphisms in OGG1 in relation to lung cancer

4.1 Introduction

No relevant meta-analyses were available, but fourteen papers were found relating to studies in which polymorphisms in the OGG1 gene were compared in lung cancer patients and healthy subjects. The results of these studies are summarized below.

4.2 Differences in the OGG1 gene between lung cancer patients and control subjects

Cases in a study carried out in Japan[11] consisted of 45 lung cancer patients, while the control group was made up of 42 unrelated healthy individuals. No further details of the cases or controls were available. DNA was extracted from samples from tumours and adjacent non-cancerous tissues

in the case group and from peripheral blood samples in the controls, and analysed for OGG1 polymorphisms using polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis. The Cys allele was present in 43.3% of the cases and 40.5% of the controls. From the data given, it was possible to estimate odds ratios for the risk of lung cancer of 0.89 (95% CI 0.35-2.29) in Ser/Cys individuals, and 1.34 (95% CI 0.41-4.43) in Cys/Cys subjects. The odds ratio for all subjects with the Cys allele was estimated at 1.01 (95% CI 0.42-2.42).

The 128 cases in a study conducted in Japan[12] were made up of lung cancer patients identified at a single hospital, from which non-cancerous lung tissue samples were obtained from surgical specimens. The 268 controls, who were matched for sex and age, were selected from individuals attending a medical institution in the same location for a general check-up. The mean age of the cases was 64.45 years compared to 57.94 years for the controls. Genomic DNA was extracted from the tissue samples and analysed for polymorphisms in exon 1 of the hMMH/OGG1 gene using polymerase chain reaction (PCR). Three alleles were identified, with variant allele 2 occurring in 5.0% of the controls and 5.1% of the cases, and allele 3 being found in 2.8% of the controls and 5.1% of the cases. After adjustment for age, sex and smoking history, the odds ratios for the risk of lung cancer were estimated at 1.33 (95% CI 0.66-2.85) and 2.60 (95% CI 1.10-6.12) for alleles 2 and 3 respectively.

In a study carried out in Japan[13], the case group consisted of 241 male lung cancer patients, with a mean age of 67.6 years, recruited from a single hospital, while the control subjects comprised 197 randomly selected male in-patients, with a mean age of 62.0 years, from the same hospital. All cancer cases were histopathologically and cytologically confirmed. DNA samples from the study participants were analysed using PCR-SSCP. The prevalence of the Ser/Ser, Ser/Cys and Cys/Cys genotypes were 35.3%, 47.7% and 17.0% respectively among the cases, and 32.0%, 54.3% and 13.7% respectively in the control group. Compared to Ser allele homozygotes, the risk of lung cancer in the Ser/Cys group was reduced (OR 0.80, 95% CI 0.52-1.21) but it was non-

significantly raised in Cys homozygotes (OR 1.13, 95% CI 0.63-2.02). Adjustment for age and smoking habits reduced the risk still further in the heterozygous group (OR 0.64, 95% CI 0.39-1.06) and increased it in Cys/Cys subjects, although it remained non-significant (OR 1.31, 95% CI 0.65-2.62). The authors reported that further adjustment for smoking variables such as number of cigarettes smoked per day did not materially alter these findings, but did not present this data.

Participants in a study conducted in Germany[8] were drawn from a larger case-control study, and consisted of 105 lung cancer patients and 105 matched controls with no history of cancer, all of whom were recruited from a single hospital. All subjects were smokers, and the cases and controls were matched to each other for age, sex and pack-years of smoking. The proportion of men was 77.1% in the both groups, and the mean age was 60.0 years in the cases and 59.5 years in the controls. All subjects provided a venous blood sample from which DNA was extracted and analysed using PCR-RFLP. The Cys variant allele frequency was 0.20 in the cases and 0.22 in the controls. Using Ser homozygotes as a reference group, the risk of lung cancer was estimated at 2.20 (95% CI 0.41-11.79) in Cys homozygotes and at 0.72 (95% CI 0.42-1.27) for all subjects with the Cys allele.

Cases in a study carried out in Japan[14] consisted of 138 lung cancer patients identified at a single hospital. The control group was made up of 241 patients undergoing gastroscopy. The case group was 49.3% male, with a mean age of 60.7 years, compared to 49.0% men, with a mean age of 56.8 years, in the control group. All subjects provided a peripheral blood sample from which DNA was extracted and analysed using a polymerase chain reaction with confronting two-pair primers (PCR-CTPP) method. The distribution of the Ser/Ser/, Ser/Cys and Cys/Cys genotypes was 28.3%, 49.2% and 22.5% respectively in the controls and 29.0%, 51.4% and 19.6% in the cases. Unadjusted odds ratios for the risk of lung cancer were 1.02 (95% CI 0.63-1.67) for the Ser/Cys genotype and 0.85 (95% CI 0.46-1.56) for the Cys/Cys genotype. Adjustment for age and sex made little difference to these

estimates (Ser/Cys: OR 1.06, 95% CI 0.64-1.76; Cys/Cys: OR 0.81, 95% CI 0.44-1.52).

In a study conducted in Hawaii[15], the case group was made up of 298 patients, aged 18-79 years, with histologically confirmed primary lung cancer, while the 405 controls were selected randomly from a list of residents interviewed as part of a health survey. One control was matched to each case for sex, ethnicity and age. All participants provided a blood sample from which DNA was extracted and the hOGG1 polymorphism assessed by polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) analysis. In the control group, the frequency of the Cys variant allele was 44.8% in Hawaiians, 42% in Japanese and 21.7% in Caucasian subjects. The odds ratios for lung cancer, adjusted for age, sex, ethnicity, smoking status, years of smoking, number of cigarettes per day, and intake of saturated fat and vegetables, were estimated at 0.7 (95% CI 0.5-1.1) and 2.1 (95% CI 1.2-3.7) for subjects with Ser/Cys and Cys/Cys genotypes respectively, compared to homozygous Ser individuals.

The case group in a study conducted in Japan[16] was made up of 198 histologically and/or cytologically confirmed lung adenocarcinoma cases, while the control group consisted of 152 randomly selected in- and out-patients at the same hospitals. There were 124 men and 74 women, with a mean age of 63 years in the case group, and 108 men and 44 women, with a mean age of 65 years, in the control group. The difference in the age distribution between the two groups reached statistical significance ($p = 0.006$). A heparinized whole-blood sample was obtained from each participant, from which genomic DNA was extracted and assessed for OGG1 polymorphisms using PCR-RFLP. The Ser/Ser genotype was found in 27.3% of the cases and 32.9% of the controls, while the Ser/Cys and Cys/Cys genotypes were seen in 53.5% and 19.2% of the cases respectively, and 42.4% and 23.7% of the controls respectively. After adjustment for sex, age and smoking habits, the OR for lung cancer in Ser/Cys subjects was estimated at 1.33 (95% CI 0.80-2.23) and that for Cys homozygotes was estimated at 0.90 (95% CI 0.48-1.70).

Participants in a study carried out in China[1] consisted of 118 primary incident cases of lung cancer and 109 controls matched on age, sex, village of residence, and type of fuel currently used for cooking and home heating. There were 78 men and 41 women in the case group and 73 men and 40 women in the control group, and the age distribution of the two groups was comparable. DNA was extracted from sputum samples using phenol-chloroform extraction and genotyping was carried out by real-time PCR. The distribution of the Ser/Ser, Ser/Cys and Cys/Cys genotypes were 31.36%, 51.69% and 16.95% respectively in the cases and 46.79%, 39.45% and 13.76% respectively in the controls. Odds ratios for lung cancer risk, adjusted for age, sex and pack-years of smoking, were estimated at 1.96 (95% CI 1.10-3.57) for Ser/Cys individuals and 1.85 (95% CI 0.83-4.11) for Cys/Cys individuals. The odds ratio for the Cys allele was 1.93 (95% CI 1.12-3.34) compared to subjects with the Ser/Ser genotype.

In a study carried out in the USA[5], the case subjects consisted of 179 patients diagnosed with histologically-confirmed primary lung cancer. Controls consisted of subjects who were visiting a cancer screening clinic, and had no previous diagnosis of cancer. Controls were matched to cases in a 1:2 ratio for age, race and sex. There were 179 cases, with a mean age of 61 years, and 358 controls, with a mean age of 65 years, and 42% of both groups were female. Buccal cell samples were collected from all study subjects, from which DNA was isolated and assessed using PCR-RFLP. Among the controls, the prevalence of the Cys allele was 0.15. Compared to Ser/Ser individuals, there was a significantly increased risk of lung cancer in both Ser/Cys subjects (OR 1.9, 95% CI 1.3-2.8) and Cys homozygotes (OR 4.1, 95% CI 1.7-10.2). Adjustment for age, sex and pack-years of smoking made little difference to the estimate for the Ser/Cys genotype (OR 1.9, 95% CI 1.2-2.9), but reduced that for Cys/Cys subjects (OR 3.8, 95% CI 1.4-10.6)

The case group in a study conducted in the Czech Republic, Hungary, Poland, Romania, Russia and Slovakia[6] consisted of subjects with histologically or cytologically confirmed lung cancer. Controls, who were

eligible if they had been diagnosed with a non-tobacco related illness, a benign disorder, common infection, eye condition or orthopaedic disease except osteoporosis, or had undergone a minor surgical procedure, were selected from among inpatients and outpatients admitted to the same hospital as the cases, and were frequency matched by sex, age, study centre and referral or residence area. In one study centre, controls were selected by random sampling of the general population. All subjects had lived in the relevant study area for at least 1 year. Each participant provided a blood sample from which genomic DNA was extracted and analysed by PCR. Among the total case group of 2188 subjects, 78% were men, compared to 74% of the 2198 controls. Details of the mean age of the two groups were not given, but the age distribution appeared to be comparable. Results for OGG1 genotypes were available for 2155 cases and 2163 controls. The Ser/Ser genotype was found in 65.0% of the cases, while the Ser/Cys and Cys/Cys genotypes occurred in 30.7% and 4.3% of this group respectively. Corresponding figures in the controls were 63.2%, 33.1% and 3.7% respectively. Compared to individuals homozygous for the Ser allele, the risk of lung cancer was slightly lower in subjects with the Ser/Cys genotype (OR 0.95, 95% CI 0.82-1.09), but non-significantly raised in homozygous Cys individuals (OR 1.34, 95% CI 0.95-1.88). These estimates were adjusted for country, age, sex and pack-years of smoking.

In a study conducted in Japan[17], 1097 cases and 394 controls were recruited. All of the cases were diagnosed with lung adenocarcinoma by cytological or histological examination in one of two hospitals. The controls were patients at the same hospitals, with no history of cancer. The mean age of the cases was 60 years, compared to 64 years in the control group, and the proportion of men varied from 60% in the cases to 62% in the controls. A whole-blood sample was obtained from each participant and genomic DNA isolated from this and subjected to genotyping by pyrosequencing. In the cases, 26% of individuals were homozygous for the Ser allele, 50% had the Ser/Cys genotype, and 24% were Cys homozygotes. Corresponding values in the control group were 31%, 48% and 21% respectively. Crude odds ratios for the risk of lung cancer were estimated at 1.2 (95% CI 0.9-1.6) for Ser/Cys subjects and 1.4 (95% CI 1.0-2.0) for Cys/Cys subjects. Adjustment for sex,

age, pack-years of smoking and hospital made no difference for the Ser/Cys genotype and barely altered the estimate for Cys homozygotes (OR 1.5, 95% CI 1.0-2.1).

Participants in a study carried out in Denmark[18] were drawn from a large prospective follow-up study of subjects aged 50-64 years, of which 57,053 had no previous diagnosis of cancer. During follow-up, a total of 431 lung cancer cases (230 men, 201 women) were identified and formed the case group. A random sample of 431 men and 365 women with the required baseline date made up the controls. DNA was isolated from frozen lymphocytes and the OGG1 polymorphism genotyped by end point reading. The proportion of cases with the Ser/Ser, Ser/Cys and Cys/Cys genotypes was 58.9%, 36.0% and 5.1% respectively, compared to 60.2%, 35.7% and 4.1% respectively in the controls. Compared to homozygous Ser individuals, crude incidence rate ratios for lung cancer in Ser/Cys and Cys/Cys subjects were 1.04 (95% CI 0.80-1.35) and 1.18 (95% CI 0.63-2.21) respectively. Adjustment for smoking duration, average smoking intensity and smoking status increased the estimate for the Ser/Cys genotype to 1.16 (95% CI 0.83-1.62), but reduced it for the Cys/Cys genotype (IRR 1.05, 95% CI 0.51-2.16).

The case group in a study carried out in Norway[19] was made up of 343 newly diagnosed lung cancer patients (75.8% men) , while the 413 controls (76.5% men) were randomly selected from individuals aged 59-60 and 75-76 who took part in general health surveys. Cases and controls were matched on age, smoking and sex. The median age of the cases was 65 years, compared to 60 years in the controls. DNA was extracted from whole blood samples or normal lung tissue and genotyping was performed by arrayed primer extension (APEX). Information on the OGG1 gene was available for only 326 cases and 386 controls. The Ser/Ser, Ser/Cys and Cys/Cys genotypes were seen in 55.8%, 30.7% and 13.5% of the cases respectively, compared to 50.3%, 30.3% and 19.4% of the controls respectively. Odds ratios for lung cancer, adjusted for age, sex and pack-years of smoking, were estimated at 1.45 (0.90-2.33) for the Ser/Cys genotype and 1.64 (1.06-2.52) for subjects who were Cys homozygotes.

In a study conducted in Belgium[3], the case group consisted of 110 patients with newly diagnosed, previously untreated, histologically confirmed primary lung cancer from the respiratory medicine department of one hospital. The 110 age and sex-matched controls, all of whom had no history of cancer, were selected from a group of 350 individuals identified from the occupational medicine and geriatric departments of the same hospital and from local senior clubs. There were 81 men and 29 women, with a mean age of 61 years, in the case group and 86 men and 24 women, with a mean age of 62 years, in the control group. A heparinized blood sample was obtained from each study subject, from which lymphocytes were isolated and frozen for genotyping. This was carried out using PCR-RFLP analysis. The frequencies of the Ser/Ser, Ser/Cys and Cys/Cys genotypes were 54.5%, 41.8% and 3.6% respectively in the control group and 67.3%, 30.0% and 2.7% respectively in the cases. Compared to Ser homozygous individuals, the risk of lung cancer was reduced in subjects with both the Ser/Cys (odds ratio 0.58, 95% CI 0.33-1.02) and Cys/Cys (odds ratio 0.61, 95% CI 0.13-2.82) genotypes. Adjustment for age, sex and pack-years of smoking reduced these estimates further (Ser/Cys: OR 0.51, 95% CI 0.27-0.95; Cys/Cys: OR 0.50, 95% CI 0.10-2.51).

4.3 Summary of study characteristics

Of the fourteen studies that investigated polymorphisms in the OGG1 gene in relation to lung cancer risk, six took place in Japan, and one each was carried out in Belgium, China, Denmark, Germany, Hawaii, Norway and the USA. One multi-centre study was conducted in the Czech Republic, Hungary, Poland, Romania, Russia and Slovakia.

The largest study[6] was based on 2155 cases, and only one other study[17] included more than 1000 cases. All but one of the remaining studies were based on case groups of between 100 and 500 subjects, with the exception of the study by[11] which included only 45 cases.

All but one of the studies were of a conventional case-control design, although in one[8] the subjects were a subset of a larger study. In the remaining study[18], the cases and controls were drawn from a prospective study.

One of the studies[13] included only male participants, and one study[11] failed to give any information on the sex of the subjects. In the remaining studies both the case and control groups were of mixed sex and were matched accordingly in eight of the studies[1,3,5,6,8,12,15,19]. Two studies[12,15] gave no further details of the sex distribution of the study participants.

Eight of the studies[1,3,5,6,8,12,15,19] matched the cases and controls for age. Despite this, the cases were older than the controls in three of these studies[5,12,19] and in two other studies[13,14] where matching had not taken place. In two studies[16,17], the cases were younger, and in one of these[16], the difference reached statistical significance. No details of the age distribution of the study subjects were available in four studies[6,11,15,18], although in two of these[6,18], cases and controls appeared to be comparable for age.

Twelve of the studies[1,5,6,8,12-19] included both smokers and non-smokers, but in four of the studies[5,6,17,18] there were more smokers in the case group. In addition, four of these studies[5,13,14,18] reported that there were more heavy smokers among the cases, a difference that reached statistical significance in one study[5]. Three of the studies[12,16,19] found that the proportion of smokers was higher in the control group, although in the study by[19] this related to the number of current vs. ex-smokers, as all study subjects had smoked at one time. Two studies[3,11] did not give any details of the smoking status of participants, but one[3] did report that there were significantly more heavy smokers in the case group than among the controls.

All but two of the studies[8,11] adjusted their results for at least some potential confounding factors. Only the study by[18] failed to adjust for age, while sex was included as an adjustment factor by 10 studies[1,3,5,6,12,15-17,19,20]. Variables relating to smoking history were included by 11 studies[1,3,5,6,12,13,15-

[19]. One study[15] also adjusted for race and dietary factors, while another[17] included hospital of diagnosis as a potential confounder.

4.4 Summary of main results and meta-analyses

The results of the individual studies are summarized in Table 1, with meta-analyses and overall prevalences of the various genotypes of the OGG1 polymorphism being presented in Tables 2 and 3 respectively. Two of the studies[1,5] reported that, compared to Ser homozygotes, the risk of lung cancer was significantly raised in the Ser/Cys genotype, while in another five studies[16-20] the risk was non-significantly raised. Five studies[3,6,11,13,15] reported that the risk of lung cancer was non-significantly reduced in these individuals. In one of these studies[3], the estimate became significant after adjustment for potential confounders. Meta-analysis of these results, using the least adjusted risk estimates where both unadjusted and adjusted estimates were presented, produced an overall estimate of lung cancer risk of 1.04 (95 % CI 0.94-1.14) using a fixed effects model and 1.08 (95% CI 0.90-1.29) with a random effects model. Substituting the most adjusted odds ratios where applicable made little difference to these findings (fixed effects model: OR 1.03, 95% CI 0.94-1.14; random effects model: OR 1.07, 95% CI 0.89-1.30). When the results for Caucasian populations were analysed separately, the overall estimates were slightly lower, but showed a similar pattern (least adjusted: fixed effects model OR 1.02, 95% CI 0.91-1.14, random effects model OR 1.04, 95% CI 0.79-1.38; most adjusted: fixed effects model OR 1.01, 95% CI 0.90-1.14, random effects model OR 1.05, 95% CI 0.77-1.42). However, the estimate for all Asian populations combined was somewhat higher, with the OR for the fixed effects and random effects models being 1.12 (95% CI 0.93-1.33) and 1.11 (0.90-1.38) respectively, using the least adjusted odds ratios where applicable. Substituting the most adjusted risk estimates made little difference to these results (fixed effects model: OR 1.11, 95% CI 0.924-1.33; random effects model: OR 1.09, 95% CI 0.84-1.41).

When Cys homozygotes were examined, four studies[5,15,17,19] found a significantly increased risk of lung cancer compared to Ser/Ser individuals,

although this association was of borderline significance in one study[17]. In another six studies[1,6,8,11,13,18], lung cancer risk was non-significantly raised. Only three studies[3,16,20] reported that lung cancer was less common in Cys homozygotes, and in none of these did the association reach statistical significance. Using least adjusted OR estimates, the overall risk of lung cancer was significantly increased, with ORs of 1.39 (95% CI 1.19-1.63) and 1.40 (95% CI 1.16-1.69) being estimated for the fixed and random effects models respectively. Again, substitution of adjusted risk estimates where available did not materially alter these results (fixed effects model: OR 1.41, 95% CI 1.19-1.66; random effects model: OR 1.40, 95% CI 1.16-1.69). This increased risk appeared to be due to the studies in Caucasian populations, for when these were analysed separately the overall risk of lung cancer was estimated at 1.50 (95% CI 1.19-1.88) for the fixed effects model and 1.53 (95% CI 1.15-2.04) for the random effects model, using the least adjusted odds ratios from the relevant studies. Adjustment reduced these estimates slightly, to 1.46 (95% CI 1.15-1.84) for the fixed effects model and 1.47 (95% CI 1.12-1.92) for the random effects model. Although the overall estimates were significantly raised in Asian subjects, the risk estimates were lower than for Caucasians (least adjusted: OR 1.26, 95% CI 1.01-1.57 for both models; most adjusted: OR 1.31. 95% CI 1.04-1.66 for both models).

Only three studies[1,8,11] reported results for all individuals with the Cys allele combined, and two of these reported increased risks of lung cancer, which reached statistical significance in one study[1], while the third study[8] found that lung cancer was non-significantly reduced in these subjects. When these results were combined by meta-analysis, the fixed effects model gave an overall estimate of lung cancer risk of 1.16 (95% CI 0.81-1.65), while the estimate using the random effects model was 1.13 (95% CI 0.59-2.18). Due to the small number of studies, no attempt was made to analyse the results by ethnicity.

In addition, one study[12] reported a higher risk of lung cancer in subjects with alleles 2 and 3 of the hMMH/OGG1 gene, with odds ratios of 1.33 (95% CI 0.62-2.85) and 2.60 (95% CI 1.10-6.12) respectively.

From Table 3 it can be seen that the prevalence of the Cys allele varies greatly according to race, and is far more common in Asian populations. The Ser/Cys genotype occurs in about one-third of Caucasians but nearly half of Asians, while Cys homozygotes are four times more common in Asians than in Caucasians, making up only about 5% of this latter population.

4.5 The effect of stratification by smoking status and intensity on risk of lung cancer according to OGG1 genotype

Seven studies[5,6,13,16-18,20] presented results for the risk of lung cancer by OGG1 genotype stratified for smoking status and/or intensity (see Table 4). For the Ser/Cys genotype compared to Ser homozygotes, one study[20] found that the risk of lung cancer was increased in never smokers but lower in ex- and current smokers, although not significantly so. Similarly, the ORs estimated by Kohno[17] were higher for non-smokers than for smokers, with the unadjusted OR for non-smokers being of borderline significance. Another study[5] found that the risk of lung cancer was increased in both current and ever smokers, with the difference reaching statistical significance in this last group, but did not include never smokers. When intensity of smoking was examined, two studies[6,13] found that the risk of lung cancer was lowest in the group with the highest level of smoking. In one study[5], the risk of lung cancer increased with the amount of smoking, and was significantly raised in heavy smokers. In the Sorensen study[18], the risk of lung cancer was significantly increased for every five years of smoking and for every five grams smoked per day, but only in subjects who smoked less than 20 grams per day. For those smoking more than 20 grams per day, the risk was non-significantly reduced. Adjustment for various potential confounders did not materially alter these findings.

When Cys homozygotes were examined, ORs for smokers were higher than those for non-smokers in one study[16], lower in one study[20], and comparable in one study[17]. One study[5] estimated similar ORs for current and ever smokers, but did not include never smokers. Heavier smokers had a

higher risk of lung cancer than lighter smokers in two studies[6,13], although in one of these[6] the ORs for all of the smoking groups were lower than for never smokers, while in the Park study[5] an OR for light smokers could not be estimated due to small numbers of subjects, but the OR for heavy smokers was significantly raised. Finally, one study[18] reported that the risk of lung cancer was significantly increased by every five years of smoking, and by every five grams of tobacco smoked per day in subjects using less than 20 grams per day. In heavier smokers, the risk was reduced for every five grams smoked per day. Again, adjustment did not substantially alter these results.

4.6 Conclusions

These findings are suggestive of a positive relationship between the Cys/Cys genotype and lung cancer risk, with 10 of the 14 studies reporting a higher frequency of this genotype in the case group, a difference that reached statistical significance in three of the studies and was of borderline significance in a third. The evidence for subjects with the Ser/Cys genotype was equivocal, with seven studies reporting a higher risk, which was statistically significant in two studies, and five studies finding a lower frequency of lung cancer in these individuals, that reached statistical significance in one study after adjustment. There were too few studies reporting on the lung cancer risk associated with the overall frequency of the Cys allele to draw any firm conclusions, and only one study reported on polymorphisms in exon 1 of the OGG1 gene.

Due partly to the small number of studies presenting results, no clear pattern emerges when the risk of lung cancer according to OGG1 genotype is stratified by smoking status and/or intensity.

Some weaknesses in the studies were noted, particularly a tendency in some studies for the age distribution to vary between the cases and the controls, and a failure by most of the studies to consider more than a very few potentially confounding factors.

5. Overall conclusions

Fourteen studies examined polymorphisms in the OGG1 gene with regard to the risk of lung cancer. Seven of the 12 studies that examined lung cancer risk in relation to the Ser/Cys genotype found it was raised in these individuals, while 10 of the 13 studies that considered lung cancer incidence in Cys homozygotes reported an increased risk. Meta-analysis of the results for this genotype suggested a significantly raised risk of lung cancer. Although a few of the studies reported results separately for subjects with differing smoking habits, this did not help to clarify the picture. There were too few studies reporting on the relationship between lung cancer and the overall prevalence of the Cys allele, or polymorphisms in exon 1 of this gene, for any firm conclusions to be drawn. Most of the studies only adjusted for a very few potential confounders, and there were also problems regarding age differences between cases and controls in several of the studies.

Table 1: Risk of lung cancer incidence in relation to OGG1 genotype

Ref.	Author (Country)	Year[a]	Cases/ controls	Genotype[b]	Odds ratios[c]	Sig[d]	Adjustment factors[e]
11	Kohno (Japan)	1998	45/42	Ser/Cys	0.89 (0.35-2.29)[f]	NS	None
				Cys/Cys	1.34 (0.41-4.43)[f]	NS	None
				All Cys	1.01 (0.42-2.42)[f]	NS	None
12	Ishida (Japan)	1999	128/268	Allele 2[g]	1.33 (0.62-2.85)	NS	A,S,SH
				Allele 3	2.60 (1.10-6.12)	p<0.03	A,S,SH
13	Sugimura (Japan)	1999	241/197	Ser/Cys	0.80 (0.52-1.21)	NS	None
					0.64 (0.39-1.06)	NS	A,SH
				Cys/Cys	1.13 (0.63-2.02)	NS	None
					1.31 (0.65-2.62)	NS	A,SH
8	Wikman (Germany)	2000	105/105	Cys/Cys	2.20 (0.41-11.79)	NS	None
				All Cys	0.72 (0.42-1.27)	NS	None
14	Ito (Japan)	2002	138/241	Ser/Cys	1.02 (0.63-1.67)	NS	None
					1.06 (0.64-1.76)	NS	A,S
				Cys/Cys	0.85 (0.46-1.56)	NS	None
					0.81 (0.44-1.52)	NS	A,S
15	Le Marchand[h] (Hawaii)	2002	298/405	Ser/Cys	0.70 (0.50-1.10)	NS	A,CPD,D, R,S,SD,SS
				Cys/Cys	2.10 (1.20-3.70)	p<0.05	A,CPD,D, R,S,SD,SS
16	Sunaga (Japan)	2002	198/152	Ser/Cys	1.33 (0.80-2.23)	NS	A,S,SH
				Cys/Cys	0.90 (0.48-1.70)	NS	A,S,SH
1	Lan (China)	2004	118/109	Ser/Cys	1.96 (1.10-3.57)	p=0.02	A,PY,S
				Cys/Cys	1.85 (0.83-4.11)	NS	A,PY,S
				Cys allele	1.93 (1.12-3.34)	p=0.02	A,PY,S
5	Park (USA)	2004	179/358	Ser/Cys	1.90 (1.30-2.80)	p<0.05	None
					1.90 (1.20-2.90)	p<0.05	A,PY,S
				Cys/Cys	4.10 (1.70-10.20)	p<0.05	None
					3.80 (1.40-10.60)	p<0.05	A,PY,S
6	Hung (Czech Republic/ Hungary/Poland/ Romania/Russia/ Slovakia)	2005	2155/2163	Ser/Cys	0.95 (0.82-1.09)	NS	A,C,PY,S
				Cys/Cys	1.34 (0.95-1.88)	NS	A,C,PY,S
17	Kohno (Japan)	2006	1097/394	Ser/Cys	1.20 (0.90-1.60)	NS	None
					1.20 (0.90-1.60)	NS	A,H,PY,S
				Cys/Cys	1.40 (1.00-2.00)	p=0.03	None
					1.50 (1.00-2.10)	p=0.04	A,H,PY,S
18	Sorensen (Denmark)	2006	431/796	Ser/Cys	1.04 (0.80-1.35)	NS	None
					1.16 (0.83-1.62)	NS	SD,SI,SS
				Cys/Cys	1.18 (0.63-2.21)	NS	None
					1.05 (0.51-2.16)	NS	SD,SI,SS
19	Zienolddiny (Norway)	2006	326/386	Ser/Cys	1.45 (0.90-2.33)	NS	A,PY,S
				Cys/Cys	1.64 (1.06-2.52)	p<0.05	A,PY,S
3	De Ruyck (Belgium)	2007	110/110	Ser/Cys	0.58 (0.33-1.02)	NS	None
					0.51 (0.27-0.95)	p<0.05	A,PY,S
				Cys/Cys	0.61 (0.13-2.82)	NS	None
					0.50 (0.10-2.51)	NS	A,PY,S

a Year of publication
b Using Ser/Ser individuals as the reference group
c 95% confidence interval shown in brackets where available
d NS = not significant ($p \geq 0.05$)
e Abbreviations used for confounders:
A = age, C = country, CPD = cigarettes per day, D = dietary factors, H = hospital, PY = pack-years of smoking, R = race, S = sex, SD = smoking duration, SH = smoking history, SI = smoking intensity, SS = smoking status
f Estimated from data given
g Relates to polymorphisms in exon 1 of hMMH/OGG1 gene
h Results were given separately for Caucasians (Ser/Cys: OR 0.6 , 95% CI 0.3-1.2; Cys/Cys: OR 1.6, 95% CI 0.5-6.1), Japanese (Ser/Cys: OR 0.8, 95% CI 0.4-1.6; Cys/Cys: OR 2.0, 95% CI 0.9-4.6) and Hawaiians (Ser/Cys: OR 1.1, 95% CI 0.4-3.2; Cys/Cys: OR 3.6, 95% CI 1.0-11.9)

Table 2: Results of meta-analysis for the risk of lung cancer in relation to OGG1 polymorphisms

Genotype	No. of studies[a]	Heterogeneity Chisquared, p	Odds ratio (95% confidence interval) Fixed effects model	Random effects model	Notes
Ser/Cys	12	28.8, p=0.002	1.04 (0.94-1.14)	1.08 (0.90-1.29)	Least adjusted
	12	29.8, p=0.002	1.03 (0.94-1.14)	1.07 (0.89-1.30)	Most adjusted
	6	19.3, p=0.002	1.02 (0.91-1.14)	1.04 (0.79-1.38)	Caucasians, least adjusted
	6	18.2, p=0.003	1.01 (0.90-1.14)	1.05 (0.77-1.42)	Caucasians, most adjusted
	7	7.84, NS	1.12 (0.93-1.33)	1.11 (0.90-1.38)	Asians, least Adjusted
	7	10.11, NS	1.11 (0.92-1.33)	1.09 (0.84-1.41)	Asians, most adjusted
Cys/Cys	13	15.3, NS	1.39 (1.19-1.63)	1.40 (1.16-1.69)	Least adjusted
	13	14.3, NS	1.41 (1.19-1.66)	1.40 (1.16-1.69)	Most adjusted
	7	7.51, NS	1.50 (1.19-1.88)	1.53 (1.15-2.04)	Caucasians, least adjusted
	7	6.70, NS	1.46 (1.15-1.84)	1.47 (1.12-1.92)	Caucasians, most adjusted
	7	5.30, NS	1.26 (1.01-1.57)	1.26 (1.01-1.57)	Asians, least Adjusted
	7	5.93, NS	1.31 (1.04-1.66	1.31 (1.04-1.66)	Asians, most adjusted
All Cys alleles	3	6.59, NS	1.16 (0.81-1.65)	1.13 (0.59-2.18)	

a Number of studies does not add up because study by {LEMARC2002} included data for both Caucasian and Asian populations

NS $p \geq 0.05$

Table 3: Overall prevalence of genotypes of the OGG1 polymorphism

Population	No. of cases	Prevalence of genotypes[a]			No. of controls	Prevalence of genotypes[a]		
		Ser/Ser	Ser/Cys	Cys/Cys		Ser/Ser	Ser/Cys	Cys/Cys
Total[b]	5441	2720 (50.0)	2072 (38.1)	649 (11.9)	5458	2963 (54.3)	2012 (36.9)	474 (8.7)
Caucasians	3432[c]	2158 (62.9)	1085 (31.6)	189 (5.5)	4077[c]	2514 (61.7)	1346 (33.0)	209 (5.1)
Asians	1934[c]	547 (28.3)	956 (49.4)	431 (22.3)	1285[c]	420 (32.7)	618 (48.1)	246 (19.1)

a Number (percent)
b Subjects in study by {ISHIDA1999} not included, as different polymorphism was studied
c Do not add up to total as Hawaiians in study by {LeMarc2002} not included

Table 4: Effect of stratification by smoking variables on lung cancer risk according to OGG1 genotype

Ref.	Author (year[a])	Smoking variable	Genotype[b]	Odds ratios[c]	Adjustment factors[d]
13	Sugimura (1999)	<800 cigarette-years	Ser/Cys	0.74 (0.39-1.42)	None
				0.74 (0.38-1.43)	A
			Cys/Cys	1.09 (0.48-2.46)	None
				0.97 (0.42-2.25)	A
		800+ cigarette-years	Ser/Cys	0.63 (0.31-1.26)	None
				0.63 (0.31-1.26)	A
			Cys/Cys	1.65 (0.50-5.46)	None
				1.73 (0.52-5.77)	A
14	Ito (2002)	Never smokers	Ser/Cys	1.36 (0.71-2.62)	A, S
			Cys/Cys	1.00 (0.46-2.36)	A, S
		Ex-smokers	Ser/Cys	0.56 (0.15-2.06)	A, S
			Cys/Cys	0.35 (0.08-1.60)	A, S
		Current smokers	Ser/Cys	0.76 (0.25-1.63)	A, S
			Cys/Cys	0.87 (0.27-2.76)	A, S
16	Sunaga (2002)	Non-smokers	Ser/Cys	1.95 (0.74-5.17)	A, S
			Cys/Cys	0.52 (0.15-1.78)	A, S
		Smokers	Ser/Cys	1.11 (0.60-2.08)	A, S
			Cys/Cys	1.15 (0.53-2.50)	A, S
5	Park (2004)	Light smokers	Ser/Cys	1.30 (0.50-3.40)	None
				1.30 (0.50-3.70)	A, PY, S
			Cys/Cys	Not available	-
		Heavy smokers	Ser/Cys	1.90 (1.10-3.30)	None
				2.00 (1.10-3.50)	A, PY, S
			Cys/Cys	7.00 (1.50-32.10)	None
				8.10 (1.70-39.10)	A, PY, S
		Current smokers	Ser/Cys	2.00 (0.90-4.30)	None
				2.10 (0.90-5.10)	A, PY, S
			Cys/Cys	5.60 (0.70-48.60)	None
				5.70 (0.60-52.10)	A, PY, S
		Ever smokers	Ser/Cys	1.80 (1.10-2.70)	None
				1.70 (1.10-2.80)	A, PY, S
			Cys/Cys	5.50 (1.70-17.70)	None
				4.90 (1.50-16.10)	A, PY, S
6	Hung (2005)	Never smokers	Ser/Cys	1.02 (0.69-1.52)	A, C, S
			Cys/Cys	1.69 (0.81-3.52)	A, C, S
		Light smokers	Ser/Cys	1.02 (0.66-1.56)	A, C, S
			Cys/Cys	1.03 (0.39-2.76)	A, C, S
		Moderate smokers	Ser/Cys	0.94 (0.76-1.17)	A, C, S
			Cys/Cys	1.26 (0.72-2.18)	A, C, S
		Heavy smokers	Ser/Cys	0.85 (0.65-1.12)	A, C, S
			Cys/Cys	1.42 (0.69-2.94)	A, C, S
17	Kohno (2006)	Non-smokers	Ser/Cys	1.50 (1.00-2.20)	None
				1.30 (0.80-2.00)	A, H, S
			Cys/Cys	1.50 (0.90-2.40)	None
				1.30 (0.80-2.30)	A, H, S
		Smokers	Ser/Cys	1.10 (0.80-1.60)	None
				1.10 (0.70-1.70)	A, H, S, SD
			Cys/Cys	1.40 (0.90-2.20)	None
				1.60 (1.00-2.60)	A, H, S, SD
18	Sorensen (2006)	Duration, per 5 years	Ser/Ser	1.57 (1.42-1.74)	None
				1.50 (1.34-1.69)	IF, IV, SI, SS
			Ser/Cys	1.50 (1.33-1.69)	None
				1.46 (1.29-1.67)	IF, IV, SI, SS
			Cys/Cys	1.55 (1.20-2.00)	None
				1.47 (1.13-1.91)	IF, IV, SI, SS

Intensity ≤ 20g/day, per 5g/day	Ser/Ser	2.32 (1.84-2.91)	None
		2.07 (1.57-2.73)	IF, IV, SI, SS
	Ser/Cys	1.87 (1.48-2.37)	None
		1.66 (1.26-2.18)	IF, IV, SI, SS
	Cys/Cys	3.26 (1.41-7.54)	None
		3.77 (1.24-6.21)	IF, IV, SI, SS
Intensity >20g/day, per 5g/day	Ser/Ser	0.93 (0.78-1.11)	None
		1.05 (0.84-1.30)	IF, IV, SI, SS
	Ser/Cys	0.94 (0.77-1.15)	None
		0.99 (0.80-1.22)	IF, IV, SI, SS
	Cys/Cys	0.55 (0.17-1.74)	None
		0.38 (0.12-1.27)	IF, IV, SI, SS

[a] Year of publication
[b] Using Ser/Ser individuals as the reference group
[c] 95% confidence interval shown in brackets where available
[d] Abbreviations used for confounders:
A = age C = country H = hospital IF = intake of fruit IV = intake of vegetables
PY = pack-years of smoking S = sex SD = smoking dosage SI = smoking intensity SS = smoking status

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