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Interactions between the *OGG1* Ser326Cys polymorphism and intake of fruit and vegetables in relation to lung cancer

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Abstract

The enzyme 8-oxoguanine glycosylase 1 (OGG1) repairs oxidatively damaged DNA and a polymorphism in the *OGG1* gene (Ser[326]Cys) has been associated with lung cancer. We examined associations between the polymorphism and intake of fruits and vegetables and smoking in the development of lung cancer, by genotyping blood samples from 431 lung cancer cases and 796 comparison persons, which were identified within a prospective cohort on 57,000 cohort members. We found no overall association between the *OGG1* polymorphism and lung cancer. There was a statistically significant interaction between the polymorphism and dietary intake of vegetables, with a 54% decrease in lung cancer risk per 50% increase in vegetable intake among homozygous Cys[326]Cys carriers and no decrease in risk among carriers of Ser[326]Ser or Ser[326]Cys. The same tendency was seen in relation to intake of fruit. There were no statistically significant interactions between the *OGG1* polymorphism and smoking.

Keywords: *OGG1, lung cancer, vegetables, tobacco smoke*

Abbreviations: *ROS, reactive oxygen species; OGG1, 8-oxoguanine glycosylase; 8-oxoG, 8-oxo-7,8-dihydroguanine; DCH, Diet; Cancer and Health; IRR, incidence rate ratios; CI, confidence interval*

Introduction

Tobacco smoking causes the vast majority of lung cancer cases. Tobacco smoke contains numerous carcinogenic substances and is a major source of reactive oxygen species (ROS) and pro-oxidants [6]. ROS can react with DNA, which results in oxidatively generated damage that probably plays a critical role in the carcinogenesis [16]. Dietary antioxidants and genetic differences in DNA repair genes may in part explain why only a minor part of smokers actually develop lung cancer.

OGG1 encodes the DNA repair enzyme 8-oxoguanine glycosylase 1 (OGG1), which excises 8-oxo-7,8-dihydroguanine (8-oxoG) and other oxidatively damaged DNA bases. The variant allele of the polymorphism *OGG1* Ser[326]Cys has been weakly associated with the risk of lung cancer [4,7,8], though not all studies can confirm this [24]. Studies have indicated that the OGG1-[326]Cys enzyme has a lower

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glycosylase activity than OGG1-^{326}Ser. When *E. coli fpg*-, which is defective in 8-oxoG repair, was complemented with a plasmid encoded *OGG1*, the OGG1-^{326}Cys enzyme repaired 8-oxoG less efficiently than the corresponding OGG1-^{326}Ser did [11]. Two studies where oxidatively generated damage was induced in human lymphocytes/peripheral blood mononuclear cells found more DNA damage in cells with the *OGG1* Cys^{326}Cys compared with cells with Ser^{326}Cys or Ser^{326}Ser genotypes [3,15]. Another study found that OGG1 Cys^{326}Cys had a lower capacity than OGG1 Ser^{326}Ser to prevent G:C to T:A transversions in a human lung cell line [26]. On the other hand, no significant difference in the 8-oxoG-specific lyase activity was found among the three *OGG1* genotypes in *in vitro* studies of the endogenous activity in human colorectal carcinoma tissue [12] or lymphocytes [10].

Most epidemiological studies have found that a frequent consumption of fruit and vegetables reduces the risk for lung cancer [17,25]. This protective effect could partly be explained by the presence of antioxidants, which are believed to prevent oxidatively generated damage through a scavenging of ROS. A protective effect of antioxidants in the diet could, thus, theoretically be stronger in persons with an impaired endogenous antioxidant defence, such as persons with an impaired OGG1. Though not statistically significant, a study surprisingly suggested that intake of vegetables had a protective effect against lung cancer only in carriers of the wild-type *OGG1* allele, whereas it had no protective effects in homozygous variant allele carriers, Cys/Cys [14].

A few studies have investigated whether the effect of tobacco smoking on lung cancer is stronger among carriers with the variant allele of *OGG1* than among carriers of the wild-type allele [7,14]. The results indicated no difference in effect.

In the present study, we investigated the relationship between the *OGG1* Ser^{326}Cys polymorphism and risk of lung cancer and interactions between the polymorphism and intake of fruit and vegetables and smoking in the development of lung cancer.

Materials and methods

Study group

Diet, Cancer and Health (DCH) is a Danish prospective follow-up study. Invited to participate were 160,725 individuals aged 50–64 years of which 57,053 individuals with no previous cancer diagnosis were recruited [22]. At enrolment (1993–1997), detailed information on diet and smoking habits were collected and blood was sampled and stored at −150°C. All participants gave informed consent. The Danish ethical committee approved the study.

Data on diet intake was obtained from a 192-item, validated food frequency questionnaire [19,21]. Forty-four of the items exclusively concerned intake of fruits, vegetables or fruit/vegetable juice. In addition, information about vegetable intake was derived from other questions as parts of recipes. Briefly, the participants were asked to report their average intake of different food and beverage items over the past 12 months within 12 possible categories ranging from never to ≥8 times/day. To adjust for a possible overestimation, the questions on frequency of intake of several specific types of fruits and vegetables were complemented by three additional questions on the overall intake of fruits, raw vegetables/salad and cooked vegetables. The intake of each type of fruit and vegetable was weighted in accordance with the answers to these additional questions. Daily intakes of specific foods and nutrients were calculated for each participant using the software program Food Calc [13], using specially developed standardized recipes and portion sizes.

Among the 57,053 persons recruited to the DCH study, 565 were later notified to the Danish Cancer Register with a cancer diagnosed before the date of enrolment and were, therefore, excluded. Among the 56,488 individuals with no previous cancer diagnosis, we identified 431 cases with lung cancer in the files of the nationwide Danish Cancer Registry [20], diagnosed between 1994 and 2003, with baseline data for smoking status, smoking duration, dietary intake of fruit and vegetables, available blood samples and for whom the *OGG1* genotype status was determined successfully. From among the cohort members, we randomly selected 431 men and 365 women with the required baseline date. This sub-cohort was used as comparison group.

Determination of OGG1 genotype

DNA was isolated from frozen lymphocytes as described [18]. Generally, 100 μg DNA was obtained from 10^7 lymphocytes. The *OGG1* Ser^{326}Cys polymorphism (rs#1052134) was genotyped by end point reading on a Sequence Detection System ABI 7500 (Applied Biosystems, Nærum, Denmark) as described using 20 ng DNA in 5 μl reactions [23]. Controls were included in each run and repeated genotyping of a random 10% subset yielded 100% identical genotypes. The genotype of 256 of the lung cancer patients have been reported previously where they were compared to a comparison group matched on sex and smoking duration [24].

Statistical methods

The data were sampled according to the case-cohort design and the unweighted case-cohort approach was used for analyses [2]. Incidence rate ratios (IRR) for lung cancer were estimated by the Cox proportional hazards model, stratified according to sex. Age was the

time axis. We calculated two-sided 95% confidence intervals (CI) and *p*-values based on robust estimates of the variance–covariance matrix [1] and Wald's test of the Cox regression parameter, that is, on the log rate ratio scale.

We estimated IRR for the heterozygous and the homozygous variant, respectively compared with the homozygous wild type. These estimates were supplemented with a trend test where the IRR is assumed to increase (or decrease) log-linearly with the number of variant type alleles. We estimated relationships between the *OGG1* genotype and lung cancer for all lung cancers combined and for each major histological type of lung cancer (small cell, adenocarcinoma and squamous cell). Moreover, we analyzed data separately for each gender and of two age groups (50–60 years and 61–70 years). The frequency distribution of the *OGG1* polymorphism was checked among the sub-cohort to verify Hardy–Weinberg equilibrium.

Interactions between the *OGG1* genotype and each of the environmental factors, smoking and dietary intake of fruit and vegetables, were analysed by estimating linear effects of each environmental factor on lung cancer risk among exposed individuals. The hypothesis of a linear association was evaluated using a linear spline with three boundaries, placed at the quartiles among cases, as covariates in the Cox model [5]. The linearity was evaluated graphically and by a numerical test using the likelihood ratio test statistic to compare the model assuming linearity with the linear spline model. Only for smoking intensity, we found a statistically significant deviation from linearity, showing a positive association with lung cancer by tobacco up to approximately 20 g/day and no further change in lung cancer risk for higher smoking intensities. Therefore, interactions between smoking intensity and the *OGG1* genotype were analysed separately for intensity below and above 20 g/day. Smoking intensity was calculated as the average of the self-reported smoking intensity for the age intervals 20–29, 30–39, 40–49 and 50–59 years and the other environmental factors refer to the time of enrolment into the cohort study. The linear effect of each environmental factor was estimated for each genotype (homozygous wild-type, heterozygous type and homozygous variant-type) and we tested the null-hypothesis that the effect of the environmental factor was the same for the three genotypes.

Results

The proportion of current smokers and the smoking intensity was substantially higher and the duration of smoking was substantially longer, among cases than among the sub-cohort members and the median dietary intake of fruit and vegetables was lower among cases than among sub-cohort members (Table I). The intake of fruits ranged from 0.1 g/day to 1451 g/day and the intake of vegetables ranged from 11 g/day to 693 g/day. The vegetables most frequently consumed are carrots, peas, leeks, cauliflower and broccoli and the fruits most frequently consumed are apples, oranges, bananas, pears and peaches. The genotype distribution among sub-cohort members was in Hardy–Weinberg equilibrium. Among the cases, 19% had a diagnosis of small cell cancer, 32% of adenocarcinoma, 23% of squamous cell carcinoma and the remaining 26% of other or unknown histological type.

There was no overall association between the polymorphism in *OGG1* and the risk of lung cancer (Table II). Women carrying the variant Cys/Cys genotype seemed to be at higher lung cancer risk than women carrying only the wild-type allele of the polymorphism, whereas among men the Cys variant allele seemed to be protective, although this was not statistically significant for either women or men (Table II). Furthermore, there was no statistically significant difference in the effect of the *OGG1* polymorphism between men and women ($P = 0.37$ in the crude analysis and $P = 0.16$ in the adjusted analysis). There were no significant effects of the genotype in either of the two age groups 50–60 years or 60–70 years or in the histological sub-groups of squamous cell adenoma, adenocarcinoma and small cell carcinoma (results not shown).

Table I. Smoking characteristics and intake of fruit and vegetables in the study population.

	Cases ($N = 431$)		Sub-cohort ($N = 796$)	
	Number (%)	Median (5–95% percentiles)	Number	Median (5–95% percentiles)
Smoking status				
Never	17 (4%)		267 (34%)	
Former	68 (16%)		248 (31%)	
Current	346 (80%)		281 (35%)	
Smoking duration (years)		40 (10–49)		20 (0–45)
Smoking intensity (g/day)		18 (5–35)		10 (0–32)
Alcohol (g/day)		16 (0.2–82)		12 (0.7–63)
Vegetables (g/day)		125 (34–332)		164 (49–365)
Fruit (g/day)		122 (16–486)		175 (28–549)

Table II. Effects of *OGG1* genotype on risk for lung cancer.

			Crude			Adjusted[†]		
	Genotype, *OGG1*	Cases/sub-cohort	IRR[‡]	CI[¶]	*P*[c]	IRR[‡]	CI[¶]	*P*[s]
Total[⋆]	Ser/Ser	254/479	1		0.61	1		0.50
	Ser/Cys	155/284	1.04	0.80–1.35		1.16	0.83–1.62	
	Cys/Cys	22/33	1.18	0.63–2.21		1.05	0.51–2.16	
Sex								
Men	Ser/Ser	143/254	1		0.57	1		0.49
	Ser/Cys	79/162	0.88	0.62–1.25		0.98	0.63–1.51	
	Cys/Cys	8/15	1.01	0.41–2.50		0.55	0.18–1.72	
Women	Ser/Ser	111/225	1		0.23	1		0.06
	Ser/Cys	76/122	1.27	0.86–1.87		1.48	0.88–2.48	
	Cys/Cys	14/18	1.35	0.57–3.21		1.95	0.77–4.94	

⋆ Stratified by sex. † Adjusted for smoking duration, average smoking intensity and smoking status (never, ever). ‡ IRR = Incidence rate ratio. ¶ CI = 95% Confidence interval. [c]Trend test.

We found a statistically significant interaction between the *OGG1* polymorphism and dietary intake of vegetables, with a 54% decrease in lung cancer risk per 50% increase in vegetable intake among homozygous carriers of the variant allele and no decrease in risk among carriers of the other genotypes (Table III). The interaction was statistically significant in both the crude analysis and in the analysis adjusted by smoking duration, smoking intensity, smoking status and intake of fruit. Though statistically insignificant, the same tendency was seen in relation to intake of fruit with a 42% decrease in lung cancer risk per 50% increase in fruit intake among homozygous carriers of the variant allele and no statistically significant decrease in risk among carriers of the other genotypes. We found no statistically significant interactions between the *OGG1* polymorphism and smoking duration or smoking intensity.

Discussion

There was no overall effect of the *OGG1* polymorphism on the risk for lung cancer. Intake of vegetables was associated with a decrease in cancer risk among homozygous carriers of the variant *OGG1* allele.

The present case-cohort study is population-based and both cases and their comparison group were selected from the same cohort, which together with complete follow-up of the participants minimizes the risk for selection bias. For all participants, information on smoking habits and dietary intake of fruit and vegetables was obtained at enrolment, i.e. before the lung cancer diagnosis for cases, which minimizes the risk for differential misclassification of these exposure variables between the cases and the comparison group. The inclusion of 431 cases and a comparison group of 796 individuals provided a relatively high-statistical power. However, an even larger sample size may be required to achieve statistically significant results for the possible gene–fruit interaction indicated by the present study.

Oxidative damages are produced continuously in the DNA as a result of endogenous oxidative stress and exposure to chemical carcinogens. If OGG1 is dysfunctional, these mutations could be left unrepaired. Some studies have suggested that the amino acid change in OGG1 affects the catalytic properties of the enzyme [11,15,26], though it has not been confirmed in all studies [10,12]. One reason to the different results could be that the polymorphism is tightly linked to other possible functional polymorphisms in *OGG1*. Another explanation as suggested by Lee et al. 2005, [15] is that the $Cys^{326}Cys$ genotype is deficient in the repair of oxidatively generated DNA damage only under conditions of cellular oxidative stress. Two recent, large epidemiological studies have indicated that the *OGG1* homozygous variant genotype is weakly associated with the risk of lung cancer: a case-control study with 2000 cases (OR = 1.34; 95% CI: 0.95–1.88) and a meta-analysis with 3500 cases (OR = 1.24; 95% CI: 1.01–1.53) [7,8]. Although our results indicate no overall effect of the *OGG1* polymorphism on the risk for lung cancer, they are not contradictive to the two larger studies as the IRRs found in our study lie within these studies confidence intervals. Together with the biological findings, this suggests that the *OGG1* Cys genotype is associated with a lowered OGG1 glycosylase activity.

In the present study, intake of vegetables was more protective against lung cancer among carriers of the Cys/Cys genotype than among carriers of the Ser/Ser and Ser/Cys genotype. After adjustment for smoking and intake of fruit, the protective effect of vegetables was only evident among Cys/Cys carriers. The same tendency was seen in relation to intake of fruit. Vegetables and fruits have a high content of antioxidants, e.g. vitamin C and E. A likely explanation for the results is that a high intake of dietary antioxidants inhibits oxidative stress that could otherwise lead to an increased number of mutations in persons with a dysfunctional OGG1. In persons carrying an *OGG1* wild-type allele, OGG1 will repair

Table III. *OGG1* genotype-specific effects of dietary intake of vegetables and fruit, and smoking on the risk for lung cancer.

Effect variable		Genotype, *OGG1*	Cases *N* (%)	Sub-cohort *N* (%)	Crude			Adjusted⋆		
					IRR†	CI‡	*P*¶	IRR†	CI‡	*P*¶
Intake of:										
Vegetables	Per 50% increase	Ser/Ser	254 (59)	479 (60)	0.87	0.80–0.96	0.05	1.07	0.95–1.21	0.02
		Ser/Cys	155 (36)	284 (36)	0.79	0.69–0.89		1.00	0.85–1.17	
		Cys/Cys	22 (5)	33 (4)	0.43	0.23–0.81		0.46	0.25–0.84	
Fruit	Per 50% increase	Ser/Ser	254 (59)	479 (60)	0.81	0.75–0.87	0.31	0.92	0.84–1.02	0.37
		Ser/Cys	155 (36)	284 (36)	0.80	0.73–0.88		0.91	0.81–1.01	
		Cys/Cys	22 (5)	33 (4)	0.59	0.39–0.88		0.58	0.30–1.11	
Smoking:										
Duration	Per 5 years	Ser/Ser	247 (60)	326 (62)	1.57	1.42–1.74	0.75	1.50	1.34–1.69	0.91
		Ser/Cys	145 (35)	181 (34)	1.50	1.33–1.69		1.46	1.29–1.67	
		Cys/Cys	22 (5)	22 (4)	1.55	1.20–2.00		1.47	1.13–1.91	
Intensity										
≤ 20 g/day	Per 5 g/day	Ser/Ser	157 (59)	240 (63)	2.32	1.84–2.91	0.15	2.07	1.57–2.73	0.18
		Ser/Cys	92 (35)	125 (33)	1.87	1.48–2.37		1.66	1.26–2.18	
		Cys/Cys	16 (6)	16 (4)	3.26	1.41–7.54		3.77	1.24–6.21	
> 20 g/day	Per 5 g/day	Ser/Ser	89 (61)	81 (58)	0.93	0.78–1.11	0.67	1.05	0.84–1.30	0.27
		Ser/Cys	52 (36)	53 (38)	0.94	0.77–1.15		0.99	0.80–1.22	
		Cys/Cys	5 (3)	6 (4)	0.55	0.17–1.74		0.38	0.12–1.27	

Data stratified by sex.

⋆ Adjusted for smoking duration, average smoking intensity and smoking status (never, ever), intake of fruit, and intake of vegetables. † IRR = Incidence rate ratio. ‡ CI = 95% Confidence interval. ¶ Test for interaction.

mutations caused by an oxidative stress and thus, be independent of the protective effect of antioxidants. Another study of *OGG1*–vegetable interactions in relation to lung cancer [14] surprisingly found a tendency of a protective effect of vegetables among carriers of the Ser wild-type allele and not among Cys/Cys carriers in a study of 298 lung cancer cases and 405 controls. They conclude that the result is unexpected and could be due to chance. The study participants lived in Hawaii and it is possible that differences in metabolism and other DNA repair genes as well as differences in dietary vegetables and fruits could explain some of the discrepancy between the two studies. Larger similar studies are needed before any firm conclusions can be drawn.

The sequencing of the human genome has revealed that single nucleotide polymorphisms are very common and it is possible that the apparent interaction between intake of vegetables and fruits and the *OGG1* polymorphism is caused by a co-segregating functional *OGG1* polymorphism or that the *OGG1* polymorphism is part of a haplotype. However, the *OGG1* Ser^{326}Cys polymorphism is the only missense polymorphism with an allele frequency above 0.03 in the *OGG1* gene [9] and there are no characterized genes in the proximity of *OGG1* that can explain the observed results. Another possibility is that a polymorphism in the *OGG1* promoter affecting the expression of *OGG1* mRNA could be responsible for the observed effects. However, the activity of OGG1-^{326}Cys and OGG1-^{326}Ser has been compared in a study where the OGG1 enzyme only differed at the 326 position [11]. The study complemented an *E. coli* defective in 8-oxoG repair (*fpg*-) with a plasmid encoding *OGG1* and the results showed that the OGG1-^{326}Cys enzyme had a lower glycosylase activity than OGG1-^{326}Ser [11]. This suggests an effect of the amino acid substitution.

Three studies have looked at the polymorphism in lymphocytes/mononuclear cells of healthy volunteers [3,10,15]. Two studies with, respectively 20 and 72 individuals found that after an induction of DNA damage, there was a higher level of DNA damage measured by the comet assay in lymphocytes/mononuclear cells with the Ser/Cys or Cys/Cys genotype than in cells with the Ser/Ser genotype [3,15]. A third study measured the OGG1 activity in lymphocytes from 34 individuals and found no difference in activity between the three genotypes [10]. In the last study, DNA damage was not induced in the lymphocytes and a likely explanation to the differences between the studies is that the OGG1-^{326}Cys enzyme is deficient of repair only under conditions of oxidative stress [15]. Many compounds present in tobacco smoke are known to induce oxidative stress. In our study, there were only 4% never smoking cases and it seems, therefore, likely that the OGG1-^{326}Cys enzyme has been deficient in repair in most of the cases. However, similar to previous studies [7,14], we did not find any *OGG1*–smoking interactions in relation to lung cancer. An explanation could be other protective agents or enzymes, such as antioxidants or other DNA repair enzymes.

In summary, the present study showed an interaction between intake of vegetables and the *OGG1* polymorphism in relation to lung cancer, which suggests that susceptible persons might lower their risk of lung cancer by increasing their intake of vegetables and fruits.

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