HANSEN, R.; SÆBØ, M.; SKJELBRED, C.F.; NEXØ, B.A.; HAGEN, P.C.; BOCK, G., LOTHE, I.M.B.; JOHNSON, E.; AASE, S.; HANSTEEN, I.L.; VOGEL, U.; KURE, E.H.;
GPX Pro198Leu and OGG1 Ser326Cys polymorphisms and risk of development of colorectal adenomas and colorectal cancer.

This is an electronic version of an article published in
Cancer Letters, Vol. 229, No. 1, 2005, p. 85-91,
available online at: http://dx.doi.org/10.1016/j.canlet.2005.04.019

GPX Pro198Leu and *OGG1* Ser326Cys polymorphisms and risk of development of colorectal adenomas and colorectal cancer

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Abstract

Little is known about genetic risk factors for colorectal cancer. We assessed the association between polymorphisms in two genes involved in DNA repair of oxidative stress, *GPX* and *OGG1*, and risk of colorectal carcinoma or adenomas. We studied 166 cases with adenocarcinoma, 974 with adenomas and 397 controls recruited from the Norwegian cohort NORCCAP. No associations were found between the polymorphism *GPX* Pro[198]Leu and risk of colorectal adenomas or carcinomas. Carriers of the variant allele *OGG1* Ser[326]Cys polymorphism had a lowered risk of colorectal cancer, OR = 0.56 (95% confidence interval 0.33–0.95), while no association were found with risk of adenomas. This indicates that a low repair capacity of oxidative DNA damage may not be a risk factor for development of colorectal adenomas or carcinoma.

Keywords: Dysplasia; Oxidative stress; Population based; Carcinoma

1. Introduction

Reactive oxygen species (ROS) are constantly generated in vivo from cell metabolism as well as from extracellular processes. When accumulated in the cell they may cause cancer by generation of oxidative DNA damage [1,2]. The DNA damage

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induced by ROS includes oxidised bases, formation of DNA adducts and strand breaks and DNA protein cross-links. Oxidative DNA damage may be counteracted by the enzymes glutathione peroxidases (GPX), selenium-dependent antioxidant enzymes that reduce H_2O_2 and lipid peroxides/hydroperoxides by oxidizing glutathione, and 8-oxoguanine glycosylase 1 (OGG1) that removes 8-oxo-7,8-dihydroguanine (8-oxoG) directly from oxidatively damaged DNA by glycosylase and apurinic lyase activity [3–5].

Chronic intestinal inflammation is a known risk factor for developing colorectal cancer [6]. Mice with disrupted *GPX1* and *GPX2* genes are more susceptible to colon cancer induced by inflammation caused by bacterial colonization [7] than are wild type mice. In humans, the selenium dependent activation of *GPX* ^{198}Leu mutant enzyme is lower than for the *GPX* ^{198}Pro wild type enzyme [8]. In recent studies, heterozygous and homozygous carriers of the variant *T*-allele (giving rise to the Pro to Leu substitution) of the *GPX* Pro^{198}Leu polymorphism were at 1.8-fold higher risk (95% confidence interval 1.2–2.8) and 2.3-fold higher risk (95% confidence interval 1.3–3.8), respectively, of lung cancer compared to homozygous carriers of the wild type allele [9]. Homozygous carriers of the variant allele were at 1.9-fold higher risk of breast cancer (95% confidence interval 1.0–3.6) [8], while in a large study by Cox et al. no association was found between polymorphism in *GPX1* Pro^{198}Leu and risk of breast cancer [10]. No association was found between the *GPX* Pro^{198}Leu polymorphism and risk of basal cell carcinoma [11].

An increased load of ROS has been shown to cause higher levels of 8-oxoG in human colorectal carcinoma compared with non-tumorous counterparts [1].

OGG1 knock out mice have higher 8-oxoG content in the DNA [2,12] and higher rates of G:C to T:A transversions than wild type mice [2,13,14]. More than 95% of G:C to T:A transversions has been found to be suppressed in the lung cancer cell line H1299, overexpressing either *OGG1* Ser^{326}Ser or Cys^{326}Cys [12]. However, *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 and thereby a lower capacity to prevent mutagenesis by 8-oxoG in vivo [12,15], while no significant difference in the 8-oxoG-specific lyase activity was found among the three genotypes (Ser^{326}Ser, Ser^{326}Cys, and Cys^{326}Cys) in in vitro studies of the endogenous activity in human colorectal carcinoma tissue [1] and lymphocytes [16]. In recent studies, heterozygous and homozygous carriers of the variant *G*-allele of the *OGG1* Ser^{326}Cys polymorphism were at 1.6-fold higher risk of orolaryngeal cancer in smokers (95% confidence interval 1.0–2.6) and 4.1-fold higher risk (CI 1.3–1.8), respectively [17]. A study has shown a 2.0- to 3.6-fold higher risk of lung cancer in Japanese and Hawaiian homozygous carriers (95% confidence interval 0.9–4.6 and 1.0–11.9 respectively) and a 1.6-fold higher risk in Caucasian (95% confidence interval 0.5–6.1) [18], while other studies found no significant associations between the *OGG1* Ser^{326}Cys polymorphism and risk of lung cancer among Caucasians [19,20] and Japanese [21]. No association was found between the *OGG1* Ser^{326}Cys polymorphism and colorectal cancer among Koreans [22] or breast cancer among Caucasians [23].

We hypothesized that the polymorphisms *GPX* Pro^{198}Leu and *OGG1* Ser^{326}Cys could be associated with the risk of colorectal cancer. To investigate this possibility, we studied 166 cases with developed adenocarcinoma, 974 cases with developed adenomas grouped in three developmental stages of dysplasia (mild, moderat, severe) according to cytological criteria [24] and 397 controls, all recruited from the Norwegian Colorectal Cancer Prevention cohort in the KAM project.

2. Subjects and methods

2.1. Subject population

The KAM biobank (Kolorektal cancer, Arv og Miljø) is based on the screening group of the Norwegian Colorectal Cancer Prevention study (The NORCCAP study) in the county of Telemark [25]. A total of 20,780 men and women, age distribution 50–64 years, drawn randomly from the population registries in Oslo (urban) and the county of Telemark (mixed urban and rural) were invited to have a flexible sigmoidoscopy screening examination with or without (1:1) an additional faecal occult blood test (FOBT). Seven hundred and seventy-seven individuals were excluded according to exclusion criteria [25].

Table 1
Distributions of gender and age among controls and cases with colorectal adenocarcinomas and adenomas

	Controls		Cases adenomas, all		Cases adeno-carcinoma	
	No.	%	No.	%	No.	%
No. of subjects	397		974		166	
Sex[a]						
Male	158	39.9	600	61.6	92	55.7
Female	238	60.1	374	38.4	73	44.3
Age[b]						
Mean (SD)	54.2 (3.6)		57.1 (4.9)		67.5 (10.7)	
<60	357	91.1	665	68.3	42	25.5
>60	35	8.9	309	31.7	123	74.5

[a] There are significant differences in the number of males and females among the control group and the case groups, $P<10^{-4}$ (test for comparison of two proportions).
[b] There are significant difference in age among the control group and the case groups, $P<10^{-4}$ (Mann–Whitney test).

The KAM biobank, consists of 170 colorectal cancer cases (still collecting samples), 1044 cases with adenomas, and 400 controls. The colorectal cancer cases of the KAM biobank consist of patients operated on at Telemark Hospital and Ulleval University Hospital in Oslo. The KAM study is approved by the Ethical Committee and the Norwegian Data Registry. In the present study, we have analyzed cases with adenocarcinomas (166), cases with adenomas (974) and controls that were polyp free in the screened region of the colon (397). The distribution of gender and age among cases with colonic adenocarcinomas and adenomas and controls are shown in Table 1.

2.2. Sample collection and DNA extraction:

EDTA blood samples were collected from both cases and controls and stored at −20 °C. All of the participants completed a questionnaire on demographic factors, dietary habits, and health status; exercise level, smoking habits and occupation.

Genomic DNA was isolated from blood samples according to standard procedures [26] with minor modifications. In brief, whole blood samples (anticoagulated) was mixed with a threefold volume of lysis buffer (155 mM NH_4Cl, 10 mM $KHCO_3$, 1 mM EDTA, pH 7.4) and incubated at 4 °C for at least 30 min. The lysate was then centrifuged, and the pellet of intact leukocytes was resuspended in 10 ml SE buffer (75 mM NaCl, 24 mM EDTA, pH 8.0), 500 μl SDS (20%) and 50 μl Proteinase K (20 mg/ml), and incubated overnight at 40 °C. After digestion 3.5 ml of 6 M NaCl was added to the lysate and the mixture was shaken vigorously and centrifuged to pellet the cellular proteins. DNA in the supernatant was then precipitated with two volumes of absolute ethanol, washed in 70% ethanol and resuspended in TE buffer (10 mM Tris, 0.1 mM EDTA, pH 7.5).

2.3. Real time-polymerase chain reaction

The *GPX* $Pro^{198}Leu$ (rs#1050450) and *OGG1* $Ser^{326}Cys$ (rs#1052134) polymorphisms were genotyped by real-time PCR on a Sequence Detection System ABI 7700 (Applied Biosystems, Nærum, Denmark) as described [9]. Controls were included in each run and repeated genotyping of a random 10% subset yielded 100% identical genotypes. The *OGG1* genotyping of samples from one control and one case with adenocarcinoma was unsuccessful.

2.4. Statistical analysis

MiniTab Statistical Software, Release 13.1 Xtra (Minitab Inc.) was used for the statistic calculations. All data are age adjusted. The data were not adjusted for sex since the incidence ratio of colorectal cancer between the genders is 1.1 in Norway [27].

3. Results

The genotype distributions were in Hardy–Weinberg equilibrium in the control groups for both

Table 2
Distribution of *GPX* Pro[198]Leu and *OGG1*Ser[326]Cys genotypes and development of colorectal adenocarcinomas and adenomas

Genotypes		No. of controls	No. of cases	OR (95% CI)
GPX Pro[198]Leu				
Adenocarcinoma	*CC* (Pro/Pro)	196	82	1[a]
	CT (Pro/Leu)	163	68	1.14 (0.66–1.95)
	TT (Leu/Leu)	38	16	0.62 (0.24–1.60)
Adenomas, all	*CC* (Pro/Pro)	196	496	1[a]
	CT (Pro/Leu)	163	398	0.92 (0.71–1.19)
	TT (Leu/Leu)	38	87	0.81 (0.53–1.26)
OGG1 Ser[326]Cys				
Adenocarcinoma	*CC* (Ser/Ser)	208	101	1[a]
	CG (Ser/Cys)	164	55	0.56 (0.32–0.97)
	GG (Cys/Cys)	24	9	0.57 (0.17–1.83)
Adenomas, all	*CC* (Ser/Ser)	208	530	1[a]
	CG (Ser/Cys)	164	376	0.92 (0.72–1.19)
	GG (Cys/Cys)	24	68	1.14 (0.68–1.90)

[a] The *CC* genotype served as reference category.

polymorphisms. The allelic frequencies of the variant allele for *GPX* Pro[198]Leu (0.300 for the control group) and *OGG1* Ser[326]Cys (0.268 for the control group) were similar to the frequencies of alleles found in two previous Scandinavian studies [9,11].

There was no association between *GPX* Pro[198]Leu and risk of colorectal adenocarcinoma and adenomas (Table 2). Furthermore, there was no trend in the association between genotype and stages of dysplasia of the adenomas (Table 3).

The variant *G*-allele of *OGG1* Ser[326]Cys was associated with a lower colorectal cancer rate with OR of 0.56 (95% confidence interval 0.32–0.97) and 0.57 (95% confidence interval 0.17–1.83) for heterozygous and homozygous carriers, respectively. Heterozygous and homozygous carriers of the variant allele as

Table 3
Distribution of *GPX* Pro[198]Leu and *OGG1* Ser[326]Cys genotypes and developmental stages of colorectal adenomas

Genotypes		No. of controls	No. of cases	*OR* (95% *CI*)
GPX Pro[198]Leu				
Severe dysplasia	*CC* (Pro/Pro)	196	32	1[a]
	CT (Pro/Leu)	163	24	0.92 (0.51–1.67)
	TT (Leu/Leu)	38	8	1.01 (0.41–2.45)
Moderate dysplasia	*CC* (Pro/Pro)	196	411	1[a]
	CT (Pro/Leu)	163	327	0.89 (0.69–1.16)
	TT (Leu/Leu)	38	72	0.80 (0.51–1.26)
Mild dysplasia	*CC* (Pro/Pro)	196	54	1[a]
	CT (Pro/Leu)	163	47	1.02 (0.64–1.64)
	TT (Leu/Leu)	38	7	0.57 (0.23–1.42)
OGG1 Ser[326]Cys				
Severe dysplasia	*CC* (Ser/Ser)	208	37	1[a]
	CG (Ser/Cys)	164	22	0.69 (0.38–1.25)
	GG (Cys/Cys)	24	5	1.07 (0.36–3.14)
Moderate dysplasia	*CC* (Ser/Ser)	208	426	1[a]
	CG (Ser/Cys)	164	326	0.98 (0.76–1.28)
	GG (Cys/Cys)	24	52	1.05 (0.61–1.78)
Mild dysplasia	*CC* (Ser/Ser)	208	67	1[a]
	CG (Ser/Cys)	164	28	0.51 (0.30–0.86)
	GG (Cys/Cys)	24	11	1.76 (0.76–4.09)

[a] The *CC* genotype served as reference category.

a group had a lowered risk of colorectal cancer with an OR = 0.56 (95% confidence interval 0.33–0.95). There was no association between *OGG1* $Ser^{326}Cys$ and risk of adenomas (Table 2). Furthermore there was no trend in the association between genotype and the different stages of dysplasia in the adenomas (Table 3).

There was no effect of the polymorphisms on the risk estimates for neither adenocarcinoma nor adenomas when dividing the case groups by gender or various age groups (data not shown).

4. Discussion

We found no association between *GPX* $Pro^{198}Leu$ polymorphism and risk of development of colorectal adenomas or adenocarcinomas. The lack of association between *GPX* $Pro^{198}Leu$ polymorphism and the development of colorectal adenocarcinomas may reflect that gene–environment interactions are required, for which the environmental exposures are not present or limited in Norway. Alternatively, that *GPX* is not important for development of adenocarcinomas or adenomas. We found that carriers of the variant *OGG1*-^{326}Cys allele had lower risk of development of adenocarcinoma than homozygous carriers of the wild-type allele. The polymorphism was not associated with risk of development of adenomas.

The design of this study is relatively strong because the controls were recruited from the same cohort. It cannot be excluded that the present findings are due to chance, especially since the *P*-value is close to 0.05. However, the size of the study group of colorectal cancer cases is comparable to most of the other published studies [19,21,22,28,29]. Recently, Starinsky et al. made a larger study on colorectal cancer but did not include polymorphisms in *OGG1* and *GPX* [30]. For the adenocarcinomas, we had an 80% chance of detecting an OR of two among homozygous and heterozygous carriers of the variant allele at a significance level of 5% assuming an allele frequency of 0.3. For adenomas, we had an 80% chance of detecting an OR of 1.5 among homozygous and heterozygous carriers of the variant allele at a 5% significance level assuming an allele frequency of 0.3.

Carriers of the Cys allele had a lowered risk of colorectal cancer with an OR = 0.56 (95% confidence interval 0.33–0.95). The same tendency may be seen in studies of lung cancer patients [20,29] and for gastric cancer [28], although the associations were not statistically significant. In the study by Ito et al. [29], the sex-age adjusted odds ratio for heterozygous and homozygous carriers of the variant G-allele of the *OGG1* $Ser^{326}Cys$ polymorphism were 1.06 (95% confidence interval 0.64–1.76) and 0.81 (95% confidence interval 0.44–1.52) respectively, and in the study by Hanaoka et al. [28] odds ratio for heterozygous and homozygous carriers of the variant G-allele were 1.01 (95% confidence interval 0.52–1.93) and 0.85 (95% confidence interval 0.57–1.26), respectively. In a recent population-based Danish study by Vogel et al. [20] homozygous carriers of the variant G-allele had a rate ratio (RR) of lung cancer of 0.65 (95% confidence interval 0.30–1.41).

In a recent study by Kim et al. [22], *OGG1* $Ser^{326}Cys$ polymorphism was not overall associated with risk of colorectal cancer, but carriers of the variant allele were at increased risk of colorectal cancer in combination with frequent meat consumption, smoking or drinking. Our results do not support this observation. Meat consumption and smoking is rather frequent in the present Norwegian population [31]. On the other hand, the very different diet in Korea and Norway may result in different gene–environment interactions in the two populations.

OGG1 knock out mice have no marked tumor predisposition [2,32] even though they had increased accumulation of 8-oxoG in the DNA over time compared with wildtype mice. Mice with inactivated *MYH*, another oxidative damage DNA repair gene, do not accumulate DNA 8-oxoG [33], but when both genes, *MYH* and *OGG1,* are inactivated 66% of the mice are predisposed to tumors [32]. This indicates that both *OGG1* and *MYH* are involved in prevention of oxidative DNA damage in mice, and that the effect of a deficiency in *OGG1* could be compensated by *MYH*. Overall, this indicates that *OGG1* is not a major cancer susceptibility gene.

The studied polymorphism in *OGG1* results in a Ser to Cys amino acid substitution. There are several indications in the literature that the *OGG1*^{326}-Cys-mutant has a somewhat lower glycosylase activity than the wild-type *OGG1*^{326}-Ser enzyme [12,15].

If *OGG1* knock out in mice are not predisposed to cancer, the partial decrease of the enzyme activity may also be without a biological effect.

We found that *OGG1* $Ser^{326}Cys$ polymorphism is not associated with risk of colorectal adenomas regardless of degree of dysplasia (Table 3) and is protective against the risk of colorectal cancer. There are two possible explanations. First, a lowered DNA repair capacity of oxidative DNA damage and lowered oxidative stress defense may not be a risk factor for development of colorectal cancer or adenomas. Increased oxidative stress and oxidative damage may lead to increased apoptosis and thereby prevent accumulation of mutations. Alternatively, we could be detecting an effect of linkage to another protective gene variant in the vicinity of *OGG1* $Ser^{326}Cys$. It is striking that we found an effect between the polymorphism and development of colorectal cancer but not on development of adenomas. A similar conclusion was drawn in a study by Tranah et al. [34]. The polymorphisms *XRCC2* $Arg^{188}His$ and *XRCC3* $Thr^{241}Met$ in the double-strand break repair genes *XRCC2* and *XRCC3* have been associated to risk of cancer [35–37], but Tranah et al. found no association to risk of colorectal adenomas. To our knowledge the KAM study is the first study including both colorectal carcinoma and colorectal adenomas in studying effects of polymorphisms in DNA repair genes.

In conclusion, we found that *GPX* $Pro^{198}Leu$ polymorphism was not associated with risk of developing colorectal cancer or adenomas, and that the variant allele of *OGG1* $Ser^{326}Cys$ polymorphism was protective against development of colorectal cancer. The polymorphism was not associated with risk of development of adenomas from mild to severe dysplasia.

Acknowledgements

This study was supported by Danish Research Council (Grant number 2052-03-0016), the Norwegian Cancer Society (Grant numbers 51024/001 and E01-0851001), Telemark University College (Grant number 22069) and the Norwegian Colorectal Cancer Prevention (NORCCAP) study (Grants from the Norwegian Cancer Society and the Department of Health and Social Affairs) and with the aid of EXTRA funds from the Norwegian Foundation for Health and Rehabilitation (2001/2/0110).

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