Polymorphisms in the oxidative stress genes, superoxide dismutase, glutathione peroxidase and catalase and risk of non-Hodgkin's lymphoma

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Background and Objectives. The risk of non-Hodgkin's lymphoma (NHL) has been associated with inflammation. One possible mechanism may involve oxidative stress as reactive oxygen species (ROS) can generate pro-inflammatory signals. Anti-oxidant enzymes including superoxide dismutase, glutathione peroxidase and catalase protect against the harmful effects of ROS. Genetic variation in the genes coding for these enzymes (*SOD2, GPX1*, and *CAT*, respectively) alters ROS production and therefore may provide a mechanism for the relationship between inflammation and NHL.

Design and Methods. Data from two population-based, case-control studies of lymphoma in the UK (700 cases and 915 controls) and USA (1593 cases and 2517 controls) were pooled to analyze polymorphisms in genes involved in the oxidative stress response (*SOD2* Val16Ala, *CAT* C-262T and *GPX1* Pro197Leu).

Results. No associations were observed between *SOD2* Val16Ala and *CAT* C-262T and total NHL, diffuse large-B cell lymphoma or follicular lymphoma. However, when we looked at marginal zone lymphoma, a specific subtype of lymphoma characterised by inflammation, we found that homozygosity for the *SOD2* 16Ala allele was associated with a decreased risk among UK study participants. The *GPX1* 197Leu allele was weakly associated with NHL and follicular lymphoma.

Interpretation and Conclusion. Analysis of genetic variation in oxidative stress genes in two lymphoma case-control studies suggests a possible role for oxidative stress in the risk of NHL. The risk modification is seen predominantly for marginal zone lymphomas which frequently arise in the context of chronic inflammation. However, in order to clarify the role of oxidative stress in the etiology of NHL analyses of additional polymorphisms and haplotypes in these and other genes involved in the oxidative stress response are needed.

Key words: non-Hodgkin's lymphoma, oxidative stress, antioxidants, single nucleotide polymorphisms.

Haematologica 2006; 91:1222-1227

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Chronic inflammation has been associated with a risk of non-Hodgkin's lymphoma (NHL).[1-3] Although the mechanisms underlying this association are uncertain, it is known that inflammation is associated with increased oxidative stress caused by the generation of reactive oxygen species (ROS). In addition to inducing oxidative DNA damage that can lead to neoplasia,[4-6] ROS propagate pro-inflammatory cytokines including interleukin-1 which stimulates B cells to produce antibodies that initiate signaling for B-cell activation. Furthermore, a number of diseases characterized by a chronic B-cell activated phenotype, including arthritis, systemic lupus erythematosus, and Sjögren's syndrome have all been associated with an increased risk of NHL.[3,7-9] Cells are protected from the harmful effects of ROS by anti-oxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase. Superoxide dismutase catalyses the dismutation of superoxide radicals (a major form of ROS) into hydrogen peroxide that glutathione peroxidase and catalase break down into water.[10-13] Thus, an imbalance in anti-oxidant mechanisms may influence cellular sensitivity to free radical damage and alter susceptibility to disease. This may be particularly important in lymphocytes and their precursors in which chronic inflammation increases the risk of neoplastic changes, as is typified by the marginal-zone group of lymphomas which have been associated with chronic inflammation.

Associations between oxidative stress and cancer have generally been investigated by measuring DNA damage, free radicals and anti-oxidants. Both increased superoxide dismutase activity[14,15] and decreased glutathione peroxidase activity[16] have previously been reported in conjunction with lymphoproliferative disorders. However, greater

insight into the relationship between oxidative stress and disease susceptibility may be gained by studying functional polymorphisms in genes that control levels of cellular oxidative damage. Candidate pathways include anti-oxidant and DNA repair mechanisms which are modulated by individual genetic variation.

A number of polymorphisms in the genes coding for superoxide dismutase, catalase and glutathione peroxidase (*SOD2*, *CAT* and *GPX1,* respectively) have been identified and associated with cancer risk.[17-22] In the mitochondrial targeting sequence for *SOD2* a T-C transition in the -9 position occurs resulting in a valine to alanine substitution (Val16Ala).[23] This substitution alters protein structure which affects localization and transport of the superoxide dismutase enzyme into mitochondria where it exerts its antioxidant effects; the valine allele has been associated with decreased enzyme transport, reduced defense against superoxide radicals and increased risk of cancer.[17-19] Several polymorphisms in *GPX1* have been identified, including Pro197Leu, which has been associated with lung cancer,[20] breast cancer[21] and cardiovascular disease.[24] The CAT C-262T polymorphism alters transcription factor binding and basal expression of catalase in red blood cells[25] and has been associated with an increased risk of breast[22] and pancreatic cancer. These and other polymorphisms that impair anti-oxidative capacity may influence NHL risk by increasing levels of pro-inflammatory cytokines leading to increased B-cell activation.

To test this hypothesis we pooled data from two population-based studies, one conducted in the UK and the other in the USA, to examine the association between single nucleotide polymorphisms (SNP) in genes involved in anti-oxidative mechanisms (*SOD2* V16A, rS4880; *GPX1* P197L, rS1050450; *CAT* C-262T, rS1001179) and NHL subtypes.

Design and Methods

Study population

Full details of both lymphoma case-control studies have been previously described.[26-29] Briefly, in the UK study, patients aged 18-64 years diagnosed with NHL between 1998 and 2001 in certain areas of the country were identified. For each case, one individually sex-, age- and ethnicity- matched control was randomly selected from the same primary care practice list as the case. In the US, NHL patients aged 21-74 years who were residents of one of six San-Francisco Bay Area counties when newly diagnosed from 1988 to 1993 were identified through the Northern California Cancer Center's rapid case ascertainment. Controls were identified by random-digit dial and supplemented by random sampling of Health Care Financing Administration lists for participants aged 65 years or older and were matched to patients by sex, in 5-year age groups and county of residence. Participants from both studies provided informed consent to interview, collection and analysis of biological samples and, in the UK, access to their medical records. NHL histological subtype and grade were coded to the Working Formulation (US study) or the International Classification for Diseases for Oncology, Third Edition (ICD-O3) (UK study) (Fritz *et al*., 2000)[30] with diagnoses grouped to reflect comparable ICD-O3 categories for analysis.

Participation rates were over 70% for cases and controls in both the UK and USA studies. The present analysis includes 2293 cases (700 UK; 1593 US) with a confirmed diagnosis of NHL and 3432 controls (915 UK; 2517 US). DNA was available from 928 and 1446 HIV-negative, white non-Hispanic cases and controls, respectively. There were no significant differences in age, sex or diagnostic sub-group between those individuals who did and did not have DNA available for genotyping. The distributions by histological subtype, sex, age and study site for genotyped NHL cases are shown in Table 1. The majority of NHL cases with available genotyping data had either diffuse large B-cell lymphomas (41%) or follicular lymphomas (35%). However, DNA was also available from a number of patients with other histological NHL subtypes including mantle cell lymphoma (n=23), marginal-zone lymphoma (MZL) (n=54) and T-cell lymphoma (n=26) in the UK study and Burkitt-like lymphomas (n=2), diffuse mixed lymphomas (n=20), diffuse small lymphomas (n=18), lymphoblastic lymphoma (n=1), mycosis fungoides (n=10) and small lymphocytic lymphoma (n=47) in the US study. In addition 18 not otherwise specified diagnoses of NHL were included in the analyses.

DNA extraction and genotyping

DNA was extracted and quantified as previously described.[26-29] Genotyping was performed using Taqman®-based assays supplied by Applied Biosystems (ABI) (Applied Biosystems, Foster City, CA, USA) on a GeneAmp PCR System 7700 ABI Sequence Detection System using the following protocol: 95°C for 10 minutes, then 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. Primer and probe sets used were 5'-TCGAAGCCCTGCTGTCTCA'-3 (forward primer), 5'-CGAGACAGCAGCACTGCAA-3' (reverse primer), VIC- AGGGCCCAGCTGT (C-specific allele probe), 6FAM-AGGGCTCAGCTGTG (T-specific allele probe) for rs1050450 (*GPX1* P197L); 5'-GGCCTGAAGGATGCTGATAACC-3' (forward primer), 5'-CTCTGGCCCAGCAATTGGA-3' (reverse primer), VIC-CCCGGGATAGCCG (C-allele specific probe) and 6FAM-CCCGGAATAGCCG (T-allele specific probe) for rs1001179 (*CAT* C-262T); and 5'-GGCTGTGCTTTCTCGTCTTCA-3' (forward primer), 5'-TCTGCCTGGAGCCCAGATAC-3' (reverse primer), VIC-

Table 1. Distribution by histological subtype, sex and age for genotyped HIV-negative non-Hodgkin's lymphoma (NHL) cases and controls by study site.

Variable	*USA San Francisco NHL Study*		*UK NHL study*		*Both sites combined*	
	Cases n (%)	*Controls n (%)*	*Cases n (%)*	*Controls n (%)*	*Cases n (%)*	*Controls n (%)*
Total	308 (100)	684 (100)	620 (100)	762 (100)	928 (100)	1446 (100)
Histological subtype[a]						
DLBCL	98 (32)	–	283 (46)	–	381 (41)	–
Follicular lymphoma	112 (36)	–	214 (34)	–	326 (35)	–
Other	98 (32)	–	123 (20)	–	221 (24)	–
Sex						
Males	174 (62)	463 (73)	319 (51)	409 (54)	493 (53)	872 (60)
Females	134 (38)	221 (27)	301 (49)	353 (46)	435 (47)	574 (40)
Age						
<45	48 (16)	231 (34)	87 (14)	159 (21)	135 (15)	390 (27)
45-<55	60 (19)	125 (18)	222 (36)	255 (33)	282 (30)	380 (26)
55-<65	93 (30)	102 (15)	311 (50)	348 (46)	404 (43)	450 (31)
65+	107 (35)	226 (33)	0 (0)	0 (0)	107 (12)	226 (16)
Mean age±SD	57.5±11.7	52.9±14.7	53.6±8.4	52.0±9.6	52.4±9.8	54.9±12.3

[a]*DLBCL, diffuse large B-cell lymphoma; other NHL cases with genotyping data from the UK lymphoma study include 23 –mantle cell lymphomas, 54 marginal-zone lymphomas, 26 T-cell lymphomas and 20 NHL not otherwise specified and from the US San Francisco NHL study include 2 Burkitt-like lymphomas, 20 diffuse mixed lymphomas, 18 diffuse small lymphomas, a lymphoblastic lymphoma, 10 mycosis fungoides, 47 small lymphocytic and 9 NHL not otherwise specified.*

CCAAAACCGGAGCCA (T-specific allele probe) and 6FAM-CCCAAAGCCGGAGC (C-specific allele probe) for rs4880 (*SOD2* V16A).

Statistical analysis

Hardy-Weinberg equilibrium for genotype frequencies was assessed in controls using standard χ^2 procedures. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from pooled data using unconditional logistic regression and adjusted for age, sex and study region. The likelihood ratio test was used to test for trend and for interaction between SNP. Results were considered statistically significant for two-sided p-values of $p<0.05$. All analyses were conducted using STATA version 8.2 (College Station, TX, USA).[31]

Results

Pooled genotype distributions for cases and controls are shown in Table 2. Genotype frequencies for controls were in Hardy-Weinberg equilibrium and, for *SOD2* and *CAT*, were similar to those previously reported in Caucasian populations.[25,32] The frequencies for *GPX1* P197L in the two control groups differed between the US (Pro/Pro 50%, Pro/Leu 40%, Leu/Leu 10%) and UK populations (Pro/Pro 58%, Pro/Leu 35%, Leu/Leu 7%) (p=0.007), although the study-specific odds ratios for NHL risk were comparable (*data not shown*).

No significant differences in the distribution of *SOD2* V16A or *CAT* C-262T polymorphisms were observed between cases and controls in pooled analyses. However, modestly increased risk estimates were observed with *GPX1* heterozygotes and homozygote variants, respectively, for all NHL (OR 1.24, 95% CI 1.04-1.48; OR 1.28, 95% 0.94-1.75), follicular lymphoma (OR 1.34; 95% CI 1.04-1.73; OR 1.29 95% CI 0.82-2.03) and diffuse large B-cell lymphoma (OR 1.24; 95% CI 0.97-1.58; OR 1.30 95% CI 0.85-1.99).

In the UK study, data were further analysed to examine the risk associated with the well-defined NHL subtype MZL (n=54 cases) which is known to have an inflammatory origin. No associations were observed with respect to the *CAT* or *GPX1* polymorphisms. However, for the *SOD2* V16A polymorphism, differences in the distribution of the genotype groups between cases (25.5% Val/Val; 60.8% Val/Ala; 13.7% Ala/Ala) and controls (23.9% Val/Val; 49.1% Val/Ala; 27.0% Ala/Ala) were observed such that homozygosity for the alanine allele was associated with a non-significant decreased risk of MZL (OR 0.45, 95% CI 0.60-1.12).

Stratification by sex for both the pooled and single study analyses revealed no differences in risk estimates. There was no evidence of gene-gene interactions for all NHL (*data not shown*).

Discussion

We examined associations between polymorphisms in genes involved in the oxidative stress response and risk of lymphoma in two population-based, case-control studies. Whereas our findings do not support a major

Table 2. Number of cases and controls, adjusted odds ratios[a] and 95% confidence intervals by subtype of non-Hodgkin's lymphoma for *SOD2* 16VA, *GPX1* P197L and *CAT* C-262T - UK and US pooled study data.

	Controls n (%)	Cases n (%)					
		NHL[b]	OR (CI)	DLBCL	OR (CI)	FL	OR (CI)
Total	1446 (100)	928 (100)	–	381 (100)	–	326 (100)	–
SOD2 16VA							
VV	358 (25)	211 (24)	1.00	97 (26)	1.00	65 (20)	1.00
VA	713 (49)	463 (51)	1.07 (0.87-1.33)	179 (49)	0.90 (0.68-1.19)	175 (55)	1.33 (0.97-1.82)
AA	371 (26)	229 (25)	1.01 (0.79-1.29)	91 (25)	0.85 (0.61-1.18)	81 (25)	1.17 (0.81-1.67)
VV v VA/AA	1071 (74)	674 (75)	1.05 (0.86-1.28)	276 (75)	0.88 (0.68-1.15)	240 (75)	1.27 (0.94-1.72)
sna	4	25		14		5	
CAT C-262T							
CC	867 (60)	554 (61)	1	218 (59)	1	205 (63)	1
CT	498 (35)	298 (33)	0.93 (0.77-1.11)	128 (34)	1.02 (0.79-1.30)	104 (32)	0.86 (0.66-1.12)
TT	72 (5)	57 (6)	1.22 (0.84-1.77)	25 (7)	1.35 (0.83-2.19)	16 (5)	0.82 (0.45-1.49)
CC v CT/TT	570 (40)	355 (39)	0.97 (0.81-1.15)	153 (41)	1.06 (0.84-1.34)	120 (37)	0.86 (0.67-1.10)
sna	9	19		10		3	
GPX1 P197L							
PP	773 (54)	453 (49)	1	186 (49)	1	156 (48)	1
PL	551 (38)	387 (42)	**1.24 (1.04-1.48)**[d]	158 (42)	1.24 (0.97-1.58)	142 (44)	**1.34 (1.04-1.73)**[f]
LL	120 (8)	81 (9)	1.28 (0.94-1.75)	33 (9)	1.30 (0.85-1.99)	28 (8)	1.29 (0.82-2.03)
PP v PL/LL	671 (46)	468 (51)	**1.25 (1.05-1.48)**[e]	191 (51)	1.25 (0.99-1.58)	170 (52)	**1.33 (1.04-1.70)**[g]
sna	2	7		4		0	
GPX1 P197L-UK	762 (100)	620 (100)		283 (100)		214 (100)	
PP	438 (58)	311 (51)	1	137	1	106 (50)	1
PL	268 (35)	259 (42)	**1.35 (1.07-1.69)**[h]	122	**1.44 (1.08-1.92)**[j]	91 (42)	**1.40 (1.02-1.93)**[l]
LL	55 (7)	43 (7)	1.12 (0.74-1.72)	20	1.17 (0.68-2.03)	17 (8)	1.35 (0.75-2.43)
PP v PL/LL	323 (42)	302 (49)	**1.31 (1.06-1.62)**[i]	142	**1.40 (1.06-1.84)**[k]	108 (50)	**1.39 (1.02-1.89)**[m]
sna	1	7		4			
GPX1 P197L-USA	684 (100)	308 (100)		98 (100)		112 (100)	
PP	335 (49)	142 (46)	1	49 (50.0)	1	50 (45)	1
PL	283 (41)	128 (43)	1.08 (0.81-1.45)	36 (36.7)	0.87 (0.55-1.38)	51 (45)	1.21 (0.79-1.85)
LL	65 (10)	38 (12)	1.42 (0.90-2.24)	13 (13.3)	1.42 (0.73-2.79)	11 (10)	1.16 (0.57-2.36)
PP v PL/LL	348 (51)	166 (54)	1.14 (0.87-1.51)	49 (50.0)	0.97 (0.63-1.49)	62 (55)	1.20 (0.80-1.80)
sna	1	0		0		0	

[a]Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression and were adjusted for age and sex; [b]NHL: non-Hodgkin's lymphoma, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, MZL: marginal zone lymphoma. sna: sample not amplified; [d]p=0.018; [e]p=0.010; [f]p=0.024; g p=0.020; [h]p=0.009; [i]p=0.014; [j]p=0.013; [k]p=0.017; [l]p=0.040; [m]p=0.035.

role for *GPX1*, *SOD2* or *CAT* in the etiology of NHL a modest increase in the risk for all NHL was observed with the *GPX1* 197Leu allele. Reduction in glutathione peroxidase activity has previously been reported in patients with lymphopoliferative disorders[16] and more recently has been associated with poor prognosis in diffuse large B-cell lymphomas[33] suggesting a possible role for this enzyme in the etiology and outcome of lymphoma.

Manganese superoxide (MnSOD) expression has also been linked with a poor prognosis of diffuse large B-cell lymphoma.[33] Although no association was observed between the *SOD2* polymorphism and diffuse large B-cell lymphoma in the present study, Wang *et al.*[32] recently reported an increased risk of this type of lymphoma in carriers of the *SOD2* 16Ala allele in a large US multicenter case control study. However, neither study found evidence of an association between *SOD2* and all cases of NHL.[32] In the UK population, fewer than expected cases of MZL were homozygous for the *SOD2* 16Ala allele such that the ala/ala genotype was associated with a decreased risk of MZL. The precise mechanism by which homozygosity for the alanine allele might result in a decreased risk for MZL is not clear. However, it may be a consequence of the improved defense against ROS conferred by the presence of alanine in the mitochondrial targeting sequence of *SOD2*. Indeed, it has been shown that the alanine form of superoxide dismutase is up to 40% more efficiently localized to the mitochondrial matrix, the major site for cellular metabolism and production of ROS, compared to the valine form.[34] Furthermore, four-fold higher levels of superoxide dismutase protein expression and activity have been observed for the alanine variant.[35] Although the NHL classification method used in the UK did not take into account of tumor site, it is likely that our population included a high proportion of gastric MZL given that gastric tissue is a more common site of MZL[36] than the

thyroid or salivary gland. Gastric MZL is associated with *Helicobacter pylori* infection which induces a chronic inflammatory response resulting in ROS and subsequent DNA damage. The lower than expected frequency of the ala/ala genotype observed in MZL is consistent with this variant having an impact on the response to infection due to its predicted increased ability to break down ROS. However, further clarification of the functional significance of the polymorphism is required since the effect on MnSOD expression is not clear.[23]

Although these findings were based on a limited number of cases (n=54), they are consistent with a previous observation of an association between inflammatory response genes and risk of MZL.[36] In this earlier study polymorphisms in interleukin-1 (*IL-1*) and glutathione S-transferase (*GST*) genes, which regulate the inflammatory response to infection and exhibit anti-oxidant properties were analyzed in a series of patients with gastric MZL. The authors concluded that risk of gastric MZL was influenced by interindividual variation in inflammatory response and anti-oxidative capacity, particularly through combined effects of the *IL-1 RN* and *GST T1* genotypes.[37]

The differential associations observed in this study between polymorphisms and NHL subtypes reflect the complexity of the disease. NHL is often referred to as a single entity when in fact it represents a group of independent lymphomas distinguished by histological subtypes that are likely to have differing etiologies. Thus, by analyzing data according to histological subtype, we may gain a greater understanding of the pathways involved in disease initiation and progression. We recently observed a similar effect by subtype for genetic polymorphisms in the folate metabolic pathway and risk of NHL subtypes.[38,39]

Our data provide some support for the hypothesis that polymorphisms that impair anti-oxidative capacity may influence NHL risk, with some aspects clearly warranting further investigation. In summary, further analyses of these and additional polymorphisms and haplotypes in *GPX1* and *SOD2* and other oxidative stress genes in large pooled studies that include well defined NHL subtypes will help to clarify their role in lymphomagenesis, and may provide a mechanism for the relationship between inflammation and NHL. In addition, evaluation of polymorphisms in oxidative stress response genes may provide useful screening and/or prognostic markers for lymphoma.

TJL and CFS: this individual should be designated as joint author as they have contributed equally to the work. They were involved in the design of the experimental work, data acquisition, interpretation of data, drafting the article and critical revision of the article; AS: contributed to data acquisition, analysis and interpretation of the data, drafting the article and critically reviewing the article. MSF: contributed to data acquisition, interpretation of data, article content and revision; PJA: contributed to analysis of pooled data and UK data, data interpretation and article preparation and revision; GJM: contributed to the initiation of the UK study, experimental design, data interpretation, manuscript preparation and revision; PMB: contributed to the conception and design of the US study, acquisition of data, analysis of US data, interpretation of results, drafting article, critical revision of article. RE: contributed to initiation, design and conduct of the UK study, acquisition of data, interpretation of results, critical revision of article; MTS: contributed to conception and design of the US study, experimental design acquisition of data, interpretation of results, critical revision of article; EAH: ontributed to the conception and design of the US study, acquisition of data, interpretation of results, critical revision of article. *This work was supported by the Leukaemia Research Fund of Great Britain, NIH grant numbers CA104862 (MTS), CA45614, CA89745, CA87014 (EAH), and by the National Foundation for Cancer Research (MT). We thank all consultants, hospital staff, general practitioners, and interviewees who participated in the study. The authors also declare that they have no potential conflict of interest.*

Manuscript received March 8, 2006. Accepted July 6, 2006.

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