COX1 and *COX2* Polymorphisms and Gastric Cancer Risk in a Polish Population

LIFANG HOU[1], PAOLO GRILLO[2], ZHONG-ZHENG ZHU[3], JOLA LISSOWSKA[4], MEREDITH YEAGER[5], WITOLD ZATONSKI[4], GUANSHAN ZHU[6], ANDREA BACCARELLI[2,7], STEPHEN J. CHANOCK[5,8], JOSEPH F. FRAUMENI Jr.[8] and WONG-HO CHOW[8]

[1]*Department of Preventive Medicine Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, U.S.A.;*
[2]*Epidemiology Unit, Department of Occupational, Clinical and Preventive Medicine, IRCCS "Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena", I-20122 Milan, Italy;*
[3]*Department of Pathology, No. 113 Hospital of the People's Liberation Army, Ningbo 315040, P.R. China;*
[4]*Division of Cancer Epidemiology and Prevention, Cancer Center and M. Sklodowska-Curie Institute of Oncology, 02-781 Warsaw, Poland;*
[5]*Core Genotyping Facility, Advanced Technology Center, National Cancer Institute, Gaithersburg, MD 20892, U.S.A.;*
[6]*Shanghai GeneCore Biotechnologies Co., Ltd, Shanghai 201203, P.R. China;*
[7]*EPOCA Research Center for Clinical, Occupational and Environmental Epidemiology, Department of Occupational Medicine, University of Milan, I-20122 Milan, Italy;*
[8]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20852, U.S.A.*

Abstract. *Background: Although a number of studies on the polymorphisms in COX1 and COX2 genes in association with risks for a number of cancers have been conducted, their relation to gastric cancer has not been well studied. Patients and Methods: Genotypes of several variants in both COX1 (Ex7+31 C>A and Ex10-4 G>A) and COX2 (-765 G>C, Ex10+837 T>C, Ex10-90 C>T, IVS5-275 T>G, and IVS7+111 T>C) were identified by TaqMan™ assays in 305 gastric cancer cases and 427 age- and gender-matched controls in a high-risk Polish population. Odds ratios for gastric cancer and 95% confidence intervals from unconditional logistic regression models were used to evaluate relative risks. Results: We found no statistically significant evidence that the polymorphisms tested in COX1 and COX2 are associated with gastric cancer risk. Conclusion: These results suggest that the polymorphisms examined in COX1 and COX2 do not affect the risk of gastric cancer.*

Non-steroidal anti-inflamatory drug (NSAID) use has been linked to reduced risks of several gastrointestinal cancers, including gastric cancer (1, 2). *In vivo* data have shown that NSAIDs reduce gastric tumor volume significantly in a dose-dependent manner (1). NSAIDs are known to inhibit production of COX-1 and COX-2 through both COX-dependent and -independent mechanisms (3). COX-1 is constitutively expressed in various tissues, including the stomach, while COX-2 is only expressed in response to growth factors, cytokines, tumor promoters, ionizing radiation and other carcinogens (4). COX2 dysregulation has been associated with gastric carcinogenesis by increasing angiogenesis (5), lymphatic invasion and metastasis (6) and depth of invasion (7). Furthermore, expression of the *COX2* gene increases with progression of gastric cancerous changes (8).

Single nucleotide polymorphisms (SNPs) in *COX1* and *COX2* genes have been examined in relation to risk for a number of cancers, including colorectal, breast, biliary tract, lung, esophageal, prostate, and gastric cancers, with several studies reporting an association (9-24). A potential role of promoter SNPs in *COX2* was suggested for gastric cancer in two separate population-based studies in China (18, 20). In the present study, we examined eight polymorphisms in these two genes in a population-based case–control study of gastric cancer in Warsaw, Poland.

Patients and Methods

Patients and samples. The present population-based case–control study of gastric cancer was carried out in Warsaw, Poland,

Correspondence to: Dr. Lifang Hou, Department of Preventive Medicine Feinberg School of Medicine, Northwestern University, 680 N Lake Shore Drive, Chicago, IL 60611, U.S.A. Tel: +312 503 4798, Fax: +312 908 9588, e-mail: l-hou@northwestern.edu

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between 1994 and 1996. The study population has been described in detail previously (25-27). Residents, aged 21 to 79 years and newly diagnosed with gastric cancer (ICD-O 151 or ICD-O-2 C16), were identified by collaborating physicians in each of the 22 hospitals serving the study area. All diagnoses were pathologically confirmed by study pathologists. Controls were randomly selected among Warsaw residents from a computerized registry of all legal residents in Poland and were frequency-matched to cases by gender and age in 5-year groups. The registry was updated monthly and the completeness of registration was estimated to be nearly 100%.

Detailed information on lifetime tobacco use, alcohol consumption, family history of gastric cancer, childhood living conditions, demographic background, history of selected medical conditions and medication use, lifetime occupational history and usual diet prior to 1990 was recorded during a personal interview, after written consent was obtained. Among the 464 gastric cancer patients and 480 controls identified for the study, genomic DNA was obtained from 305 (65.7%) patients and 427 (90.0%) controls (27).

Genotyping. Two SNPs in *COX1* (Ex7+31 C>A, rs5789; and Ex10-4 G>A, rs5794) and six SNPs in *COX2* (-765 G>C, rs20417; IVS5-275 T>G, rs20432; IVS7+111 T>C, rs4648276; Ex10-90 C>T, rs689470; and Ex10+837 T>C, rs5275) were tested by either TaqMan Assays (Applied Biosystems, Foster City, CA, USA) or MGB Eclipse Assays (Epoch Biosciences, Bothell, WA, USA) at the National Cancer Institute's Core Genotyping Facility. Details on assay design and conditions are available at http://snp500cancer.nci.nih.gov. Assays were validated and optimized as described in the SNP500 Cancer website (28). For each genotype, as a lab internal quality control, four human DNA controls (Coriell DNA) as well as no template controls were run with study samples. *COX2* Ex3-8 G>C (rs5277) was tested by TaqMan Assays (Applied Biosystems, Foster City, CA, USA) at Shanghai GeneCore Biotechnologies Co., Ltd, Shanghai, China. Approximately 8% blind quality control samples from 2 individuals were interspersed with the study samples, showing greater than 99% concordance for each genotype. Genotyping data for each tested SNP were successfully obtained for ≥95% of the samples.

Statistical analyses. Hardy-Weinberg equilibrium was tested for each SNP using the asymptotic Pearson's Chi-square test. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). For all genotypes, the homozygote of the common allele was used as the referent. The HaploView software was used to assess the pair-wise linkage disequilibrium (LD) between the markers within each gene (29). Haplotypes were reconstructed from genotype data by means of Phase software (Version 2.1) (http://www.stat.washington.edu/stephens/software.html). The statistical significance of a multiplicative interaction term was tested using the likelihood ratio test, comparing logistic regression models with and without the appropriate interaction term.

Further adjustment for other potential confounding variables, including family history of cancer, pack-years of cigarette smoking, dietary intake, history of gastro-esophageal reflux and use of ulcer medications did not affect the risks meaningfully. All statistical analyses were conducted using the Stata 9.0 (Stata Corporation, College Station, TX, USA) statistical package. All tests were two-sided at the 0.05 significance level.

Table I. *Gastric cancer risk and polymorphisms in COX1 and COX2 in a Polish population.*

	Cases	Controls	OR (95% CI)*	*P*-value for trend
COX1				
Ex7+31C>A, rs5789				
CC	292	402	1.00 (Referent)	
CA	13	14	1.41 (0.64-3.12)	
AA	0	0	-	0.39
Ex10-4 G>A, rs5794				
GG	317	429	1.00 (Referent)	
GA	4	3	2.06 (0.45-9.43)	
AA				
0	0	-	0.35	
COX2				
–765 G>C, rs20417				
GG	210	288	1.00 (Referent)	
GC	70	110	0.85 (0.59-1.22)	
CC	10	11	1.21 (0.5-2.96)	0.66
Ex3-8 G>C, rs5277				
GG	230	285	1.00 (Referent)	
GC	63	115	0.67 (0.47-0.97)	
CC	9	10	1.11 (0.44-2.82)	0.12
IVS5-275 T>G, rs20432				
TT	218	298	1.00 (Referent)	
TG	81	114	0.94 (0.66-1.32)	
GG	12	9	1.89 (0.77-4.67)	0.63
IVS7+111 T>C, rs4648276				
TT	221	307	1.00 (Referent)	
TC	68	105	0.89 (0.62-1.27)	
CC	10	9	1.85 (0.72-4.72)	0.83
Ex10-90 C>T, rs689470				
CC	289	399	1.00 (Referent)	
CT	19	10	2.09 (0.91-4.81)	
TT	0	0	-	0.08
Ex10+837 T>C, rs5275				
TT	137	165	1.00 (Referent)	
TC	132	202	0.77 (0.56-1.07)	
CC	35	49	0.80 (0.49-1.33)	0.18

*Adjusted for gender, age, education, smoking.

Results

All SNPs fell within the expected distributions of Hardy-Weinberg equilibrium in controls. Overall, SNPs in both genes were not significantly associated with the risk for gastric cancer (Table I). Non-significant increases in risk were observed among carriers of the *COX1*-Ex10-4 G/C genotype (OR=2.06, 95% CI=0.45-9.43), *COX2*-IVS5-275 G/G (OR=1.89, 95% CI=0.77-4.67), *COX2*-IVS7+111C/C (OR=1.85, 95% CI=0.72-4.72) and *COX2*-Ex10-90G/A (OR=2.09, 95% CI=0.91-4.81) when compared to their most common genotypes. A significant reduction in risk (OR=0.67, 95% CI=0.47-0.97) was observed in carriers of *COX2* Ex3-8 G/C genotype, but not in the homozygote

Table II. *Summary of published studies of the COX polymorphisms examined in the present study in relation to cancer risk.*

Polymorphism	Study	Location	Study design	Disease	Cases	Controls	Results
COX2	Langsenlehner *et al.* (9)	Austria	Case–control	Breast cancer	500	500	Increased
(Ex10+837T>C,	Campa *et al.* (10)	Norwegian	Case–control	Non-small cell lung cancer	250	214	Increased
rs5275)	Sakoda *et al.* (11)	Chinese	Case–control	Bile duct cancer	127	786	Increased
	Hu *et al.* (12)	Chinese	Case–control	Lung cancer	322	323	Decreased
	Gallicchio *et al.* (13)	US	Cohort	Breast cancer	91	1376	No association
	Park *et al.* (14)	Korea	Case–control	Lung cancer	582	582	No association+
	Cox *et al.* (15)	Spain	Case–control	Colorectal cancer	292	274	No association
	Sorensen (16)	Danish	Cohort	Lung cancer	265	272	No association
	Shahedi (17)	Sweden	Case–control	Prostate cancer	1378	782	No association
COX2	Campa *et al.* (10)	Norwegian	Case–control	Non-small cell lung cancer	250	214	No association
(-765 G>C,	Cox *et al.* (15)	Spain	Case–control	Colorectal cancer	292	274	No association
rs20417)	Liu *et al.* (18)	Chinese	Case–control	Gastric cancer	248	1523	No association
	Zhang *et al.* (19)	Chinese	Case–control	Esophageal cancer	1026	1270	Increased
	Zhang *et al.* (20)	Chinese	Case–control	Gastric cancer	323	646	Increased
	Panguluri *et al.* (21)	Multiethnicity*	Case–control	Prostate cancer	370	366	No association+
	Koh *et al.* (22)	Singapore Chinese	Cohort	Colorectal cancer	310	1177	No association+
	Hamajima *et al.* (23)	Japanese	Case–control	Colorectal cancer	148	241	No association
COX2	Campa *et al.* (10)	Norwegian	Case–control	Non-small cell lung cancer	250	214	No association
(Ex3-8 G>C,	Sakoda *et al.* (11)	Chinese	Case–control	Biliary tract cancers	411	786	No association
rs5277)	Cox *et al.* (15)	Spain	Case–control	Colorectal cancer	292	274	No association
COX2	Campa *et al.* (10)	Norwegian	Case–control	Non-small cell lung cancer	250	214	No association
(IVS5-275T>G,	Sakoda *et al.* (11)	Chinese	Case–control	Biliary tract cancers	411	786	No association
rs20432)	Cox *et al.* (15)	Spain	Case–control	Colorectal cancer	292	274	No association
	Shahedi (17)	Sweden	Case–control	Prostate cancer	1378	782	Decreased
COX2	Sakoda *et al.* (11)	Chinese	Case–control	Biliary tract cancers	411	786	No association
(IVS7+111T>C,	Shahedi 17)	Sweden	Case–control	Prostate cancer	1378	782	No association
rs4648276)							
COX2	Sakoda *et al.* (11)	Chinese	Case–control	Biliary tract cancers	411	786	No association
(Ex10-90 C>T,	Shahedi 17	Sweden	Case–control	Prostate cancer	1378	782	Decreased
rs689470)							
COX1							
(Ex7+31C>A,							
rs5789)	Goodman *et al.* (24)	US	Case–control	Colon cancer	293	533**	No association
COX1							
(Ex10-4 G>A,							
rs5794)	Goodman *et al.* (24)	US	Case–control	Colon cancer	293	533**	No association

*African Americans; European Americans and Nigerians; +results from stratification analysis was partly positive; **hospital-based (229) and population-based (304).

carriers of the minor alleles (OR=1.11, 95% CI=0.44-2.82). Haplotypes of *COX1* and *COX2* were also not associated with case–control status (data not shown). Stratification by gastric cancer risk factors and tumor characteristics, including age, gender, smoking, alcohol consumption, Lauren classification, tumor grade, site of tumor origin, metastasis status and *Helicobacter pylori* infection status, produced comparable results (data not shown). Gene–gene interaction tests between the SNPs in COX1 and COX2 did not reveal any meaningful results, although power was low to detect such effects (data not shown). In addition, we observed no association between *H. pylori* infection and the tested SNPs among controls (data not shown).

Discussion

In the present study, we found no evidence that the seven SNPs tested in *COX1* (Ex7+31 C>A and Ex10-4 G>A) and *COX2* (Ex3-8 G>C; IVS5-275 T>G; IVS7+111 T>C; Ex10-90 G>A; and Ex10+837 T>C) are associated with gastric cancer risk. Some of the SNPs tested in the present study have been examined in relation to other types of cancer (Table II). Ex10+837 T>C in *COX2* has been most widely evaluated, with mixed results (9-17). A majority of the studies reported no association with the minor genotype, while three studies reported a positive association involving breast, lung, and bile duct cancers (9-11), and another study of lung cancer

reported an inverse association (12). Although the –765 G>C promoter polymorphism in *COX2* has been observed to confer risks for esophageal and gastric cancers in a Chinese population (19, 20), no association was found with gastric cancer risk in our study. Due to the rarity of the minor alleles in Caucasians (http://snp500cancer.nci.nih.gov), two other promoter polymorphisms previously studied in relation to gastric cancer risk in two Chinese populations (18-20) were not investigated in the present study. Similar to our findings, a study of colon cancer conducted in the United States reported no association with *COX1* Ex7+31 C>A and Ex10-4 G>A, or with several additional SNPs in COX1 that were not evaluated in our study (24).

Our study has the advantage of high participation rates and population-based design. Misclassification was minimal due to the high reproducibility and accuracy of genotyping.

Several limitations of the current study should be considered in interpreting the results: (i) low frequencies of the minor alleles of most studied SNPs and the relatively small sample size made it difficult to detect possible low magnitude associations, particularly for haplotype effects and gene–gene interactions; (ii) the selection of SNPs was limited and an effect of untested SNPs in these two genes could not be ruled out; (iii) lack of information on NSAID use hindered our ability to examine gene–environment interactions; and (iv) we did not have reliable data on *H. pylori* infection status among patients since *H. pylori* colonization of gastric mucosa may be cleared in the multi-stage progression to gastric cancer (30). However, over 81% of controls in our study were seropositive for *H. pylori* and exclusion of seronegative controls did not alter the genotype results substantially.

Conclusion

Despite the null associations reported in this study, overexpression of the *COX-2* gene has been shown in several gastrointestinal malignancies, including gastric cancer (31), suggesting that more comprehensive studies into the *COX1* and *COX2* pathways and relevant exposures such as NSAID use may provide insights into carcinogenic mechanisms and possible chemopreventive strategies.

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