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A Population-based Study of the *Arg399Gln* Polymorphism in X-Ray Repair Cross-Complementing Group 1 (*XRCC1*) and Risk of Pancreatic Adenocarcinoma[1]

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ABSTRACT

XRCC1 (X-ray repair cross-complementing group 1) is a base excision repair protein that plays a central role in the repair of DNA strand breaks and base damage from a variety of endogenous and exogenous oxidants including tobacco smoke. One genetic polymorphism (G→A, Arg→Gln at codon 399) occurs within a poly(ADP-ribose) polymerase binding region and within the central breast cancer susceptibility gene 1 product COOH terminus domain of XRCC1. The variant *399Gln* allele of *XRCC1* has been associated with elevated biomarkers of DNA damage in human cells. We conducted an analysis of the *Arg399Gln* polymorphism in *XRCC1* using genomic DNA, and questionnaire information from 309 cases of pancreatic adenocarcinoma and 964 controls that were part of a population-based, case-control study conducted in the San Francisco Bay Area between 1994 and 2001. We genotyped individuals using a mass spectrometry-based method. Because smoking and obesity are known and suspected pancreas cancer risk factors, and have been associated with DNA damage and oxidative stress in target tissues, we estimated odds ratios (ORs), interaction contrast ratios (ICRs), and 95% confidence intervals for the combined effects of *XRCC1* genotype and smoking or body mass index (in kg/m^2). We also assessed potential gene-gene interactions between polymorphisms in *XRCC1* and *CYP1A1*, *GSTT1*, and *GSTM1*. We found little or no evidence for an association between *XRCC1* genotype and pancreatic cancer among Caucasians, African-Americans, or Asians. There was evidence for interaction between *XRCC1 399Gln* and smoking that was stronger among women than men. Relative to never active or passive smokers with the *Arg/Arg* genotype, the age- and race-adjusted ORs and ICRs (95% confidence limits) for heavy smoking (≥41 pack-years) were: for *Gln/Gln* or *Arg/Gln* genotypes [women OR = 7.0 (2.4, 21), ICR = 3.1 (0.03, 6.2); men OR = 2.4 (1.1, 5.0), ICR = 1.3 (−0.20, 2.8)]; and for the *Arg/Arg* genotype [women OR = 2.2 (0.73, 6.4); men OR = 1.5 (0.68, 3.2)]. Analyses of combined genotypes suggested an interaction between *XRCC1* (*Gln/Gln* or *Arg/Gln*) and *GSTT1/GSTM1-null/null* among women but not among men. There was no evidence of interaction between *XRCC1* genotype and body mass index. Our results suggest that the *XRCC1 399Gln* allele is a potentially important determinant of susceptibility to smoking-induced pancreatic cancer. Our findings, including stronger associations and interactions among women, require replication in additional study populations.

INTRODUCTION

Adenocarcinoma of the exocrine pancreas is the fifth leading cause of cancer mortality among men and women in the United States (1). The aggressive nature of most pancreas tumors combined with a lack of markers for early detection, and an unclear understanding of etiology has made this one of the deadliest of human cancers. Tobacco smoking, the only established environmental risk factor for pancreatic cancer (2), may account for a slightly higher fraction of the disease among women (29%) than among men (26%; Ref. 3). Exposure to tobacco smoke has been associated with elevated oxidative stress and DNA damage endpoints in animal and human pancreata (4–9). Oxidative stress and lipid peroxidation also have been linked with obesity (10, 11), a potential risk factor for pancreatic cancer (3, 12–14).

DNA damage that is associated with oxidative stress is repaired by the BER[3] pathway (15). In general, BER targets endogenous oxidative DNA damage, but it also repairs strand breaks, base damage, and nonbulky adducts induced by exogenous agents such as ionizing radiation, alkylating agents, and oxidizing agents including complex carcinogens such as tobacco smoke (16). DNA repair capacity is known to be variable in the human population, and because a part of this variation is believed to be genetic, a number of DNA repair genes have been screened recently and discovered to be polymorphic (17–19). *XRCC1* (located on 19q13.2) is a polymorphic BER gene that encodes a M_r 70,000 protein. The XRCC1 protein acts as a scaffold for interaction with other BER-associated proteins including human AP endonuclease (APE1), DNA polymerase β, DNA ligase III, polynucleotide kinase, and PARP (20–24). One polymorphism (G→A) in *XRCC1* results in an arginine to glutamine change at codon 399 within a breast cancer susceptibility gene 1 product COOH terminus domain and PARP binding site (23, 25). The variant *XRCC1 399Gln* allele has been linked with DNA damage phenotypes in human tissues (26–30). It also has been associated with cancer susceptibility in case-control studies of numerous cancers including head and neck, colon, stomach, lung, bladder, breast, esophagus, and skin, although results have been inconsistent with regard to at-risk alleles and definitions of exposure (31–39).

We examined the role of *XRCC1* as a candidate susceptibility gene for pancreatic cancer using DNA samples and exposure information collected from 309 cases of pancreatic adenocarcinoma and 964 controls from a population-based case-control study in the San Francisco Bay Area. We hypothesized that the *XRCC1 399Gln* allele confers an increased risk for pancreatic cancer induced by oxidative stress; namely, that having one or two copies of *XRCC1 399Gln* increases the effects of smoking (active smoking, duration of smoking, and smoking intensity) and obesity (elevated BMI, in kg/m^2) on pancreatic cancer risk. Because age is a known risk factor for pancreatic cancer, and because we previously found significantly elevated endogenous DNA adducts among older nondiseased individuals (65 years or older) with variant *XRCC1* codon 399 genotypes (*Gln/Gln or Arg/Gln;* Ref. 27), we tested the data for interactions between age and *XRCC1* genotype in relation to the risk of pancreatic cancer. Finally, because alleles in *XRCC1* may act synergistically with alleles in carcinogen metabolism genes to additionally increase cancer risk (40), we examined genotype-genotype interactions between *XRCC1* and the carcinogen metabolism genes *GSTT1*, *GSTM1*, and *CYP1A1*.

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[3] The abbreviations used are: BER, base excision repair; BMI, body mass index; CI, confidence interval; OR, odds ratio; PARP, poly(ADP-ribose) polymerase; XRCC1, X-ray repair cross-complementing group 1; RDD, random digit dial; HCFA, Health Care Finance Administration; CL, confidence limit; ICR, interaction contrast ratio; RR, risk ratio.

MATERIALS AND METHODS

Study Population. Patients with primary adenocarcinoma of the exocrine pancreas who were diagnosed between 1994 and 2001 were identified by the Northern California Cancer Center (Union City, CA) using rapid case ascertainment in the six San Francisco Bay Area counties of Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara. Eligible participants resided in one of the six counties at the time of diagnosis, were 21 to 85 years of age, and were alive and able to communicate in English. All of the case diagnoses were subsequently confirmed using Surveillance, Epidemiology, and End Results program abstracts. Additional out-of-area cases who met all of the study criteria other than their place of residence at the time of diagnosis were obtained through clinical files at University of California San Francisco Medical Center and were included in the full case-control study to improve sample size. The majority of these cases were from other counties in northern California. As none of the out-of-area participants was asked to provide a blood sample, these could not be included in the present analyses. Control participants were identified using RDD and the HCFA lists for those who were 65 years and older, and were frequency matched to cases by sex and age within 5-year categories. Out-of-area controls, also identified by RDD, were frequency matched to out-of-area cases by telephone area code and prefix of residence, and by sex and age. Detailed in-person interviews were conducted in the homes of the participants or at a location of their choice for Bay Area participants and by telephone interview for out-of-area participants. No proxy interviews were conducted. The University of California San Francisco institutional review board approved all of the study procedures, and written informed consent was obtained from each study participant before interview and before collection of blood for genetic analyses.

A total of 530 eligible pancreatic cancer patients were interviewed for our larger case-control study. Sixty-five percent ($n = 466$) of the San Francisco Bay Area pancreatic cancer cases and 80% ($n = 64$) of those from outside the six-county area who were eligible completed their interviews. The analyses for this study are based on 309 patients who gave blood as part of the laboratory portion of the study and whose specimens were available for genotyping. Blood was not obtained from the out-of-area cases and from the remainder of the case participants for the following reasons: patient was too ill, patient had died, patient or physician refused, or the blood draw was unsuccessful or insufficient. Among cases, there were no statistical differences (all of the *P*s were >0.05) between those who provided blood and those who did not provide blood by variables for age, sex, race, education, smoking status (never, former, current), or pack-years of smoking.

A total of 1701 eligible control participants were interviewed. Of these, 59% were obtained by RDD in the six-county San Francisco Bay Area, 4% by out-of-area RDD, and 37% from HCFA lists. Sixty percent of eligible San Francisco Bay Area RDD control subjects, 69% of eligible out-of-area RDD control subjects, and 53% of eligible HCFA control participants completed interviews. Analyses presented here are based on 964 control participants who gave blood as part of the laboratory portion of the study and whose specimens were available for genotyping. Blood was not obtained from out-of-area controls and from the remainder of the control participants for the following reasons: participant refused, participant had moved since the interview, participant was ill, the blood draw was unsuccessful or insufficient, or the participant had died. Among controls, there were no statistical differences between those who provided blood and those who did not provide blood by age, education, and pack-years of smoking (all of the *P*s were > 0.05). Overall, case or control status was not related to providing blood ($P = 0.6$). Among controls, there were statistically significant differences between those who provided blood and those who did not by race ($P = 0.002$, a higher proportion of Caucasian participants provided blood), sex ($P = 0.002$, a higher proportion of men provided blood), and smoking status ($P < 0.001$, a smaller proportion of never-smokers provided blood).

Exposure Information. Exposure history was obtained at interview by self-report using structured questionnaires. No proxy interviews were conducted. The interview for all of the subjects included questions about tobacco use, alcohol consumption, diet, occupational exposures, family history, medical history, and demographic information. Race was based on self-report and was broadly defined as Caucasian, African-American, or Asian.

Participants were defined as never-smokers if they never had smoked >100 cigarettes in their lifetime and had not smoked cigars or pipes at least once per month for 6 months or more. Because there was a substantial number of participants who had never smoked and who reported a history of passive smoke exposure at home as an adult (women: 32 cases, 95 controls; men: 5 cases, 21 controls), these individuals were removed from the referent group of never-smokers. Smoking duration was defined as the total number of years of cigarette smoking. Smoking intensity (pack-years) was defined as the number of packs of cigarettes smoked per day multiplied by the number of years smoked. Cut-points for pack-years or duration of smoking were based on quartiles of the distribution among all of the control participants who smoked. Recent smoking was assessed using pack-years or duration restricted to within 15 calendar years of the date of diagnosis among cases or interview among controls.

BMI (weight in kilograms divided by height in meters squared) was based on self-reported usual adult height and weight. Cut-points for elevated BMI were based on the upper tertile (25.75 kg/m^2 or more) or upper quartile (26.60 kg/m^2 or more) of the distribution among the 964 controls who participated in the laboratory portion of the main study.

Laboratory Methods. Genomic DNA was extracted from peripheral blood lymphocytes using the QIAmp DNA Blood Mini kit (Qiagen, Inc., Valencia, CA) and according to the manufacturer's instructions. Genotyping for *XRCC1* (G→A at nucleotide 28152 in exon 10, Arg→Gln at codon 399) was performed using the Masscode assay (Qiagen Genomics, Inc., Bothell, WA; Ref. 41). This mass spectrometry-based method uses standard PCR amplification of the region containing the polymorphism followed by hybridization with oligonucleotide primers that have been modified with photocleavable linkers attached to tags of variable composition (cleavable mass spectrometry tags) such that each allele-specific oligonucleotide primer is of different mass. For homozygotes, the mass spectrometer detects a single allele-specific tag, and for heterozygotes it detects two tags. In unpublished pilot data, we compared this mass spectrometry method with a standard PCR-RFLP method (27) using 100 samples of genomic DNA from Caucasians in the Boston area. In this comparison of two different methods for assaying the same *XRCC1 Arg399Gln* polymorphism, we observed no discordant pairs. For the full genotyping sample, we included a blinded 10% random sample of repeats ($n = 128$ pairs). Pairs discordant on genotype ($n = 4$; 3%) were dropped from subsequent analyses.

PCR-RFLP analysis was used to genotype *CYP1A1 m1* (T→C, nucleotide 6235 in 3′ flanking region), *GSTM1-null* (homozygous gene deletion), and *GSTT1-null*. Detailed methods and results of analyses of polymorphisms in *CYP1A1*, *GSTM1*, and *GSTT1* in this subset of the San Francisco Bay Area pancreatic cancer study have been described previously (40).

Statistical Methods. Tests for Hardy-Weinberg equilibrium among controls were conducted using observed genotype frequencies and a χ^2 test with one degree of freedom. ORs and 95% CIs were estimated using unconditional logistic regression in SAS (v. 8; SAS Institute, Cary, NC). Risk factors for pancreatic cancer and potential confounders were kept in multivariable models if their removal caused β parameter estimates to change by $>10\%$. Final multivariable models are presented stratified by sex and include terms for age (continuous) and race (Caucasian, African American, and Asian) unless otherwise noted. In general, ORs did not differ substantially by race, so results for combined effects of *XRCC1* genotype and exposure are presented among all of the racial groups combined. Other potential confounders that were evaluated but not included in multivariable models were: alcohol consumption, coffee consumption, education (high school or less, college, graduate work), annual household income, first-degree family history of pancreatic cancer, and medical conditions (history of pancreatitis, diabetes, ulcer, gallbladder disease, allergy, and vitamin B12 deficiency). Hormonal factors and reproductive history (age at menarche, age at menopause, parity, age at first full-term birth, oral contraceptive use, and hormone replacement therapy use) were also evaluated in separate multivariable models among women. Women who reported cessation of menstrual periods at the time of interview were defined as menopausal, and women who reported their menses had begun to cease (3 cases, 12 controls) or had not ceased (8 cases, 47 controls) were categorized as premenopausal women. With the exception of age at menopause, none of these factors were identified as confounders or risk factors for pancreatic cancer among women in this subset of our San Francisco Bay Area population.

Gene-environment and gene-gene interactions were estimated by evaluating departures from additivity. Departures from additivity were evaluated by estimating multivariable ORs for the combined effect of *XRCC1* codon 399

genotype and exposure (heavy smoking, elevated BMI, or older age) or genotypes for polymorphic carcinogen-metabolizing genes (*CYP1A1*, *GSTM1*, *GSTT1*). Variables for combined effects were coded using a common referent group (*e.g.*, *XRCC1* codon 399 *Arg/Arg* and never-smoker). The magnitude of an interaction effect was determined by estimating age- and race-adjusted ICRs with 95% CLs using PROC LOGISTIC in SAS (42). We calculated the ICR using the following formula:

$$ICR = RR_{11} - RR_{10} - RR_{01} + 1,$$

where RR_{11} is the RR for exposure with a variant *XRCC1* genotype, RR_{10} is the RR for a variant *XRCC1* genotype among the nonexposed, and RR_{01} is the RR for exposure with a nonvariant *XRCC1* genotype. ORs were used to estimate RRs. ICRs > 0 imply greater than additive effects (interaction), whereas ICRs of zero imply additive effects (no interaction), and ICRs < 0 imply less than additive effects (negative interaction; Ref. 43). For the present study, we considered ICRs of magnitude 1 or higher as indicative of an interaction. CLs for ICRs that exclude the null value of zero can be considered statistically significant at α level 0.05. For estimation of ICRs, cigarette smoking and genotypes were dichotomized using the highest quartile of pack-years or duration for smoking (for example, 41 or more pack-years *versus* all of the others), and variant-allele containing genotypes (variant/variant + variant/wild-type *versus* wild-type/wild-type), as the exposed groups.

RESULTS

Characteristics of this subset of the San Francisco Bay Area study population have been published previously (40). Heavy cigarette smoking (upper quartile: 41 or more pack-years) was positively associated with pancreatic cancer (age, sex- and race-adjusted OR, 2.4; 95% CI, 1.6–3.4). ORs for cigarette smoking and pancreatic cancer were similar between women and men (data not shown). However, among women, ORs for heavy cigarette smoking increased 20% when those with passive exposure at home were removed from the referent group of nonsmokers (data not shown). A similar increase was absent among men, but fewer men reported exposure to passive cigarette smoke (5 cases and 21 controls). There was a positive but weak association between BMI (kg/m^2, in tertiles $<$23.01, 23.01–25.74, $\geq$25.75) and pancreatic cancer among women and men (age-, sex- and race-adjusted OR, 1.2; 95% CI , 0.84–1.6 middle compared with lower tertile; OR, 1.4; 95% CI, 0.99–1.9 upper compared with lower tertile). ORs for BMI and pancreatic cancer were similar between women and men (data not shown).

Allele and genotype frequencies and ORs for *XRCC1 Arg399Gln* by race are presented in Table 1. A χ^2 test of observed genotype *versus* expected genotype frequencies for *XRCC1* was suggestive of deviations from Hardy-Weinberg equilibrium among Caucasian controls ($P = 0.053$; Table 1). In general, there was no evidence for a main effect of the *XRCC1 Arg399Gln* polymorphism on pancreatic cancer. Among African-American participants, homozygous variant genotypes were combined with heterozygous genotypes to estimate ORs because of small numbers. Among all of the participants, age- and race-adjusted ORs for *XRCC1* and pancreatic cancer were higher among women (OR, 1.3; 95% CI, 0.87–2.1 heterozygotes compared with wild-types; OR, 1.6; 95% CI, 0.86–2.9 homozygous variants compared with wild-types) compared with men (OR, 0.96; 95% CI, 0.66–1.4 heterozygotes compared with wild-types; OR, 1.0; 95% CI, 0.58–1.9 homozygous variants compared with wild-types). *XRCC1* genotypes were not associated with either age at diagnosis among cases or age at interview among controls of either sex or by race (data not shown).

Because the results of analyses for gene effects, exposure effects, and gene-environment or gene-gene interactions did not differ substantially among the racial groups used in this study (Caucasians, African-Americans, and Asians), we have presented ORs adjusted for age and race separately for women and men, unless otherwise noted.

ORs for the combined effect of *XRCC1* genotype and tobacco smoking variables are given in Table 2. Among women in our study, *XRCC1* genotype did not modify the effect of passive smoking exposure on pancreatic cancer. Among women who reported no active cigarette use, two controls reported pipe and/or cigar use, and the remaining women were exposed to passive smoke or were classified as "never-active or passive" smokers. Among women who reported that they were former cigarette smokers ("former-active") or current cigarette smokers ("current-active"), ORs were higher among genotypes with one or two copies of the *XRCC1 399Gln* allele (*Arg/Gln* or *Gln/Gln*). For the combined effect of *XRCC1* genotype and number of pack-years of smoking or duration on pancreatic cancer, ORs again were higher for heavy smoking among those with one or two copies of the *XRCC1 399Gln* allele. Results did not substantially differ (by $>$10%) when pack-years or duration of smoking was restricted to within 15 calendar years of diagnosis among cases or interview among controls (data not shown).

ORs for the combined effect of *XRCC1* genotype and smoking among women were stronger when age (in years) at menopause (premenopausal, $\leq$45, 46–54, $\geq$55) was included in multivariable models (data not in Table). The age- and race-adjusted ORs for age at menopause and pancreas cancer (relative to premenopausal women) were 1.2 (95% CI, 0.51–2.7) for ages $\leq$45, 1.8 (95% CI, 0.82–4.1) for ages 46–54, and 2.2 (95% CI, 0.85–5.6) for ages $\geq$55. Among women, the age-, race-, and age at menopause-adjusted OR for heavy smokers (41 or more pack-years) with the *XRCC1 Gln/Gln* or *Arg/Gln*

Table 1 *Allele and genotype frequencies and ORs for XRCC1, stratified by race/ethnicity, San Francisco Bay Area, California 1994-2001*

	Caucasians					African Americans					Asians				
	Cases $n = 261$		Controls $n = 860$			Cases $n = 26$		Controls $n = 36$			Cases $n = 17$		Controls $n = 53$		
XRCC1	*n*	(%)	*n*	(%)	OR[a] (95% CI)	*n*	(%)	*n*	(%)	OR[a] (95% CI)	*n*	(%)	*n*	(%)	OR (95% CI)
Allele															
Arg		0.65		0.68			0.81		0.85			0.76		0.74	
Gln		0.35		0.32			0.19		0.15			0.24		0.26	
Genotype															
Arg/Arg	110	(44)	398	(48)	1.0 (referent)	16	(62)	25	(69)	1.0 (referent)	11	(65)	29	(57)	1.0 (referent)
Arg/Gln	105	(42)	337	(40)	1.1 (0.83–1.5)	10	(38)	11	(31)	1.4 (0.48–4.0)	4	(23)	17	(33)	0.90 (0.22–3.7)
Gln/Gln	35	(14)	97	(12)	1.3 (0.84–2.0)	0	(0)	0	(0)		2	(12)	5	(10)	1.1 (0.18–6.7)
Missing	11		28			0		0			0		2		
H-W χ^{2b}			3.7					2.3					0.84		
P			0.053					0.12					0.36		

[a] Adjusted for age and sex.
[b] Test for Hardy-Weinberg equilibrium comparing observed to expected genotype frequencies among controls ($df = 1$).

Table 2 *ORs for the joint effects of tobacco smoking and XRCC1 genotype, stratified by sex, San Francisco Bay Area, California 1994–2001*

		Women					Men				
		Cases $n = 141$		Controls $n = 433$			Cases $n = 168$		Controls $n = 531$		
	XRCC1	*n*	(%)	*n*	(%)	OR[a] (95% CI)	*n*	(%)	*n*	(%)	OR[a] (95% CI)
Smoking status											
Never active or passive[b]	Arg/Arg	7	(5)	40	(10)	1.0 (referent)	15	(9)	49	(10)	1.0 (referent)
	Arg/Gln + Gln/Gln	12	(9)	57	(14)	1.2 (0.45–3.5)	11	(7)	59	(12)	0.64 (0.27–1.5)
Adult passive/cigar/pipe use[c]	Arg/Arg	19	(14)	56	(13)	1.6 (0.61–4.3)	10	(6)	29	(6)	1.1 (0.45–2.9)
	Arg/Gln + Gln/Gln	13	(10)	41	(10)	1.7 (0.60–4.8)	5	(3)	32	(6)	0.51 (0.17–1.6)
Former active	Arg/Arg	22	(16)	90	(21)	1.4 (0.54–3.5)	39	(24)	135	(26)	0.95 (0.48–1.9)
	Arg/Gln + Gln/Gln	32	(24)	84	(20)	2.2 (0.87–5.4)	44	(27)	150	(29)	1.0 (0.51–2.0)
Current active	Arg/Arg	11	(8)	25	(6)	2.1 (0.69–6.3)	17	(10)	33	(6)	1.7 (0.74–3.9)
	Arg/Gln + Gln/Gln	18	(13)	28	(7)	3.9 (1.4–10.7)	23	(14)	26	(5)	3.0 (1.3–6.9)
Missing[d]		7		12			4		18		
Pack-years											
Never active or passive	Arg/Arg	7	(5)	40	(10)	1.0 (referent)	15	(10)	49	(10)	1.0 (referent)
	Arg/Gln + Gln/Gln	12	(9)	57	(14)	1.3 (0.46–3.6)	11	(7)	59	(12)	0.62 (0.26–1.5)
<41/adult passive	Arg/Arg	40	(30)	140	(34)	1.5 (0.60–3.6)	39	(25)	128	(27)	0.98 (0.49–2.0)
	Arg/Gln + Gln/Gln	44	(33)	130	(32)	2.0 (0.81–4.8)	35	(23)	142	(30)	0.86 (0.43–1.7)
≥41	Arg/Arg	11	(8)	29	(7)	2.2 (0.73–6.4)	22	(14)	50	(11)	1.5 (0.68–3.2)
	Arg/Gln + Gln/Gln	18	(14)	15	(4)	7.0 (2.4–20.7)	32	(21)	46	(10)	2.4 (1.1–5.0)
Missing[e]		9		22			14		57		
Duration (years)											
Never active or passive	Arg/Arg	7	(5)	40	(10)	1.0 (referent)	15	(10)	49	(10)	1.0 (referent)
	Arg/Gln + Gln/Gln	12	(9)	57	(14)	1.3 (0.45–3.5)	11	(7)	59	(12)	0.62 (0.26–1.5)
<40/adult passive	Arg/Arg	37	(28)	134	(32)	1.5 (0.62–3.7)	45	(29)	136	(29)	1.1 (0.54–2.1)
	Arg/Gln + Gln/Gln	41	(31)	120	(29)	2.0 (0.82–4.9)	43	(28)	151	(32)	0.98 (0.50–1.9)
≥40	Arg/Arg	15	(11)	36	(9)	2.1 (0.74–5.9)	16	(10)	42	(9)	1.3 (0.56–3.0)
	Arg/Gln + Gln/Gln	22	(16)	30	(7)	4.3 (1.6–11.7)	24	(16)	37	(8)	2.4 (1.1–5.3)
Missing[e]		7		16			14		57		

[a] Adjusted for age and race.
[b] Passive smoking exposure at home as an adult; active cigarette smoking.
[c] Passive smoke exposure: women (32 cases, 95 controls), men (5 cases, 21 controls); pipe/cigar users: women (0 cases, 2 controls), men (10 cases, 39 controls).
[d] Missing data on smoking or genotype.
[e] Missing data includes cigar or pipe users.

genotype was 8.6 (95% CI, 2.9–25.8), whereas the age-, race-, and age at menopause-adjusted OR for heavy smokers with the *XRCC1 Arg/Arg* genotype was 2.5 (95% CI, 0.83–7.4). The age-, race-, and age at menopause-adjusted OR for light smokers (less than 41 pack-years or passive) with the *XRCC1 Gln/Gln* or *Arg/Gln* genotype was 2.2 (95% CI, 0.89–5.4), whereas the age-, race-, and age at menopause-adjusted OR for light smokers with the *XRCC1 Arg/Arg* genotype was 1.6 (95% CI, 0.64–3.8). The age-, race-, and age at menopause-adjusted OR for never-active/passive smokers with the *XRCC1 Gln/Gln* or *Arg/Gln* genotype was 1.4 (95% CI, 0.48–3.9).

Among men who reported no active cigarette smoking, passive smoking exposure was less common (5 cases and 21 controls) than among women. However, self-reported pipe and/or cigar use was more common among men (10 cases and 40 controls) who were never-active cigarette smokers than among women (Table 2). Among men, never-smoking and passive or cigar/pipe smoking were inversely associated with pancreatic cancer among variant *399Gln* containing genotypes, possibly because of small sample size. Among men, ORs for current-active smoking and heavy smoking (≥41 pack-years or >40 years) were greater among variant genotypes (*Gln/Gln* or *Arg/Gln*) than among nonvariant genotypes. In general, combined ORs for *XRCC1* genotype and smoking were stronger among women than among men (Table 2).

We estimated the magnitude of interaction effects by calculating the ICR. The age- and race-adjusted ICR and 95% CLs for smoking pack-years (≥41 *versus* never-active or passive smoker) and *XRCC1* (*Gln/Gln* or *Arg/Gln versus Arg/Arg*) for all of the participants was 1.8 (0.47, 3.1); for women ICR = 3.1 (0.03, 6.2); for men ICR = 1.3 (−0.20, 2.8), suggesting moderate interaction effects between *XRCC1* genotype and heavy smoking.

XRCC1 genotype was not associated with BMI (kg/m^2, in tertiles or quartiles) among controls of either sex (Mantel-Haenszel χ^2, all $P > 0.1$). We then evaluated joint ORs for BMI (tertiles or quartiles) and *XRCC1* genotype, and found no evidence for association with case/control status or OR modification by sex (data not shown). Likewise, there was no evidence of elevated ORs for the combined effect of *XRCC1* genotype and age (≥65 years *versus* <65 years) on risk of pancreatic cancer (data not shown).

ORs for the combined effect of *XRCC1* and *CYP1A1 m1* genotypes are presented in Table 3. Among women with variant alleles for both

Table 3 *ORs for the combined effect of XRCC1 and CYP1A1 ml genotypes, stratified by sex, San Francisco Bay Area, California 1994–2001*

		Women			Men		
		Cases	Controls		Cases	Controls	
CYP1A1 ml	XRCC1	$n = 141$	$n = 433$	OR[a] (95% CI)	$n = 168$	$n = 531$	OR[b] (95% CI)
Wt/Wt	Arg/Arg	41	161	1.0 (referent)	63	164	1.0 (referent)
	Arg/Gln + Gln/Gln	47	157	1.5 (0.92–2.5)	60	206	0.80 (0.52–1.2)
Wt/ml + ml/ml	Arg/Arg	18	49	1.7 (0.86–3.4)	17	79	0.54 (0.28–1.0)
	Arg/Gln + Gln/Gln	26	52	3.0 (1.6–5.7)	23	60	1.1 (0.60–2.0)
Missing[c]		9	14		5	22	

[a] Adjusted for age, race, pack-years of smoking, and age (yr) at menopause (premenopausal, 45 or less, 46–54, 55 or more).
[b] Adjusted for age, race, and pack-years of smoking.
[c] Missing data on either genotype.

Table 4 *ORs for the combined effect of XRCC1 genotype, and GSTM1 and GSTT1 deletion genotypes, stratified by sex, San Francisco Bay Area, California 19941–2001*

		Women			Men		
		Cases	Controls		Cases	Controls	
	XRCC1	n = 141	n = 433	OR[a] (95% CI)	n = 168	n = 531	OR[b] (95% CI)
GSTM1							
Present	Arg/Arg	31	95	1.0 (referent)	36	119	1.0 (referent)
	Arg/Gln + Gln/Gln	33	93	1.5 (0.82–2.8)	42	131	1.1 (0.65–1.9)
Null	Arg/Arg	28	115	0.89 (0.48–1.6)	44	126	1.2 (0.71–2.1)
	Arg/Gln + Gln/Gln	42	116	1.5 (0.86–2.8)	41	134	1.1 (0.66–2.0)
Missing[c]		7	14		5	21	
GSTT1							
Present	Arg/Arg	45	173	1.0 (referent)	69	188	1.0 (referent)
	Arg/Gln + Gln/Gln	59	178	1.6 (1.0–2.6)	65	215	0.91 (0.60–1.4)
Null	Arg/Arg	14	36	1.5 (0.74–3.2)	11	57	0.56 (0.27–1.2)
	Arg/Gln + Gln/Gln	16	32	2.6 (1.2–5.4)	18	50	0.98 (0.50–1.9)
Missing[c]		7	14		5	21	
GSTM1/GSTT1							
Both present	Arg/Arg	23	79	1.0 (referent)	32	93	1.0 (referent)
	Arg/Gln + Gln/Gln	31	79	1.8 (0.95–3.6)	33	106	1.0 (0.56–1.8)
Either null	Arg/Arg	30	111	1.1 (0.59–2.2)	41	121	0.98 (0.55–1.7)
	Arg/Gln + Gln/Gln	30	112	1.4 (0.70–2.7)	41	134	0.90 (0.50–1.6)
Both null	Arg/Arg	6	20	1.2 (0.41–3.6)	7	31	0.77 (0.29–2.0)
	Arg/Gln + Gln/Gln	14	18	3.6 (1.5–8.9)	9	25	1.3 (0.54–3.4)
Missing[c]		7	14		5	21	

[a] Adjusted for age, race, pack-years of smoking, and age (yr) at menopause (premenopausal, 45 or less, 46–54, 55 or more).
[b] Adjusted for age, race, and pack-years of smoking.
[c] Missing data on either genotype.

XRCC1 and *CYP1A1 m1*, there was a 3-fold increased risk of pancreatic cancer compared with women with wild-type genotypes for both genes. Among men, the joint OR for *CYP1A1* variant genotypes (*m1/wt + m1/m1*) and wild-type *XRCC1* (*Arg/Arg*) was inversely associated with case status (Table 3). The age-, race-, and smoking-adjusted ICR and 95% CLs for *XRCC1* (*Gln/Gln* or *Arg/Gln versus Arg/Arg*) and *CYP1A1* (*m1/m1* or *m1/wt versus wt/wt*) for all of the participants was 0.64 (−0.035, 1.3); for women ICR = 0.79 (−1.4, 3.0); for men ICR = 0.77 (0.045, 1.5), suggesting little or no interaction between *XRCC1* and *CYP1A1* genotypes.

ORs for the combined effect of *XRCC1* genotype and *GSTM1* and/or *GSTT1* homozygous gene deletion (null) genotypes are presented in Table 4. There was little evidence among women or men for a combined effect of variant *GSTM1* and *XRCC1* genotypes. For *GSTT1-null*, a 2.6-fold increase in risk was observed among women (but not men) with variant *XRCC1* genotypes. For the combined effect of variant *XRCC1* and *GSTM1-null* and *GSTT1-null*, we observed a 3.6-fold positive association with risk of pancreatic cancer among women. The age-, race-, and smoking-adjusted ICR and 95% CLs for *XRCC1* (*Gln/Gln* or *Arg/Gln versus Arg/Arg*) and *GSTM1/T1* (*null/null versus present/present* or *null/present*) for all of the participants was 1.0 (−0.16, 2.2); for women ICR = 2.0 (−1.1, 5.0); for men ICR = 0.59 (−0.75, 1.9), suggesting a weak to moderate interaction between *XRCC1* and *GSTT1/GSTM1* genotypes.

DISCUSSION

We investigated the role of the *XRCC1 Arg399Gln* polymorphism in pancreatic adenocarcinoma in a subset of a population-based, case-control study from the San Francisco Bay Area. We found evidence for synergy between *XRCC1-399Gln* and cigarette smoking, in particular, current or heavy smoking (≥41 pack-years or ≥40 years in duration). Because most of the heavy smokers in our study also were current smokers, it was difficult to separate the effect of high-intensity exposure from the effect of recent exposure. However, the interaction between *XRCC1* and smoking was strongest when smoking was based on intensity (pack-years) suggesting dose may be as important as timing of exposure. Insofar as *XRCC1* alleles are determinants of XRCC1 function and BER capacity, the observed interaction between *XRCC1* codon 399 genotype and cigarette smoking suggests that XRCC1 protein and BER capacity are important in protecting pancreatic cells from the damaging effects of tobacco smoking. Furthermore, the magnitude of ORs and interaction effects consistently was stronger among women than men. Whereas the incidence of pancreas cancer is about 20–25% higher in men than in women, recent trends indicate that rates may be declining less in women than in men (44, 45).

There are several potential explanations for our observations including biological differences between women and men in the response to tobacco carcinogens, as well as nonbiological differences in smoking behavior and in the prevalence of unmeasured risk factors correlated with smoking (such as occupational exposures). In support of the first premise, a recent study of autoantibodies to oxidative DNA-based damage found significantly higher levels among women who smoke than among men who smoke (46). Observational evidence suggests that estrogens may increase levels of triglycerides and total lipids in human pancreas (47, 48), and, thus, increase the level of reactive oxygen species and subsequent DNA damage in the pancreas. Moreover, endogenous estrogens themselves may damage DNA (49) or synergistically increase the DNA-damaging properties of tobacco smoke. Other potential biological explanations include lower DNA repair capacity in women (50), differences in response to DNA-damaging agents between women and men (51–53), and sex-specific expression of receptors for gastrin-releasing peptide, which has been demonstrated in pancreas cells (54) and has been hypothesized recently to play a role in observed gender differences in smoking-related lung cancer susceptibility (55). Analogous to the lung cancer susceptibility issue, a number of previous studies of pancreatic cancer among men and women, including observations in our San Francisco Bay Area population, have reported stronger smoking-related associations among women than among men (3, 40, 56–58). Because of the inherent limitations of the case-control study design, we cannot rule out the possibility that the background risk of pancreatic cancer for male never-smokers is higher than that for female never-smokers. Such a difference in background risks could contribute to the larger relative risks for smoking and pancreatic cancer among women than among men as observed in this study and in other studies (3, 40, 56,

57). However, this phenomenon is unlikely to explain all of the gender differences in relative risk for the combined effect of *XRCC1* genotype and smoking, because our relative risk estimates for heavy smoking and pancreatic cancer were only 20% higher among women than among men when passive smoking was removed from the referent group of never smokers.

The mechanism by which tobacco carcinogens act in the human pancreas is currently unknown. Smoking has been associated with oxidative stress and DNA damage in animal and human pancreatic specimens (4–9). Thus, efficient repair of oxidative DNA damage in pancreas tissue may be important in highly exposed individuals. The *Arg399Gln* amino acid change occurs within the central breast cancer susceptibility gene 1 product COOH terminus domain of human XRCC1 (codons 314–402; Ref. 25), a protein-binding motif present in several cell cycle and repair proteins including BRCA1. This motif appears to be important in DNA damage detection, DNA end binding, multimerization, and genetic stability (59). The *Arg399Gln* polymorphism also occurs within a PARP binding region (codons 301–402; Refs. 24, 60). Thus, this polymorphism has the potential to influence XRCC1 function. In studies using human cells and tissues, the variant allele (*399Gln*) has been associated with biomarkers of DNA damage including higher glycophorin (GPA) mutant frequency (26), elevated DNA adduct levels (26, 27, 30), higher baseline sister chromatid exchange frequency (27, 28), and increased sensitivity to ionizing radiation as measured by prolonged mitotic delay (29).

In analyses of genotype-genotype interaction, ORs and ICRs were strongest for combined *XRCC1*, *GSTT1*, and *GSTM1* variant genotypes. Furthermore, these interactions were observed predominantly among women. The observed (age-, race-, and smoking-adjusted) interactions between *XRCC1* genotype and metabolic genotypes suggest that these genes in combination may be important in determining susceptibility to pancreatic cancer irrespective of tobacco carcinogen exposure and that women could be more susceptible within a given genetic background than are men. These observations also raise the possibility that other (nontobacco) sources of carcinogens or oxidant stress play a role in pancreatic carcinogenesis. Indeed, tobacco smoking is believed to account for 26–29% of pancreatic cancer incidence (3, 56, 61). However, the magnitude of such estimates of population attributable fraction may vary depending on the genetic background of the population under study, including variation in alleles of genes for carcinogen-metabolism, DNA repair, and other key biochemical pathways that may interact with constituents in tobacco smoke (40).

We conducted tests for Hardy-Weinberg equilibrium among controls and found evidence of possible deviations for *XRCC1* alleles among Caucasians. Deviations from Hardy-Weinberg equilibrium can result from systematic errors in genotyping, population stratification, or inbreeding. We cannot rule out the possibility that biased sampling may have contributed to stratification in our population sample; however, bias from stratification and inbreeding is unlikely in a dynamic and heterogeneous ("outbred") Caucasian population such as that found in the San Francisco Bay Area (62). In unpublished pilot data, we compared the Masscode genotyping assay for *XRCC1* codon 399 with a standard PCR-RFLP method (27). In this comparison of two different genotyping methods, we observed no discordant pairs, suggesting no systematic bias for *XRCC1* genotyping using the mass spectrometry-based assay. Furthermore, random error was low because the proportion of discordant pairs among all of the repeated pairs ($n = 128$) using this assay was 3% ($n = 4$). Nevertheless, because our allele and genotype frequencies for *XRCC1 399Gln* were lower than expected, our estimates of ORs are likely to be conservative, because the true type I error (the chance of rejecting the null hypothesis of no association when it is true) is likely lower than assumed (63).

Potential weaknesses in our study include possible recruitment bias among pancreatic cancer cases associated with the rapidly fatal course of this disease and the potential role of chance in some gender-specific comparisons. If *XRCC1* genotype is associated with lower mortality, our data are likely to underestimate the true effect of *XRCC1* alleles on risk of pancreatic cancer. Whereas we cannot rule out the potential influence of systematic differences between participants and nonparticipants in the laboratory portion of the study on measures of association and interaction, these differences would also have to vary accordingly by *XRCC1* genotype.

In summary, our data provide evidence for synergy between the *XRCC1 399Gln* allele and tobacco smoking in relation to the risk of pancreas cancer. Our finding of stronger associations and interactions among women is suggestive but requires replication in additional study populations. A number of case-control studies have evaluated the role of *XRCC1* polymorphisms in human cancer including such diverse sites as head and neck, colon, stomach, esophagus, lung, bladder, breast, and skin (31–39). Our results are consistent with the genotype-phenotype studies that suggest *XRCC1 399Gln* is the at-risk allele (26–30) and with some case-control studies (31–34, 39) but not with others (35–38). Inconsistencies across studies could result from variations in tissue-specific XRCC1 expression levels, exposure-specific effects of *XRCC1* alleles, and competing or overlapping biochemical pathways (16, 64). Nevertheless, we believe that the *XRCC1* codon 399 polymorphism warrants additional study in the context of cancer susceptibility, and that basic research on the function of this protein, its allelic variants, and other BER proteins should continue.

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