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Genetic variation in *CYP17A1* and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California

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Pancreatic cancer is the fourth leading cause of cancer-related death in men and women in the United States. Reproductive factors and steroid hormones have been suspected risk factors for many years, but the results from epidemiologic studies to date have been inconclusive. *CYP17A1* encodes cytochrome P450c17α, an enzyme with 17α-hydroxylase and 17,20-lyase activities in estradiol biosynthesis. A polymorphism in the 5′UTR promoter region of *CYP17A1*-34T/C(A1/A2) has been associated with circulating estrogens in premenopausal women and with susceptibility to breast, prostate, and endometrial cancer. Questionnaire data and germline DNA collected in a San Francisco Bay Area population-based case-control study of pancreatic cancer (cases = 532, controls = 1701) were used to conduct analyses of pancreatic cancer susceptibility related to the *CYP17A1* polymorphism and whether effects associated with smoking and reproductive risk factors were modified by this polymorphism. Mass spectrometry– and TaqMan-based methods were used to determine *CYP17A1* genotypes in DNA samples from 308 cases and 964 controls. Results showed that carriers of the A2 allele (*vs.* A1/A1) were significantly less likely to have been diagnosed with pancreatic cancer (A1/A2, adjusted odds ratio (OR) = 0.77, 95% confidence interval (CI) = 0.58-1.0; A2/A2, OR = 0.63, 95%CI = 0.42-0.93; *p*-trend = 0.01). ORs for *CYP17A1* genotypes did not differ by sex, but the observed inverse association was stronger in postmenopausal women. ORs for smoking and pancreatic cancer were not modified by *CYP17A1* genotype. Our results suggest that the *CYP17A1* A2 allele may be associated with a lower risk of pancreatic cancer in both men and women.

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States.[1] Few environmental risk factors have been identified, including smoking and some dietary factors.[2,3] Incidence rates are approximately 25-50% higher in men than in women, but this difference becomes less marked at older ages (>75 years).[2] Combined with evidence from cell line and animal studies, these data have been used as a rationale to investigate the association between pancreatic cancer and hormonal and reproductive factors.[4–7] However, the results from most studies[8–30] have been inconclusive partly because of design and analysis methods such as the use of proxy data in earlier studies, inconsistencies in analytic approach, small sample size and inadequate control for smoking, as well as other potential confounders.

Cytochrome P450c17alpha (*CYP17A1*) is located in the 10q24.32 chromosomal region and encodes cytochrome P450c17α, an enzyme with 17α-hydroxylase and 17,20-lyase activities at branch points in estrogen and testosterone biosynthesis.[31] One extensively studied polymorphism in *CYP17A1* (-34T/C, A1/A2, rs743572) is located in the 5′untranslated promoter region.[32] The *CYP17A1*-34C (A2) allele was reported to result in higher P450c17α mRNA levels[32] and possibly higher endogenous levels of sex steroids. However, results from studies that have evaluated the functional effects of *CYP17A1* alleles have been inconsistent.[31,33,34] *CYP17A1* A2 genotypes may

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influence circulating estrogen levels, but this appears to be limited to premenopausal women.[31,34–37] A number of studies have reported an association between this polymorphism and age at menarche and estrogen use.[31] Finally, the *CYP17A1* A2 allele has been associated with the hormone-related cancers endometrial (A2 allele associated with lower risk, OR range 0.62 to 0.44 based on 5 studies each with fewer than 200 cases, and no association for one study with 497 cases), breast (A2 allele associated with a slight increased risk, summary OR = 1.05; 95% CI = 0.87-1.21 based on 15 case-control studies) and prostate (A2 associated with increased risk in men of African descent, summary OR = 1.56; 95% CI = 1.07-2.28, on the basis of 3 studies).[34,36,38–43]

The association between the *CYP17A1*-34 C/T (A1/A2) polymorphism and pancreatic cancer was investigated as a follow-up to previous analyses of reproductive factors and pancreatic cancer risk in our large population-based case-control study in the San Francisco Bay Area.[11] Here, we determined the main effects of the *CYP17A1* polymorphism with pancreatic cancer, as well as potential gene-environment interactions with smoking and reproductive factors in patients with ductal adenocarcinoma of the pancreas and population-based controls.

Material and Methods

Population

A population-based case-control study of pancreatic cancer was conducted in 6 San Francisco Bay Area counties (Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara) between 1994 and 2005. Detailed methods on the study design and selection methods for the full study have been previously published.[11,44–49] Briefly, cases with ductal adenocarcinoma of the pancreas diagnosed in 1995 to 1999 were identified by use of rapid case ascertainment at the Northern California Cancer Center with the goal of ascertaining cases within 1 month of pancreatic cancer diagnosis. Cases were between 21 and 85 years of age, resided in 1 of the 6 counties at diagnosis, were alive when first contacted and were able to complete an interview in English. A total of 532 eligible cases completed the interview for a 67% response rate.[47–49] Cancer diagnoses were confirmed by use of the Surveillance, Epidemiology, and End Results abstracts and by participants' physicians.

Control participants were identified with random-digit dial and were frequency matched to the cases in an approximate 3:1 ratio by sex and 5-year age group. Eligibility criteria were identical for control and case participants with the exception of pancreatic cancer status. Recruitment for controls older than 65 years was supplemented with Health Care Finance Administration (now Center for Medicare and Medicaid Services) lists for the 6 Bay Area counties. A total of 1,701 eligible control participants completed the interview for a 67% response rate.[47–49]

The present analyses are based on 308 cases and 964 controls who gave a blood sample as part of the laboratory protocol of the parent study. Detailed methods for the laboratory part of the study, including a detailed comparison of participants who gave blood and those who did not, have been previously published.[50–53] The study interviewers obtained separate written informed consent from all participants before conducting the interview or venipuncture. Study methods and protocols were approved by the University of California Committee on Human Research.

Exposure and demographic information were obtained from the participants during in-person interviews conducted by trained interviewers using structured questionnaires. No proxy interviews were conducted. Race groups were based on self-report and defined as white or Caucasian, black or African American, Asian or other (5 cases, 15 controls of mixed race). Results are not presented separately for "other race" because of sparse data. Smokers were those who had smoked more than 100 cigarettes in their lifetime and had smoked cigars or pipes at least once per month for 6 months or more. Never smokers who reported a history of involuntary (passive) smoking at home as an adult (women: 32 cases, 95 controls; men: 5 cases, 21 controls) were combined with former active smokers and pipe or cigar smokers to form 3 groups (never, former and current) used in analyses of smoking status.

Laboratory

Genomic DNA was extracted from whole blood with the QIAmp DNA Blood Mini kit (Qiagen, Hilden, Germany). *CYP17A1* -34 C/T (A1/A2) (*rs*743572) genotyping was performed with a mass spectrometry method (MassCode, Qiagen Genomics, Inc) and was repeated on a 10% random sample of DNA specimens and found to be discordant in 3 of 128 pairs. MassCode genotyping resulted in no-calls for 8.4% of cases and 4.2% of controls. Specimens that did not replicate or that were "no calls" (plus a random 5%) were repeated with a previously designed TaqMan assay. After repeat genotyping, all no-calls and discordant genotypes were resolved; thus there were no missing values for *CYP17A1* genotypes used in these analyses.

Statistical analysis

Tests for Hardy-Weinberg equilibrium among controls were conducted with observed genotype frequencies and a χ^2 test with 1 degree of freedom. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated by use of unconditional logistic regression in SAS (version 9.1, SAS Institute, Cary, NC). All models were adjusted for age and sex, the frequency-matched variables. Tests for trend were based on the χ^2 p value from the adjusted unconditional logistic regression models where genotype was included as an ordinal variable representing the number of variant alleles present, e.g. 0, 1, 2. False-positive report probabilities (FPRP) were provided for a range of priors (0.01 to 0.1) on the basis of previous reports of associations of the 5′UTR A1/A2 polymorphism with cancer and the existence of functional data,[31,34,37,38,40–42,54,55]

Table 1. Odds ratios for *CYP17A1* and pancreatic cancer, San Francisco Bay Area, California 1995–1999

	All participants			Non-Hispanic white			<70 yr		
	Cases	Controls	OR* (95% CI)	Cases	Controls	OR** (95% CI)	Cases	Controls	OR* (95% CI)
***CYP17A1* 5′UTR**									
A1/A1	131	339	1.0 (referent)	101	287	1.0 (referent)	81	207	1.0 (referent)
A1/A2	133	440	0.77 (0.58-1.0)	113	372	0.82 (0.60-1.1)	83	259	0.80 (0.55-1.2)
A2/A2	44	185	0.63 (0.42-0.93)	32	141	0.66 (0.42-1.0)	27	127	0.55 (0.33-0.91)
p-trend			0.01			0.06			0.02

*Adjusted for age, sex, race and smoking status. **Adjusted for age, sex and smoking status.

Table 2. Odds ratios for *CYP17A1* and pancreatic cancer by sex, San Francisco Bay Area, California 1995–1999

	All Women			Post-Menopausal Women			Men		
	Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
***CYP17A1* 5′UTR**									
A1/A1	60	156	1.0 (referent)	57	138	1.0 (referent)	71	183	1.0 (referent)
A1/A2	61	197	0.80 (0.52-1.2)	58	167	0.82 (0.53-1.3)	72	243	0.73 (0.50-1.1)
A2/A2	19	79	0.62 (0.34-1.1)	14	68	0.48 (0.24-0.93)	25	106	0.62 (0.37-1.0)
p-trend			0.1			0.04			0.05

*Adjusted for age, race and smoking status.

and assuming FPRP noteworthiness at values below 0.5.[56] For ease of presentation, interactions (departures from multiplicative effects) were evaluated by use of stratified methods. Continuous variables for reproductive factors were compared across *CYP17A1* genotypes with a Kruskal-Wallis test. The following reproductive factors were evaluated as continuous variables in analyses to detect differences by *CYP17A1* genotype in control women: age at menarche (years), age at menopause (years), age at first use of oral contraceptives (OC, years), age at first use of estrogen replacement therapy (ERT, years), total duration of OC use (months) and body mass index (BMI, kg/m^2).

Results

The *CYP17A1* 5′UTR -34 T/C polymorphism satisfied Hardy-Weinberg equilibrium for each control group by race (all p values >0.1, data not shown). The *CYP17A1* 5′UTR polymorphism was inversely associated with pancreatic cancer in all participants combined (adjusted for age, sex, race, and smoking status) (Table 1), and in each group by race [adjusted for age, sex, and smoking status, in African Americans: A1/A2 OR = 0.39, 95% CI = 0.12-1.3; A2/A2 OR = 0.16, 95% CI = 0.03-1.0 (both compared to A1/A1); in Asian Americans: A1/A2 OR = 0.33, 95% CI = 0.08-1.5; A2/A2 OR = 0.49, 95% CI = 0.11-2.1 (both compared to A1/A1)]. Decreasing trends in *CYP17A1* genotype ORs also were observed in non-Hispanic whites, and in participants under 70 years of age (Table 1), but not among those 70+ years of age (data not shown). Consistent inverse associations were observed by sex and were somewhat stronger in postmenopausal women (Table 2). Although smoking was not a confounder of the associations between *CYP17A1* genotype and pancreatic cancer, we kept this variable in all final models because it is an established risk factor.

False-positive report probabilities (FPRP) for the associations between A2/A2 and pancreatic cancer reported in Table 1 were as follow (for prior probabilities ranging from 0.01 to 0.1) for all participants (FPRP = 0.769, 0.232); for non-Hispanic whites (FPRP = 0.908, 0.474); and for participants <70 yr. (FPRP = 0.798, 0.264). For the lower range of priors (0.01), these results were not considered noteworthy (all FPRP >0.5), but for the higher end of the range of priors (0.1), the results were all considered noteworthy (all FPRP <0.5). FPRP values for the associations between A2/A2 and pancreatic cancer reported in Table 2 were as follow (for prior probabilities ranging from 0.01 to 0.1) for all women (FPRP = 0.953, 0.648); for postmenopausal women (FPRP = 0.854, 0.348) and for men (FPRP = 0.908, 0.474). For the lower range of priors (0.01), the results in Table 2 were not noteworthy (all FPRP >0.5). For the higher end of the range of priors (0.1), the results were noteworthy in postmenopausal women and in men (all FPRP <0.5), but not in all women (FPRP >0.5).

Mean or median age at menarche (in years), age at menopause, age at first OC use, and body-mass index (kg/m^2) were independent of *CYP17A1* genotypes in control women (data not shown). A shorter mean total duration of OC use was observed in control women with the *CYP17A1* A2 allele (A1/A1: 58.7 months; A1/A2: 48.6 months; A2/A2: 47.1

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Table 3. Odds ratios for smoking status and exogenous hormone use and pancreatic cancer, by *CYP17A1* genotype, San Francisco Bay Area, California 1995–1999

	CYP17A1 A1/A1		*CYP17A1* A1/A2 +A2/A2	
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)
Men and Women*				
Smoking status				
Never	21/80	1.0 (referent)	26/128	1.0 (referent)
Former	83/221	1.4 (0.79-2.4)	108/419	1.2 (0.77-2.0)
Current	27/38	2.7 (1.3-5.5)	43/78	2.7 (1.5-4.7)
All women†				
ERT/OC Use				
Neither	12/29	1.0 (referent)	21/50	1.0 (referent)
OC only	10/30	1.0 (0.31-3.4)	19/53	1.1 (0.46-2.7)
ERT only	21/51	1.0 (0.43-2.4)	21/75	0.67 (0.33-1.4)
ERT and OC	16/43	1.1 (0.40-2.8)	18/91	0.55 (0.25-1.2)
p-trend		0.6		0.04
Postmenopausal women†				
ERT/OC Use				
Neither	12/27	1.0 (referent)	20/42	1.0 (referent)
OC only	7/17	1.1 (0.31-4.2)	12/26	0.95 (0.34-2.6)
ERT only	21/50	1.0 (0.41-2.5)	21/74	0.61 (0.29-1.3)
ERT and OC	16/41	1.2 (0.40-3.5)	18/86	0.45 (0.18-1.1)
p-trend		0.8		0.03

*OR adjusted for age, sex and race. †Adjusted for age, race and smoking status. Abbreviations: ERT, estrogen replacement therapy; OC, oral contraceptive.

months), although differences in duration of use could have been due to chance (p value = 0.6).

Odds ratios for smoking status and pancreatic cancer were not modified by *CYP17A1* genotype (Table 3). In analyses of ERT and oral contraceptives (OC) used either alone or in combination (stratified by *CYP17A1* genotype), there was some suggestion of an inverse association (in all women and in postmenopausal women) with a combination of A2 allele genotypes and exogenous hormone use, although estimates were imprecise (Table 3).

Discussion

Our analyses of the *CYP17A1* 5′UTR -34 T/C (A1/A2) polymorphism and pancreatic cancer showed that the A2 allele conferred a 23 to 37% decreased risk. These results were consistent across race groups and observed in both men and postmenopausal women.

If *CYP17A1* A2 is associated with an increase in endogenous hormone levels such as estradiol, then our observation of an inverse association between this allele and pancreatic cancer risk would provide support for the hypothesis that estrogens reduce the risk of pancreatic cancer. However, results from several studies showed little or no association between *CYP17A1* A2 genotypes and levels of sex steroids, except possibly in younger premenopausal women.[31,34–37]

Associations between *CYP17A1* A2 genotypes have been observed in several hormone-related cancers including endometrial,[34] and breast in women,[38,39,57] and prostate cancer in men of African ancestry.[43,58] Some studies of *CYP17A1* and breast cancer have reported interactions with reproductive factors, ERT use and BMI.[38,57] A number of studies have reported associations between *CYP17A1* A2 and earlier age at menarche,[31] and a recent Swedish study found associations with menstrual cycle length, age at first use of OC, and *BRCA* non-carrier mutation status in women from known *BRCA1/2* families.[54] In contrast, among women in our study population, there were no statistically significant associations between *CYP17A1* genotypes and self-reported age at menarche, age at menopause, age of first OC use, age of first ERT use, duration of OC use and BMI.

The putative functional effect of *CYP17A1* alleles, whether in linkage disequilibrium (LD) or not, may be more subtle than a direct effect on serum hormone levels. Tissue specificity for *CYP17A1* or other hormone metabolites and pathways are likely to be involved. For example, 2-methoxyestradiol, an endogenous metabolite of 17β-estradiol can trigger pancreatic cancer cells to up-regulate cell death pathways.[59]

We cannot rule out the potential for recall bias and measurement error related to poor recall of past events (such as

ages at menarche or menopause, or exogenous hormone use). Replication of these results in other study populations, and analyses of pooled data from pancreatic cancer consortia are needed to confirm or refute a possible role of the *CYP17A1* A2 allele in pancreatic cancer etiology.

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