Null Results in Brief

Single Nucleotide Polymorphisms in Obesity-Related Genes and the Risk of Esophageal Cancers

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Abstract

Rates of adenocarcinoma of the esophagus (EAC) and esophagogastric junction (EGJAC) have been rising rapidly in recent decades, in contrast to the declining rates of esophageal squamous cell carcinomas (ESCC). Obesity is a major risk factor for both EAC and EGJAC, but not ESCC, and there is speculation that obesity promotes adenocarcinoma development through endocrine and related pathways. We therefore compared the prevalence of 12 single nucleotide polymorphisms (SNPs) in nine candidate genes previously implicated in obesity pathways (*LEP, LEPR, ADIPOQ, POMC, PPARα, PPARγ, RXRγ, GHRL*, and *INSIG2*) in a large Australian case-control study comprising DNA samples from 260 EAC cases, 301 EGJAC cases, 213 ESCC cases, and 1,352 population controls. No SNPs were associated with EGJAC or ESCC. Although several SNPs seemed to be associated with EAC on crude analysis [*ADIPOQ* (rs1501299), *LEP* (5′-untranslated region), *PPARγ* (H447H), and *GHRL* (M72L)], effect sizes were modest and none of the associations was significant after correcting for multiple comparisons. Further, we found no consistent evidence that any of the genotypes were associated with risk of EAC or EGJAC within strata of body mass index (<25.0 kg/m^2, 25.0-29.9 kg/m^2, >30 kg/m^2). In conclusion, our data suggest that these SNPs do not play a major role in esophageal carcinogenesis. (Cancer Epidemiol Biomarkers Prev 2008;17(4):1007–12)

Introduction

The incidence of adenocarcinomas of the esophagus (EAC) and esophagogastric junction (EGJAC) has been rising in many Western populations, whereas the incidence of esophageal squamous cell carcinomas (ESCC) has been declining (1-3). Obesity has been identified as a major risk factor for EAC and EGJAC (4-8), and it is likely that the increasing prevalence of obesity (9) underlies the rising incidence of these cancers. Because obesity has been associated with increased risks of several cancers (10), there is speculation that obesity may promote tumor development through endocrine and related pathways. Leading candidate genes include *leptin* (*LEP*; ref. 11), *leptin receptor* (*LEPR*; ref. 12), *adiponectin* (*ADIPOQ*; ref. 13), *proopiomelanocortin* (*POMC*; ref. 14), *peroxisome proliferative-activated receptor α* (*PPARα*; ref. 15), *peroxisome proliferative-activated receptor γ* (*PPARγ*; ref. 16), *retinoid X receptor γ* (*RXRγ*; ref. 17), *ghrelin* (*GHRL*; ref. 18), and *insulin-induced gene 2* (*INSIG2*; ref. 19). To address the hypothesis that single nucleotide polymorphisms (SNPs) in these genes are specifically associated with EAC, we investigated possible associations between SNPs in these genes and risk of developing EAC, EGJAC, and ESCC in a population-based case-control study conducted in Australia.

Materials and Methods

Study Population. Full details of the study have been published previously (8). Briefly, we recruited patients diagnosed between July 1, 2002 (July 1, 2001 in the state of Queensland) and June 30, 2005 with histologically confirmed EAC, EGJAC, or ESCC. Simultaneously, we recruited 1,580 matched controls selected at random from a population register. Detailed information was collected about height, weight 1 y before diagnosis (before recruitment for controls), cigarette smoking, alcohol consumption, and frequency of symptoms of gastroesophageal acid reflux, as reported previously (8, 20). Complete epidemiologic data and DNA were available for 260 EAC cases, 301 EGJAC cases, 213 SCC cases, and 1,352 controls. Approval was obtained from the human research ethics committees of the Queensland Institute of Medical Research and participating hospitals throughout mainland Australia and written informed consent was obtained from all participants.

Received 1/14/08; accepted 2/12/08.

Grant support: Queensland Cancer Fund project grant and National Health and Medical Research Council of Australia Program grant 199600. N.K. Hayward, P.M. Webb, and D.C. Whiteman are supported by Research Fellowships from the National Health and Medical Research Council of Australia.

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doi:10.1158/1055-9965.EPI-08-0023

Table 1. Associations between polymorphisms in multiple obesity-related genes and risk of EAC, EGJAC, and ESCC

Locus description	Genotype	Control proportion (n = 1,352)	EAC		
			Proportion (n = 260)	P*	OR† (95% CI)
rs1501299	GG	0.56	0.63		1.0 (reference)
ADIPOQ	GT	0.37	0.34		0.75 (0.54-1.03)
Intron	TT	0.07	0.03		0.38 (0.17-0.83)
	Minor allele	0.26	0.20	0.008	
rs2167270	GG	0.40	0.36		1.0 (reference)
LEP	GA	0.46	0.50		1.41 (1.02-1.95)
5′-UTR	AA	0.13	0.13		1.21 (0.75-1.95)
	Minor allele	0.36	0.39	0.4	
rs1137100 (K109R)	AA	0.53	0.52		1.0 (reference)
LEPR	AG	0.39	0.38		0.93 (0.67-1.27)
Nonsynonymous coding	GG	0.09	0.09		1.20 (0.70-2.05)
	Minor allele	0.28	0.29	0.8	
rs1137101 (Q223R)	AA	0.31	0.28		1.0 (reference)
LEPR	AG	0.49	0.54		1.25 (0.88-1.76)
Nonsynonymous coding	GG	0.20	0.18		1.08 (0.69-1.68)
	Minor allele	0.44	0.45	0.9	
rs8179183 (K656N)	GG	0.69	0.69		1.0 (reference)
LEPR	GC	0.28	0.28		1.12 (0.80-1.57)
Nonsynonymous coding	CC	0.03	0.03		1.09 (0.48-2.52)
	Minor allele	0.17	0.17	1.0	
rs1042571	GG	0.66	0.65		1.0 (reference)
POMC	GA	0.31	0.31		1.05 (0.76-1.44)
3′-UTR	AA	0.03	0.04		2.08 (0.95-4.58)
	Minor allele	0.18	0.20	0.5	
rs1800206 (L162V)	CC	0.88	0.87		1.0 (reference)
PPARα	CG	0.12	0.13		1.26 (0.81-1.98)
Nonsynonymous coding	GG	0.00	0.01		2.59 (0.34-19.7)
	Minor allele	0.06	0.07	0.6	
rs3856806 (H447H)	CC	0.79	0.73		1.0 (reference)
PPARγ	CT	0.20	0.25		1.36 (0.95-1.93)
Synonymous coding	TT	0.01	0.02		2.09 (0.74-5.94)
	Minor allele	0.11	0.15	0.04	
rs1128977 (A140A)	GG	0.38	0.41		1.0 (reference)
RXRγ	GA	0.46	0.42		0.81 (0.59-1.13)
Synonymous coding	AA	0.15	0.18		1.07 (0.70-1.64)
	Minor allele	0.39	0.39	1.0	
rs4684677 (L90Q)	AA	0.88	0.91		1.0 (reference)
GHRL	AT	0.11	0.09		0.77 (0.46-1.29)
Nonsynonymous coding	TT	0.00	0.00		
	Minor allele	0.06	0.05	0.2	
rs696217 (M72L)	CC	0.85	0.79		1.0 (reference)
GHRL	CA	0.14	0.21		1.69 (1.14-2.50)
Nonsynonymous coding	AA	0.01	0.00		
	Minor allele	0.08	0.10	0.05	
rs7566605	GG	0.46	0.48		1.0 (reference)
INSIG2	GC	0.44	0.40		0.82 (0.59-1.13)
10 kb upstream	CC	0.11	0.12		1.0 (0.61-1.65)
	Minor allele	0.32	0.32	0.9	

*P control versus case comparison.
† ORs and 95% CIs adjusted for age (in years), sex, smoking, BMI, and frequency of gastroesophageal reflux symptoms.

SNP Selection and Genotyping. Twelve SNPs were selected from nine obesity-related genes: *LEP, LEPR, ADIPOQ, POMC, PPARα, PPARγ, RXRγ, GHRL*, and *INSIG2*. SNP selection was based on previously published results showing allelic associations between these polymorphisms and obesity (11-22). Polymorphisms included six coding region nonsynonymous mutations, two synonymous mutations, three 5′ and 3′ SNPs, and one intronic SNP (Table 1). Genotyping was conducted using the Sequenom iPLEX protocol (Sequenom) as previously published (20).

Statistical Analyses. We calculated Hardy-Weinberg equilibrium and allele frequencies and assessed linkage disequilibrium using Haploview (21). Minor allele frequencies between case and control groups were tested using χ^2 analyses, with P values presented in Table 1. To estimate the relative risk of cancer associated with each SNP, we calculated the odds ratio (OR) and 95% confidence interval (95% CI) using multivariable logistic regression in Statistical Analysis System version 9.1 (SAS Institute, Inc.). Initial models were adjusted only for age and sex; final models included terms for age, sex, body mass index (BMI), smoking history, and frequency of gastroesophageal reflux symptoms 10 y before diagnosis. Additional adjustment for alcohol consumption, frequency of nonsteroidal anti-inflammatory drug use, and education made essentially no difference to the risk

Table 1. Associations between polymorphisms in multiple obesity-related genes and risk of EAC, EGJAC, and ESCC (Cont'd)

EGJAC			ESCC		
Proportion (n = 301)	P*	OR † (95% CI)	Proportion (n = 213)	P*	OR † (95% CI)
0.53		1.0 (reference)	0.60		1.0 (reference)
0.36		0.96 (0.72-1.29)	0.34		0.89 (0.64-1.25)
0.10		1.50 (0.94-2.39)	0.05		0.72 (0.36-1.43)
0.29	0.2		0.22	0.2	
0.38		1.0 (reference)	0.40		1.0 (reference)
0.44		1.04 (0.77-1.39)	0.49		1.09 (0.77-1.53)
0.18		1.40 (0.94-2.08)	0.12		0.87 (0.52-1.45)
0.40	0.2		0.36	0.9	
0.53		1.0 (reference)	0.54		1.0 (reference)
0.42		1.0 (0.76-1.33)	0.38		0.89 (0.64-1.25)
0.05		0.72 (0.40-1.31)	0.08		1.0 (0.55-1.80)
0.26	0.3		0.27	0.5	
0.27		1.0 (reference)	0.30		1.0 (reference)
0.53		1.28 (0.93-1.75)	0.50		1.01 (0.70-1.45)
0.20		1.30 (0.87-1.93)	0.20		1.08 (0.68-1.70)
0.46	0.3		0.45	1.0	
0.68		1.0 (reference)	0.66		1.0 (reference)
0.27		0.98 (0.72-1.33)	0.32		1.16 (0.82-1.64)
0.04		1.51 (0.77-2.96)	0.02		0.91 (0.34-2.44)
0.18	0.6		0.18	0.5	
0.67		1.0 (reference)	0.64		1.0 (reference)
0.28		0.93 (0.69-1.25)	0.31		1.09 (0.77-1.54)
0.04		1.56 (0.76-3.22)	0.04		1.85 (0.84-4.10)
0.19	0.9		0.20	0.4	
0.88		1.0 (reference)	0.85		1.0 (reference)
0.11		0.96 (0.63-1.48)	0.15		1.21 (0.77-1.92)
0.01		3.42 (0.65-18.0)	0.00		1.23 (0.12-12.8)
0.06	1.0		0.08	0.4	
0.74		1.0 (reference)	0.80		1.0 (reference)
0.24		1.24 (0.90-1.71)	0.19		1.03 (0.69-1.53)
0.02		1.58 (0.54-4.61)	0.01		1.14 (0.24-5.28)
0.14	0.1		0.11	0.8	
0.33		1.0 (reference)	0.39		1.0 (reference)
0.52		1.28 (0.95-1.72)	0.46		0.98 (0.69-1.38)
0.14		1.06 (0.70-1.61)	0.15		0.95 (0.59-1.53)
0.41	0.3		0.38	1.0	
0.90		1.0 (reference)	0.90		1.0 (reference)
0.09		0.70 (0.44-1.13)	0.10		0.81 (0.48-1.37)
0.01		1.28 (0.23-7.03)	0.00		
0.05	0.4		0.05	0.4	
0.84		1.0 (reference)	0.88		1.0 (reference)
0.16		1.13 (0.77-1.66)	0.11		0.81 (0.49-1.33)
0.00		0.43 (0.05-3.39)	0.01		1.20 (0.26-5.62)
0.08	0.6		0.06	0.5	
0.46		1.0 (reference)	0.42		1.0 (reference)
0.45		0.98 (0.74-1.32)	0.48		1.13 (0.81-1.58)
0.09		0.81 (0.49-1.32)	0.11		1.13 (0.66-1.94)
0.32	0.7		0.34	0.5	

estimates. In further analyses, we assessed genotypic associations within strata of BMI using standard WHO cut points (22). We assessed statistical significance at $\alpha = 0.05$, which became 0.004 after Bonferroni correction (0.05/12).

Results

All SNPs were in Hardy-Weinberg equilibrium. Table 1 shows genotype and allele frequencies for each SNP in controls compared with the three case groups. P values are presented for the minor allele comparisons. Although several SNPs seemed to be associated with EAC {*ADIPOQ* (rs1501299), *LEP* [5′-untranslated region (UTR)], *PPARγ* (H447H), and *GHRL* (M72L)}, these were not statistically significant following Bonferroni correction.

After stratification for BMI, the effect sizes for *PPARα*, *PPARγ*, and *GHRL* markedly increased for persons with BMI <25 kg/m^2 (Table 2, EAC only), whereas the OR for *POMC* was significantly increased in the BMI ≥30 kg/m^2 group. There were no other consistent patterns across BMI strata for EAC, and none for EGJAC or ESCC.

Discussion

The Australian Cancer Study constitutes one of the largest available collections of tissue and risk factor data

Table 2. Associations between polymorphisms in multiple obesity-related genes and the risk of EAC, EGJAC, and ESCC and BMI

Locus description	Genotype	EAC		
		BMI ≤25 kg/m^2	BMI 25-29.9 kg/m^2	BMI ≥30 kg/m^2
		OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
rs1501299	GG	1.0 (reference)	1.0 (reference)	1.0 (reference)
ADIPOQ	GT	0.52 (0.25-1.11)	0.89 (0.56-1.43)	0.69 (0.40-1.20)
Intron	TT		0.80 (0.31-2.03)	0.22 (0.05-1.05)
rs2167270	GG	1.0 (reference)	1.0 (reference)	1.0 (reference)
LEP	GA	2.13 (0.98-4.63)	1.92 (1.15-3.20)	0.84 (0.49-1.45)
5′-UTR	AA	1.76 (0.59-5.25)	1.87 (0.94-3.74)	0.54 (0.22-1.33)
rs1137100 (K109R)	AA	1.0 (reference)	1.0 (reference)	1.0 (reference)
LEPR	AG	1.65 (0.82-3.34)	1.03 (0.64-1.66)	0.57 (0.33-0.98)
Nonsynonymous coding	GG	0.91 (0.19-4.42)	2.20 (1.08-4.47)	0.53 (0.19-1.50)
rs1137101 (Q223R)	AA	1.0 (reference)	1.0 (reference)	1.0 (reference)
LEPR	AG	1.56 (0.71-3.4)	1.78 (1.03-3.05)	0.74 (0.41-1.33)
Nonsynonymous coding	GG	1.10 (0.39-3.08)	2.11 (1.09-4.10)	0.48 (0.22-1.05)
rs8179183 (K656N)	GG	1.0 (reference)	1.0 (reference)	1.0 (reference)
LEPR	GC	1.73 (0.85-3.51)	0.66 (0.39-1.12)	1.64 (0.91-2.95)
Nonsynonymous coding	CC	1.95 (0.36-10.7)	0.63 (0.18-2.24)	2.43 (0.48-12.3)
rs1042571	GG	1.0 (reference)	1.0 (reference)	1.0 (reference)
POMC	GA	1.42 (0.70-2.89)	0.76 (0.47-1.25)	1.26 (0.72-2.20)
3′-UTR	AA	1.49 (0.30-7.43)	1.50 (0.44-5.07)	7.48 (1.31-42.6)
rs1800206 (L162V)	CC	1.0 (reference)	1.0 (reference)	1.0 (reference)
PPARα	CG	3.98 (1.85-8.57)	0.76 (0.35-1.64)	0.71 (0.30-1.71)
Nonsynonymous coding	GG		3.20 (0.26-39.8)	1.54 (0.09-26.7)
rs3856806 (H447H)	CC	1.0 (reference)	1.0 (reference)	1.0 (reference)
PPARγ	CT	0.98 (0.43-2.25)	0.94 (0.54-1.65)	2.58 (1.41-4.72)
Synonymous coding	TT	9.45 (1.35-66.2)	0.40 (0.04-3.63)	4.81 (0.83-27.7)
rs1128977 (A140A)	GG	1.0 (reference)	1.0 (reference)	1.0 (reference)
RXRγ	GA	1.29 (0.61-2.74)	0.86 (0.53-1.41)	0.59 (0.34-1.04)
Synonymous coding	AA	1.63 (0.62-4.32)	1.11 (0.59-2.09)	0.75 (0.35-1.58)
rs4684677 (L90Q)	AA	1.0 (reference)	1.0 (reference)	1.0 (reference)
GHRL	AT	0.70 (0.25-1.99)	0.67 (0.30-1.52)	1.09 (0.43-2.78)
Nonsynonymous coding	TT			
rs696217 (M72L)	CC	1.0 (reference)	1.0 (reference)	1.0 (reference)
GHRL	CA	3.26 (1.50-7.09)	1.74 (0.96-3.14)	1.01 (0.49-2.10)
Nonsynonymous coding	AA			
rs7566605	GG	1.0 (reference)	1.0 (reference)	1.0 (reference)
INSIG2	GC	0.81 (0.39-1.67)	0.73 (0.44-1.19)	1.08 (0.61-1.89)
10 kb upstream	CC	1.28 (0.46-3.60)	0.82 (0.39-1.72)	1.34 (0.53-3.38)

*ORs and 95% CIs adjusted for age (in years), sex, smoking, and frequency of gastroesophageal reflux symptoms.

from esophageal cancer patients and has an estimated 80% power to detect ORs between 1.4 and 2.0 for allele frequencies between 0.05 and 0.45. Thus, our case-control sample had adequate power to find moderate risk alleles in the selected genes if they existed. Of the 12 SNPs tested, we identified modest positive associations for two mutations [*PPARγ* (H447H) and *GHRL* (M72L)] and a sizable inverse association for one SNP [*ADIPOQ* (rs1501299)]; however, none of the associations was statistically significant at the Bonferroni corrected threshold. To the best of our knowledge, this is the first study to comprehensively evaluate obesity-related SNPs in relation to risk of esophageal cancer. A recent review (23) examined all studies before February 2007 regarding polymorphisms and risk of EAC and ESCC. From 100 studies reviewed, no obesity-related genes were examined.

We further investigated the potential role of selected SNPs within strata of BMI. We observed some evidence of decreasing risks of EAC associated with *LEP* (5′-UTR), *RXRγ* (A140A), and *GHRL* (M72L) with increasing adiposity; however, these trends were not statistically significant. The other SNPs tested displayed inconsistent trends across BMI strata, indicating no relationship with esophageal cancer risk regardless of BMI.

In summary, we tested 12 SNPs across three groups of cases compared with controls. We found no convincing associations between any of the SNPs tested and risk of EGJAC or SCC. However, the finding of weak associations between *LEP*, *ADIPOQ*, and *GHRL* and risk of EAC suggests that further investigation of the SNPs tested here, and other SNPs within the same genes, may be warranted.

Appendix A The Australian Cancer Study: Esophageal Cancer

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Table 2. Associations between polymorphisms in multiple obesity-related genes and the risk of EAC, EGJAC, and ESCC and BMI (Cont'd)

EGJAC			ESCC		
BMI ≤25 kg/m^2	BMI 25-29.9 kg/m^2	BMI ≥30 kg/m^2	BMI ≤25 kg/m^2	BMI 25-29.9 kg/m^2	BMI ≥30 kg/m^2
OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.74 (0.42-1.30)	1.25 (0.8-1.96)	0.82 (0.48-1.41)	0.92 (0.57-1.50)	0.98 (0.55-1.74)	1.05 (0.48-2.30)
1.29 (0.54-3.12)	1.46 (0.7-3.05)	1.63 (0.67-3.98)	0.52 (0.19-1.49)	0.93 (0.30-2.85)	1.01 (0.20-4.95)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1.39 (0.79-2.47)	0.97 (0.60-1.54)	0.92 (0.54-1.57)	1.24 (0.76-2.03)	0.85 (0.47-1.54)	1.05 (0.48-2.30)
1.53 (0.71-3.30)	1.67 (0.92-3.03)	1.03 (0.47-2.27)	0.63 (0.28-1.41)	1.08 (0.49-2.40)	1.12 (0.33-3.84)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1.22 (0.71-2.08)	0.96 (0.61-1.49)	0.85 (0.50-1.42)	1.18 (0.73-1.89)	0.81 (0.45-1.47)	1.05 (0.48-2.30)
0.58 (0.17-2.03)	0.86 (0.34-2.21)	0.75 (0.28-2.02)	0.56 (0.20-1.56)	0.78 (0.26-2.38)	2.60 (0.90-7.50)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1.39 (0.77-2.53)	1.25 (0.76-2.04)	1.12 (0.62-2.03)	1.05 (0.62-1.76)	1.41 (0.74-2.68)	1.05 (0.48-2.30)
1.28 (0.60-2.74)	1.67 (0.90-3.10)	0.90 (0.43-1.87)	0.89 (0.45-1.75)	1.29 (0.56-2.96)	1.05 (0.39-2.88)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1.10 (0.62-1.94)	0.86 (0.53-1.41)	0.99 (0.55-1.76)	1.16 (0.71-1.89)	1.22 (0.67-2.22)	1.05 (0.48-2.30)
1.75 (0.52-5.88)	1.44 (0.54-3.85)	1.38 (0.29-6.59)	0.99 (0.25-3.90)	0.45 (0.06-3.52)	5.33 (0.52-55.1)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.83 (0.46-1.47)	0.83 (0.52-1.33)	1.13 (0.66-1.94)	0.97 (0.59-1.60)	0.94 (0.50-1.76)	1.05 (0.48-2.30)
0.95 (0.26-3.46)	1.56 (0.54-4.48)	3.50 (0.49-24.9)	1.15 (0.35-3.73)	3.14 (0.93-10.6)	3.72 (0.30-46.8)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1.12 (0.53-2.39)	1.13 (0.59-2.15)	0.56 (0.22-1.43)	1.12 (0.59-2.15)	1.30 (0.57-2.94)	1.05 (0.48-2.30)
	7.63 (1.02-57.3)	1.24 (0.09-17.8)		2.92 (0.22-39.0)	
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.95 (0.50-1.80)	1.25 (0.76-2.05)	1.65 (0.90-3.0)	0.89 (0.50-1.60)	1.12 (0.59-2.16)	1.05 (0.48-2.30)
5.59 (0.90-34.8)	1.22 (0.28-5.30)		3.21 (0.33-31.3)	1.15 (0.13-9.93)	
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1.66 (0.92-2.99)	1.41 (0.89-2.24)	0.90 (0.53-1.54)	1.16 (0.70-1.90)	0.81 (0.44-1.49)	1.05 (0.48-2.30)
1.84 (0.85-4.0)	1.01 (0.52-1.96)	0.66 (0.30-1.47)	0.92 (0.46-1.87)	1.18 (0.55-2.53)	0.59 (0.15-2.30)
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.46 (0.17-1.25)	0.83 (0.40-1.70)	0.79 (0.33-1.89)	0.65 (0.30-1.42)	0.41 (0.12-1.38)	1.05 (0.48-2.30)
	12.68 (0.7-229)	0.80 (0.08-8.38)			
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1.71 (0.83-3.55)	0.86 (0.45-1.63)	1.23 (0.62-2.44)	1.03 (0.52-2.03)	0.49 (0.17-1.42)	1.05 (0.48-2.30)
3.82 (0.35-42.2)			3.50 (0.31-39.2)	1.32 (0.15-11.8)	
1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.88 (0.50-1.53)	1.10 (0.69-1.73)	1.0 (0.59-1.70)	0.93 (0.58-1.51)	1.58 (0.88-2.86)	1.05 (0.48-2.30)
0.57 (0.20-1.61)	1.03 (0.51-2.09)	0.72 (0.27-1.94)	0.86 (0.38-1.94)	0.93 (0.33-2.61)	2.97 (1.0-8.97)

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Laboratory staff: Peter Schultz, Lauren Aoude, Loralie Parsonson, and Stephen Walsh.

Acknowledgments

We thank Shahram Sadeghi, M.D., and Harish Babu, M.D., for assisting with pathology abstractions; Nirmala Pandeya, M.Med.Sci., for data cleaning and programming; and all the study participants.

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Cancer Epidemiol Biomarkers Prev 2008;17:1007-1012.