Published in final edited form as:
Int J Cancer. 2009 April 1; 124(7): 1716–1720. doi:10.1002/ijc.23919.

Genetic variation in *SIPA1* in relation to breast cancer risk and survival after breast cancer diagnosis

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Abstract

Genetic variation in *SIPA1*, *signal-induced proliferation-associated gene 1*, has been proposed to be associated with aggressive breast tumor characteristics related to metastasis and worse prognosis in humans and rodents. To test this hypothesis, we genotyped three single nucleotide polymorphisms (SNP) located at −3092 (A<G, rs931127), exon 3 −135 (C>T, rs3741378), and exon 14+14 (C>T, rs746429), and examined them in relation to breast cancer risk and overall survival, stratified by tumor characteristics in two independent case-control studies conducted in Poland (1,995 cases, 2,296 controls) and in Britain (2,142 cases, 2,257 controls). Vital status (n=396 deaths) was available for 911 Polish and 1,919 British breast cancer cases with an average follow-up time of 5.5 years. Overall, we found no significant associations between genetic variants of *SIPA1* SNPs and breast cancer risk (per allele odds ratios, 95% confidence intervals (CI): rs931127 - 0.99, 0.93–1.06; rs3741378 - 1.03, 0.94–1.13; and, rs74642 - 0.98, 0.92–1.04). In both studies, *SIPA1* polymorphisms were not related to overall mortality (per allele hazard ratios, 95% CI: 1.02, 0.88–1.17; 0.90, 0.72–1.11; 1.04, 0.90–1.21, respectively). Our results do not support a relationship between *SIPA1* polymorphisms and breast cancer risk or subsequent survival.

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Authors' Contributions

MMG performed all statistical analyses and drafted the manuscript. KH contributed to the conception and interpretation of the data. PP conceived of the SEARCH study, and participated in its design and coordination. AMD and KD contributed to sample collection and genotyping for the SEARCH study. MG, MS, JL, BP, LAB contributed to the conception of the PBCS and participated in its design and coordination, and helped to draft the manuscript. All authors read, contributed to, and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

Introduction

Accumulating evidence suggests that genetic predisposition of the host, in addition to acquisition of somatic mutations during tumor progression, may determine metastatic potential of tumors and prognosis 1, 2. Studies of inbred transgenic mice have demonstrated that metastatic potential may be related to germline genetic variation located in the metastasis efficiency modifier locus, *Mtes1* 3. Evidence from bioinformatics, sequence analysis, as well as *in vitro* and *in vivo* experiments suggest that *signal-induced proliferation-associated gene 1* (*SIPA1*) is a strong candidate gene underlying the *Mtes1* locus 4. Its enzyme, SIPA1 (also known as Spa1) may be linked to metastatic potential through its role as a Rap1 GTPase-activating protein, which down-regulates cell adhesion 5, 6. As a signal transduction protein, SIPA1 also likely plays a role in cell differentiation and proliferation 6.

In humans, *SIPA1*, located on chromosome 11q13.3, contains at least three common (minor allele frequency >5%) single nucleotide polymorphisms (SNPs) within regulatory or coding regions 7. rs931127 is an A-to-G SNP located in the promoter region, rs3741378 is a C-to-T SNP that encodes for a serine-to-phenylalanine amino acid substitution in exon 3, and rs746429 is a G-to-A SNP that encodes for a synonymous amino acid change (alanine) in exon 14. In an analysis of 300 cases 8, the variant alleles of these SNPs were associated with lymph node involvement and hormone receptor negative tumors after age-adjustment. These results support the hypothesis that *SIPA1* may represent genetic predisposition to aggressive breast cancer behavior, such as lymph node involvement and lack of hormone receptor expression, which predict tumor metastasis and have poorer prognosis 9, 10. To evaluate this hypothesis, we estimated the associations between the three SNPs in *SIPA1* and breast cancer risk, as well as overall survival, stratified by tumor characteristics in two large and independent case-control studies in Poland and England.

Material and Methods

The present analysis used data from two case-control studies conducted in the Polish Breast Cancer Study (PBCS) 11 and the SEARCH study 12 that have been previously described in detail. Both studies received approval from their respective institutional review committees and all study respondents provided informed consent.

PBCS Population

The study was conducted between 2000 and 2003 among women residing in Warsaw and Lodz, Poland 11. Eligible cases were women aged 20 to 74 years who were newly diagnosed with either histologically or cytologically confirmed *in situ* or invasive breast cancer. Study personnel identified cases through a rapid identification system and cancer registries to ensure complete case ascertainment. Controls with no history of breast cancer were randomly selected through a database of all Polish residents. Controls were frequency matched to cases by city and age in 5-year categories. A total of 1,995 cases (65% of eligible cases identified) and 2,296 controls (63% of eligible controls identified) provided a personal interview on known and suspected risk factors and donated a venous blood sample.

Medical records and the surgical pathology form were abstracted for all cases. Stage at diagnosis was assigned based on tumor size and extent of nodal involvement from the pathology reports. Data on distal metastasis was not available at the time of analysis. Therefore, tumors measuring <2 cm and involving 1–3 nodes were classified as stage II tumors (n=393, 21.1%) and there was no further discrimination between stages III and IV cancer (n=47, 2.5%). A total of 381 cases had missing data for tumor size and/ or nodal involvement and could not be assigned stage. Vital status was determined via review of

medical records every five years. At the time of analysis, data was available for a subset of cases diagnosed in Warsaw during the first year of study recruitment (2000).

SEARCH Study Population

Cases were drawn from SEARCH breast cancer study with cases ascertained through the East Anglian Cancer Registry. All patients diagnosed with invasive, epithelial breast cancer below age 55 years since 1991 and still alive in 1996 (prevalent cases, median age 48 years), together with all those diagnosed <70 years between 1996 and the present (incident cases, median age 54 years), were eligible to take part. Sixty-three percent of eligible breast cancer patients returned a questionnaire and provided a blood sample for DNA analysis. Female controls were selected from the Norfolk component of EPIC (European Prospective Investigation of Cancer) in approximate order of recruitment through general practice age-sex registers. EPIC is a prospective study of diet and cancer being carried out in nine European countries. The EPIC-Norfolk cohort comprises 25,000 individuals resident in Norfolk, East Anglia – the same region from which the cases have been recruited. Controls were not matched to cases, but are broadly similar with respect to age (range= 42–81 years).

This analysis is based on a subset of 2,142 cases and 2,257 controls all of whom completed an epidemiological questionnaire and provided a blood sample for DNA analysis. Tumor characteristics of the cases were based on review of pathology reports and medical records conducted by the cancer registry. Vital status was determined based on a combination of follow-up through national death registrations and follow-up every five years by the cancer registry.

Genotyping

SIPA1 does not appear to be highly polymorphic in Caucasian populations based on HapMap (http://www.hapmap.org) and dbSNP (http://www.ncbi.nlm.nih.gov/sites/entrez) databases. We selected 2 of 3 SNPs (rs3741378 and rs931127) in *SIPA1* that were genotyped in HapMap. The additional *SIPA1* SNP (rs2448490) is in linkage with rs3741378 (D'=1.0, r^2=0.10) and rs931127 (D'=1.0, r^2=0.63), and was not genotyped in our study. We also genotyped rs746429 that was found in dbSNP to have a minor allele frequency of 29–31% in Caucasian populations.

Description and methods for PBCS genotype assays can be found at http://snp500cancer.nci.nih.gov 7. A total of 100 duplicate DNA pairs interspersed throughout the PBCS DNA samples. All pairs were >98% concordant for each SNP. Completion proportions were >99% for all SNPs. Genotype frequencies for all loci were in Hardy-Weinberg equilibrium among controls (p-value >0.28).

SEARCH DNA samples were genotyped using a fluorescent 5' exonuclease assay (Taqman) and the ABI PRISM 7900 Sequence Detection Sequence (PE Biosystems). Cases and controls were arrayed together in twelve 384-well plates and a 13^{th} plate contained 8 duplicate samples from each of the 12 plates. The concordance proportions for all loci were 100%. Genotype assays were complete for 94% of samples.

Statistical Analyses

Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for study site (Warsaw, Lodz, or England), for the association between individual SNPs and breast cancer, using STATA (version 8.2). The less frequent allele was considered the variant allele. Genotypes were evaluated using indicator variables. We assumed an additive mode of inheritance to calculate the p for trend. Individual SNP associations were examined by stage (I, II, III/ IV), grade (well, moderately,

or poorly differentiated), and estrogen receptor status of the tumors using polytomous logistic regression models. The presence of study heterogeneity was assessed by the Q test 13.

Survival analyses were based on 2,830 breast cancer cases (45.7% of PBCS and 89.6% of SEARCH) with available follow-up time data. Time at risk was calculated from the date of blood collection (left truncation) to the date of death or the end of observation truncated at 10 years. The Kaplan-Meier method stratified by genotype was used to generate survival curves for preliminary analysis of the data 14. Hazard ratios (HR) and 95% confidence intervals (CI) for mortality associated with genotype, adjusted for age and study site, were estimated using Cox proportional hazard models 15. We checked for violations of the proportional hazards assumption for genotype variables and covariates by visual inspection of the log (-log) plots and analytically using Schoenfeld residuals 16. The proportional hazards assumption for estrogen receptor status was violated. We therefore did not include it as a covariate in the Cox model, but stratified on it. We evaluated the potential confounding of tumor stage and grade by inclusion into the model and of ER status by stratification of the baseline hazard. None of the potential confounders were retained in the final model as they did not change the association between genotype and survival by more than 10%.

All analyses were conducted using STATA v.9 for Windows (College Station, TX).

Results

Description of Study Populations

The average age of the Polish women in PBCS was 55.7 (± 10.0) years and all were white. The British women in SEARCH were slightly older (mean age=57.8 ± 10.7) and >98% were self-reported white. SEARCH cases tended to be diagnosed with ER+ (79.1%), early stage (stage I=50.4%, II=44.7%, III/IV=5.0%), and moderately differentiated (well differentiated=25.2%, moderately=45.6%, poorly=29.2%) breast tumors. Smaller percentages of PBCS than SEARCH cases were diagnosed with ER+ (65.1%) tumors, and more were diagnosed at a later stage (stage I=40.2%, II=57.3, III/IV=2.5%) and as poorly differentiated (well differentiated=15.7%, moderately=47.7%, poorly=36.6%) tumors.

Associations with Overall Breast Cancer Risk

The minor allele frequencies for controls by study were 40% for rs931127, 12% for rs3741378, and 44% for rs746429 in PBCS; 47%, 13%, and 35% in SEARCH; and, 43%, 13%, and 40% overall, respectively. Individually, these SNPs were not significantly associated with breast cancer risk (Table 1). However, there was a suggestion of an increased risk of breast cancer associated with the variant TT genotype of rs3741378, although results were not significant. The results for both studies were similar for rs3741378 and rs746429 (p for heterogeneity=0.82 and 0.19, respectively); however, there was evidence of study heterogeneity for rs931127 results (p for heterogeneity=0.04), though both estimates hover around an OR of 1.0.

Breast Tumor Subtypes

In the pooled analyses, stratifying results by stage (Table 2), grade (Supplemental Table 4), or estrogen receptor status (Supplemental Table 3) did not reveal significant associations between *SIPA1* and breast tumor subtypes. Of note, women carrying the TT genotype for rs3741378 had a 2.4 times higher risk of a stage III/ IV tumor compared to women carrying the CC genotype, but this result was based on 5 cases (OR=2.44, 95% 0.96–6.22; Table 2). Results for breast tumor subtypes did not significantly differ by study (Supplemental Tables 1–3, 5–6).

Survival Analyses

Cases were followed up for a median of 5.4 years (range, from 13.8 days to 9.7 years) overall, 4.1 years (13.8 days to 6.8 years) for PBCS, and 6.6 years (1.2 months to 9.7 years) for SEARCH. Cases were followed-up for a total of 15,678 person-years with the occurrence of 396 deaths (78 deaths from PBCS and 318 deaths from SEARCH). Survival did not differ by genotype for the *SIPA* SNPs under study (Table 3) as observed for both studies (p for study heterogeneity >0.36).

Discussion

In a pooled analysis of 4,511 cases and 4,667 controls, we did not find significant overall associations between breast cancer risk and *SIPA1* SNPs, nor did we identify significant evidence of heterogeneity by stage at diagnosis, grade, and estrogen receptor status. We did not replicate the findings of a previous case-only study of *SIPA1* variants and breast tumor characteristics 8. In this previous study of 300 breast cancer cases with a family history of breast and ovarian cancer, *SIPA1* variation was associated with tumors that did not express hormone receptors and had lymph node involvement 8. The reason for these inconsistencies is unclear, but may be due to random variation in studies and a lack of a true effect between genetic variation of *SIPA1* and breast tumor characteristics.

No additional published data are available. However, recent results from the genome-wide scan of 1,140 breast cancer cases and 1,140 controls (17; http://caintegrator.nci.nih.gov/cgems) that genotyped 5 markers to capture the majority of common variation in *SIPA1* as well as the neighboring regions (that included the genes *PCNXL3* and *MAP3K11*) found that rs931127 examined in our study, as well as the other tagSNPs, were not associated with breast cancer risk. Although the coverage of genetic variation in *SIPA1* is unclear for the SNPs genotyped in our study, the genome-wide scan data provide additional evidence that there is no association between genetic variants of SIPA1 and breast cancer risk.

Survival among 2,830 breast cancer cases did not differ by *SIPA1* genotypes in our studies. In particular, rs3741378 was associated with better, rather than worse, survival as suggested by observations that this SNP is associated with more aggressive tumor characteristics in a previously published study 8. The associations between *SIPA1* polymorphisms and mortality have not been previously evaluated in human populations. In rodent models, genetic variation in *SIPA1* is suspected to be responsible for the underlying *Mtes1* locus found to be related to metastasis potential of mammary tumors 4. While metastases at distant sites are the main cause of death among women with breast cancer diagnoses 2 and is suspected to be a heritable trait 1, our findings do not support that genetic variation in *SIPA1* is responsible for predisposition of greater metastatic potential and poorer prognosis among women with breast cancer.

To combine tumor stage data from the East Anglian Cancer Registry in the British study, we assigned tumor stage in the Polish study based on tumor size and nodal involvement, because information about distal metastasis was not available at the time of analysis. The incomplete information for the Polish cases resulted in the misclassification of some stage III tumors as stage II tumors. As evidence, the distribution of breast tumor stage among a subgroup of 372 Polish cases with final stage information was 43% diagnosed with stage I, 49% stage II, and 8% stage III/IV tumors, whereas the distribution in Warsaw, Poland is 40.1% localized, 41.0 % regional, and 7.2% distal metastases (Warsaw Cancer Registry, 2007). However, the observed association between the homozygous variant of rs3741378 and stage III/IV, if truly causal, is unlikely to be biased by misclassification since observed

large, metastatic tumors reported at the time of the Polish analysis were correctly assigned as stage III/IV.

Selection bias would not be expected to substantially affect our results, because carrier status is unlikely to be associated with participation. Furthermore, population stratification is unlikely to substantially account for our results, as the study populations had minimal ethnic diversity, particularly in the Polish study. In addition, potential biases in the data are unlikely to be similar in the two studies, and are unlikely to account for the lack of consistent associations observed in both study populations.

The complete course of treatment for the initial, primary breast cancer diagnosis was not available at the time of analysis for PBCS or SEARCH. Treatment likely affected survival among cases but unlikely to be related to genotype and thus was not suspected to be a confounder in the survival analyses. We are further confident that the lack of association between survival and *SIPA1* polymorphisms was not confounded by breast cancer treatment because tumor characteristics that would determine treatment course did not affect HR estimates. While our results are based on a range of follow-up time from 13.8 days to 9.7 years, deaths that occurred quickly after diagnosis (and before study entry) may have been under-represented in our study population. However, we accounted for potential survival bias in our analyses by truncating follow-up time to the date of blood draw rather than the date of diagnosis.

Genetic variants of *SIPA1* were not associated with breast cancer risk or survival in two studies totaling over 4,000 cases and 4,000 controls. Although we cannot exclude the possibility that other unmeasured genetic variants of *SIPA* or of other linked genes may reveal relationships with tumor metastasis and prognosis, it is unlikely that *SIPA1* variation has a profound effect on risk of breast cancer metastasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

CI	Confidence interval
HR	Hazards ratio
OR	Odd ratio
SIPA1	*signal-induced proliferation-associated gene 1*

Acknowledgments

This research was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. SEARCH is funded by a grant from Cancer Research UK and PDPP is a Senior Clinical Research Fellow of Cancer Research UK. The authors are thankful for: the contributions of Neonila Szeszenia-Dabrowska of the Nofer Institute of Occupational Medicine (Lodz, Poland) and Witold Zatonski of the Department of Cancer Epidemiology and Prevention, Cancer Center and M. Sklodowska-Curie Institute of Oncology (Warsaw, Poland) for their contribution to the Polish Breast Cancer Study; and the SEARCH team. Anita Soni (Westat, Rockville, MD, USA) and Pei Chao (IMS, Silver Spring, MD, USA) have been invaluable to the management of the study. This work would not be possible without the dedicated efforts of the physicians, nurses, interviewers and study participants.

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Table 1

OR[1] and 95% CI[1] for associations between *SIPA1* SNPs and breast cancer

	PBCS			SEARCH			Pooled Study		
rs# (Location)	**No.[3] (%) Controls**	**No.[3] (%) Cases**	**OR[3] (95% CI)**	**No.[3] (%) Controls**	**No.[3] (%) Cases**	**OR[3] (95% CI)**	**No.[3] (%) Controls**	**No.[3] (%) Cases**	**OR[3] (95% CI)**
rs931127 (−3092 A>G)									
AA	681 (30.6)	814 (34.2)	1.00	622 (31.0)	623 (28.4)	1.00	1306 (32.9)	1437 (32.2)	1.00
AG	947 (42.5)	1107 (46.6)	1.02 (0.90, 1.17)	970 (48.4)	1099 (50.1)	0.88 (0.77, 1.02)	1917 (48.3)	2209 (49.6)	0.95 (0.86, 1.05)
GG	330 (14.8)	342 (14.4)	1.15 (0.96, 1.38)	412 (20.6)	470 (21.4)	0.88 (0.74, 1.04)	742 (18.7)	812 (18.2)	1.00 (0.88, 1.13)
per allele			1.06 (0.97, 1.16)			0.93 (0.86, 1.02)			0.99 (0.93, 1.06)
rs3741378 (Ex3−135 C>T)									
CC	1514 (68.0)	1759 (74.0)	1.00	1525 (74.9)	1640 (74.7)	1.00	3040 (75.7)	3402 (76.1)	1.00
CT	432 (19.4)	476 (20.0)	1.06 (0.92, 1.23)	472 (23.2)	524 (23.9)	0.97 (0.84, 1.12)	905 (22.5)	1000 (22.4)	1.01 (0.91, 1.12)
TT	31 (1.4)	37 (1.6)	0.97 (0.60, 1.58)	40 (2.0)	30 (1.4)	1.43 (0.89, 2.31)	72 (1.8)	67 (1.5)	1.20 (0.86, 1.68)
per allele			1.04 (0.92, 1.19)			1.02 (0.90, 1.16)			1.03 (0.94, 1.13)
rs746429 (Ex14+14 C>T)									
GG	637 (28.6)	697 (30.93)	1.00	816 (40.9)	917 (42.3)	1.00	1454 (36.7)	1616 (36.5)	1.00
GA	969 (43.5)	1113 (49.4)	0.95 (0.83, 1.10)	950 (47.6)	992 (45.7)	1.08 (0.95, 1.23)	1920 (48.5)	2106 (47.6)	1.02 (0.93, 1.12)
AA	356 (16.0)	445 (19.7)	0.87 (0.73, 1.04)	231 (11.6)	261 (12.0)	0.99 (0.81, 1.22)	588 (14.8)	706 (15.9)	0.93 (0.82, 1.07)
per allele			0.94 (0.86, 1.02)			1.02 (0.93, 1.12)			0.98 (0.92, 1.04)

[1] Abbreviations: OR=odds ratio, CI=confidence intervals,

[2] Cases and controls may not add up the totals because of missing values;

[3] Adjusted for age and study site.

Table 2

Pooled OR[1] and 95% CI[1] for associations between *SIPA1* SNPs and breast cancer stratified by breast tumor stage[2]

rs# (Location)	Stage I vs. Controls			Stage II vs. Controls		Stage III/IV vs. Controls		p-value for heterogeneity across stage
	No.[3] (%) Controls	No.[3] (%) Cases	OR[4] (95% CI)	No.[3] (%) Cases	OR[4] (95% CI)	No.[3] (%) Cases	OR[4] (95% CI)	
rs931127 (−3092 A>G)								
AA	1437 (32.2)	527 (33.0)	1.00	563 (32.0)	1.00	43 (32.3)	1.00	
AG	2209 (49.6)	774 (48.5)	0.93 (0.82, 1.06)	856 (48.7)	0.99 (0.87, 1.12)	66 (49.6)	0.94 (0.63, 1.38)	
GG	812 (18.2)	296 (18.5)	0.93 (0.79, 1.10)	338 (19.2)	1.06 (0.90, 1.25)	24 (18.0)	0.86 (0.52, 1.43)	
per allele			0.96 (0.88, 1.04)		1.02 (0.95, 1.11)		0.93 (0.72, 1.19)	0.63
rs3741378 (Ex3−135 C>T)								
CC	3402 (76.1)	1229 (75.6)	1.00	1345 (76.1)	1.00	107 (78.1)	1.00	
CT	1000 (22.4)	365 (22.5)	0.99 (0.86, 1.14)	396 (22.3)	1.00 (0.88, 1.14)	25 (18.2)	0.76 (0.49, 1.18)	
TT	67 (1.5)	31 (1.9)	1.27 (0.83, 1.97)	27 (1.5)	1.02 (0.65, 1.60)	5 (3.6)	2.44 (0.96, 6.22)	
per allele			1.03 (0.91, 1.16)		1.00 (0.89, 1.13)		0.98 (0.68, 1.41)	0.46
rs746429 (Ex14+14 C>T)								
CC	1616 (36.5)	602 (37.6)	1.00	633 (36.3)	1.00	52 (39.1)	1.00	
CT	2106 (47.6)	763 (47.7)	1.01 (0.89, 1.15)	859 (49.2)	1.04 (0.92, 1.18)	61 (45.9)	0.99 (0.68, 1.44)	
TT	706 (15.9)	234 (14.6)	0.98 (0.82, 1.18)	254 (14.5)	0.92 (0.78, 1.09)	20 (15.0)	1.07 (0.63, 1.82)	
per allele			1.00 (0.92, 1.08)		0.98 (0.90, 1.06)		1.02 (0.79, 1.32)	0.80

[1] Abbreviations: OR=odds ratio, CI=confidence intervals,

[2] Stage was defined by tumor size and nodal involvement only;

[3] Cases and controls may not add up the totals because of missing values;

[4] Adjusted for age and study site.

Table 3

Pooled HR[1] and 95% CI[1] for associations between *SIPA1* SNPs and all cause mortality among breast cancer cases

	PBCS			SEARCH			Pooled Study		
rs# (Location)	**No. Deaths**	**Person-Time**	**HR[2] (95% CI)**	**No. Deaths**	**Person-Time**	**HR[2] (95% CI)**	**No. Deaths**	**Person-Time**	**HR[2] (95% CI)**
rs931127 (−3092 A>G)									
AA	19	1,119	1.00	95	3,702	1.00	114	4,821	1.00
AG	35	1,539	1.34 (0.77, 2.34)	160	5,655	1.10 (0.86, 1.42)	195	7,195	1.15 (0.91, 1.44)
GG	12	538	1.32 (0.64, 2.72)	57	2364	0.94 (0.68, 1.31)	69	2,902	1.00 (0.74, 1.35)
per allele			1.17 (0.83, 1.65)			0.99 (0.84, 1.15)			1.02 (0.88, 1.17)
rs3741378 (Ex3−135 C>T)									
CC	54	2,421	1.00	241	8,919	1.00	295	11,340	1.00
CT	14	784	0.80 (0.44, 1.44)	73	2,746	0.98 (0.76, 1.28)	87	3,530	0.95 (0.74, 1.20)
TT	0	36	N/E	4	243	0.60 (0.22, 1.61)	4	279	0.53 (0.20, 1.43)
per allele			0.74 (0.42, 1.31)			0.92 (0.74, 1.17)			0.90 (0.72, 1.11)
rs746429 (Ex14+14 C>T)									
GG	21	1,054	1.00	124	4,700	1.00	145	5,754	1.00
GA	34	1,614	1.06 (0.61, 1.82)	146	5,608	0.99 (0.78, 1.25)	180	7,221	1.00 (0.80, 1.25)
AA	14	488	0.83 (0.38, 1.81)	4	302	1.21 (0.85, 1.70)	53	1,912	1.12 (0.82, 1.54)
per allele			0.94 (0.66, 1.34)			1.07 (0.90, 1.26)			1.04 (0.90, 1.21)

[1] Abbreviations: HR=hazard ratio, CI=confidence intervals,

[2] Adjusted for age and study site.