Polymorphisms of peroxisome proliferator-activated receptors and survival of lung cancer and upper aero-digestive tract cancers

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Abstract

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Background—Peroxisome proliferator-activated receptors (PPARs) are transcriptional factors involved in several biological processes such as inflammation, cancer growth, progression and apoptosis that are important in lung and upper aero-digestive tract (UADT) cancer outcomes. Nonetheless, there are no published studies of the relationship between *PPARs* gene polymorphisms and survival of patients with lung cancer or UADT cancers.

Methods—1,212 cancer patients (611 lung, 303 oral, 100 pharyngeal, 90 laryngeal, and 108 esophageal) were followed for a median duration of 11 years. We genotyped three potentially functional single nucleotide polymorphisms (SNPs) using Taqman--rs3734254 of the gene *PPARD* and rs10865710 and rs1801282 of the gene *PPARG*--and investigated their associations with lung and UADT cancer survival using Cox regression. A semi-Bayesian shrinkage approach was used to reduce the potential for false positive findings when examining multiple associations.

Results—The variant homozygote CC (vs. TT) of *PPARD* rs3734254 was inversely associated with mortality of both lung cancer (adjusted hazard ratio [aHR] = 0.63, 95% confidence interval [CI] = 0.42, 0.96) and UADT cancers (aHR = 0.51, 95% CI = 0.27, 0.99). Use of the semi-Bayesian shrinkage approach yielded a posterior aHR for lung cancer of 0.66 (95% posterior limits = 0.44, 0.98) and a posterior aHR for UADT cancers of 0.58 (95% posterior limits = 0.33, 1.03).

Conclusion—Our findings suggest that lung-cancer patients with the CC variant of *PPARD* rs3734254 may have a survival advantage over lung-cancer patients with other gene variants.

Keywords

Introduction

Lung cancer and upper aero-digestive tract (UADT) cancers are common cancers that are responsible for serious morbidity and mortality. According to Globocan 2012, lung cancer ranks third in incidence and first in mortality of cancers in the world; and third in incidence and first in mortality of cancers in the United States (U.S.) [1]. The overall 5-year survival of lung cancer is 16.6% in the U.S. in 2013 [2, 3]. UADT cancers comprise the cancers of the airway and upper digestive tract, specifically, oral cavity, pharynx, larynx and esophagus, which are contiguous and commonly exposed to inhaled and sometimes swallowed substances. Collectively, UADT cancers rank fifth in incidence and fourth in mortality of cancers in the world and seventh in incidence and sixth in mortality of cancers in the U.S. in 2012 [1]. The overall 5-year survival is 61% for head and neck cancer (HNC) and 17.3% for esophagus cancer in the U.S. in 2013 [2]. Despite advances in understanding the pathogenesis of lung and UADT cancers, improvements in surgical procedures and the introduction of newer treatment regimens, survival, especially for lung and esophageal cancers has not changed much [2, 4]. At the present time, stage, histology and treatment are thought to be related to cancer prognosis [5]; however there is only a limited amount of information available on genetic factors and cancer prognosis for both lung cancer and UADT cancers.

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily [6–8]. Initially, PPARs are found to regulate genes that control glucose and lipid metabolism and are linked to type 2 diabetes mellitus risk [9, 10]. Later it is discovered that they are involved in many other important biological functions, including early development, inflammation, cell differentiation, proliferation, and apoptosis [6, 11].

Several studies on lung cancer illustrate that the activation of PPAR-γ could constrain cancer cell growth and oral administration of synthesized PPAR-γ ligand could inhibit lung cancer progression and metastases [12–14]. Compared to extensive research on PPAR-γ, studies on PPAR-δ are fewer and focus mostly on the digestive system, with inconsistent results [15–17]. Limited studies of non-small cell lung cancer (NSCLC) show that the function of PPAR-δ is different from that of PPAR-γ and that the former increases cancer proliferation [18]. Considering the cancer-related links with PPARs and the lack of epidemiologic studies examining their relation with lung- and UADT- cancer survival, we conducted this study to explore the association between PPARs gene polymorphisms and survival among patients with lung and UADT cancers.

Methods

Study Population

The study population consisted of newly diagnosed cancer cases identified for the University of California at Los Angeles (UCLA) and University of Southern California (USC) population-based case-control study between 1999 and 2004 in Los Angeles County (LAC) [19]. These subjects included pathologically confirmed new cases of lung cancer or UADT cancers (oral cancer, pharyngeal cancer, laryngeal cancer and esophageal cancer) identified by the rapid ascertainment system of the LA County Cancer Registry under the Cancer Surveillance Program at USC [19]. Recurrent cancer cases were excluded from our study.

Recruitment occurred from 1999 to 2004. All participants were residents of LAC, aged 18 to 65 years old at the time of diagnosis and able to speak either English or Spanish or had a translator on site. Vital status was determined through linking the cases with the Social Security Death Index. The survival time was calculated as the interval between the date of diagnosis and the date of death, or the date of the last follow-up which was July 13th, 2012. The median follow-up time was 11.1 years in all cases, and 11.5 years in lung cancer cases and 10.8 years in UADT cancer cases, respectively.

Recruitment rates among eligible cancer patients were 39%, 54%, 45%, 42% and 35% for lung, oral, pharyngeal, laryngeal and esophageal cancer, respectively. A total of 1,212 patients were included in our study. There were 611 patients with lung cancer, including 95 squamous carcinomas (SQC), 297 adenocarcinomas (ADC), 115 large cell carcinomas (LCC), 75 small cell lung cancers (SCLC) and 29 others. There were a total of 601 patients with UADT cancers, including 303 patients with oral cancer, 100 with pharyngeal cancer and 90 with laryngeal cancer; and 108 esophageal cancer patients. 497 UADT cancer

patients were squamous carcinomas, 74 were esophageal adenocarcinomas, and 30 were other cell types.

Data Collection

Trained interviewers used study specific standardized questionnaires to collect subject-reported data including age, gender, ethnicity, education level, smoking and alcohol drinking. Tobacco smokers were defined as those who smoked more than 100 cigarettes in their lifetimes. Alcohol drinkers were defined as those who drank at least one alcoholic drink per month for a period of at least six months. Cumulative level of smoking was measured by pack-years, which were calculated by summing packs per day times the number of years that a subject smoked that amount prior to the diagnosis of cancer. One pack-year is equivalent to smoking one pack per day for one year. Alcohol drinking was measured by the average number of drinks (including wine, beer or liquor) consumed per day. Interviews occurred within six months of diagnoses for 89% of cases.

Buccal cells were collected for DNA analysis by asking subjects to brush their buccal mucosa and rinse with mouthwash. Response rates for interviewed participants providing buccal cells were 89%, 68%, 88%, and 90% for lung, oral and pharyngeal, laryngeal and esophageal cancer cases, respectively.

All specimens were transported and stored at −70°C in the Molecular Epidemiology Laboratory at UCLA, Fielding School of Public Health. DNA samples were isolated by using a modified phenol-chloroform assay [20]. We selected single nucleotide polymorphisms (SNPs) of which the minor allele frequencies (MAFs) in Caucasians were 5%; when the pairwise linkage disequilibrium (LD) r^2 was 0.8, we picked non-synonymous SNPs or SNPs located in regions regulating gene transcriptions, such as promoter areas from the National Center for Biotechnology Information SNP database. A total of one SNP in the gene *PPARD* (rs3734254) and four SNPs in the gene *PPARG* (rs10865710, rs1801282, rs3856806, and rs13306747) were selected. SNP genotyping was done using TaqMan (Applied Biosystems (ABI, Foster City, CA) 7900HT). Samples were first held at 92°C for 10 minutes; then underwent 60 thermocycles of denaturing at 92°C for 15 seconds and annealing at 62°C for 80 seconds. After PCR amplification, end-point fluorescence was read using the ABI 7900HT Sequence Detection System, and genotypes were coded using the SDS 2.3 Allelic Discrimination Software. SNPs that did not meet the criteria of Hardy-Weinberg equilibrium (HWE) p-value Bonferroni-adjusted p-value of 0.01 and a genotyping call rate 95% were excluded, leaving rs3734254, rs10865710 and rs1801282 in the analysis.

Statistical Analysis

We first analyzed SNP genotypes (TT, TC, CC or CC, CG, GG) as dummy variables. These results were used to decide the appropriateness of the dominant or recessive model. Cox regression was used to estimate crude and adjusted hazard ratios (cHRs and aHRs) and their corresponding 95% confidence intervals (CIs). SNP genotypes were also treated as ordinal variables to be tested for p-trends. For lung cancer, we adjusted for age, gender, ethnicity, education level, and smoking; we also adjusted for cell differentiation and morphology that

included lung SQC, lung ADC, LCC and SCLC. For UADT cancers, we adjusted for age, gender, ethnicity, education level, and smoking and alcohol drinking; we also adjusted for morphology including UADT SQC and ADC, and cell differentiation. Proportionality assumptions were checked in each model, and no noteworthy violations were detected. We also performed semi-Bayesian shrinkage to adjust for potential false discoveries caused by multiple comparisons [21, 22]. Due to lack of previous relevant epidemiology studies and based on existing biology evidence, we applied a Normal coefficient prior with mean 0 and variance 0.5 (corresponding to HR = 1.0, 95% prior limits = 0.25, 4.00, after exponentiation) for the adjustment. All statistical analyses were conducted using SAS v9.3 software (SAS Institute Inc., Cary, NC). We used R 2.15.1 (The R Foundation for Statistical Computing) to construct Kaplan-Meier curves for each SNP.

The study was approved by the institutional review boards of UCLA and USC. Informed consents were obtained from all participants.

Results

Study Population

Table 1 shows the demographic characteristics of the deaths and censored survivors of lung cancer and UADT cancers separately. For lung cancer, the median survival time was 2.5 years; while the median survival time of UADT cancers was 9.4 years.

For lung cancer, the proportion of deaths was higher in the age group 55 or older (72%), comparing to those younger than 55 years of age (62%). It was higher in the male (71%) than in the female (62%). Among different morphological types, SCLC was associated with the highest mortality (80%), and lung SQC, the lowest (56%). Mortality increased with cell differentiation, varying from 54% to 74%. More deaths occurred in smokers than in nonsmokers (69% vs. 55%), and the proportion increased slightly with increasing number of pack-years.

For UADT cancers, the mortality was higher in the patients aged 55 years or older (47%) than in the younger patients (35% – 39%); and higher in esophageal adenocarcinomas (57%) than other morphological types (37% – 39%). Higher proportion of deaths was observed among smokers than among nonsmokers (46% vs. 29%); also more in alcohol drinkers than in non-alcohol drinkers (42% vs. 38%).

SNP Analysis

Table 2 presents the crude and adjusted hazard ratios for lung cancer mortality and corresponding adjusted posterior estimates after semi-Bayesian shrinkage of selected SNPs, stratified by morphological types.

For lung cancer overall, only the SNP of the gene *PPARD* was associated with mortality. The CC (vs. TT) variant of rs3734254 was inversely associated with mortality (cHR = 0.65; 95% CI = 0.44, 0.96). After adjusting for age, gender, ethnicity, education levels, pack-years of smoking, tumor cell differentiation and morphology, the association changed little (aHR = 0.63; 95% CI = 0.42, 0.96). Moreover, the association persisted after semi-Bayesian

shrinkage (posterior aHR = 0.66; 95% posterior limits = 0.44, 0.98). We observed similar associations in the recessive model (CC vs. TT+TC), both from the actual data (cHR = 0.64; 95% CI = 0.44, 0.94 and aHR = 0.61; 95% CI = 0.41, 0.92) and the posterior estimations (posterior aHR = 0.64; 95% posterior limits = 0.43, 0.94). When stratified by morphological types, we observed the CC (vs. TT) genotype of rs3734254 was associated with decreased risk of death in LCC in the crude model (cHR = 0.34; 95% CI = 0.12, 0.95) but not in the adjusted model (aHR = 0.32; 95% CI = 0.09, 1.06) or in the recessive models (CC vs. TT +TC). The crude association was weakened after semi-Bayesian shrinkage (posterior cHR = 0.49; 95% posterior limits = 0.23, 1.03) (presented in the supplementary table 1).

Similar to the lung cancer findings, the CC (vs. TT) variant of rs3734254 was inversely associated with UADT cancer mortality (aHR = 0.51; 95% CI = 0.27, 0.99). However, semi-Bayesian shrinkage weakened the association and increased the width of the posterior interval (posterior aHR = 0.58; 95% posterior limits = 0.33, 1.03).

No associations were observed between SNP variants of the _PPARG_ gene and lung cancer or UADT cancer mortality.

We further combined genotypes of all three SNPs (rs3734254, rs10865710 and rs1801282) based on the results from recessive models to evaluate joint effects on survival. However, the combined PPAR genotypes did not provide additional information on survival of lung or UADT cancer patients (data not shown).

Kaplan-Meier survival curves by gene variants of each SNP for both lung and UADT cancers are shown in Figures 1 and 2. Lung cancer patients with the CC variant of rs3734254 showed a clear survival advantage over the lung cancer patients of the other two genotypes (Log-rank test: p = 0.02, Figure 1a). In UADT cancers, better survival was observed for the rs10865710 GG variant carriers, in comparison with that of the CC/CG carriers; however, the log rank p-value was 0.20 (Figure 2b).

Gene-environment interactions

Due to the importance of smoking in lung cancer and UADT cancer development, its potential interactions with gene polymorphisms were also explored. We noted that the inverse association of the CC variant of rs3734254 with cancer mortality was observed primarily in lung-cancer smokers (in the recessive model CC vs. TT+TC: aHR = 0.55; 95% CI = 0.35, 0.87). Among lung-cancer non-smokers, the associations were much weaker (in the recessive model CC vs. TT+TC: aHR = 0.84; 95% CI = 0.31, 2.28); and p-value for the interaction between ever vs. never smokers and the CC vs. TT+TC variants was 0.21. We also explored the potential discrepancies of SNP-survival associations between ever and never drinkers in UADT cancer patients and did not observe any apparent variations.

Discussion

We found that the CC variant of rs3734254 of the gene _PPARD_ was inversely associated with mortality in lung cancer and UADT cancers, and the association persisted in lung cancer with semi-Bayesian shrinkage which reduced the issue of false positive findings

resulting from multiple comparisons. To date, most published studies have explored the relationship between the gene polymorphisms of *PPARG* with the incidence of cancer. Among those studies that examined multiple types of cancer, one study on lung cancer in the Chinese population shows that rs2972162 of *PPARG* is inversely associated with lung cancer, and this association differs little between smokers and non-smokers [23]. Our study was the first to examine the association of polymorphism of *PPARs* on survival of lung and UADT cancers and we did not find any associations between selected SNPs of *PPARG* and survival from either lung cancer or UADT cancers. Although rs1801282 coding non-synonymous protein resulting Pro-to-Ala exchange of PPAR-γ2--one isoform of PPAR-γ-- causes reduced transcriptional activity, the lack of expression of PPAR-γ2 in the lung/ UADT tissues may have resulted in the null findings [24–27]. Also, several studies have suggested that PPAR-γ may play a role in the early stage of lung cancer development rather than its progression and metastasis [12, 28].

PPARD rs3734254 is located on chromosome 6 and at a 3 prime untranslated region(3'-UTR) [29]. Two other SNPs of the gene *PPARD* are in LD with rs3734254. One is rs2076167 that results in a synonymous change to an asparagine residue and the other is rs1053049 within the *PPARD* 3'-UTR. [30, 31]. The synonymous SNP (rs2076167) may alter the mRNA structure that might influence protein translation and folding [32]. SNPs at 3'-UTR (rs3734254 included in our study and rs1053049 in LD) might impact the stability of the corresponding mRNAs, all of which may affect the activity of PPAR-δ and influence the fate of cancer cells.

PPAR-δ is ubiquitously expressed in multiple tissues [33, 34]. Studies have shown that PPAR-δ has a compound effect on cancer progression of which the exact mechanism is still under investigations [35–37]. For example, in a lung cancer model, down-regulation of phosphatase and tensin homolog (PTEN) and the activation of the PI3 kinase/AKT pathway have been postulated as underlying mechanisms connecting PPAR-δ and cancer progression[37–40]. In addition, studies have found that PPAR-δ impacts angiogenesis via vascular endothelial growth factor receptors (VEGFRs) depending on the concentration of its agonist [41–43]. PPAR-δ could also directly interact with DNA response elements of target genes and repress transcription activities, in turn to suppress the cell cycle, initiate cell differentiation or apoptosis [44–47]. Inflammation may provide another link between PPAR-δ and cancer. The role of inflammation in lung and UADT cancer progression, metastasis and prognosis has been extensively investigated and acknowledged [48–52]. The NF-κB pathway and the COX2 pathway have been identified as main connections[53, 54]. PPAR-δ is inversely associated with inflammation-related genetic factors, including NF-κB and COX2; also PPAR-δ can inhibit NF-κB-dependent signaling by combining with the p65 subunit of NF-κB, suggesting its potential anti-inflammatory function [47, 55, 56].

Since PPAR-δ plays a pivotal role from energy and blood supply and inflammation reactions to cell differentiation, growth and apoptosis [9, 10, 57–60], it is reasonable to assume that the CC genotype of rs37342574 at 3'-UTR of *PPARD* identified by our study could affect the transcription of *PPARD* and change the expression of PPAR-δ, eventually increase survival through the interactive network PPAR-δ entangled. However, future studies employing functional assays and deep sequencing of the *PPARD* gene would help elucidate

the precise polymorphism of functional consequence and the characteristics of a mutated gene product. The inverse association between the CC (vs. TT) genotype of rs37342574 and morphology specific cancer survival was strongest for large cell carcinomas (LCC). However, the association between the CC (vs TT) genotype of rs37342574 and LCC mortality was weakened when adjusted for multiple testing and the 95% posterior limits contained the null after introducing a moderate prior to the actual data, which might indicate that the observation was simply due to chance.

We also explored the potential interactions between gene polymorphisms and environmental risk factors including alcohol drinking and cigarette smoking. The inverse association between the CC (vs. TT) genotype of rs37342574 and cancer death was much stronger in lung-cancer smokers than in non-smokers, but the power for testing this interaction in our data was low. This is the first study on *PPARD* gene polymorphisms and lung/UADT cancer survival. A major limitation of our study is the partial gene coverage. We analyzed only three SNPs and might have failed to identify functionally important markers. However, our SNP selection strategy of focusing on potential functional SNPs of >=5% MAF increased the chance for identifying relevant markers at the population-level. Another drawback is that there was no tumor-node-metastasis (TNM) cancer staging information in our database. Although we treated the cell differentiation as a proxy, it could not fully substitute for TNM staging and might introduce measurement errors. Measurement errors could also arise from genotyping and disease diagnoses, which would bias the results; unfortunately, we cannot predict the direction or magnitude of such bias. The recruitment rates were relatively low in our study. Nonparticipation of eligible cancer cases due to early death or sickness, especially for lung and esophageal cancers with poor prognoses, might favor less severe patients included in the study. The potential selection bias limits our ability to generalize our findings to all lung cancer patients and might distort our observed associations. It is difficult to predict the direction of the selection bias or to correct it in the analysis, since the imputation of the SNP distribution in the nonparticipants is problematic. However, by employing the semi-Bayesian shrinkage approach with a null prior, the estimated associations were conservative and the validity of our results would be reliable. In fact, for the CC variant of *PPARD* rs3734254 that was still inversely related with lung cancer death even after semi-Bayesian shrinkage with a null prior, the missing of severe lung cancer patients with shorter survival would bias the association towards the null. The small numbers of certain cancers or morphological subtypes also limit the power and precision with which we could estimate the effects of low-penetrance SNPs. Finally, the biological mechanisms involving PPAR-δ are still not fully understood and controversial [61]. Various mechanisms mentioned above on PPAR-δ have been proposed by different researchers, but they have not been replicated by independent laboratories [57], which prevent an definite explanation about our findings.

Conclusion

We found that the CC variant of *PPARD* rs3734254 was inversely associated with lung-cancer mortality among diagnosed cases. If replicated in larger populations with higher recruitment rates, these findings may be valuable in lung cancer treatment and prognostic predictions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- We explore single nucleotide polymorphisms and cancer survival.

- Peroxisome Proliferative Activated Receptor Beta and Delta are major interests.

- We apply semi-Bayesian shrinkage to adjust for potential false discoveries.

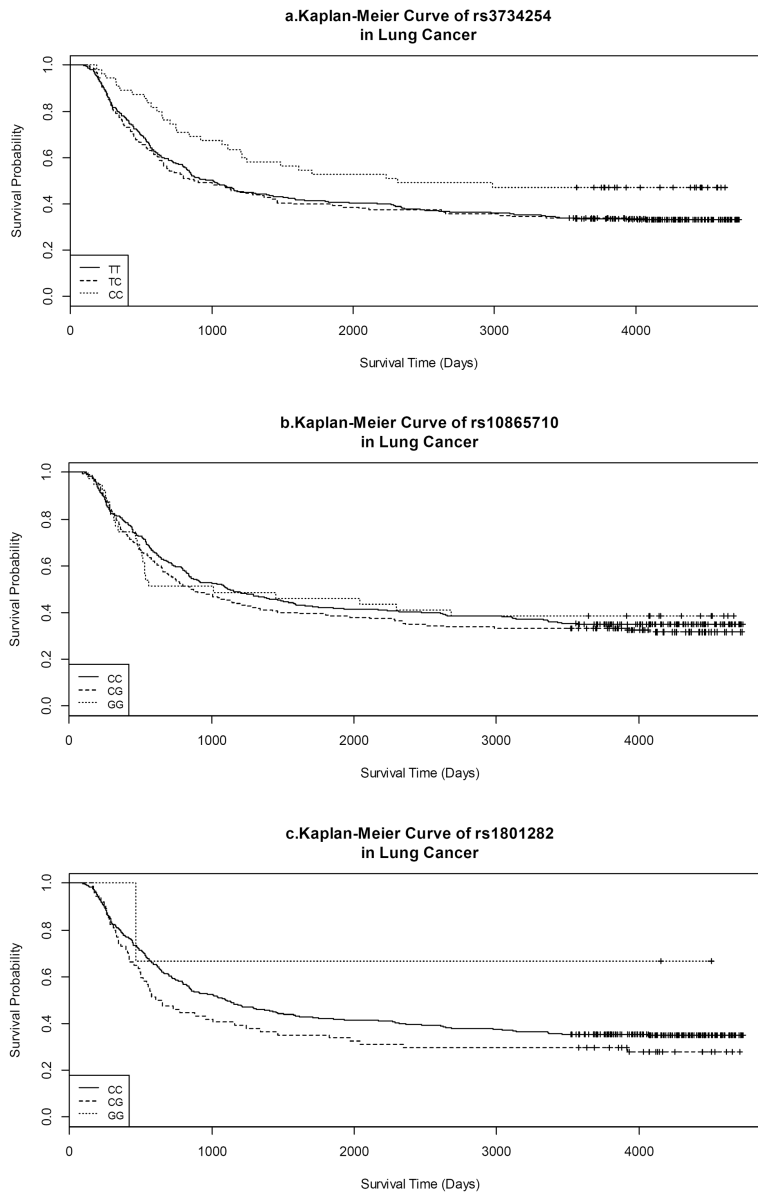- Lung-cancer cases with the CC variant of rs3734254 may have a survival advantage.

Figure 1.
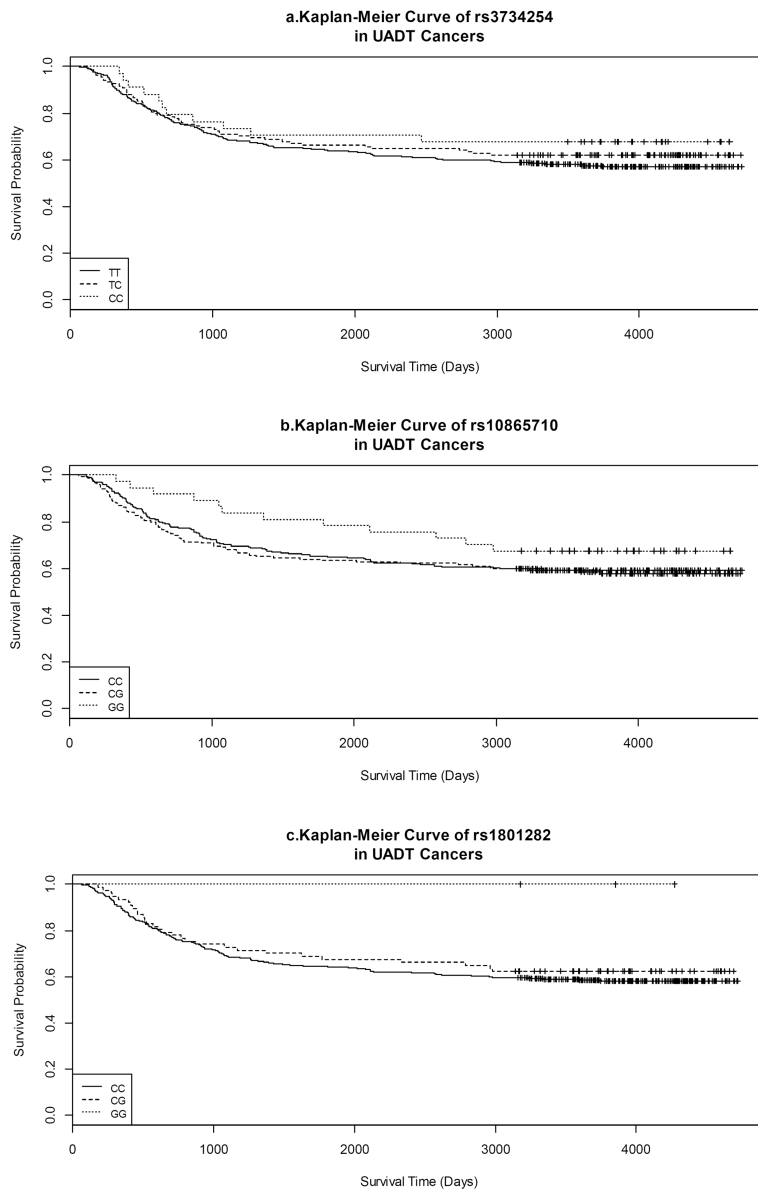Kaplan-Meier Curves of selected SNPs in lung cancer.

Figure 2.
Kaplan-Meier Curves of selected SNPs in UADT cancers.

Table 1

Demographic characteristics in lung and UADT cancer cases, respectively.

	Lung cancer (N = 611)				UADT (N = 601)			
	All, n	Death, n (%)	Censored, n (%)	Median survival years	All, n	Death, n (%)	Censored, n (%)	Median survival years
Survival	611	406 (66)	205 (34)	2.5	601	248 (41)	353 (59)	9.4
Age of Diagnosis, mean (SD)		52.6±5.3	51.5±5.7			51.2±7.3	49.8±7.7	
<45	61	38 (62)	23 (33)	3.0	109	38 (35)	71 (65)	10.1
45–54	301	188 (62)	113 (38)	2.9	267	105 (39)	162 (61)	9.6
55+	249	180 (72)	69 (28)	2.2	225	105 (47)	120 (53)	9.0
Sex								
Male	303	215 (71)	88 (29)	2.0	454	191 (42)	263 (53)	9.3
Female	308	191 (62)	117 (38)	3.7	147	57 (39)	90 (61)	9.7
Ethnicity								
Caucasian	359	245 (68)	114 (32)	2.4	341	135 (40)	206 (60)	9.4
Hispanic	70	44 (63)	26 (37)	2.2	109	46 (42)	63 (58)	9.4
Aincan-Amerian	96	60 (62)	36 (38)	3.0	69	39 (56)	30 (43)	5.6
Asian-American	70	46 (66)	24 (34)	2.8	64	21 (33)	43 (67)	99
Other	15	10 (67)	5 (33)	4.1	16	6 (33)	10 (62)	9.0
Morphology								
Squamous cell	95	53 (56)	42 (44)	5.8	497	195 (39)	302 (61)	9.6
Adenocarcinoma	297	186 (63)	111 (34)	3.4	74	42 (57)	32 (43)	3.6
Large cell	115	85 (74)	30 (26)	2.1		-	-	
Small cell	75	60 (80)	15 (20)	1.4		-	-	
Other	29	22 (76)	7 (24)	1.5	30	11 (37)	19 (63)	9.9
Education (years of schooling)		13.2±3.3	13.4±3.5			12.9±3.6	13.3±3.7	
0–12	265	181 (68)	84 (32)	2.6	273	117 (43)	156 (57)	9.3
13–16	275	181 (66)	94 (34)	2.4	259	110 (42)	149 (58)	9.4
>16	71	44 (62)	27 (38)	2.8	69	21 (30)	48 (70)	10.1
Tumor cell differentiation								
Well to moderate	168	90 (22)	78 (38)	7.1	397	171 (43)	226 (57)	9.3
Poor to very poor	222	154 (38)	68 (33)	2.0	121	42 (35)	79 (65)	9.8

	Lung cancer (N = 611)				UADT (N = 601)			
	All, n	Death, n (%)	Censored, n (%)	Median survival years	All, n	Death, n (%)	Censored, n (%)	Median survival years
Undetermined	219	161 (40)	58 (28)	2.0	81	34 (42)	47 (58)	9.6
Smoking (pack-years)		33.11±24.78	27.89±25.35			28.3±25.8	18.4±22.5	
Never	110	61 (55)	49 (44)	5.5	182	53 (29)	129 (71)	10.1
Ever	501	345 (69)	156 (31)	2.2	419	195 (46)	224 (53)	9.0
less than 20	98	63 (64)	35 (36)	2.6	145	51 (35)	94 (65)	9.7
20 – 40	201	139 (69)	62 (31)	2.5	146	71 (49)	75 (51)	8.8
40 or more	202	143 (71)	59 (29)	1.9	128	73 (57)	55 (43)	6.8
Alcohol drinking status (drinks-day)		1.62±3.08	1.63±5.06			3.1±4.6	2.1±4.6	
Never	170	111 (65)	59 (34)	2.8	117	45 (38)	72 (62)	9.8
Ever	440	294 (67)	146 (33)	2.5	482	202 (42)	280 (58)	9.4
< 2 drinks/day	302	200 (66)	102 (34)	2.4	279	97 (35)	182 (65)	9.8
>=2 drinks/day	138	94 (68)	44 (32)	2.8	203	105 (52)	93 (48)	8.2

Table 2

Selected crude and adjusted hazard ratio of PPAR SNPs and lung cancer survival, stratified by morphological types[*].

	PPARD rs3734254 T>C				PPARG rs10865710 C>G				
Genotype	Death/All	cHR (95% CI)	aHR[**] (95% CI)	Posterior aHR[**] (95% posterior limits)	Genotype	Death/All	cHR (95% CI)	aHR[**] (95% CI)	Posterior aHR[**] (95% posterior limits)
Lung Cancer (N=611)									
TT	193/289	1.00	1.00	1.00	CC	186/286	1.00	1.00	1.00
TC	112/168	1.02(0.81, 1.29)	1.07(0.83, 1.37)	1.08(0.84, 1.37)	CG	130/192	1.11(0.88, 1.38)	1.06(0.84, 1.34)	1.06(0.85, 1.33)
CC	29/55	*0.65(0.44, 0.96)*	*0.63(0.42, 0.96)*	*0.66(0.44, 0.98)*	GG	24/39	0.99(0.65, 1.51)	1.11(0.71, 1.73)	1.10(0.72, 1.68)
P_trend		0.10	0.15	0.16	P_trend		0.62	0.54	0.54
Recessive	29/55	*0.64(0.44, 0.94)*	*0.61(0.41, 0.92)*	*0.64(0.43, 0.94)*	Recessive	24/39	0.95(0.63, 1.44)	1.07(0.70, 1.66)	1.07(0.71, 1.62)
Non-SCLC (N=536)									
TT	162/251	1.00	1.00	1.00	CC	162/254	1.00	1.00	1.00
TC	97/150	1.04(0.81, 1.34)	1.04(0.80, 1.36)	1.05(0.80, 1.36)	CG	105/162	1.05(0.82, 1.34)	1.03(0.80, 1.33)	1.03(0.80, 1.32)
CC	24/46	0.69(0.45, 1.06)	0.69(0.44, 1.09)	0.72(0.47, 1.10)	GG	22/36	1.00(0.64, 1.55)	1.14(0.71, 1.33)	1.12(0.72, 1.76)
P_trend		0.24	0.28	0.28	P_trend		0.83	0.63	0.63
Recessive	24/46	0.68(0.45, 1.03)	0.68(0.44, 1.05)	0.70(0.47, 1.06)	Recessive	22/36	0.98(0.63, 1.51)	1.12(0.71, 1.78)	1.11(0.72, 1.72)
SQC (N=95)									
TT	23/43	1.00	1.00	1.00	CC	18/35	1.00	1.00	1.00
TC	16/27	1.22(0.65, 2.32)	1.51(0.74, 3.05)	1.40(0.75, 2.60)	CG	22/37	1.27(0.68, 2.37)	1.35(0.68, 2.67)	1.26(0.69, 2.29)
CC	5/10	0.94(0.36, 2.46)	0.91(0.30, 2.71)	0.92(0.39, 2.13)	GG	4/8	0.95(0.32, 2.80)	1.21(0.35, 4.19)	1.09(0.43, 2.75)
P_trend		0.87	0.75	0.77	P_trend		0.76	0.50	0.53
Recessive	5/10	0.86(0.34, 2.20)	0.74(0.26, 2.09)	0.82(0.36, 1.86)	Recessive	4/8	0.84(0.30, 2.34)	1.01(0.31, 3.27)	1.01(0.41, 2.47)
ABC (N=297)									
TT	82/137	1.00	1.00	1.00	CC	83/141	1.00	1.00	1.00
TC	54/87	1.13(0.80, 1.60)	1.19(0.82, 1.73)	1.18(0.83, 1.68)	CG	57/89	1.22(0.87, 1.71)	1.11(0.77, 1.58)	1.09(0.78, 1.54)
CC	13/23	0.88(0.49, 1.58)	0.99(0.51, 1.92)	0.99(0.55, 1.79)	GG	13/20	1.37(0.76, 2.46)	1.24(0.65, 2.33)	1.19(0.66, 2.12)
P_trend		0.97	0.64	0.64	P_trend		0.16	0.45	0.46
Recessive	13/23	0.84(0.48, 1.49)	0.90(0.48, 1.69)	0.92(0.52, 1.63)	Recessive	13/20	1.27(0.72, 2.24)	1.18(0.64, 2.17)	1.15(0.65, 2.02)
LCC (N=115)									
TT	45/56	1.00	1.00	1.00	CC	50/64	1.00	1.00	1.00

| | | PPARD rs3734254 T>C | | | | | PPARG rs10865710 C>G | | |
Genotype	Death/All	cHR (95% CI)	aHR** (95% CI)	Posterior aHR** (95% posterior limits)	Genotype	Death/All	cHR (95% CI)	aHR** (95% CI)	Posterior aHR** (95% posterior limits)
TC	23/31	0.82(0.50, 1.35)	0.68(0.37, 1.25)	0.75(0.44, 1.30)	CG	19/27	0.74(0.44, 1.26)	0.85(0.48, 1.48)	0.87(0.52, 1.45)
CC	4/9	0.34(0.12, 0.95)	0.32(0.09, 1.06)	0.50(0.22, 1.15)	GG	4/7	0.55(0.20, 1.52)	0.87(0.26, 2.92)	0.93(0.38, 2.29)
P_{trend}		0.04	0.03	0.04	P_{trend}		0.14	0.59	0.61
Recessive	4/9	0.37(0.13, 1.01)	0.36(0.11, 1.20)	0.54(0.24, 1.23)	Recessive	4/7	0.60(0.22, 1.65)	0.94(0.28, 3.07)	0.96(0.39, 2.36)
SCLC (N=75)									
TT	31/38	1.00	1.00	1.00	CC	24/32	1.00	1.00	1.00
TC	15/18	1.04(0.56, 1.92)	1.22(0.61, 2.45)	1.19(0.64, 2.22)	CG	25/30	1.28(0.73, 2.25)	1.03(0.54, 1.95)	1.03(0.58, 1.84)
CC	5/9	0.43(0.17, 1.10)	0.67 (0.20, 2.18)	0.78(0.32, 1.91)	GG	2/3	1.17(0.28, 4.93)	0.80(0.17, 3.69)	0.90(0.33, 2.46)
P_{trend}		0.13	0.84	0.85	P_{trend}		0.45	0.91	0.92
Recessive	5/9	0.42(0.17, 1.07)	0.63(0.20, 2.03)	0.76(0.32, 1.84)	Recessive	2/3	1.04(0.25, 4.27)	0.79(0.18, 3.43)	0.89(0.33, 2.39)

*
Due to many 0 counts of PPARG rs1801282, the corresponding results were presented in supplementary tables.

**
Adjusted by age, gender, ethnicity, education level, smoking as packyears and tumor cell differentiation and morphology including squamous carcinoma, adenocarcinoma and large cell carcinoma and small cell carcinoma, if applicable.

Table 3

Selected results of crude and adjusted hazard ratio of PPAR SNPs and UADT cancer survival, stratified by morphological types [*].

		PPARD rs3734254 T>C					PPARG rs10865710 C>G		
Genotype	Death/All	cHR (95% CI)	aHR[**] (95% CI)	Posterior aHR[**] (95% posterior limits)	Genotype	Death/All	cHR (95% CI)	aHR[**] (95% CI)	Posterior aHR[**] (95% posterior limits)
UADT (N=601)									
TT	123/286	1.00	1.00	1.00	CC	96/235	1.00	1.00	1.00
TC	51/134	0.88 (0.63, 1.21)	0.90 (0.64, 1.27)	0.92 (0.66, 1.27)	CG	73/175	1.06 (0.78, 1.43)	1.07 (0.78, 1.46)	1.07 (0.79, 1.45)
CC	11/54	0.71(0.33, 1.31)	**0.51 (0.27, 0.99)**	0.58 (0.33, 1.03)	GG	12/37	0.70 (0.38, 1.28)	0.79 (0.42, 1.46)	0.82 (0.47, 1.43)
P$_{trend}$		0.20	0.07	0.07	P$_{trend}$		0.52	0.77	0.78
Recessive	11/34	0.74(0.40, 1.35)	0.53 (0.28, 1.01)	0.59 (0.34, 1.04)	Recessive	12/57	0.69 (0.38, 1.23)	0.76 (0.42, 1.40)	0.80 (0.46, 1.38)
SQC (N=497)									
TT	91/227	1.00	1.00	1.00	CC	71/187	1.00	1.00	1.00
TC	34/106	0.78 (0.53, 1.16)	0.84 (0.56, 1.26)	0.86 (0.59, 1.27)	CG	52/143	0.99 (0.69, 1.42)	0.98 (0.68, 1.41)	0.98 (0.69, 1.39)
CC	11/31	0.87 (0.47, 1.63)	0.60 (0.30, 1.18)	0.66 (0.37, 1.20)	GG	11/30	0.91 (0.48, 1.71)	0.92 (0.48, 1.77)	0.94 (0.52, 1.68)
P$_{trend}$		0.32	0.12	0.12	P$_{trend}$		0.80	0.81	0.81
Recessive	11/31	0.94 (0.51, 1.73)	0.63 (0.33, 1.23)	0.69 (0.38, 1.24)	Recessive	11/30	0.91 (0.49, 1.69)	0.93 (0.50, 1.76)	0.95 (0.53, 1.67)
Oral and oropharyngeal (N=335)									
TT	53/145	1.00	1.00	1.00	CC	42/116	1.00	1.00	1.00
TC	20/67	0.80 (0.48, 1.35)	1.05 (0.62, 1.79)	1.05 (0.64, 1.72)	CG	28.91	0.85 (0.52, 1.37)	0.86 (0.52, 1.44)	0.89 (0.55, 1.43)
CC	6/15	1.18 (0.51, 2.74)	0.91 (0.37, 2.27)	0.94 (0.44, 2.00)	GG	7/19	0.98 (0.44, 2.19)	0.75 (0.32, 1.74)	0.81 (0.40, 1.65)
P$_{trend}$		0.80	0.96	057	P$_{trend}$		0.69	0.43	0.44
Recessive	6/15	1.26 (0.55, 2.90)	0.90 (0.36, 2.21)	0.93 (0.44, 1.96)	Recessive	7/19	1.05 (0.48, 2.29)	0.79 (0.35, 1.81)	0.84 (0.42, 1.69)
Laryngeal (N=90)									
TT	16/39	1.00	1.00	1.00	CC	16/41	1.00	1.00	1.00
TC	6/24	0.58 (0.23, 1.48)	0.62 (0.20, 1.94)	0.69 (0.30, 1.59)	CG	11/29	1.04 (0.48, 2.24)	0.98 (0.42, 2.31)	1.01 (0.49, 2.09)
CC	5/12	1.07 (0.39, 2.91)	2.11 (0.57, 7.83)	1.57 (0.60, 4.07)	GG	1/5	0.43 (0.06, 3.24)	0.50 (0.05, 4.87)	0.81 (0.26, 2.53)
P$_{trend}$		0.76	0.50	0.55	P$_{trend}$		0.60	0.69	0.72
Recessive	5/12	1.28 (0.48, 3.38)	2.69 (0.81, 8.91)	1.74 (0.68, 4.44)	Recessive	1/5	0.42 (0.06, 3.11)	0.50 (0.05, 4.76)	0.81 (0.26, 2.52)

[*] Due to the very small sample size of esophageal cancer and many 0 counts of *PPARG* rs1801282, the corresponding results were presented in supplementary tables.

** Adjusted by age, gender, ethnicity, education, smoking as packyears, alcohol drinking as alcoholic drinks per day and tumor cell differentiation and morphology including squamous carcinoma and adenocarcinoma, if applicable.