Improved survival associated with somatic *PIK3CA* mutations in copy-number low endometrioid endometrial adenocarcinoma

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Abstract. The phosphoinositide-3-kinase (PI3K) signaling pathway has been implicated in the development of endometrioid endometrial adenocarcinoma (EEC). Recently, The Cancer Genome Atlas (TCGA) project stratified EEC into four molecular subgroups, with the majority of tumors falling into the copy-number low-EEC (CNL-EEC) molecular subgroup. The aim of the present study was to investigate whether alterations of the PI3K pathway are associated with specific survival outcomes in patients with EEC. The clinical and genomic data of 307 patients with endometrioid-type tumors were obtained from TCGA project, including 90 patients in the CNL-EEC subgroup. Patients were evaluated in terms of survival and clinicopathological characteristics, as well as mutations in the PI3K catalytic subunit alpha (*PIK3CA*) gene and their effect on *PIK3CA* function. In CNL-EEC subgroup patients, somatic PIK3CA mutations (48/90 cases) were associated with significantly improved overall survival compared with that of wild-type *PIK3CA* (P=0.018). Furthermore, this improved survival was specific to the CNL-EEC subgroup and was not observed in other TCGA molecular subgroups. The majority of CNL-EEC cases were low-stage (stage I) and low-to-intermediate grade (grades 1-2) endometrioid tumors. There were no significant differences in age, stage, histology or International Federation of Gynecology and Obstetrics grade between *PIK3CA*-mutated and non-mutated patient groups (P>0.05). In addition, the majority of cases contained activating *PIK3CA* mutations. Overall, in the TCGA cohort, *PIK3CA* mutations had a favorable effect on the survival of patients with EEC, and this effect was dependent on tumoral molecular sub-stratification. Future studies on larger independent cohorts with long term follow-up are warranted to further analyze this association.

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Introduction

Endometrial adenocarcinoma is the most frequently diagnosed type of gynecological malignancy, with 280,000 cases reported worldwide in 2008 (1). In the United States, it is estimated that there were ~40,000 new cases per year, with 7,500 mortalities reported in 2008 (2). The majority of cases are grade 1 endometrioid-type adenocarcinoma confined to the uterus for which total hysterectomy and bilateral salpingo-oophorectomy is standard treatment (1,2). However, a small but significant percentage of cases recur following total hysterectomy. This recurrence, or cases that are metastatic upon presentation, exhibit a limited response to systemic therapy (chemotherapy, hormonal therapy or radiation). The five-year survival rate is >95% for women with disease confined to the uterus (stage I) and ~15% for distant, high-stage disease (3). Recently, The Cancer Genome Atlas (TCGA) project stratified endometrioid endometrial adenocarcinoma (EEC) into four different molecular subgroups, each with distinct survival outcomes: i) Copy-number low (CNL) alterations; ii) copy-number high alterations (serous-like); iii) polymerase ε (*POLE*) ultramutated; and iv) microsatellite instability hypermutated (4). In this stratification system, the CNL-EEC molecular subgroup exhibited intermediate progression-free survival compared with the *POLE* ultramutated (best prognosis) and copy-number high, serous-like (worst prognosis) tumors (4).

Similar to previous studies, which revealed a high percentage of somatic phosphatase and tensin homolog (*PTEN*), phosphoinositide-3-kinase catalytic subunit alpha (*PIK3CA*) and PI3K regulatory subunit 1 (*PIK3R1*) mutations in EECs, the TCGA study revealed that a significant number of endometrial adenocarcinomas had genetic alterations in the PI3K/AKT pathway, suggesting a potential for targeted therapy with specific inhibitors (4-11). More specifically, TCGA demonstrated that the PI3K pathway was altered in 92% (83/90) CNL-EEC cases, as evidenced by somatic mutations in the *PTEN*, *PIK3CA* and *PIK3R1* genes (4). The majority of CNL-EEC tumors (77%; 69/90) exhibited somatic *PTEN* mutations, while approximately half (53%; 48/90) exhibited somatic *PIK3CA* mutations and one-third (33%; 30/90) contained somatic *PIK3R1* mutations. Furthermore, approximately two-thirds of tumors (68%; 61/90) exhibited somatic mutations in >1 member of the PI3K pathway (4). These and previous findings (4-11) support the hypothesis that activation of the PI3K signaling pathway is an important step in the development of EEC.

The aim of the present study was to investigate whether mutations of PI3K pathway members are associated with specific survival outcomes in patients with endometrial adenocarcinomas and whether these outcomes are specific to a particular molecular subgroup.

Materials and methods

Survival analysis. The clinical data of 307 newly diagnosed endometrial carcinoma patients with endometrioid-type histology, including 90 cases of CNL-EEC, was obtained from TCGA Research Network (4) and integrated with *PIK3CA* mutation data from TCGA Data Portal Open-Access directory (https://tcga-data.nci.nih.gov/tcga/). Overall and disease-free survival analysis were then performed using the cBio Cancer Genomics Portal (http://cbioportal.org). The present study was approved by the Beth Israel Deaconess Medical Center-HCC Institutional Review Board.

Review of pathological data. Pathology reports were downloaded from TCGA Data Portal Open-Access directory or via the cBio Cancer Genomics Portal. Quality control hematoxylin and eosin (H&E) images from frozen and permanent sections were re-analyzed by a board-certified gynecological pathologist (Dr Douglas Lin) at the Department of Pathology, Beth Israel Deaconess Medical Center (Boston, MA, USA) to determine that tumors were indeed of the endometrioid histological subtype. Re-analysis was performed via TCGA BioSig website (http://tcga.lbl.gov:8080/biosig/tcgadownload.do) hosted by Lawrence Berkeley National and via the Cancer Digital Slide Archive (http://cancer.digitalslidearchive.net; Emory University, Atlanta, GA, USA). Tumor stage (12) and overall International Federation of Gynecology and Obstetrics (FIGO) grade (13) were also independently re-evaluated where possible, however, this was deferred to the available pathology reports, as only limited virtual images from each case were publicly available for review.

Analysis of PIK3CA mutations. Somatic *PIK3CA* mutations derived from Next Generation exome sequencing were retrieved from TCGA Data Portal Open-Access directory via the cBio Portal (http://www.cbioportal.org/public-portal/). The effect of specific somatic mutations on *PIK3CA* function was determined by cross-referencing them with previously published studies, wherein the effect of specific *PIK3CA* mutations on p110-α activation or gain-of-function was demonstrated *in vitro* or *in vivo* (9,14-16). p110-α is the protein encoded by the *PIK3CA* gene and represents the catalytic subunit of PI3K. The presence of specific *PIK3CA* somatic mutations in other cancer types was determined by analyzing the Catalogue of Somatic Mutations in Cancer database (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/). All websites were accessed between July 1, 2013 and May 1, 2014.

Statistical analysis. Kaplan-Meier overall and disease-free survival curves and corresponding P-values were calculated using the cBio Cancer Genomics Portal (http://cbioportal.org; Memorial Sloan Kettering Cancer Center, New York, NY, USA) with significance estimated by log-rank test (17,18).

Table I. Clinicopathological characteristics of patients in The Cancer Genome Atlas copy-number low endometrioid endometrial carcinoma molecular subgroup with and without somatic *PIK3CA* mutations.

	PIK3CA		
Characteristic	Non-mutated	Mutated	P-value
Cases, n	42	48	
Age, years			0.902
Range	37-90	34-89	
Mean	60.6	60.3	
Median	59	60	
Stage, n (%)			0.406
I	34 (81.0)	40 (83.3)	
II	1 (2.3)	2 (4.0)	
III	6 (14.3)	6 (13.0)	
IV	1 (2.3)	0 (0.0)	
Grade, n (%)			0.074
1	22 (52.4)	23 (47.9)	
2	18 (42.9)	21 (43.8)	
3	2 (4.8)	4 (8.3)	

Statistical analysis of clinicopathological characteristics (age and tumor stage and grade) were assessed using the t-test and paired t-test, respectively. P<0.05 was considered to indicate a statistically significantly difference.

Results

Clinical data from 307 newly diagnosed endometrial carcinoma patients with endometrioid-type histology, including 90 cases of the CNL-EEC subtype, was obtained from TCGA Research Network (4) and integrated with *PIK3CA* mutation data from TCGA Data Portal via the cBio Cancer Genomics Portal (4,17,18). Survival analysis of all TCGA tumors with endometrioid-type histology (n=307), regardless of molecular subtype, revealed that patients with somatic *PIK3CA* mutations exhibited significantly improved overall survival and marginally prolonged progression-free survival compared with those possessing wild-type *PIK3CA* (log-rank test P=0.001 and P=0.077, respectively; Fig. 1A and B).

The overall survival outcome difference was specific to the CNL-EEC patients (n=90; P=0.018; Fig. 1C and D), as no significant association with overall and disease-free survival was observed in the three other TCGA molecular subgroups (copy-number high, P=0.442 and P=0.225; *POLE* ultramutated, no mortality or recurrence; or microsatellite instability hypermutated tumors, P=0.108 and P=0.949) (data not shown). For this reason, the remainder of the study was focused on the CNL-EEC subgroup. In CNL-EEC, the mean follow-up times for patients with mutated and wild-type *PIK3CA* were 33 and 26 months, respectively. The median follow-up times for patients with mutated *PIK3CA* and wild-type *PIK3CA* were 29 and 21 months, respectively. There were no reported mortalities among patients with *PIK3CA* mutations (0%;
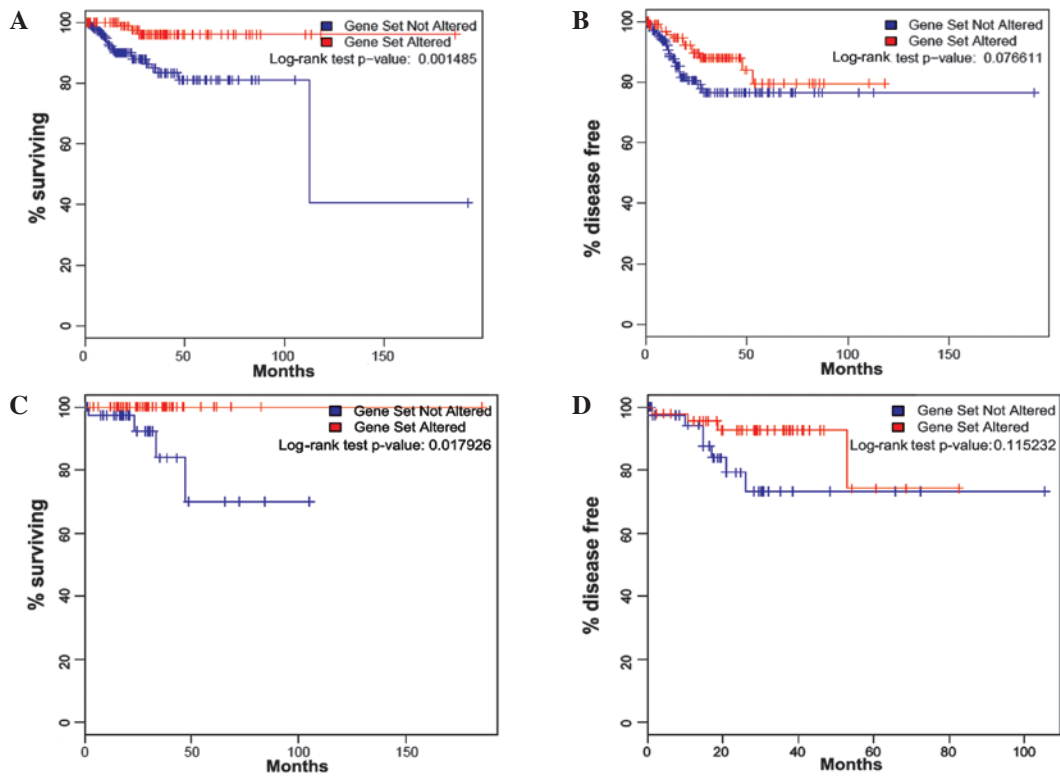
Figure 1. Kaplan-Meier survival curves for *PIK3CA*-mutated tumors. (A) Overall and (B) disease-free survival of all TCGA patients with endometrioid-type tumors (n=307), regardless of molecular sub-stratification, with (red) or without (blue) *PIK3CA* mutations. (C) Overall and (D) disease-free survival of TCGA patients in the copy-number low endometrioid endometrial adenocarcinoma molecular subgroup (n=90) with (red) or without (blue) *PIK3CA* mutations. TCGA, The Cancer Genome Atlas.
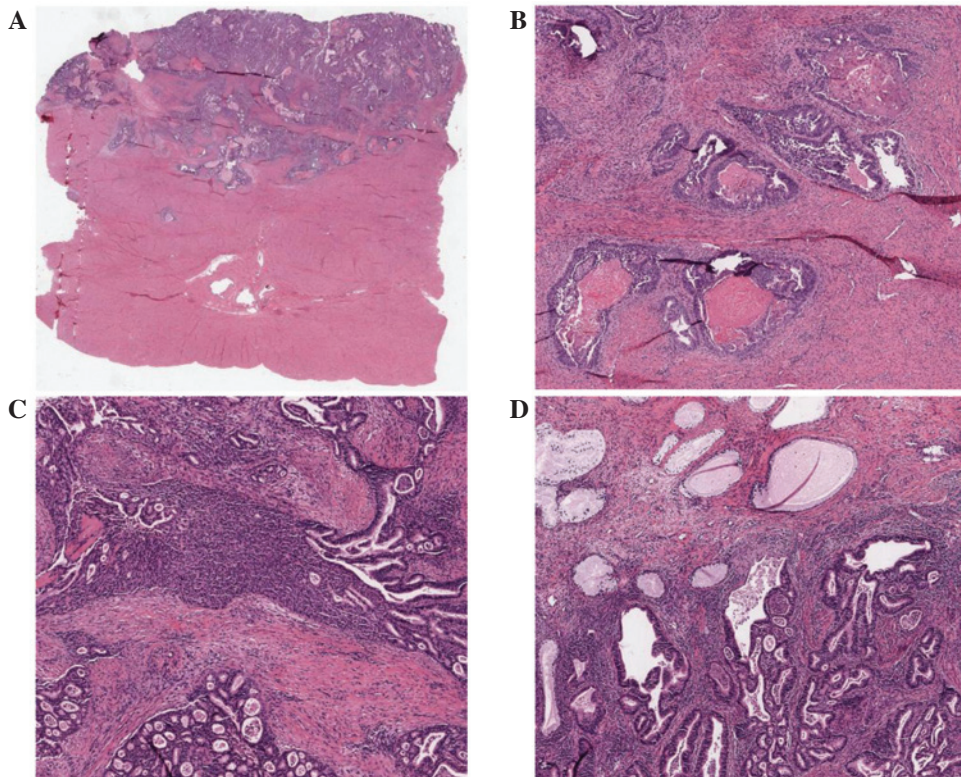

Figure 2. Histology of *PIK3CA*-mutated tumors (hematoxylin and eosin staining) from patients in TCGA. Patient no. TCGA-D1-A16D: (A) Full-thickness permanent section of well-differentiated tumor, demonstrating stage I myometrial invasion (magnification, x10). (B) Higher magnification of the same tumor characterized by well-formed, endometrioid-type glands and no significant nuclear atypia [FIGO grade 1 (of 3)] (magnification, x40). Patient no. TCGA-D1-A16J: (C) Endometrioid endometrial adenocarcinoma, characterized by cribriform and solid growth patterns [FIGO grade 2 (of 3)] (magnification, x40). (D) Different section of the same tumor involving stage II endocervical stroma (magnification, x40). Images and data obtained from the cBio Cancer Genomics Portal (http://cbioportal.org). TCGA, The Cancer Genome Atlas; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Summary of somatic *PIK3CA* mutations in the copy-number low endometrioid endometrial adenocarcinoma subgroup.

Mutation	n	Effect on function	Type	Domain	Present in other cancers
WGIHLMPP11del	1	Unknown	IF del	ABD	No
R88Q	2	Activating	Missense	ABD	Yes
R93Q	2	Activating	Missense	ABD	Yes
I102del	1	Unknown	IF del	ABD	No
N107S	1	Unknown	Missense	ABD	No
K111E	1	Activating	Missense	ABD	Yes
L113del	1	Unknown	IF del	ABD	Yes
R115L	1	a	Missense	ABD	Yes
G118D	1	Activating	Missense	ABD	Yes
V344M	1	Unknown	Missense	C2	Yes
N345K	2	Activating	Missense	C2	Yes
C420R	2	Activating	Missense	C2	Yes
463_465GSN>D	1	Unknown	IF del	C2	No
E542K	5	Activating	Missense	Helical	Yes
E542A	1	Activating	Missense	Helical	Yes
E545K	8	Activating	Missense	Helical	Yes
E545A	1	Activating	Missense	Helical	Yes
E545G	1	Activating	Missense	Helical	Yes
E545D	1	a	Missense	Helical	Yes
Q546P	2	Activating	Missense	Helical	Yes
Q546K	1	Activating	Missense	Helical	Yes
Q546R	1	a	Missense	Helical	Yes
C901F	1	Unknown	Missense	Kinase	Yes
D939G	2	Unknown	Missense	Kinase	Yes
G1007R	1	Unknown	Missense	Kinase	Yes
M1043V	2	Activating	Missense	Kinase	Yes
M1043I	2	Activating	Missense	Kinase	Yes
H1047R	7	Activating	Missense	Kinase	Yes
H1047L	2	Activating	Missense	Kinase	Yes
H1047Q	1	a	Missense	Kinase	Yes

Six tumors exhibited >1 somatic mutation. a, mutation occurring in a position previously implicated in *PIK3CA* activation; ABD, adaptor-binding domain; C2, protein kinase-C homology 2; IF del, in-frame deletion.
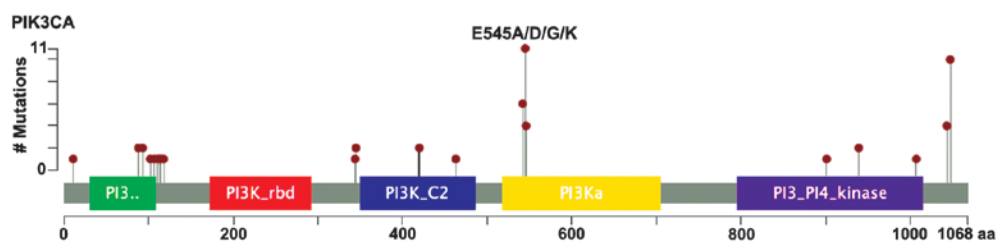

Figure 3. Distribution of somatic *PIK3CA* mutations in the copy-number low endometrioid endometrial adenocarcinoma molecular subgroup. Mutations occurred predominantly in hotspots centered on the following *PIK3CA* functional domains: Adaptor-binding domain (green), protein kinase-C homology 2 (blue), helical (yellow) and kinase (purple). PI3K, phosphoinositide-3-kinase.

0/48), while 4 mortalities were reported among the patients with wild-type *PIK3CA* (9.5%; 4/42). Of the patients with somatic *PIK3CA* mutations, 5 exhibited recurrent disease (10.4%; 5/48), while 8 patients with wild-type *PIK3CA* had recurrent disease (19.0%; 8/42).

Next, the pathological data was re-reviewed in terms of patient age, tumor type, stage and FIGO grade via the tools available at TCGA Data Portal Open-Access directory and the cBio portal. Patient age in *PIK3CA*-mutated cases ranged from 34-89 years (mean, 60.3 years; median, 60 years), which was

similar to that of the non-mutated cases (range, 37-90 years; mean, 60.6 years; median, 59 years) (Table I). The majority of *PIK3CA*-mutated cases were of stage I (83%; 40/48) and FIGO grade 1 or 2 disease (48 and 44%, respectively) (Table I and Fig. 2). There were no significant differences in age, tumor stage and FIGO grade between *PIK3CA*-mutated and non-mutated cancers (Table I). For all cases in the CNL-EEC subgroup, the tumors were of endometrioid histological type. This was confirmed by the presence of back to back atypical endometrial type glands with complex architecture, no intervening stroma and varying differentiation upon review of available H&E images (Fig. 2).

Pathological analysis of 3 *PIK3CA*-mutated cases also demonstrated the presence of a serous carcinoma component. However, the images that were available for review were more consistent with endometrioid-type tumors. In addition, these 3 cases exhibited no *TP53* mutations or homozygous deletion, indicating that the histological type was not serous carcinoma. These findings suggest that survival differences between *PIK3CA* mutated and non-mutated cases may not be attributed to differences in patient age, tumor stage, FIGO grade or histological subtype.

A total of 56 somatic *PIK3CA* mutations were identified in 48 patients with CNL-EEC, and a subset of these mutated tumors (12.5%; 6/48) contained >1 *PIK3CA* mutation. *PIK3CA* mutations occurred predominantly in hotspots centered on p110-α functional domains (Fig. 3), and around 30% (17/56) occurred within exons 1-7, which encode the N-terminal domains of p110-α, including the p85/adaptor-binding domain and the protein kinase-C homology 2 domain. In addition, around 70% (39/56) of *PIK3CA* mutations occurred within exons 9 and 20, which encode the C-terminal helical and kinase domains (Fig. 3). The majority of cases (79% of patients and 75% of overall mutations) contained mutations implicated in *PIK3CA* activation and gain-of-function (Table II). The following recurrent activating mutations were also identified: R88Q, R93Q, N345K, C420R, E542K, E545K (most common), Q546P, D939G, M1043V, M1043I, H1047R (second most common) and H1047L (Fig. 3 and Table II). These findings support the hypothesis that endometrial adenocarcinomas possess a unique spectrum of somatic *PIK3CA* mutations in which a significant number of mutations occur in the amino terminal domain of p110-α compared with other cancer types, such as colorectal, breast or bladder carcinomas (4,9).

Discussion

Despite its growth-promoting properties, the effect of *PIK3CA* mutation on patient prognosis varies according to the cancer subtype. In patients with colorectal or lung cancer, mutations of *PIK3CA* are associated with poor prognosis. By contrast, *PIK3CA* mutations have been associated with favorable prognosis in patients with breast cancer and esophageal squamous cell carcinomas (19-22). In endometrial cancer patients, the influence of *PIK3CA* mutations on survival and prognosis has been unclear, as there is data to suggest an association between *PIK3CA* mutations and both favorable and unfavorable prognoses (23-25).

The TCGA Data Portal on endometrial adenocarcinoma offers a host of tools that can be used to interrogate specific genetic events relative to survival and clinicopathological characteristics, as well as to generate hypotheses for future testing. In the present study, we hypothesized that *PIK3CA* mutations in EEC may be associated with favorable survival outcomes, possibly specific to a molecularly sub-defined cohort of tumors that exhibit low somatic copy-number alterations and microsatellite stability. The significantly improved overall survival observed in all patients with endometrioid-type adenocarcinomas exhibiting *PIK3CA* mutations, regardless of the molecular subtype, may reflect the fact that the majority of TCGA tumors were in the CNL-EEC subgroup.

However, due to the limitations of the TCGA study (i.e., small sample size of the CNL-EEC subgroup, relatively short follow-up time, lack of information on co-morbidities), these findings are exploratory and hypothesis-generating in nature, rather than definitive. For this reason, future studies with multivariate analyses and long-term follow-up to determine the effect of other clinical co-variables (including race, body mass index, estrogen receptor/progesterone receptor status, co-morbidities and treatment regimens) on survival outcome are required. In addition, long-term multivariate analyses with increased power are essential to determine the effect of other molecular co-variables. For example, Liang *et al* (11) previously reported that *ARID1A* mutations co-occur with PI3K pathway mutations in endometrial cancer and lead to activation of the PI3K signaling pathway. In the TCGA CNL-EEC subgroup, somatic mutations of *ARID1A* occurred in 42% of cases (38/90) with a trend towards improved overall survival (P=0.0517) and no differences in progression-free survival (P=0.86). By contrast, significantly improved overall survival was observed in cases with *PIK3CA-ARID1A* co-occurring mutations (P=0.00026), with no differences in progression-free survival (P=0.88; data not shown).

Finally, the mechanism by which *PIK3CA* mutations affect patient survival and the mechanism that explains why there appears to be no association between *PIK3R1* mutations and survival outcome are unclear, as *PIK3CA* and *PIK3R1* are subunits of the same kinase (8,11). One possible explanation for this is that *PIK3CA*- and *PIK3R1*-mutated tumors may have different driver mutations.

In conclusion, the results presented in the current study suggest that *PIK3CA* mutations may serve as a favorable prognostic biomarker in EEC, depending on further molecular sub-stratification of the tumors. Therefore, future studies on larger independent cohorts with long term follow-up are warranted to further analyze this association and to validate the findings of the TCGA project.

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