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# PTPN14 Mutations and Cervical Cancer

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**Abstract.** *Background/Aim: It was recently shown that rare germline loss-of-function variants in the tyrosine-protein phosphatase non-receptor type 14 (PTPN14) gene conferred substantial risk of basal cell carcinoma (BCC). A follow-up investigation of 24 cancers and three benign tumor types showed that PTPN14 loss-of-function variants were associated with high risk of cervical cancer and early age at diagnosis. We used the Cancer Genome Atlas (TCGA) to further evaluate the PTPN14 – cervical cancer association. Materials and Methods: We analyzed the Genomic Data Commons (GDC) TCGA Cervical Cancer (CESC) data set. We used cBioPortal for Cancer Genomics to access data in TCGA. cBioPortal provides visualization, analysis and download options for large-scale cancer genomic data sets. We also accessed TCGA data with the University of California Santa Cruz (UCSC) Xena Browser. UCSC Xena allows users to explore functional genomic data sets for assessing correlations between genomic and/or phenotypic variables. Results: Ten patients with PTPN14 mutations had significantly better survival than 266 patients without PTPN14 mutations (p=0.05 log rank test). In the Human Protein Atlas, low expression of PTPN14 in 85 TCGA cervical cancer specimens was associated with better survival than high expression in 206 cervical cancer specimens. Conclusion: In general, factors that affect the risk of a cancer have the same effect on prognosis. For example, history of allergy reduces risk of malignant brain tumors and improves prognosis. However, this relationship is not the case for PTPN14. We conclude that in TCGA cervical cancer specimens, PTPN14 mutation is a favorable prognostic factor. However, germline variants of PTPN14 confer a worse prognosis. Further studies of the specific mutations would be worthwhile.*



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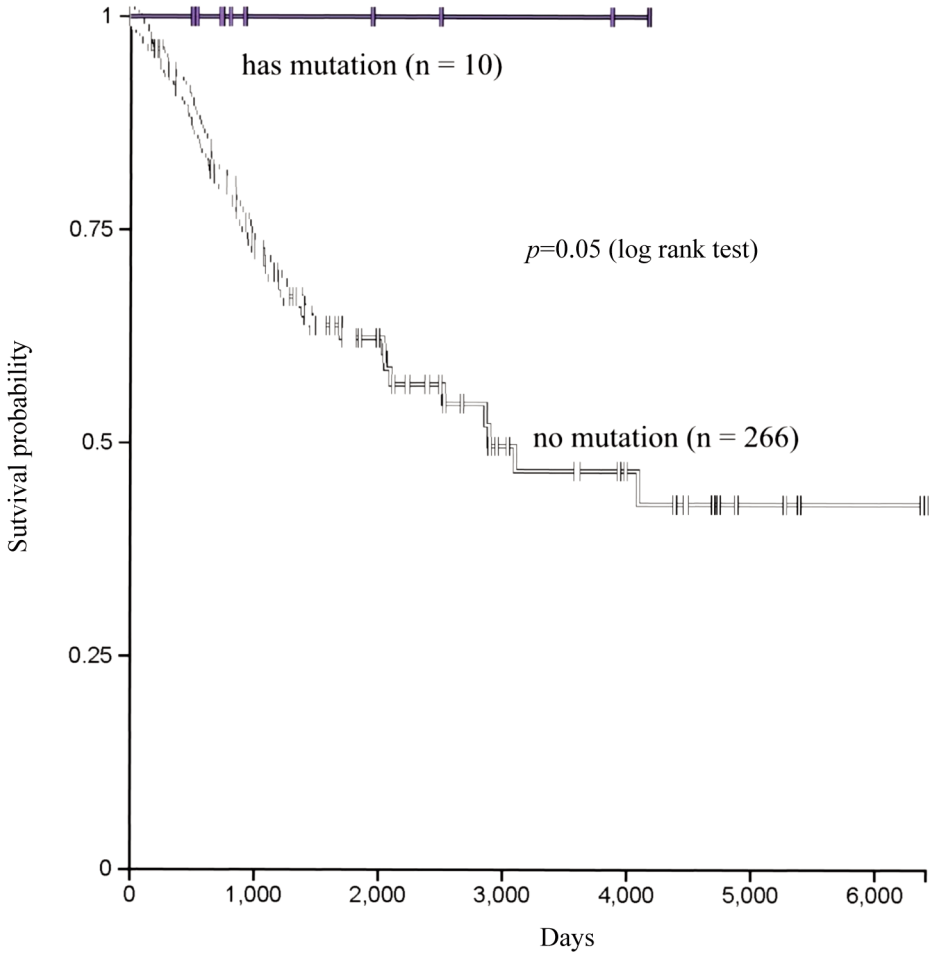
In a recent study, Olafsdottir *et al*. showed that rare germline loss-of-function variants in the Tyrosine-protein phosphatase non-receptor type 14 (PTPN14) gene conferred substantial risk of basal cell carcinoma (BCC). One fourth of PTPN14 carriers developed BCC before 70 years of age and over half of PTPN14 carriers developed BCC in their lifetime. Moreover, common variants at the PTPN14 locus were associated with BCC, suggesting PTPN14 as a new, high-impact BCC predisposition gene. A follow-up investigation of 24 cancers and three benign tumor types showed that PTPN14 loss-of-function variants were associated with high risk of cervical cancer and early age at diagnosis (1). We used the Cancer Genome Atlas (TCGA) to further evaluate the PTPN14 – cervical cancer association.

## Materials and Methods

We used cBioPortal for Cancer Genomics to analyze data in TCGA. cBioPortal provides visualization, analysis and download options of large-scale cancer genomics data sets (2). We also accessed TCGA data with the University of California Santa Cruz (UCSC) Xena Browser (https://xenabrowser.net) (3). UCSC Xena allows users to explore functional genomic data sets for assessing correlations between genomic and/or phenotypic variables. The UCSC Xena system was developed to enable cancer researchers to explore large public datasets. Xena hosts datasets from cancer genomics resources including TCGA, International Cancer Genome Consortium (ICGC) and the Genomic Data Commons (GDC). The system easily supports tens of thousands of samples and has been tested up to as many as a million cells. Using Xena we analyzed the GDC TCGA Cervical Cancer (CESC) data set.

## Results

The age of cervical cancer patients was 48±14 years (mean±SD). Of the 276 cases of cervical cancer, 10 had PTPN14 mutations: 2 intron variants, one 5 prime UTR variant, 3 missense variants, 3 synonymous variants, and one stop gained variant. 7 of these mutations were identified in




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| 266 | 90 | 35 | 18 | 12 | 4 | 2 |
| 10 | 4 | 3 | 2 | 1 | 0 | 0 |

Figure 1. *Survival of 276 cervical cancer patients with or without PTPN14 tumor mutations. Table shows number at risk, upper row, no mutation, lower row, has mutation.*

cBioPortal, which did not classify them as germline. The significance of these mutations is not known.

The 10 patients with PTPN14 mutations were significantly older (55±9 years) than the 266 patients without mutations (48±14 years, $p$=0.046) as shown by two-tailed test, with equal variances not assumed.

The 10 patients with PTPN14 mutations had significantly better survival than 266 patients without PTPN14 mutations ($p$=0.05 log rank test) (Figure 1). In the Human Protein Atlas, low expression of PTPN14 in 85 TCGA cervical cancer specimens was associated with better survival than high expression in 206 cervical cancer specimens (3).

## Discussion

The protein encoded by PTPN14 is a member of the protein tyrosine phosphatase (PTP) family and PTPN14 subfamily of tyrosine protein phosphatases. Protein tyrosine phosphatases are a group of enzymes that remove phosphate groups from phosphorylated tyrosine residues on proteins. Protein tyrosine phosphorylation is a common post-translational modification. In addition, PTPs are signalling molecules that regulate multiple cell processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. In cancer, PTPN14 interacts with and

negatively regulates the oncogenic function of YAP, part of the Hippo signaling pathway determining cellular proliferation and survival (4).

In general, factors that affect the risk of a cancer have the same effect on prognosis. For example, history of allergy reduces the risk of malignant brain tumors and improves prognosis (5). However, this relationship does not hold in the case of PTPN14.

We conclude that in TCGA cervical cancer specimens, PTPN14 mutation is a favorable prognostic sign. However, germline variants of PTPN14 confer a worse prognosis, as reported by Olafsdottir *et al*. (1). Further studies of the specific mutations would be worthwhile.

## Conflicts of Interest

The Authors declare no conflicts of interest.

## Authors' Contributions

Dr. Lehrer and Dr. Rheinstein contributed equally to the conception and analyses in this study.

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