Original Article

Mutation Frequencies in Endometrial Cancer Patients of Different Ethnicities and Tumor Grades: An Analytical Study

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Abstract

Background: Endometrial carcinoma is a predominant health problem for women worldwide. However, there is a lack of data on genetic mutation frequencies in endometrial cancer patients of different ethnicities and tumor grades.

Objective: The objective of this study is to provide data regarding mutation frequencies in endometrial cancer patients of different ethnic groups and tumor grades by analyzing large-scale cancer genomic datasets of a database.

Materials and Methods: The following databases of cBioPortal were explored for possible mutation frequency variations in endometrial cancer patients: the Uterine Corpus Endometrial Carcinoma (TCGA, PanCancer Atlas) database for ethnicity-based studies; the Uterine Corpus Endometrial Carcinoma (TCGA, Nature 2013) database for tumor grade-based study; and GDC Data Portal database for calculating survival rates using the Kaplan–Meier method.

Results: *PTEN* mutation frequency was almost identical in all ethnic groups studied (White, Black/African American, Asian, Native Hawaiian or other Pacific Islander, and American Indian or Asian Native). *PIK3CA* and *ARID1A* mutation frequencies were higher in White and Asian patients compared with other ethnicities; *TP53* and *FAT1* mutation frequencies were higher in Black/African Americans; and *CTNNB1* and *RYR2* mutation frequencies were higher Native Hawaiians or Asian Natives. *TTN* mutation frequency was lower in Asian patients. With regards to mutation frequencies at different tumor stages, in all genes, >50% of the mutations occurred during the first stage, except in *TP53* and *POLQ*. In terms of prognosis in endometrial cancer considering the 10 most frequently mutated genes, *PIK3CA* and *ARID1A* mutations were correlated with good prognosis, whereas *TP53* and *PIK3R1* mutations were correlated with poor prognosis; mutations in all other genes did not show significant differences.

Conclusion: This study revealed a new mutation frequency profile for different ethnicities and tumor grades in endometrial cancer patients. However, because this is a retrospective study, future prospective studies should be conducted including large sample sizes and more controlled measurements.

Keywords: Cancer stage, cBioPortal, endometrial cancer, ethnicity, frequency, genetic mutation

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INTRODUCTION

Endometrial cancer is the most common gynecological cancer in the United States. According to the American Cancer Society, in 2018, there would be 63,230 new cases of endometrial cancer, and about 11,350 patients will die from this cancer.[1,2] In fact, endometrial cancer is a predominant health problem for women worldwide.[3] In women from developed countries, endometrial cancer is usually detected after the age of 60 years.[4] Nearly 90% of the diagnosed cases are sporadic, while 10% are attributed to genetic factors.[5]

Endometrial cancer is a multifactorial disease. Obesity and long-term therapeutic administration of estrogen are the most common risk factors, while pathological production of estrogen has also found to be associated.[6-9] In addition, nulliparity and infertility are among factors that increase the risk of endometrial cancer.[10]

Endometrial cancer is classified into Type I or Type II, based on clinical and pathological differences. Type I endometrial cancer accounts for 80% of all cases and is linked to excess estrogen exposure. It is associated with low-grade tumors and has a good prognosis.[11,12] Type II accounts for 20% of all new cases of endometrial cancer and is a highly differentiated papillary serous-cell carcinoma that is not linked to estrogen exposure. It is commonly detected at later stages and is associated with poor prognosis.[11]

Genetic mutations in cancers have been shown to be influenced by patients' ethnicity and grade of tumor.[13-20] These variations in mutations affect therapeutic regimes.[21-24] Conceptually, precision medicine requires knowledge of the exact mutation present in each patient along with the tumor stage. Currently, there is a lack of data regarding genetic mutation frequencies (GMFs) in endometrial cancer patients of different ethnic groups and tumor grades. To obtain significant data regarding any such differences in mutation frequencies, a large-scale, multicenter study that includes endometrial cancer patients with different ethnicities and tumor stages is required. However, such studies are difficult to conduct and require concerted efforts at several levels. Nonetheless, an analytical study of large-scale endometrial cancer genomics datasets can provide initial data on GMFs of different ethnic groups and tumor grades. Accordingly, this study was conducted using cBioPortal, an open source database of large-scale cancer genomics data sets, to search for variability in genetic mutations of endometrial cancer in different ethnic groups and stages.

MATERIALS AND METHODS

Data collection

Data were retrieved from cBioPortal (http://www.cbioportal.org/), an open access platform with data distribution under the terms of CC-BY-4.0 license, to assess the variability in genetic mutations among endometrial cancer patients. After a preliminary analysis of the database, the author searched for the following genes that displayed differences in mutation frequencies across ethnic groups and tumor grades: *PTEN, PIK3CA, TTN, TP53, PIK3R1, KMT2D, CTNNB1, CTNND1, USH2A, DMD, KRAS, MACF1, FAT4, FAT1, MTOR, MUC16, CTCF, RYR2, ZFHX3, CSMD3, MUC5B, OBSCN, SYNE1, CHD4, FLG*, and *ZFHX4*. The ethnic groups included in the study were White, Black/African American, Asian, Native Hawaiian or other Pacific Islanders and American Indian or Asian Native. A preliminary search on the database showed that the following genes had significant mutation frequencies at different stages of endometrial cancer: *CTNNB1, PTEN, ARID1A, KRAS, PIK3CA, PIK3R1, ZFHX3, FAT4, DMD, FAT1, MUC5B, ERCC6 L2, RYR2, CSMD3, NEB, PPP2R1A, TP53,* and *POLQ*. Stages I–IV of endometrial cancer were compared to determine frequency differences. The author also tested the prognostic potential of 10 most frequently mutated genes, namely, *PTEN, KRAS, TNN, CTNNB1, MUC16, CSMD3, PIK3CA, ARID1A, TP53* and *PIK3R1*, to assess the overall survival rates for patients with endometrial carcinoma.

Data analysis

To assess the GMF of different ethnicities, the Uterine Corpus Endometrial Carcinoma (TCGA, PanCancer Atlas) database was used through cBioPortal.[25] For GMFs of different grades, information was obtained from the Uterine Corpus Endometrial Carcinoma (TCGA, Nature 2013) database.[26] Finally, the Kaplan–Meier method was used to determine the survival rates of endometrial cancer patients in the GDC Data Portal database of cBioPortal.[27] The frequencies of genetic mutations were then normalized to the total patient number in each group using Microsoft Excel for Mac 2011. Using Prism 7 for Mac software (GraphPad Software, La Jolla, CA, USA), a heat plot of the genes most frequently mutated was generated for each ethnic group and grouped for analysis of different tumor stages.

Ethical issues

This work used anonymous, open-access data, and thus did not involve any personal information of individuals.

RESULTS

Mutation frequency by ethnicity

To explore the variation in the frequency of endometrial cancer-associated genetic mutations among different ethnicities, a hotspot model was used. As shown in Figure 1, there was a clear variation in the GFM between individual genes. The *PTEN* gene showed nearly identical mutation frequencies in White, Asian and American Indian or Asian Native endometrial cancer patients, but Black/African American patients possessed a lower mutation frequency. *PIK3CA* displayed high mutation frequency in Asians compared with other ethnicities. However, mutations were less frequent in Asians compared to other ethnic groups. *CTNNB1* and *RYR1* mutation were found more frequently in Native Hawaiian or other Pacific Islanders compared with other ethnic groups. *FAT1* exhibited a high mutation frequency in Black/African American and Asian populations; *FAT4* mutations were more frequent in Asians; *MUC5B* mutations occurred more frequent in American Indian or Asian Native; while ZFHX4 and *FLG* were more frequently mutated in Asians. *TP53* and *RYR2* mutation frequencies were very high in Black/African American and Native Hawaiian or Other Pacific Islander, respectively, compared with other ethnicities. *TNN* mutation frequencies were high in all ethnicities, except among Asian patients, in whom it was very low.

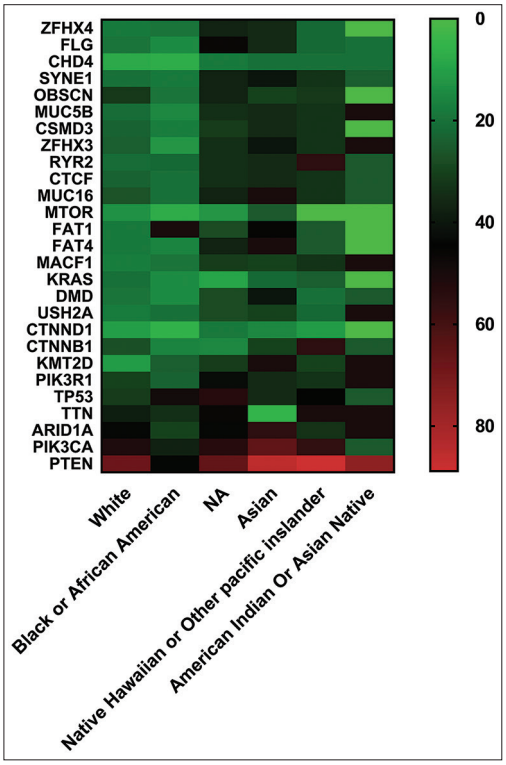

Figure 1: Genetic mutation frequency of selected genes for each ethnicity (green = low genetic mutation frequency; black = moderate genetic mutation frequency; dark red to light red = high to very high genetic mutation frequency)

Mutation frequency by endometrial carcinoma stage

To study the distinct mutation frequencies in each stage of endometrial cancer, the author compared the GMFs of 18 genes that were found to be most commonly mutated in endometrial cancer patients [Figure 2]. All genes, except TP53 and *POLQ*, showed high mutation frequencies in the first stage of the cancer. The *PTEN*, *PPP2R1A* and *ARID1A* genes were less frequently mutated in the second stage of cancer than the other genes studied. The third stage of the cancer exhibited the most frequent genetic mutations, with *TP53*, *POLQ*, *PPP2R1A*, *NEB*, *RYR2* and *ERCC6 L2* displaying the highest mutation frequencies. In the fourth stage, mutation frequencies were much lower than that in the other stages of endometrial cancer.

Survival rates

With regards to the potential prognostic value of the mutated genes in endometrial cancer, it was found that patients with mutations in *PIK3CA* and *ARID1A* have a significantly better prognosis than patients with the wild-type gene ($P < 0.05$). Similarly, patients with mutations in *PTEN*, *KRAS*, *TNN*, *CTNNB1* and *MUC16* had a better prognosis than patients with the wild-type genes [Figure 3], although this finding is not significant ($P > 0.05$). However, patients with a mutation in *CSMD3* did not have any prognostic difference from patients with its wild-type counterpart. In contrast, patients with the wild-type *TP53* and *PIK3R1* genes displayed a better prognosis relative to patients with mutations in these genes.

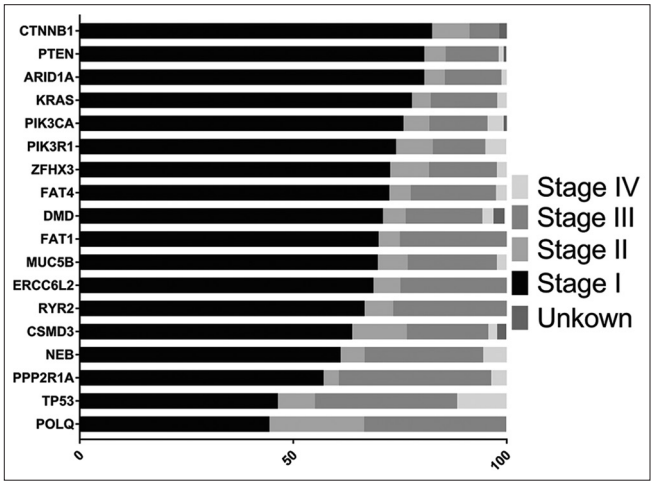

Figure 2: Genetic mutation frequencies in selected genes according to different stages of endometrial cancer

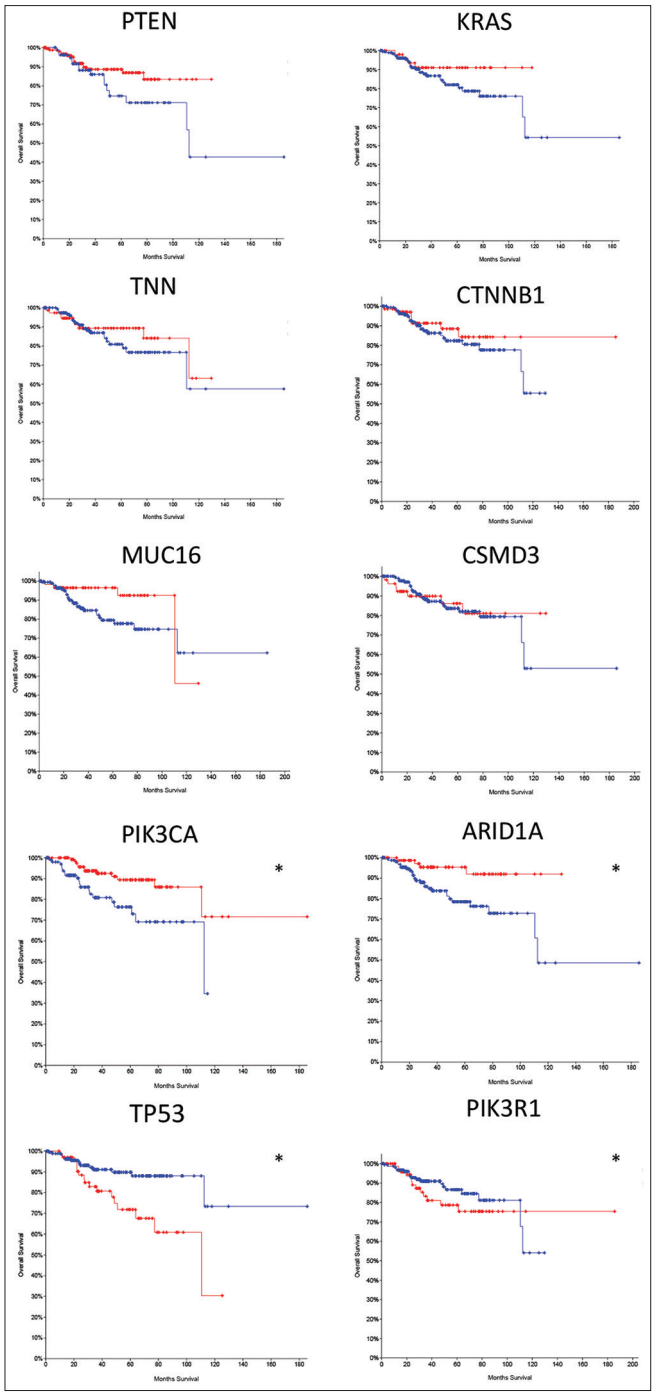

Figure 3: Kaplan–Meier survival curves demonstrating correlations between mutated (red) and wild-type (blue) gene expression and survival rates (*indicates significant difference)

DISCUSSION

Genetic mutations in cancers are likely to be influenced by patients' ethnicity and grade of tumor.[13-20] However, there is a lack of knowledge on GMFs in endometrial cancer patients of different ethnic groups. The current analytical study found that GMFs in endometrial cancer patients vary by ethnicity. Variations in GMFs can help understand biological differences between ethnic groups, which in turn could be used for targeted therapy. Further, this study also demonstrates altered activity of certain genes during different cancer stages.

In African Americans with prostate cancer, recurrent loss-of-function mutations has been shown in the *ERF* gene, which is a tumor suppressor gene.[28] Increased mutations in *KRAS* have been reported in African Americans with colon cancer compared with Caucasians patients.[29] In non-small cell lung cancer, Black women have been found to be at a higher risk of *EGFR* mutations than White women.[30] *BRCA1* mutations in breast cancer patients have been shown to be more prevalent in Hispanics compared with other ethnicities.[15] Further, *BRCA1* exon 2 mutations are more frequent in Ashkenazi Jewish women relative to Caucasians.[31] Such differences in GMFs between women of different ethnicities were also observed in several other studies.[32-34] These and the current study results collectively show that genetic mutations vary by ethnicity, and thus could potentially be used to determine and administer precise therapy for a subset of patients within an ethnic group. Therefore, a larger study, including more ethnic groups, could potentially aid in improving endometrial cancer diagnosis and therapy.

The current study also demonstrated differences in the mutation frequency between endometrial cancer stages, which could potentially be used to better understand the progression of cancer and to monitor its treatment. The frequent mutation of *PTEN* in early-stage endometrial cancer has also been suggested previously.[35] However, in that study, endometrial carcinoma *PTEN* mutations were compared with that of endometrial hyperplasia, thereby limiting the validity of the finding. Therefore, a large population study should be conducted to elucidate the genetic mutation patterns in each stage of endometrial cancer. This would further contribute to the implementation of precise therapy. Previously, in studies of other cancers, GMFs have been found to vary in different stages of cancer.[36-40] However, to the best of the author's knowledge, this is the first study demonstrating GMF variation in different stages of endometrial carcinoma.

Endometrial carcinoma is characterized by mutations in many genes, with microsatellite instability genes *PTEN*, *KRAS*, *PIK3CA* and *β-catenin* most commonly involved.[19,41-43] The mechanisms that initiate and drive endometrial cancer have been explored. Mutations in the pro-survival genes, such as *KRAS*, *Akt*, *mTOR* and *β-catenin*, or pro-apoptotic genes, such as *PTEN* and *p53*, have all exhibited a role in the pathological findings of this

cancer.[44-46] Understanding the molecular background of uterine cancers could help in determining future therapy for endometrial cancer.[44-46] Small molecules capable of targeting and inhibiting these genes have been found to potentially reduce mortality rates of endometrial cancer patients.[45] Further, inhibitors can be combined with hormonal or cytotoxic agents, thereby focusing on multiple targets.[46] For example, the *PI3K/AKT/mTOR* pathways have been used for uterine cancer therapy.[12,47] In fact, the effectiveness of mTOR inhibitors such as AZD8055, OSI-027 and INK128 for treating endometrial cancer are being evaluated in clinical trials.[48] Other inhibitors have also been tested *in vivo* but have not yet been introduced into trials.[46]

The results of this study's survival rates of patients could potentially be used as prognostic markers for clinical outcome. This study found that mutations in *TP53* and *PIK3R1* are correlated with poor prognosis in endometrial cancer. These results conform to the findings of previous study results on other cancers. For example, *TP53* has been shown to correlate with poor prognosis in breast cancer,[49,50] lymphoma,[51] colon cancer,[52] lung cancer[53] and leukemia,[54] while *PIK3R1* is associated with poor prognosis in glioblastoma.[55] In patients with late-stage endometrial cancer, poor prognosis may be related to the observed increased frequency of *TP53* mutations.

It should be noted that because the current study is a retrospective study that is more exploratory and hypothesis generating in nature, its findings cannot be considered conclusive. Therefore, future work should comprise large sample sizes, including more ethnic groups such as Arabs from different countries, and long-term follow-up, including detailed information on patient body weight, morbidity, mortality and treatment regimens administered.

CONCLUSION

The findings of the current retrospective study illustrate a new GMF profile for endometrial cancer patients of different ethnicities. Further, this study demonstrates the altered activity of certain genes during different cancer stages and that the survival rates of patients with endometrial carcinoma could be predicted using the set of genes investigated. Nonetheless, to validate the findings of this study, future prospective studies should be conducted with large sample sizes, more diverse ethnic groups and long-term follow-up.

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Conflicts of interest
There are no conflicts of interest.

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