Gynecologic Oncology Reports 55 (2024) 101498

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Short communication

Germline genetic testing reveals pathogenic variants in uterine serous carcinoma patients

Katelyn Tondo-Steele [a], Kara J. Milliron [b], Jean H. Siedel [a], Shitanshu Uppal [a], Sofia D. Merajver [b], Karen McLean [a,c,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Michigan, 1500 E. Medical Center Dr., Ann Arbor, MI 48109, USA
[b] Breast and Ovarian Cancer Risk Evaluation Program, Department of Internal Medicine, Rogel Cancer Center, Michigan Medicine, 1500 E. Medical Center Dr., Ann Arbor, MI 48109, USA
[c] Department of Gynecologic Oncology and Department of Pharmacology and Therapeutics, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, NY 14263, USA

ARTICLE INFO

Keywords:
Genetic testing
Genetic counseling
Pathogenic variant
Uterine serous carcinoma
BRCA

ABSTRACT

An increase in the risk of developing uterine serous carcinoma (USC) has been observed among *BRCA1* and *BRCA2* germline pathogenic variant carriers in the published literature. However, routine germline genetic testing is not currently incorporated into USC management guidelines. The primary objective of this study is to define the incidence of germline pathogenic variants identified through genetic counseling referrals for USC patients at our institution. A retrospective cohort study was performed of patients diagnosed with USC at a single institution over a seven-year interval. A total of 91 patients with uterine serous carcinoma were identified. Almost half of the patients were referred to genetic counseling, and just over half of referred patients (24/43, 56%) ultimately underwent germline genetic testing. Pathogenic variants were noted in 12.5% (3/24) of the patients who were tested. Pathogenic mutations were found in *BRCA1*, *BRCA2,* and *MSH6*. Variants of unknown significance (VUS) were seen in 16.6% (4/24) of patients. Based on our findings, we recommend integration of germline testing into the standard management of patients with USC.

1. Introduction

It is estimated that approximately 67,880 new cases of uterine cancer will be diagnosed in 2024 (American Cancer Society, 2024). A rising incidence of endometrial cancer has been observed in the past decade by about 1 % per year in white women and 2–3 % per year in women of all other racial/ethnic groups (American Cancer Society, 2024).

There are multiple histologic subtypes of endometrial adenocarcinoma, with unique molecular profiles and clinical behaviors. The Cancer Genome Atlas (TCGA) molecular classification identifies four distinct genetic subgroups: POLE (ultramutated), microsatellite instability (MSI, hypermutated), copy-number low (endometrioid), and copy-number high (serous-like) (Cancer Genome Atlas Research Network, 2013; Alexa et al., 2021). The histologic subtype uterine serous carcinoma (USC) falls within the copy-number high molecular subgroup and is characterized by *TP53* mutation. USC is both genetically and clinically similar to high-grade serous ovarian carcinoma (HGSC), with a propensity for earlier distant metastases and a poorer clinical prognosis than other histologic subtypes.

Based on these similarities, it has been proposed that USC may be associated with germline or somatic genetic alterations in the same genes altered in HGSC, such as *BRCA1* and *BRCA2* (Pennington et al., 2013; de Jonge et al., 2021; Thompson and Easton, 2002; Shu et al., 2016). In support of this association, a 12-fold and a 5-fold increased risk of developing USC has been observed for *BRCA1* and *BRCA2* germline pathogenic variant carriers, respectively, compared to the general population (de Jonge et al., 2021). The Breast Cancer Linkage Consortium showed an increased risk of developing uterine cancer in *BRCA1* mutation carriers (Thompson and Easton, 2002). Thus, screening for germline *BRCA1/2* pathogenic variants has been proposed as a consideration for USC (Pennington et al., 2013). However, such testing is not currently uniformly incorporated into guidelines by the National Comprehensive Cancer Network (NCCN) or other national organizations. Current NCCN guidelines state “consider germline testing” in

* Corresponding author at: Department of Gynecologic Oncology and Department of Pharmacology and Therapeutics, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, NY 14263, USA.
E-mail address: Karen.McLean@RoswellPark.org (K. McLean).

https://doi.org/10.1016/j.gore.2024.101498
Received 9 July 2024; Received in revised form 30 August 2024; Accepted 31 August 2024
Available online 2 September 2024

Table 1
Patient demographics.

	All (*n* = 91)	Referred (n = 43)	Not Referred (n = 48)	p-value	Pathogenic Variant (#)
Age					
Median, IQR* – yr	69.6 (51, 90)	69.0 (51, 90)	70.2 (56, 83)	0.504	
Race – # (%)					
White	73 (80.2)	35 (47.9)	38 (52.1)	0.935†	3
Black	14 (15.4)	6 (42.9)	8 (57.1)		0
Asian	3 (3.3)	1 (33.3)	2 (66.7)		0
Other/Unknown	1 (1.1)	1 (100)	0 (0)		0
Hispanic/Non-Hispanic – # (%)					
Non-Hispanic	89 (97.8)	42 (47.2)	47 (52.8)	>0.999	3
Hispanic	2 (2.2)	1 (50)	1 (50)		0
Stage at Diagnosis – # (%)					
IA	43 (47.3)	16 (37.2)	27 (62.7)	0.461†	1
IB	10 (10.9)	4 (40)	6 (60)		0
II	8 (8.8)	7 (87.5)	1 (12.5)		1
IIIA	11 (12.1)	7 (63.6)	4 (36.3)		0
IIIB	0 (0)	0 (0)	0 (0)		0
IIIC1	3 (3.3)	2 (66.7)	1 (33.3)		1
IIIC2	3 (3.3)	1 (33.3)	2 (66.7)		0
IVA	1 (1.1)	0 (0)	1 (100)		0
IVB	12 (13.2)	6 (50)	6 (50)		0
History of Breast Cancer – # (%)					
Yes	8 (8.8)	5 (62.5)	3 (37.5)	0.469	0
No	83 (91.2)	38 (45.8)	45 (54.2)		3

* IQR: inter-quartile range.
† To calculate p-values, the categories were collapsed to eliminate zero value entries. Race was collapsed to White, Black, Asian + Other. Stage was collapsed to I, II, III, IV.

patients diagnosed with uterine neoplasms (Abu-Rustum et al., 2023), in contrast to the stronger recommendation that ovarian cancer patients "should be referred for a genetic risk evaluation and germline… testing" (Armstrong et al., 2022).

In 2017, our gynecologic oncology division integrated into our multidisciplinary tumor board conference the recommendation of genetic counseling referral for patients diagnosed with USC. The purpose of this current study is to define the incidence of germline pathogenic variants identified through genetic counseling referrals for USC patients at our institution.

2. Methods

We conducted a retrospective analysis of patients diagnosed with USC at the University of Michigan during the seven-year interval from 1/1/2017 through 12/31/2023. We reviewed medical records and documented patient demographics, cancer stage, personal history of breast cancer, whether or not the patient was referred to genetic counseling, if the patient underwent genetic counseling and germline testing, the number of genes evaluated, and results of this testing. Statistical comparisons between the patients that were referred and were not referred were carried out using Student's *t*-test for the continuous variable of age and chi-squared or Fisher's exact test for the categorical variables as appropriate. A p-value of less than 0.05 was considered statistically significant. This study was reviewed and approved (exempt) by the University of Michigan Institutional Review Board (HUM00119046).

3. Results

A total of 91 patients with USC were identified during the queried interval (Table 1). Among those patients, the median age was 69.6 years (range 51–90), 80 % were white, and 98 % were non-Hispanic. Fifty-eight percent of patients (N=53/91) had stage I disease at the time of diagnosis, whereas 33 % (N=30/91) had stage III or IV disease. Eight patients (8 %) had a history of breast cancer prior to endometrial cancer diagnosis.

Of these 91 patients in our overall cohort, 43 (47.2 %) were referred to cancer genetics at the University of Michigan. There was no statistically significant difference in age, race, Hispanic identity, stage, or history of breast cancer between the referred and not referred populations (Table 1). Stage I disease trended toward patients not being referred (33 patients with stage I disease in the not referred group versus 20 patients in the referred group, p = 0.461, Table 1). Just over half of referred patients (24 out of 43, 56 %) elected to pursue germline genetic testing (Fig. 1). Panels utilized for testing ranged from 1 to 86 genes tested, with the one gene panel used for a patient with family history of a *MSH6* pathogenic variant. Excluding that patient, the number of genes tested in the panels utilized ranged from 13 to 86, with a median of 36 genes included. Commercially available panels were used for all patients except one, who underwent testing using an in-house panel at their hospital.

Pathogenic variants were noted in 12.5 % (3/24) of the patients who underwent genetic testing. Pathogenic mutations involved a diverse group of genes (Table 2), including *BRCA1*, *BRCA2,* and *MSH6*. The patient with the *MSH6* mutation was known to be a carrier prior to the diagnosis of endometrial cancer. Her USC was detected through an annual endometrial biopsy performed as part of her Lynch Syndrome cancer screening and she had stage IA disease (FIGO 2018 staging) at the time of diagnosis.

Variants of unknown significance (VUS) were seen in 16.6 % (4/24) of patients. VUS were detected in both *PALB2* and *RAD50* in one patient, *POLE*, both *POLD1* and *SDHA* in one patient, and *BRCA1*.

To further assess the impact of these findings on cancer detection and risk reduction, we assessed the frequency of cascade testing among the

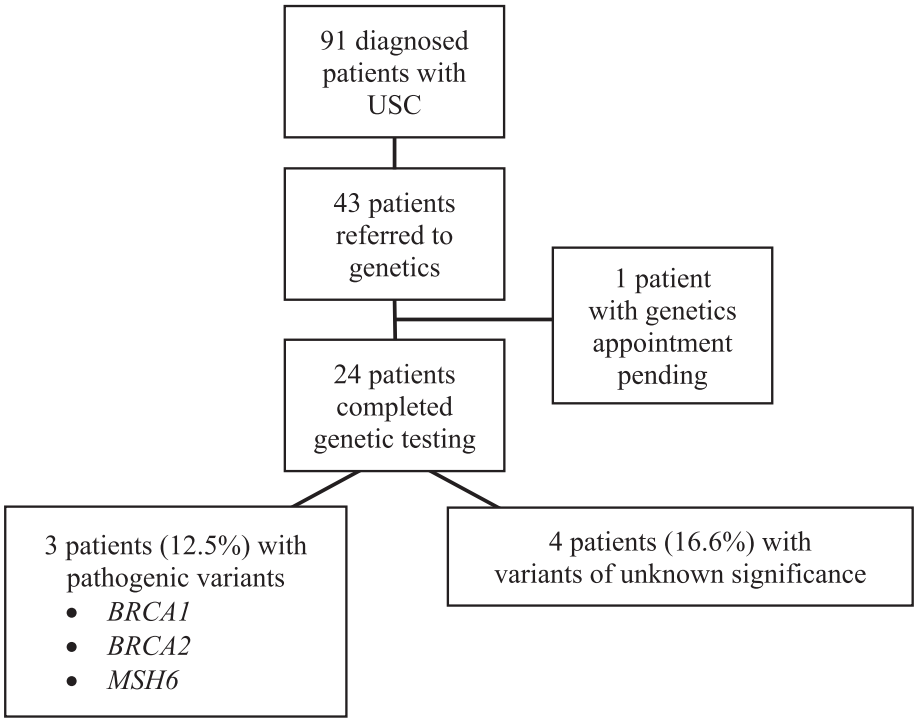

Fig. 1.

Table 2
Pathogenic variants identified on germline testing.

Gene	Rate	Molecular Function
BRCA1	1/24 (4.2 %)	Tumor suppressor gene; role in DNA double-strand break repair by regulation of homologous recombination
BRCA2	1/24 (4.2 %)	Tumor suppressor gene; role in DNA double-strand break repair by regulation of homologous recombination
MSH6	1/24 (4.2 %)	DNA mismatch repair (MMR) gene

families of patients determined to carry pathogenic variants. All patients in whom a germline pathogenic variant is detected are provided with a letter summarizing the findings to give to their family members. In assessing cascade testing among our cohort, we determined that for the patient with a *BRCA1* germline pathogenic variant, two first-degree and one second-degree family member tested positive for the same pathogenic variant. For the patient with the *BRCA2* germline pathogenic variant, all four of her children were tested and two of them tested positive.

4. Discussion

In this study, we assessed the outcomes of genetic counseling and germline genetic testing for women diagnosed with USC over the past seven years at our institution. This testing yielded an overall pathogenic variant rate of 12.5 % for patients with USC, with 8.3 % associated with *BRCA1/2*. These findings in combination with previous reports support the association between USC and hereditary breast and ovarian cancer syndrome.

The germline pathogenic variant rates reported herein are in alignment with those previously reported in the USC population (Pennington et al., 2013; Thompson and Easton, 2002). A previous study looking at the frequency of mutation in 30 tumor suppressor genes among specimens from 151 women with USC and no personal history of breast cancer at the time of testing demonstrated a 4.6 % pathogenic variant rate, with 2 % within *BRCA1* (Pennington et al., 2013). Factors potentially contributing to the higher rate of detecting pathogenic variants in our population than in this previous study are the fact that our study did not exclude patients with a personal history or family history of breast cancer as well as our small sample size of tested patients. Approximately 8 % of patients in our study had a personal diagnosis of breast cancer, although none of these patients had a pathogenic variant on germline testing (Table 1).

Additionally, it is noted that in our study, despite attempts to integrate genetic counseling referrals into our multidisciplinary tumor board recommendations, referrals were submitted for only approximately half of USC patients. There were no statistically significant predictors of which patients were not referred (Table 1), although there was a trend toward patients with stage I disease not receiving a referral. If consider the hypothetical situation in which everyone who did not undergo testing in our cohort had a negative test (a conservative estimate), the overall pathogenic variant rate would be 3.3 % (3/91). We believe that this pathogenic variant rate still warrants routine germline testing.

Our data add significantly to the literature by demonstrating the role of genetic counseling and testing to both detect clinically actionable pathogenic variants and to provide the opportunity for cascade testing of family members. The identification of *BRCA* pathogenic variants among women with USC adds to the literature supporting hysterectomy in *BRCA* carriers at the time of risk-reducing bilateral salpingo-oophorectomy (Shu et al., 2016). Furthermore, in our study, we found documentation of five additional individuals that tested positive for pathogenic variants for *BRCA* genes through cascade testing, providing the opportunity for risk-reducing strategies in these individuals.

Additionally, one subject in our cohort (4.1 %) had a germline *MSH6* pathogenic variant that had been identified prior to her uterine cancer diagnosis due screening recommended as part of management of a known Lynch Syndrome family. Data suggest that the likelihood of Lynch Syndrome in patients with USC is much lower than that in patients with endometrioid endometrial carcinomas (Pennington et al., 2013; Meyer et al., 2009). However, the diagnosis of Lynch Syndrome through genetic testing triggered by USC pathology diagnosis has many beneficial implications including treatment options, additional cancer screening for the patient, and family member cascade testing and

subsequent risk-tailored cancer screening.

In addition to our detection of pathogenic variants, a number of patients also were noted to harbor germline variants of undetermined significance (VUS). Our observed rate of VUS in 16.6 % of patients is lower than the 32.6 % VUS rate for multi-gene panels in one recent report (Rehm et al., 2023).

Finally, the identification of pathogenic variants has important implications for potential treatment options for patients. The recent phase III DUO-E study investigated the efficacy of chemotherapy alone versus chemotherapy plus immunotherapy versus chemotherapy plus immunotherapy plus poly (ADP-ribose) polymerase (PARP) inhibition in newly diagnosed advanced or recurrent endometrial cancer (Westin et al., 2023). Twenty percent of study patients had USC. This study found a 45 % reduction in disease progression or death with immunotherapy plus PARP inhibition with chemotherapy arm and a 29 % reduction with immunotherapy with chemotherapy arm compared with chemotherapy only control arm. As with HGSC arising from the ovaries, the largest responses may be in patients with alterations in homologous recombination repair pathway genes, such as *BRCA1* and *BRCA2*. Additionally, USC patients with pathogenic variants that result in homologous recombination deficiency may benefit from PARP inhibitor maintenance following systemic chemotherapy. Thus, routine tumor testing including assessment of homologous recombination deficiency and somatic *BRCA1/2* gene alterations can further expand the pool of patients potentially eligible for PARP inhibitor therapy.

Strengths of our study include assessment of a structured approach to genetic counseling and testing of USC patients, as well as the ability to robustly collect the data across their clinical care as both gynecologic oncology care and genetic counseling were performed at the same institution. Limitations include the small sample size with a proportion of patients that did not undergo testing, as discussed above. Therefore, the absolute number of patients with pathogenic variants in this cohort is relatively small.

In conclusion, we found that germline genetic testing of USC patients identified a subset of patients with germline pathogenic variants. We found an overall pathogenic variant rate of 12.5 % (3/24), with alterations in *BRCA1*, *BRCA2* and *MSH6* genes. These results have significant implications for cancer screening for the patient, potential cancer treatment options for the patient, and genetic testing and screening benefits for family members. Based on the findings of this study, we strongly recommend that germline genetic testing be integrated as a routine test into the standard management of patients with newly diagnosed USC.

CRediT authorship contribution statement

Katelyn Tondo-Steele: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Kara J. Milliron:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Jean H. Siedel:** Writing – review & editing, Resources, Conceptualization. **Shitanshu Uppal:** Writing – review & editing, Resources, Conceptualization. **Sofia D. Merajver:** Writing – review & editing, Resources, Project administration. **Karen McLean:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

Dr. Jean Siedel is an Editorial Board for *Gynecologic Oncology Reports* and was not involved in the editorial review or the decision to publish this article. Other than this declaration, the authors have no financial interests/personal relationships which may be considered as potential competing interests.

Acknowledgements

This work was supported by National Institutes of Health grant R01CA251198 (McLean) and by the Breast Cancer Research Foundation (Merajver, Milliron).

References

Abu-Rustum, N., et al., 2023. Uterine neoplasms, version 1.2023, NCCN clinical practice guidelines in oncology. J. Natl. Compr. Canc. Netw. 21 (2), 181–209.
Alexa, M., et al., 2021. The TCGA molecular classification of endometrial cancer and its possible impact on adjuvant treatment decisions. Cancers (Basel) 13 (6), 1478.
American Cancer Society, 2024. Cancer Facts & Figures 2024. Atlanta: American Cancer Society.
Armstrong, D.K., et al., 2022. NCCN guidelines insights: ovarian cancer, version 3.2022. J. Natl. Compr. Canc. Netw. 20 (9), 972–980.
Cancer Genome Atlas Research Network, et al., 2013. Integrated genomic characterization of endometrial carcinoma. Nature 497 (7447), 67–73.
de Jonge, M., et al., 2021. Endometrial cancer risk in women with germline BRCA1 or BRCA2 mutations: multicenter cohort study. J Natl Cancer 113 (9), 1203–1211.
Meyer, L., et al., 2009. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control 16 (1), 14–22.
Pennington, K., et al., 2013. BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. Cancer 119 (2), 332–338.
Rehm, H., et al., 2023. Medical genome initiative steering committee. The landscape of reported VUS in multi-gene panel and genomic testing: time for a change. Genet. Med. 25 (12), 100947.
Shu, C., et al., 2016. Uterine cancer after risk-reducing Salpingo-oophorectomy without hysterectomy in women with BRCA mutations. JAMA Oncol. 2 (11), 1434–1440.
Thompson, D., Easton, D., 2002. Breast cancer linkage consortium. Cancer incidence in BRCA1 mutation carriers. J. Natl Cancer Inst. 94 (18), 1358–1365.
Westin, S., et al., 2023. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. J. Clin. Oncol. 42 (3), 283–299.