Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Prior breast cancer and tamoxifen exposure does not influence outcomes in women with uterine papillary serous carcinoma

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HIGHLIGHTS

- Women with a history of breast cancer are at increased risk of developing uterine papillary serous carcinoma (UPSC).
- Breast cancer history was not associated with survival outcomes in patients with UPSC.
- Tamoxifen exposure was not associated with survival outcomes in patients with UPSC and breast cancer.

ARTICLE INFO

Article history:
Received 7 October 2016
Received in revised form 19 December 2016
Accepted 27 December 2016
Available online xxxx

Keywords:
Uterine papillary serous cancer
Breast cancer
Tamoxifen
Survival

ABSTRACT

Objectives. To evaluate progression-free survival (PFS) and overall survival (OS) outcomes in women diagnosed with uterine papillary serous carcinoma (UPSC) who have had (UPSCBR+) or have not had (UPSCBR−) an antecedent history of breast cancer and to correlate their outcomes to prior tamoxifen exposure.

Methods. Data were collected for women diagnosed with UPSC at two academic institutions between January 1997 and July 2012. Patient demographics, tumor histology, stage, and treatments were recorded. Patients were divided into two groups: those with and without a personal history of breast cancer. Within the UPSCBR+ cohort, we identified those with a history of tamoxifen use. Cox regression modeling was used to explore associations between selected covariates of interest and the time-to-event outcomes of PFS and OS.

Results. Of 323 patients with UPSC, 46 (14%) were UPSCBR+. Of these, 15 (33%) had a history of tamoxifen use. UPSCBR+ patients were older than UPSCBR− (median years, 72 vs. 68, $p = 0.004$). UPSCBR+ women showed no significant difference in PFS or OS compared to UPSCBR− ($p = 0.64$ and $p = 0.73$ respectively), even after controlling for age ($p = 0.15$ and $p = 0.48$ respectively). Within the UPSCBR+ cohort, there was no difference in PFS or OS with or without tamoxifen exposure ($p = 0.98$ and $p = 0.94$ respectively).

Conclusions. There was no difference in PFS or OS between the UPSCBR+ and UPSCBR− cohorts. We did not demonstrate significant OS or PFS differences in women who took tamoxifen prior to their endometrial cancer diagnosis. These findings have implications for counseling, and should be encouraging to women who are facing their second cancer diagnosis.

1. Introduction

In contrast to global incidence, endometrial cancer (EC) remains the most common gynecologic cancer in developed countries with nearly 60,050 new cases expected in the United States in 2016 [1]. Uterine papillary serous cancer (UPSC) is an aggressive histological subtype of EC that is associated with an increased risk for distant metastases and high rates of recurrence even in women with early stage disease [2–4]. Though relatively rare, accounting for 10% of EC diagnoses,

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http://dx.doi.org/10.1016/j.ygyno.2016.12.024
0090-8258/

UPSC is responsible for up to 39% of EC-related deaths [3] and has significantly worse 5-year outcomes than both clear cell and grade 3 endometrioid endometrial cancer (EEC) [5].

Several studies have investigated the association between breast cancer and endometrial cancer. In a study by Gehrig et al., women with a diagnosis of breast cancer who subsequently developed endometrial cancer were 2.6 times more likely have UPSC than the less aggressive endometrioid histology [6]. Synchronous or subsequent breast cancers develop more frequently in women with UPSC when compared to endometrioid histology (25% vs. 3.2%, $p < 0.001$) [7]. There is a growing body of literature that suggests association between UPSC and hereditary breast and ovarian cancer syndromes. Five percent of patients diagnosed with UPSC carry germline mutations in the tumor suppressor genes BRCA1, CHEK2, or TP53. The carrier rate of BRCA1 in UPSC patients is 2%, higher than the 0.06% carrier rate seen in general population [8–10]. These elevated gene frequencies as well as associations with hormone replacement therapy provide a pathophysiologic basis for how breast cancer history could impact EC outcomes.

Tamoxifen, a selective estrogen receptor modulator, improves overall survival in patients with early and metastatic breast cancer. Tamoxifen exposure is associated with a two to seven- fold increase in the development of uterine cancers [11–14]. A recent update of the National Surgical Adjuvant Breast and Bowel Project, randomized, placebo-controlled trial, reinforced that tamoxifen exposure increases a woman's risk for endometrial cancer 3.28 fold (95% CI = 1.87 to 6.03) [15]. Though the biological mechanism is unclear, this increased risk is likely due to a combination of estrogenic effects, overexpression of p53, modulation of multidrug resistance genes, and other currently unknown factors, and has impacted EC outcomes [14]. A debate continues over evidence that tamoxifen exposure is associated with development of aggressive subtypes of endometrial cancer, including UPSC [10,14,16].

To date there are little data evaluating survival outcomes in women with both UPSC and a history of breast cancer. Our study evaluated progression-free survival and overall survival outcomes in women diagnosed with UPSC who have had (UPSCBR+) or not had (UPSCBR−) a prior history of breast cancer and to correlate their outcomes to prior tamoxifen use.

2. Methods

This is a retrospective cohort analysis of all women treated for endometrial cancer at the University of North Carolina, Chapel Hill (UNC) and Duke University Medical Center (DUMC) between 1/1997 and 7/2012. Institutional Review Board approval was granted at each institution (#12-1601). A cohort of UPSC endometrial cancer patients was identified from departmental records and abstracted into a database. Abstracted data included demographics (age, race), clinical (comorbidities, medications), histopathology (grade and stage), adjuvant treatment information (chemotherapy, radiation therapy) and outcomes data. This cohort was further divided into patients with and without a history of breast cancer. Within the UPSCBR+ cohort, those with a history of tamoxifen use were identified. Medication use was defined as any documented or patient reported use prior to or after diagnosis. Overall survival (OS) was defined as the time from UPSC diagnosis to death from any cause. Progression-free survival (PFS) was defined as the time from UPSC diagnosis to the date of documented disease progression. Electronic medical records and the social security death index were used to gather information regarding the date of death.

Cox regression modeling was used to explore associations between selected covariates of interest and the time-to-event outcomes of PFS and OS. For models of interest, relevant hazard ratios (HR) with their 95% confidence intervals have been given. The Kaplan-Meier method was used to estimate PFS and OS functions and the log-rank test was used to test for significant differences. Fisher's exact tests were used to evaluate general association for data categorized into contingency tables. The Wilcoxon rank-sum test (using Van der Waerden or normal scores) was used for two-group comparisons of continuous covariates. The nonparametric Jonckheere-Terpstra method was used to test for significant differences across ordered categories for contingency tables where at least one of the variables was ordinal, and had at least 3 categories. With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories.

Statistical analyses were performed using both SAS and R statistical software. SAS statistical software used was Version 9.3, from the SAS Institute, Inc., Cary, NC. R is from the R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria ISBN 3-900051-07-0, URL http://www.R-project.org/.

3. Results

A total of 323 patients were diagnosed with UPSC during our study period. Two hundred and seventy-seven women (86%) did not have a personal history of breast cancer (UPSCBR−) while 46 (14%) did (UPSCBR+). In the UPSC cohort, only 15 patients (4.6%) had a prior history of tamoxifen exposure prior to their endometrial cancer diagnosis. Within our UPSCBR+ group, 15/46 (33%) had used tamoxifen (Fig. 1).

There was no statistical difference in race between these two groups; UPSCBR− were 42% (n = 116) African American (AA), while UPSCBR+ were 35% (n = 16) AA (p = 0.42). UPSCBR+ women were significantly older (72 years vs 68, p = 0.004) and weighed less (73 kg vs 79, p = 0.03). There was no significant difference in stage between the two groups. The majority of malignancies were early stage (I/II) in both UPSCBR+ and UPSCBR− (66% vs. 54%, p = 0.20). Patients with a history of breast cancer appeared more likely to receive adjuvant radiation therapy for treatment of their endometrial cancer (59% vs 44%) but this difference was not statistically significant (p = 0.08) (Table 1). The median follow-up for survivors was 29 months.

A history of breast cancer was not significantly associated with either PFS or OS in univariable modeling (p = 0.64 and p = 0.73 respectively), or in a multivariable model controlling for age, stage, grade, and adjuvant treatment (p = 0.15 and p = 0.48 respectively). When examining UPSCBR+ patients alone (n = 46), tamoxifen use was not associated with either PFS or OS (p = 0.98 and p = 0.94 respectively). The Kaplan-Meier curves are presented in Fig. 2A–D.

4. Discussion

To date, the current study is the largest retrospective analysis of uterine papillary serous cancer patients with a history of breast cancer. We found that a prior history of breast cancer was not associated with either PFS or OS in women with UPSC. This result is congruent with

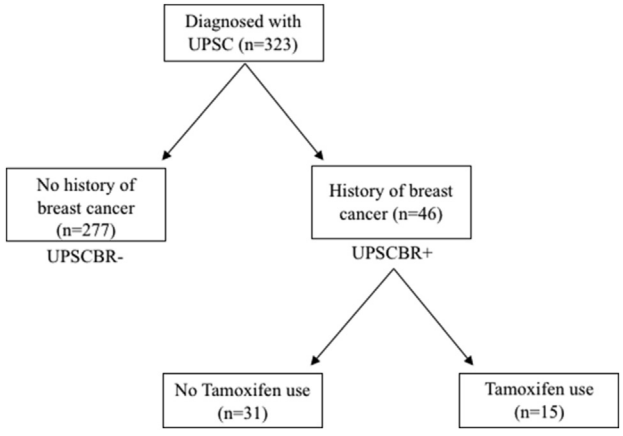

Fig. 1. Consort diagram of cohort selection. Abbreviations: UPSC, uterine papillary serous carcinoma.

Please cite this article as: S.R. Pierce, et al., Prior breast cancer and tamoxifen exposure does not influence outcomes in women with uterine papillary serous carcinoma, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.12.024