Extended Abstract

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Statin Use Prior to Diagnosis Predicts High Risk Features in Early Stage Endometriosis Endometrial Cancer

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There is increasing evidence that statin use decreases the incidence and improves survival of gynecologic malignancies, but the role in endometrial cancer (EC) has not been defined. Our primary aim is to investigate statin use and its association with high intermediate risk (HIR) features in early stage EC. We hypothesize those women who develop early stage EC while taking statins have less aggressive features on pathology at the time of hysterectomy. Our secondary aim is to determine if concurrent use of other medications demonstrating anti-cancer effects; metformin, NSAIDs and bisphosphonates may reduce the risk of development of HIR early stage EC.

Keywords Endometrial cancer; Gynecologic cancer; Hypertension; Metabolic-syndrome

Introduction:

Statins are an effective and commonly used cholesterol-lowering medication class, but their hypothesized effects on cancer risk remain uncertain. Statins act by inhibition of HMG-CoA reductase preventing the conversion of HMG-Coo to mevalonate, and thereby reducing levels of mevalonate and its downstream products [1]. Many of these products are necessary for critical cellular functions and disruption of these processes in neoplastic cells by statins may result in control of tumor initiation, growth and metastasis [1]. Recent reports have suggested that statins induce cell death in certain epithelial cancers and that patients taking statins to reduce cholesterol levels possess lower cancer incidence. This has been observed in various organs such as the colon, lungs, liver, and breast [1].

Seven observational studies evaluating statin use and risk of female reproductive organ cancer have been performed to date. The largest cohort study by Yu et al. evaluated 550 gynecologic cancer cases and found a clinically useful but non-statistically significant reduction in risk of endometrial cancer among Statin users versus non-users [2]. Lavie et al. published results from a case control trial of newly diagnosed gynecologic malignancies. They found a significant negative association between use of statins for more than one year and endometrial cancer risk in 430 patients as well as significantly improved survival when statins were taken only after the diagnosis [3].

Although the use of statins for chemoprevention of gynecologic cancer has not been established, there does appear to be mounting evidence for reduction of risk of development of gynecologic malignancies and influence on survival [3].

Anti-inflammatory agents [4], anti-hyperglycemics [5] and bisphosphonates [6] have also been demonstrated as chemo- preventative agents and improved outcomes in many different tumor sites.

All studies to date have included all comers with a diagnosis of gynecologic malignancy without comparison of clinico-pathologic factors that influence recurrence rate and survival. There are no studies to date evaluating the effect of statin use on clinical and pathologic characteristics of endometrial cancer that increase a patient's recurrence risk and the need for adjuvant therapy.

Materials and Methods:

Institutional review board approval (#509556-1:10/2013) was obtained to review all patients who underwent hysterectomy for endometrial cancer at UC Davis Medical Center over a seven year period. Exclusion criteria for analysis were less than two years of electronic medical records, non-endometrioid histology, or equivocal pathology reports. Seven hundred and sixty four patients were identified, pathology reports were reviewed and 400 FIGO Stage I EC were identified. Cases were identified the presence of any high intermediate risk feature: Grade 2 or 3 histology, greater than 50% myoinvasion, or lymph vascular space invasion.

Results:

Of the 764 patients with endometrial cancer who underwent hysterectomy with or without staging we identified 400 with FIGO Stage I disease. Of the total cohort, 75 (18.8%) had at least one high intermediate risk feature, and 114 (28.5%) were taking a statin at the time of diagnosis. Thirty one percent of our patients had BMI >30, 74% of our patients were younger than 70, 21% had a diagnosis of diabetes, 36% of hypertension. On multivariate analysis, statin use was associated with increased high risk features (OR 2.4, 95% CI 1.3-4.3) at the time of hysterectomy even when controlled for patient age, parity, diabetes, obesity, hypertension, metformin use, NSAID and bisphosphonate. Metformin use was associated with increased HIR features (OR 1.6, 95% CI 0.7-3.5) but not statistically significant. Concurrent NSAID and bisphosphonate suggested a protective effect against high risk features, but was not significant either. Average follow up time was 35 months for both groups. There was a non-significant higher percentage of patients who recurred in the Statin users 10.5%(12/114) v 6.3% (18/286) in non-users. (p=0.15) Mean months to recurrence for statin users was 20.8 months v 28.1 months for non- users (p= 0.26).

Discussion:

In our single institution retrospective case-control study, statin use increased the risk of having high risk features over two-fold at the time of hysterectomy for FIGO stage I endometrioid endometrial cancer patients. There was also a trend in increase recurrence rate in statin users, consistent with a higher risk patient population. We may have identified a patient population at higher risk for poor prognosis.

The Prostate Cancer Prevention Trial, a randomized placebo- controlled trial found that finasteride decreased prostate cancer risk by 25% [10]. However, high-grade prostate cancer was more common in the finasteride group 6.5% v 5.1% with a relative risk of high grade tumor of 1.67 [95% CI, 1.44 to 1.93]; P=0.005 [10]. The decrease in di- hydro-testosterone related to finasteride use may help reduce the risk of low-grade prostate cancer in men [11]. Their data may suggest that some high-grade prostate cancers may not require androgen for progression.

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