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

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Abstract

Objective: 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.

Study Design: Four-hundred patients with stage I EC who underwent hysterectomy at a single institution from 2008-2013 were reviewed to determine presence of any HIR features. lymph vascular space invasion, Grade 2 or 3 and greater than 50% my invasion. Associations between statin use and presence of any HIR features at the time of hysterectomy were examined using multivariate logistic regression adjusting for age, BMI, parity, diabetes, and hypertension. Baseline metformin, NSAIDs, and bisphosphonate use was also included in the analysis.

Results: Of the 400 patients, 75 (18.8%) had at least one high intermediate risk feature, and 124 (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. Statin use was associated with increased high risk features (OR 2.4, 95% CI 1.3-4.3) at the time of hysterectomy. 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).

Conclusion: Our findings suggest that statin use confers a two times greater risk of having high risk features at the time of hysterectomy for early stage endometrial cancer. Statin use may prevent early stage low risk endometrial cancer, leading to an increased number of patients with HIR features in our statin user population.

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. We sought to determine an association with statin use and development of high-intermediate risk features in early stage endometrial cancer in a retrospective case-control study.

		Controls	Cases: HIR Features	P-value
Total patients		325 (81.3%)	75 (18.8%)	
Age	50-69	244 (82.7%)	52 (17.3%)	0.209
	70-89	81(77.1%)	24 (22.9%)	
Parity	0	33	3	0.525
	1	34	7	
	2	77	26	
	> 3	100	21	
	Missing	99	18	
Diabetes	No	259 (82.5%)	55 (17.5%)	0.227
	Yes	66 (76.7%)	20 (23.3%)	
Obesity	No	224 (81.8%)	50 (18.2%)	0.705
	Yes	101 (80.2%)	25 (19.8%)	
Hypertension	No	214 (83.9%)	41 (16.1%)	0.07
	Yes	111(76.6%)	34 (23.4%)	
Statin Use	No	245 (85.7%)	41 (14.3 %)	<0.0001
	Yes	80 (70.2%)	34 (29.8%)	
Metformin Use	No	255 (82.8%)	53 (17.2%)	0.148
	Yes	70 (76.1%)	22 (23.9%)	
Asa/Nsaids Use	No	204 (81.3%)	47 (18.7%)	0.987
	Yes	121 (81.2%)	28 (18.8%)	
Bisphospanate Use	No	303 (81%)	71 (19%)	0.649
	Yes	22 (84.6%)	4 (15.4%)	

Table 1: Characteristics of the 400 patients with low and high intermediate risk (HIR) FIGO Stage 1 endometrioid endometrial cancer.

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. Controls were those without any high intermediate risk features. Statin use was determined by review of medication reconciliations at the time of initial consultation.

Relevant exposure variables known to be associated with risk of cancer in the endometrium were tested as possible confounders or effect modifiers. These included: age greater than 70, BMI greater than 30, parity and a diagnosis of diabetes or hypertension. The concomitant use of metformin, NSAIDS, and bisphosphonates was obtained from medical reconciliation at the time of initial consultation. Time to cancer recurrence was documented for each patient.

Associations between statin use and presence of any HIR features at the time of hysterectomy were examined using multivariate logistic regression adjusting for age, BMI, parity, diabetes, and hypertension. Baseline metformin, NSAIDs, and bisphosphonate use was also included in the analysis.

Difference of categorical (or continuous) confounding variables between the two groups were tested by Chi-square test (or T-test) with reported two-sided P values. All analysis was performed using SAS V9.3

		OR	**(95% CI)**
Statin Use		2.4	(1.3 - 4.3)
Age 70-89 VS 50-69		1.4	(0.8 - 2.5)
Parity	1 vs 0	2.4	(0.5 - 10.2)
	2 vs 0	3.6	(1.0 - 13.0)
	3= vs 0	2.3	(0.6-8.5)
Diabetes		0.7	(0.3-1.7)
Obesity (bmi > 30)		1.1	(0.6-1.9)
Hypertension		1.5	(0.8-2.7)
Concomittent Medications	Metformin	1.6	(0.7-3.5)
	ASA/NSAID	0.8	(0.5-1.4)
	Bisphosphanate	0.8	(0.3-2.4)

Table 2: Adjusted OR for risk of high-intermediate risk (HIR) features at the time of hysterectomy.

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.

Nevadunsky et al recently demonstrated an improved disease-specific survival for women with endometrial cancer who were taking statins, and when stratified for histologic subtype the association persisted with type 2, but not type 1 disease [12]. Our study findings conflict with previous studies demonstrating improved overall survival [3], but may be related to study design and sample size.

As the obesity epidemic continues to rise, so will the prevalence of metabolic syndrome, with definitions encompassing insulin resistance, hyperlipidemia, obesity, and hypertension, all risk factors for endometrial cancer. [13] Statin use has been shown to decrease cardiovascular risk in metabolic syndrome patients and they are a recommended treatment strategy. [14] Our findings suggests that use of statins may prevent the low risk early stage endometrioid tumors, and could indicate a possible chemoprevention strategy. Although the etiology is unclear, statin use may actually have a filter effect in that people who are taking statins don't get low risk cancers, leading to an increased number of statin users having high risk disease.

The limitations of our study include retrospective data collection as well as lack of data regarding type, duration, and compliance with statin use and other concomittent medications. We did not investigate staging or adjuvant therapy, as this may play a role in survival and recurrence rate, but not initial clinic-pathologic findings at diagnosis.

Early stage endometrial cancer patient represents a heterogeneous group [15], and known risk factors for low risk early stage endometrial cancer may differ from those who present with high risk features. Metabolic syndrome in itself has increased risk for development of endometrial cancer, and majority are diagnosed early stage. The finding of an association between statin use and high risk disease in early stage endometrial cancer may reflect the identification of an alternative biologic pathway altered by statin use or a subset of patient population at risk for endometrial cancer with a worse prognosis. The molecular mechanism of statins on endometrial cancer needs to be more clearly understood in order to determine if statins can be used as a chemo preventative option for low grade disease or alter disease course and therefore recommendation on surgical management and adjuvant therapy. Future studies are in order.

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