Clinical Obstetrics, Gynecology and Reproductive Medicine

Research Article

Ultrasound monitoring of endometriomas—is there evidence of benefit for ovarian cancer detection?

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Abstract

Objective: To evaluate the potential impact of ultrasound monitoring of detected endometriomas on stage at diagnosis of clear cell and endometrioid type ovarian cancer.

Methods: Retrospective observational study of women diagnosed with clear cell or endometrioid type ovarian cancer between 1/1/2007 and10/15/2015 within a closed integrated health system. Electronic medical records were reviewed to determine the proportion of women with these cancers who had a suspected endometrioma described on ultrasound prior to their cancer diagnosis, the time interval between the report and diagnosis of cancer, whether follow-up imaging was done, and stage at diagnosis.

Results: Among 335 women diagnosed with clear cell or endometrioid ovarian cancer, 11 women (3.3%, 95%CI: 1.65% -5.8%) had a suspected endometrioma reported more than 1 year prior to cancer diagnosis with no intervening evidence of removal or resolution. The median time interval from first report of an endometrioma to diagnosis was 15 years (range: 5-18 years). In no cases, did monitoring in the absence of new symptoms lead to diagnosis of cancer. At surgery, 8 women were found to have stage 1 disease, two women had stage 2 disease, and one woman had stage 3 disease.

Conclusions: Prolonged ultrasound monitoring of suspected endometriomas is unlikely to significantly affect ovarian cancer stage at diagnosis.

Introduction

Clear cell and endometrioid ovarian carcinomas account for approximately 10-20% of ovarian cancers and, in contrast to high grade serous cancers, are frequently diagnosed at early stage [1]. The distinct clinical behavior and biology of these subtypes supports a dualistic model of ovarian carcinogenesis in which Type 1 cancers, which include clear cell and endometrioid histologies, are thought to arise from benign ovarian precursor lesions, whereas Type 2 cancers such as high grade serous carcinoma arise primarily from fallopian tube dysplasia [2]. Strong observational as well as molecular data support the notion that endometriomas and endometriotic implants can act as precursors for clear cell and endometrioid ovarian cancers [3-7]. Given this paradigm, the question arises whether long-term ultrasound monitoring of endometriomas, which are common benign ovarian lesions, leads to meaningful benefit in terms of early detection of clear cell or endometrioid adenocarcinoma. In order to assess the potential benefit of prolonged monitoring of suspected endometriomas on cancer stage at diagnosis, we determined the proportion of women diagnosed with clear cell or endometrioid ovarian cancer who had a documented history of a suspected endometrioma remote from their diagnosis, and evaluated the clinical presentation leading to diagnosis.

Methods

Study design, setting, and study cohort

Retrospective observational cohort study. Following approval from the Kaiser Permanente Northern California Institutional Review Board for Health Services, all women diagnosed with clear cell and endometrioid ovarian cancer between January 1, 2007 and October 15, 2015 within Kaiser Permanente Northern California (KPNC) were identified via the institution's tumor registry and confirmed by manual electronic medical record (EMR) review. Electronic medical record systems were implemented throughout KPNC during 2006. The study interval was selected in order to capture the maximum number of clear cell and endometrioid ovarian cancer cases during the time frame in which ultrasound reports and clinical notes would be reliably captured in the EMR. Demographic characteristics as well as the length of time that women had been members of the health plan prior to cancer diagnoses were determined from health plan enrollment records. Using electronic database searches of pelvic ultrasound transcripts and confirmatory chart review, all non-obstetric pelvic ultrasounds > 12 months prior to the diagnosis of cancer for each patient were identified in which a mass was described as a possible or probable endometrioma. Women with at least one such ultrasound report were considered to be those for whom long-term monitoring of an endometrioma could potentially have facilitated diagnosis of cancer. Women were excluded from this group if subsequent to the report, there was documented surgical removal or resolution of the lesion on follow-up imaging prior to cancer diagnosis.

The clinical presentation that led to cancer diagnosis was assessed from the medical records, reviewing outpatient or emergency room visit notes as well as the indications for ultrasound or other imaging

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Received: March 20, 2017; **Accepted:** April 04, 2017; **Published:** April 07, 2017

that was ordered. The time from the first ultrasound description of the endometrioma to cancer diagnosis was determined. Surgical pathology reports were reviewed for histology and stage at diagnosis. Staging was considered complete if both omental and retroperitoneal nodal evaluation were performed in addition to removal of the tumor.

Statistical analysis

Comparisons involving categorical variables were performed using Chi-square or Fisher's exact test. Normally distributed continuous variables were compared using Student's t-test. Comparisons of non-normally distributed continuous variables were conducted using the Wilcoxon rank-sum test. All analyses were performed using Statistical Analysis Systems (SAS) version 9.3 (SAS Institute, Cary, North Carolina). We considered a 2-sided P value less than 0.05 to be statistically significant.

Results

We identified 335 women diagnosed with primary clear cell/endometrioid ovarian cancer between January 1, 2007 and October 15, 2015. Prior to cancer diagnosis, women had been members in the health plan for an average of 10 years (median 11 years' range: 0 - 18 years). The average age at cancer diagnosis was 57 years old. Of the 335 women, 104 had at least one pelvic ultrasound done at least 1 year prior to cancer diagnosis and in 11 cases (3.3%, 95%CI: 1.65% -5.8%), the report described a possible or probable endometrioma. The average age at first detection of the endometrioma was 46 years old. The demographic characteristics of women with and without a history of reported endometrioma are shown in Table 1.

The median time interval from initial report of an endometrioma to diagnosis for 10 of the 11 women was 15 years (range: 5-18 years). For one woman, an endometrioma was reported in May 2005, she discontinued membership between Aug 2005 and March 2014, and cancer was diagnosed shortly after resumption of membership.

The clinical presentation leading to diagnosis of cancer is shown in Table 2. Three women had a history of previous surgery for endometriosis and/or endometrioma. Pain was the most common presenting complaint (8/11). All women underwent staging with assessment of retroperitoneal lymph nodes and omentum in addition to total hysterectomy and bilateral salpingooophorectomy. At surgery, 8 women were found to have stage 1 disease, two women had stage 2 disease, and one woman had stage 3 disease.

Discussion

Several observational studies have reported an association between endometrioma, endometriosis and ovarian cancer [3-7]. An increased incidence of ovarian cancer was reported among women who were entered into a registry of women with clinical endometriomas in Japan [8]. With a median ot 12.8 years of follow-up, 0.72% of women developed ovarian cancer, 74% of which were either clear cell or endometrioid histology. The investigators found that older age as well as large size of the endometrioma increased the risk of subsequent cancer [9]. A pooled analysis of 13 case-control studies found an increased risk of clear cell (OR, 3.05) and endometrioid (OR, 2.21) ovarian cancer among women who reported a history of endometriosis [3]. In addition to observational data, recent studies provide molecular support for the hypothesis that endometrioid and clear cell carcinomas arise out of endometriotic implants and endometriomas. Mutations in both PTEN and the tumor suppressor gene ARIDIA have been observed in up both clear cell and endometrioid cancers as well as adjacent endometrioitic epithelium [10-14].

The failure of ovarian screening trials to demonstrate survival benefit is partially explained by the heterogeneity of ovarian cancers. It is now recognized that Type 2 cancers, which represent the majority of ovarian malignancies, arise primarily from fallopian tube precursors. While the pathogenesis of Type I cancers would appear to make them more amenable to detection by screening, as noted by Kurman "the

Table 1. Demographic characteristics of women with and without a prior ultrasound reporting endometrioma.

Characteristics	Total cohort (N=335)	Women with documented history of endometrioma (N=11)	Women without documented history of endometrioma (N=324)	P-value
Race/Ethnicity				
White/Caucasian, n (%)	176 (53)	4 (36)	172 (53)	Fisher exact test p-value=0.087
African-American, n (%)	22 (7)	1 (9)	21 (7)	
Hispanic, n (%)	40 (12)	4 (36)	36 (11)	
Asian Pacific Islander, n (%)	74 (22)	1 (9)	72 (23)	
Native American/other, n (%)	23 (7)	1 (9)	22 (7)	
Age at cancer diagnosis, median (interquartile range)	56 (49-64)	55 (44-60)	56 (50-64)	Wilcoxon rank-sum testp-value=0.354

Table 2. Clinical presentation and stage at diagnosis for women with history of endometrioma.

#	Age at first detection of endometrioma	Age at cancer diagnosis	Hx of surgically documented endometriosis endometrioma	Presenting complaint	Stage
1	42	57	No	Pain	1a
2	54	68	No	Pain and postmenopausal bleeding	2b
3	59	69	No	Pain	1a
4	49	57	No	Postmenopausal bleeding	1a
5	36	39	No	Pain	1c
6	46	60	No	Mass on exam	1c
7	40	45	Yes	Pain	1a
8	44	53	No	Right pleural effusion and postmenopausal bleeding	1a
9	54	55	Yes	Pain	1c
10	41	44	No	Pain	1a
11	40	44	No	pain	3c

tumors that present in stage I are type I neoplasms, which account for 10% of deaths from ovarian cancer," [15] underscoring the fact that screening is only beneficial if it detects a cancer earlier than it would otherwise be detected. The main potential benefit of monitoring an asymptomatic adnexal mass is the possibility that the mass represents either an early cancer or a cancer precursor and that monitoring will lead to earlier stage at diagnosis. Since women with symptomatic endometriomas are generally offered surgical removal, the clinical question is whether monitoring asymptomatic endometriomas can be justified based on potential benefit.

The strengths of this study are the population-based nature of the cohort, the length of observation, and the completeness of data regarding prior imaging, clinical presentation and treatment. Identification of patients did not rely on referral and draws on a racial and ethnically diverse population. Limitations of the study include those inherent to retrospective review. The duration of time that women had been within the health plan prior to cancer diagnosis was variable. It is possible that women may have had ultrasounds done prior to becoming health plan members. The study identified women whose ultrasound reports specifically described a mass as a possible or probable endometrioma. It did not identify women based on ultrasound characteristics themselves. There may have been some women with prior endometriomas who were not recognized either due to the inherent limitations of ultrasound and/or variability in radiology reporting, or due to the fact that they never had an ultrasound or other imaging study prior to cancer diagnosis. Because it is impossible for any study to accurately identify all women with endometriomas independent of imaging, the absolute risk of clear cell or endometrioid cancer arising from an endometrioma cannot be determined, and was not the goal of the study. Rather, we sought to assess the potential yield of prolonged ultrasound monitoring of known endometriomas on cancer detection and stage at diagnosis.

We found that the proportion of women with clear cell and endometrioid ovarian cancer who had a prior ultrasound reporting an endometrioma is small at 3.3%, the average time interval between endometrioma detection and cancer was 15 years, and that among these women, evaluation prompted by clinical symptoms led to early stage diagnosis in 10/11 cases. These findings suggest that although a history of endometrioma and endometriosis is a risk factor for development of clear cell or endometrioid ovarian cancer, long-term ultrasound monitoring of suspected endometriomas is unlikely to significantly affect ovarian cancer stage at diagnosis.

Funding

Funding for the study was provided by the Community Benefits Program of Kaiser Permanente Northern California.

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