Gynecologic Oncology 132 (2014) 328–333

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Prior appendectomy does not protect against subsequent development of malignant or borderline mucinous ovarian neoplasms

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HIGHLIGHTS

- Prior appendectomy is not protective against subsequent mucinous ovarian neoplasms.
- Occult mucinous tumors in the appendix at the time of surgery are rare events.
- Immunohistochemistry may help resolve the origin of some mucinous neoplasms.

ARTICLE INFO

Article history:
Received 17 October 2013
Accepted 9 December 2013
Available online 14 December 2013

Keywords:
Mucinous ovarian neoplasms
Epidemiology
Risk factors
Appendectomy

ABSTRACT

Background. Due to concern that mucinous malignant or borderline ovarian neoplasms (MON) may represent metastatic deposits from appendiceal primaries, gynecologic oncologists routinely perform appendectomy in these cases. However, a multidisciplinary critique of this practice is lacking.

Methods. The New England Case–Control study database was utilized to compare the effect of prior appendectomy against known risk factors for MON. Pathology and operative reports of local cases of MON were reviewed to estimate the frequency of microscopic mucinous lesions in the appendix. Protein expression patterns among mucinous ovarian, colorectal, and appendiceal cancers were compared by immunohistochemistry.

Results. From the New England Case–Control study, 287 cases of MON were compared against 2339 age-matched controls. Prior appendectomy did not reduce the risk of MON (OR 1.28, 95% CI 0.83–1.92, $p = 0.23$), while prior tubal ligation, parity, and breastfeeding were each protective against MON. Active smoking (OR 2.04, 95% CI 1.48–2.80, $p < 0.001$) was associated with an increased risk of MON. Among 196 mucinous adnexal tumors, appendectomy did not reclassify any MON as appendiceal in origin. By immunohistochemistry, mucinous ovarian carcinomas tended to be CK7 +/CK20 −/MUC2 −/CDX2 −, whereas mucinous colorectal and appendiceal adenocarcinomas were typically CK7 −/CK20 +/MUC2 +/CDX2 +, although with some overlap in immunophenotype. Additionally, PAX8 was positive in a subset of MOC and negative in all appendiceal carcinomas.

Conclusion. Prior appendectomy is not protective against development of malignant or borderline MON. Routine appendectomy during surgery for MON seldom reveals an unsuspected GI primary in early stage tumors but may aid in final diagnosis in advanced stage cases.

Funding. National Cancer Institute grants P50-CA105009 and R21 CA-156021; The Honorable Tina Brozman 'Tina's Wish' Foundation; the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF); Dana-Farber Cancer Institute — Susan Smith Center for Women's Cancers; Robert and Deborah First Fund; The Gamel Family Fund; Mary Kay Foundation; Sandy Rollman Ovarian Cancer Foundation; Arthur Sachs/Fulbright/Harvard; La Fondation Philippe; La Fondation de France.

Introduction

Epithelial ovarian carcinomas (EOC) are the leading cause of death among gynecologic tumors [1]. EOC are histologically classified into four major subtypes: serous, clear cell, endometrioid, and mucinous

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http://dx.doi.org/10.1016/j.ygyno.2013.12.011

[2,3]. Mucinous ovarian carcinomas have been the least studied of these, probably because of their relative rarity, comprising about 3% or less of EOC [4]. Mucinous tumors can exist as both invasive and borderline tumors, here collectively referred to as mucinous ovarian neoplasms (MON). Although it has been argued that MON bear some relationship to the endocervix, the mucinous epithelium that characterizes MON more frequently resembles gastrointestinal (GI) epithelium [5]. Even when excluding cases of pseudomyxoma peritonei, which are now generally accepted to occur almost exclusively in association with appendiceal primaries, most pathologists still maintain that the diagnosis of primary MON requires consideration and exclusion of metastases from other GI carcinomas [6,7]. Indeed, the epidemiology, histology, and molecular biology of MON are routinely compared to GI mucinous carcinomas, in particular those arising in the colon [8]. Coupled with rare case reports of goblet cell carcinoids ("adenocarcinoid" tumors) presenting as isolated adnexal masses, these reports have advanced the notion that a significant proportion of MON are subsequently found to have arisen from an occult appendiceal or other GI primary, and therefore that the appendix should be routinely removed at the time of surgery for any malignant or borderline MON [9–12]. In addition, other authors have advocated routine appendectomy in all EOC cytoreductive surgeries regardless of histology to exclude isolated metastases from the ovary to the appendix [13–15]. As a result, routine appendectomy at the time of surgery for a suspected or confirmed (by frozen section) MON of malignant or borderline potential has become common.

In this study, we examine the relationship between malignant and borderline MON and mucinous appendiceal tumors. We test the idea that some seemingly isolated MON are actually derived from the appendix by using a large regional case–control study to compare the effect of prior appendectomy against established risk factors for EOC. We then report our recent clinical experience with regard to the issue of occult appendiceal primaries at the time of surgery for suspected malignant or borderline MON and microscopic metastases from MON to the appendix. Finally, we compare the immunohistochemical (IHC) pattern of mucinous ovarian carcinomas (MOC) to mucinous appendiceal and colorectal carcinomas to test the ability of pathologists to discriminate among these clinical entities.

Materials and methods

New England Case–Control study

Data derived from four phases of a case–control study of ovarian cancer, the New England Case–Control (NECC) study, were used [16,17]. Cases were enrolled from 7/1984 to 9/1987 (NECC2), 5/1992 to 3/1997 (NECC3), 8/1998 to 4/2003 (NECC4), and 10/2003 to 11/2008 (NECC5). Data from an earlier phase between 1978 and 1981 (NECC1) were no longer available electronically and not included. NECC2 identified ovarian cancer cases from ten hospitals in Boston; NECC3, 4, and 5 used statewide cancer registries and tumor boards to identify cases diagnosed in Eastern Massachusetts and the State of New Hampshire. The four phases enrolled 2475 cases including 2274 with epithelial ovarian cancers, of which 287 were mucinous. Controls for NECC3 were identified by random-digit dialing supplemented with residents lists for older controls. About 10% of households dialed had an eligible control and of these, 421 (72%) agreed to participate. All controls for NECC2, 4, and 5 were identified through town residents' lists in Massachusetts and Driver License Registries in New Hampshire. Of 5151 potential controls identified through town books in all phases, 1671 were ineligible due to bilateral oophorectomy, 1562 declined participation, and 1918 were enrolled. In total, 2339 controls were enrolled. This study is approved by the Brigham and Women's Hospital and Dartmouth Medical Center Institutional Review Boards.

Chart review

The medical charts of 106 patients from the NECC study population were available for review by virtue of being operated on at either Brigham and Women's Hospital or Massachusetts General Hospital. These were combined with an additional 64 patients operated on at Brigham and Women's from 2006 to 2011 not enrolled in NECC. Operative reports and pathology reports from these cases were read to determine the frequency of appendectomy at the time of surgery and the incidence of microscopic metastases to the appendix from the ovary. In addition, the medical charts of an additional 26 patients operated on by the gynecologic oncology service at Brigham and Women's Hospital for an adnexal mass with the subsequent finding of a GI primary cancer were assessed by a member of the gynecologic oncology division (KME) for the frequency of a microscopic GI primary that would have been diagnosed only by routine appendectomy and not by examination of the other pathologic specimens obtained via oophorectomy or other cytoreductive procedures. Chart review was approved by the Partners Healthcare Institutional Review Board.

Statistical methods

For the case control study, continuous variables were categorized based on quartiles of the control distributions. Subjects with missing exposures were excluded on an exposure-specific basis. Unconditional logistic regression models were used to assess the associations between exposures and MON. All models were adjusted for the matching factors (age, study site, and study phase), as well as parity, breastfeeding, OC use, genital talc exposure, Jewish ethnicity, and tubal ligation. All analyses were performed with SAS (SAS Institute, Cary, NC). Immunohistochemical staining results were compared using Fisher's exact test (GraphPad Software, La Jolla, CA).

Pathology samples

A total of 65 cases of mucinous tumors were selected from the surgical pathology files of the Brigham and Women's Hospital including 21 mucinous ovarian carcinomas, 18 mucinous colon carcinomas (MCCs), and 26 mucinous appendiceal carcinomas (MACs). Sites of origin of all tumors were known before this study on the basis of clinical and radiologic information in addition to surgical specimen examination. The tissues had been routinely fixed in 10% neutral formalin and embedded in paraffin. At least one paraffin tissue block with tumor was selected from each case by a pathologist with expert training in gynecologic or gastrointestinal pathology (MSH or JLH and LAD, respectively).

Immunohistochemistry

Commercially available antibodies to keratin 7 (CK7), keratin 20 (CK20), CDX-2, β-catenin, MUC-2, SMAD4, and PAX-8 were evaluated in all cases (Table S1). The sections were deparaffinized and rehydrated in graded alcohol. The sections were then brought to an automated stainer (DAKO Corporation,Carpinteria, CA). For epitope retrieval, the sections for MUC-2, CDX-2, PAX-8, β-catenin, and SMAD4 were subjected to Dako TRS Retrieval buffer, and the sections for CK20 and CK7 were enzyme digested. DAKO Envision + polymer detection methods were used. Appropriate positive and negative (without primary antibodies) controls were used simultaneously for each antibody. The scoring was semi-quantitative as follows: 0, 1+ (1–5%), 2+ (6–25%), 3+ (26–50%), or 4+ (>50%) based on cytoplasmic (CK7, CK20), membranous (MUC2), or nuclear (CDX-2, PAX8) positivity; only cases ≥2+ were scored as "positive." SMAD4 was considered positive if there was complete loss of nuclear and cytoplasmic staining. β-Catenin was evaluated for a membranous (negative) or nuclear (positive) staining pattern.