Gynecologic Oncology 132 (2014) 280–286

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Outcome of unexpected adnexal neoplasia discovered during risk reduction salpingo-oophorectomy in women with germ-line *BRCA1* or *BRCA2* mutations

James R. Conner [a], Emily Meserve [a], Ellen Pizer [b], Judy Garber [c], Michael Roh [d], Nicole Urban [e], Charles Drescher [f], Bradley J. Quade [a], Michael Muto [h], Brooke E. Howitt [a], Mark D. Pearlman [g], Ross S. Berkowitz [h], Neil Horowitz [h], Christopher P. Crum [a,*,1], Colleen Feltmate [h,1]

[a] *Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, USA*
[b] *Cell-Netix, Seattle, USA*
[c] *Dana Farber/Brigham and Women's Cancer Center, Boston, MA, USA*
[d] *Department of Pathology, University of Michigan Medical School, Ann Arbor, USA*
[e] *Fred Hutchinson Cancer Research Center, Seattle, WA, USA*
[f] *University of Washington School of Medicine, Seattle, WA, USA*
[g] *Department of Obstetrics and Gynecology, University of Michigan Medical School, Ann Arbor, USA*
[h] *Division of Gynecologic Pathology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, USA*

HIGHLIGHTS

- Adnexal neoplasia was found in ~5% of risk reduction surgeries for BRCA1 or BRCA2 mutations.
- Recurrences developed from 9 to 17% over a median of 5 year follow-up.
- There were no ovarian cancer-related deaths at 5 years.

ARTICLE INFO

Article history:
Received 28 September 2013
Accepted 5 December 2013
Available online 12 December 2013

Keywords:
BRCA
Fallopian
Ovarian cancer
Serous cancer

ABSTRACT

Objective. This study computed the risk of clinically silent adnexal neoplasia in women with germ-line *BRCA1* or *BRCA2* mutations ($BRCA^{m+}$) and determined recurrence risk.

Methods. We analyzed risk reduction salpingo-oophorectomies (RRSOs) from 349 $BRCA^{m+}$ women processed by the SEE-FIM protocol and addressed recurrence rates for 29 neoplasms from three institutions.

Results. Nineteen neoplasms (5.4%) were identified at one institution, 9.2% of *BRCA1* and 3.4% of *BRCA2* mutation-positive women. Fourteen had a high-grade tubal intraepithelial neoplasm (HGTIN, 74%). Mean age (54.4) was higher than the $BRCA^{m+}$ cohort without neoplasia (47.8) and frequency increased with age ($p < 0.001$). Twenty-nine $BRCA^{m+}$ patients with neoplasia from three institutions were followed for a median of 5 years (1–8 years.). One of 11 with HGTIN alone (9%) recurred at 4 years, in contrast to 3 of 18 with invasion or involvement of other sites (16.7%). All but two are currently alive. Among the 29 patients in the three institution cohort, mean ages for HGTIN and advanced disease were 49.2 and 57.7 ($p = 0.027$).

Conclusions. Adnexal neoplasia is present in 5–6% of RRSOs, is more common in women with *BRCA1* mutations, and recurs in 9% of women with HGTIN alone. The lag in time from diagnosis of the HGTIN to pelvic recurrence (4 years) and differences in mean age between HGTIN and advanced disease (8.5 years) suggest an interval of several years from the onset of HGTIN until pelvic cancer develops. However, some neoplasms occur in the absence of HGTIN.

Introduction

Ovarian cancer is the fifth leading cause of cancer related deaths in women in the United States, with approximately 22,000 new cases and 14,000 deaths annually [1]. High-grade carcinomas – mostly serous

* Corresponding author at: Department of Pathology, Brigham and Women's Hospital, Boston, MA 02115, USA. Fax: +1 617 264 5125.
E-mail address: ccrum@partners.org (C.P. Crum).
URL: http://www.pointproject.org (C.P. Crum).
[1] These authors contributed equally as senior authors.

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.12.009

type – have the worst outcome. They typically present in late stage, seeding the peritoneal cavity and metastasizing early in the disease course [2].

The anatomic origin of high grade serous carcinoma has been ascribed both to the ovarian surface and to the distal fallopian tube, supported by the presence of high-grade serous tubal intraepithelial neoplasia (HGTIN), also termed serous tubal intraepithelial carcinoma (or STIC) in over 40% of women with disseminated high grade serous carcinoma [3]. Identification of HGTIN or early tubal carcinoma in risk reducing salpingo-oophorectomy (RRSO) specimens of asymptomatic women with presumed germ-line mutations in *BRCA1* or *BRCA2* genes ($BRCA^{m+}$) further supports a tubal origin [4–10]. Moreover, "latent" precursors with mutations in the p53 gene, known as "p53 signatures," are commonly found in the fallopian tube epithelium and have been shown to be genetically linked to some high-grade serous carcinomas [11].

RRSO is routinely offered to $BRCA^{m+}$ patients or those with a strong personal or family history of breast and ovarian cancers or a family history of ovarian cancer alone. Unsuspected carcinomas have been reported in the fallopian tubes or ovaries of these women between 2% and 17%, more precise estimates following the widespread adoption of the SEE-FIM protocol for more careful examination of the distal tube, including the fimbriae [4,8,12–15]. The clinical outcome of these small, clinically unsuspected neoplasms of the fallopian tube has not to date been characterized in great detail, owing to their relatively low frequency and non-uniform sampling of fallopian tubes. As a result, management of these patients and their prognosis have been uncertain.

A single study in 2004 reported one recurrence in a patient with a *BRCA1* mutation among four patients undergoing RRSO [16]. Two recent studies with larger numbers reported recurrence rates for HGTIN alone at 0 and 7% [17,18]. Our institution began using the SEE-FIM protocol to evaluate RRSO specimens in 2005 for $BRCA^{m+}$ women, providing up to 8 years of clinical follow-up [5]. This population provides an opportunity to study both the detection frequency and longer term outcome of clinically unsuspected adnexal neoplasia in this unique population.

Methods

This study was approved by the human investigation committees at Brigham and Women's Hospital, the University of Michigan Medical School and the Pacific Ovarian Cancer Research Consortium (POCRC). The material for the two major analyses was derived from two distinct clinical sources. The first analysis explored the frequency of neoplasia in a series of consecutive RRSOs conducted at Brigham and Women's Hospital and the Dana Farber Cancer Institute (DFCI). The second pooled high-grade TINs or carcinomas were diagnosed following RRSO at BWH/DFCI, POCRC and University of Michigan and ascertained the risk of a pelvic cancer outcome (www.pointproject.org). All were reviewed by a second observer (CPC) to verify the diagnosis. For this study, cases were limited to high grade serous or endometrioid neoplasms detected in asymptomatic women that were small or microscopic and were tubal, ovarian or unclear in their origin. Histologic sections and p53 immunostains of representative early carcinomas with and without associated spread were reviewed. The term HGTIN in this study connotes a high-grade non-invasive serous tubal intraepithelial neoplasm unless otherwise specified. Histologic criteria for the diagnosis of HGTIN have been detailed previously, consisting of a combination of marked nuclear atypia and some loss of cell polarity, typically accompanied by an increased proliferative index and either strong or absent (due to a deletion mutation) immuno-positivity for p53. In essence, HGTIN corresponded to serous tubal intraepithelial carcinomas as described previously [2,3].

Frequency and clinicopathologic features of early carcinoma in patients with BRCA gene mutations

The case files of the Women's and Perinatal Division in the Department of Pathology at Brigham and Women's Hospital were searched for terms containing the sequence "BRCA" received between January 1, 2005 and February 15, 2013. From this data set, cases in which ovarian or tubal carcinoma was suspected preoperatively based on clinical, radiographic, or laboratory data were excluded. Although no standard pre-operative testing was performed, the stated impressions took into account standard imaging studies along with physical exam findings, and prior pathologic diagnoses when relevant. CA125 values were not obtained as part of the pre-operative management of patients in this cohort. Asymptomatic $BRCA^{m+}$ cases, including cases in which carcinoma was identified during or after surgery, were included. The clinic records of each case were then reviewed for evidence corroborating a *BRCA1* or *BRCA2* mutation (Fig. 1).

RRSOs were entirely submitted for microscopic examination according to the SEE-FIM protocol previously described [5]. Clinically unsuspected carcinomas were divided into three categories: Group I consists of cases with HGTIN alone; Group II had HGTIN and evidence of advanced disease, including ovarian/serosal surfaces and positive peritoneal cytology; Group III had the latter findings without evidence of HGTIN (Table 1).

Age was recorded for all and the mean or median age of patients with early carcinoma was compared to the median age of patients without disease using an independent sample two-tailed *t*-test analysis. The proportion of patients with carcinoma at each year of age was calculated and used in a linear regression analysis to determine the correlation between age at the time of RRSO and risk of early carcinoma (Fig. 2).

Clinical outcomes of early carcinoma

The cohort of patients with neoplasia detected in RRSO specimens from Brigham and Women's Hospital, POCRC, and University of Michigan Medical School was identified. Patients were followed for signs of recurrent disease at the discretion of the managing physician using standard clinical, imaging, and laboratory (CA-125) signs. Recurrence was defined either by a direct cytologic or histologic diagnosis or by two consecutively rising CA-125 values above the patient's established baseline levels.

Results

RRSO specimens from patients with BRCA1 and BRCA2 mutations

Frequency of neoplasia

The initial results returned 452 reports with the term "BRCA" in the pathology report clinical history. After excluding cases of symptomatic malignancy, 385 were eligible for further analysis from a single major academic medical center (BWH) from January 2005 to February 2013. All but 3 were bilateral salpingo-oophorectomies. Within this group are 122 cases (and 7 early cancers) that have been previously reported [12]. Fig. 1 summarizes the breakdown of cases. In 36 a *BRCA1* or *BRCA2* gene mutation was not corroborated in the clinical record. In 345, a *BRCA1* or *BRCA2* mutation was specified in the clinical record; 34 were documented in clinical notes alone and 311 provided in addition a sequence report from Myriad Genetics. In four others, mutations in both genes or unspecified BRCA mutations were reported in the clinic notes. Cases specified as *BRCA1* or *BRCA2* mutation positive included those with a documented deleterious mutation (del+) or mutation of uncertain significance (del−) based on sequence data, and *BRCA1* or *BRCA2* mutation without further information (UK) (Fig. 1).

Mean ages for all of the 173 *BRCA1* and 172 *BRCA2* mutation-positive cases were 46.4 and 48.7 years respectively ($p = 0.024$). Overall, neoplasia was identified in 19 of 349 (5.4%) cases with *any* record of mutation and 18 of 313 (5.8%) cases with a documented deleterious mutation in *BRCA1*, *BRCA2* or both. Neoplasia was discovered in 13/154 (9.2%) and 5/148 (3.4%) cases with documented deleterious mutations in *BRCA1* or *BRCA2* respectively ($p = 0.09$). Mean ages for patients with neoplasia in the two groups were 52.8 and 58.4 respectively ($p = .32$).

Table 1
Genetic, pathologic, and clinical features of unsuspected carcinomas detected in BWH patients at RRSO.

Age[a]	Gene with mutation	*BRCA* mutation	Fallopian tube involvement	Ovarian surface involvement	Other peritoneal involvement	Peritoneal washing cytology	Subsequent surgical staging	FIGO stage	Other Malignancies
Group I									
41	*BRCA1*	243T>C	HGTIN	None	None	Negative	Yes	0	None
41	*BRCA1*	3717C>T	HGTIN	None	None	Negative	Yes	0	None
44	*BRCA1*	1294del40	HGTIN	None	None	Negative	No	0	Breast
46	*BRCA1*	Not available	HGTIN	None	None	Negative	No	0	Breast
51	*BRCA1*	4184del4	HGTIN	None	None	Negative	No	0	None
66	*BRCA2*	5301insA	HGTIN	None	None	Negative	Yes	0	None
Group II									
43	*BRCA2*	W2586X	HGTIN	None	None	Positive	Yes	1c	Breast
57	*BRCA1*	943ins10	HGTIN with associated invasive serous carcinoma	None	None	Negative	Yes	1a	Breast
60	*BRCA1*	4794G>A	HGTIN with associated invasive serous carcinoma	None	None	Negative	No	1a	Breast (DCIS)
56	*BRCA1*	4154delA	HGTIN	Bilateral (multiple foci)	None	Negative	Yes	1c[a]	Breast
46	*BRCA1*	2953delGTAinsC	Endometrioid TIN	Endometrioid adenocarcinoma	Anterior abdominal wall implant	Positive	Yes	2c/3a[ab]	Breast
65	*BRCA1*	2798del4	HGTIN	Present on contralateral surface, ipsilateral surface covered by thin pseudocapsule	None	Positive	No (full staging performed with RRSO after frozen section diagnosis)	2c[a]	None
65	*BRCA1*	2798del4	HGTIN	Present on contralateral surface, ipsilateral surface covered by thin pseudocapsule	None	Positive	No (full staging performed with RRSO after frozen section diagnosis)	2c[a]	None
56	*BRCA2*	L2653P	HGTIN	Ipsilateral	None	Suspicious for malignancy	Yes	2a	None
48	*BRCA1*	Exon 13 in. 6 kb	HGTIN	Bilateral	None	Positive	Yes	2c	None
Group III									
62	*BRCA1*	187delAG	Invasive endometrioid adenocarcinoma (grade 2/3), involving fimbriae	None	None	Atypical, favor reactive mesothelial cells	Yes	1a	Breast
73	*BRCA1*	2953delGTAinsC	Invasive serous carcinoma, involving fimbriae	None	None	Negative	No	1a	Breast
49	*BRCA1*	Q1240X	Moderately differentiated (likely endometrioid) adenocarcinoma	Ipsilateral	None	Negative	Yes	2a	None
76	*BRCA2*	6174delT	Bilateral serous carcinoma involving fimbriae	None	Gross tumor seen on omentum and multiple other peritoneal surfaces	Positive	No (full staging performed with RRSO after frozen section diagnosis)	3b	Pancreatic
51	*BRCA2*	3331G>T	None	Bilateral serous carcinoma	None	Positive	Yes	1c[a]	None

[a] Cases staged as primary ovarian carcinoma.
[b] A single focus of microscopic disease was found in the pelvis on the anterior abdominal wall.

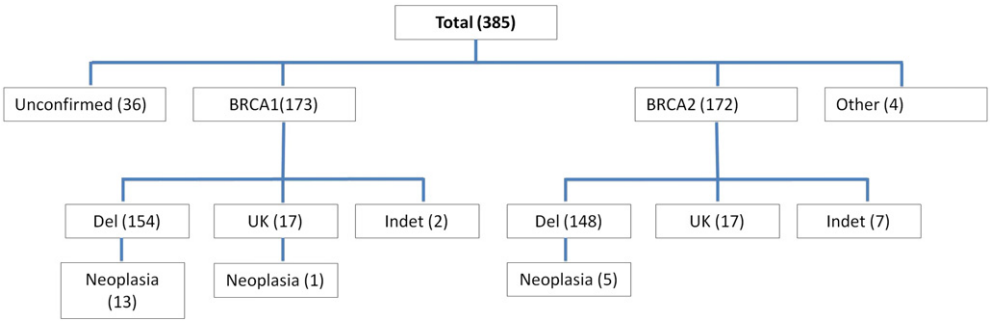

Fig. 1. *BRCA1* and *BRCA2* gene mutation status in the BWH cohort. A total of 385 patients were designated as having a BRCA gene mutation on the pathology requisition submitted at the time of RRSO. Subsequent chart review revealed documented mutations in *BRCA1*, *BRCA2*, or both (classified as "other") in 349, whereas 36 cases were not confirmed. The nature of the mutations (del = known deleterious, UK = exact mutation unknown after chart review, indet = effect of mutation indeterminate) and frequency of neoplasia in each category are shown.

Histologic findings in unsuspected neoplasms detected at or following RRSO

As shown in Fig. 2A and B, patients with neoplasia were significantly older than patients without evidence of disease (median age of patients with neoplasia 51, mean 54.4; range 41–76, $p = 0.0009$). Logistic regression analysis revealed a significant relationship between age at the time of surgery and likelihood of an unsuspected carcinoma ($p < 0.001$).

Thirteen of 19 cases had serous HGTIN and another endometrioid HGTIN for a total of 74% with evidence of an origin in the tubal mucosa. *BRCA1* germ-line mutations were found in 14 of 19 (74%) overall, and 5 of 6 in Group I, 7 of 9 in Group II and 3 of 5 in Group III.

Mean age at the time of diagnosis was 48.2 years for 6 cases with HGTIN alone, 58.1 years for 7 cases with HGTIN and peritoneal involvement and 62.2 years for tumors without HGTIN (two-tailed *t*-test comparing cases with HGTIN alone to more advanced lesions, $p = 0.63$).

Clinical outcomes of early tubal-ovarian carcinoma: retrospective experiences from three academic centers

To estimate the risk of recurrence following RRSO, 29 patients with *BRCA1* and/or *BRCA2* mutations with unsuspected neoplasia identified in RRSO specimens from three institutions were followed. Median follow-up was 5 years; (range <1 year to 8 years). The cases were subdivided into Groups I (11), II (12) and III (6). Two of 11 in Group I received chemotherapy versus all in Groups II and III. Mean ages in this multi-institutional data set for Groups I, II and III were 49.2, 56.9, and 61.0 years respectively. The differences in mean age between groups I and II and I and III approached statistical significance ($p = 0.052$ and 0.064, *t*-test) and patients with HGTIN alone (group I) were significantly younger than those with more advanced disease (groups II and III; $p = 0.027$).

Twelve patients with invasive or more advanced carcinoma underwent a second staging laparoscopy, some including lymphadenectomy and omentectomy. Chemotherapy consisted of platinum and paclitaxel based combinations in all cases with all patients receiving intravenous therapy and one patient with a serosal metastasis documented at the time of surgery receiving intraperitoneal therapy. One patient who recurred subsequently received gemcitabine for the recurrence.

Two patients (both without evidence of early spread) have died; one each attributed to breast cancer and pneumonia.

A recurrence was observed in 1 of 11 in Group I (9.1%), 2 of 12 in Group II (16.7%) and 1 of 6 in Group III (16.7%). The recurrence in the patient with HGTIN alone was presumptive, based on ascites and increasing CA125, but no tissue diagnosis. Recurrence developed at 4 years for the case in Group I, and 5, 5, and 6 years for the cases in Groups II and III. There was no significant association between age and risk of recurrence (logistic regression analysis $p = .06$). No recurrences developed within the follow-up period in treated patients with microscopic serosal or ovarian metastases or peritoneal cytology in the absence of gross metastatic disease.

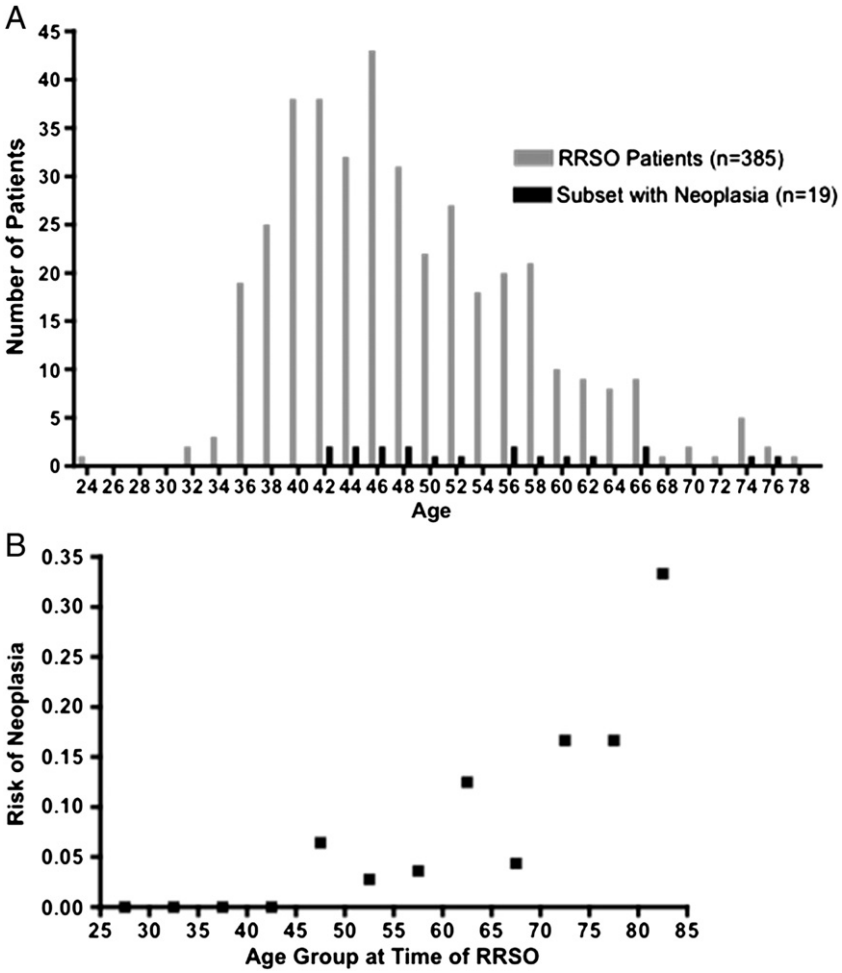

Fig. 2. Age distribution of patients undergoing risk-reducing salpingo-oophorectomy and patients with neoplasia. A. Histogram showing ages for all patients undergoing risk-reducing salpingo-oophorectomy at BWH (gray) and the subset of patients with neoplasia (red). Patients with neoplasia were significantly older than patients without evidence of disease ($p = 0.0009$). B. Age-related risk of unsuspected neoplasia at RRSO. Patients were grouped into 5 year age bins and the proportion of cases positive for neoplasia was plotted against age. Logistic regression analysis demonstrated a significant relationship between age at the time of surgery and likelihood of an unsuspected neoplasia ($p < 0.001$).

Discussion

This study addresses three questions concerning ovarian cancer in BRCA^{m+} women: 1) relationship of BRCA status to frequency of asymptomatic disease, 2) frequency of disease in RRSOs and 3) risk of recurrence on follow-up. Estimates of occult neoplasia in RRSOs range from 2 to 17% [4,8,12–15,18]. In 2005, the SEE-FIM protocol was instituted at Brigham and Women's Hospital and specified more thorough sectioning of the fimbriated end to increase the amount of surface area evaluated in the distal tube [5]. Since then, 100% of every fimbria has been examined in this manner in BRCA^{m+} women, including the remainder of the tube, excepting rare instances when a segment in the proximal one-third was retained for research.

The overall frequency of early neoplasia in this population ranged from 5.4% (for any record of mutation) to 5.8% (deleterious mutations only). This is similar to a prior study by Callahan et al. from this institution that identified 7 cancers in 122 consecutive cases (5.7%) [12]. As shown in Fig. 2, the frequency of cases in which neoplasia was detected increased significantly as a function of age. This indicates that the age of the cohort could influence the detection rate. A similar size study of women with a somewhat younger mean age (44) reported occult cancers in 8 of 360 (2.2%), including 6 HGTINs [19]. Another variable that might influence detection and age of presentation is BRCA mutation status. In this study both the population and neoplasms associated with *BRCA1* mutations were younger than the *BRCA2* mutation positive group. These differences were not highly significant; however, *BRCA1* mutation-positive women with symptomatic high grade pelvic carcinoma are significantly younger than their *BRCA2* mutation-positive counterparts [20]. Evidence thus suggests that *BRCA1* mutation-positive individuals may be more susceptible and at a younger age, in keeping the higher overall risk of malignancy and adverse outcome in this subset [20,21].

BRCA^{m+} women who have undergone a RRSO with normal pathology have a reported 4–5 percent risk of a pelvic serous cancer on follow-up, an approximately 4–9 fold greater risk than the general population [22]. Going forward, this risk will likely be revised downward with the widespread adoption of protocols to thoroughly examine the distal fallopian tube. Such protocols should lower the miss rate for microscopic tubal neoplasia (HGTIN) that could later recur, but may not address other potential sources of disease [3,5,8]. Irrespective of site of origin, the risk of later recurrence when carcinoma is discovered is substantial. Powell et al. noted a recurrence rate of 47% for cases with invasive carcinoma and in this study more advanced disease recurred in 17% (3 of 18) of cases with invasion [23]. These individuals invariably are counseled to receive adjunctive therapy. The principal question is how to manage non-invasive neoplasia (HGTIN). One of 17 (5.8) % high-grade intraepithelial neoplasms in the study by Powell et al. recurred at 43 months. In the current study 1 of 11 (9%) cases with HGTIN alone recurred (Table 2). If the data from these two studies are combined, the risk of recurrence following invasion or other evidence of spread (11 of 32) is significantly higher than that for intraepithelial neoplasia (2 of 26; $p = .024$ by Fishers exact test). Wethington et al. noted no recurrences in 12 HGTINs over a median of 28 months [18]. This supports aggressive management when the tumor has spread or advanced, but does not support prophylactic chemotherapy for HGTIN alone, pending additional data that would clarify which patients with HGTIN were more likely to have a recurrence.

The BRCA^{m+} population plays an important role in efforts to devise models of frequency of HGTIN and transit time from HGTIN to serous cancer. They bear on both efforts to estimate the effectiveness of prophylactic salpingectomy in preventing this disease and screening efforts to interrupt potentially curative stages of neoplasia. RRSO provides the unique opportunity to detect disease early and crudely estimate the timing of progression from early (such as HGTIN) to advanced disease by either following women with HGTIN or comparing the mean ages of patients at different stages of disease. Several confounders are unavoidable. The decisions of when to screen for BRCA mutations and when to perform RRSO influence the age at which an asymptomatic neoplasm will be detected. The timing of testing is patient dependent and often influenced by concerns raised with the prior detection of breast cancer. Moreover, *BRCA2* mutation positive cohorts with or without neoplasia tend to be slightly older than their *BRCA1* counterparts, further confounding the interpretation of age differences.

Three findings in this study and others suggest that there might be a substantial interval from the onset of HGTIN to either asymptomatic or symptomatic spread. First, most HGTINs are not associated with recurrences, indicating that the acquisition of metastatic potential takes time after a HGTIN emerges. Second, the mean ages for patients with localized HGTIN vs HGTIN with advanced disease were 49.2 and 56.9 years, a difference that approached significance. Third, the lag time from discovery of a HGTIN to (presumed) recurrence was 43 and 48 months in the two recurrences recorded in this study and that of Powell et al. The first two observations imply that the tubal serous carcinogenic pathway conceivably might be interrupted by detecting pre-metastatic neoplasia, the removal of which would prevent subsequent disease.

Although the above findings merit further studies to determine their relevance to serous cancer prevention, an equally compelling question remains to be answered, which is a paradox between the frequency of HGTIN in RRSOs vs cases of symptomatic, advanced high-grade serous carcinoma. Estimates of associated HGTIN in unselected women with symptomatic high grade cancer range from 19 to 59%, a distinct contrast to the rate of 74% in the asymptomatic population in this study. This implies that many cancers are not initiated in recognizable HGTINs [24]. Interestingly, Powell et al. noted that the mean age of their cases with invasion was significantly younger than those with intraepithelial neoplasia only (50 vs. 55, $p = 0.04$) [23]. Whether these discrepancies are a function of demographics, tissue sampling, different transit times, or variable pathways and organs (peritoneum, ovary etc.) involved in the pathogenesis of pelvic serous cancer remains to be determined. However, it leaves open the possibility that more than one carcinogenic pathway is involved in the development of high grade serous carcinoma, including one that manifests rapidly and not clearly of tubal origin. In a study of registry data of 63 BRCA^{m+} cancers, Piek et al. noted that only 6% were reported as tubal in origin. This figure is a likely underestimation of tubal involvement, but nonetheless contrasts sharply with the detection rate in asymptomatic women [25]. In a histologic analysis of tubes of symptomatic BRCA^{m+} women with carcinoma using the SEE-FIM protocol, we have found STIC in less than 40% of cases (Meserve, Schulte and Crum, unpublished). Thus, more thorough analysis of high-grade serous cancers in symptomatic BRCA^{m+} women is needed to shed light on this question [24].

In summary, this study has shown a detection rate of 5.4% for early adnexal cancer in BRCA^{m+} women undergoing RRSO and recurrence rates from 9 to 17% over 5 years depending on the extent at the time of RRSO. There is a low-rate of recurrence overall following chemotherapy for local spread and high cancer-free survival rate in the first 5 years following diagnosis. At this point there is no compelling justification for prophylactic chemotherapy in cases with TIC alone. The precise lag time from localized to more advanced disease remains unclear. Alternate pathways to neoplasia should be excluded by meticulous pathologic studies of advanced high grade serous carcinomas in these women.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

The study is supported by grants from the National Cancer Institute (NCI P50 CA083636 to NU) (1R21CA124688-01A1 to CPC) and the Department of Defense (W81XWH-10-1-0289 to CPC).

Table 2
Pathologic features and clinical outcomes of incidental carcinomas detected at RRSO from 3 institutions.

Age[a]	Institution	Pathology	Chemotherapy[b]	Recurrence	Current status	Years of follow-up
Group I						
41	BWH	HGTIN	No	No	Alive	5
41	BWH	HGTIN	No	No	Alive	1
44	BWH	HGTIN	Yes	No	Alive	8
46	BWH	HGTIN	No	Yes - positive ascites cytology and elevated CA-125; 4 yrs after BSO	Alive	6
51	BWH	HGTIN	No	No	Lost to follow-up 2009	<1
53	FHCRC	HGTIN	NO	NO	Alive	3
49	UMICH	HGTIN	No	No	Alive	2
37	UMICH	HGTIN	No	No	Alive	2
53	FHCRC	HGTIN	No	No	Alive; last follow-up 2011	7
60	BWH	HGTIN	Yes	No	Alive	7
66	BWH	HGTIN	Yes (2 cycles)	No	Alive	8
Group II						
57	BWH	HGTIN and focal invasive tubal carcinoma	Yes	No	Expired 2010 (metastatic breast cancer)	2
57	FHCRC	HGTIN and invasive tubal carcinoma	Yes	No	Alive	6
67	FHCRC	HGTIN and invasive tubal carcinoma	Yes (3 cycles)	Yes – elevated CA-125; 5 yrs after BSO	Alive	6
60	FHCRC	HGTIN (2 foci) and metastatic carcinoma on ovarian surface	Yes	No	Alive	5
49	UMICH	HGTIN with associated invasive carcinoma and positive peritoneal cytology	Yes	No	Alive	<1
43	BWH	HGTIN and positive peritoneal cytology	Yes	No	Alive	8
48	BWH	HGTIN and metastatic carcinoma on ovarian surface, positive peritoneal cytology	Yes	No	Alive	4
56	BWH	HGTIN and metastatic carcinoma on ovarian surface	Yes	No	Alive	<1
56	BWH	HGTIN and metastatic carcinoma on ovarian surface	Yes	No	Alive	1
65	BWH	HGTIN and metastatic carcinoma on ovarian surface, positive peritoneal cytology	Yes	No	Lost to follow-up 2008	1
76	BWH	HGTIN with associated invasive carcinoma and Multiple serosal metastases, positive peritoneal cytology	Yes	Yes — elevated ca-125 and tissue diagnosis at 6 yrs.	Alive	8
49	BWH	Endometrioid adenocarcinoma (moderately differentiated) involving fallopian tube and metastatic carcinoma on ovarian surface	Yes	No	Alive	6
Group III						
73	BWH	Invasive serous carcinoma, involving fimbriae	Yes	Yes - elevated CA-125; 5 yrs after BSO	Alive	6
62	BWH	Endometrioid adenocarcinoma (grade 2/3), involving fimbriae	Yes (1 cycle)	No	Alive	8
50	FHCRC	Invasive carcinoma, bilateral fallopian tubes	Yes	No	Alive	6
74	FHCRC	Invasive tubal carcinoma	Yes (3 cycles)	No	Expired 2008 (pneumonia)	<1
46	BWH	Endometrioid adenocarcinoma (grade 3 of 3) involving ovarian surface and positive peritoneal cytology, abdominal wall nodule	Yes	No	Alive	5
51	BWH	High grade serous carcinoma, involving ovarian surface and positive peritoneal cytology	Yes	No	Alive	4

[a] Age at the time of prophylactic BSO.
[b] All chemotherapy patients received 6 courses unless otherwise stated.

References

[1] Cancer facts and figures. Atlanta, Georgia, USA: American Cancer Society; 2013.
[2] Carlson J, Roh MH, Chang MC, Crum CP. Recent advances in the understanding of the pathogenesis of serous carcinoma: the concept of low- and high-grade disease and the role of the fallopian tube. Diagn Histopathol 2008;14(8):352–65.
[3] Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. Am J Surg Pathol 2007;31(2):161–9.
[4] Finch A, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol 2006;100(1):58–64.
[5] Medeiros F, Muto MG, Lee Y, Elvin JA, Callahan MJ, Feltmate C, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol 2006;30(2):230–6.
[6] Rose PG, Shrigley R, Wiesner GL. Germline BRCA2 mutation in a patient with fallopian tube carcinoma: a case report. Gynecol Oncol 2000;77(2):319–20.
[7] Paley PJ, Swisher EM, Garcia RL, Agoff SN, Greer BE, Peters KL, et al. Occult cancer of the fallopian tube in BRCA-1 germline mutation carriers at prophylactic oophorectomy: a case for recommending hysterectomy at surgical prophylaxis. Gynecol Oncol 2001;80(2):176–80.
[8] Powell CB, Kenley E, Chen LM, Crawford B, McLennan J, Zaloudek C, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol 2005;23(1):127–32.
[9] Werness BA, Ramus SJ, Whittemore AS, Garlinghouse-Jones K, Oakley-Girvan I, Dicioccio RA, et al. Histopathology of familial ovarian tumors in women from families with and without germline BRCA1 mutations. Hum Pathol 2000;31(11):1420–4.
[10] Werness BA, Ramus SJ, DiCioccio RA, Whittemore AS, Garlinghouse-Jones K, Oakley-Girvan I, et al. Histopathology, FIGO stage, and BRCA mutation status of ovarian cancers from the Gilda Radner Familial Ovarian Cancer Registry. Int J Gynecol Pathol 2004;23(1):29–34.
[11] Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol 2007;211(1):26–35.
[12] Callahan MJ, Crum CP, Medeiros F, Kindelberger DW, Elvin JA, Garber JE, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol 2007;25(25):3985–90.
[13] Leeper K, Garcia R, Swisher E, Goff B, Greer B, Paley P. Pathologic findings in prophylactic oophorectomy specimens in high-risk women. Gynecol Oncol 2002;87(1):52–6.
[14] Mingels MJ, Roelofsen T, van der Laak JA, de Hullu JA, van Ham MA, Massuger LF, et al. Tubal epithelial lesions in salpingo-oophorectomy specimens of BRCA-mutation carriers and controls. Gynecol Oncol 2012;127(1):88–93.
[15] Manchanda R, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, Brunell C, et al. Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG 2011;118(7):814–24.
[16] Agoff SN, Garcia RL, Goff B, Swisher E. Follow-up of in situ and early-stage fallopian tube carcinoma in patients undergoing prophylactic surgery for proven or suspected BRCA-1 or BRCA-2 mutations. Am J Surg Pathol 2004;28(8):1112–4.

[17] Bijron JG, Seldenrijk CA, Zweemer RP, Lange JG, Verheijen RH, van Diest PJ. Fallopian tube intraluminal tumor spread from noninvasive precursor lesions: a novel metastatic route in early pelvic carcinogenesis. Am J Surg Pathol 2013;37(8):1123–30.
[18] Wethington SL, Park KJ, Soslow RA, Kauff ND, Brown CL, Dao F, et al. Clinical outcome of isolated serous tubal intraepithelial carcinomas (STIC). Int J Gynecol Cancer 2013;23(9):1603–11.
[19] Reitsma W, de Bock GH, Oosterwijk JC, Bart J, Hollema H, Mourits MJ. Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens. Eur J Cancer 2013;49(1):132–41.
[20] Liu J, Cristea MC, Frankel P, Neuhausen SL, Steele L, Engelstaedter V, et al. Clinical characteristics and outcomes of BRCA-associated ovarian cancer: genotype and survival. Cancer Genet 2012;205(1–2):34–41.
[21] Hyman DM, Zhou Q, Iasonos A, Grisham RN, Arnold AG, Phillips MF, et al. Improved survival for BRCA2-associated serous ovarian cancer compared with both BRCA-negative and BRCA1-associated serous ovarian cancer. Cancer 2012;118(15):3703–9.
[22] Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA 2006;296(2):185–92.
[23] Powell CB, Swisher EM, Cass I, McLennan J, Norquist B, Garcia RL, et al. Long term follow up of BRCA1 and BRCA2 mutation carriers with unsuspected neoplasia identified at risk reducing salpingo-oophorectomy. Gynecol Oncol 2013;129(2):364–71.
[24] Crum C, Herfs M, Ning G, Bijron J, Howitt B, Jimenez C, et al. Through the glass darkly: intraepithelial neoplasia, top-down differentiation and the road to ovarian cancer. J Pathol 2013;231:402–12.
[25] Piek JM, Torrenga B, Hermsen B, Verheijen RH, Zweemer RP, Gille JJ, et al. Histopathological characteristics of BRCA1- and BRCA2-associated intraperitoneal cancer: a clinic-based study. Fam Cancer 2003;2(2):73–8.