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Editorial

Risk reducing salpingo-oophorectomy for BRCA mutation carriers: Twenty years later

It has been twenty years since the region of the BRCA1 mutation was identified on chromosome 17q. There are now over 3000 risk reducing salpingo-oophorectomy (RRSO) cases reported and an estimated 150 cases describing unsuspected cancers of the ovaries and tubes or in situ lesions. Connor et al. in their current study add to the literature on RRSO outcomes [1]. They report on 345 cases of RRSO in BRCA mutation carriers from a single institution, finding a HGTIN/cancer rate of 5.4%, 9.2% in BRCA1 and 3.4% in BRCA2. Mean age of neoplasia was 54.4 years which was higher than those without neoplasia (47.8 years). The authors then present 29 cases collected from 3 institutions of HGTIN/cancer followed for a median of 5 years. 1/11 HGTIN recurred and 3/18 invasive cancers recurred (17%).

What have we learned about RRSO in these 2 decades since the identification of BRCA1 mutations? The rate of unsuspected neoplasia at RRSO of 5.4% in Connor's study, is consistent with other reports from Finch et al. of 4.4%, Manchanda et al. of 5.1%, Mingels et al. of 7.1% and Powell et al. of 7.9% [2–5]. Unsuspected lesions are more likely to be detected in BRCA1 mutation carriers as compared with BRCA2, when rigorous microsectioning protocols are used for processing ovaries and tubes and at increasing age at the time of RRSO (as shown so clearly in Connor's figure 2).

Pooling 9 studies, and 2035 RRSO describing STIC[1], there are 62 independent reports of STIC without concomitant invasion or ovarian involvement, an overall rate of 3.0% (Table 1a). Connor adds a third case to the reports of Manchanda and Powell of recurrence or peritoneal primary after a finding of STIC at RRSO, all three associated with BRCA1 [1,3,6]. RRSO and recurrences occurred respectively at age 44 and 6 years later, age 49 and 3.5 yrs later and at age 46 with recurrence 4 years later. Cytology was performed in 2 of the 3 and was negative. Are the 3 reports of peritoneal primary after STIC different from the baseline rate of 1–4% peritoneal primary after RRSO? This low incidence and the 100% overall survival in Connor and Powell's reports supports not adding adjuvant chemotherapy when STIC is discovered.

Performing cytology at RRSO may be helpful as positive cytology may increase the index of suspicion for an occult lesion and will upstage an early invasive cancer. Some have advocated for adjuvant chemotherapy if STIC is associated with positive cytology. Data is extremely limited (10 cases,) with about half receiving chemotherapy and half not. No recurrences have been reported when positive cytology is associated with only STIC [7].

Initially we performed routine omental and peritoneal biopsies at the time of RRSO. However no case of random omental biopsy or peritoneal biopsy was positive so the practice was abandoned. No case of only STIC has been reported with a positive staging finding outside of cytology. It is therefore reasonable to conclude that staging is not necessary for cases of only STIC and negative cytology. With STIC and positive cytology, attention should be directed to rule out invasion in the tube or adjacent ovary but formal staging is unlikely to have yield. As most invasive lesions are not visible at surgery, formal staging for unsuspected invasive lesions at a second surgery seems more appropriate than random biopsies.

Pooling 13 reports of 3030 RRSOs, there are 82 invasive cancers, a rate of 2.7% (Table 1b). The majority of invasive cancers are BRCA1 related (78%). Connor's finding of 74% tubal involvement is consistent with the 70% from pooled data.

Mean age of Connor's HGTIN associated with invasion or other sites of disease was 57.7 years and occurred 8.5 years after the age of HGTIN lesions. It is tempting to postulate that the time for progression of HGTIN lesions might therefore be in the order of 8 years. Our study ironically showed that invasive lesions occurred younger than preinvasive lesions, which makes no intuitive sense and suggests that data may be limited by the small numbers. Indeed in reviewing the cases in the 9 studies reporting 52 cases of STIC with age documented, the median age is 50 years (49 for BRCA1 and 53.5 for BRCA2). The median age for invasive cancer from the pooled studies is 51 years (49.5 for BRCA1 and 54.5 for BRCA2).

The second contribution of Connor's study is the report of 5 year follow up of those patients with unexpected neoplasia at RRSO. This report complements our recent study describing long term clinical outcomes after RRSO with 7 year follow up. We can now be confident that STIC is associated with a favorable prognosis. Connor also reports 3 of 18 invasive cancer recurrences. This 17% is lower than Powell's 47% [7,15]. Both studies have small numbers contributing to the wide range. One patient in Powell's series also recurred at 83 months, so recurrence rate will likely increase with longer follow up. Median time to recurrence was 34 months pooling both studies. Powell's overall disease specific survival at a median follow up of 80 months was relatively favorable at 80%, with a disease free survival of 66%. While 40% of Powell's invasive cases were stage 2 or greater, 60% of Connor's were Stage 2 or greater. It is concerning that both studies show a high stage at diagnosis of unexpected cancers at RRSO. If comprehensive staging including nodes was performed in all cases, the stage might be shifted even more. As the cancers are found with increasing age, this suggests that we need to offer older women RRSO sooner.

The reports of RRSO cases collected over the past twenty years have contributed significantly to our understanding of the pathogenesis of

[1] STIC and HGTIN (serous tubal intraepithelial carcinoma and high grade serous tubal intraepithelial neoplasia are used to describe essentially the same histology by different authors.

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Table 1a
Isolated STIC lesions reported in BRCA mutation carriers.

Author	Total N	STIC N	BRCA1	BRCA2	Cytology positive	Treatment	F/u (mths)
Connor [1]	345	7	5	2	1	3	58
Powell [2]	407	17	13	4	3	4	80
Mingels [4]	226	14	9	5	Uk[a]	Uk	
Reitsma [8]	303	2	0	2	0	Uk	17
Wethington [9]	396	10	6	4	1	0	24.1
Manchanda [3]	118	7	5	2	1	0	41.3
Carcangiu [10]	50	3	3	0	0	0	44
Finch [11]	159	1	1	0	0	Uk	Uk
Colgan [12]	31	1	1	0	1	Uk	12
Total	2035	62 (3.0%)	43/62 (69%)	19/62 (31%)	7/51 (14%)	7/48 (15%)	
Median age		50	49	53.5			

Earlier studies from the same institution are not included.
5 HGTIN cases from outside institutions in Connor's report are not included as the total number of RRSOs from those institutions is not known.
[a] Uk = unknown.

Table 1b
Invasive lesions at RRSO in BRCA mutation carriers.

Author	Total	Invasive N	BRCA1	BRCA2	Recurrences (mths)	Stage of recurrences
Connor [1]	345[a]	13	10	3	60, 60, 72	Uk, 1a, 3b
Powell [6]	407	15	13	2	34, 29, 83, 17,31, 47, 25	2c, 2c, 1a, 1c, 3c, 1a, 1a
Schmeler [16]	65	1	Uk			
Domchek [18]	647	16	12	4		
Finch [2]	490	10	8	2		
Finch [11]	159	6	5	1	48	1a
Laki [17]	89	4	3	1	48	3c
Olivier [14]	65	5	5		20, 11	3b, Uk
Manchanda [7]	117	4	2	2		
Mingels [4]	226	2		2		
Reitma [8]	303	4	4		66	2c
Meeuwissen [15]	86	1	1			
Deligdisch [13]	31	1	1			
Total	3030	82 (2.7%)	64/82 (78%)	17/82 (21%)		
Median age		51.0	49.5	54.5		

[a] Total RRSO was only given from Brigham Women's Hospital, recurrences include 1 from another institution.

serous pelvic cancers and the potential origin in the fallopian tube in many of these cases. We can counsel our patients more effectively based on these collective reports. But at the start of a new year, we also wonder what our focus should be for women with BRCA mutations undergoing RRSO. Questions remain. Lacking the evidence to determine a right answer but showing an "all in" editorial spirit, I have committed to my opinions in parenthesis: Should women also have hysterectomy at RRSO? (*For other reasons but not BRCA risk reduction*). Should hysterectomy be performed for STIC (*if multifocal/involving isthmus*). Should STIC with positive cytology be staged or treated with chemotherapy? (*One or the other, not both, maybe just observation*). Should invasive cancers be treated with chemotherapy? (*In general yes as recurrences occur after the small Stage 1a cancers.*) What should surveillance be after RRSO? (*No routine CA 125 as risk of recurrence is so low, but follow CA 125 after untreated positive cytology*). Several areas bear attention for future research: Why are women having RRSOs so late? While we can debate whether RRSO can be delayed from the recommended under age 40 and at what cost to breast cancer risk, the majority of women are significantly older than the recommended age of 40. Many women are well over age 50 and 60. The oldest patient with an unexpected invasive cancer at RRSO was 78! We must encourage RRSO earlier than this if we wish to prevent cancer. Since most women are choosing RRSO quickly after receiving their positive test results the question is really: Can we diagnose BRCA earlier so that younger women can consider options of oral contraception, salpingectomy followed by oophorectomy and choose their preferred and reasonable timing of oophorectomy. How can we strategize to improve the identification of women at hereditary risk of ovarian cancer? Only 20% of women with ovarian cancer are currently referred in community settings for genetic counseling [19]. Improved referral of these women and others who clearly meet guidelines, would translate directly into the number of young women relatives without cancer, who know their risk status. What can we offer the 30% of women who decline salpingo-oophorectomy, what screening strategies can be offered to detect ovarian cancer? How effective in risk reduction is salpingectomy? We still have a limited understanding of noncancer outcomes and the health risks of premature menopause and the safety of hormonal replacement that women experience after RRSO. What health surveillance should these women do for bone and heart health? This is the work that still needs to be accomplished and where the improvements in our RRSO outcomes now lie.

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