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Serous tubal intraepithelial carcinoma (STIC) outcomes in an average risk population

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A B S T R A C T

Objective: Serous tubal intraepithelial carcinoma (STIC) are precursors for high grade serous carcinomas (HGSC) of tubo-ovarian origin. It is a rare entity, most commonly described in patients with a *BRCA* pathogenic variant (PV) undergoing risk-reducing surgery. Little is known about the risk of subsequent HGSC in patients found to have an isolated STIC without a genetic PV. The objective of this study is to report the outcomes of STIC diagnosed in patients with negative genetic testing ("average risk").

Methods: Retrospective population-based cohort study from British Columbia, Canada. Chart review of patients diagnosed with an isolated STIC from January 2012 to May 2022. Average risk patients are defined as individuals with known negative genetic testing results. Treatment and outcomes are described in the "average risk", *BRCA* PV, and total cohorts.

Results: Twenty-nine patients with isolated STIC were identified. Ten patients had a *BRCA* PV, four had other variants identified (*BRIP1*, *MLH1*, *BRIP1 VUS*, *BRCA 2 VUS)*, nine had no PV identified ("average risk"), and six were unknown (no genetic testing). Of the nine "average risk" patients, eight (89%) underwent surgical staging. Three (33.3%) had subsequent HGSC diagnosed 29, 70 and 86 months after STIC diagnosis.

Conclusions: STIC identified in patients with negative genetic testing are at risk of subsequent HGSC. Patients developed primary peritoneal HGSC despite surgical staging. These patients should also be included in future *meta*-analysis to determine outcomes and optimal treatment.

1. Introduction

High grade serous carcinoma (HGSC) is the most common form of ovarian cancer, accounting for 70–80% of cases (Bray et al., 2018). It often presents at advanced stages, and is associated with high mortality rates (Bray et al., 2018). Those at highest risk of HGSC are individuals with germline pathogenic variants (PV) in *BRCA* 1 or 2 (Kuchenbaecker et al., 2017). As there is still no effective screening test for this cancer, these individuals are advised to undergo risk-reducing bilateral salpingo-oophorectomy ("risk-reducing surgery") to reduce their risk of HGSC. Close pathological examination of risk-reducing specimens using the SEE-FIM (Sectioning and Extensively Examining the FIMbriated end) protocol identified serous tubal intraepithelial carcinoma (STIC) in the fallopian tubes (Singh et al., 2016). Investigation into STIC has identified it as the immediate precursor to HGSC (Bogaerts et al., 2021; Singh et al., 2016). This has provided evidence over the last decade supporting tubal origin of HGSC (Bogaerts et al., 2021; Reade et al., 2014; Gilks et al., 2015; Singh et al., 2017).

Isolated STIC are rare lesions, with a prevalence rate of 3.5–5.6% in patients with *BRCA* PV undergoing risk-reducing surgery (Wethington et al., 2013). The prevalence and outcomes of STIC in patients without an underlying *BRCA* PV is unknown. Samimi and colleagues reported an incidence of < 0.01 % in a population who underwent surgery for benign indications (Samimi et al., 2018). "Opportunistic salpingectomy" is now recommended for average-risk women to reduce their risk of ovarian cancer (Hanley et al., 2022). This has led to an increased removal of fallopian tube specimens in average-risk patients (Mandelbaum et al., 2020). With more fallopian tubes being assessed pathologically, combined with a better understanding of STIC diagnostic criteria, this may lead to more patients being diagnosed with STIC who do not have a *BRCA* PV.

The primary objective of this study is to report the outcomes of STIC diagnosed in patients with negative genetic testing ("average risk"). The secondary objective is to report the outcomes of a population-based cohort of patients with a STIC diagnosis.

2. Methods

This is a retrospective population-based cohort study of patients diagnosed with STIC in British Columbia (BC), Canada. Patients were

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identified through a keyword search of "STIC" or "serous tubal intraepithelial carcinoma" in an electronic pathology database which includes cases from British Columbia which are reviewed by expert gynecologic pathologists at Vancouver General Hospital and BC Cancer. The identified cases were then reviewed and excluded from this study if they had a concurrent high grade serous carcinoma. A chart review was performed for patient demographic information, genetic testing results, STIC diagnostic criteria, treatment, and outcomes. "Average risk" patients were defined as those with known negative genetic testing. A "high risk" cohort was defined as patients with *BRCA* 1 or 2 PV. An "other" cohort included the remaining patients with non-*BRCA* PV, variants of unknown significance (VUS), and no genetic testing results available. Data cut off for follow up was April 22, 2023. Data was analyzed using descriptive statistics for the total, average risk, *BRCA* PV, and other cohorts. To calculate estimated prevalence of STIC, a keyword search for "fallopian tube" was performed in the same database to provide a denominator. Ethics approval was obtained by the University of British Columbia Research Ethics Board (H19-03611).

3. Results

From January 1, 2012 to May 1, 2022, 22,558 patients underwent salpingectomy in British Columbia. In those patients, 196 were identified through the keyword search of "STIC" or "serous tubal intraepithelial carcinoma". Of those, 167 (85.2%) were excluded for diagnosis of concurrent HGSC. The remaining 29 patients were included in this study. SEE-FIM was performed in 58.6% of specimens (Table 1*)*. One STIC was diagnosed retrospectively on review of previously sectioned pathology specimens at the time of presentation of primary peritoneal HGSC. The estimated prevalence of isolated STIC in patients undergoing salpingectomy over a 10 year period in British Columbia was 0.1%.

In the overall cohort, the mean age of diagnosis was 58.3 years (+/-11.6). Median follow up was 56.9 months (7–103 months). The main indications for surgery were for benign gynecological conditions (48.3%, n = 14) such as pelvic organ prolapse, fibroids, abnormal uterine bleeding, benign ovarian cysts, contraception, and opportunistic salpingectomy (Table 1*)*. Nine patients (31%) underwent risk-reducing bilateral salpingo-oophorectomy for a known *BRCA* PV. The remaining six patients (20.7%) underwent surgery for other malignancy (five low grade endometrial cancer and one advanced high grade bladder primary). Prior to primary surgery, nine patients (31%) were known to have *BRCA* PV and 20 patients (69%) had unknown genetic status. After primary surgery and STIC diagnosis, 14 additional patients underwent genetic testing. Genetic testing was available for a total of 23 patients (79%) (Table 1*)*. There were ten patients who had a *BRCA* PV. There were nine patients who had no abnormality and were deemed the "average risk" cohort. Of note, one patient with no abnormality initially tested for a *BRCA 1 VUS*, however on routine re-examination by the genetic testing program, was deemed a benign variant in 2019. There were two patients with non-*BRCA* PV (*BRIP1*, *MLH1*), another two with variants of unknown significance (*BRCA 2 VUS, BRIP1 VUS*), and 6 patients who did not have any genetic testing. These 10 patients were classified as the "other" cohort. Surgical staging was the most common management for STIC (n = 22, 75.9%) (Table 1*)*. Two surgically staged patients had abnormalities at staging (atypical cells on cytology; 2 mm focus of HGSC) and received adjuvant chemotherapy. Five patients (17%) developed subsequent primary peritoneal HGSC after STIC diagnosis.

In the "average risk" cohort (n = 9), the mean age at diagnosis was 57.7 (+/-12.5) years. The median follow up was 43.4 months (11–90 months) (Table 1*)*. The main indication for primary surgery was for benign gynecologic conditions for seven patients (78%), and two (22%) had low grade endometrial cancer. Eight (89%) underwent surgical staging as STIC treatment, and one (11%) had surveillance. Three (33%) developed primary peritoneal HGSC (Table 2*)*.

Table 1
Cohort demographics and outcomes by total, *BRCA* pathogenic variant, average risk and other cohorts. *BSO – bilateral salpingo-oophorectomy, USO – unilateral salping-oophorectomy, BS – bilateral salpingectomy, VUS – variant of unknown significance, SEEFIM – sectioning and extensively examining the fimbriated end.*

Demographic	Total (n = 29)	*BRCA* pathogenic variant (n = 10)	"Average risk" (n = 9)	Other (n = 10)
Age (mean) years (+/- SD)	58.3 (+/-11.6)	57 (+/- 6.6)	57.7 (+/-12.5)	60.3 (+/-15.1)
Follow up (median) months (range)	56.9 (7–103)	73 (42–98)	43.4 (11–90)	52.9 (7–103)
Menopausal status				
Pre	11	3	5	3
Post	18	7	4	7
Indications for primary surgery				
Benign	14	1	7	6
Other Malignancy	6	0	2	4
Risk reducing BSO	9	9	0	0
Type of primary surgery				
BSO	12	9	2	1
Hysterectomy and BSO	8	1	3	4
Hysterectomy, BS	5	0	3	2
BS	2	0	1	1
BS, USO	1	0	0	1
USO	1	0	0	1
Genetic Testing				
No	6	0	0	6
Yes	23	10	9	4
BRCA 1	*6*	*6*	0	0
BRCA 2	*4*	*4*	0	0
BRIP1	*1*	0	0	*1*
MLH1	*1*	0	0	*1*
BRCA 1 VUS subsequent negative	*1*	0	*1*	0
BRCA 2 VUS	*1*	0	0	*1*
BRIP1 VUS	*1*	0	0	*1*
No abnormality	*8*	0	*8*	0
Unknown	*6*	0	0	*6*
Pathology				
SEEFIM	17	7	5	5
Sections	11	2	4	5
Retrospective review of previous section	1	1	0	0
Treatment of STIC				
Surgery	20	7	8	5
Surgery then chemotherapy	2	1	0	1
Chemotherapy	0	0	0	0
Surveillance	5	2	2	3
Treatment for primary malignancy	2	0	0	2

The first patient had a remote history of breast cancer 15 years prior and initially was found to have a *BRCA 1 VUS* on genetic testing. She underwent routine review by the genetic screening program in 2019 and the *VUS* was reclassified as a benign variant. Her indication for primary surgery was for pelvic organ prolapse and uterine fibroids, for which she had a total abdominal hysterectomy and bilateral salpingo-oophorectomy. STIC was diagnosed with SEE-FIM protocol. She did not have any further treatment after that initial surgery (therefore surveillance alone). She developed primary peritoneal HGSC 86 months after STIC diagnosis.

The second patient had a total laparoscopic hysterectomy, bilateral salpingo-oophorectomy for a Stage 1A Grade 1 endometroid endometrial cancer. STIC was diagnosed with pathological sections. STIC

Table 2
"Average risk" patients (negative genetic testing) outcomes, organized by duration of follow up. Hyst – hysterectomy, BSO - bilateral salpingo-oophorectomy, BS - bilateral salpingectomy.

Patient	Indication for Primary Surgery	Age at Primary Surgery (Yrs)	Type of primary surgery	Genetic Testing results	Treatment of STIC	Subsequent primary peritoneal HGSC	Time to subsequent HGSC (months)	Length of follow up (months)
1	Pelvic organ prolapse, fibroid	78	Hyst, BSO	BRCA 1 VUS, subsequently negative	Surveillance	Yes	86	90
2	Low grade endometrial cancer	68	Hyst, BSO	Negative	Surgery	Yes	70	72
3	Pelvic organ prolapse, opportunistic salpingectomy *Note: low grade endometrial cancer on final pathology*	56	Hyst, BS, prolapse repair	Negative	Surgery	No	n/a	62
4	Pelvic organ prolapse, opportunistic salpingectomy	49	Hyst, BS, prolapse repair	Negative	Surgery	Yes	29	52
5	Benign ovarian cyst	65	BSO	Negative	Surgery	No	n/a	51
6	Abnormal uterine bleeding, fibroids, opportunistic salpingectomy	50	Hyst, BS	Negative	Surgery	No	n/a	26
7	Benign ovarian cyst	67	BSO	Negative	Surgery	No	n/a	15
8	Contraception	39	BS	Negative	Surgery	No	n/a	12
9	Low grade endometrial cancer	47	Hyst, BSO	Negative	Surgery	No	n/a	11

management included genetic testing (negative), and staging surgery (laparoscopic omentectomy and washings). She developed primary peritoneal HGSC 70 months afterwards.

The third patient had a total vaginal hysterectomy, bilateral salpingectomy, and prolapse repair for pelvic organ prolapse and opportunistic salpingectomy. STIC was diagnosed with SEE-FIM protocol. STIC management included genetic testing (negative), and staging surgery (laparoscopic omentectomy, bilateral oophorectomy, and washings). She was diagnosed with primary peritoneal HGSC 29 months after STIC diagnosis.

In the *BRCA* PV cohort (n = 10), the mean age at diagnosis was 57 (+/- 6.6) years. The median follow up was 73 months (range 42–98) (Table 1). Nine patients were known to have a *BRCA* PV prior to their initial surgery and underwent risk-reducing salpingo-oophorectomy. Of these, one patient (11%) developed primary peritoneal HGSC 80 months after primary surgery. This patient had a germline *BRCA* 1 PV and underwent risk reducing surgery at age 59. There were no intraoperative abnormalities and pelvic washings were negative. STIC was diagnosed with SEE-FIM protocol. STIC was managed with staging surgery (laparoscopic hysterectomy, omentectomy, and washings).

The remaining patient in the *BRCA* PV cohort had primary surgery (total laparoscopic hysterectomy, bilateral salpingo-oophorectomy) at age 57 for fibroids and post-menopausal bleeding. The fallopian tubes were examined with pathological sections, and the results were benign. Eighteen months later, she presented with advanced primary peritoneal high grade serous carcinoma, and genetic testing at this time revealed a *BRCA* 1 PV. Retrospective pathology review of her salpingectomy specimens revealed an isolated STIC.

For the "other" cohort, the median age at diagnosis was 60.3 (+/- 15.1) years. The median follow up was 52.9 months (7–103 months) (Table 1). There were no cases of primary peritoneal HGSC.

4. Discussion

STIC are rare, and the infrequency of these lesions make them challenging to study, with most studies representing small numbers, or *meta*-analyses of small cohorts (Chong et al., 2020; Ruel-Laliberté et al., 2022). This study represents the largest single cohort in the literature of outcomes in patients diagnosed with an isolated STIC in an "average risk" (negative genetic testing) population.

The frequency of STIC in an "average-risk" population is unknown. In our study, the estimated prevalence of STIC in salpingectomy specimens was approximately 0.1%. Several limitations exist in our calculation of the estimated prevalence. Firstly, the use of SEE-FIM (Sectioning and extensively examining the fimbriated end) protocol was not universally conducted. This may have led to under identification of STIC, or in patients with STIC an under identification of concurrent HGSC. In four of five patients with subsequent primary peritoneal HGSC, it is unlikely a concurrent HGSC was missed as the interval after STIC diagnosis was between 29 and 86 months. The remaining case had only an 18 month interval between STIC and HGSC diagnosis. In that case, the STIC was diagnosed on retrospective review of salpingectomy specimens at the time of primary peritoneal HGSC diagnosis. It is plausible that a HGSC could have been missed at the time of primary surgery. Secondly, the indication for salpingectomy (the denominator in our calculation) did not exclude surgeries for known ovarian cancers and patients with *BRCA* PV. Nonetheless, the rarity of isolated STIC with negative genetic testing is confirmed with only nine cases over a 10 year period.

Three of nine (33%) in the "average-risk" cohort developed primary peritoneal HGSC at 29, 70, and 86 months after STIC diagnosis. This is similar to the 43 to 75 month interval between STIC and HGSC in the literature for patients with a *BRCA* PV undergoing risk-reducing surgery (Wethington et al., 2013; Stanciu et al., 2019). Although this is a small sample size, this finding demonstrates that patients with an isolated STIC lesion are at risk of subsequent primary peritoneal HGSC even if the absence of a *BRCA* PV. The remaining six patients in the "average risk" cohort are only 11 to 62 months from STIC diagnosis, and additional diagnoses of primary peritoneal HGSC may be yet to come. In contrast, of the 10 patients in the "other" cohort (*BRIP1*, *MLH1*, *BRCA 2 VUS, BRIP1 VUS*, and six without genetic testing), there have been no diagnoses of peritoneal HGSC after 7–103 months. However, the majority have been followed less than five years, and it remains to be seen if any of these patients will develop HGSC.

The majority of the patients in this study had genetic testing and surgical staging (typically omentectomy, washings, and completion oophorectomy and/or hysterectomy) following the diagnosis of STIC. Despite this surgical staging, patients subsequently developed HGSC. It is difficult to study the optimal management of STIC given the low

incidence, and there is no consensus on preferred treatment in the literature. Future international collaborative efforts are necessary to identify effective treatments that can reduce the risk of subsequent HGSC.

As we better understand the significant clinical implications of STIC, identification of these lesions becomes increasingly important. Future work should focus on techniques that may better identify this rare precursor. The frequency of finding a STIC is dependent on how meticulously the fallopian tube is sectioned, but SEE-FIM protocol is not routinely performed in average-risk specimens (Samimi et al., 2018). Simple tests such as p53 immunohistochemistry as a screening tool are also unrealistic given P53 signature are extremely common in the fallopian tubes even in patients with benign disease (Folkins et al., 2008). As demonstrated in our study, isolated STIC are often found at the time of benign or non-risk reducing gynecologic surgery that, in our setting, are commonly done at non-tertiary centres. Therefore it is important for ongoing knowledge translation with pathologists to maximize the identification of STIC. Scientific and knowledge translation work with general gynecologists will be important to ensure appropriate referral to genetic counselling and centralized cancer centres for up-to-date treatment recommendations for this rare, but significant, precursor lesion.

5. Conclusions

This study represents a large cohort of patients diagnosed with an isolated STIC, and the largest cohort in the literature of patients with "average risk". This sample demonstrates that patients with negative genetic testing are at risk of subsequent primary peritoneal HGSC. The importance of genetic testing is highlighted after a STIC diagnosis, not only for the identification of *BRCA* PV, but also other high-risk variants. In this cohort, surgical staging was the most common management method, and despite this, patients were still at risk of subsequent HGSC. Effective treatment of STIC has not yet been identified.

CRediT authorship contribution statement

Kimberly T. Stewart: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Lien Hoang:** Data curation, Writing – review & editing, Supervision. **Janice S. Kwon:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Bogaerts, J., Steenbeek, M.P., van Bommel, M.H., Bulten, J., van der Laak, J.A., de Hullu, J.A., et al., 2021. Recommendations for diagnosing STIC: a systematic review and meta-analysis. Virchows Arch. 1–13.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68 (6), 394–424.

Chong, G.O., Park, J.Y., Lee, H.J., 2020. Incidental Serous Tubal Intraepithelial Carcinoma that Developed into Primary Peritoneal Serous Carcinoma in a Patient without BRCA Mutation. Am J Case Rep. 21, e921146–e921151.

Folkins, A.K., Jarboe, E.A., Saleemuddin, A., Lee, Y., Callahan, M.J., Drapkin, R., et al., 2008. A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. Gynecol Oncol. 109 (2), 168–173.

Gilks, C.B., Irving, J., Köbel, M., Lee, C., Singh, N., Wilkinson, N., et al., 2015. Incidental nonuterine high-grade serous carcinomas arise in the fallopian tube in most cases: further evidence for the tubal origin of high-grade serous carcinomas. Am J Surg Pathol. 39 (3), 357–364.

Hanley, G.E., Pearce, C.L., Talhouk, A., Kwon, J.S., Finlayson, S.J., McAlpine, J.N., et al., 2022. Outcomes From opportunistic salpingectomy for ovarian cancer prevention. JAMA Netw Open. 5 (2), e2147343–e.

Kuchenbaecker, K.B., Hopper, J.L., Barnes, D.R., Phillips, K.A., Mooij, T.M., Roos-Blom, M.J., et al., 2017. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. Jama. 317 (23), 2402–2416.

Mandelbaum, R.S., Adams, C.L., Yoshihara, K., Nusbaum, D.J., Matsuzaki, S., Matsushima, K., et al., 2020. The rapid adoption of opportunistic salpingectomy at the time of hysterectomy for benign gynecologic disease in the United States. Am J Obstet Gynecol. 223 (5), 721.e1–721.e18.

Reade, C.J., McVey, R.M., Tone, A.A., Finlayson, S.J., McAlpine, J.N., Fung-Kee-Fung, M., et al., 2014. The fallopian tube as the origin of high grade serous ovarian cancer: review of a paradigm shift. J Obstet Gynaecol Can. 36 (2), 133–140.

Ruel-Laliberté, J., Kasasni, S.M., Oprea, D., Viau, M., 2022. Outcome and Management of Serous Tubal Intraepithelial Carcinoma Following Opportunistic Salpingectomy: Systematic Review and Meta-Analysis. J Obstet Gynaecol Can. 44 (11), 1174–1180.

Samimi, G., Trabert, B., Duggan, M.A., Robinson, J.L., Coa, K.I., Waibel, E., et al., 2018. Processing of fallopian tube, ovary, and endometrial surgical pathology specimens: A survey of U.S. laboratory practices. Gynecol Oncol. 148 (3), 515–520.

Singh, N., Gilks, C.B., Hirschowitz, L., Kehoe, S., McNeish, I.A., Miller, D., et al., 2016. Primary site assignment in tubo-ovarian high-grade serous carcinoma: Consensus statement on unifying practice worldwide. Gynecol Oncol. 141 (2), 195–198.

Singh, N., McCluggage, W.G., Gilks, C.B., 2017. High-grade serous carcinoma of tubo-ovarian origin: recent developments. Histopathology. 71 (3), 339–356.

Stanciu, P., Ind, T., Barton, D., Butler, J., Vroobel, K., Attygalle, A., et al., 2019. Development of peritoneal carcinoma in women diagnosed with serous tubal intraepithelial carcinoma (STIC) following risk-reducing salpingo-oophorectomy (RRSO). J Ovarian Res. 12 (1), 1–6.

Wethington, S.L., Park, K.J., Soslow, R.A., Kauff, N.D., Brown, C.L., Dao, F., et al., 2013. Clinical outcome of isolated serous tubal intraepithelial carcinomas (STIC). Int J Gynecol Cancer. 23 (9).