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Clinical outcomes following identification of an incidental p53 signature in the fallopian tube

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ABSTRACT

Fallopian tube pathology in patients with *BRCA1* and *BRCA2* mutations suggests a possible pathway to high grade serous ovarian carcinoma originates with a p53 signature, which is thought to represent a potential precursor to serous tubal intraepithelial carcinoma (STIC). The clinical implications of an isolated p53 signature in the average-risk population has not been well-established. This study aims to describe clinical outcomes in patients with incidentally noted p53 signature lesions.

All patients diagnosed with a p53 signature lesion on final pathology from 2014 to 2022 were identified at a large academic institution. P53 signature is defined by our lab as morphologically normal to mildly atypical tubal epithelium with focal p53 over-expression on immunohistochemistry. Incidental p53 signature was defined as identification of a fallopian tube lesion excised for benign or unrelated indications in patients without a known hereditary disposition. Demographic, clinicopathologic, and genetic data were collected.

A total of 127 patients with p53 signatures were identified. Thirty-six patients were excluded for established ovarian cancer or high-risk history leaving 91 total patients. Five patients (5.5%) developed a malignancy, none of which were ovarian or primary peritoneal, at the end of the eight and a half year follow up period. Twenty-four (26.4%) patients had salpingectomy without any form of oophorectomy at the time of initial surgery, while 67 (73.6%) patients had at least a unilateral oophorectomy at the time of their salpingectomy. Seven patients (7.7%) had additional surgery after p53 signature diagnosis; however, the final pathology yielded no evidence of malignancy in all these patients. After subsequent surgeries, 19 (20.9%) patients maintained their ovaries. The diagnosis of an incidental p53 signature was not associated with any primary peritoneal or ovarian cancer diagnoses during our follow up, and the majority of patients were managed conservatively by their providers with no further intervention after diagnosis.

1. Introduction

Ovarian high grade serous carcinoma has a relatively poor prognosis, with a 5-year survival rate of approximately 49 % (Ovarian Cancer — Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/ovary.html. Accessed January 25, 2022). As a result, investigation into screening and earlier identification has been expansive. Examination of the fallopian tubes in patients with pathogenic *BRCA* mutations and a known predisposition for ovarian high grade serous carcinoma has yielded potential precursor lesions, notably serous tubal intraepithelial carcinoma (STIC) lesions. (Folkins et al., 2008; Lim and Oliva, 2013; Soong et al., 2019) The p53 signature has been proposed to be a putative precursor to STIC lesions based on current step-wise paradigm of pathogenesisWu et al., 2020 (The Role of the Fallopian Tube in Ovarian Cancer – Hematology Oncology. https://www.hematologyandoncology.net/archives/may-, 2022). The hypothesis lies in the epithelium of the fimbriated end of the fallopian tube, where injury to the secretory fallopian tube leads to DNA damage, cell cycle arrest and ultimately mutations in *TP53* (The Role of the Fallopian Tube in Ovarian Cancer, 2022). This lesion, noted during histologic evaluation of the fallopian tube, shows aberrant p53 immunohistochemical expression, and is called the p53 signature (Lee et al., 2007; Nakamura et al., 2019). This well-established stepwise paradigm in carcinogenesis for high risk BRCA1 and BRCA2 patients led to development of the SEE-FIM protocol

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for fimbria evaluation, specifically designed to better identify precursor lesions (Medeiros et al., 2006).

While p53 signatures have been studied in patients with *BRCA1* and *BRCA2* pathogenic variants, the implications of a p53 signature in the fallopian tube in the average-risk population has not been established. This is particularly important as p53 signatures are not obligate precursors and may not share the same *TP53* mutations as concurrent STIC lesions or high-grade serous carcinomas (Soong et al., 2018; Hatano et al., 2018). Recommendations for the management of an incidentally identified STIC lesion are vague. The National Comprehensive Cancer Network (NCCN) recommends referral to a gynecologic oncologist and genetics evaluation if not previously performed with unclear recommendations for additional treatment and surveillance (Armstrong et al., 2021). No guidelines exist for management of incidental p53 signature. Due to concern for a similar possible premalignant potential, providers may likewise be compelled to pursue further workup, given the dearth of guiding information available. This poses a dilemma when patients without a known hereditary predisposition to ovarian cancer are found to have an incidental p53 signature.

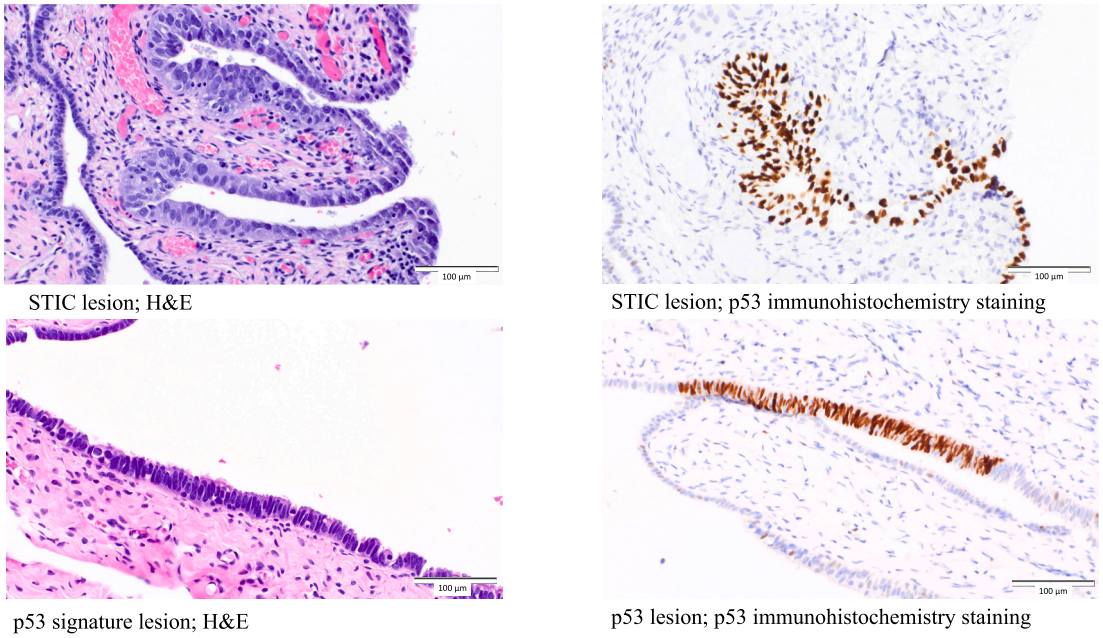
The aim of this study is to describe our institutional experience with incidental p53 signature lesions as well as the outcomes of patients found to have this pathology over our modest follow up period to add to the literature regarding this uncommon diagnosis.

2. Materials and Methods

Following IRB approval, all patients diagnosed with a p53 signature lesion on pathology from 2014 − 2022 were identified at a single large academic institution. A p53 signature was defined as 12 or more consecutive tubal epithelial cells with aberrant p53 immunohistochemical expression (demonstrated in Fig. 1). Typically, p53 signatures are morphologically indistinguishable from normal tubal epithelium and therefore can only be detected by p53 immunostaining. Immunostaining for p53 is routinely performed by our pathology department when standard evaluation reveals nuclear atypia, loss of polarity, presence of mitoses, loss of normal tubal differentiation, and/or elevated Ki67 index from background epithelium. Incidental p53 signature was defined as a lesion identified in a specimen removed during surgery performed for benign indications or indications unrelated to ovarian carcinoma. Patients undergoing risk-reducing surgery for any known hereditary predisposition (which in this population included *BRCA1* and *BRCA2*) were excluded. All patients incidentally found to have an occult ovarian or fallopian tube malignancy were excluded. Finally, patients found to have both an incidental p53 and STIC lesion were excluded from this analysis. Demographic and clinicopathologic data were collected for each patient from the electronic medical record.

3. Results

We identified 13,936 total patients who underwent salpingectomy at our institution from 2014 to 2022. Of these, 127 patients (0.9 %) with a p53 signature lesion were identified. After excluding those with concurrent ovarian malignancy, a concurrent STIC lesion, and/or hereditary predisposition for ovarian cancer, there were 91 patients (0.6 %) with an incidental p53 signature (Fig. 2). Demographic information for this cohort is available in Table 1. Indications for surgery included pelvic organ prolapse (N = 15), adnexal mass (N = 22), abnormal uterine bleeding (N = 12), uterine cancer or complex atypical endometrial hyperplasia (N = 29), and other (N = 13). Specimens removed at initial surgery are detailed in Table 2. Of those 91 patients, five (5.5 %) were diagnosed with a malignancy during the follow up period: one appendiceal, one breast, two endometrial which were incidentally noted at the time of surgery, and one primary lung cancer. In terms of oncologic history, 30 patients (33.0 %) had a personal history of non-ovarian cancer. Ten patients had a cancer diagnosis prior to this encounter while the remainder had a concurrent primary uterine carcinoma (N = 20) which was the indication for surgery. The non-uterine carcinomas included one cervical cancer, one tonsillar cancer, one rectal cancer, six breast cancers and one lymphoma diagnosis. In terms of family history, 19/91 (20.9 %) patients reported a family history of ovarian cancer, 28/91 (30.8 %) reported a family history of breast cancer, and 7/91 (7.7 %) reported a family history of uterine cancer. Seven patients (7.7 %) had additional surgery after the p53 signature diagnosis including removal of one (N = 2) or both (N = 5) ovaries and completion of ovarian cancer staging (N = 2); the final pathology of all yielded no evidence of malignancy. Subsequent surveillance strategies for these patients postoperatively varied widely among providers, with some recommending annual ultrasounds, some recommending annual CA-125 lab collection, and some recommending no further surveillance. Nineteen patients (20.9 %) maintained their ovaries at the time of final follow up. Of the



STIC lesion; H&E

STIC lesion; p53 immunohistochemistry staining

p53 signature lesion; H&E

p53 lesion; p53 immunohistochemistry staining

Fig. 1. Sample immunohistochemistry STIC lesion and p53 signature in comparison with H&E slides.

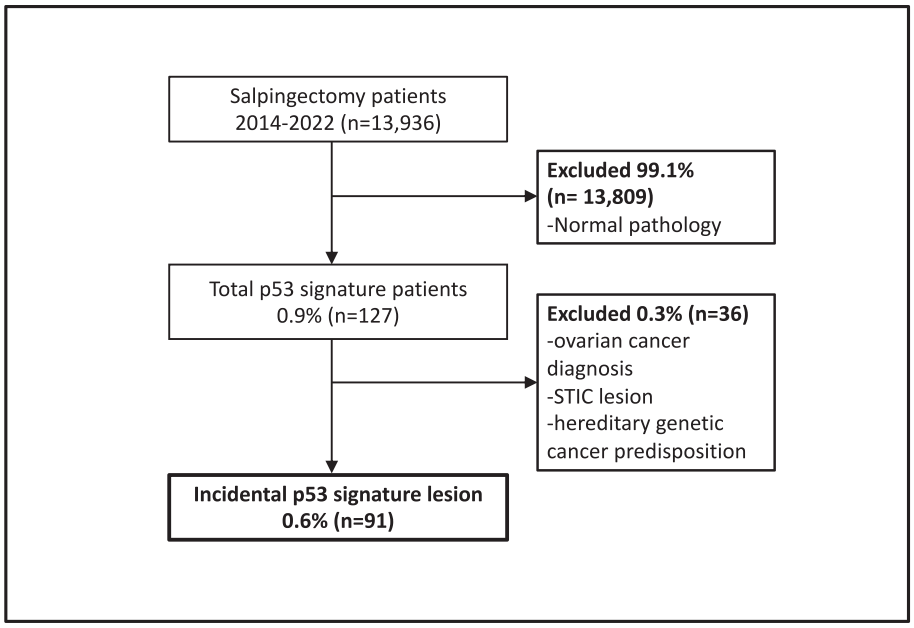


Fig. 2. Inclusion/Exclusion Criteria.

Table 1
Demographics.

	Frequency (n = 91)	Percentage (%)
Age		
30–49	17	18.7
50–69	50	54.9
70–89	24	26.4
BMI		
<30.00	41	45.0
30.00–40.00	37	40.7
>40.00	13	14.3
Race		
White	87	95.6
Hispanic	1	1.1
Non-Hispanic	86	94.5
Black	2	2.2
Indian	1	1.1
Unknown	1	1.1

BMI: Body mass index.

Table 2
Procedures and Specimens.

Initial Surgery	n=91 (%)
Bilateral salpingectomy	3 (3.2)
Bilateral salpingo-oophorectomy	9 (9.9)
Hysterectomy and bilateral salpingectomy	18 (19.8)
Hysterectomy and bilateral salpingo-oophorectomy	54 (59.3)
Other*	7 (7.7)
Follow up Surgery	**7 (7.7)**
Bilateral oophorectomy	5 (5.5)
Unilateral oophorectomy	2 (2.2)
Full staging procedure	2 (2.2)

* Includes removal of ovarian remnant; hysterectomy/bilateral oophorectomy/left salpingectomy; exploratory laparotomy with bilateral salpingectomy and right oophorectomy; hysterectomy and right salpingectomy; right salpingo-oophorectomy; cesarean section with bilateral tubal ligation; and cesarean section with left salpingectomy.

two patients who underwent completion of ovarian cancer staging, neither had any personal history of cancer or family history of a genetic cancer syndrome. One of these patients had a family history of breast cancer, and she was also offered genetic counseling which she did not complete. Sixty-seven (73.6 %) were seen primarily by or referred to a gynecologic oncologist for possible further workup. At these visits, 8 patients were recommended for further surgery which seven patients completed. Two were recommended for a CA-125 and imaging (one CT scan and one pelvic ultrasound), which were negative. Two were recommended for follow up every 6 months for 2 years. The remainder did not have recommendations made for follow up or did not address the p53 signature diagnosis during the postoperative period. Median time of follow up was 27 months, ranging from 1 to 103 months. All but one of the 91 patients were living at the time of last follow up and there were no ovarian cancer or primary peritoneal cancer diagnoses identified. The cause of death for this patient was unrelated to p53 signature diagnosis.

The majority of patients had p53 signature identified in a unilateral tube, although seventeen patients (18.6 %) were found to have bilateral lesions. Pathologic data is summarized in Table 3.

4. Conclusions

Our limited findings suggest that the diagnosis of an incidental p53 signature has modest clinical implications in this group of patients undergoing salpingectomy for non-malignant and/or high-risk prophylactic indications. None of the patients in this cohort developed a subsequent ovarian or primary peritoneal cancer during our eight and a

Table 3
Pathologic testing and data.

	Frequency	Percentage
Location		
Bilateral	17	18.7
Unilateral	74	81.3
Ki 67 Expression		
Not increased	29	36.7
Low proliferation	22	27.8
Scattered positive	17	21.5
Increased	11	13.9

half year follow up period. While the majority of patients were referred to gynecologic oncology, very little actionable follow-up resulted from these consultations. Very few patients had further work-up, additional surgery, or surveillance. Those patients that went on to have further surgery (n = 7), including two undergoing staging surgery after p53 signature diagnosis, had no occult ovarian or peritoneal cancer diagnoses at the time of surgery. Notably, nineteen patients did report a family history of ovarian cancer; however, no malignancies were seen at the culmination of our review. Our small case series of data reveals that a variety of approaches to the incidental finding of a p53 signature lesion in the fallopian tube of an average-risk patient may be pursued. In the setting of the rarity of this finding and our limited data set, it is not clear what, if any further workup, surgery, or surveillance is indicated for these patients.

To our knowledge, this is the largest reported cohort of patients to date reporting clinical outcomes of patients with incidental p53 signature. Saleemuddin et al did examine p53 signature prevalence in the *BRCA* mutated population and noted that 38 % of women had at least one p53 signature at time of risk-reducing surgery (Lee et al., 2007; Saleemuddin et al., 2008). While this data is useful for the known high-risk *BRCA1* and *BRCA2* population, it has limited transference to the average-risk population. Several studies examining the rate of p53 alterations in the fallopian tubes of the *BRCA1* and *BRCA2* mutated population also describe these lesions in their control population, who do not have *BRCA1* and *BRCA2* mutations. These authors report rates between 26 and 50 % in the control population, which may also be related to the amount of tube sampled and evaluated (Norquist et al., 2010 Nov 15). However, these studies do not comment on clinicopathologic data or follow up for these patients. As such, this data represents a unique addition to the literature on this topic.

This data largely serves to support providers as they counsel patients in the setting of an incidentally noted p53 signature, which is a rare finding with uncertain significance. We recognize that further understanding of the relationship between p53 signature and STIC lesions may help identify other prognostic factors for which further surgery and workup are indicated. Contrary to recommendations for a STIC lesion, the necessity of gynecologic-oncologist referral for this diagnosis is unclear. If generalist providers feel comfortable counseling about this diagnosis, it may be reasonable to avoid a gynecologic-oncologist referral for this diagnosis given the dearth of information available to provide patients, while also considering the reassurance some patients may feel by having this discussion with an oncologist. It is notable that 20.9 % of these patients maintained their ovaries after their p53 diagnosis with no ovarian cancer diagnosis during our eight and a half year follow up period, however this study was underpowered to make a recommendation as to if completion oophorectomy is warranted. Even if ovaries are removed, it is not clear there is an indication for long-term follow-up, especially considering the lack of evidence-based screening guidelines for primary peritoneal cancer in even high-risk patients. Further data will be needed to make specific recommendations.

As a significant proportion of patients had concurrent endometrial carcinoma at the time of p53 signature identification (n = 20), this relationship may also warrant further investigation. Fallopian tube abnormalities are reported to be found in association with uterine serous carcinoma. In one study, the rate of p53 lesion was as high as 17.9 % in patients with this pathology(Steenbeek et al., 2020). Of the 20 patients with uterine carcinoma in our cohort, 19 (95 %) had endometrioid type endometrial adenocarcinoma, representing a new association not previously reported in the literature. There may be molecular and genetic associations to be evaluated in this population as well; however, the final outcome data remain unchanged.

The major strength of this study is the descriptive data on incidental p53 signature in an average-risk population. Another strength is the single institution providing an internal control for the diagnosis of p53 signature and well-annotated data. There are several weaknesses. Although our follow-up was up to 8.5 years, this is an insufficient period to fully exclude the development of ovarian and/or peritoneal cancer. However, the median age of our patient population was 60 years, consistent with the median age of primary peritoneal and ovarian malignancy patients, which places our patient population in the general timeline when we would expect to see this diagnosis. We acknowledge that this is a relatively small case series and a larger, more diverse patient population (including race, ethnicity, and location) would be better powered to provide more generalizable data. However, we also recognize that the finding of an p53 signature is itself relatively rare, with an overall incidence at our institution of 0.9 % in all patients undergoing salpingectomy. The incidence of an incidental p53 signature was even lower, at 0.6 %. At our institution, we have seen a general increase in this diagnosis over the past ten years, and if this increase continues, we anticipate over time even more cases and longer follow-up, which can add to this data. Continued follow up of these patients prospectively and those additionally diagnosed with an incidental p53 signature lesion will help to support our conclusions. Finally, we also have limited data as to genetic history and testing. It is unclear if genetic testing is warranted for STIC lesions, let alone in p53 signature lesions, although the presence of pathogenic mutations could clearly alter the clinical indications for further surgery and/or follow-up.

In conclusion, the finding of an incidental p53 signature in the average-risk population undergoing salpingectomy for benign indications has unclear clinical implications. This finding has not yet been shown to warrant further testing, therapy, or surgical intervention; however, a discussion with the patient of the current data and consideration of other patient risk factors is prudent. A high proportion of p53 signature was found in concurrent endometrial cancer patients, although the significance of this is not clear and bears further investigation.

Condensation

A retrospective case-series of patients with incidental p53 signature found at the time of surgery and related long-term clinical outcomes.

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CRediT authorship contribution statement

Emily C. MacARTHUR: Investigation, Data Curation, Writing – original draft, Visualization. **Mackenzy RADOLEC:** Data curation, Investigation, Resources, Writing – review & editing. **T. Rinda SOONG:** . **Esther ELISHAEV:** Resources, Writing – review & editing. **Ronald BUCKANOVICH:** Writing – review & editing. **Sarah E. TAYLOR:** Writing – review & editing. **Jamie LESNOCK:** Conceptualization, Methodology, Supervision, Writing – review & editing.

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