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Review

Cancer Prevention Research

Rationale for Developing a Specimen Bank to Study the Pathogenesis of High-Grade Serous Carcinoma: A Review of the Evidence

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Abstract

Women with clinically detected high-grade serous carcinomas (HGSC) generally present with advanced-stage disease, which portends a poor prognosis, despite extensive surgery and intensive chemotherapy. Historically, HGSCs were presumed to arise from the ovarian surface epithelium (OSE), but the inability to identify early-stage HGSCs and their putative precursors in the ovary dimmed prospects for advancing our knowledge of the pathogenesis of these tumors and translating these findings into effective prevention strategies. Over the last decade, increased *BRCA1/2* mutation testing coupled with performance of risk-reducing surgeries has enabled studies that have provided strong evidence that many, but probably not all, HGSCs among *BRCA1/2* mutation carriers appear to arise from the fallopian tubes, rather than from the ovaries. This shift in our understanding of the pathogenesis of HGSCs provides an important opportunity to achieve practice changing advances; however, the scarcity of clinically annotated tissues containing early lesions, particularly among women at average risk, poses challenges to progress. Accordingly, we review studies that have kindled our evolving understanding of the pathogenesis of HGSC and present the rationale for developing an epidemiologically annotated national specimen resource to support this research. *Cancer Prev Res; 9(9); 713–20. ©2016 AACR.*

Overview of the Problem

Ovarian carcinoma accounts for more than 22,000 incident cases and 14,000 deaths annually in the United States (1). The most common histopathologic subtype of ovarian carcinoma is high-grade serous carcinoma (HGSC), which characteristically presents with symptomatic, late-stage, high-volume disease. Even with aggressive treatment, the prognosis of advanced-stage HGSC is poor, with 5-year survival rates estimated at less than 50% (2).

Among women with deleterious *BRCA1/2* mutations, risk-reducing salpingo-oophorectomy (RRSO) is effective in reducing ovarian cancer incidence and mortality (3). Unexpectedly, early pathology studies of RRSO specimens led to the identification of putative clinically occult HGSC precursors in the fimbria of the fallopian tubes, rather than in the ovarian surface epithelium (OSE), as anticipated (4). Subsequently, many studies have described putative HGSC precursors in tubes of *BRCA1/2* mutation carriers (reviewed in ref. 5); however, descriptions of these lesions among noncarriers, especially in the absence of concurrent HGSC, remain rare (6, 7), and developing the specimen resource required to investigate such lesions is challenging. Herein, we review recent advances in the understanding of the pathogenesis of HGSC and provide evidence that the development of a tissue bank may facilitate translation of recent findings into improved prevention strategies.

Screening and Prevention Approaches for HGSC

To date, approaches for ovarian/tubal cancer screening and prevention in the general population (8–10) have been disappointing. Screening using CA-125 blood testing at a fixed threshold in combination with pelvic ultrasound did not reduce ovarian cancer mortality in the Prostate, Lung, Colorectal and Ovarian

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Cancer Screening Trial (11) or earlier studies (summarized in ref. 12). In the United Kingdom Collaborative Trial of Ovarian Cancer Screening), serial CA-125 serum levels analyzed with the risk of ovarian cancer algorithm in combination with transvaginal ultrasound also did not demonstrate a statistically significant mortality reduction (13), despite a favorably stage shift (14). Although long-term use of oral contraceptives reduces risk of developing ovarian cancer by up to 50% (15), uptake for this indication has been limited by concerns related to increased risks of thrombotic complications, stroke, and breast cancer (16).

Despite the aforementioned challenges, the discovery that many HGSCs found among asymptomatic *BRCA1/2* mutation carriers seem to arise from the fallopian tubes offers hope of achieving a breakthrough in the early detection and prevention of this disease. However, the percentage of HGSCs that originate in the fallopian tube among *BRCA1/2* mutation carriers and non-carriers is unclear. Further, lack of sufficiently annotated benign gynecologic tissues, putative HGSC precursors and early-stage HGSCs from non-carriers poses an obstacle to pursuit of this work.

Evolving Views on the Molecular Histology and Pathology of the Fallopian Tube

Prior to implementation of RRSO as a prevention strategy among *BRCA1/2* mutation carriers, pathologists rarely encountered specimens containing low-volume HGSC, and when such tumors were identified, attention was routinely focused on the ovaries (17). HGSC was presumed to develop from OSE because tumor was frequently present on the ovarian surface, OSE was presumed to represent the source of a unique progenitor of HGSC, and the risk of HGSC increases with a woman's number of lifetime ovulations. In this model, each ovulation would subject the OSE to injury and repair that could lead to accumulation of deleterious mutations (18). Among cases of HGSC, ovarian and peritoneal involvement is often extensive, whereas tubal involvement is comparatively subtle, easily overlooked, and was seldom sought historically. Thus, the failure to identify dysplastic changes in OSE in older studies was generally ascribed to destructive overgrowth of invasive carcinoma (19).

Recognition that *BRCA1/2* mutations confer lifetime risks of HGSC of 18% to 40% (20) led to increased use of RRSO, enabling Piek and colleagues (21), Crum and colleagues and others (22–25) to identify serous tubal intraepithelial carcinoma (STIC) in the fallopian tube epithelium (predominantly the fimbria) in the context of preserved microanatomy. When STIC and HGSC were present concurrently, the relatedness of the lesions was often suggested by the following: similar morphology with marked cytologic atypia; identical *TP53* mutations in paired lesions (26, 27), comparable immunohistochemical staining for p53, Ki-67, apoptotic markers, and DNA damage response proteins (28–31), and topographic continuity (32). Further, STICs demonstrated shorter telomeres than adjacent normal appearing tubal epithelial cells, suggesting their status as a possible precursor of HGSC (33). In one study, 61% of *TP53* mutations were missense and demonstrated strong p53 protein staining by immunohistochemistry; the remaining cases showed frameshift, splice junction, or nonsense mutations, which were p53 null by immunohistochemistry (26). Thus, most STICs overexpress p53 protein, but a minority is null, and may be identified with other immunohistochemical stains, such as stathmin 1, p16INK4A, and laminin C1 (34–36). Other studies have also reported STICs that were negative by p53 immunostaining (6, 7).

STIC (alone or with concurrent carcinoma) has been identified in 2% to 8% of RRSO specimens, reflecting differences among populations, intensity of sampling for microscopic pathology, and diagnostic criteria (5, 7, 19, 37, 38). In the general population, STIC has been found concurrently with HGSC in approximately 20% to 70% of cases when the tube is extensively scrutinized (39–41), but the presence of cancer limits inferences regarding whether STIC is a cancer precursor. Further, the frequency of detecting STIC may vary with the histopathologic pattern of the associated HGSC and the patient's *BRCA1/2* mutation status, but studies have not identified an alternate origin of HGSC when STIC is not found (42, 43). Thus, at this point, many, but probably not all, HGSCs among *BRCA1/2* carriers appear to arise from STICs, although little is known about the frequency of STICs in the general population (44–46).

STICs have been found in approximately 0.5% of RRSO specimens removed from women at elevated risk of developing HGSC related to a positive family history who tested negative for *BRCA1/2* mutations (5), and anecdotally in tubes removed for benign indications among women in the general population (7, 19, 47). Sensitive protocols for pathology processing to optimize histologic detection of tubal precursors of HGSC have been developed (48, 49), and as pathologists apply these methods more routinely, detection will certainly increase, providing more opportunities for research. Utility of these tissues is enhanced by targeted next-generation sequencing methods that may enable molecular characterization of these lesions in fixed tissues, despite their minimal size (50). These studies may also provide molecular evidence suggesting that some "STIC" lesions represent secondary deposits from endometrial carcinomas (50) and that the clonal relationships of multiple foci of STIC and carcinoma within a single woman are complex (51, 52).

In addition, the development of genetically engineered mouse models that recapitulate the origin of HGSC from the fallopian tube, provide opportunities to perform mechanistic studies that will complement clinical research (53–56). Studies aimed at understanding how ovulation might damage fallopian tube epithelium may suggest new prevention strategies (57, 58).

Approaches to HGSC Research in the General Population

Translating advances in our understanding of the early pathogenesis of HGSC among *BRCA1/2* mutation carriers to the general population is limited by several factors, including: (i) rarity of detecting STIC among women who are *not BRCA1/2* mutation carriers and who do *not* have advanced-stage HGSC; (ii) the microscopic size of almost all STIC lesions; (iii) incomplete standardization of the extent of pathology processing of gynecologic tissue specimens (especially when performed for benign indications; refs. 59, 60); and (iv) limited epidemiologic and clinical annotation of samples. Given that STIC requires salpingectomy for diagnosis, the natural history of these lesions will likely remain unknown. Consequently, comparative molecular analysis of STIC, early-stage HGSC, and benign tissues may

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represent the best available approach to study the biology of these lesions.

Detection and Characterization of HGSC and Putative Precursors

The Sectioning and Extensively Examining the Fimbria pathology protocol ("SEE-Fim") was developed to enable detailed comprehensive microscopic study of the fallopian tube in RRSO specimens (Fig. 1; ref. 49). Dissemination of data regarding detection of STIC at RRSO, and guidelines that emphasize microscopic examination of the tube when cancer is present, have undoubtedly led to increased use of SEE-Fim (61). However, pathology processing of surgical specimens removed from women with wild-type *BRCA1/2* for benign indications is likely more variable, particularly if the tubes and the ovaries appear unremarkable on microscopic examination of the "representative sections" initially submitted for histologic processing.

Among 523 sequential surgical pathology specimens removed for benign indications that were processed according to a modified SEE-Fim approach for research, 4 STICs and 11 additional examples of epithelial atypia were identified (47). A recent study found STICs in 3 (0.17%) of 1,747 specimens from women 50 years of age and older who neither harbored a concurrent pelvic or uterine HGSC, nor were known *BRCA1/2* mutation carriers (E. Meserve and C. Crum, unpublished). Experience suggests that if these specimens had been processed routinely, many STIC lesions may have been missed. In contrast, among 966 high-risk women with or without deleterious *BRCA1/2* mutations who elected immediate risk-reducing surgery in Gynecologic Oncology Group Protocol-0199, STICs were identified in four and invasive fallopian tube cancers in five women (5). Among women who are not *BRCA1/2* carriers, STIC is infrequent; however, the *absolute number* of STICs in this group may be substantial given that these women account for 85% to 90% of HGSCs in the population. Further, germline mutations in genes other than *BRCA1/2* may increase risk of HGSC and these women may also harbor STIC or other cancer precursors (62).

The "molecular histology" of the fallopian tube, broadly conceptualized as the morphology, molecular biology, and function of benign tubal tissues in relation to risk exposures has not been extensively studied; however, similarities have been found between the transcriptome of benign tubal epithelium of *BRCA1/2* carriers and HGSC (63, 64), prompting a hypothesis that mutation carriers may respond abnormally to post-ovulatory inflammation (65). In addition, stretches of p53 immunopositive cells have been identified in approximately 24% of carriers of *BRCA1/2* mutations and 33% of women undergoing benign surgery (ref. 27; Fig. 2). These "p53 signatures," which may appear cytologically normal or show only mild cytologic atypia, are not highly proliferative, but frequently demonstrate *TP53* mutations and stain positively for γH2Ax, a histone that is phosphorylated by ATM kinase at sites of double-strand DNA breaks. Compared with STIC and HGSC, p53 signatures are much more common, especially with intensive scrutiny (59), suggesting that many would not progress to neoplasia if left intact, although a minority of such lesions may represent early steps in carcinogenesis. Areas of secretory cell outgrowths (SCOUTs) composed of stretches of non-ciliated cells expressing wild-type *p53* have also been recognized in otherwise histopathologically unremarkable fallopian

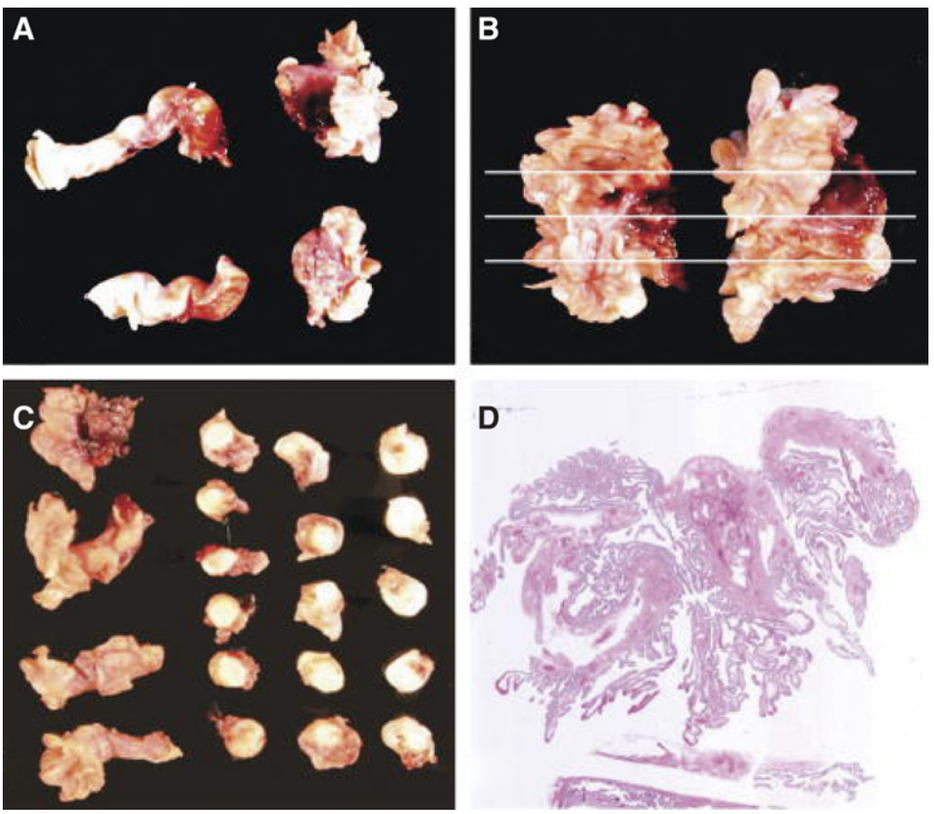

Figure 1.
Macroscopic appearance of fallopian tube demonstrating SEE-Fim protocol (**A–C**). Approach to longitudinal sectioning of fimbria (**B**) and preparing cross-sections of tubes (**C**). Hematoxylin and eosin–stained section of fimbria (**D**). This figure was published in Diagnostic Gynecology and Obstetrics Pathology, Christopher Crum, Marissa Nucci and Kenneth Lee, Chapter 21, The Fallopian Tube and Broad Ligaments, p. 701, copyright Elsevier.

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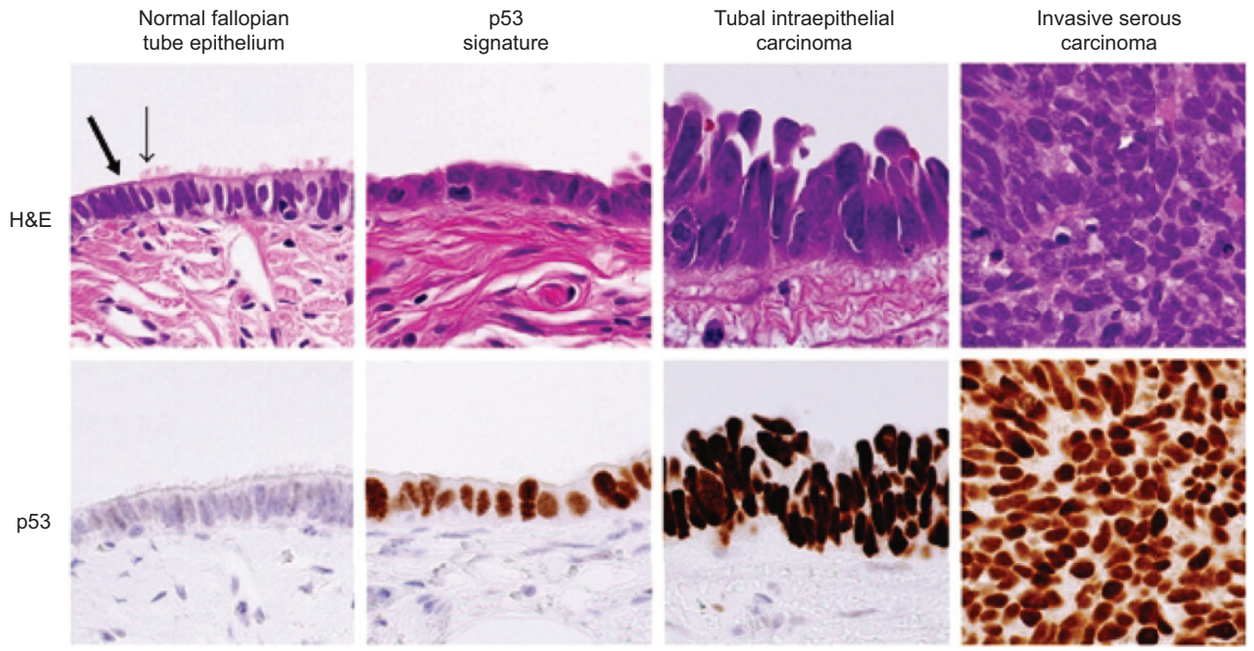

Figure 2.
Sections of fallopian tube epithelium stained with hematoxylin and eosin top and immunohistochemistry for p53 bottom, showing normal, p53 signature, STIC, and invasive serous carcinoma (left to right). Adapted from: Ovarian cancer pathogenesis: A model in evolution. Karst AM, Drapkin R. *J Oncol* 2010.

tube epithelium, but whether this is a variant of normal or a subtle alteration associated with greater cancer risk is also uncertain (66).

Fallopian Tube Pathology in Clinical Practice and Translational Research

The interobserver reproducibility of the diagnosis of STIC based on morphology is suboptimal. Although use of immunohistochemical stains may improve agreement (28, 31, 67–69), expert consensus is the only available measure of diagnostic accuracy. Establishing reproducible and accurate diagnoses of STIC is a prerequisite for developing clinical studies to improve management. Accurate diagnosis of STIC will likely pose an increasing clinical problem, as *BRCA1/2* mutation testing, performance of RRSO, and meticulous examination of surgically removed fallopian tube increases. Moreover, only 6% to 10% of STICs encountered in RRSOs of women with *BRCA1/2* mutations have an outcome of metastatic HGSC, raising important questions about the risk of progression of this putative early form of HGSC (70, 71).

"Opportunistic salpingectomy" has been proposed as a public health strategy to lower incidence rates of ovarian/tubal cancer (72–76). Salpingectomy with deferred oophorectomy offers the potential to prevent HGSC while limiting harms associated with premature estrogen deprivation. Opportunities to perform incidental salpingectomy occur in conjunction with (i) sterilization (in place of tubal ligation); (ii) hysterectomy for benign diseases and (iii) non-gynecologic abdominal or pelvic surgery. Opportunistic salpingectomy offers considerable theoretical appeal; however, prospective proof-of-safety and effectiveness will require decades of surveillance. Population-based registry analyses from Scandinavia have demonstrated that women that have undergone salpingectomy, particularly if bilateral, have a substantially reduced incidence of "ovarian cancer," supporting the hypothesis that a sizeable percentage of HGSC arises from the fallopian tube (77, 78).

Anecdotal observations suggest that cells from STIC lesions may exfoliate from the fallopian tube mucosa and implant on the ovary or peritoneum without invading through the basement membrane of the tube (79). Staging procedures may demonstrate invasive HGSC in cases initially diagnosed as STIC (80). Interest in the topic of prophylactic salpingectomy with deferred oophorectomy will likely magnify unaddressed concerns regarding whether detection of STIC or STIC-like lesions necessitates immediate oophorectomy, and possibly, formal cancer staging. In fact, clinical observations (81) and studies of animal models (53) suggest that ovarian involvement may potentiate the malignant behavior of early HGSC. Further, the value of offering *BRCA1/2* genetic testing to women with incidental STIC is unknown. It is also unclear whether high-risk women who undergo salpingectomy will return for delayed oophorectomy, and if so, when that should be performed to maximize cancer risk reduction, while minimizing negative effects of estrogen deprivation, including osteoporosis and cardiovascular disease.

National Gynecological Specimen Bank: Considerations

The overarching goal of creating a national gynecological specimen bank would be to provide epidemiologically annotated samples to the research community to pursue high-quality research related to the pathogenesis of early-stage HGSC. Although investigators have collected RRSO samples, and a campaign promoting "opportunistic salpingectomy" with benign

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hysterectomy as a means of lowering the incidence of HGSC has been promulgated in British Columbia (73), these resources have limitations, including (i) rare numbers of STIC lesions and early cancers, (ii) exhaustion of small lesions by histopathology processing and molecular testing, (iii) variable pathology processing, (iv) incomplete epidemiological and clinical annotation, and (v) lack of associated germline DNA. The goal of the proposed bank is to augment available resources and to complement registry efforts, such as the recently established Pelvic-Ovarian Cancer Interception (POINT) Project (Pointproject.org/POINT/).

Historically, pathologists have examined grossly unremarkable fallopian tubes sparingly, mainly for documentation purposes; however, clinical practices are likely changing. Thus, by leveraging the shift toward routinely examining tubes more thoroughly, it may be practical to efficiently identify the rare cases of STIC among non-carriers of *BRCA1/2* mutations, without vastly modifying routine pathology protocols for research. Specifically, electronic searches of surgical pathology reports may be sufficient to identify a useful number of women with STIC, even if such cases are rare. Further, more extensive sampling of the ovary and endometrium may reveal unsuspected non-tubal HGCSC precursors, such as endometrial intraepithelial carcinoma, the probable precursor of uterine serous carcinoma (82).

BRCA1/2 carriers are diagnosed with HGSC at earlier ages, respond better to treatment, and in a recent meta-analysis, had improved survival compared with non-carriers at a median of 6.3 years (83). Further, studies suggest HGSC comprises multiple histopathologic patterns, which may be differentially associated with loss of *BRCA1/2* function, STIC, age at onset or prognosis (42, 43). Similarly, HGSC may include multiple molecular subtypes with different clinical behaviors (84). Accordingly, the hypothesis that most HGSCs among non-carriers develop from STICs represents an untested hypothesis, which could be evaluated using tissue bank resources. Defining whether tubal lesions are associated with HGSC among women who are not carriers of *BRCA1/2* mutations would be useful, either confirming a common approach to HGSC prevention, irrespective of mutation status, or redirecting attention to other approaches.

The proposed bank would collect pathology specimens from three contexts: (i) selected procedures performed for benign indications, such as hysterectomy or surgical sterilization; (ii) RRSO or risk-reducing salpingectomy; and (iii) HGSC, especially stages, I, II, or IIIA (Fig. 3). An important aspect of the resource would be the collection of specimens from non-carriers that were removed for benign indications, but which revealed occult STIC or minimal HGSC on microscopic review. In addition, the bank would collect tissues from all RRSOs, HGSC cases, especially those defined as stage I or II or stage IIIA1i (disease volume $\leq$ 10 mm), and a judiciously selected sample of matching normal tissues from benign surgeries, including fallopian tubes. Each sample would be annotated with minimal medical history as required to estimate risk of developing HGSC within a reasonable logistical framework (85). Centers contributing specimens to the bank would agree to process pathology material according to a standard protocol (Fig. 1). Given that SEE-Fim processing is recommended for cases with STIC or HGSC (61) and that many pathologists are probably examining the tubal fimbria routinely, finding pathology laboratories that are currently processing samples that can identify HGSC precursors and early HGSC may be possible, without altering existing practices. This would enable a *post hoc* selection of a small percentage of specimens from a large pool by re-contacting patients after surgery for consent as needed and further collection of data and specimens. A survey of pathology

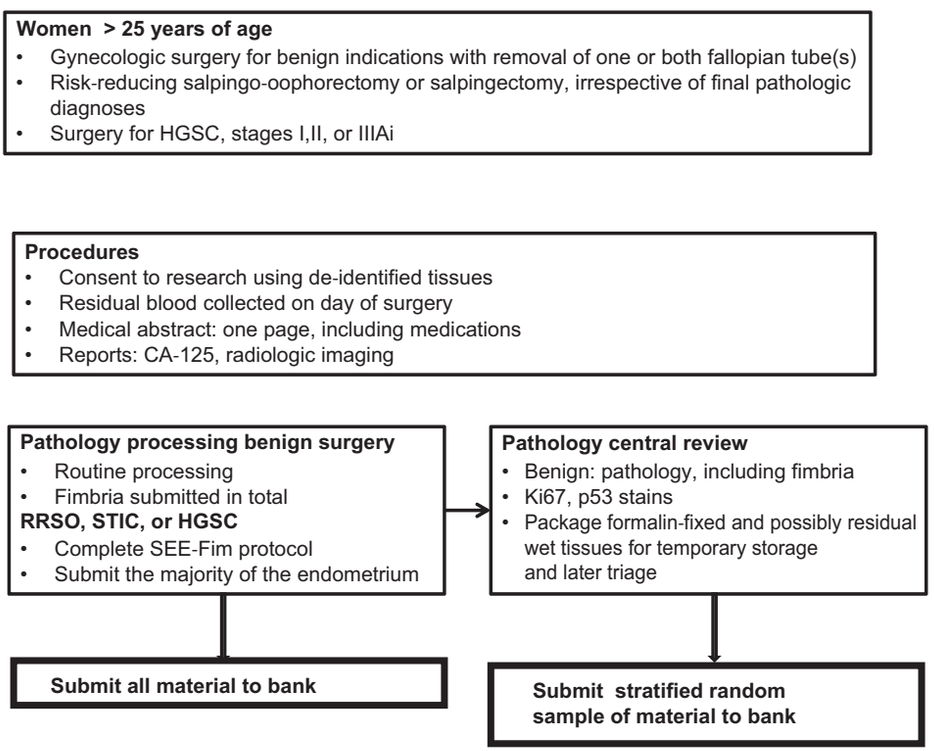

Figure 3.

Centers participating in the proposed bank would perform SEE-Fim on all fallopian tubes for microscopic examination. The bank would include the following specimens: RRSO, risk-reducing salpingectomy, any specimen with a diagnosis of STIC, or HGSC (multiple annotated samples of primary and metastatic deposits, SEE-Fim processing, and extensive endometrial sampling to assess the presence of early uterine serous carcinoma). Benign specimens would be selected randomly to create a set of tissues for comparison with those showing putative or diagnostic lesions. Clinical and epidemiologic annotation and source of germline DNA (e.g., unused blood drawn clinically) would be collected as permitted. Residual liquid-based cytology samples would also be banked.

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laboratories to assess usual tissue sampling procedures for specimens by clinical indication as would be needed to develop a pilot project is ongoing.

The bank could be pilot tested in pathology laboratories that perform SEE-Fim on all tubes and meticulously sample ovaries and endometrium. Benign surgical pathology specimens removed from non-carriers could be handled using a two-stage approach. Specifically, the fimbria of fallopian tubes from procedures with a benign diagnosis would be processed in their entirety for clinical diagnosis and later centrally reviewed for research. On a rolling basis, a stratified random sample of benign specimens without STIC or HGSC would be chosen with oversampling of those at greatest risk (85). These samples could be used in comparative molecular analyses.

Goals of Research Using Banked Gynecologic Tissue Samples

Potentially, data from medical charts could be supplemented by questionnaires. Data and materials from the proposed bank could be used to address a wide range of potential questions related to the pathogenesis of HGSC, including (but not limited) to those defined below.

- Does the molecular histology of the fallopian tube, particularly the epithelium of the fimbria and/or its microenvironment, vary by critical factors including *BRCA1/2* mutation status, age, menopausal status, family history of breast or ovarian cancer, medications, parity or other factors?
  - Are factors associated with risk of developing HGSC associated with the "omic" profile of the benign appearing tubal epithelium?
  - How do molecular profiles of the fimbria and non-fimbria tubal epithelia compare, and what are the similarities and differences?
  - Does the frequency of detecting p53 protein over-expression by immunohistochemistry vary by risk of HGSC among carriers and among non-carriers?
    - Does the frequency, extent or molecular profile of microdissected "p53 signatures" vary by risk factors among non-carriers or carriers of deleterious *BRCA1/2* mutations? Are certain specific *p53* mutations in "p53 signatures" related to HGSC, while other mutations are not?
  - Are ovarian cancer risk factors associated with important characteristics of the microenvironment, including number and immunophenotype of mononuclear cells, microvessel density, collagen, or matrix factors or biophysical characteristics?
  - Are ovarian cancer risk factors associated with markers of cell stress, DNA damage, DNA repair, proliferation, apoptosis, inflammation, and telomere length in benign appearing tubal epithelium?
- How do molecular profiles of STIC, normal appearing epithelium adjacent to STIC and small foci of HGSC deposits compare within and between patients? What evidence is there for clonal relationships between classes of lesions and metastatic deposits and what specific molecular abnormalities are likely drivers of early events in the pathogenesis of these lesions?
- How do molecular profiles of benign appearing fallopian tube epithelium among women with small cancers that are not associated with STIC compare with those that are associated with STIC?
- How heterogeneous is the molecular profile of HGSC and does it vary by age and ovarian cancer risk factors? Do molecular signatures vary by proposed histological subtypes of HGSC?
  - Is there evidence of intratumoral molecular heterogeneity at the earliest stages of HGSC?
  - Given that ovarian involvement may be linked to accelerated dissemination of malignant cells, are there differences in gene expression between tubal and ovarian foci of HGSC?

Conclusions

The development of a national gynecologic tissue bank to study early-stage HGSC and its precursors holds promise for enabling researchers to identify improved methods for early cancer detection and prevention because an important challenge to conducting this research is the scarcity of carefully annotated tissue specimens representing different hypothesized stages in the development of HGSC. However, assembling this resource would require a complex multi-institutional effort, substantial investment, and equitable access based on objective merit of proposed studies. Accordingly, assessment of feasibility and pilot testing to define a cost-effective approach are important prerequisites for considering this project.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Cancer Prevention Research

Rationale for Developing a Specimen Bank to Study the Pathogenesis of High-Grade Serous Carcinoma: A Review of the Evidence

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