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Review Article

The fallopian tube, "precursor escape" and narrowing the knowledge gap to the origins of high-grade serous carcinoma

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HIGHLIGHTS

- High grade serous carcinomas (HGSCs) have been linked to serous tubal intraepithelial carcinomas (STICs) by TP53 mutations.
- However, many disseminated HGSCs are not associated with STICS.
- Many tubes without STICs contain benign-appearing early serous proliferations (ESPs) with TP53 mutations.
- Many ESPs share TP53 mutations with HGSCs, implying early "precursor escape" with later intraperitoneal transformation.
- "Precursor escape" further links the tube to HGSC but with potential challenges for prevention and early detection of HGSC.

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ABSTRACT

Most ovarian carcinomas are high-grade serous carcinomas (HGSC) that contain *TP53* mutations, present at advanced stage, and eventually become resistant to chemotherapy. The rapid evolution of this disease has been attributed to an origin in the distal fallopian tube, in the form of serous tubal intraepithelial carcinomas (STICs). This has led to a disease model where malignancy develops first in the tube and spreads to the peritoneum or regional lymph nodes. However, although most early or incidentally discovered HGSCs manifest in the tube with STICs, many advanced HGSCs are not accompanied by a malignancy in the fimbria. To resolve this paradox, the focus has shifted to earlier, premalignant serous proliferations (ESPs) in the tubes, which lack the cytomorphologic features of malignancy but contain *TP53* mutations. These have been termed p53 signatures or serous tubal intraepithelial lesions (STILs). Although they have not been presumed to have cancer-causing potential by themselves, some ESPs have recently been shown to share identical *TP53* mutations with concurrent HGSCs, indicating a shared lineage between these early mucosal changes and metastatic malignancy. This discovery supports a paradigm by which HGSCs can emerge not only from STICs but also from exfoliated precursor cells (precursor escape) that eventually undergo malignant transformation within the peritoneal cavity. This paradigm unifies both localized and widespread HGSCs to a *visible pre-existing cellular alteration in the tubal epithelium*, and highlights a consistent and necessary biologic event (*TP53* mutation) rarely encountered in the ovary or secondary Mullerian system. This dual pathway to HGSCs underscores the subtle nature of many serous cancer origins in the tube, explains contrasting clinico-pathologic presentations, and explains why, until recently, the fallopian tube was unappreciated as the principal origin of HGSCs. Moreover, it highlights additional challenges faced in preventing or intercepting HGSCs at a curable stage.

Contents

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1. Introduction

From the perspectives of pathogenesis, early detection, and treatment, ovarian cancer has been one of the most challenging diseases to manage over the last half-century. It is also a disease that is particularly emblematic of the importance of tumor origin and evolution to therapeutic and preventive strategies. Therapeutic interventions have done little to alter the ultimate outcome, notwithstanding the value of cytotoxic chemotherapy in shifting the curve for disease-free survival [1].

Similarly, despite the promise of early detection with the use of ultrasound and other disease-related biomarkers such as CA125, there has been no compelling evidence to suggest that such markers will have a decisive impact on lowering the death rate in the population in a cost-effective manner [2]. This is due largely to the fact that up to 70% of ovarian cancers are high-grade serous carcinomas (HGSCs). Unlike primary ovarian endometrioid, clear cell, and mucinous adenocarcinomas, which are presumed to originate within ovarian endometriotic or other epithelial inclusion cysts and which can often be detected at an early stage, approximately 95% or more HGSCs are not detected until they have involved either the ovarian or fallopian tube serosal and/or peritoneal surfaces [3]. These differences in presentation and outcome underscore the likelihood that the development of HGSCs is distinct from the other malignancies and emphasize that pathogenesis not only determines how a particular tumor type will evolve but also how it must be approached to achieve successful management and prevention. This fact was highlighted in a paper by Bell and Scully, who observed from a large consultation practice that an exceedingly small fraction of HGSCs were diagnosed while confined to the ovary, prompting the admonition that prevention of this disease by early detection would be a challenge [4]. What has transpired since then has been a revolution in our understanding of the origins of the most lethal "ovarian" carcinoma. New insights and questions, as well as alternative theories of pathogenesis have been superimposed upon or dovetailed with the old. The purpose of this review is to summarize the evolution in this field, address the emerging knowledge gaps and add some insights to the tubal theory of serous carcinogenesis in the light of recent discoveries.

Ovarian surface epithelium (OSE) and serous carcinogenesis (Fig. 1).

Up until the year 2000, the prevailing theory of ovarian carcinogenesis centered on the ovarian surface epithelium. The connection between HGSCs and OSE has remained circumstantial. The OSE or nearby Mullerian epithelial inclusion cysts in the ovarian cortex (CICs) were thought to be the logical predecessor to ovarian carcinoma [5]. Theories for the development of the Mullerian OSE and CICs included trans-differentiation of mesothelium, a modified epithelium capable of both Mullerian and mesothelial differentiation and epithelial implants from the tubal fimbria [6]. Irrespective of the pathway proposed, a very high percentage of HGSCs involve the ovarian cortex or are present on the ovarian surface. This strong physical association between HGSCs and the ovarian surface has been the most enduring argument for the OSE or CIC as a site of origin [7]. The principal weaknesses in the argument have been the following: 1) As mentioned previously, very early carcinomas are rarely discovered on the ovarian cortex alone and 2) data addressing the role of CICs are conflicting. On one hand,

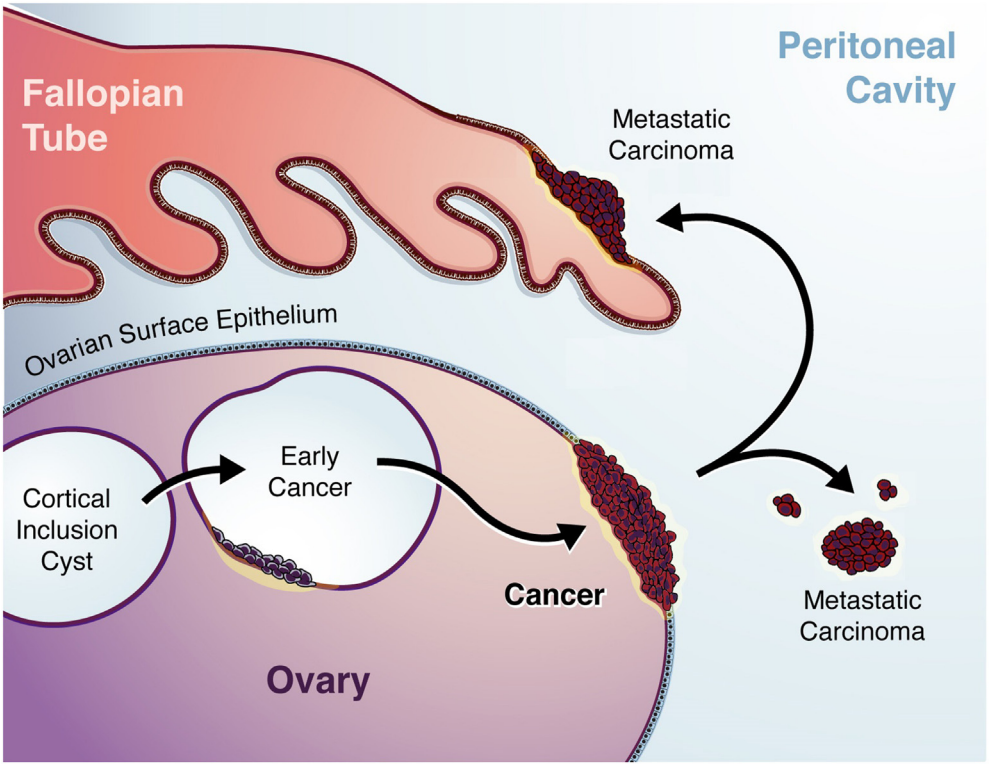

Fig. 1. Depiction of the ovarian theory of high grade serous carcinogenesis. In this model, serous carcinomas would develop from either cortical inclusion cysts or the ovarian surface epithelium.

examples of p53-immunopositive CICs have been described alone or in association with HGSCs, albeit in very small case studies [8,9,10]. On the other hand, two comprehensive immunohistochemical analyses of CICs in risk-reduction salpingo-oophorectomies for germ-line mutations in *BRCA1* or *BRCA2* failed to identify any evidence of *TP53* mutations [11,12]. Notwithstanding, there is a wealth of experimental evidence indicating that under the appropriate conditions adenocarcinomas can be produced in vitro from ovarian surface or nearby(reviewed in [6]) [13]. Moreover, altered expression of biomarkers that could be germane to ovarian carcinogenesis has been identified in the OSE (reviewed in [6]) [14,15]. OSE has been credited with HGSCs in some studies based on molecular profile, and some mouse models have successfully generated HGSC in the absence of fallopian tubes [16,17,18]. Facilitation of OSE or CIC transformation by the aging ovarian cortical stroma has been suggested in another experimental study [19]. Nevertheless, with the exception of occasional examples of CICs with inactivating *TP53* mutations, a consistent precursor lesion in the ovary with absent P53 expression and/or lineage link to HGSCs– a prerequisite for HGSC precursor candidate– has not been histologically confirmed *in vivo* in humans [8,20].

Some arguments supporting an ovarian origin for HGSCs take a different tact, incorporating multiple factors to explain why the tumors often appear to "come out of nowhere". One hypothesis to explain this would be neoplastic transformation occurring in the OSE or inclusions followed by rapid tumor development facilitated by growth stimulating stromal factors [6]. This hypothesis is supportable by experimental data from animal and cell culture models but is otherwise impossible to prove as no visible related precursor can be identified in human samples under microscopic examination. Similarly, the proposition that mesothelium could abruptly trans-differentiate to Mullerian epithelium in the course of neoplastic transformation is plausible on embryologic grounds; however, it is nearly impossible to come up with visual or histologic evidence to support this mechanism for the development of HGSC in the ovary [21]. Nevertheless, this mysterious property of HGSCs to suddenly appear is a critical piece of the pathogenetic puzzle and one that will be revisited later in the review.

2. Secondary Mullerian system

The "secondary Mullerian system" is defined as Mullerian remnants distributed across the serosal surfaces of the pelvic and abdominal peritoneum. These remnants include epithelial cysts resembling fallopian tube (endosalpingiosis) and endometrium (endometriosis). They are present presumably either by transport from the uterus or as the residua of embryonic development, the classic example being paratubal Mullerian cysts, vestiges of the paramesonephric ducts [22]. This "system" has been designated by some as the probable source for serous and endometrioid carcinomas found in the ovaries or elsewhere [23]. Plausible arguments have been made that the Mullerian cortical cysts in the ovaries are derived from this system and give rise to epithelial ovarian carcinomas [5]. The coelomic metaplasia theory, by which the Mullerian cortical inclusions emerge from mesothelium via trans-differentiation, has been criticized as far less likely [23]. The origin of so-called primary peritoneal carcinomas is likewise assigned to these Mullerian remnants, similar to the presumed origin of many low-grade or borderline serous tumors that seem to arise spontaneously in the peritoneal cavity. Thus, the secondary Mullerian system has been displayed to both refute the theory that Mullerian metaplasia arises in coelomic epithelium and provide an alternative and more plausible origin for many "ovarian" cancers.

The secondary Mullerian system is a reasonable source of endometrioid and low grade serous neoplasia, which are often associated with endometriosis and endosalpingiosis respectively [24]. However, the theory has far less momentum as an explanation for disseminated HGSCs. First, as mentioned above, whether being of mesothelial or Mullerian origin, ovarian cortical inclusion cysts rarely display immunohistochemical evidence of *TP53* mutations [11,12]. Second, there is no evidence of *TP53* mutations in extra-ovarian endosalpingiosis beyond rare occurrences. It might be argued that the cystic nature of ovarian or peritoneal serous carcinomas could signify an origin within cysts; however, cystic architecture also often occurs in the setting of metastatic disease. Third, if ovulatory fluid cytokineso or other exposures are integral to DNA damage - related carcinogenesis, their access to inclusion cysts might be limited, both anatomically and temporally, particularly the latter if the inclusions develop after menopause [25]. In summary, there is little visible evidence for a precursor to implicate the secondary Mullerian system in the development of HGSCs.

3. The fallopian tube (Figs. 2 & 3)

The fallopian tube emerged as a strong candidate for a site of origin for HGSCs following the discovery of the *BRCA* cancer susceptibility genes and promotion of risk-reducing salpingo-oophorectomy (RRSO) as a cancer preventive strategy in these vulnerable patients with *BRCA* germline mutations [26,27]. With close scrutiny of the fallopian tube, including the introduction of the SEE-FIM protocol, a number of studies analyzed the fallopian tubes in detail, specifically the fimbriated end [28,29,30]. What transpired was the discovery that approximately 5% of women with germline *BRCA* mutations harbor an unsuspected early serous carcinoma in the fimbria or distal one third of the fallopian tube [31]. Many such early neoplasms were intramucosal, and were designated serous tubal intraepithelial carcinomas (STIC). When found in isolation, STICS carried an approximately 5% risk of a subsequent disseminated HGSC, albeit based on a small number of cases [32,33,34]. Brown and Palmer presented a model for the progression of HGSCs based on STICs. They estimated that following the development of STIC, there was a latent time window of approximately 5 years prior to the onset of full-blown metastatic HGSC [35].

The fact that a very high percentage of *early* cancers discovered manifested as STICs or STICS with early invasion was a strong endorsement of the fallopian tube as an important if not the only source of HGSCs [36]. However, subsequent studies of women who presented with *advanced* cancer, including those with and without germline *BRCA* mutations, reported a much lower frequency of STICs in the fallopian tube [29]. Even with the aid of the SEE-FIM protocol, the percentages have ranged from as low as 10 to 60% [37,38]. Thus, in a significant percentage of women with HGSC there is no visible intramucosal carcinoma in the fallopian tubes.

The above paradox - high frequency of STICs in early or incidentally discovered carcinomas but low frequency in advanced carcinomas - has until recently gone largely unresolved albeit not without proposed explanations. One explanation was that advanced HGSCs simply overran preexisting STICs, obliterating evidence of the earlier intramucosal component [39]. Another was that there was more than one pathway to HGSCs. Proponents of an origin in the OSE, mesothelium or secondary Mullerian system could argue that their explanations was equally plausible [6]. We noted in two studies that HGSCs with endometrioid or SET (solid, endometrioid like or transitional) morphology were less likely to manifest with STICs, suggesting an alternative pathway could exist for some of those tumors, whether it was in the fallopian tube or elsewhere [40,41]. However, although this observation suggested a second pathway to HGSCs, clinical and genetic data did not strongly support a dualistic model for HGSCs [17,42]. From another perspective, the notion that STICs invariably serve as the source(s) of HGSC has been challenged by studies using next generation sequencing or whole exome sequencing. These studies have suggested that some STICs are *metastatic* rather than primary lesions in the fallopian tube [43,44]. This casts further doubt on STIC as a consistent and reliable marker of tubal origin for HGSC, and has not solved the mystery of seemingly instantaneous development of widespread HGSCs in the apparent absence of a tubal mucosal carcinoma.

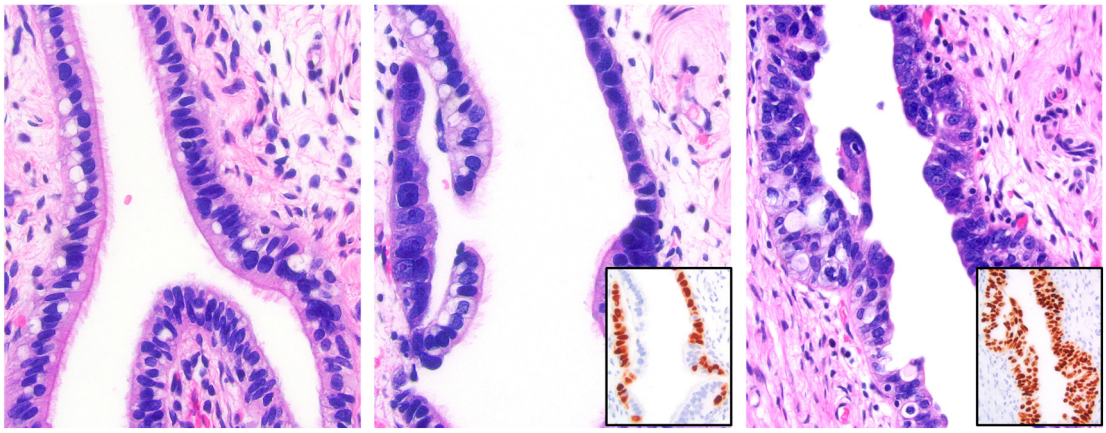

Fig. 2. A) Normal fallopian tubal mucosa. B) An early serous tubal proliferation (ESP) of the fallopian tube containing a *TP53* mutation. C) A serous tubal intraepithelial carcinoma for contrast (see text).

4. Fallopian tube precursors and precursor escape

Previous studies have uncovered epithelial proliferations in the fallopian tube that, like precancerous changes in the cervix, are credible predecessors to intraepithelial carcinomas and by association, HGSCs (Fig. 2) [45,46]. Although receiving rather little attention in the past, with the increased scrutiny of fallopian tubes in risk-reduction procedures, these small genetic lesions with *TP53* mutations have been noticed and incorporated into the serous carcinogenic sequence. Whether termed mucosal dysplasias, atypias, P53 signatures or serous tubal intraepithelial lesions (STILs), these entities share several features in common with HGSC or STICs [47,48]. First, they are most likely to be found in the fimbria, like STICs [46]. Second, they contain *TP53* mutations as evidenced via immunohistochemistry or direct sequencing as well as other biomarkers [46]. Third, they are found within non-ciliated (secretory) cells, the same cell type from which HGSCs develop [49]. Fourth, they demonstrate evidence of DNA damage, visible as punctate staining for gamma H2AX in the affected cells [46]. Fifth, physical and lineage continuity between these early proliferations and STIC has been documented with compelling arguments that some ultimately give rise to STICs and consequently, HGSCs [46,50].

This range of early serous proliferations (ESPs) have previously been viewed as having little or no metastatic potential per se beyond their possible role as occasional precursors to STIC. Moreover, in one form or the other they can be detected in the fallopian tubes of as high as 50-70% of healthy women [51]. Thus, while they shared some of the

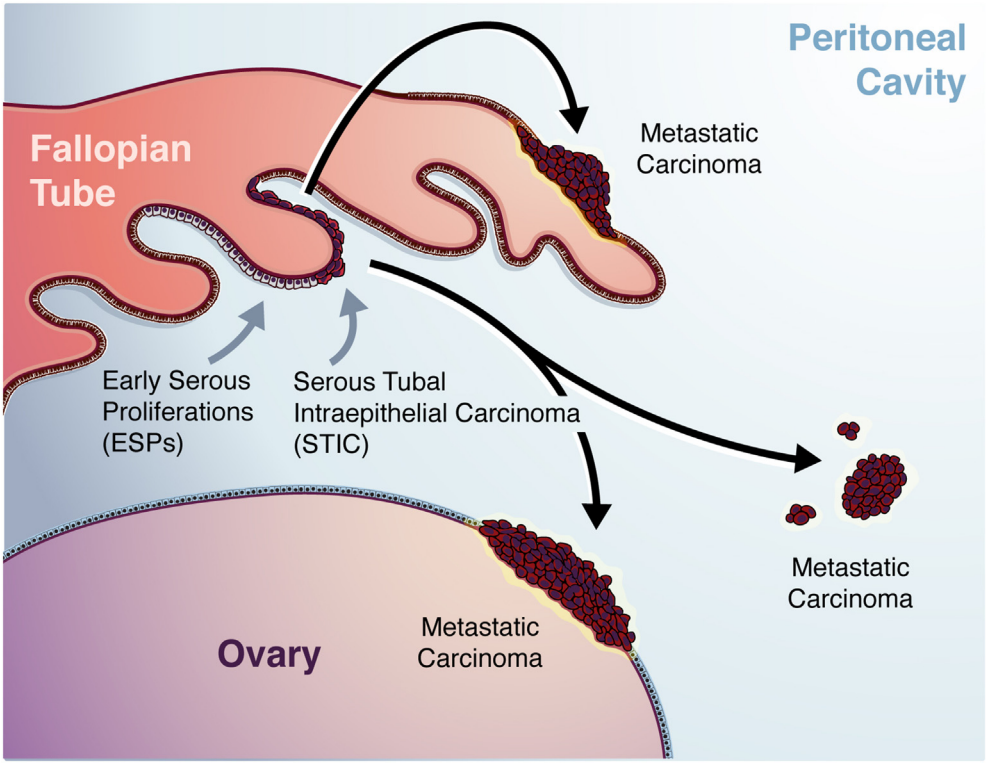

Fig. 3. The fallopian tubal theory of high-grade serous carcinogenesis. In this model DNA damage in non-ciliated epithelial cells of the distal tube leads to an early serous proliferation (p53 signature or serous tubal intraepithelial lesion) with a mutation in *TP53*. Some may progress to a serous tubal intraepithelial carcinoma (STIC), which in turn might disseminate to the ovary and/or peritoneal surfaces leading to HGSC.

attributes of STIC (*TP53* mutations, location in the distal tube, secretory cell type, and presence of DNA damage), ESPs were viewed more as potential precursors to STIC than as an independent start-point for HGSC.

Given the high frequency of *TP53* mutations in HGSCs and the similarity in genetics across all HGSCs irrespective of their association with STICs, we reasoned that if the fallopian tube played an even more dominant role in serous cancer development, then some ESPs would have to function as direct precursors to HGSCs. In an earlier study we had found that 54% of STICs were associated with ESPs either nearby or in another remote site in the fallopian tube [46]. Moreover, in a recent report by others in which fallopian tubes of women with HGSCs were carefully examined, STICs were found in 28% of HGSCs and ESPs were detected in an additional 46%, bringing the number of cases with an associated tubal STIC or precursor to 74% [52]. However, ultimately the question was whether an ESP could be linked to HGSC in the absence of an intervening STIC.

Previously, lineage identity between STICS and concurrent HGSCs has been clearly established by the sharing of common *TP53* site-specific mutations [37,53]. Thus, a similar question was addressed, being whether isolated ESPs shared the same *TP53* mutation with concurrent HGSCs. In a recent study, 32 benign-appearing fallopian tubes from women with HGSCs were exhaustively sectioned and immunostained for evidence of ESPs. Occult STICs were uncovered in 3 cases with extensive sectioning. ESPs were seen in 41% (13/32) of the cases, including one with concurrent occult STIC, and 12 of these 13 ESPs had detectible *TP53* mutations. *TP53* mutations in 9 of 12 ESP cases were identical to those in concurrent HGSCs at varying allele frequency. The findings provide strong evidence of lineage identity between ESPs in the distal tube and some metastatic HGSCs via a shared site-specific *TP53* mutation in a significant portion of cases [42].

Most gynecologic cancers arise from defined precursor lesions that are nearby and are not malignant, requiring further genetic events before invasion and spread occurs. A prime example is HPV-associated carcinogenesis in the cervix or endometrioid carcinoma of the endometrium. In both, the precancers give rise to nearby cancers but by themselves are not able to metastasize. A less common pathway involves the development of a "non-invasive" or intraepithelial carcinoma that has the potential to spread directly to the peritoneal or other mucosal surfaces. This pathway exemplifies serous carcinomas in the endometrium and fallopian tube, both of which can lead to peritoneal carcinomatosis without invasion of the underlying stroma [54,55]. In contrast, precancers or ESPs that precede intraepithelial carcinomas were not known to have metastatic potential [56,57].

The sharing of site-specific *TP53* mutations between isolated ESPs and concurrent HGSCs implies that genetically altered epithelial cells could detach from the tubes and eventually culminate in a widespread serous cancer (Fig. 4). This notion of "precursor escape", while novel from the perspective of serous carcinogenesis, has a precedent in the endometriosis-endometrioid adenocarcinoma model. Multiple deposits of endometriosis have been shown to share genetic markers that infer a common lineage. Similarly, synchronous ovarian and endometrial adenocarcinomas are now presumed to share a common cell of origin, possibly from the endometrium [58,59,60].

The significance of the model of "precursor escape" for high-grade serous carcinogenesis is that it satisfies at least four precepts. First, despite some inevitable genetic variations, all HGSCs share *TP53* mutations and the only visible precursors with these mutations have been found in the distal fallopian tube, not on the ovarian surface or in the secondary Mullerian system. Second, the precursor-cancer sequence has a *visible start point*, whether it be STIC or ESP. Third, the disparity in STIC frequency between early and late HGSC can be expected by the occurrence of precursor escape, which accounts for the dual manner of tumor presentation. For example, early HGSCs will *by definition* only be recognizable as STIC because this is the *only* form of tubal HGSC that can be detected when localized or has undergone limited spread. At the same time, malignant transformation following precursor escape explains the presence of widespread HGSC in the absence of STIC, inasmuch as the HGSC will not be detected until after a clinically latent period during

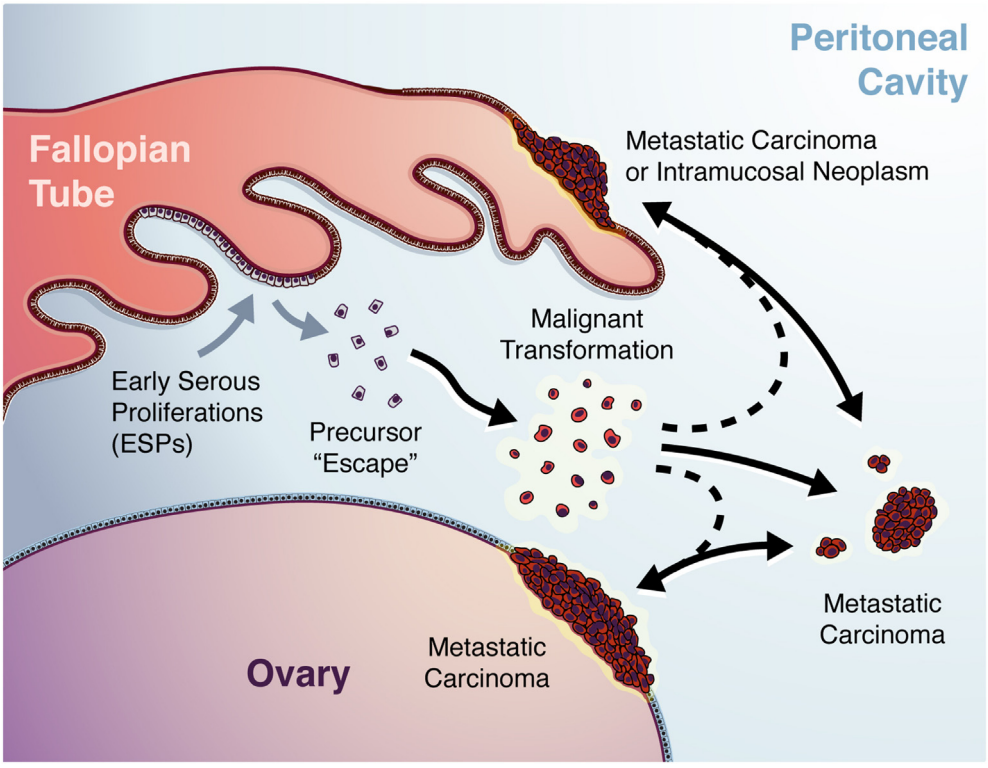

Fig. 4. The "precursor escape" theory of high-grade serous carcinogenesis complements the conventional fallopian tube theory. In this model, cells within early serous proliferations with *TP53* mutations become detached and exfoliate into the peritoneal cavity. In some cases the cells eventually undergo malignant transformation, creating the appearance of a spontaneous HGSC with no obvious origin in the fallopian tube, and with metastatic carcinoma spreading to the ovary, peritoneum and/or back to the tube itself, or vice versa.

which the ESP undergoes malignant transformation and the tumor grows and spreads throughout the peritoneum. The latter would also explain the so called "primary peritoneal" carcinoma, roughly half of which are not associated with STIC. As mentioned previously, based on genomic profiling, there is no measurable difference between tumors with or without an associated STIC, indirectly supporting a common cell of origin [17]. Finally, the subtle nature of many precursors in the fallopian tube explains why the tubal theory of serous carcinogenesis did not get significant attention until recently, inasmuch as so many early but potentially important precursors - ESPs - would not have been appreciated.

5. Caveats, challenges and opportunities

In addition to potentially explaining the absence of STICs in many HGSCs, consideration of multiple pathways to HGSC development might help evaluate a number of mysteries and study findings that lack proven biologic explanations based on current knowledge. The first mystery is the fact that there is relatively little difference in mean age for women with isolated STICs versus symptomatic HGSC in women with *BRCA* mutations, a surprising observation when considering that an interval of years would be expected between STIC-onset and disseminated HGSC [61] Second, over 90% of incidentally discovered STICs - a rare occurrence - are not followed by disseminated HGSCs, casting doubt on the STIC-HGSC pathogenic pathway as the *only* mechanism for generating disseminated cancer. Third, the recent UK Collaborative Trial of Ovarian Cancer Screening reported a survival benefit from screening but only after 7 years on study [62]. One explanation would be that tumors arising in the fallopian tubes might progress more slowly, and therefore would more likely be detected earlier in their metastatic course and modestly influence overall survival after years of screening. In contrast, the outcomes of those emerging rapidly from the peritoneal surfaces would remain unchanged. These speculations and recent study findings together raise the possibility of multiple pathways to HGSC. We previously found an association between parity and p53 signatures in women with *BRCA* mutations [63]. However, a recent epidemiological study of precursors did not identify specific protective factors associated with STICs that linked them directly to HGSCs, although a multiplicity of precursor lesions, including p53 signatures, might impose a greater risk of HGSCs. The implication was that HGSCs with and without STICs/STILs might be epidemiologically separate entities, leaving open the possibility of more than one pathway to HGSC development, including extra-tubal origins [64].

Although circumstantial molecular evidence from shared *TP53* mutations in ESPs and HGSCs suggests that non-malignant cells with *TP53* mutations could escape the tube and emerge later as widespread pelvic HGSCs, the models centering on STIC and precursor escape do not yet account for all of the HGSCs encountered. Solutions to this puzzle will invariably be offered in the context of competing philosophies, each with their own perspective. To summarize what has been detailed above, there are basically three schools of thought. The first is the emergence of neoplasia from either CICs or the secondary Mullerian system. The two are combined here because evidence of *TP53* mutations in benign Mullerian mucosa is the subject of rare observations and not verified by extensive analysis of either CICs or endosalpingiosis [8–12,23]. Thus the mechanism of HGSC development must entail a step-wise acquisition of genetic lesions culminating suddenly in HGSC concurrent with or immediately following inactivation of *TP53*. HGSCs involving ovarian cortex rarely contain adjacent benign mucosa with evidence of loss of *TP53* function. However, support for this model can be found in one report describing a single allelic mutation in the OSE adjacent to HGSC (which contained the second and inactivating mutation) [65]. This model awaits further confirmation. Another is the description of an ovarian genetic signature in 12% of HGSCs [17].

A second school of thought has HGSC emerging from stem cells in the region of the ovarian hilus in a mouse model, a surface epithelium/mesothelium "signature" in some HGSCs [13]. There is little histologic evidence of this mechanism based on examination of surgical pathology specimens, although an ovarian surface epithelium (OSE) phenotype has been described in a subset of HGSCs [18]. Again, immunohistochemical studies of the OSE have not detected pre-existing *TP53* mutations in a benign condition, again requiring that the acquisition of the mutation coincide with the onset of HGSC as mentioned above.

A third school of thought involves the evaluation for ESPs as the "tip of the iceberg" of subtly altered fallopian tubal epithelium that is responsible for the genesis of HGSC. The strength of this argument lies in the evidence linking ESPs to HGSC by genetic as well as several histologic characteristics not seen in other models. The theory, however, does not address the subset of HGSCs in which no evident ESPs or STICs can be detected histologically in pelvic resections specimens. Possibilities that one can consider include [1] a non-tubal origin of HGSC as described above; [2] colonization of normal fallopian tubal epithelium on the ovarian or peritoneal surface, which then acquires *TP53* mutation and undergo carcinogenesis; [3] adhesion of salpingeal epithelium that already contains *TP53* mutation on the ovarian or peritoneal surface; [4] previously existing ESPs might have involuted over time resulting in benign-appearing tubal epithelium and apparent absence of explainable precursor lesion, while exfoliated ESPs persist and undergo malignant transformation elsewhere in the peritoneal cavity.

Taking into account the possibility that HGSCs could arise not only in the tube but also on the peritoneal surface, strategies that rely on detecting cancer and reducing the cancer death rate by either ultrasound or CA125 screening face significant obstacles. Over 95% of women present with FIGO stage 3 (or above) HGSC disease. As the number of women harboring early serous proliferations in their tubes greatly exceeds the incidence of HGSC, the only strategies currently viable for cancer prevention are widespread testing for germ-line mutations in cancer susceptibility genes and opportunistic salpingectomy. In a retrospective meta-analysis, salpingectomy alone was associated with a significant reduction in ovarian cancer frequency relative to retention of the fallopian tubes [66]. Clearly, salpingectomy holds promise as a cancer preventive in women with germ-line *BRCA* mutations by removing the site of precursor development [67]. The questions remaining that will affect all women will be whether precursor escape predates removal of the tubes and whether preservation of the ovaries will maintain a hormonal milieu more permissive to malignant transformation of residual cells with *TP53* mutations. In any event, more needs to be learned about the cell biology of precursors and the events that transpire between their escape from a healthy fallopian tube and the emergence of a lethal malignancy months or years later.

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Contributions

Drs. Soong, Howitt, Nucci and Crum wrote the initial drafts and contributed the pathologic observations. Dr. Horowitz contributed clinical expertise and materials relevant to the review. All authors reviewed the manuscript.

Conflicts of interest

The authors have no conflicts of interest.

References

[1] S.A. Cannistra, Cancer of the ovary, N. Engl. J. Med. 351 (2004) 2519–2529 (Erratum in: N Engl J Med. 2005 Jan 6;352(1):104).
[2] J.T. Henderson, E.M. Webber, G.F. Sawaya, Screening for Ovarian Cancer: An Updated Evidence Review for the U.S. Preventive Services Task Force [Internet], Agency for Healthcare Research and Quality (US), Rockville (MD), 2018 Feb. (Report No.: 17-05231-EF-1. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews).
[3] J. Prat, E. D'Angelo, I. Espinosa, Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics, Hum. Pathol. 80 (2018) 11–27.
[4] D.A. Bell, R.E. Scully, Early de novo ovarian carcinoma. A study of fourteen cases, Cancer 73 (1994) 1859–1864.
[5] N. Banet, R.J. Kurman, Two types of ovarian cortical inclusion cysts: proposed origin and possible role in ovarian serous carcinogenesis, Int. J. Gynecol. Pathol. 34 (2015) 3–8.
[6] N. Auersperg, The origin of ovarian carcinomas: a unifying hypothesis, Int. J. Gynecol. Pathol. 30 (2011) 12–21.
[7] N. Auersperg, Ovarian surface epithelium as a source of ovarian cancers: unwarranted speculation or evidence-based hypothesis? Gynecol. Oncol. 130 (2013) 246–251.
[8] R. Hutson, J. Ramsdale, M. Wells, p53 protein expression in putative precursor lesions of epithelial ovarian cancer, Histopathology 27 (1995) 367–371.
[9] B. Pothuri, M.M. Leitao, D.A. Levine, A. Viale, A.B. Olshen, C. Arroyo, F. Bogomolniy, N. Olvera, O. Lin, R.A. Soslow, M.E. Robson, K. Offit, R.R. Barakat, J. Boyd, Genetic analysis of the early natural history of epithelial ovarian carcinoma, PLoS One 5 (4) (2010 Apr 26), e10358. .
[10] P.W. Schlosshauer, C.J. Cohen, F. Penault-Llorca, C.R. Miranda, Y.J. Bignon, J. Dauplat, L. Deligdisch, Prophylactic oophorectomy: a morphologic and immunohistochemical study, Cancer 98 (12) (2003 Dec 15) 2599–2606.
[11] A.K. Folkins, E.A. Jarboe, A. Saleemuddin, et al., 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 (2008) 168–173.
[12] R.R. Barakat, M.G. Federici, P.E. Saigo, et al., Absence of premalignant histologic, molecular, or cell biologic alterations in prophylactic oophorectomy specimens from BRCA1 heterozygotes, Cancer 89 (2000) 383–390.
[13] A. Fleskin-Nikitin, C.I. Hwang, C.Y. Cheng, et al., Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche, Nature 495 (2013) 241–245.
[14] I.H. Roland, W.L. Yang, D.H. Yang, et al., Loss of surface and cyst epithelial basement membranes and preneoplastic morphologic changes in prophylactic oophorectomies, Cancer 98 (2003) 2607–2623.
[15] H. Okamura, H. Katabuchi, Pathophysiological dynamics of human ovarian surface epithelial cells in epithelial ovarian carcinogenesis, Int. Rev. Cytol. 242 (2005) 1–54.
[16] J. Kim, D.M. Coffey, L. Ma, et al., The ovary is an alternative site of origin for high-grade serous ovarian cancer in mice, Endocrinology 156 (2015) 1975–1981.
[17] J. Ducie, F. Dao, M. Considine, et al., Molecular analysis of high-grade serous ovarian carcinoma with and without associated serous tubal intra-epithelial carcinoma, Nat. Commun. 8 (2017) 990.
[18] M.A. Merritt, S. Bentink, M. Schwede, et al., Gene expression signature of normal cell-of-origin predicts ovarian tumor outcomes, PLoS One 8 (2013), e80314. .
[19] K. Lawrenson, B. Grun, E. Benjamin, et al., Senescent fibroblasts promote neoplastic transformation of partially transformed ovarian epithelial cells in a three-dimensional model of early stage ovarian cancer, Neoplasia 12 (2010) 317–325.
[20] B. Pothuri, M.M. Leitao, D.A. Levine, et al., Genetic analysis of the early natural history of epithelial ovarian carcinoma, PLoS One 5 (2010), e10358. .
[21] Y. Saijad, Development of the genital ducts and external genitalia in the early human embryo, J. Obstet. Gynaecol. Res. 36 (2010) 929–937.
[22] S.C. Lauchlan, The secondary mullerian system revisited, Int. J. Gynecol. Pathol. 13 (1994) 73–79.
[23] L. Dubeau, The cell of origin of ovarian epithelial tumours, Lancet Oncol. 9 (2008) 1191–1197.
[24] W.T. McCaughey, M.E. Kirk, W. Lester, et al., Peritoneal epithelial lesions associated with proliferative serous tumours of ovary, Histopathology 8 (1984) 195–220.
[25] K. Bahar-Shany, H. Brand, S. Sapoznik, et al., Exposure of fallopian tube epithelium to follicular fluid mimics carcinogenic changes in precursor lesions of serous papillary carcinoma, Gynecol. Oncol. 132 (2014) 322–327.
[26] L.S. Friedman, E.A. Ostermeyer, C.I. Szabo, et al., Confirmation of BRCA1 by analysis of germline mutations linked to breast and ovarian cancer in ten families, Nat. Genet. 8 (1994) 399–404.
[27] R.P. Zweemer, P.J. van Diest, R.H. Verheijen, et al., Molecular evidence linking primary cancer of the fallopian tube to BRCA1 germline mutations, Gynecol. Oncol. 76 (2000) 45–50.
[28] F. Medeiros, M.G. Muto, Y. Lee, et al., The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome, Am. J. Surg. Pathol. 30 (2006) 230–236.
[29] E.E.K. Meserve, J. Brouwer, C.P. Crum, Serous tubal intraepithelial neoplasia: the concept and its application, Mod. Pathol. 30 (2017) 710–721.
[30] I. Cass, C. Holschneider, N. Datta, et al., BRCA-mutation-associated fallopian tube carcinoma: a distinct clinical phenotype? Obstet. Gynecol. 106 (2005) 1327–1334.
[31] M. Zakhour, Y. Danovitch, J. Lester, et al., Occult and subsequent cancer incidence following risk-reducing surgery in BRCA mutation carriers, Gynecol. Oncol. 143 (2016) 231–235.
[32] J.R. Conner, E. Meserve, E. Pizer, et al., Outcome of unexpected adnexal neoplasia discovered during risk reduction salpingo-oophorectomy in women with germ-line BRCA1 or BRCA2 mutations, Gynecol. Oncol. 132 (2014) 280–286.
[33] C.B. Powell, E.M. Swisher, I. Cass, J. McLennan, B. Norquist, R.L. Garcia, J. Lester, B.Y. Karlan, L. Chen, Long term follow up of BRCA1 and BRCA2 mutation carriers with unsuspected neoplasia identified at risk reducing salpingo-oophorectomy, Gynecol. Oncol. 129 (2013) 364–371.
[34] M.G. Patrono, M.D. Iniesta, A. Malpica, et al., Clinical outcomes in patients with isolated serous tubal intraepithelial carcinoma (STIC): a comprehensive review, Gynecol. Oncol. 139 (2015) 568–572.
[35] P.O. Brown, C. Palmer, The preclinical natural history of serous ovarian cancer: defining the target for early detection, PLoS Med. 6 (2009), e1000114. .
[36] C.B. Gilks, J. Irving, M. Köbel, et al., 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 (2015) 357–364.
[37] D.W. Kindelberger, Y. Lee, A. Miron, et al., Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship, Am. J. Surg. Pathol. 31 (2007) 161–169.
[38] F. Chen, K. Gaitskell, M.J. Garcia, et al., Serous tubal intraepithelial carcinomas associated with high-grade serous ovarian carcinomas: a systematic review, Brit. J. Obstet. Gynecol. 124 (2017) 872–878.
[39] N. Singh, C.B. Gilks, L. Hirschowitz, et al., Primary site assignment in tubo-ovarian high-grade serous carcinoma: consensus statement on unifying practice worldwide, Gynecol. Oncol. 141 (2016) 195–198.
[40] M.H. Roh, Y. Yassin, A. Miron, et al., High-grade fimbrial-ovarian carcinomas are unified by altered p53, PTEN and PAX2 expression, Mod. Pathol. 23 (2010) 1316–1324.
[41] B.E. Howitt, S. Hanamornroongruang, D.I. Lin, et al., Evidence for a dualistic model of high-grade serous carcinoma: BRCA mutation status, histology, and tubal intraepithelial carcinoma, Am. J. Surg. Pathol. 39 (2015) 287–293.
[42] T.R. Soong, B.E. Howitt, A. Miron, et al., Evidence for lineage continuity between early serous proliferations (ESPs) in the fallopian tube and disseminated high-grade serous carcinomas, J. Pathol. 25 (2018 Jul).
[43] A.S. McDaniel, J.N. Stall, D.H. Hovelson, et al., Next-generation sequencing of tubal intraepithelial carcinomas, JAMA Oncol. 1 (2015) 1128–1132.
[44] E.E. Meserve, K.C. Strickland, A. Miron, et al., Evidence of a monoclonal origin for bilateral serous tubal intraepithelial neoplasia, Int. J. Gynecol. Pathol. (2018) (in press).
[45] J.M. Piek, P.J. van Diest, R.P. Zweemer, et al., Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer, J. Pathol. 195 (2001) 451–456.
[46] Y. Lee, A. Miron, R. Drapkin, et al., A candidate precursor to serous carcinoma that originates in the distal fallopian tube, J. Pathol. 211 (2007) 26–35 (Erratum in: *J Pathol* 2007; 213: 116).
[47] R. Vang, K. Visvanathan, A. Gross, et al., Validation of an algorithm for the diagnosis of serous tubal intraepithelial carcinoma, Int. J. Gynecol. Pathol. 31 (2012) 243–253.
[48] S. Lee, G. Nelson, Q. Duan, et al., Precursor lesions and prognostic factors in primary peritoneal serous carcinoma, Int. J. Gynecol. Pathol. 32 (2013) 547–555.
[49] R.T. Marquez, K.A. Baggerly, A.P. Patterson, et al., Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon, Clin. Cancer Res. 11 (2005) 6116–6126.
[50] S.I. Labidi-Galy, E. Papp, D. Hallberg, et al., High grade serous ovarian carcinomas originate in the fallopian tube, Nat. Commun. 8 (2017) 1093.
[51] K.K. Mehra, M.C. Chang, A.K. Folkins, et al., The impact of tissue block sampling on the detection of p53 signatures in fallopian tubes from women with BRCA 1 or 2 mutations (BRCA+) and controls, Mod. Pathol. 24 (2011) 152–156.
[52] T. Kar, A. Kar, I. Dhal, et al., Serous tubal carcinogenesis: the recent concept of origin of ovarian, primary peritoneal and fallopian tube high-grade serous carcinoma, J. Obstet. Gynaecol. India 67 (2017) 432–441.
[53] E. Kuhn, R.J. Kurman, R. Vang, et al., TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma—evidence supporting the clonal relationship of the two lesions, J. Pathol. 226 (2012) 421–426.
[54] R.A. Ambros, M.E. Sherman, C.M. Zahn, et al., Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation, Hum. Pathol. 26 (1995) 1260–1267.
[55] W. Zheng, L. Xiang, O. Fadare, et al., A proposed model for endometrial serous carcinogenesis, Am. J. Surg. Pathol. 35 (2011) e1–e14.
[56] E.A. Jarboe, E.S. Pizer, A. Miron, et al., Evidence for a latent precursor (p53 signature) that may precede serous endometrial intraepithelial carcinoma, Mod. Pathol. 22 (2009) 345–350.
[57] J.M. Piek, P.J. van Diest, R.P. Zweemer, et al., Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer, J. Pathol. 195 (2001) 451–456.
[58] M.S. Anglesio, A. Bashashati, Y.K. Wang, et al., Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden, J. Pathol. 236 (2015) 201–209.
[59] M.S. Anglesio, Y.K. Wang, M. Maassen, et al., Synchronous endometrial and ovarian carcinomas: evidence of clonality, J. Natl. Cancer Inst. 108 (6) (2016).
[60] D.M. Dinulescu, T.A. Ince, B.J. Quade, et al., Role of K-ras and Pten in the development of mouse models of endometriosis and endometrioid ovarian cancer, Nat. Med. 11 (2005) 63–70.
[61] J. Kotsopoulos, J. Gronwald, B. Karlan, et al., Hereditary ovarian cancer clinical study group. Age-specific ovarian cancer risks among women with a BRCA1 or BRCA2 mutation, Gynecol. Oncol. 150 (2018) 85–91.
[62] I.J. Jacobs, U. Menon, A. Ryan, et al., Ovarian cancer screening and mortality in the UK collaborative trial of ovarian Cancer screening (UKCTOCS): a randomised controlled trial, Lancet 387 (10022) (2016 Mar 5) 945–956.
[63] A. Saleemuddin, A.K. Folkins, L. Garrett, et al., Risk factors for a serous cancer precursor ("p53 signature") in women with inherited BRCA mutations, Gynecol. Oncol. 111 (2008) 226–232.

[64] K. Visvanathan, P. Shaw, B.J. May, et al., Fallopian tube lesions in women at high risk for ovarian Cancer: a multicenter study, Cancer Prev. Res. (Phila.) 11 (2018) 697–706.
[65] K.Q. Cai, H. Wu, A.J. Klein-Szanto, et al., Acquisition of a second mutation of the Tp53 alleles immediately precedes epithelial morphological transformation in ovarian tumorigenicity, Gynecol. Oncol. 114 (2009) 18–25.
[66] T.R. Rebbeck, N.D. Kauff, S.M. Domchek, Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers, J. Natl. Cancer Inst. 101 (2009) 80–87.
[67] L.L. Holman, S. Friedman, M.S. Daniels, et al., Acceptability of prophylactic salpingectomy with delayed oophorectomy as risk-reducing surgery among BRCA mutation carriers, Gynecol. Oncol. 133 (2014) 283–286.