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Low-stage high-grade serous ovarian carcinomas: support for an extra-ovarian origin

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Summary

Many adnexal high-grade serous carcinomas (HGSCs) may derive from microscopic precursors in the fallopian tube. By studying a series of low-stage ovarian carcinomas, we anticipated that HGSCs would be distributed in a pattern suggesting secondary involvement, helping to indirectly validate the fallopian tube origin theory, and that most ovarian carcinomas other than SCs would demonstrate features consistent with derivation from precursors located in or transplanted to the ovary. Seventy-six patients with low-stage (FIGO I/II) sporadic ovarian carcinoma who underwent primary surgical management at Memorial Sloan Kettering Cancer Center from 1980 to 2000 were included in the study. Histologic type was assigned using Gilks' criteria.¹³ Similar to the approach taken when distinguishing primary and metastatic mucinous or endometrioid carcinoma involving ovary, cases interpreted as showing a "primary" pattern of ovarian involvement had 3 or more of the following features: unilateral tumor, size greater than 12 cm, no surface involvement, no multinodularity, no destructive stromal invasion. All other cases were considered to show a "metastatic" pattern of ovarian involvement. Cases were evaluated for p53 and WT-1 expression, using standard techniques on a tissue microarray. *TP53* gene sequencing was also performed. Cases comprised HGSC (n=22), endometrioid carcinoma (n=30), clear cell carcinoma (n=13) and mucinous carcinoma (n=11). HGSCs displayed substantially more "metastatic features" than the non-HGSC group and a mean overall size that was smaller (8.85 cm vs 14.1 cm). Statistically significant differences were found for bilaterality (63% vs 7.3%), $p = 0.0001$; multinodularity (55% vs 7.3%), $p = 0.0001$; tumor size, $p = 0.003$; and surface involvement (50% vs 13%), $p = 0.002$. Five of 22 (23%) of HGSCs showed a "primary pattern" of ovarian involvement. There were no significant differences between these cases and "metastatic pattern" HGSCs when comparing morphology, immunophenotype, *TP53* mutational status, and clinical outcomes. Most low-stage HGSCs demonstrate patterns of ovarian involvement that suggest metastasis from another source, such as the fallopian tube. Both metastatic pattern HGSCs and unilateral, low-stage HGSCs can behave aggressively.

Keywords

serous carcinoma; ovary; low-stage; metastasis; fallopian tube

Introduction

Recent studies suggest that many high-grade serous carcinomas (HGSCs) that present as ovarian carcinomas may derive from microscopic precursors in the fallopian tube, termed serous tubal intraepithelial carcinomas (STICs).¹⁻⁵ One study demonstrated that HGSCs show expression profiles and immunophenotypes more closely related to tubal epithelium than to the ovarian surface epithelium (OSE)^{6,7}; another study demonstrated different telomere lengths in STIC with matched ovarian carcinomas,^{8,9} providing further evidence that STICs are ovarian HGSC precursors. Alternative theories include derivation from the ovarian surface epithelium or ovarian epithelial inclusion cysts. Gene expression profiling studies have demonstrated more similarity between the epithelium of ovarian inclusion cysts and carcinoma than the ovarian surface, bolstering the inclusion cyst theory, and further diminishing the OSE hypothesis that asserts that ovarian carcinoma arises from the OSE and/or cortical invaginations.¹⁰ Profiling studies also indirectly strengthen the overarching theory that HGSCs arise in epithelium showing tubal differentiation, including not only fallopian tube epithelium, but also ovarian epithelial inclusions cysts, since these may be derived from tubal epithelium that has secondarily implanted onto the ovarian surface and subsequently become incorporated into the cortex.¹¹

While the concept of HGSC developing from STIC is no longer novel and has been examined from a variety of different perspectives, a recent search of the literature reveals that a comparative clinicopathological analysis of low-stage HGSC that focuses on the site of origin has not yet been performed. Evaluation of low-stage disease is advantageous because a major obstacle in the evaluation of carcinogenetic pathways in HGSC is that the overwhelming majority of cases present at high stage, which frequently precludes determination of the site of origin. Approximately 70% of ovarian carcinomas are HGSCs and 90% of patients with high-stage (FIGO III/IV) have HGSC.¹² By thoroughly examining a series of low-stage ovarian carcinomas, we hoped to circumvent this problem and gain insight into the source of HGSC at the earliest possible stages of disease. We anticipated that most ovarian cancers other than serous carcinomas (SCs) would demonstrate features consistent with derivation from precursors located in or transplanted to the ovary and that the majority of HGSCs would be distributed in a pattern suggesting secondary involvement, helping to further validate the fallopian tube origin theory.

Materials and Methods

Seventy-six patients with low-stage (FIGO I/II) sporadic ovarian carcinoma who underwent primary surgical management at Memorial Sloan Kettering Cancer Center from 1980 to 2000 were included in the study. Clinical and histologic features of this cohort were previously reported in 2004¹³ and 2013.¹⁴ The cases were processed prior to the implementation of the Sectioning and Extensively Examining the Fimbriae (SEE-FIM) protocol. H&E slides were reviewed and histologic type assigned using *Gilks, Soslow et al* criteria.¹⁵ Twenty-two HGSCs, 30 endometrioid, 13 clear cell, and 11 mucinous ovarian carcinomas were studied to determine primary or metastatic origin, which was assigned based on the presence of parameters evaluated when distinguishing between primary and

secondary ovarian mucinous or endometrioid neoplasms.^{16,17} These parameters, termed “metastatic parameters” for the purposes of this study, included bilaterality, multifocality, surface involvement, size, and pattern of invasion.

Cases interpreted as “primary” showed 3 or more of the following features: unilateral tumor, size greater than 12 cm, no surface involvement, no multinodularity, no destructive stromal invasion. All other cases were considered “metastatic.” We also assessed the HGSCs’ growth pattern and stratified them into 5 categories: BRCA-like (FIG 1), intracystic (FIG 2), adenofibromatous (FIG 3), infiltrative micropapillary (FIG 4), and mixed epithelial (FIG 5). The BRCA-like pattern was based on HGSC features in patients with *BRCA1* mutations elaborated in a study by *Soslow et al* in 2012.¹⁸ In the absence of findings that suggested secondary ovarian involvement, an intracystic growth pattern was assumed to represent a “primary” pattern. Mixed epithelial carcinomas with a high-grade serous component were coded as HGSC for the purposes of this study (n=1). The distribution and number of epithelial inclusion cysts was also assessed.

All of the cases were evaluated for p53 and WT-1 expression immunohistochemically¹⁴ and for *TP53* mutation via molecular studies.¹³ Immunohistochemical studies were performed using standard techniques on a tissue microarray. p53 expression was considered aberrant if there was complete absence of staining or “null” phenotype, or if there was strong diffuse staining in at least 75% of the tumor cells. Staining for p53 in less than 75% of cells, indistinguishable from the background of physiologic expression in non-neoplastic tissue, was considered normal.¹⁴ Direct gene sequencing of the entire coding region of *TP53* was performed on all cases with available tissue.¹³ Categorical variables were compared using Chi-square or Fisher exact tests as appropriate. Continuous variables were compared using Mann-Whitney U or Kruskal-Wallis tests as appropriate. Progression-free survival was determined from date of diagnosis to recurrence, death, or last follow-up. Overall survival was determined from date of diagnosis to death or last follow-up. Survival was estimated using Kaplan-Meier estimates and compared with log-rank test.

Results

In total, 76 cases of ovarian carcinoma were evaluated, including HGSC (n=22), endometrioid carcinoma (n=30), clear cell carcinoma (n=13), and mucinous carcinoma (n=11).¹⁴ Sections of fallopian tube were available for examination in only 9 HGSCs. A comparison of the “metastatic” parameters for HGSCs vs non-HGSCs is displayed in Table 1. As expected, HGSCs displayed a higher percentage of metastatic features than the non-HGSC group across all 4 categories (bilaterality, multifocality, surface involvement, and pattern of infiltration) and displayed a mean overall size that was smaller than the non-HGSC group (8.85 cm vs 14.1 cm). These differences reached statistical significance in the categories of bilaterality (63% vs 7.3%), $p = 0.0001$; multinodularity (55% vs 7.3%), $p = 0.0001$; difference in median size, $p = 0.003$; and surface involvement (50% vs 13%), $p = 0.002$.

When the 22 HGSCs were independently evaluated for these parameters, a subset of 5 cases emerged which possessed a “primary” pattern of ovarian involvement. These results are

displayed in Table 2. Four of these cases were pure HGSCs and one case was a mixed low-grade endometrioid and HGSC, but for the purposes of the study was included under the HGSC category. These primary pattern HGSCs tended to be unilateral, lacked surface involvement and gross multinodularity, and were of an overall larger mean size than other HGSCs. All 5 of these tumors were Stage I whereas only 18% of the metastatic pattern tumors presented as Stage I, with the majority of the tumors (58%) being stage IIC (Table 3).

To determine whether there were underlying genetic or morphologic differences between the primary and metastatic pattern HGSC, tumor slides were reviewed and cases stratified into five broad categories in terms of growth pattern. These patterns included BRCA-like, cystic, adenofibromatous, infiltrative micropapillary, and mixed epithelial (Table 4). The tumors were also evaluated with immunohistochemistry for WT-1 and aberrant p53 expression and with molecular analysis for *TP53* gene mutation (Table 5); there proved to be no significant difference between the two groups for these factors. We attempted to record the number and distribution of epithelial inclusion cysts, but a meaningful correlation was not possible because the ovaries were subtotally replaced by carcinoma in most cases studied.

We then studied clinical outcomes in the primary and metastatic HGSC groups by examining 10-year progression free- and overall survival. There were no significant differences between the two groups of HGSC (Table 6).

Finally we examined the group of five primary pattern HGSC to determine whether any further subsets emerged. The results of this comparison are displayed in Table 7. The one mixed low-grade endometrioid and HGSC was different from the four pure HGSC in that it was the only one without WT-1 expression, it was of significantly larger size, it lacked *TP53* mutation (although aberrant p53 expression was present), and the patient had a favorable clinical course, with no evidence of disease at 151 months follow-up.

Discussion

There have been many theories as to the precursor of ovarian HGSC and until recently it was generally accepted that HGSCs arose from the ovarian “surface epithelium” or even juxta-ovarian mesonephric remnants.¹⁹ A number of more recent molecular, genetic, and immunohistochemical studies have provided evidence that many or most pelvic and extrauterine high-grade serous carcinomas likely originate in the fallopian tubes.^{1–11} The current study, an examination of a series of low-stage ovarian carcinomas including low-stage HGSCs, supports the idea that many HGSCs do not arise within the ovary; as compared to the other major ovarian carcinoma subtypes, low-stage HGSCs are significantly more often distributed bilaterally and multifocally with ovarian surface involvement of relatively small ovaries, patterns which, with the exception of SC, are almost always equated with metastasis to the ovaries. The morphology, immunophenotype, and *TP53* mutational status of low-stage HGSC is identical to that reported for the far more common high-stage HGSCs. Survivals in this cohort, composed of cases diagnosed 15–35 years ago, are equivalent to modern survival estimates for HGSCs including both low- and high-stage cases. Although this suggests that stage designation may not be a major indicator of clinical

outcomes in HGSC, it also leaves open the possibility that these low-stage patients might have experienced better survivals had they been treated with modern therapy.

Although most HGSCs exhibited patterns that suggested secondary ovarian involvement, we found a small subset of HGSCs that were compatible with an ovarian primary. A publication from our group explored the possibility that some HGSCs might arise within epithelial inclusion cysts that acquire morphologic and genetic features similar to STIC.¹⁰ The index HGSC, a predominantly intraepithelial carcinoma that partly colonized the lining of an epithelial inclusion cyst, was found in a prophylactic risk-reducing bilateral salpingo-oophorectomy specimen. At least one additional example of this type has been described (personal communication, T. Longacre). Kurman et al have also made reference to the possibility that non-neoplastic tubal epithelium may implant and secondarily become incorporated into the ovarian cortex during ovulation, setting the stage for progression to carcinoma in a manner similar to that described within the eutopic fallopian tube.¹¹ We attempted to test this theory by assessing the number and distribution of epithelial inclusion cysts among the study cases but this proved to be impossible due to the fact that while the tumors were overall low-stage, they for the most part completely or subtotally replaced non-neoplastic ovarian parenchyma. There were no significant differences in the distribution of intracystic carcinomas between groups, but the number of relevant cases was very small.

Review of the literature revealed a number of studies examining the role of ovarian inclusion cysts in the development of ovarian epithelial carcinoma. In a series of studies by Deligdisch and colleagues, the ovaries of “at risk” women (first degree relatives with a history of ovarian carcinoma, *BRCA* mutation positive, etc) who underwent prophylactic oophorectomy were compared against a control cohort.^{20,21} Features that occurred at higher frequency in the at risk or “cancer-prone” population as compared to control groups included not only the expected findings of surface epithelial pseudostratification, surface papillations, and deep cortical invaginations, but also an increased number of epithelial inclusion cysts.^{22,23} Although differences in the numbers of inclusions in the “at risk” ovaries vs the control ovaries did not reach statistical significance in these studies, a separate study by Salazar et al demonstrated a significant difference in the number of inclusion cysts between the two groups ($p = 0.006$).²⁴ Differences in the characteristics of inclusion cysts on an immunohistochemical level were also identified in a study by Hutson et al.²⁵ They utilized p53 immunohistochemical staining, a hallmark of high-grade serous carcinoma,^{26,27} to evaluate epithelial inclusion cysts with atypia and identify differences at the between epithelial inclusion cysts adjacent to and contralateral to serous carcinoma. The comparison group included normal ovaries and those containing borderline tumors. The authors reported that cysts associated with serous carcinomas were more likely to abnormally express p53 than those associated with borderline tumors or benign ovaries (62.5% vs 0%).²⁵ Therefore, the number and type of inclusion cysts may play a role in the genesis of ovarian HGSC.

Tumors resembling or representing HGSC can also theoretically arise from other precursors within the ovary, notably endometriosis^{28,29} or a low-grade serous or endometrioid neoplasm. A series of studies have examined the phenomenon of HGSCs or undifferentiated carcinomas that arose in association with LGSC or serous borderline tumor. McCluggage and colleagues described a series of 7 low-grade ovarian carcinomas associated with high-

grade carcinomas.³⁰ While the majority of the tumors in this study were high stage (IIIC and above), there were 2 cases that presented as IC. Both of these tumors were originally diagnosed as serous borderline tumors (one specifically seromucinous borderline tumor) and both recurred as HGSC. These findings were also identified in similar studies performed by two other groups.^{31,32} While these studies clearly document the occurrence of transformation from low-grade to HGSC, they do not explain the phenomenon of low-stage high-grade serous carcinoma. None of the HGSCs in our study was associated with a low-grade serous tumor.

Literature review produced two studies by Silva and Tornos that described the characteristics of mixed low-grade endometrioid and HGSC. They reported that regardless of its extent, the presence of a serous component in an otherwise low-grade endometrioid carcinoma conferred a significantly more aggressive biologic behavior (higher rate of metastasis at presentation, decreased disease-free and overall survival, etc) than purely endometrioid counterparts.^{33,34} We identified one tumor diagnosed as mixed endometrioid and HGSC in this series and, interestingly, despite the presence of a high-grade component that resembled HGSC, the tumor's distribution, immunophenotype, and clinical evolution were more in keeping with a primary ovarian endometrioid carcinoma than a HGSC. This would account for the absence of WT-1 expression. It is possible that the higher grade component had a *TP53* mutation that resulted in the observed aberrant expression pattern. The reported absence of a *TP53* mutation could be explained if only the low-grade endometrioid component had been inadvertently subjected to *TP53* gene sequencing. Whether this tumor represents a mixed epithelial carcinoma with an HGSC component or an endometrioid carcinoma showing intratumoral heterogeneity is an open question.

In summary, while many studies have evaluated the origin of HGSC by looking at intraepithelial lesions within the fallopian tube, we sought to look at the problem from a different perspective. We demonstrated that low-stage HGSC usually involves the ovary in a pattern compatible with metastasis from an extra-ovarian primary, in contrast to endometrioid and clear cell carcinomas, which are known to arise in association with ovarian endometriosis in a significant percentage of cases.^{28,29} Although we were unable to find an inclusion cyst precursor for HGSCs with a primary pattern of involvement, we noted one primary ovarian carcinoma resembling primary HGSC that arose in a background of a low-grade ovarian endometrioid carcinoma. Whether they arise from low-grade precursors within the ovary or displaced epithelium from fallopian tube HGSCs, there is little evidence to support the idea that HGSCs arise from ovarian "surface epithelium." Our findings demonstrate a strong association between HGSC and a metastatic pattern of ovarian involvement, adding to existing data that support the extra-ovarian origin of "ovarian" HGSCs.

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Figure 1. High-grade serous carcinoma with “BRCA-like” features. The tumor has a solid growth pattern, high nuclear grade, high proliferative rate, and tumor-infiltrating lymphocytes (A and B).

Figure 2.
Intracystic high-grade serous carcinoma.

Figure 3. High-grade serous carcinoma with an “adenofibromatous” growth pattern. The tumor forms glands and nests deposited in a fibromatous stroma lacking a desmoplastic reaction (**A** and **B**).

Figure 4.
High-grade serous carcinoma with an infiltrative micropapillary growth pattern.

Figure 5. Mixed serous and endometrioid carcinoma. The low power image demonstrates predominantly endometrioid features, but transition to a higher grade component is found at left (**A**). The low-grade component (**B**) is endometrioid, while the high-grade component (**C**) was interpreted as high-grade serous carcinoma.

Table 1

Comparison of different types of low-stage ovarian carcinoma

Parameter	HGSC (n =22)	Endo (n=30)	Mucinous (n=11)	Clear cell (n= 13)	p-value
Bilateral	14 (63%)	4 (13%)	0%	0%	0.0001
Multinodularity	12 (55%)	2 (7%)	0%	2 (15%)	0.0001
Surface involvement	11 (50%)	5 (17%)	0%	2 (15%)	0.002
Size (median) (range)	8.85 cm (2–28 cm)	12.5 cm (4–45 cm)	17.4 cm (9–35 cm)	11 cm (4–20 cm)	0.003
Infiltrative	8 (36%)	7 (23%)	0%	5 (38%)	0.25

HGSC, high-grade serous carcinoma; Endo, endometrioid.

Table 2

Comparison of HGSCs with and without a metastatic pattern of adnexal involvement.

	Primary (n=5)	Metastatic (n=17)	p-value
Bilateral	1 (20%)	12 (71%)	0.12
Multifocal	0	11 (65%)	0.04
Surface Involvement	0	11 (65%)	0.04
Size, median (range)	17 cm (12–27 cm)	7.5 cm (2–28 cm)	0.01
Infiltrative	2 (40%)	8 (47%)	1.0
STIC	0/1	1/8	

HGSC, high-grade serous carcinoma; STIC, serous tubal intraepithelial carcinoma; SEE-FIM, Sectioning and Extensively Examining the Fimbriae.

Note: SEE-FIM protocol not applied.

Table 3

Stage comparison of HGSCs with and without a metastatic pattern of adnexal involvement

Stage at diagnosis	Primary (n=5)	Metastatic (n=17)	p-value
IA	3 (60%)	-	0.007
IB	1 (20%)	-	0.23
IC	1 (20%)	3 (18%)	1.0
IIA	-	1 (6%)	1.0
IIB	-	3 (18%)	1.0
IIC	-	10 (58%)	0.04

HGSC, high-grade serous carcinoma.

Table 4

Growth pattern comparison of HGSCs with and without a metastatic pattern of adnexal involvement.

Pattern	Primary (n=5)	Metastatic (n=17)	p-value
BRCA-like	3 (60%)	12 (71%)	1.0
Cystic	1 (20%)	2 (12%)	1.0
Adenofibromatous	0 (0%)	2 (12%)	1.0
Infiltrative micropapillary	0 (0%)	1 (5%)	1.0
Mixed epithelial	1 (20%)	0 (0%)	0.23

HGSC, high-grade serous carcinoma.

Table 5

Immunohistochemical and genotypic comparison of HGSCs with and without a metastatic pattern of adnexal involvement

	Primary (n=4)	Metastatic (n=17)	p-value
WT1 (+)	3 (75%)	12 (71%)	1.0
P53 (aberrant)	4 (100%)	12 (71%)	0.5322
TP53 Mutation	3 (75%)	12 (71%)	1.0

HGSC, high-grade serous carcinoma.

Table 6

Clinical comparison of HGSCs with and without a metastatic pattern of adnexal involvement

	Primary (n=5)	Metastatic (n=17)	p-value
10-year PFS - % (+/-SE)	40% (+/-21.9%)	57.4% (+/-12.3%)	0.6
10-year OS - % (+/-SE)	40% (+/-21.9%)	70.1% (+/-11.2%)	0.5

HGSC, high-grade serous carcinoma; PFS, progression free survival; OS, overall survival.

Table 7

Comparison of mixed low grade endometrioid and HGSC with other HGSCs showing a primary pattern of adnexal involvement*

	Mixed epithelial (n=1)	Other “primary” CA (n=4)
Bilateral	1/1	0%
Size (cm)	17	13, 18
Stage	IIB	IA (3), IC (1)
WT1 positive	0/1	100%
p53 aberrant	1/1	100%
<i>TP53</i> mutation	0/1	100%
Survival (median, months)	177	117.75

* Sample size too small to perform statistical analyses

HGSC, high-grade serous carcinoma.