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Molecular Alterations of *TP53* are a Defining Feature of Ovarian High-Grade Serous Carcinoma: A Rereview of Cases Lacking *TP53* Mutations in The Cancer Genome Atlas Ovarian Study

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Summary

The Cancer Genome Atlas has reported that 96% of ovarian high-grade serous carcinomas (HGSCs) have *TP53* somatic mutations suggesting that mutation of this gene is a defining feature of this neoplasm. In the current study, 5 gynecologic pathologists independently evaluated hematoxylin and eosin slides of 14 available cases from The Cancer Genome Atlas classified as HGSC that lacked a *TP53* mutation. The histologic diagnoses rendered by these pathologists and the accompanying molecular genetic data are the subject of this report. Only 1 case (Case 5), which contained a homozygous deletion of *TP53*, had unanimous interobserver agreement for a diagnosis of pure HGSC. In 1 case (Case 3), all 5 observers (100%) rendered a diagnosis of HGSC; however, 3 observers (60%) noted that the histologic features were not classic for HGSC and suggested this case may have arisen from a low-grade serous carcinoma (arisen from an alternate pathway compared with the usual HGSC). In 2 cases (Cases 4 and 12), only 3 observers (60%) in each case, respectively, interpreted it as having a component of HGSC. In the remaining 10 (71%) of tumors (Cases 1, 2, 6–11, 13, and 14), the consensus diagnosis was not HGSC, with individual diagnoses including low-grade serous carcinoma, high-grade endometrioid carcinoma, HGSC, metastatic carcinoma, clear cell carcinoma, atypical proliferative (borderline) serous tumor, and adenocarcinoma, not otherwise specified. Therefore, 13 (93%) of the tumors (Cases 1–4 and 6–14) were either not a pure HGSC or represented a diagnosis other than HGSC, all with molecular results not characteristic of HGSC. Accordingly, our review of the *TP53* wild-type HGSCs reported in The Cancer Genome Atlas suggests that 100% of *de novo* HGSCs contain *TP53* somatic mutations or deletions, with the exception of the rare HGSCs that develop from a low-grade serous tumor precursor. We, therefore, propose that lack of molecular alterations of *TP53* are essentially inconsistent with the diagnosis of ovarian HGSC and that tumors diagnosed as such should be rigorously reassessed to achieve correct classification.

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Keywords

The Cancer Genome Atlas; TCGA; *TP53*; High-grade serous carcinoma

Ovarian cancer is the most lethal gynecologic malignancy accounting for approximately 21,980 new cases in 2014 and resulting in 14,270 deaths annually in the United States (1). High-grade serous carcinoma (HGSC) accounts for approximately 75% of all ovarian carcinomas and is responsible for nearly 90% of the fatalities (2). The recent recognition of a microscopic precursor lesion in the fallopian tube, serous tubal intraepithelial carcinoma, which is morphologically similar to ovarian HGSC and contains a *TP53* mutation in >90% of cases, (3,4) suggests that mutation of *TP53* is an early and important molecular event in the pathogenesis of HGSC. A genome-wide analysis of HGSC by The Cancer Genome Atlas (TCGA) Research Network reported *TP53* mutations in 96% of specimens (5), supporting this view. In that study, only 15 HGSCs analyzed lacked a *TP53* mutation raising the question as to what distinguished this small group from the remainder. The aim of the present study was to evaluate the morphologic features and molecular genetic data of this particular group of tumors to determine whether the lack of *TP53* mutations characterized a rare subset of HGSCs or whether the tumors had been misclassified.

MATERIALS AND METHODS

All samples were part of the previously reported TCGA study on ovarian cancer that was IRB approved at all participating sites (5). In the TCGA study, cases were included based on the original pathology report. Specimens were reviewed by the Biospecimen Core Resource (a centralized laboratory that reviews and processes specimens and their associated data for all of the TCGA Research Network). However, whether specific histologic criteria were used is unknown. Immunohistochemistry was not employed as inclusion/exclusion criteria in the TCGA, and the original pathology reports for the cases in the current study do not indicate that immunohistochemistry was performed at the time of the initial diagnosis.

All tumor-bearing slides from the 15 TCGA cases with wild-type *TP53* sequences were retrieved from tissue source sites. One case with insufficient tissue for review was excluded. All hematoxylin and eosin slides from the remaining 14 cases were reviewed by 1 author (R.J.K.), and representative slides were selected for this study. Those representative slides were reviewed independently by 5 gynecologic pathologists (R.V., I.-M.S., R.A.S., C.Z., R.J.K.) who were blinded to all clinical and molecular information with the exception that all cases lacked a *TP53* mutation, and a diagnosis was rendered based on criteria used in routine practice. Molecular data were obtained from the cBioPortal for Cancer Genomics website (6), and those results were then correlated with the rendered rereview diagnoses.

RESULTS

The 5 pathologists' diagnoses in this study and reported molecular data for each tumor are shown in Table 1. All 5 pathologists agreed in 8 (57%) of the 14 cases, and at least 3 pathologists agreed in 11 (79%) of the cases. Of the 8 cases with a unanimous diagnosis, 4 were classified as low-grade serous carcinoma (LGSC) (Cases 6, 11, 13, and 14), 1 as an

atypical proliferative serous tumor (typical serous borderline tumor) (Case 9), 1 as a high-grade endometrioid carcinoma (Case 8), 1 as an unusual HGSC with features suggesting evolution from LGSC (Case 3), and 1 as a pure HGSC (Case 5). Therefore, the panel of observers uniformly agreed that only 1 (7%) of 14 TCGA *TP53* wild-type cases originally diagnosed as HGSC was unequivocally an HGSC (Case 5) (Fig. 1). This tumor had a *BRCA1* germline mutation, substantial level of somatic copy number alterations, high number of mutations, and homozygous *TP53* deletion.

The other tumor diagnosed by all panel members as an HGSC, but for which 3 of 5 observers noted features suggesting evolution from LGSC (Case 3) (Fig. 2) had a substantially lower number of mutations and relatively lower level of somatic copy number alterations. Morphologically, this tumor had a micropapillary-rich architecture but exhibited greater cytologic atypia and more mitotic figures than the usual LGSC, warranting a diagnosis of HGSC. It lacked the molecular features characteristic of HGSC, specifically a *TP53* mutation, large number of mutations, and high level of somatic copy number alterations (6–9). In contrast, it lacked *KRAS* and *BRAF* mutations, which are found in approximately half of LGSCs (10,11). Thus, neither the morphologic nor molecular findings allowed for the definitive classification of this neoplasm.

In each of 2 cases (Cases 4 and 12), 3 of 5 observers, respectively, diagnosed a component of HGSC. In Case 4 (Fig. 3), 1 of the 3 observers that diagnosed a component of HGSC also noted a mixed component of LGSC. However, 2 observers in this case interpreted the tumor as clear cell carcinoma. In Case 12 (Fig. 4), 2 of the observers diagnosed the tumor as something other than HGSC: 1 as clear cell carcinoma and the other as adenocarcinoma, not otherwise specified. On the basis of morphology and the relatively low level of somatic copy number alterations, both cases were not unequivocally HGSC.

In the remaining 10 cases (Cases 1, 2, 6–11, 13, and 14), between 0 and 2 observers per case rendered a diagnosis of HGSC, with non-HGSC diagnoses including LGSC, high-grade endometrioid carcinoma, metastatic carcinoma, and atypical proliferative (borderline) serous tumor (Table 1). Therefore, these cases were morphologically misclassified or unclassifiable, and some had numbers of mutations and/or levels of somatic copy number alterations that were not characteristic of HGSC (Table 1).

DISCUSSION

An accurate diagnosis of HGSC is important for proper clinical management and clinical trial stratification. HGSCs are exquisitely sensitive to platinum- based agents and respond to poly-(ADP-ribose) polymerase (PARP) inhibitors, unlike other histologic subtypes (12). In addition, HGSC is the most common subtype associated with *BRCA* germline mutations and warrants genetic testing, particularly in women with a strong family history of ovarian and/or breast carcinoma. Serous tubal intraepithelial carcinoma, the proposed precursor of ovarian/peritoneal HGSC, also exhibits *TP53* mutations in 93% of cases, (3,4,13–16) implicating this molecular alteration as an early event in the pathogenesis of HGSC. Current screening tests for ovarian cancer utilizing serum measurement of CA125 and transvaginal ultrasound have failed to demonstrate a survival benefit (17–21). However, the recognition

that nearly 100% of ovarian HGSCs contain a *TP53* mutation suggests that detection of this molecular alteration may be a promising screening test. Accordingly, the likely success of such an approach is borne out by a recently reported screening test (PapGene test) that used a panel of genes commonly mutated in ovarian carcinomas, including *TP53*, and successfully detected 41% of ovarian cancers (22).

To properly classify a tumor as HGSC, reproducible histologic features must be utilized. Per the 2014 WHO Classification for gynecologic tumors, ovarian HGSC is characterized by solid, papillary, glandular, and cribriform architecture with slit-like spaces, necrosis, high-grade nuclei with bizarre forms, prominent nucleoli, abundant mitotic figures, and psammoma bodies (23). In a study of primary ovarian carcinomas published before the 2014 WHO Classification, Köbel et al. (24) demonstrated that, using histologic criteria for HGSC similar to those above, excellent interobserver reproducibility can be achieved for all histologic types combined. Particularly in the validation set in that study, 94% of cases originally diagnosed as HGSC were concordant with the central review diagnosis. For the discordant cases, 4% and 2% of those originally diagnosed as HGSC were interpreted as LGSC and endometrioid carcinoma, respectively, upon central review. Their overall frequency of misclassification of HGSC is similar to the readjusted data for the TCGA although only the HGSCs lacking a *TP53* mutation were rereviewed in our study. Nevertheless, the findings in our study show the value of rigorous histologic assessment for properly defining HGSC.

Although it was not the goal of this study to immunohistochemically evaluate cases without *TP53* mutations or those having nonconsensus, the use of immunohistochemical stains for the assessment of carcinomas involving the ovary can be useful to improve diagnostic accuracy and interobserver reproducibility of primary ovarian carcinomas in general, as well as distinguish LGSC from HGSC and exclude some metastatic adenocarcinomas (25–35). In particular, ovarian HGSC is usually positive for PAX8, ER, PR, and WT-1, exhibits an abnormal pattern of p53 expression (either diffuse strong or complete absence of staining), and often but not always shows diffuse expression of p16. Thus, careful attention to histologic features and selected use of immunohistochemical stains can help avoid misclassification as HGSC.

Even though consensus guidelines have not yet been established as to whether immunohistochemistry is necessary for diagnosing all cases of HGSC, the use of immunohistochemical stains should be performed at the discretion of the pathologist, particularly based on his/her level of experience with ovarian tumors. For cases in which histologic features are considered classic, morphology alone should suffice. However, in cases where there is diagnostic uncertainty or the distinction between HGSC and other primary ovarian carcinomas is unclear, immunohistochemical staining for WT-1, p53, and p16, as described above, should be performed. Nonetheless, it must be emphasized that establishing/excluding a diagnosis of HGSC should not be based solely on one immunohistochemical stain. This is because some HGSCs can be negative for WT-1 or lack aberrant expression patterns of p53, occasional endometrioid carcinomas can be WT-1-positive, and some nonserous carcinomas can show aberrant expression patterns of p53 (23).

Thus, those immunohistochemical stains must be interpreted together as a panel of markers in the context of the morphologic appearance.

In addition to histology, it is also important to understand what defines HGSC at the molecular level. Prior work, including that of the TCGA, has established that molecular aberrations of HGSC consist of *TP53* mutations in >96% of cases, *BRCA* mutations (germline or somatic) in 20%, recurrent mutations in other genes in 2% to 6%, 20 to 60 mutations in the majority of cases, a high fraction of copy number altered genome in most cases with particular chromosomal gains and losses, and various patterns of promoter methylation, mRNA expression, and miRNA expression (5,6,8,9,36). Given the significant pathogenic role of *TP53* mutations and their high frequency in HGSC, their absence in select HGSCs in the TCGA was puzzling. The goal of the current study was to evaluate the histologic features of these *TP53* wild-type tumors to determine whether they represented a specific subset of HGSCs or if these were misclassified.

Rereview of hematoxylin and eosin slides in our study showed that the panel of pathologists uniformly agreed that only 1 of 14 TCGA *TP53* wild-type originally diagnosed as HGSC was unequivocally a pure HGSC (Case 5). This tumor had a *BRCA1* germline mutation, extensive somatic copy number alterations, and a homozygous *TP53* deletion instead of the more common somatic point mutation, underscoring the importance of loss of p53 function. Hence, our findings further support that unequivocal HGSCs have molecular alterations involving *TP53*. The other case diagnosed by all panel members as HGSC (Case 3) had histologic features suggestive of evolution from LGSC. The tumor lacked the molecular findings characteristic of HGSC, specifically a *TP53* mutation and high level of DNA copy number alterations (7). It has been reported that, on rare occasion, HGSCs may develop along a pathway evolving from a low-grade serous tumor (borderline tumor or LGSC) independent of the more common pathway for the usual HGSC, which involves *TP53* mutations and, presumably origin from serous tubal intraepithelial carcinoma (37,38). On the basis of interobserver histologic assessment and lack of molecular findings typical of HGSC (Table 1), the remaining cases in this study were either not a pure HGSC or represented a diagnosis other than HGSC.

The results of another study also support our findings. In an analysis of 126 extrauterine HGSCs, 94% were originally found to harbor *TP53* mutations (36). Seven cases were mutation-negative, and rereview of those showed that 3 were not pure HGSC (1 LGSC, 1 high-grade carcinoma of uncertain primary site, and 1 mixed LGSC-HGSC). The remaining 4 cases were interpreted as HGSC after rereview. After adjusting for the 3 mutation-negative non-HGSC cases, the frequency of *TP53* mutation in HGSC was 97%. Although alternative mechanisms of p53 dysfunction, such as amplification of *MDM2* and *MDM4*, were suggested for *TP53* mutation-negative HGSCs, it is unknown if these 4 *TP53* mutation-negative HGSCs were subjected to rigorous interobserver testing as was done in our study, which potentially may have increased the reclassification frequency of those cases and yielded an even higher proportion of *TP53* mutations in HGSC.

Of note, a recent study analyzing the clinical data from the *TP53* mutation-negative cases in the ovarian TCGA reported that women with *TP53* mutation-negative tumors had a

significantly shorter survival and their tumors had higher chemoresistance compared with the *TP53*-mutated cases (39). These findings should be interpreted in the light of our study showing that nearly all of the “*TP53* mutation-negative” cases were misclassified highlighting the importance of rigorous pathology rereview.

A potential limitation of the current study is that our pathology review panel was aware of the *TP53* status of these cases before slide review. However, we do not believe that this introduces any significant bias as this was not a traditional interobserver reproducibility study. The goal of the study was actually to simply determine what were the real diagnoses of the *TP53* wild-type cases in the TCGA. Moreover, the possibility that the panel members would not diagnose HGSC because they knew that the case lacked a *TP53* mutation was limited as Table 1 shows that a number of HGSC diagnoses were rendered by individual pathologists for various cases. Thus, the importance of our study is that it demonstrates that the vast majority of *TP53* wildtype cases diagnosed as HGSC in the TCGA were not HGSC.

In conclusion, the findings in this study complement and extend those reported by the TCGA by showing that all *de novo* ovarian HGSCs contain alterations of *TP53*, most frequently through somatic mutation. Although certain morphologic features are characteristic of HGSC, we propose that the lack of a *TP53* mutation is inconsistent with that diagnosis. These findings, in conjunction with genome-wide analysis of other gynecologic neoplasms, including ovarian clear cell carcinoma, (40,41) ovarian LGSC, (10) uterine endometrioid carcinoma, (42,43) and uterine serous carcinoma, (7,42,44) set the stage for the potential development of a morphologic-molecular classification of gynecologic neoplasms, similar to what has been achieved for breast carcinoma. This study demonstrates the need for establishing a rigorous definition of HGSC for enrollment in research studies and clinical trials. It also underscores the importance of careful pathology review in comprehensive cancer genome studies of cases with unusual molecular findings to determine if they represent variants of the particular tumor type or misclassifications.

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FIG. 1.

Case 5: all 5 observers classified this case as high-grade serous carcinoma. **(A)** The architectural features are notable for large papillae lined by stratified epithelium with irregular slit-like spaces. Numerous detached and small epithelial clusters are present. **(B)** The cytologic features consist of large nuclei, nuclear pleomorphism, hyperchromasia, bizarre nuclear atypia, and mitotic activity (arrow).

FIG. 2.

Case 3: all 5 observers classified this case as high-grade serous carcinoma; however, 3 noted features suggestive of evolution from lowgrade serous carcinoma. **(A)** The tumor is predominantly composed of a micropapillary-rich pattern, commonly seen in invasive low-grade serous carcinoma, in which small micropapillary nests within clear lacunar spaces haphazardly infiltrate through stroma. **(B)** The nuclei are not as large as frequently seen in high-grade serous carcinoma and more uniform than in most such cases. However, the combined presence of some degree of both chromatin irregularity and variation in nuclear shape and mitotic activity (arrows) favor classification as high-grade serous carcinoma.

FIG. 3.

Case 4: this case was classified as high-grade serous carcinoma by 2 observers, serous carcinoma with a mixture of low-grade and high-grade features by 1, and clear cell carcinoma by 2. **(A)** This tumor featured areas with tubulocystic-like architecture and a vague suggestion of hobnail cell shapes. **(B)** The papillae in other foci were lined by a single layer of low-cuboidal cells with a slight degree of monotony and without the degree of stratification seen in many high-grade serous carcinomas. A vague suggestion of hobnail cell shapes is also present. **(C)** Some areas had solid architecture consisting of polygonal cells with abundant clear cytoplasm.

FIG. 4.

Case 12: this case was classified as high-grade serous carcinoma by 3 observers, clear cell carcinoma by 1, and adenocarcinoma, not otherwise specified by 1. **(A)** The tumor shows solid architecture with variably sized nests haphazardly arranged within stroma. **(B)** Many areas had polygonal cells with round and relatively uniform nuclei and abundant clear cytoplasm. **(C)** A bizarre atypical cell (upper left) is present. **(D)** Some foci exhibited cord-like architecture. Note the presence of high-grade nuclei.

TABLE 1
Rereview diagnoses and molecular data for TP53 wild-type high-grade serous carcinomas from the TCGA study

Case	TCGA*	Rereview pathologist					Molecular data from the TCGA(6)			
		A	B	C	D	E	TP53 HD†	BRCA‡	No. Muts§	CNA (%)
1	09-2056	LGSC	HG Endo	LGSC	HGSC	HGSC	-	-	68	46
2	10-0933	Met	HG Endo	HG Endo	Met	Met	-	-	33	47
3	13-0727	HGSC¶	HGSC¶	HGSC¶	HGSC¶	HGSC	-	-	21	22
4	13-0755	CCC	LG/HGSC#	CCC	HGSC	HGSC	-	-	73	18
5	13-1408	HGSC	HGSC	HGSC	HGSC	HGSC	+	+	78	31
6	13-1477	LGSC	LGSC	LGSC	LGSC	LGSC	-	-	42	9
7	24-1544	Met	Met	Met	HGSC	HGSC	-	-	17	31
8	24-1565	HG Endo	HG Endo	HG Endo	HG Endo	HG Endo	-	-	25	9
9	24-2038	APST	APST	APST	APST	APST	-	-	10	11
10	25-1316	LGSC	HG Endo	LGSC	HGSC	HGSC	-	-	13	30
11	25-1328	LGSC	LGSC	LGSC	LGSC	LGSC	-	-	10	NA
12	25-2042	CCC	Adeno, NOS	HGSC	HGSC	HGSC	-	-	56	19
13	25-2408	LGSC	LGSC	LGSC	LGSC	LGSC	-	-	13	9
14	61-2095	LGSC	LGSC	LGSC	LGSC	LGSC	-	-	109	1

* TCGA study number.

† Homozygous deletion of *TP53*.

‡ Mutation of *BRCA1* or *BRCA2*.

§ No. mutations.

|| Fraction of copy number altered genome.

¶ HGSC with LGSC architecture.

Serous carcinoma with features of both LGSC and HGSC.

+ indicates Present; -, Absent; Adeno, adenocarcinoma; APST, atypical proliferative serous tumor (typical serous borderline tumor); CCC, clear cell carcinoma; HG Endo, high-grade endometrioid carcinoma; HGSC, high-grade serous carcinoma; LGSC, invasive low-grade serous carcinoma; Met, metastatic carcinoma; NA, not available; NOS, not otherwise specified; TCGA, The Cancer Genome Atlas