Research Square

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Divergent Mutational Landscapes and Clinical Outcomes in P53-Negative High-Grade Serous Ovarian Carcinoma Versus Cervical Cancer

Ping Qin
Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University
Tonghui Cai
Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University
Zilong Song
Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University
Tianyu Wang
Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University
Ruichao Chen
Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University
Li Zhao
Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University
Wei Zhang
Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University
Qingping Jiang
jiangqingping@gzhmu.edu.cn

Third Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University

Research Article

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Abstract

Objective

P53 negativity is a shared diagnostic feature of both some high-grade serous ovarian carcinoma (HGSOC) and cervical cancer, yet the underlying mechanisms remain poorly defined. This study aimed to elucidate the distinct pathogenic mechanisms and signaling dependencies that distinguish P53-negative HGSOC from P53-negative cervical cancer.

Methods

Hematoxylin and eosin (H&E) and P53 immunohistochemistry (IHC) were performed on archival HGSOC and cervical cancer cohorts. Clinical parameters were collected for P53-negative cases, followed by comprehensive molecular profiling using targeted next-generation sequencing (NGS). Differentially mutated genes were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses.

Results

Patients with P53-negative HGSOC were significantly older (≥ 50 years: 81.25% vs. 50%, $P < 0.05$) and exhibited a five-fold higher mortality rate (25% vs. 5%) than the P53-negative cervical cancer cohort. Molecular profiling revealed that all 16 P53-negative HGSOC cases harbored deleterious *TP53* mutations, whereas P53-negative cervical cancers showed wild-type *TP53* but high mutation frequencies in *PIK3CA* (33.33%) and *TERT* (27.78%); notably, the P53-negative phenotype in cervical cancer was attributable to E6 oncoprotein-driven ubiquitin-mediated proteasomal degradation of wild-type P53 rather than to *TP53* gene inactivation. Pathway analysis further distinguished these entities: P53-null HGSOC mutations preferentially enriched the *PI3K/AKT/mTOR* axis, whereas cervical cancer mutations converged on the *MAPK/ERK* pathway.

Conclusion

P53 negativity masks divergent oncogenic trajectories driven by fundamentally different mechanisms. In HGSOC, the P53-negative phenotype arises from intrinsic *TP53* loss-of-function mutations, whereas in cervical cancer it predominantly reflects HPV E6-mediated post-translational degradation of wild-type P53 protein. Consequently, cervical carcinogenesis appears to rely on alternative pathway dysregulation (e.g., *MAPK/ERK* activation) independent of primary *TP53* inactivation. These findings highlight the necessity of histology-specific, mechanism-driven therapeutic strategies that incorporate HPV status in P53-negative gynecological malignancies.

Introduction

Cervical cancer and ovarian cancer rank among the most lethal gynecological malignancies worldwide. According to the most recent global cancer statistics, they are the second and third leading causes of cancer-related deaths in women residing in transitioning countries, following breast cancer [1, 2]. Histologically, epithelial ovarian cancer comprises several subtypes, with high-grade serous ovarian carcinoma (HGSOC) being the most prevalent, accounting for approximately 70% of cases and the majority of ovarian cancer mortality [3, 4]. Cervical cancer is primarily classified into squamous cell carcinoma and adenocarcinoma, with persistent high-risk Human Papillomavirus (HPV) infection serving as the etiological driver in the vast majority of cases [5, 6].

The tumor suppressor P53, encoded by the *TP53* gene, is a central regulator of genomic stability. In HGSOC, somatic *TP53* mutations are near-universal events (> 96%), and these alterations manifest as either missense mutations—associated with aberrant nuclear accumulation of the protein—or null mutations, which produce a truncated protein subject to nonsense-mediated decay and result in complete absence of P53 expression by IHC [7, 8, 9]. Approximately 10%–30% of HGSOC cases harbor *TP53* null mutations corresponding to the IHC "null" pattern [7, 8]. In contrast, approximately 70% of cervical cancers exhibit low or negative P53 expression [10], most commonly attributed to HPV E6 oncoprotein-mediated ubiquitination and proteasomal degradation of wild-type P53 rather than primary genetic loss [6, 11, 12].

This divergence in underlying biology raises a critical clinical question: do P53-negative phenotypes in HGSOC and cervical cancer share similar oncogenic trajectories? Current evidence suggests that a shared IHC "null" pattern may mask fundamentally distinct molecular pathologies—intrinsic *TP53* gene ablation in HGSOC versus post-translational P53 inactivation in HPV-driven cervical cancer [10, 13]. To date, no direct comparative analysis has elucidated whether these tumors rely on convergent or divergent downstream signaling pathways [14, 15].

Therefore, this study aimed to bridge this knowledge gap by performing a comparative clinicopathological and genomic analysis of P53-negative HGSOC and cervical cancer cohorts. By characterizing their distinct mutational profiles and enriched signaling pathways (i.e., *PI3K/AKT/mTOR* versus *MAPK/ERK*), we sought to delineate their unique oncogenic mechanisms and to advocate for divergent, histology-specific therapeutic strategies.

Materials and Methods

Specimen and Data Collection

Formalin-fixed paraffin-embedded (FFPE) specimens from patients diagnosed with HGSOC and cervical cancer at the Third Affiliated Hospital of Guangzhou Medical University (June 2015–October 2020) were retrospectively collected. All diagnoses were confirmed by two senior pathologists based on H&E staining following current WHO classification criteria [14]. After P53 IHC screening, 16 P53-null HGSOC

cases, 18 P53-negative cervical cancer cases, and 11 P53-wild-type cervical cancer cases (control group), in line with previously established null-pattern frequencies [7, 8] (control group) were included, in line with previously established null-pattern frequencies [7, 8]. Clinical data—including age, tumor diameter, FIGO stage, treatment modality, and follow-up outcome—were retrieved from electronic medical records. Patients were stratified by age into < 50 years and ≥ 50 years. The study was approved by the Institutional Ethics Committee (approval No. [[2026]098]).

Immunohistochemical Detection of P53

Sections (4–5 μm) were deparaffinized and subjected to heat-induced epitope retrieval. P53 IHC was performed using a Roche auto-stainer (EnVision method) with anti-P53 antibody (clone DO7, 1:5000; Zhuhai QuanHui, China). Interpretation followed established criteria [7, 9, 10]: (i) overexpression—diffuse strong nuclear positivity in ≥ 75% of tumor cells; (ii) null-type—≤5% of tumor cells show nuclear staining (with positive internal stromal controls); (iii) wild-type—heterogeneous nuclear staining in 5%–75% of tumor cells. Null-type cases were defined as P53-negative for this study.

Next-Generation Sequencing (NGS)

Tumor tissue wax rolls were submitted for targeted NGS covering 671 cancer-related genes (Illumina platform; Zhiben Medical Technology, Shanghai, China). The gene panel included all recurrently altered drivers of HGSOC and cervical cancer, including *TP53, BRCA1/2*, *PIK3CA*, *KRAS*, and *TERT* [3, 5, 16]. Variants were classified according to ACMG/AMP guidelines as pathogenic, likely pathogenic, or variants of uncertain significance (VUS). Only confirmed somatic mutations of clinical significance or VUS with high functional impact were retained for downstream analysis ("report" and "reportVUS").

GO and KEGG Pathway Enrichment Analysis

Gene symbols were converted to Entrez IDs using the R package org.Hs.eg.db. Enrichment of GO biological processes, cellular components, molecular functions, and KEGG pathways was performed in R v4.x using clusterProfiler [17] against reference datasets derived from The Cancer Genome Atlas (TCGA) and published gynecological cancer cohorts [3, 4, 5]. Terms with adjusted $P < 0.05$ were considered significant. The top enriched terms were visualized as bar plots and bubble plots.

Statistical Analysis

Categorical variables were expressed as n (%) and compared using the χ^2 test or Fisher's exact test, and continuous variables as mean ± SD and compared using the independent-samples t-test. Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. $P < 0.05$ was considered statistically significant. All analyses were performed in R and SPSS 22.0.

Results

Clinicopathological Characteristics

Among 16 P53-negative HGSOC patients (age range 46–71 years, Table 1) and 29 cervical cancer patients (18 P53-negative, 11 P53 wild-type; age range 39–67 years, Table 2-4), P53-negative HGSOC patients were significantly older (≥50 years: 81.25% vs. 50%, P< 0.05) and exhibited a higher mortality rate during follow-up (25% vs. 5% in P53-negative cervical cancer; 0% in P53 wild-type cervical cancer, Table 3-4).

TP53 Mutation Status and Divergent Genomic Profiles

All 16 P53-negative HGSOC cases harbored deleterious *TP53* mutations (100% mutation frequency, Fig. 1A), comprising nonsense (n=10), frameshift (n=4), and splice-site (n=2) alterations—consistent with the null IHC phenotype reflecting true gene-level loss-of-function. By contrast, none of the 18 P53-negative cervical cancers nor the 11 P53 wild-type cervical cancers harbored *TP53* mutations(Fig. 1B). Instead, P53-negative cervical cancers showed high mutation frequencies in *PIK3CA* (33.33%), *TERT* (27.78%), *KMT2C*, *EP300*, *FBXW7*, and *NECTIN4* (each 22.22%), whereas P53 wild-type cervical cancers were dominated by *PIK3CA* (36.36%) without *TP53* involvement(Supplementary Table 1). TCGA cohort validation confirmed *TP53* as the top mutated gene in HGSOC (98%) but a low-frequency event in cervical cancer (8%, Fig. 2) [18].

GO and KEGG Pathway Enrichment

GO analysis revealed distinct biological processes: P53-negative HGSOC mutant genes were enriched in DNA damage response, cell cycle checkpoint regulation, and apoptotic signaling, whereas P53-negative cervical cancer mutant genes were enriched in epithelial proliferation, glandular development, and telomere maintenance—consistent with HPV-driven immortalization via *TERT* upregulation(Fig. 3A-C) [5,6,24].

KEGG analysis demonstrated a fundamental signaling dichotomy: P53-negative HGSOC mutations predominantly converged on the *PI3K/AKT/mTOR* signaling axis (adj. P< 0.05) [19,20,21], while P53-negative cervical cancer mutations primarily enriched the *MAPK/ERK* pathway and HPV infection signaling pathway (Fig. 3D-F) [16,22]. These findings indicate that, despite a shared P53 IHC null appearance, the two entities activate divergent survival and proliferative cascades.

Protein–Protein Interaction (PPI) Network and Core Mutated Genes

PPI network analysis identified *TP53*, *BRCA1*, *CTNNB1*, *PIK3CA*, *KRAS*, *ERBB4*, and *KMT2D* as core hub genes in P53-negative HGSOC(Fig. 4A-B), with TP53 showing the highest degree centrality—supporting its role as the initiating driver [23]. In P53-negative cervical cancer, core hubs included *PIK3CA*, *KMT2D*, *KRAS*, *STK11*, *EP300*, *TERT*, and *FBXW7*(Fig. 4C-D), reflecting alternative pathway dysregulation independent of *TP53* loss [5,13].

Discussion

This exploratory, hypothesis-generating study demonstrates that P53 protein negativity in HGSOC and cervical cancer represents biologically distinct entities—a concept we define as "same shadow, different substance" [14, 25]. While the absence of P53 expression serves as a critical diagnostic marker in both malignancies, our multi-omics analysis reveals that this shared phenotype conceals divergent genomic landscapes and signaling dependencies.

In HGSOC, P53 negativity is the phenotypic readout of an intrinsic *TP53* null mutation, representing a catastrophic loss-of-function event that initiates genomic instability and chromosomal aberrations [3, 4, 23]. Our finding that 100% of P53-null HGSOC cases harbor deleterious *TP53* mutations aligns with the consensus that HGSOC originates from a "P53-first, *TP53*-mutant" state [7, 8]. In stark contrast, P53 negativity in cervical cancer reflects HPV E6-mediated proteasomal degradation of wild-type P53 protein rather than primary gene loss [6, 10, 11]. This explains why none of our P53-negative cervical cancer cases harbored *TP53* alterations, instead displaying high frequencies of *PIK3CA* and *TERT* mutations—hallmarks of viral-driven carcinogenesis in which E6/E7 oncogenes cooperate with somatic alterations to drive transformation [5, 16, 13].

The most clinically relevant discovery lies in the differential pathway addiction between these entities. We observed a fundamental schism: P53-null HGSOC mutations predominantly enriched the *PI3K/AKT/mTOR* axis, whereas cervical cancer mutations converged on the *MAPK/ERK* pathway. Mechanistically, in HGSOC, loss of P53 removes a critical brake on cell survival, creating a compensatory dependency on *PI3K* signaling. Hyperactivation of *PI3K/AKT/mTOR* is a well-established driver of cisplatin resistance in ovarian cancer, primarily through upregulation of anti-apoptotic proteins (e.g., Bcl-2, Survivin) and promotion of DNA repair [19, 20, 21]. Our data suggest that for P53-null HGSOC patients—particularly those with co-occurring *PI3K* pathway mutations—standard platinum-taxane chemotherapy may be insufficient; future trials should consider combining *PARP* inhibitors (given the *TP53* null/HRD background) with *PI3K* or *mTOR* inhibitors to overcome chemoresistance [14, 25]. This paradigm has recently received clinical support: the phase II OCTOPUS trial of the *mTOR* inhibitor vistusertib plus paclitaxel [26] and the PROFECTA-II trial of the *AKT* inhibitor afuresertib plus paclitaxel [27] both showed activity in platinum-resistant HGSOC, while alpelisib has demonstrated clinical efficacy in *PIK3CA*-mutated gynecological cancers [28].

Conversely, in cervical cancer, the reliance on the *MAPK/ERK* pathway highlights [16, 22] a distinct vulnerability. Unlike HGSOC, where P53 loss is genetic, cervical carcinogenesis involves the viral hijacking of cellular machinery. The enrichment of *TERT* mutations and *MAPK* signaling in our cohort suggests a proliferative advantage driven by growth factor signaling rather than genomic chaos [5, 13]. For recurrent or refractory P53-negative cervical cancers, our findings imply that targeting the *MAPK/ERK* axis (e.g., MEK inhibitors) or *TERT*-mediated telomere maintenance might offer therapeutic efficacy beyond conventional chemoradiotherapy, especially in patients with high *PIK3CA/TERT* mutational burdens [13].

These findings call for a paradigm shift in the diagnostic workup of gynecological tumors. Currently, P53 IHC is often interpreted in isolation. We propose an integrated clinical workflow: (1) identify P53-null status via IHC; (2) perform targeted NGS to distinguish between *TP53* mutational loss (HGSOC-like) and *PIK3CA/TERT* alterations (cervical-like); (3) tailor therapy accordingly—prioritizing DNA damage response inhibitors (e.g., *PARP* inhibitors) for HGSOC and pathway-specific targeted agents for cervical cancer.

Study Limitations

This study is limited by its modest sample size (n = 16 HGSOC, n = 18 P53-negative cervical cancer) drawn from a single institution and by its retrospective design. Findings should therefore be interpreted as exploratory and hypothesis-generating. Validation in larger multicenter cohorts and functional studies confirming the inferred pathway dependencies are warranted before clinical translation.

Declarations

Author Contributions

Ping Qin, Tonghui Cai contributed to the reviewing the literature, integrating and analyzing the literature results and the collection of patient data. Zilong Song, Tianyu Wang designed the study and analyzed the data. Ruichao Chen, Li Zhao performed the immunohistochemistry, and Wei Zhang participated in the immunohistochemical scoring. Qingping Jiang contributed to the statistical analysis. QPJ supervised all the work. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

Ethics Statement

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University (No. [[2026]098]). Written informed consent was waived due to the retrospective nature of the study.

Data Availability Statement

The raw sequencing data are available from the corresponding author upon reasonable request. TCGA data were accessed via the GDC portal (https://portal.gdc.cancer.gov/).

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Tables

Table 1.Clinical and pathological characteristics of 16 ovarian cancer patients

Clinical and pathological characteristics of 16 ovarian cancer patients			
Clinical and pathological characteristics		Number	Percentage□%□
Age	□50	3	18.75
	≥50	13	81.25
Treatment	Surgery only	2	12.50
	Surgery+Chemotherapy	14	87.50
Prognosis	Death	4	25.00
	Living	10	62.50
	Lost to follow-up	2	12.50
Cancer Stage	I+II	8	50.00
	III+IV	8	50.00
Histological Type	HGSOC	16	100.00
P53	Null-type	16	100.00
	Other	0	0.00

HGSOC,high-grade serous ovarian carcinoma

Table 2.Clinical and pathological characteristics of 29 cervical cancer patients

Clinical and pathological characteristics of 29 cervical cancer patients

Clinical and pathological characteristics		Number	Percentage□%□
Age	□50	15	51.72
	≥50	14	48.28
Treatment	Surgery only	12	41.38
	Surgery+Chemotherapy	17	58.62
Prognosis	Death	1	3.45
	Living	25	68.21
	Lost to follow-up	3	10.34
Cancer Stage	I+II	25	86.21
	III+IV	4	13.79
Histological Type	Squamous cell carcinoma	14	48.28
	Adenocarcinoma	9	31.03
	Adenosquamous carcinoma	5	17.24
	Adenocarcinoma, mesonephric type	1	3.45
P53	Null-type	18	62.07
	Wild-type	11	37.93
P16	Strongly positive	28	3.45
	Negative	1	96.55
HPV	Negative	2	100.00
	Positive	27	0.00

Table 3.Clinical and pathological characteristics of 11 cases of P53 wild-type cervical cancer

Clinical and Pathological characteristics of 11 Cases of P53 Wild-Type Cervical Cancer

Clinical and pathological characteristics		Number	Percentage□%□
Age	□50	5	45.45
	≥50	6	54.55
Treatment	Surgery only	5	45.45
	Surgery+Chemotherapy	6	54.55
Prognosis	Death	0	0.00
	Living	9	81.81
	Lost to follow-up	2	18.19
Cancer Stage	I+II	9	81.81
	III+IV	2	18.19
Histological Type	Squamous cell carcinoma	4	36.36
	Adenocarcinoma	2	18.19
	Adenosquamous carcinoma	4	36.36
	Adenocarcinoma, mesonephric type	1	9.09
P53	Null-type	0	0.00
	Wild-type	11	100.00
HPV	Negative	2	18.19
	Positive	9	81.81
P53 AND HPV	P53 Wild-type and HPV-	2	18.19
	P53 Wild-type and HPV+	9	81.81

Table 4.Clinical and pathological characteristics of 18 P53 null-type cervical cancer patients

Clinical and Pathological Characteristics of 18 P53 null-type Cervical Cancer Patients

Clinical and pathological characteristics		Number	Percentage□%□
Age	□50	9	50.00
	≥50	9	50.00
Treatment	Surgery only	8	44.44
	Surgery+Chemotherapy	10	55.56
Prognosis	Death	1	5.55
	Living	16	88.90
	Lost to follow-up	1	5.55
Cancer Stage	I+II	16	88.90
	III+IV	2	11.10
Histological Type	Squamous cell carcinoma	10	55.56
	Adenocarcinoma	7	38.89
	Adenosquamous carcinoma	1	5.55
P53	Null-type	18	100.00
	Wild-type	0	0.00
HPV	Negative	0	0.00
	Positive	18	100.00
P53 AND HPV	P53 null-type and HPV-	0	0.00
	P53 null-type and HPV+	18	100.00

Figures

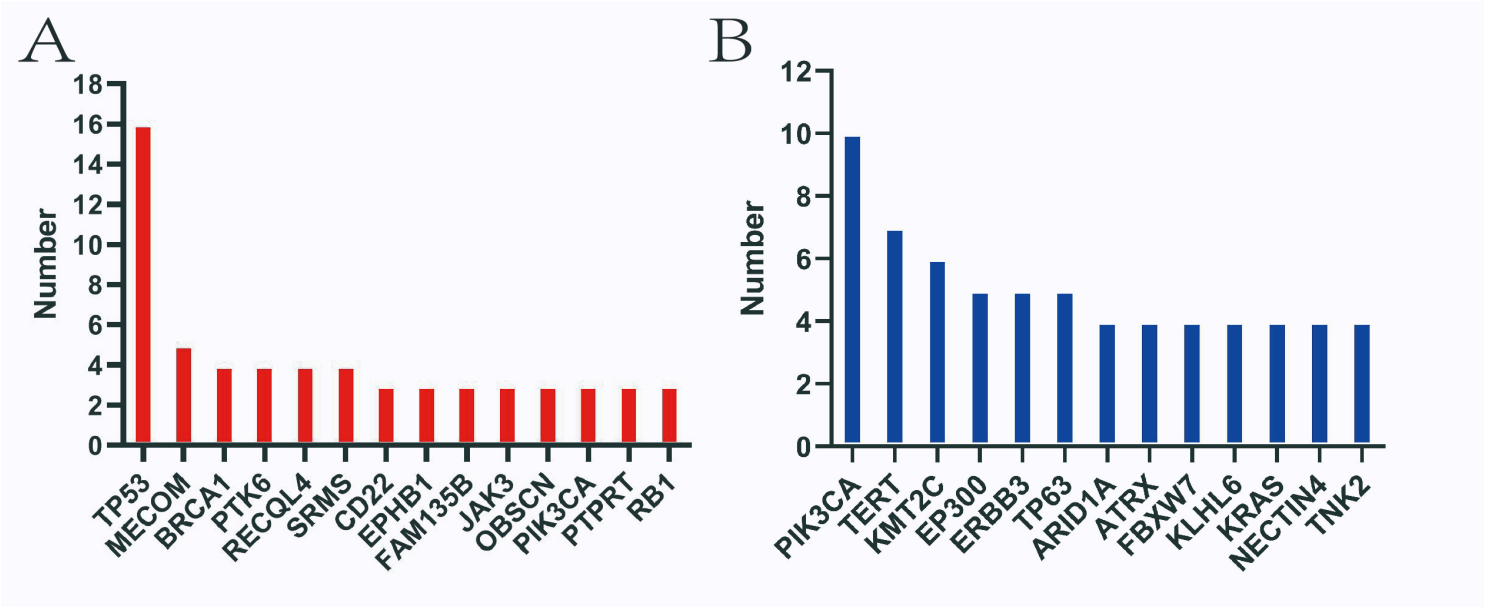


Figure 1

Gene mutation status of ovarian cancer and cervical cancer

A: Genetic mutation status in 16 cases of ovarian cancer,B: Genetic mutation status in 29 cases of cervical cancer

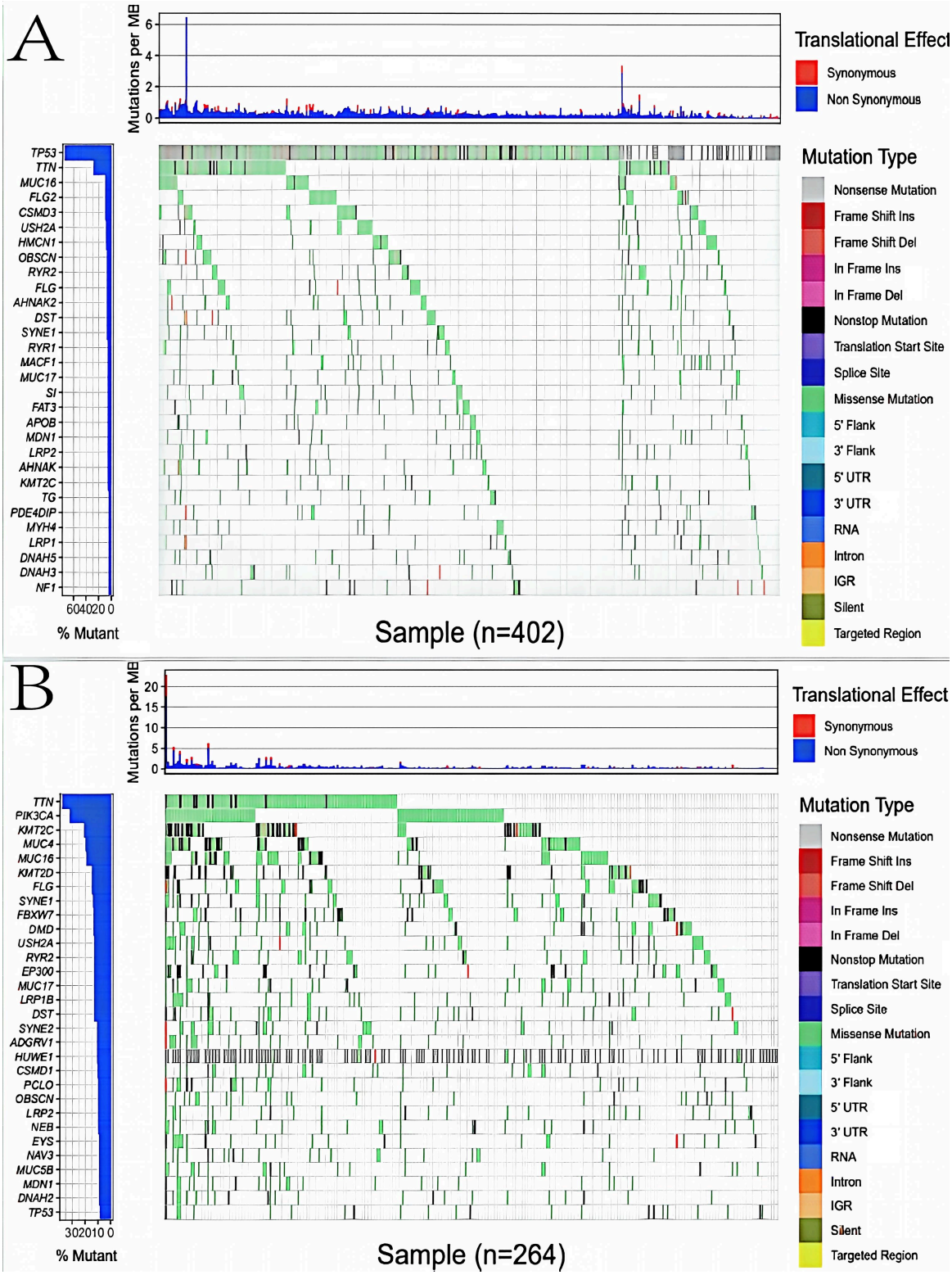


Figure 2

TCGA data analysis of mutation gene distribution characteristics in ovarian cancer and cervical cancer

A: Distribution characteristics of gene mutations in 402 cases of ovarian cancer

B: Distribution characteristics of gene mutations in 264 cases of cervical cancer

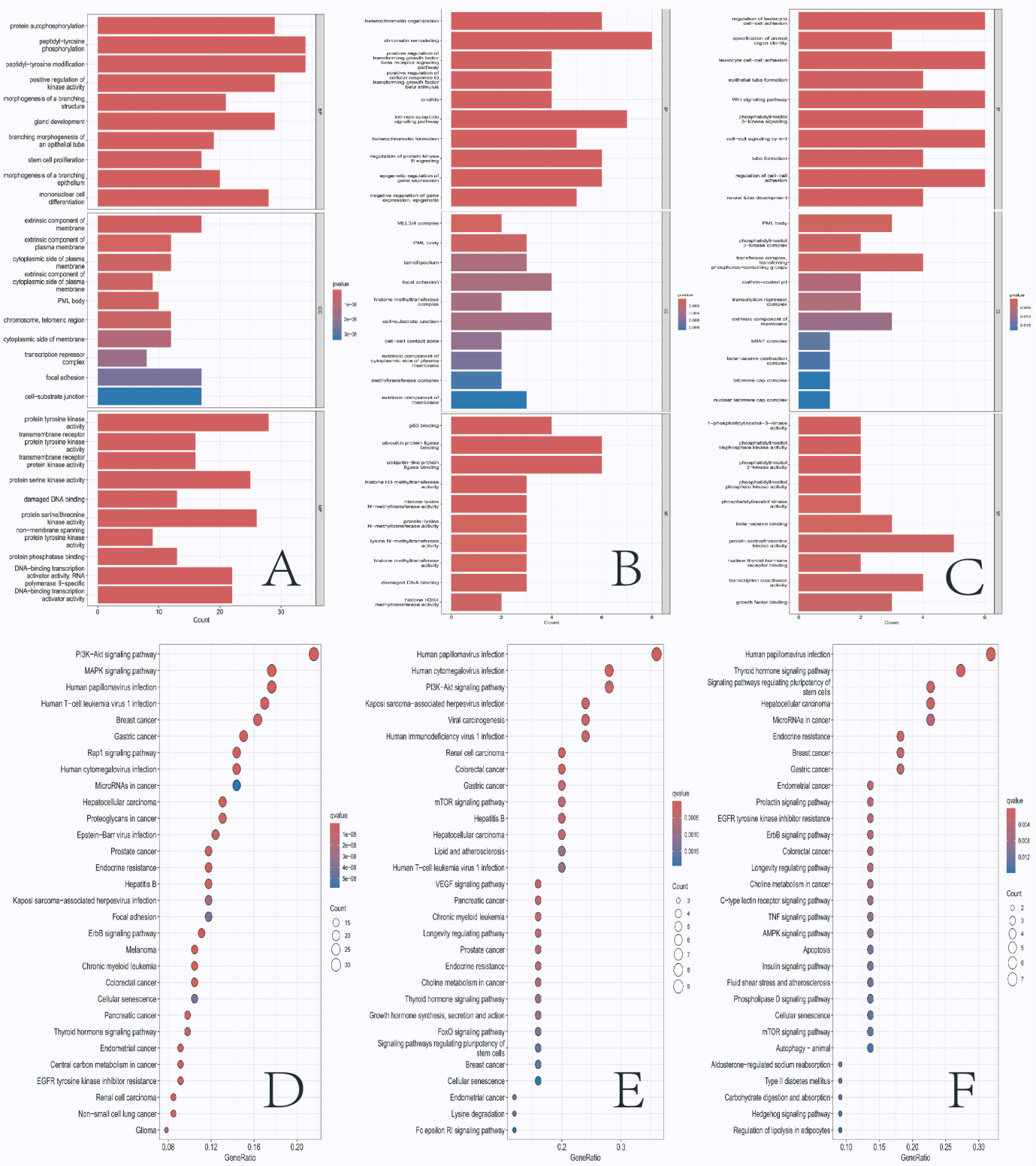


Figure 3

GO and KEGG enrichment analysis results of mutated genes in two types of tumors

A: GO analysis results of mutated genes in P53 null-type ovarian cancer,B: GO analysis results of mutated genes in P53 null-type cervical cancer,C: GO analysis results of mutated genes in P53 wild-type cervical cancer,D: Major KEGG pathways involved in mutated genes of P53 null-type ovarian cancer,E:

Major KEGG pathways involved in mutated genes of P53 null-type cervical cancer,F: Major KEGG pathways involved in mutated genes of P53 wild-type cervical cancer

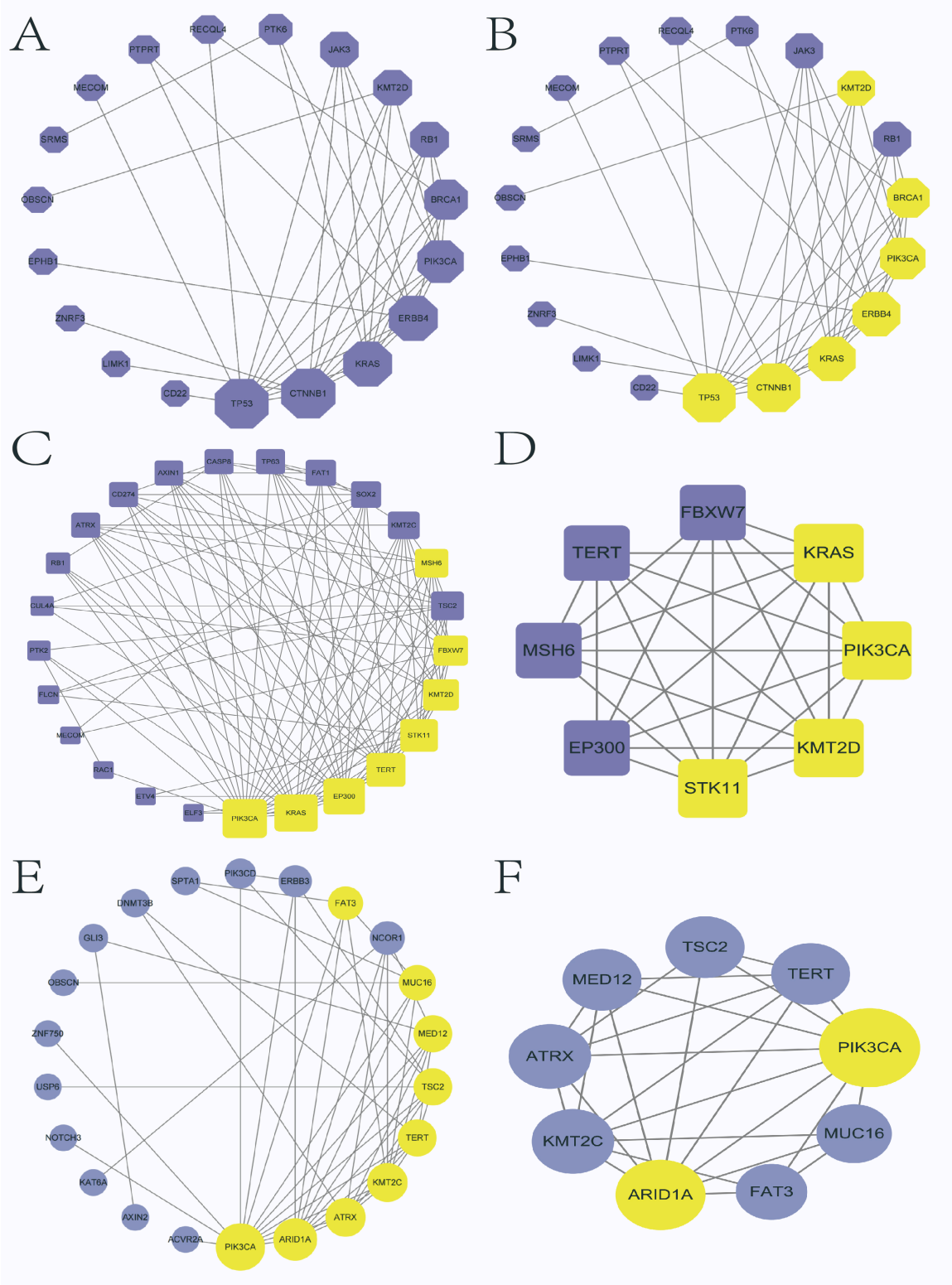


Figure 4

The core mutated genes with the highest mutation frequency in two types of tumors

A: P53 null-type ovarian cancer mutant gene,B: P53 null-type ovarian cancer core mutant gene,C: P53 null-type cervical cancer mutant gene,D: P53 null-type cervical cancer core mutant gene,E: P53 wild-type cervical cancer mutant gene,F: P53 wild-type cervical cancer core mutant gene

Supplementary Files

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- OriginalFiguresandTables.docx
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- SupplementaryTables.xlsx