

# Bach1 Promotes the Malignant Phenotype of Ovarian Cancer Through the Pi3k/Akt Signaling Pathway

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## ARTICLE INFO

**Received:** 📅 October 13, 2026

**Published:** 📅 October 22, 2026

**Citation:** Yutong Zheng, Yuan Gao, Yan Tu, Ruotong Wang, Hairu Xie, Xiufeng Xie and Jun Li. Bach1 Promotes the Malignant Phenotype of Ovarian Cancer Through the Pi3k/Akt Signaling Pathway. Biomed J Sci & Tech Res 67(2)-2026. BJSTR.MS.ID.010451.

## ABSTRACT

**Background:** Ovarian cancer (OC) is one of the most common gynecologic malignancies. Its increasing incidence and heterogeneous clinical outcomes highlight the need for new therapeutic targets. This study investigated the oncogenic role of BTB and CNC homology 1 (BACH1), a heme-dependent transcription factor whose function in OC remains poorly understood.

**Methods:** BACH1 expression and its association with prognosis were evaluated using The Cancer Genome Atlas (TCGA) data, western blotting, Kaplan-Meier analysis, Cox regression, and a nomogram. BACH1 function was examined using cell proliferation, colony formation, wound-healing, migration, and invasion assays after siRNA-mediated knockdown or overexpression. Potential mechanisms were investigated by Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and gene set enrichment analysis (GSEA) of BACH1-related differentially expressed genes. Western blotting assessed BACH1, epithelial-mesenchymal transition (EMT) markers, and PI3K/AKT pathway proteins.

**Results:** BACH1 expression was significantly higher in ovarian cancer tissues and cell lines, and higher expression was associated with poorer prognosis. BACH1 knockdown inhibited ovarian cancer cell proliferation, migration, and invasion, whereas overexpression promoted these phenotypes ( $P < 0.05$ ). Bioinformatic analyses linked BACH1 to PI3K/AKT signaling and EMT. Western blotting showed that BACH1 knockdown increased E-cadherin and decreased N-cadherin, vimentin,  $\beta$ -catenin, and phosphorylated AKT; BACH1 overexpression produced the opposite changes.

**Conclusion:** BACH1 is overexpressed in ovarian cancer and is associated with poor prognosis. It promotes malignant phenotypes in ovarian cancer cells by inducing EMT through activation of the PI3K/AKT pathway, supporting its potential as a prognostic biomarker and therapeutic target.

**Keywords:** Ovarian Cancer; Bach1; Epithelial-Mesenchymal Transition; Pi3k/Akt Signaling Pathway

**Abbreviations:** OC: Ovarian Cancer; TCGA: The Cancer Genome Atlas; GO: Gene Ontology KEGG: Kyoto Encyclopedia of Genes and Genomes; GSEA: Gene Set Enrichment Analysis; EMT: Epithelial-Mesenchymal Transition; BACH1: BTB and CNC Homology 1; OV: Ovarian Cancer; TPM: Transcripts Per Million; ROC: Receiver Operating Characteristic; GTEX: Genotype-Tissue Expression

## Introduction

Ovarian cancer (OC) is the most lethal gynecologic malignancy worldwide. According to GLOBOCAN 2024 estimates, OC is the 18th most commonly diagnosed cancer and the 14th leading cause of cancer death among women, with approximately 330,731 new cases and 203,850 deaths in 2024 [1]. Most deaths are attributable to

high-grade serous carcinoma. Despite advances in surgery and targeted agents such as poly (ADP-ribose) polymerase inhibitors, only about half of patients survive beyond 5 years, and survival is lower among patients without BRCA1/BRCA2 mutations who present with advanced disease [2]. Early OC often causes vague, nonspecific symptoms, so most patients are diagnosed at an advanced stage. At that

point, the 5-year survival rate may be as low as 20%, compared with more than 90% for localized disease [3]. Current screening methods, including transvaginal ultrasonography and serum markers such as CA-125 and human epididymis protein 4, lack sufficient sensitivity and specificity for early detection. Recurrence and chemoresistance further limit long-term survival, even among patients who initially respond to treatment [4, 5]. New molecular biomarkers are therefore needed to predict prognosis and clarify the mechanisms that drive OC progression and metastasis. BTB and CNC homology 1 (BACH1) is a heme-dependent basic leucine zipper transcription factor.

Under low-heme conditions, it heterodimerizes with small musculoaponeurotic fibrosarcoma proteins and represses genes involved in heme and iron metabolism, oxidative stress responses, and cell-cycle regulation [6,7]. Evidence from several cancers indicates that BACH1 has multiple oncogenic functions. It can enhance glycolysis by upregulating hexokinase 2 and glyceraldehyde-3-phosphate dehydrogenase while suppressing mitochondrial oxidative metabolism, thereby supporting tumor-cell proliferation [8]. BACH1 can also activate angiogenesis-related genes and increase tumor vascularity independently of hypoxia-inducible factor signaling [9]. BACH1 promotes epithelial-mesenchymal transition (EMT) and metastatic dissemination by repressing epithelial genes and activating mesenchymal programs. This function has been demonstrated in non-small cell lung cancer, bladder cancer, clear cell renal cell carcinoma, and hepatocellular carcinoma [10-14]. BACH1 also interacts with oncogenic pathways, including MAVS-mediated and CLCF1/STAT3 signaling [15,16]. EMT is a central process in metastasis: epithelial cells lose intercellular adhesion and apical-basal polarity while acquiring a motile, invasive phenotype. These changes include reduced E-cadherin expression and increased expression of N-cadherin and vimentin. EMT is regulated by pathways that include TGF- $\beta$ , Wnt/ $\beta$ -catenin, and PI3K/AKT, and it is increasingly understood as a continuum of transitional states rather than a binary switch [17,18].

Aberrant PI3K/AKT activation promotes tumor-cell proliferation, survival, invasion, EMT, and chemoresistance in OC [19,20]. Because BACH1 interacts with oncogenic signaling networks and drives EMT in other tumor types, we hypothesized that BACH1 promotes malignant phenotypes in OC cells through the PI3K/AKT pathway.

## Materials and Methods

### Data Acquisition and Processing

RNA-sequencing data in fragments per kilobase of transcript per million mapped reads (FPKM) and corresponding clinical information for ovarian cancer (OV) were downloaded from The Cancer Genome Atlas (TCGA; <https://portal.gdc.cancer.gov/>). FPKM values were converted to transcripts per million (TPM) to facilitate cross-sample comparisons. Cases without survival time, survival status, or complete clinicopathological data were excluded. When normal ovarian tissue was required for comparison, expression data from the Genotype-Tis-

sue Expression (GTEx) project were obtained through the UCSC Xena platform (<https://xenabrowser.net/>). BACH1 mRNA expression was compared between tumor and normal tissues, and its associations with clinicopathological variables, including FIGO stage, histological grade, and residual tumor status, were analyzed.

### Survival and Prognostic Analyses

Patients were classified into BACH1-high and BACH1-low groups using the median BACH1 expression value or the optimal cutoff identified with the `surv_cutpoint` function in the R package `survminer`. Kaplan-Meier curves were compared with the log-rank test. Time-dependent receiver operating characteristic (ROC) curves for 1-, 2-, 3-, and 5-year overall survival (OS) were generated with the R package `timeROC`, and the corresponding areas under the curve (AUCs) were calculated. The R package `pheatmap` was used to visualize risk-score distributions, signature-gene expression, and survival status in the high- and low-risk groups. Univariate and multivariate Cox proportional hazards models were used to assess whether BACH1 expression was an independent prognostic factor; results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Variables with  $P < 0.05$  in univariate analysis were entered into the multivariate model. A nomogram was constructed with the R package `rms` and internally validated by bootstrap resampling with 1,000 iterations. Calibration curves compared predicted and observed 1-, 3-, and 5-year OS. Analyses were performed in R version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and  $P < 0.05$  was considered statistically significant.

### Differentially Expressed Genes and Functional Enrichment

Patients were divided into high- and low-BACH1-expression groups using the median expression value. Differentially expressed genes (DEGs) were identified with DESeq2 using thresholds of  $|\log_2 \text{fold change}| > 1$  and adjusted  $P < 0.05$  after Benjamini-Hochberg correction. Gene Ontology (GO) analyses of biological process, cellular component, and molecular function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were performed with clusterProfiler;  $P < 0.05$  was considered statistically significant. Gene set enrichment analysis (GSEA) was also performed on the complete gene list ranked by correlation with BACH1 expression, using KEGG gene sets from the Molecular Signatures Database. Significance was defined by the normalized enrichment score and a false discovery rate  $q < 0.25$ , or  $q < 0.05$  according to the adopted criterion.

### Cell Culture

Human ovarian cancer cell lines SKOV3, A2780, NIH:OVCA3, CAOV3, and UWB1.289 and the normal human ovarian epithelial cell line IOSE80 were obtained from the American Type Culture Collection. Cells were cultured in DMEM or RPMI-1640 supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>. Cell-line identity was

confirmed by short tandem repeat profiling, and cultures were routinely tested for mycoplasma contamination.

### siRNA Transfection and BACH1 Overexpression

Small interfering RNAs targeting BACH1 (si-BACH1), the corresponding negative control (si-NC), BACH1 overexpression plasmids (OE-BACH1), and empty-vector controls (OE-NC) were designed and synthesized by JinTuoSi (Wuhan, China). Cells in logarithmic growth were seeded in 6-well plates and transfected with Lipofectamine 3000 (Invitrogen, USA; L3000001) according to the manufacturer's instructions at 70-80% confluence. Transfection efficiency was confirmed by western blotting 48 h after transfection before functional assays.

### Cell Proliferation Assay

Cell proliferation was measured with the CCK-8 assay (Meilun, China; MA0212). Transfected cells were seeded in 96-well plates at  $3 \times 10^3$  cells per well and cultured for 24, 48, 72, and 96 h. At each time point, 10  $\mu$ L of CCK-8 reagent was added to each well, followed by incubation at 37 °C for 1-2 h. Absorbance was measured at 450 nm with a microplate reader. Each experiment included at least three biological replicates, and proliferation curves were plotted.

### Colony Formation Assay

Transfected cells were seeded in 6-well plates at 500-1,000 cells per well and cultured for 10-14 days under standard conditions; the medium was replaced every 3 days. Colonies were fixed with 4% paraformaldehyde for 15-20 min and stained with 0.1% crystal violet for 15-20 min. Colonies containing at least 50 cells were counted manually or with ImageJ, and the colony-formation rate was calculated relative to the number of seeded cells. Experiments were performed in triplicate.

### Wound-Healing Assay

Transfected cells were seeded in 6-well plates and grown to approximately 90-100% confluence. A linear scratch was made with a sterile 200- $\mu$ L pipette tip, and detached cells were removed by washing with phosphate-buffered saline. Cells were then cultured in serum-free or low-serum medium, and wound closure was imaged with an inverted microscope at 0 and 24 or 48 h. Migration was calculated as the percentage reduction in wound area using ImageJ.

### Transwell Migration and Invasion Assays

Cell migration and invasion were assessed in Transwell chambers with 8-micrometer pores (Corning, USA; 725001). For invasion assays, the upper membrane was coated with Matrigel (BD Biosciences, USA; 356237) diluted in serum-free medium; uncoated chambers were used for migration assays. Transfected cells ( $2.5 \times 10^5$ ) in serum-free medium were placed in the upper chamber, and medium containing 10-20% fetal bovine serum was added to the lower chamber as a chemoattractant. After 24 or 48 h, cells remaining on the up-

per surface were removed with a cotton swab. Cells on the lower surface were fixed with 4% paraformaldehyde, stained with 0.1% crystal violet, and counted in five randomly selected microscopic fields. The mean number of migrated or invaded cells per field was calculated.

### Protein Extraction and Western Blotting

Total protein was extracted from tissues or cells with RIPA lysis buffer containing protease and phosphatase inhibitors. Protein concentrations were measured with a bicinchoninic acid assay. Equal amounts of protein were separated by SDS-PAGE and transferred to polyvinylidene fluoride membranes. Membranes were blocked with 5% nonfat milk and incubated overnight at 4°C with primary antibodies against BACH1 (CST; 33059S),  $\beta$ -catenin (CST; 8480T), E-cadherin (Proteintech; 20874-1-AP), N-cadherin (Proteintech; 22018-1-AP), vimentin (Proteintech; 10366-1-AP), PI3K (CST; 4257), AKT (CST; 4691), p-AKT (Ser473; CST; 4060), and  $\beta$ -actin (CST; 8480T). After incubation with the appropriate horseradish peroxidase-conjugated secondary antibodies, protein bands were visualized with enhanced chemiluminescence.

### Statistical Analysis

In vitro data are presented as the mean  $\pm$  standard deviation of at least three independent biological replicates. Two groups were compared with Student's t test, and multiple groups were compared by one-way analysis of variance. Survival differences were evaluated with the log-rank test, and Cox regression was used for prognostic modeling as described above. Analyses of in vitro experiments were performed with GraphPad Prism version 9.0. All tests were two-sided, and  $P < 0.05$  was considered statistically significant.

## Results

### BACH1 Expression Is Associated with Prognosis in Ovarian Cancer

TCGA analysis showed that BACH1 mRNA expression was higher in ovarian cancer tissues than in normal ovarian tissues (Figure 1A). Patients with high BACH1 expression had significantly shorter overall survival than patients with low expression (Figure 1B). Risk-score and survival-status distributions similarly showed shorter survival in the high-risk group (Figure 1D & 1E). Time-dependent ROC analysis yielded AUCs of 0.682, 0.640, and 0.570 for 1-, 3- and 5-year OS, respectively, indicating stronger short-term than long-term discrimination (Figure 1C). Univariate Cox regression identified age and risk score as significant predictors of OS (both  $P < 0.001$ ; Figure 1F). Both remained independently associated with OS in multivariate analysis (age,  $P = 0.005$ ; risk score,  $P < 0.001$ ; Figure 1G). Age, tumor stage, and risk score were incorporated into a nomogram for individualized survival estimates (Figure 1H). Calibration curves showed close agreement between predicted and observed 1-, 3-, and 5-year OS probabilities (Figure 1I).

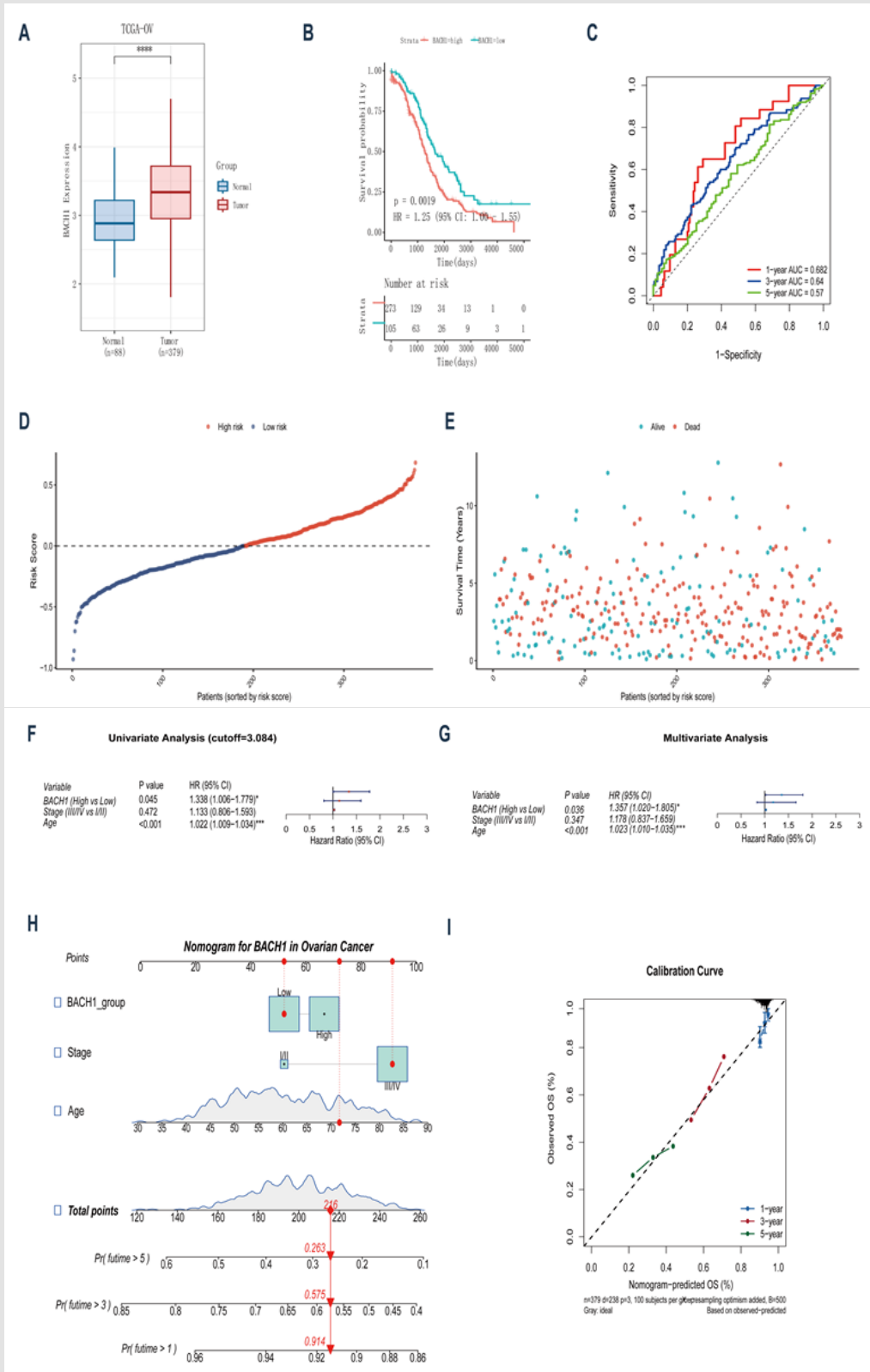


**Figure 1:** Association of BACH1 Expression with Prognosis in Patients with Ovarian Cancer and Development of a Prognostic Nomogram.

## BACH1 Is Upregulated in Ovarian Cancer Tissues and Cell Lines

BACH1 expression was examined in clinical specimens and cell lines to validate the bioinformatic findings. Expression was sig-

nificantly higher in ovarian cancer tissues than in matched adjacent non-tumor tissues ( $P < 0.05$ ). Similarly, all five ovarian cancer cell lines examined (SKOV3, UWB1.289, NIH:OVCAR3, A2780, and CAOV3) expressed more BACH1 than the normal ovarian epithelial cell line IOSE80 ( $P < 0.05$ ; Figure 2).

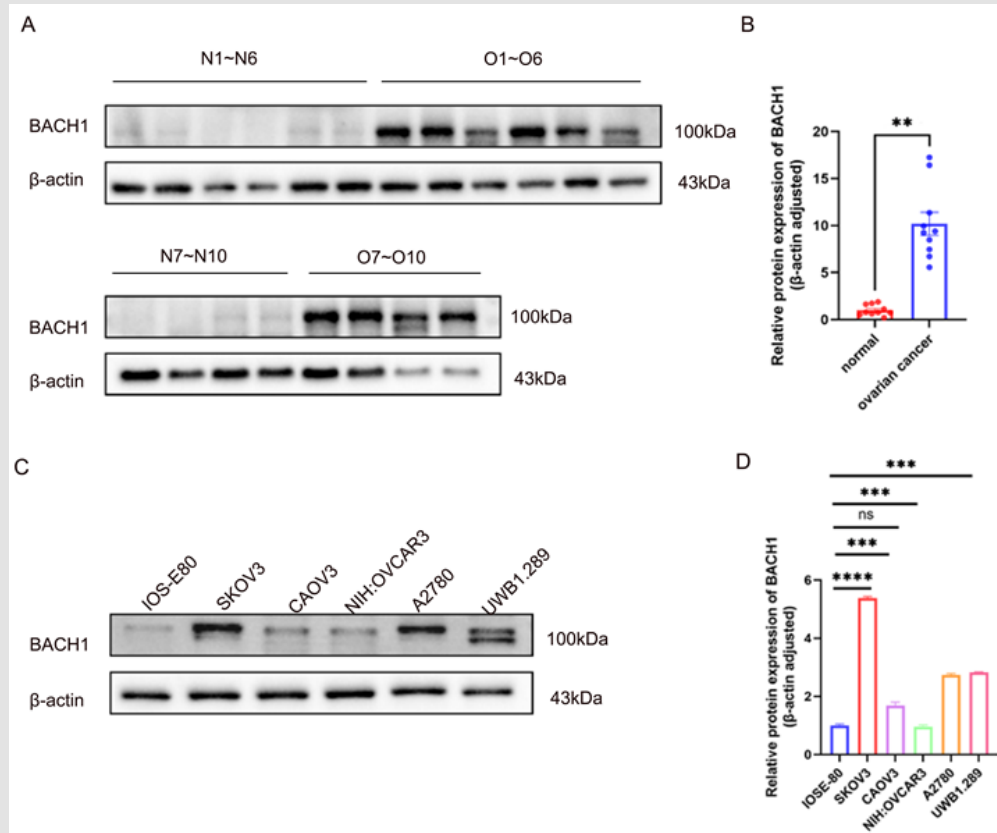


**Figure 2:** BACH1 Is Upregulated in Ovarian Cancer.

(A, B) BACH1 expression in ovarian cancer tissues and paired adjacent non-tumor tissues.

(C, D) BACH1 expression in ovarian cancer cell lines.

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , and \*\*\*\* $P < 0.0001$ .

## BACH1 Promotes Ovarian Cancer Cell Proliferation

Loss- and gain-of-function experiments were used to assess the role of BACH1 in ovarian cancer. BACH1 knockdown reduced cell proliferation and colony formation relative to the si-NC control. BACH1 overexpression increased both outcomes relative to the OE-NC control (all  $P < 0.05$ ; Figure 3).

## BACH1 Promotes Ovarian Cancer Cell Migration and Invasion

BACH1 knockdown reduced ovarian cancer cell migration and invasion, whereas BACH1 overexpression increased both behaviors ( $P < 0.05$ ; Figure 4). These findings indicate that BACH1 promotes malignant phenotypes in ovarian cancer cells.

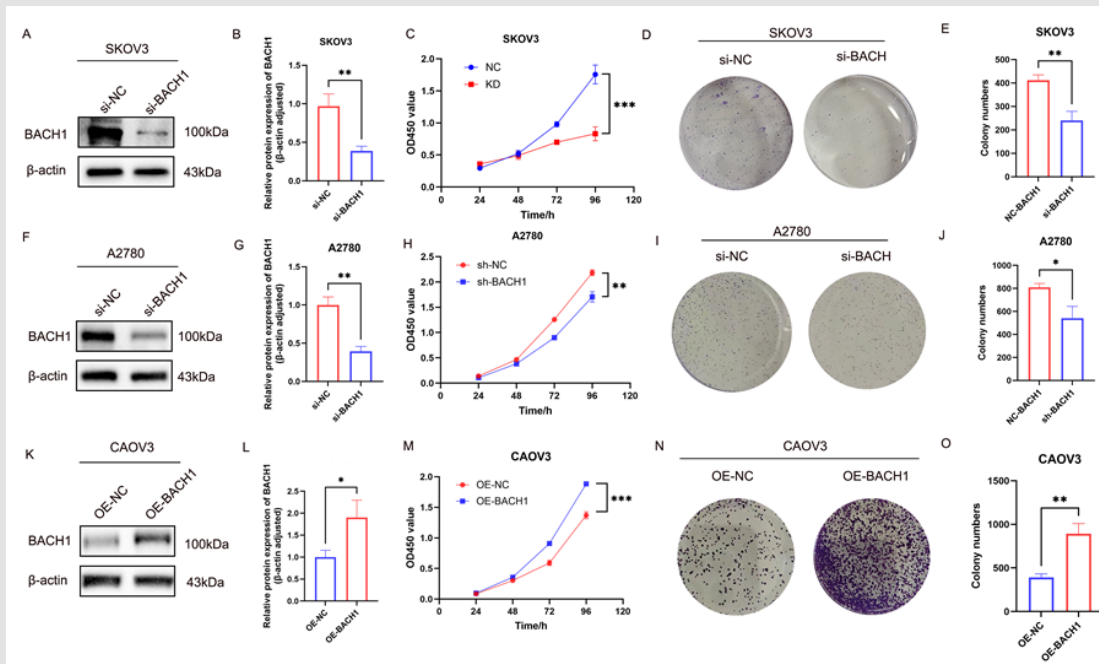


**Figure 3:** Ovarian Cancer Cell Proliferation After BACH1 Knockdown or Overexpression.  
 (A, B, F, G, K, L) Western blot analysis confirming BACH1 knockdown or overexpression in ovarian cancer cell lines.  
 (C, H, M) Cell proliferation measured by the CCK-8 assay.  
 (D, E, I, J, N, O) Colony formation assay.  
 \*P < 0.05, \*\*P < 0.01, and \*\*\*P < 0.001.

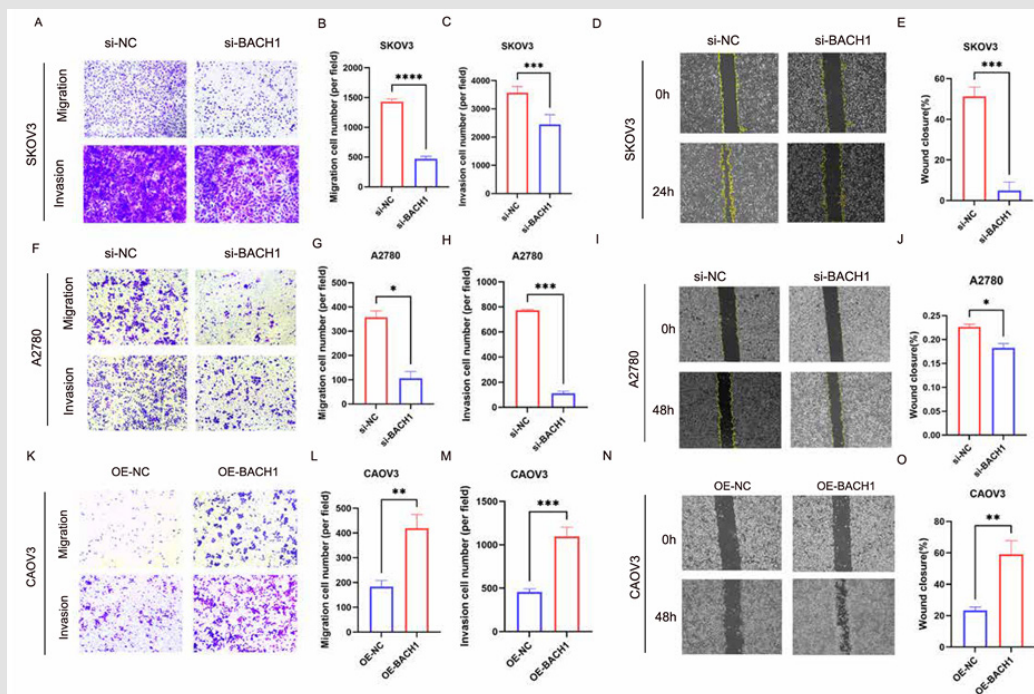


**Figure 4:** Migration and Invasion of Ovarian Cancer Cells After BACH1 Knockdown or Overexpression.  
 (A-C, F-H, K-M) Transwell migration and invasion assays.  
 (D, E, I, J, N, O) Wound-healing assay of ovarian cancer cell migration.  
 \*P < 0.05, \*\*P < 0.01, and \*\*\*P < 0.001.

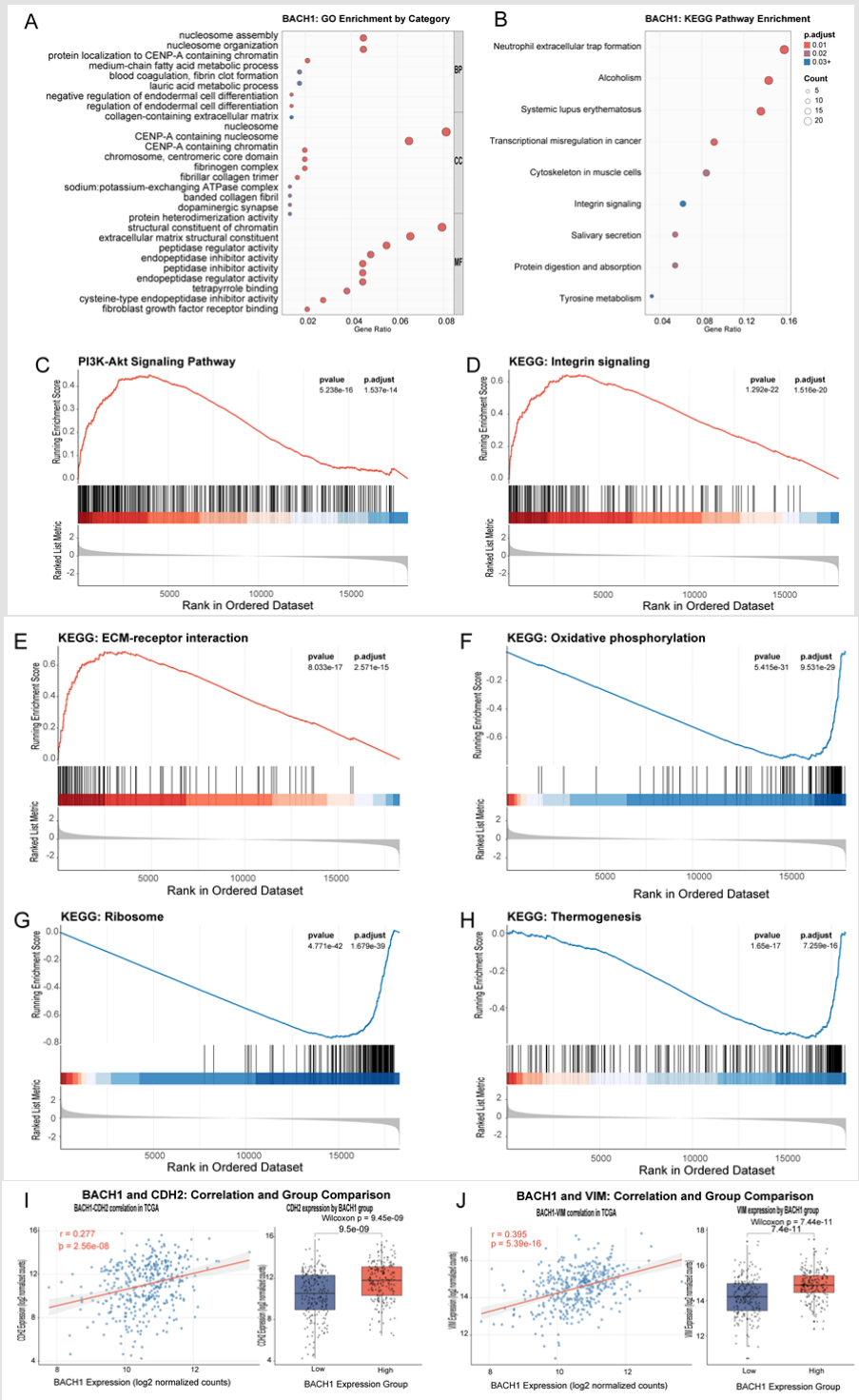


**Figure 5:** Functional Enrichment Analysis of BACH1 in Ovarian Cancer. (A) Gene Ontology enrichment analysis of BACH1-associated differentially expressed genes. (B-H) Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis of BACH1-associated differentially expressed genes. (I, J) Pearson correlations between BACH1 expression and mesenchymal markers.

BACH1 Is Associated with PI3K/AKT Signaling and a Mesenchymal Phenotype

Functional enrichment analyses were performed to investigate mechanisms that may underlie BACH1-mediated tumor progression. GO analysis associated BACH1 with nuclear localization, heterodimerization, nucleosome remodeling, centromere stability, and extracellular-matrix metabolism, suggesting links between genomic regulation and remodeling of the extracellular microenvironment (Figure 5A). KEGG analysis showed enrichment of PI3K/AKT signaling in the BACH1-high group (Figure 5C), together with integrin signaling, extracellular matrix-receptor interactions, oxidative phosphorylation, ribosomal function, and thermogenesis (Figure 5D-H). Because PI3K/AKT signaling is closely linked to EMT, correlations between BACH1 and mesenchymal markers were examined. In TCGA data, BACH1 ex-

pression correlated positively with vimentin and N-cadherin expression (Figure 5I & 5J), suggesting an association with a mesenchymal phenotype.

BACH1 Promotes EMT Through PI3K/AKT Activation

Western blotting was used to test the predicted effects of BACH1 on EMT and PI3K/AKT signaling. BACH1 knockdown increased the epithelial marker E-cadherin and decreased N-cadherin, vimentin, and  $\beta$ -catenin. Total PI3K and AKT levels were unchanged, whereas phosphorylated AKT decreased. BACH1 overexpression produced the opposite changes in EMT markers and  $\beta$ -catenin, did not alter total PI3K or AKT, and increased phosphorylated AKT (all  $P < 0.05$ ; Figure 6). These findings indicate that BACH1 promotes EMT in ovarian cancer cells, at least in part, through PI3K/AKT activation.

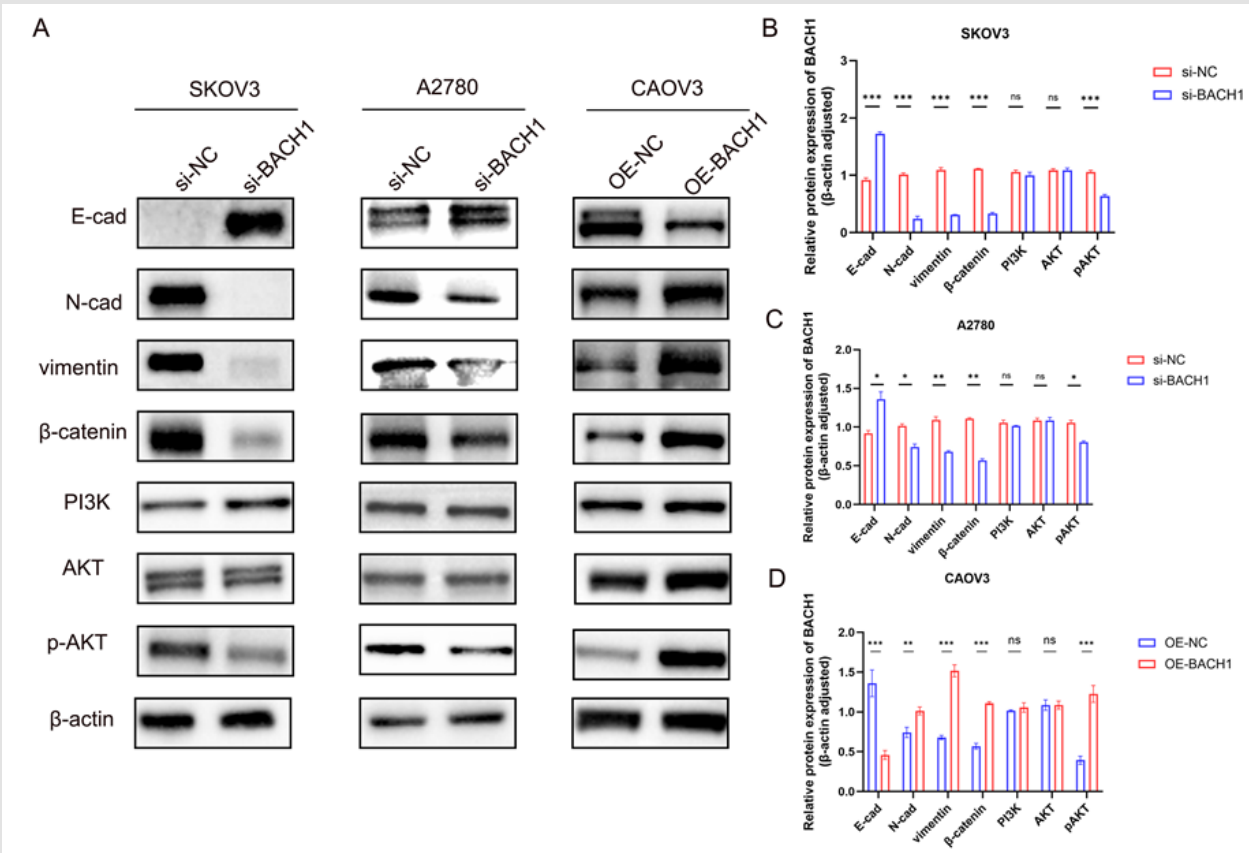


**Figure 6:** BACH1 Regulates Epithelial-Mesenchymal Transition Through PI3K/AKT Signaling. (A-D) Western blot analysis of EMT-related and PI3K/AKT pathway proteins in SKOV3 and A2780 cells.

## Discussion

This study identifies BACH1 as a promoter of malignant phenotypes in OC. BACH1 was overexpressed in ovarian cancer tissues and cell lines, and higher expression was associated with shorter overall survival. The BACH1-based risk score remained independently prognostic in multivariable Cox regression. A nomogram incorporating age, tumor stage, and risk score yielded AUCs of 0.682, 0.640, and 0.570 at 1, 3, and 5 years, respectively, indicating that discrimination decreased with longer follow-up. Functional experiments showed that BACH1 promoted proliferation, colony formation, migration, and invasion. The molecular findings further linked these effects to EMT and PI3K/AKT activation. BACH1 silencing reduced phosphorylated AKT without altering total PI3K or AKT, which is consistent with regulation of pathway activity rather than protein abundance. Because PI3K/AKT signaling controls cell growth and survival and is frequently hyperactivated in cancer [21-24], this result provides a plausible mechanism for the observed proliferative effects. BACH1 knockdown also increased E-cadherin and decreased N-cadherin and vimentin, linking BACH1 to EMT and to the reduced migration and invasion observed in the functional assays. EMT is a well-established driver of metastasis [17,18,25-27]. This study has several limitations. All functional experiments were performed in vitro, so the role of BACH1 in ovarian tumorigenesis requires validation in animal models. The PI3K/AKT pathway also interacts with other signaling networks, including MAPK/ERK and JAK/STAT [28-30].

Whether BACH1 directly binds the promoter regions of PIK3CA, AKT1, or PTEN remains unknown and requires further molecular investigation. The present findings are consistent with the reported pro-tumorigenic role of BACH1 in pancreatic cancer, glioma, clear cell renal cell carcinoma, esophageal squamous cell carcinoma, and hepatocellular carcinoma, in which BACH1 promotes invasion, metastasis, and poor prognosis [12,31-34]. In ovarian cancer, BACH1 has been reported to recruit the chromatin-remodeling protein HMG2 to the SNAIL and SLUG promoters while increasing AKT and p70S6K phosphorylation and cyclin D1 expression. This coordinated EMT and proliferation mechanism is consistent with the changes in EMT markers and phosphorylated AKT observed in this study [35]. TCGA data and analyses of multiple ovarian cancer cell lines consistently showed BACH1 overexpression, and higher expression was associated with shorter overall survival. BACH1 knockdown reduced proliferation, colony formation, migration, and invasion in SKOV3 and A2780 cells, whereas overexpression in CAOV3 cells produced the opposite effects. The magnitude of these effects varied among cell lines, possibly because SKOV3 cells have a more mesenchymal phenotype and greater migratory capacity, whereas CAOV3 cells have a more epithelial phenotype. This variation suggests that the effect of BACH1 may depend on cellular context or upstream regulatory signals.

BACH1 is a heme-regulated transcription factor involved in the tumor microenvironment, ferroptosis, and cellular metabolism. In

ovarian cancer, chronic inflammation and an iron-rich environment, such as that found in endometriotic cysts, can promote DNA damage and oxidative stress and may support the pro-tumorigenic activity of BACH1 [36]. GO and KEGG analyses further associated BACH1 with the cell cycle, mitosis, and PI3K/AKT signaling. Western blotting showed that BACH1 knockdown decreased N-cadherin, vimentin, and  $\beta$ -catenin and increased E-cadherin, whereas overexpression reversed these changes. BACH1 did not affect total PI3K or AKT but increased AKT phosphorylation at Ser473, suggesting that it activates the pathway by promoting AKT phosphorylation. Activated AKT can phosphorylate downstream GSK3 $\beta$ , stabilize Snail and  $\beta$ -catenin, and induce EMT [37]. AKT can also phosphorylate  $\beta$ -catenin at Ser552, increasing its transcriptional activity and promoting EMT [37,38]. BACH1 may therefore promote ovarian cancer progression through an AKT- $\beta$ -catenin axis. Chromatin immunoprecipitation, luciferase reporter, and rescue experiments are needed to test this hypothesis. Ovarian cancer has a high case-fatality ratio among gynecologic malignancies, partly because prognostic tools and targetable drivers remain limited [1,39]. The prognostic value of the BACH1-based nomogram should be tested in independent, multi-institutional cohorts with longer follow-up.

Animal models are also needed to determine whether the effects of BACH1 observed in vitro occur under physiological conditions. Finally, rescue experiments with PI3K/AKT inhibitors are needed to establish causality within the BACH1-PI3K/AKT-EMT axis and to assess its relevance to combination therapy.

## Conclusion

BACH1 is overexpressed in ovarian cancer tissues and cell lines, and higher expression is associated with poor prognosis. BACH1 promotes ovarian cancer cell proliferation, migration, and invasion and is associated with EMT and PI3K/AKT activation. These findings support further evaluation of BACH1 as a prognostic biomarker and therapeutic target in ovarian cancer.

## Acknowledgements

None.

## Funding

This study was supported by the National Natural Science Foundation of China (grant No. 82404043).

## Conflict of Interest

All authors completed the ICMJE uniform disclosure form and declared no conflicts of interest.

## Ethics Statement

All experiments were performed in accordance with relevant guidelines and regulations. The Ethics Committee of the Chinese PLA General Hospital approved the study (approval No. 2022-268-01).

The study complied with the ethical principles of the Declaration of Helsinki for research involving human participants, and all participants provided informed consent.

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**ISSN: 2574-1241**DOI: [10.26717/BJSTR.2026.67.010451](https://doi.org/10.26717/BJSTR.2026.67.010451)

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