Reduced expression of SOX7 in ovarian cancer: a novel tumor suppressor through the Wnt/β-catenin signaling pathway

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Outline

- 1. Background
- 2. Research Goal
- 3. Data
- 4. Discussion

Conclusion,

Acknowledgements

Estimated New Cases

Females

Breast	232,340	29%
Lung & bronchus	110,110	14%
Colorectum	69,140	9%
Uterine corpus	49,560	6%
Thyroid	45,310	6%
Non-Hodgkin lymphoma	32,140	4%
Melanoma of the skin	31,630	4%
Kidney & renal pelvis	24,720	3%
Pancreas	22,480	3%
Ovary	22,240	3%
All Sites	**805,500**	**100%**

Cancer Statistics, 2013.

Estimated Deaths

Females

Lung & bronchus	72,220	26%
Breast	39,620	14%
Colorectum	24,530	9%
Pancreas	18,980	7%
Ovary	14,030	5%
Leukemia	10,060	4%
Non-Hodgkin lymphoma	8,430	3%
Uterine corpus	8,190	3%
Liver & intrahepatic bile duct	6,780	2%
Brain & other nervous system	6,150	2%
All Sites	**273,430**	**100%**

Cancer Statistics, 2013.

Late diagnosis results in poor survival

If diagnosed at the localised stage, the 5-year survival rate is 93%.
However, only about 15% of all cases are diagnosed at this stage.

Localised
Confined to primary site

15% at diagnosis

Regional
Spread to regional lymph nodes

17% at diagnosis

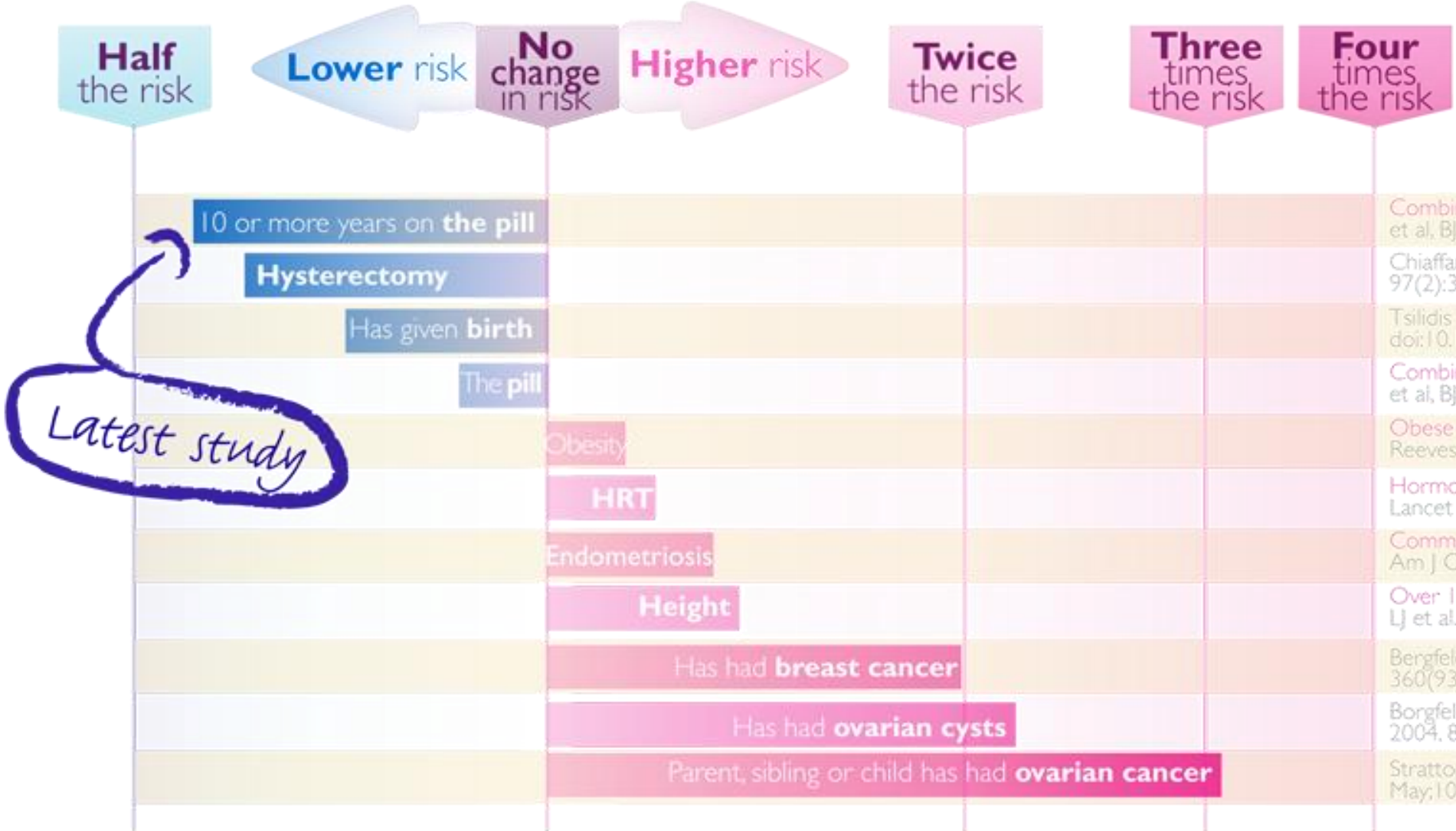
Distant
Cancer has metastasised

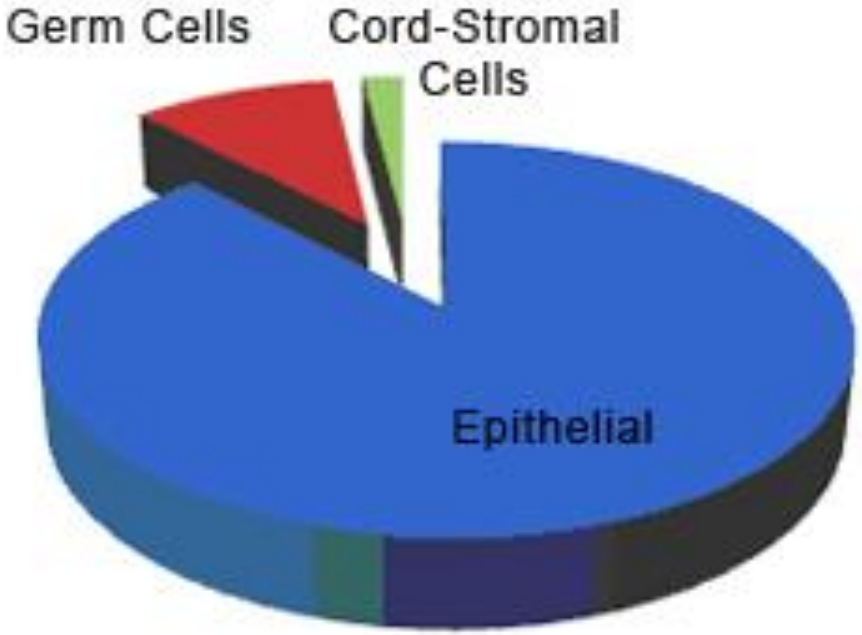
62% at diagnosis

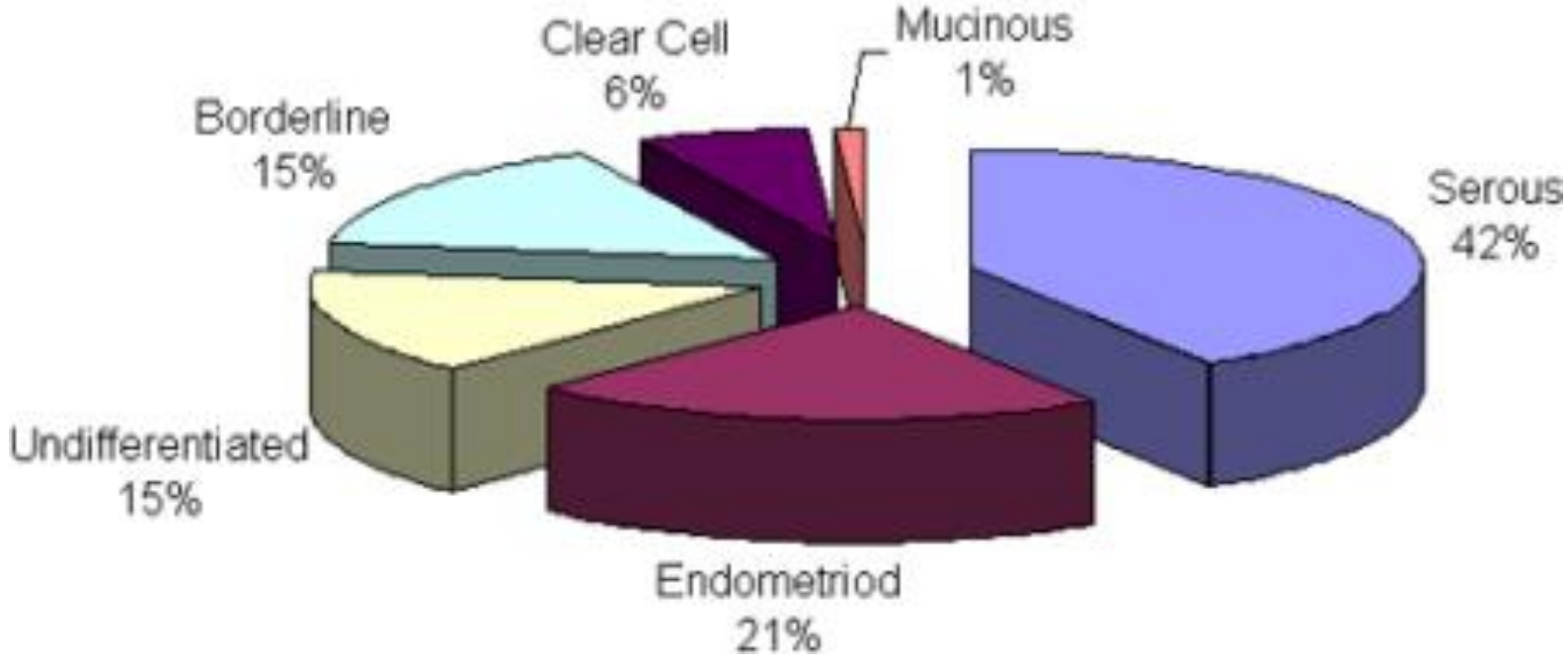
Unknown
Unstaged

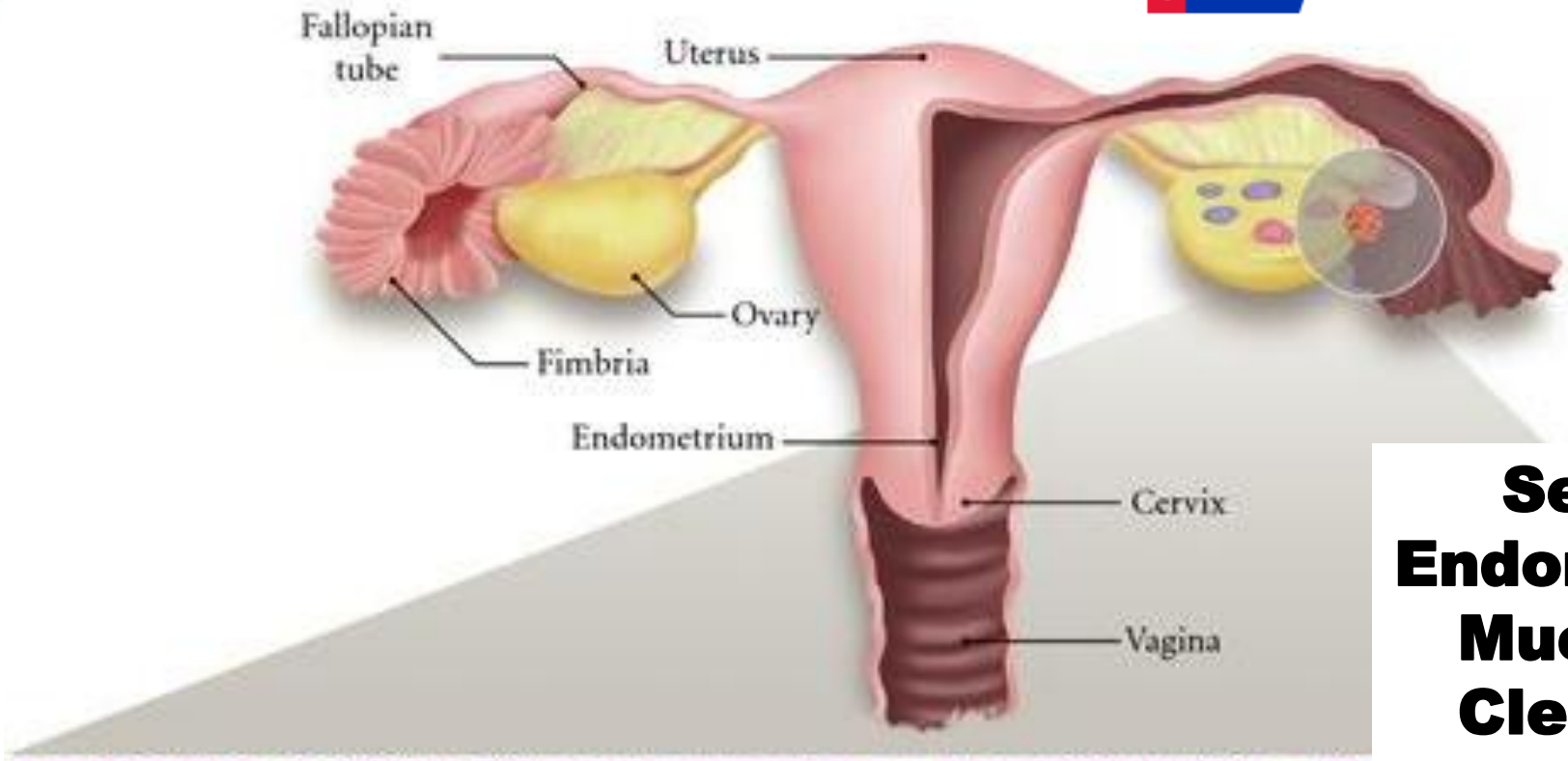
7% at diagnosis

What affects **ovarian cancer** risk?

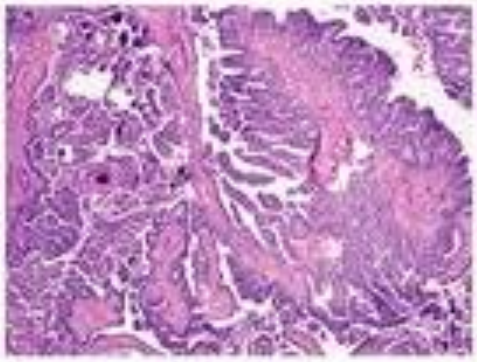


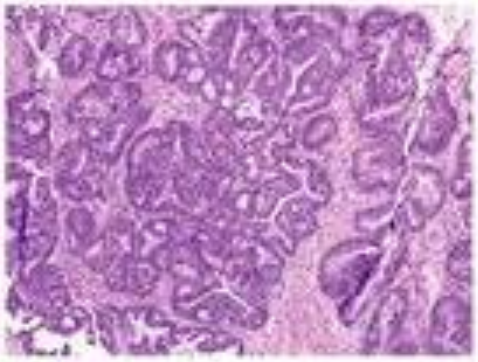




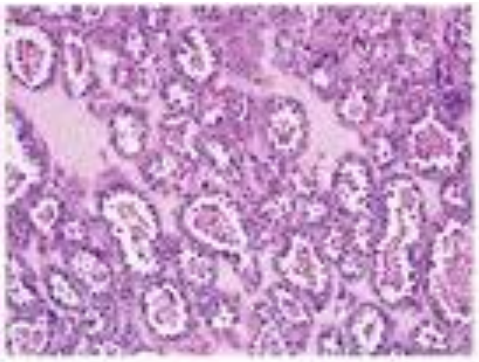


Serous
Endometrioid
Mucinous
Clear cell


Serous


Endometrioid


Mucinous

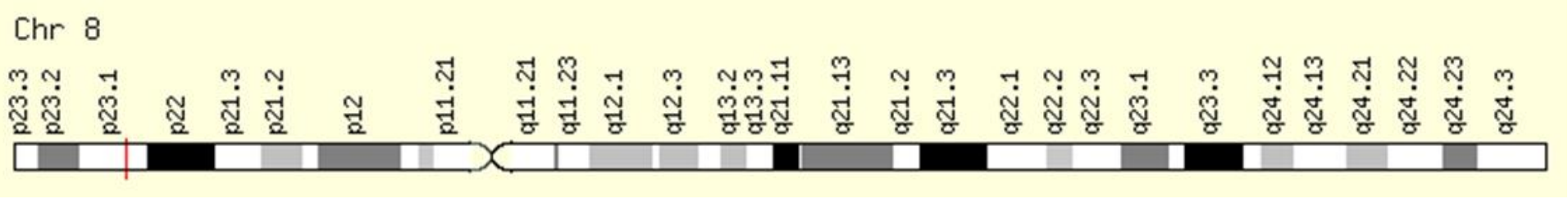

Clear cell

SOX7

SRY (sex determining region Y)-boxes

- **SOX7, a member of subfamily SOX F along with SOX17 and SOX18, has been identified as a developmental regulator in hematopoiesis and cardiogenesis.**

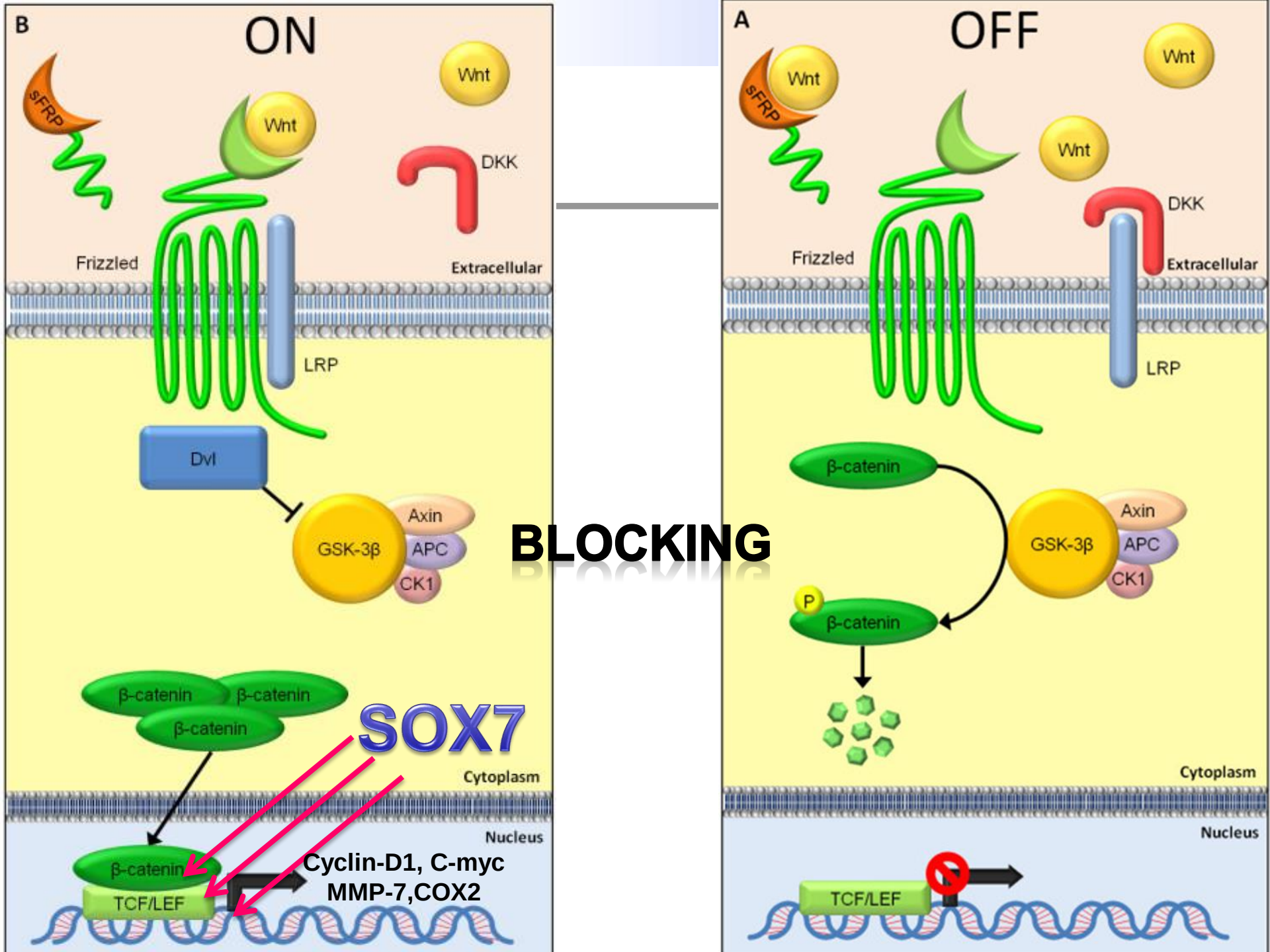
- **Genomic location for SOX7 gene: 8p23.1**



Wnt/β-catenin signal pathway

- It is reported that SOX7 can directly bind β-catenin and negatively regulate its activity.

- As SOX7 negatively regulates the Wnt/β-catenin signaling pathway by impeding the transcriptional machinery of β-catenin/TCF/LEF-1.

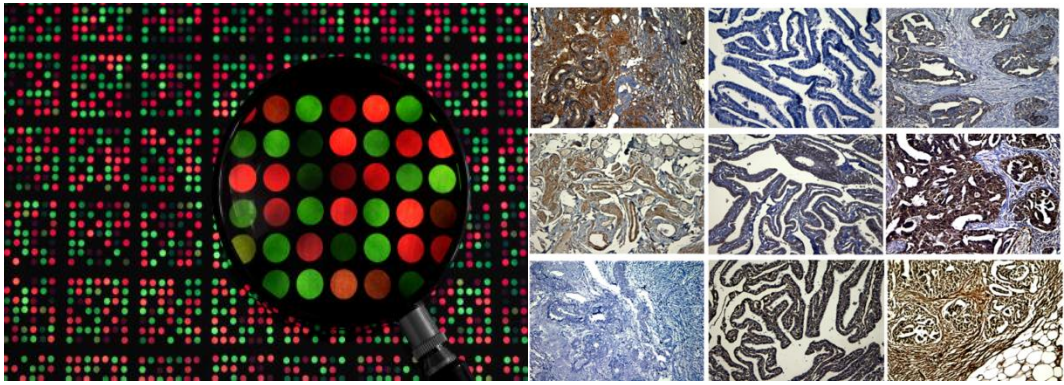

B
ON
sFRP
Wnt
Wnt
DKK
Frizzled
Extracellular
LRP
Dvl
GSK-3β
Axin
APC
CK1
β-catenin
β-catenin
β-catenin
SOX7
Cytoplasm
Nucleus
β-catenin
TCF/LEF
Cyclin-D1, C-myc
MMP-7,COX2
BLOCKING
A
OFF
sFRP
Wnt
Wnt
DKK
Frizzled
Extracellular
LRP
β-catenin
GSK-3β
Axin
APC
CK1
P
β-catenin
Cytoplasm
Nucleus
TCF/LEF

SOX7

- **SOX7 is frequently down-regulated in many human cancers, such as prostate, colon, lung and breast cancer, and its reduced expression often correlates with poor prognoses.**

Research Goal

- **We investigated the contributions and molecular mechanisms of SOX7 in ovarian cancer.**

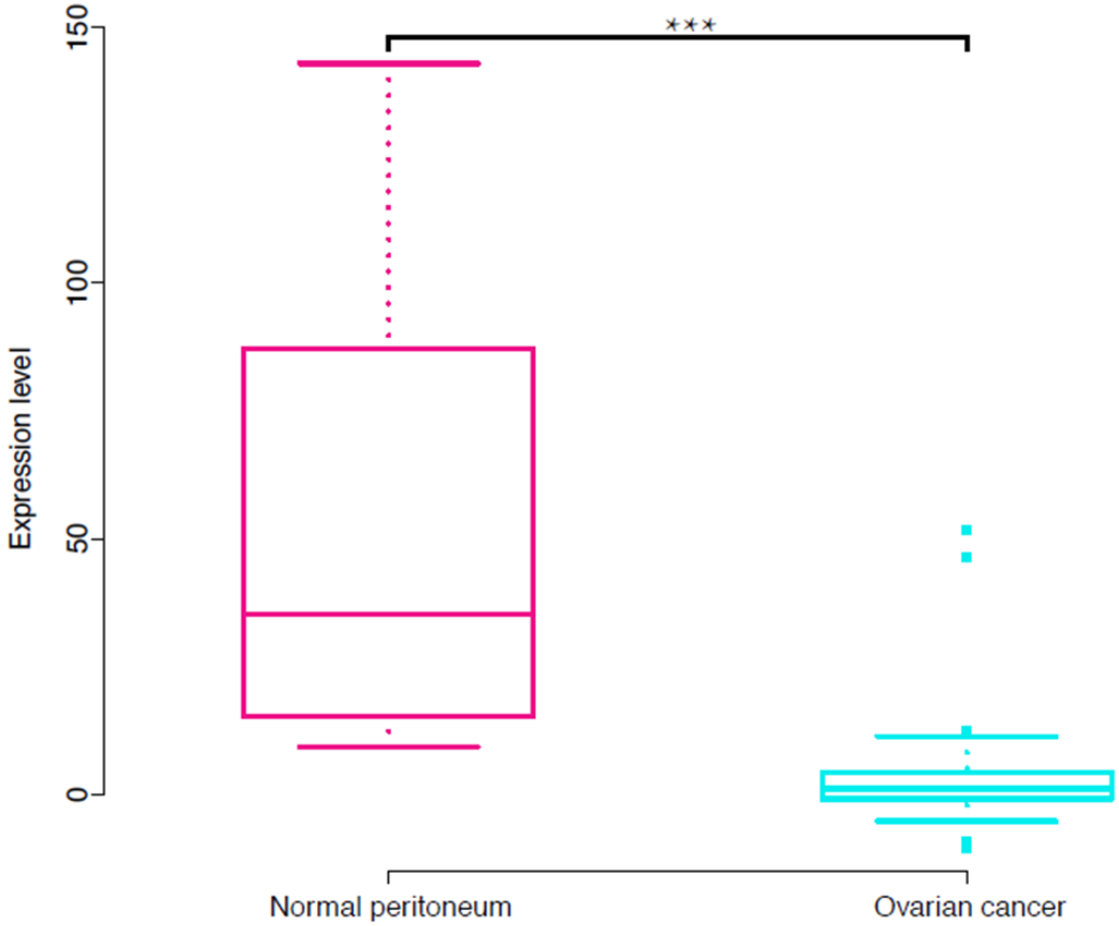


Materials & Methods

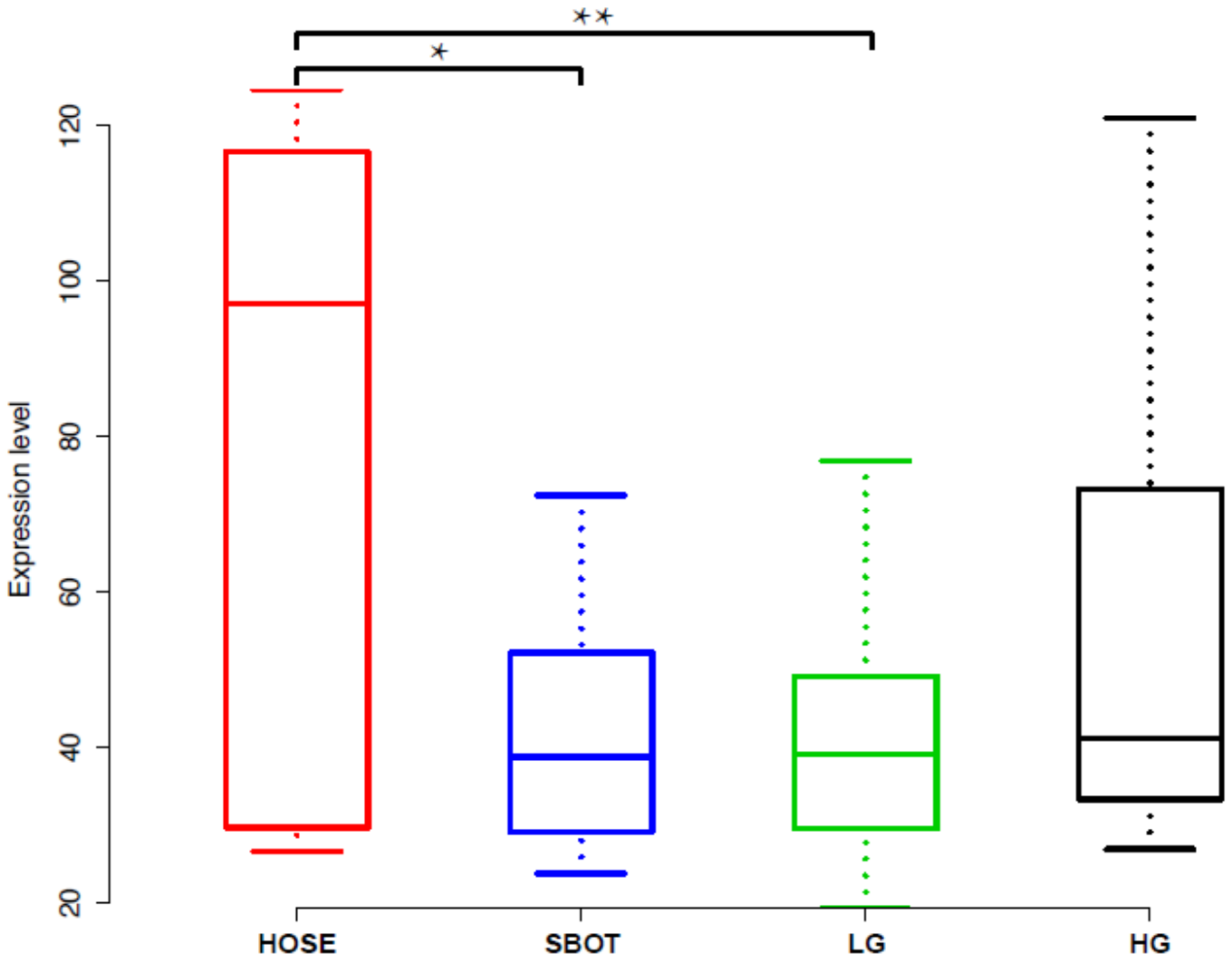
- Chemicals and antibodies
- Datasets and preprocessing
- Functional enrichment analysis
- Clinical specimens
- Immunohistochemistry
- Standard for evaluation
- Statistical analysis

Results

- **Expression levels of SOX7 in ovarian cancer and normal tissues.**



- **Correlation of reduced SOX7 expression with tumor progression**



- **Correlation of reduced SOX7 expression with tumor progression**

HOSE: Human ovarian surface epithelia

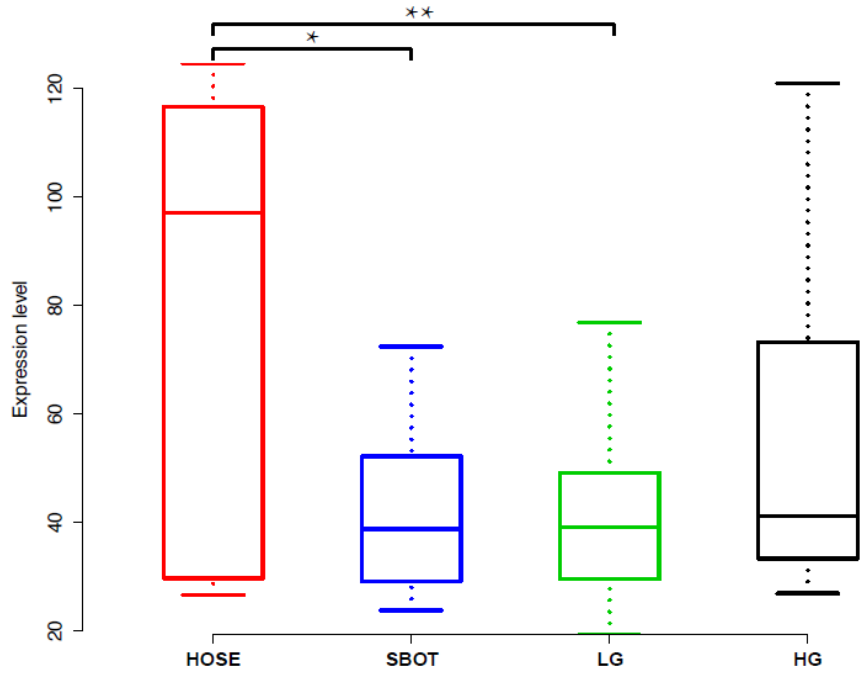
SBOT: Serous borderline ovarian tumors

LG: Low-grade serous ovarian carcinomas

HG: High-grade serous ovarian carcinomas

Malignant:
LG>SBOT>HG>HOSE

SOX7:
HOSE>HG>SBOT>LG



- **SOX7 as a negative regulator in Wnt/β-catenin pathway in ovarian cancer**

To investigate the mechanism by which SOX7 is involved in the oncogenesis and progression of ovarian cancers,

We analyzed genes that were co-expressed with SOX7 and short-listed 7933 genes by Pearson correlation (FDR < 0.01) in GSE27651 (Additional file 1).

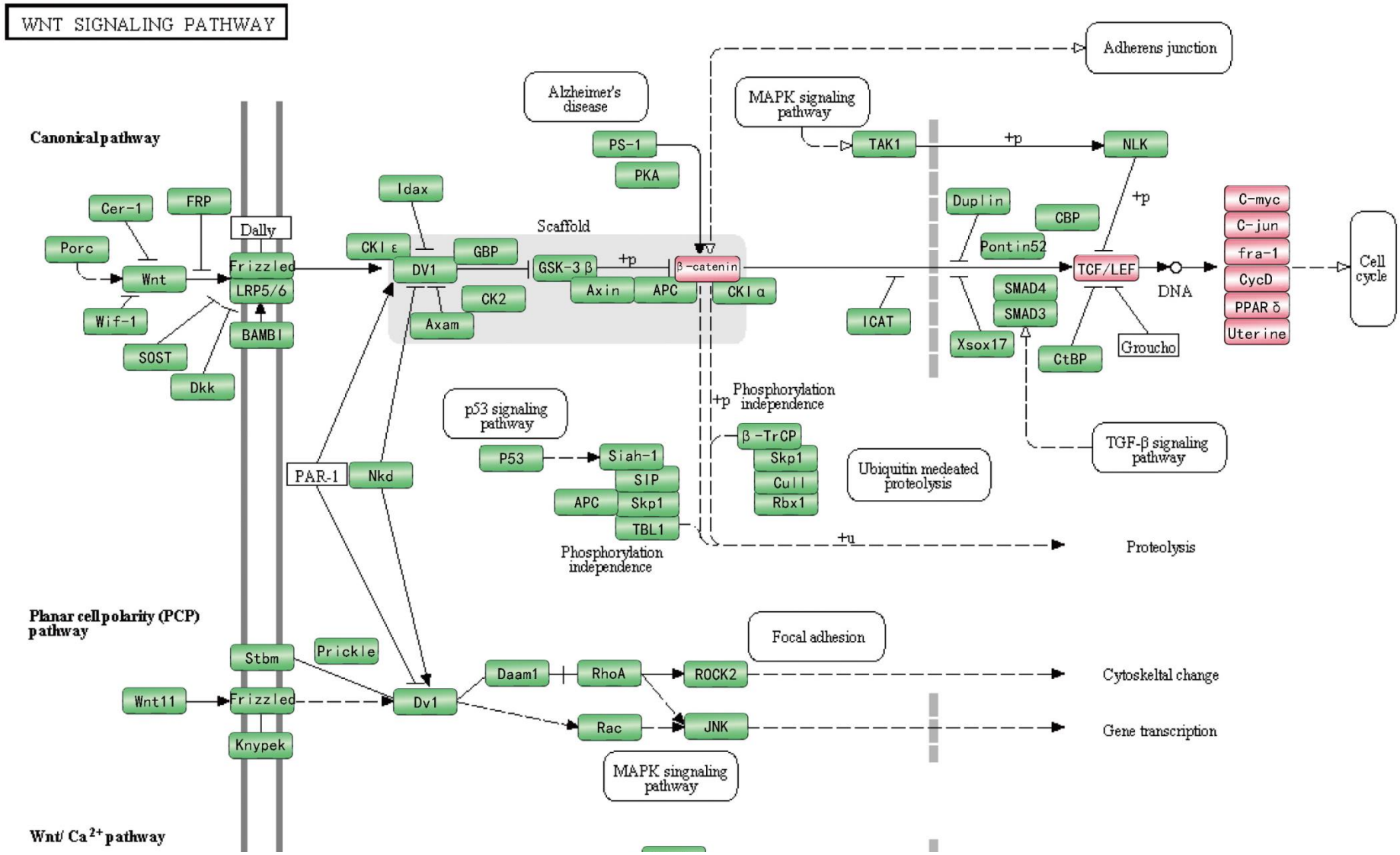
Short-listed 7933 genes were co-expressed with SOX7 by Pearson correlation (*FDR* < 0.01) in GSE27651

Number	Gene	EntrezGene	Fdr	Correlation Coefficient
1	NAT2	10	0.000513216	0.521953398
2	AAMP	14	0.002578854	-0.463809284
3	AANAT	15	4.50E-07	0.687615139
4	ABCA2	20	0.00033142	0.535889973
5	ABCB7	22	0.000125177	-0.56417787
6	ABCF1	23	4.98E-08	0.72395679
7	ABCA4	24	5.65E-07	0.683662042

- **Using DAVID with a 5% FDR control, we found that the 7933 genes were significantly overrepresented in eleven GO-biological processes involved mainly in transcription activities (Table 1)**

Table 1 Biological processes enriched with genes dysregulated to a larger extent in ovarian cancer

Accession	Term	*P*-Values	FDR
GO:0006414	translational elongation	4.692062542984977E-29	9.047961108371685E-26
GO:0006412	translation	2.049129117345554E-22	3.951447873919316E-19
GO:0006396	RNA processing	2.7244884076177707E-10	5.253780188674284E-7
GO:0022613	ribonucleoprotein complex biogenesis	1.3552603187281535E-9	2.6134227004703803E-6
GO:0016071	mRNA metabolic process	3.895055800131527E-8	7.511046692387778E-5
GO:0006397	mRNA processing	5.7556740309817435E-8	1.1098975527534805E-4
GO:0000375	RNA splicing, via transesterification reactions	3.5239047199996375E-7	6.795316527141715E-4
GO:0000377	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	3.5239047199996375E-7	6.795316527141715E-4
GO:0000398	nuclear mRNA splicing, via spliceosome	3.5239047199996375E-7	6.795316527141715E-4
GO:0042254	ribosome biogenesis	5.134416394199803E-7	9.900929787476365E-4
GO:0008380	RNA splicing	1.103477760861063E-6	0.0021278751



We chose thirteen genes from KEGG that were annotated in the Wnt/β-catenin pathway as down-stream or pivotal hub genes (Figure 3)

- **The Pearson correlation coefficients of expression levels between the 13 genes and SOX7**

Table 2 The Pearson correlation coefficients between the expression levels of 13 genes and SOX7

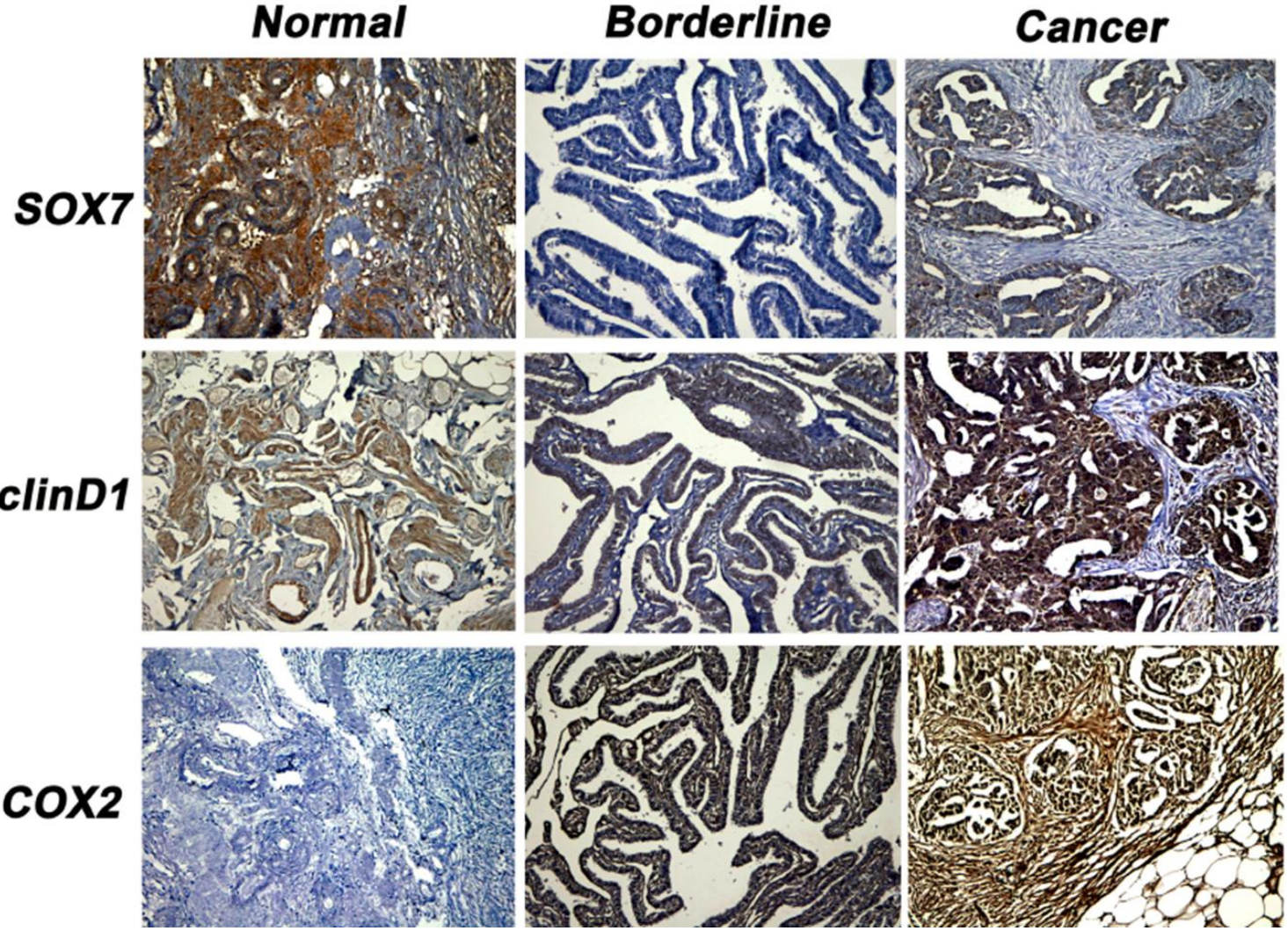
Gene name	r	*p*
CCN-D1	−0.2753514639	0.0555052128
CCND2	−0.2083737906	0.1507783665
CCND3*	−0.3789749206	0.0072460704
CTNNB1	−0.2298744109	0.1120735508
JUN*	−0.328410818	0.0212317742
MMP7	−0.1436013727	0.3249317121
MYC*	−0.3794897149	0.0071609446
PPARD(NR1C2)	0.0113166546	0.9384851238
TCF7*	−0.4721329855	0.0006148219
TCF7L2*	−0.5079689459	0.00019461
FOSL1	0.1976706188	0.1733712192
LEF1*	−0.4230961749	0.0024547299
TCF7L1	0.014360968	0.9219826098

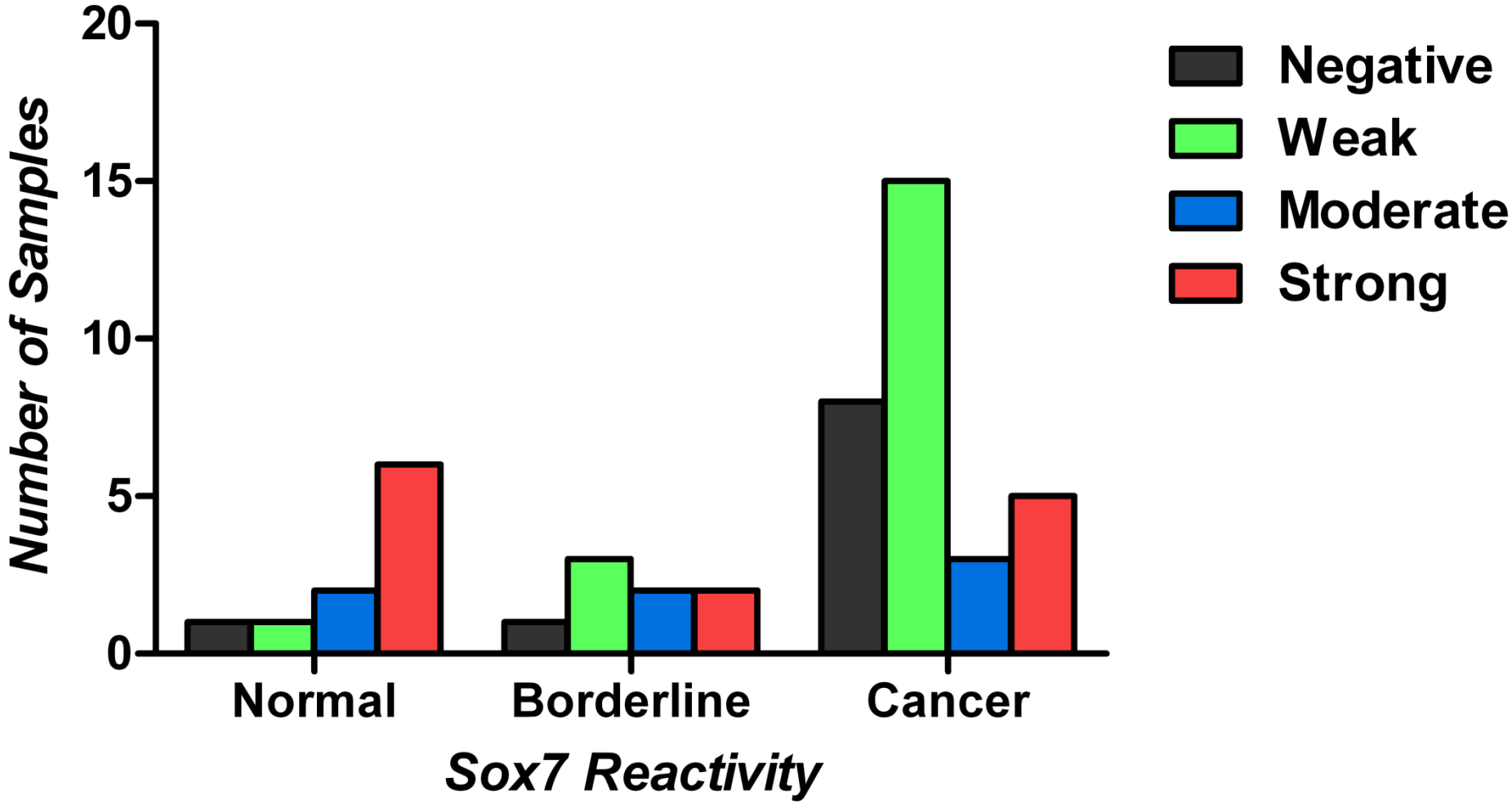
Bold front denotes downstream genes in wnt signal pathway list in KEGG.
*Presents significant correlation.

11/13 genes
Negative

SOX7
Negative regulator

- **Expression of SOX7, cyclin-D1 and COX2 proteins in normal ovarian tissues, borderline ovarian tumors and ovarian cancer.**




20
15
10
5
0
Number of Samples
Normal
Borderline
Cancer
Sox7 Reactivity
Negative
Weak
Moderate
Strong

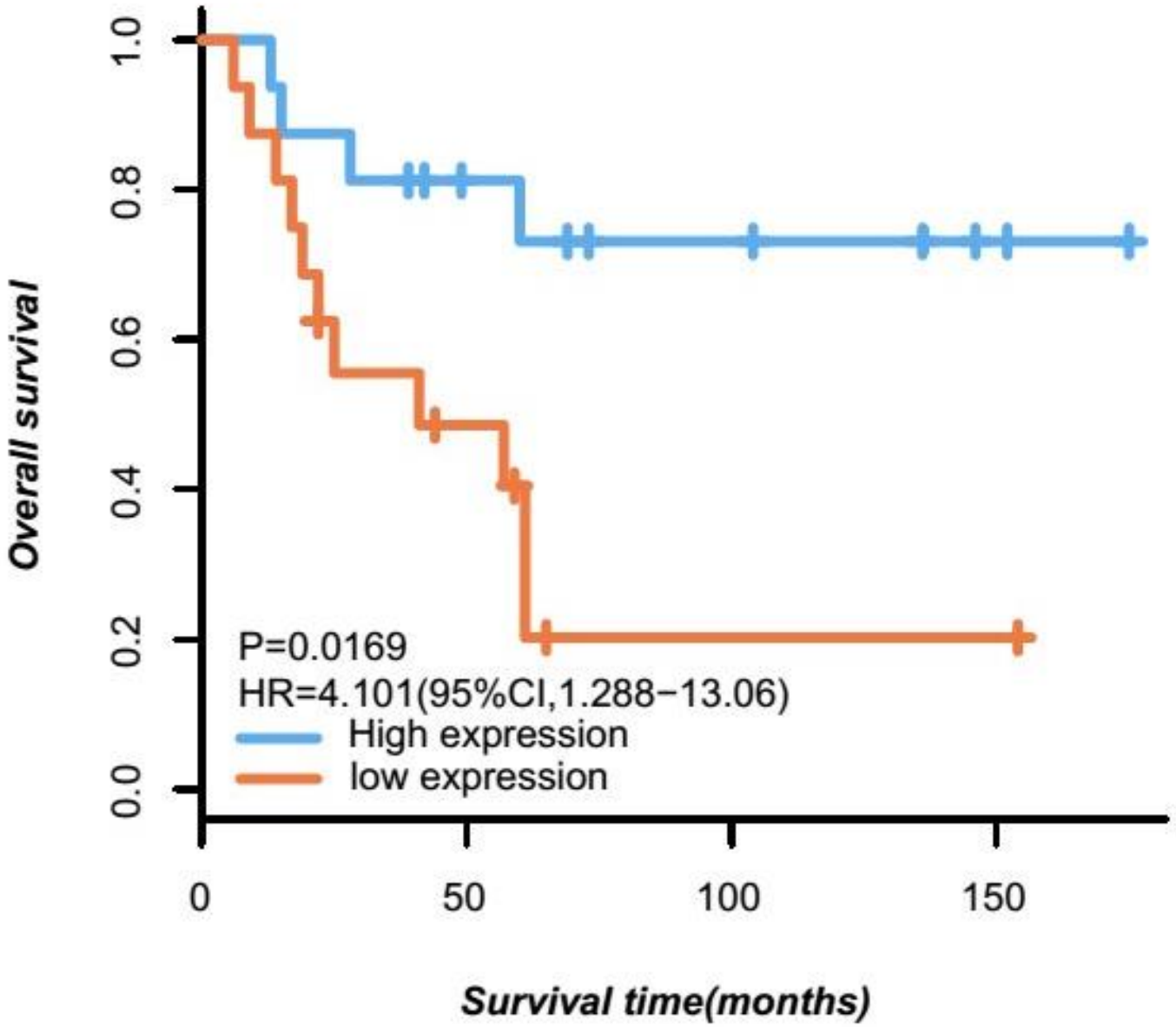
• Relations between SOX7 and clinical or pathological characteristics in patients with epithelial ovarian carcinoma

- The down-regulation of SOX7 was significantly associated with the advanced stages (III-IV; 14/31, p = 0.037) .

- The negative correlation of SOX7 with COX2 and cyclinD1 indicates a trend of inverse expression pattern of SOX7 to COX2 and cyclin D1.

Characteristic	Total	SOX7 expression		P
		Over-expression	Low-exeression	
All cases	31			
Pathology type				NS
Serous	26	7	19	
Mucinous	2	0	2	
Endometrioid	3	1	2	
FIGO stage				0.037
Early(I-II)	16	7	9	
Advance(III-IV)	15	1	14	
Pathology grade				NS
Low(1)	4	1	3	
High(2+3)	27	7	20	
Age (years)				NS
≦60	21	5	16	
≧60	10	3	7	
COX2				r_s=-0.618,p<0.001
Over-expression	27	5	22	
Low-exeression	4	3	1	
CyclinD1				r_s=-0.583,p<0.001
Over-expression	26	8	18	
Low-exeression	5	0	5	

- **Expression of SOX7 v.s. Overall survival**



Discussion

- In this study, we chose ovarian cancer to work on due to that relatively little has been done on SOX7 in ovarian cancer.

- Our results obtained from different platforms indicate that the expression levels of SOX7 were significantly reduced in all types of ovarian cancers studied here.

- **Our results demonstrated that the expression levels of SOX7 and its targets, COX-2 and cyclin D1, have an inverse relationship.**

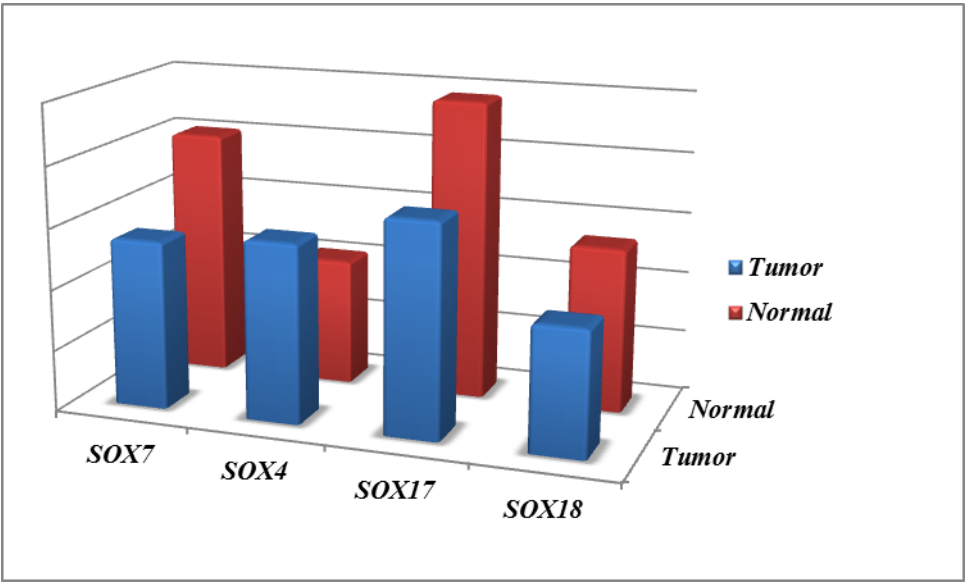
- **Further supporting our hypothesis that SOX7 is a negative regulator in the Wnt/β-catenin signaling pathway in ovarian cancer.**

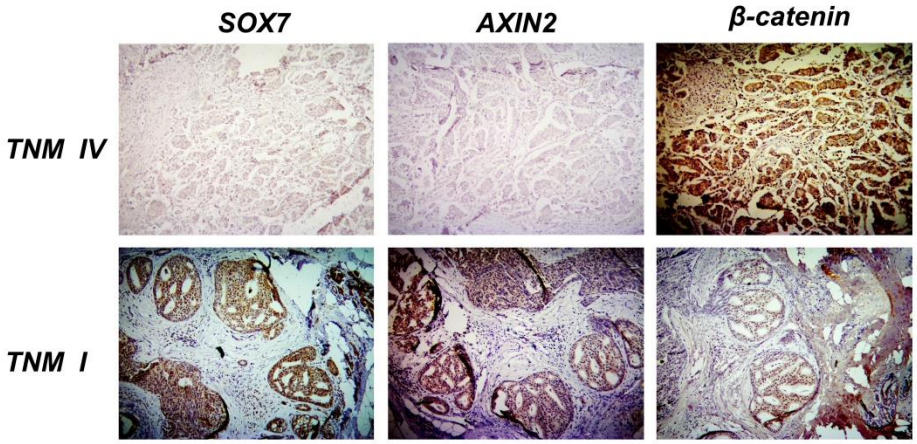
Conclusions

- Our work reported here suggests, for the first time, that SOX7 may play an important role as a tumor suppressor in ovarian cancer progression.
- Our results also revealed SOX7 as a negative regulator in the Wnt/β-catenin signaling pathway in ovarian cancer.
- Our result demonstrates the suppressive function of SOX7 in the carcinogenic process of ovarian cancer.

Future Direction

- **Current data showed that the expression of SOX7 was significantly reduced in breast cancer and this effect might be positively correlated with AXIN2.**





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