Identifying SOX17 as a sensitive and specific marker for ovarian and endometrial tumors

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Abstract

Like PAX8, SOX17 was recently identified as a master transcription factor of ovarian cancer based on RNA sequencing data. We explored SOX17's utility in diagnosing ovarian tumors and other gynecologic tumors. We systematically evaluated SOX17 expression on tissue microarrays from 398 ovarian tumors of various types, 93 endometrial carcinomas, 80 cervical carcinomas, and 1,055 non-gynecologic carcinomas from kidney, thyroid, breast, colon, bladder, liver and bile duct. In addition, SOX17 expression was evaluated on whole tissue sections from 60 gynecologic carcinomas and 10 angiosarcomas. The results demonstrated that SOX17 was highly expressed in most ovarian and endometrial tumors with strong intensity, but unlike PAX8, it was predominately negative in other tested tumor types including kidney and thyroid tumors. Specifically, SOX17 was highly expressed in the following types of ovarian tumors: serous carcinoma, clear cell carcinoma, endometrioid carcinoma, and germ cell tumors. SOX17 was mostly negative in mucinous carcinoma and sex cord stromal tumors. In addition, SOX17 was expressed in vascular endothelial cells and positive in all tested angiosarcomas. In summary, our results demonstrate that SOX17 is a sensitive and specific marker for ovarian non-mucinous carcinomas and endometrial carcinomas with a comparable sensitivity, but better specificity than PAX8. Furthermore, SOX17's positivity in endothelial cells serves as an internal positive control, making it an excellent marker.

Introduction

The utility of different markers to confirm tumor origin is essential in pathology practice. In diagnostic pathology, there has been an increasing interest in the application of the transcription factor immunohistochemistry (IHC) due to their distinct nuclear reactivity and easy interpretation. For example, paired-box gene 8 (PAX8) is a member of the paired-box family of genes and PAX8 IHC is routinely used as an adjunctive tool in diagnosing kidney, thyroid and Mullerian tumors.[1–10] However, challenges exist when using PAX8 to diagnose ovarian and endometrial tumors in clinical practice. PAX8 expression in thyroid and kidney tumors may occasionally cause diagnostic pitfalls when ovarian, renal, and thyroid tumors are in the differential diagnosis. Furthermore, PAX8 is reportedly expressed in up to 40% of breast carcinomas and estrogen receptor (ER) can be expressed in ovarian, endometrial, and breast cancer, which can cause a diagnostic challenge. [11–15]

A recent study identified PAX8 and Sry-related HMG box gene 17 (*SOX17*) as ovarian cancer master transcription factors by using pan-cancer RNA sequencing data from 34 tumor types and 140 subtypes.[16] *SOX17* is a member of SOX F subfamily which also contains SOX7 and SOX18. SOX17 protein is a transcription factor that controls the first step of gene expression and regulates cellular growth and differentiation in the endoderm, during hematopoiesis, and in the cardiovascular system. [17–23] Recent studies have demonstrated that SOX17 is involved in tumorigenesis of endometrial and ovarian carcinomas,[16,24–28] but no study to date has investigated its diagnostic utility as a Mullerian tumor marker. In this study, we systematically evaluated SOX17 expression in various tumors of gynecologic and non-gynecologic origin using tissue microarray (TMA) and whole tissue sections.

Materials And Methods

Specimens

This study was approved by The Ohio State University institutional research board. The following TMAs were included: 398 ovarian tumors (OV20810 and V20813, Biomax, Rockville, MD), 93 endometrial carcinomas (FUR1021b, US Biolab, Rockville, MD), 80 cervical carcinomas (CR1001b, Biomax, Rockville, MD), 110 kidney carcinomas (KD1201, Biomax, Rockville, MD), 70 thyroid carcinomas (TH8010a, Biomax, Rockville, MD), 208 breast carcinomas (BR20724, US Biolab, Rockville, MD), (CO20813, US Biolab, Rockville, MD), 142 bladder tumors (UBD2082b, US Biolab, Rockville, MD), 208 liver hepatocellular carcinomas and cholangiocarcinomas (LV2161, Biomax, Rockville, MD), and 109 bile duct cholangiocarcinomas (made at The Ohio State University). Additional whole tissue sections from 25 ovarian tumors, 25 endometrial tumors, 10 cervical tumors and 10 angiosarcomas were also included.

Evaluation of SOX17 expression using immunohistochemistry

IHC staining was performed with a rabbit monoclonal antibody against human SOX17 (EPR20684 from Abcam, Waltham, MA) on a Leica Bond III autostainer system (Leica Biosystems, Buffalo Grove, IL). Formalin-fixed paraffin-embedded (FFPE) tissue sections were deparaffinized/rehydrated, and antigen retrieval was performed with Bond ER1 (Leica Biosystems, equivalent to citrate buffer, pH 6.0) or Bond ER2 (Leica Biosystems, equivalent to EDTA buffer, pH 8;0) at 100°C for 20 min. Primary antibody (1:1,000) was incubated for 15 min at room temperature. The primary antibody was detected by using the Bond Polymer Refine Detection kit (Leica Biosystems, Cat# DS9800), and diaminobenzidine (DAB) chromogen. Tissue was then counterstained using Leica Hematoxylin as part of the Leica Bond Polymer Refine Detection kit. Normal breast tissues were used as positive control.

All immunostains were reviewed by at least two pathologists and difficult cases with discordant results were reviewed by all pathologists together to obtain a consensus. Only nuclear staining was counted as specific positive staining. The IHC results were categorized based on the percentage of immunoreactive tumor cells as the following: negative (< 1%), low positive (1–9%), intermediate positive (≥ 10%, but < 50%), or high positive (≥ 50%). We used a cut off value of 1% for all four proteins' positivity in current study.

Results

SOX17 expression in normal tissues

SOX17 expression was examined in multiple normal tissues and was found in fallopian tube epithelium, endometrium, endocervical glandular epithelium, and vascular endothelial cells. SOX17 was not expressed in breast ductal epithelial cells or myoepithelial cells, kidney tubules, thyroid follicular cells, bladder urothelial cells, bile ductal epithelial cells, colorectal mucosa, or liver hepatocytes. (Table 1) (Fig. 1)

Table 1
SOX17 expression in normal tissue.

Tissue type	SOX17 expression
Fallopian tube epithelium	Positive
Endometrium	Positive
Endocervical epithelium	Positive
Endothelial cells (blood vessel)	Positive
Breast ductal epithelial cells	Negative
Kidney tubules	Negative
Thyroid follicular cells	Negative
Bladder urothelium	Negative
Bile ductal epithelial cells	Negative
Colorectal mucosa	Negative
Liver hepatocytes	Negative

SOX17 expression in various types of ovarian tumors using tissue microarray and whole tissue sections

We investigated the SOX17 expression in various types of ovarian tumors on TMA sections. 74% (294/398) of ovarian tumors showed positive nuclear expression, while 26% (105/398) showed negative expression. When stratified by tumor type, SOX17 was positive in most serous carcinomas (high grade and low grade) (91%, 234/256), clear cell carcinomas (91%, 10/11), endometrioid carcinomas (74%, 14/19), dysgerminomas (75%, 6/8), and yolk sac tumors (100%, 7/7). Most mucinous carcinomas (77%, 50/65) and all stomal and sex cord tumors (100%, 22/22) were negative for SOX17 expression. Furthermore, almost all positive cases showed strong staining intensity with either high or intermediate percentage of positively stained tumor cells. (Table 2)

Table 2
SOX17 expression in gynecologic tumors using tissue microarray.

		Negative		Low positive (< 10%)		Intermediate positive (10–49%)		High positive (≥ 50%)		Total positive		Total
Ovary	Total	105	26%	5	1%	16	4%	272	68%	293	74%	398
	Serous carcinoma	22	9%	5	2%	9	4%	220	86%	234	91%	256
	Clear cell carcinoma	1	9%	0	0%	1	9%	9	82%	10	91%	11
	Endometrioid carcinoma	5	26%	0	0%	2	11%	12	63%	14	74%	19
	Mucinous carcinoma	51	77%	0	0%	2	3%	13	20%	15	23%	65
	Adenocarcinoma	3	33%	0	0%	1	11%	5	56%	6	67%	9
	Neuroendocrine carcinoma	0	0%	0	0%	0	0%	1	100%	1	100%	1
	Dysgerminoma	2	25%	0	0%	1	13%	5	63%	6	75%	8
	Yolk sac tumor	0	0%	0	0%	0	0%	7	100%	7	100%	7
	Stromal and sex cord tumor	22	100%	0	0%	0	0%	0	0%	0	0%	22
Uterus	Total	10	11%	0	0%	2	2%	81	87%	83	89%	93
	Endometrioid carcinoma	10	11%	0	0%	2	2%	81	87%	83	89%	93
Cervix	Total	74	93%	0	0%	0	0%	6	8%	6	8%	80
	Adenocarcinoma	34	85%	0	0%	0	0%	6	15%	6	15%	40
	Squamous cell carcinoma	40	100%	0	0%	0	0%	0	0%	0	0%	40

We further studied the SOX17 expression on whole tissue sections of various types of ovarian carcinomas including high grade serous carcinomas (n = 5), low grade serous carcinomas (n = 5), clear cell carcinomas (n = 5), endometrioid carcinomas (n = 5), and Mucinous carcinomas (n = 5). All high- and low-grade serous carcinomas, clear cell carcinomas, and endometrioid carcinomas were diffusely positive (> 50%) for SOX17 expression. All five mucinous carcinomas cases were negative for SOX17 expression. (Table 3) (Figs. 2 and 3)

Table 3
SOX17 expression in gynecologic tumors using whole tissue sections.

		Negative		Low positive (< 10%)		Intermediate positive (10–49%)		High positive (≥ 50%)		Total positive		Total cases
Ovary	Total	5	20%	0	0%	0	0%	20	80%	20	80%	25
	High grade serous carcinoma	0	0%	0	0%	0	0%	5	100%	5	100%	5
	Low grade serous carcinoma	0	0%	0	0%	0	0%	5	100%	5	100%	5
	Clear cell carcinoma	0	0%	0	0%	0	0%	5	100%	5	100%	5
	Endometrioid carcinoma	0	0%	0	0%	0	0%	5	100%	5	100%	5
	Mucinous carcinoma	5	100%	0	0%	0	0%	0	0%	0	0%	5
Uterus	Total	1	4%	3	12%	0	0%	21	84%	24	96%	25
	Endometrioid carcinoma	0	0%	0	0%	0	0%	5	100%	5	100%	5
	Endometrioid carcinoma with mucinous feature	0	0%	0	0%	0	0%	5	100%	5	100%	5
	Serous carcinoma	0	0%	0	0%	0	0%	5	100%	5	100%	5
	Clear cell carcinoma	1	20%	0	0%	0	0%	4	80%	4	80%	5
	Carcinosarcoma	0	0%	3	60%	0	0%	2	40%	5	100%	5
Cervix	Total	8	80%	1	10%	1	10%	0	0%	2	20%	10
	Adenocarcinoma	3	60%	1	20%	1	20%	0	0%	2	40%	5
	Squamous cell carcinoma	5	100%	0	0%	0	0%	0	0%	0	0%	5

SOX17 expression in endometrial carcinomas using tissue microarray and whole tissue sections

Next, we investigated the SOX17 expression in uterine endometrial carcinomas using TMAs and whole tissue sections. On TMAs, 83 out of 93 (89%) endometrial endometrioid carcinomas showed positive staining for SOX 17, while 10 (11%) cases showed negative expression for SOX17. Majority of cases (98%, 81/83) demonstrated diffusely strong staining (> 50%), while only 2 out of 83 cases showed intermediate positivity. Similar findings were obtained when analyzing SOX17 expression of endometrioid carcinomas on whole tissue sections. (Table 2)

We further analyzed SOX17 expression in endometrial carcinomas on whole tissue sections, including endometrioid carcinomas (n = 5), endometrioid carcinomas with mucinous features (n = 5), serous carcinomas (n =

5), clear cell carcinomas (n = 5), and carcinosarcomas (n = 5). All tested cases except one clear cell carcinoma were positive for SOX17 with most cases showing diffuse strong staining. (Table 3) (Fig. 4)

SOX17 expression in cervical carcinomas using tissue microarray and whole tissue sections

Next, we analyzed SOX 17 expression in two types of cervical carcinomas on TMA sections: cervical adenocarcinomas (n = 40) and squamous cell carcinoma (n = 40). All (100%, 40/40) squamous cell carcinomas and 85% (34/40) cases of cervical adenocarcinomas were negative for SOX17 staining. Only 6 out of 40 (15%) cases of cervical adenocarcinomas showed positive nuclear expression for SOX17. (Table 2)

On whole tissue sections, SOX17 was negative in 100% of squamous cell carcinomas (5/5) and 60% of cervical adenocarcinomas (3/5), while was focally positive in two adenocarcinomas (40%). (Table 3) (Fig. 5)

SOX17 expression in kidney carcinomas and thyroid carcinomas using tissue microarray

Since PAX8 is positive in kidney and thyroid tumors, we investigated SOX17 expression in these tumors. As shown in Table 4, all kidney tumors (n = 110) including clear cell (n = 79), papillary (n = 3), chromophobe (n = 2), sarcomatoid (n = 6), and urothelial (n = 20) showed negative nuclear expression for SOX17. Similarly, all thyroid tumors (n = 70) including the papillary (n = 51), follicular (n = 13), and anaplastic (n = 6) subtypes showed negative nuclear expression of SOX17. (Fig. 6A and 6B)

Table 4
SOX17 expression in non-gynecologic carcinomas using tissue microarray.

		Negative		Low positive (< 10%)		Intermediate positive (10–49%)		High positive (≧ 50%)		Total positive		Total
Kidney	Total	110	100%	0	0%	0	0%	0	0%	0	0%	110
	Clear cell	79	100%	0	0%	0	0%	0	0%	0	0%	79
	Papillary	3	100%	0	0%	0	0%	0	0%	0	0%	3
	Chromophobe	2	100%	0	0%	0	0%	0	0%	0	0%	2
	Sarcomatoid	6	100%	0	0%	0	0%	0	0%	0	0%	6
	Urothelial	20	100%	0	0%	0	0%	0	0%	0	0%	20
Thyroid	Total	70	100%	0	0%	0	0%	0	0%	0	0%	70
	Papillary	51	100%	0	0%	0	0%	0	0%	0	0%	51
	Follicular	13	100%	0	0%	0	0%	0	0%	0	0%	13
	Anaplastic	6	100%	0	0%	0	0%	0	0%	0	0%	6
Breast	Total	208	100%	0	0%	0	0%	0	0%	0	0%	208
	Invasive ductal	206	100%	0	0%	0	0%	0	0%	0	0%	206
	Invasive lobular	2	100%	0	0%	0	0%	0	0%	0	0%	2
Colorectal	Total	208	100%	0	0%	0	0%	0	0%	0	0%	208
	Adenocarcinoma	195	100%	0	0%	0	0%	0	0%	0	0%	195
	Signet ring cell	7	100%	0	0%	0	0%	0	0%	0	0%	7
	Adenosquamous	4	100%	0	0%	0	0%	0	0%	0	0%	4
	Carcinoid	2	100%	0	0%	0	0%	0	0%	0	0%	2
Bladder	Total	140	99%	0	0%	1	1%	1	1%	2	1%	142
	High grade urothelial	137	99%	0	0%	1	1%	1	1%	2	1%	139
	Sarcomatoid	3	100%	0	0%	0	0%	0	0%	0	0%	3
Liver	Total	204	98%	2	1%	0	0%	2	1%	4	2%	208
	Hepatocellular	175	98%	2	1%	0	0%	2	1%	4	2%	179
	Cholangiocarcinoma	29	100%	0	0%	0	0%	0	0%	0	0%	29
Bile duct	Cholangiocarcinoma	103	94%	1	1%	0	0%	5	5%	6	6%	109

SOX17 expression in other non-gynecologic carcinomas using tissue microarray

We also examined SOX17 expression in commonly encountered tumors from other organs including breast, colorectal, bladder, liver and bile ducts. All tested breast carcinomas (n = 208), including 206 invasive ductal carcinomas and 2 invasive lobular carcinomas, and all colorectal carcinomas (n = 208), including 195 adenocarcinomas, 7 signet ring cell carcinomas, 4 adenosquamous cell carcinomas and 2 low-grade neuroendocrine tumors, were negative for SOX17.

We also investigated the SOX17 expression in bladder carcinomas (n = 142) including 139 high grade urothelial carcinomas and 3 sarcomatoid carcinomas. 99% of cases were negative for SOX17. SOX17 was also negative in 98% (204/208) of liver tumors including 175 hepatocellular carcinomas and 29 cholangiocarcinomas. SOX17 was negative in 94% (103/109) of bile duct cholangiocarcinomas. (Table 4) (Fig. 6)

SOX17 expression in angiosarcoma

Since SOX17 was expressed in normal vascular endothelial cells, we examined SOX17 expression in 10 breast angiosarcomas. All cases of angiosarcoma showed SOX17 nuclear staining with 8 cases showing high positivity and 2 cases showing intermediate positivity. (Fig. 7)

Discussion

In summary, we examined SOX17 expression in 1,696 tumors from different organs including 1,626 tumors on TMAs and 70 tumors on whole tissue sections. We found that SOX17 was highly expressed in ovarian non-mucinous carcinomas and germ cell tumors, endometrial carcinomas, and angiosarcomas, while mostly/completely negative in kidney, thyroid, breast, colorectal, bladder, hepatocellular carcinomas and cholangiocarcinomas.

PAX8 has been routinely used as an adjunctive tool in diagnosing Mullerian tumors together with thyroid and kidney tumors.[1–10] In Table 5, we summarized SOX17 and PAX8 expression in different tumors based on our current study and previous studies. SOX17 shows a comparable sensitivity to PAX8 in labeling ovarian and endometrial carcinomas ranging between 70–90%, except in ovarian mucinous carcinomas. However, SOX17 was completely negative in the thyroid and kidney carcinomas tested, while PAX8 usually shows positivity in 70–100% of these tumors. Therefore, SOX17 can be confidently used to identify ovarian/endometrial carcinomas and can be an effective diagnostic tool when differentiating between ovarian clear cell carcinoma (positive) from clear cell renal cell carcinoma (negative).

Table 5
Comparison of SOX17 and PAX8 expression in different tumor types.

Organ	Tumor type	SOX17 positive % (Current study)	PAX8 positive % (references)
Ovary	Serous carcinoma	91 (TMA), 100 (WTS)	79–99 [4,36,40]
	Clear cell carcinoma	91 (TMA), 100 (WTS)	76–100 [4,36,40]
	Endometrioid carcinoma	74 (TMA), 100 (WTS)	38–92 [4,36,40]
	Mucinous carcinoma	24 (TMA), 0 (WTS)	0–50 [4,36,40,41]
	Germ cell tumor	75 (TMA)	0 [4,35,36]
	Stromal and sex cord tumor	0 (TMA)	5 [4]
Uterus	Endometrioid carcinoma	89 (TMA), 100 (WTS)	73–100 [4,36,42]
	Endometrioid with mucin	100 (WTS)	10–100 [42,43]
	Serous carcinoma	100 (WTS)	100 [42]
	Clear cell carcinoma	80 (WTS)	100 [42]
	Carcinosarcoma	100 (WTS)	60–100 [4,42]
Cervix	Adenocarcinoma	15 (TMA), 40 (WTS)	0–50 [4,43,44]
	Squamous cell carcinoma	0 (TMA), 0 (WTS)	0-100 [4,42]
Thyroid	Papillary	0	78–100 [4,8,36,45–47]
	Follicular	0	63–100 [4,8,36,45–47]
	Anaplastic	0	76–100 [4,8,36,45,47,48]
Kidney	Clear cell carcinoma	0	83–100 [35,36,44]
	Papillary	0	71–100 [35,36,44]
	Chromophobe	0	57–88 [35,36,44]
	Sarcomatoid	0	44–100 [35,36,44]
	Urothelial	0	0–24 [35,44,49]
Breast	Invasive carcinoma	0	6–41 [11–15]
Angiosarcoma		100 (WTS)	0 [39,50]

Abbreviations: TMA: tissue microarray; WTS: whole tissue section.

SOX17 showed similar low/negative expression in cervical carcinomas as PAX8. It is not surprising that cervical squamous cell carcinomas were negative for SOX17 since cervical squamous epithelial cells showed no SOX17

staining. Surprisingly, most cervical adenocarcinomas were also negative for SOX17, while normal endocervical glandular epithelial cells exhibited diffuse strong staining. These findings suggest that SOX17 may be lost during cervical adenocarcinoma tumorigenesis and it may be used to differentiate cervical adenocarcinomas from benign cervical glands and endometrial adenocarcinomas, which are the most commonly encountered pitfalls in practice. Indeed, SOX17 has been shown to function as tumor suppressor in many cancer types including breast and colon cancers, etc.[29–34] However, additional studies with large cohorts are necessary to further examine SOX17 expression in cervical adenocarcinomas.

PAX8 is rarely expressed in germ cell tumors,[4,35,36] while our data showed SOX17 was expressed in 75% of ovarian germ cell tumors, consistent with previous reports of high SOX17 expression in testicular germ cell tumors.[37,38] Initially, we focused our evaluation on SOX17 expression in tumor cells, but we also noticed that SOX17 was diffusely expressed in vascular endothelial cells within both tumoral areas and non-tumoral areas. We examined SOX17 expression in 10 angiosarcomas and found that SOX17 was positive in all tested samples. A previous study examined PAX8 expression in 10 thyroid angiosarcomas and all cases showed negative staining.[39]

Although SOX17 is expressed in germ cell tumors and angiosarcomas, these entities are rarely involved in the differential diagnosis of ovarian/endometrial carcinomas. In addition, SOX17 may be used as a marker for these tumors given its high expression. Sample numbers of these tumors are limited in our cohort; therefore, future studies with larger sample sizes are warranted. Furthermore, it would be beneficial to compare the sensitivity of SOX17 with specific markers in germ cell tumors (SALL4, LIN28, etc) and angiosarcoma (ERG, CD31). The expression of SOX17 in normal endothelial cells can be used as an internal positive control, especially in SOX17 negative tumor samples, which is usually beneficial in routine practice.

Our study has several limitations. First, most cases were from TMAs, which have limited material. Therefore, negative expression of SOX17 in certain cases needs to be confirmed on whole tissue sections in future studies. Second, PAX8 IHC was not performed in concordance with SOX17 in our samples. However, we believe that the literature has provided comprehensive data of PAX8 expression in various tumors, and we were able to effectively compare our findings to previously reported data.

In summary, our data indicates that SOX17 is a highly sensitive marker for ovarian non-mucinous carcinomas and endometrial carcinomas with a comparable sensitivity to PAX8. Furthermore, SOX17 provides better specificity than PAX8 due to its negative staining in thyroid and kidney tumors. In addition, SOX17's positivity in endothelial cells can serve as an internal positive control, a very useful tool to evaluate negatively stained tumors.

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Figures

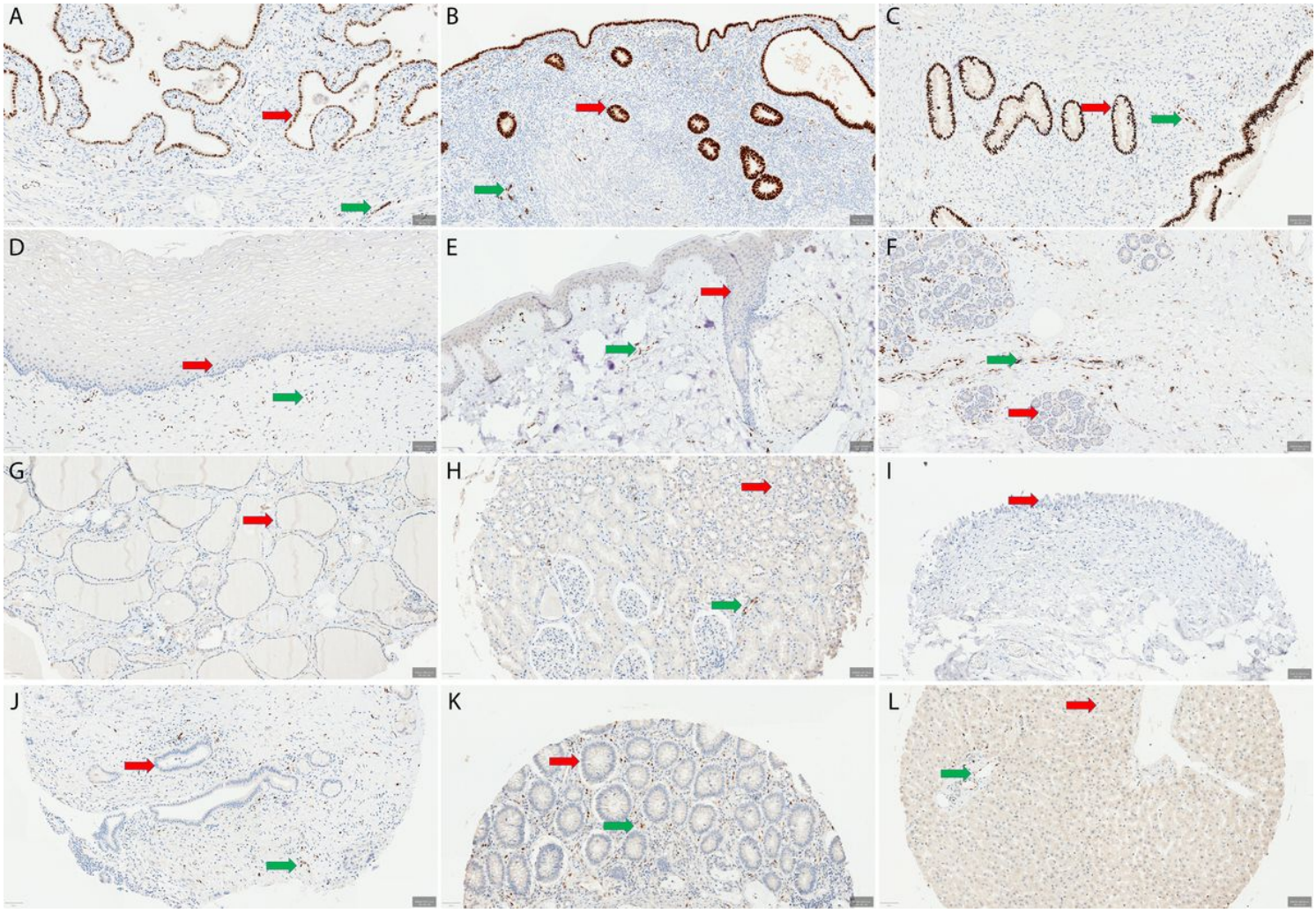

Figure 1

SOX17 expression in various normal tissues. SOX17 immunostain showed positive nuclear staining in A) fallopian tube; B) endometrial glands; C) endocervical glands; but showed negative staining in D) ectocervical squamous epithelium; E) skin squamous epithelium; F) breast ductal epithelial cells; G) thyroid follicular cells; H) kidney tubules; I) bladder urothelium; J) bile ductal epithelial cells; K) colonic glands; and L) liver hepatocytes. SOX17 showed nuclear staining in vascular endothelial cells (red arrows). The red arrows indicate various epithelial cells, and the green arrows indicate blood vessels. Immunostain, 200x.

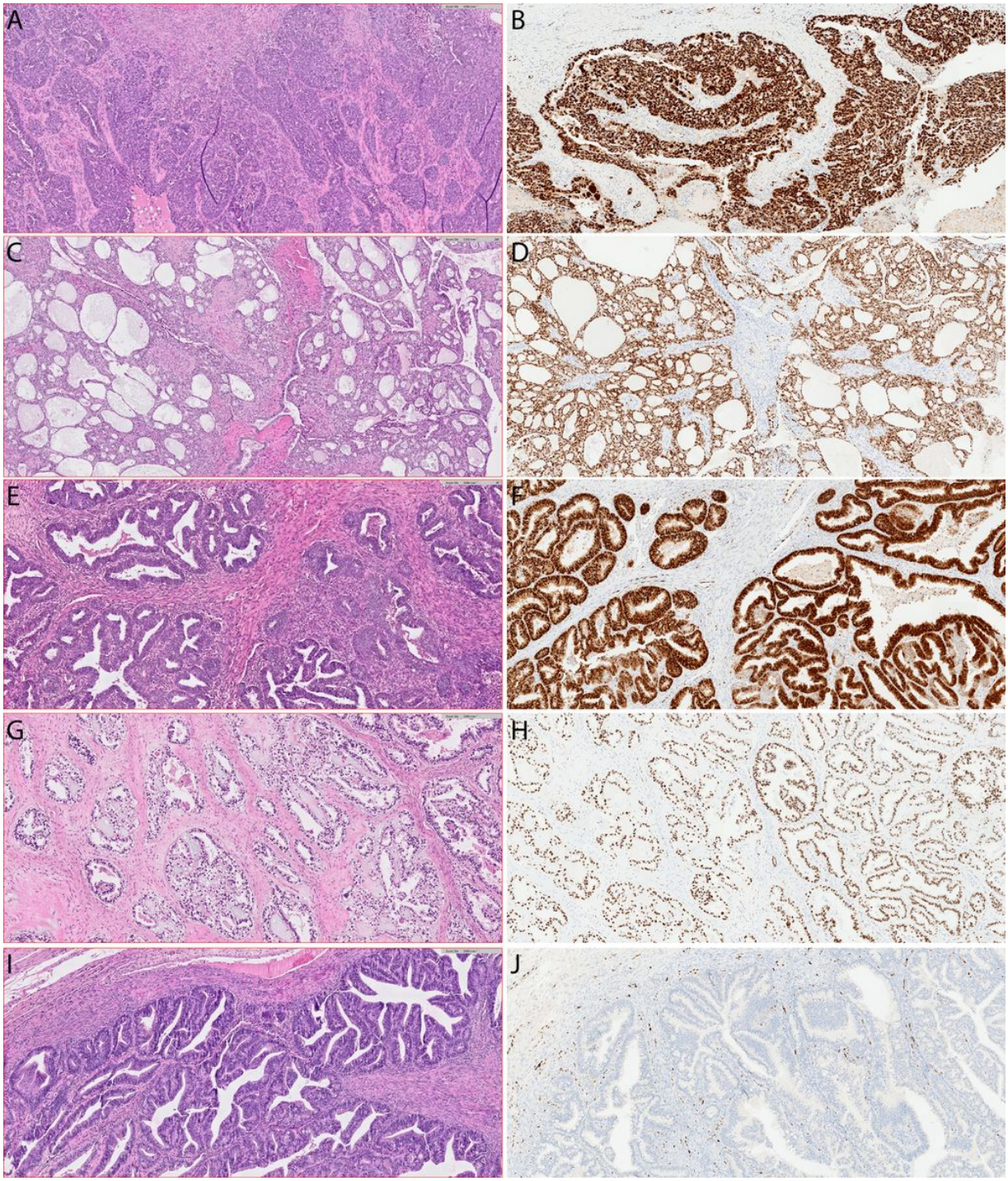

Figure 2

SOX17 expression in various ovarian carcinomas. SOX17 immunostain showed positive nuclear staining in ovarian high grade serous carcinoma (A, B); low grade serous carcinoma (C, D); endometrioid carcinoma (E, F); and clear cell carcinoma (G, H), but negative staining in mucinous carcinoma (I, J). A, C, E, G and I: H&E staining; B, D, F, H and J: SOX18 immunostain. 100x.

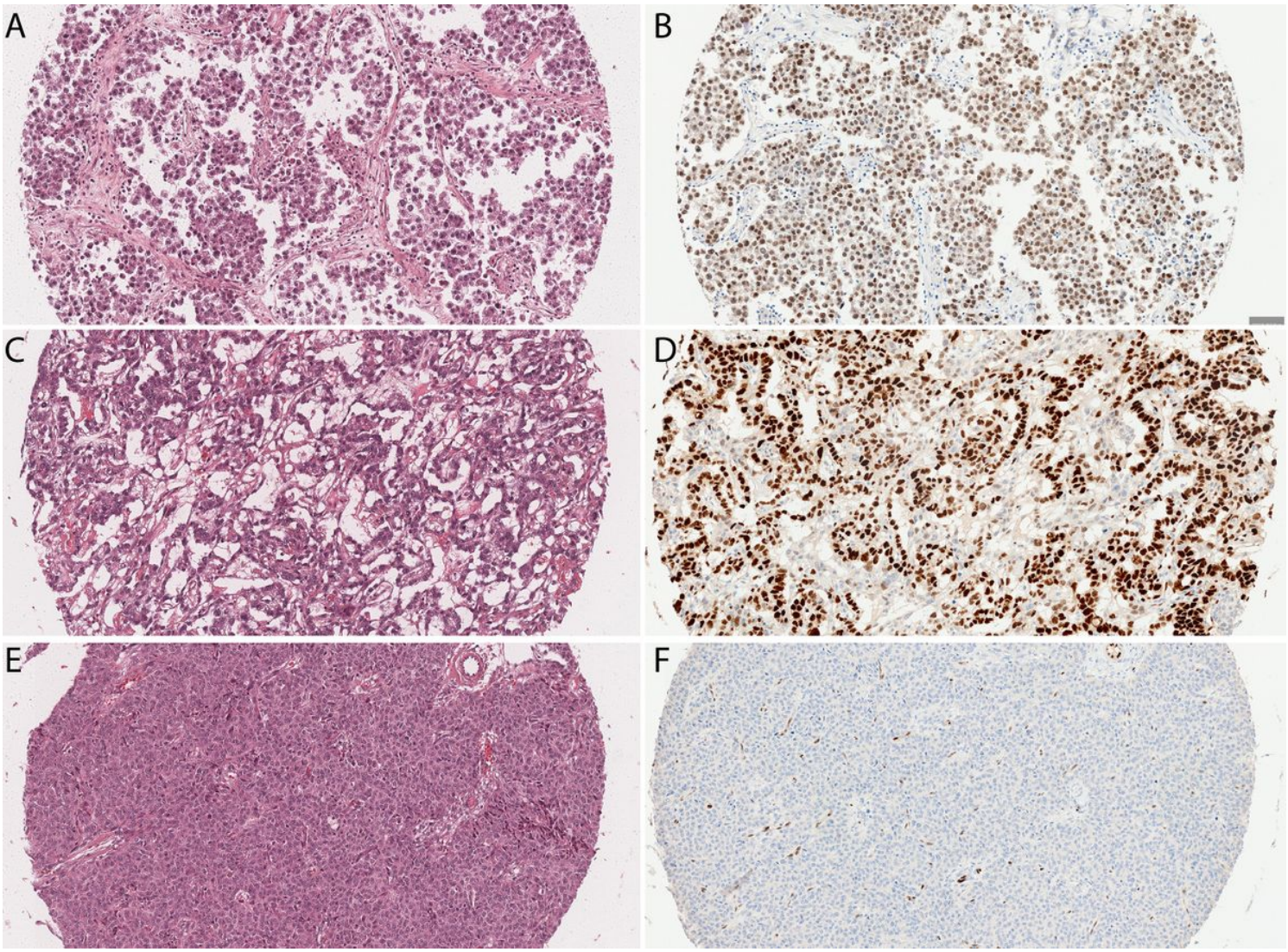

Figure 3

SOX17 expression in ovarian germ cell tumors and sex cord stromal tumors. SOX17 immunostain showed positive nuclear staining in dysgerminoma (A, B) and yolk sac tumor (C, D), but negative staining in granulosa cell tumor (E, F). A, C and E: H&E staining; B, D and F: SOX17 immunostain. 200x.

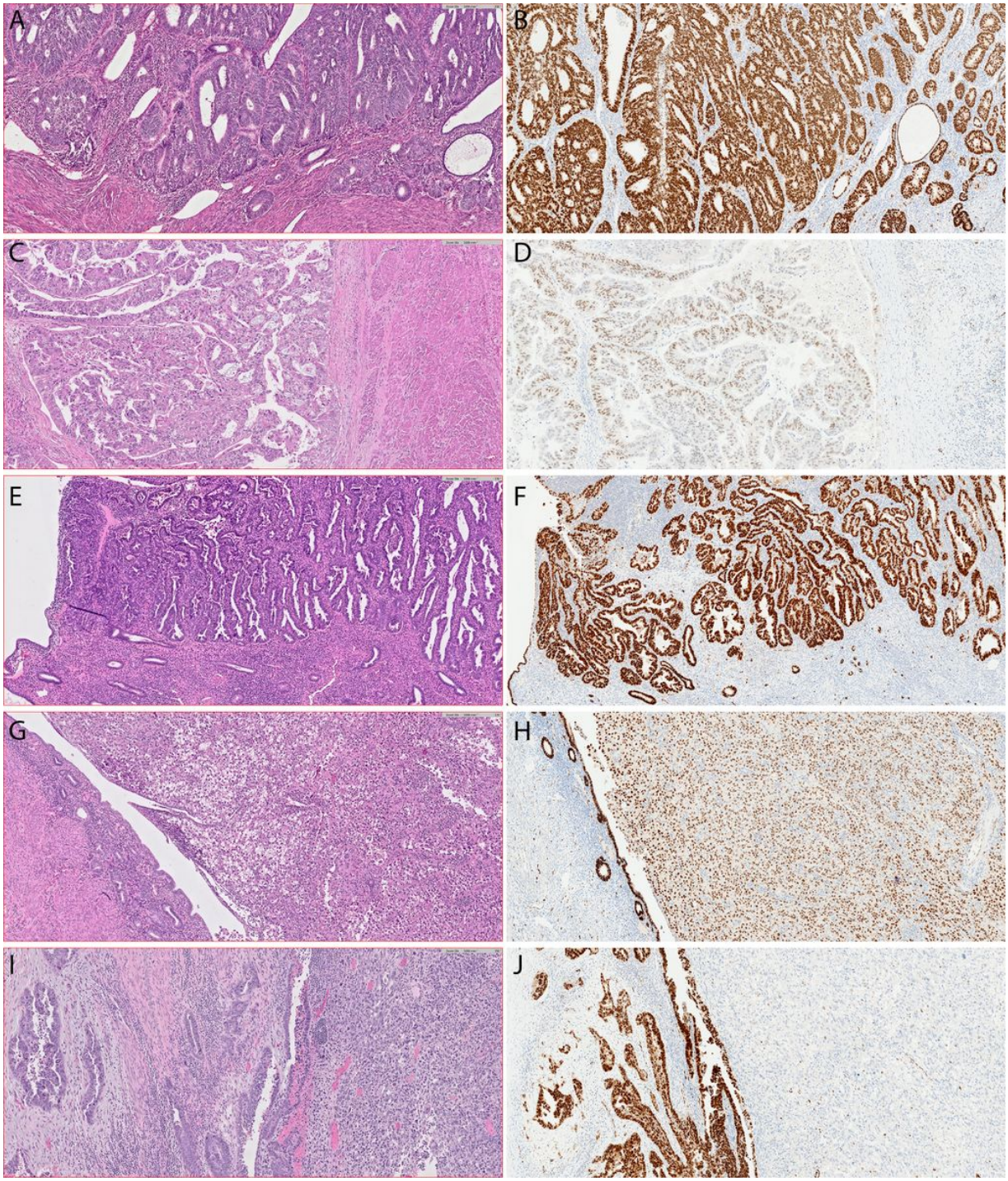

Figure 4

SOX17 expression in various endometrial carcinomas. SOX17 immunostain showed positive nuclear staining in endometrial endometrioid carcinoma (A, B); endometrioid carcinoma with mucinous feature (focal and moderate staining) (C, D); serous carcinoma (E, F); clear cell carcinoma (G, H); and carcinosarcoma (mostly positive in carcinoma components) (I, J). A, C, E, G and I: H&E staining; B, D, F, H and J: SOX17 immunostain. 100x.

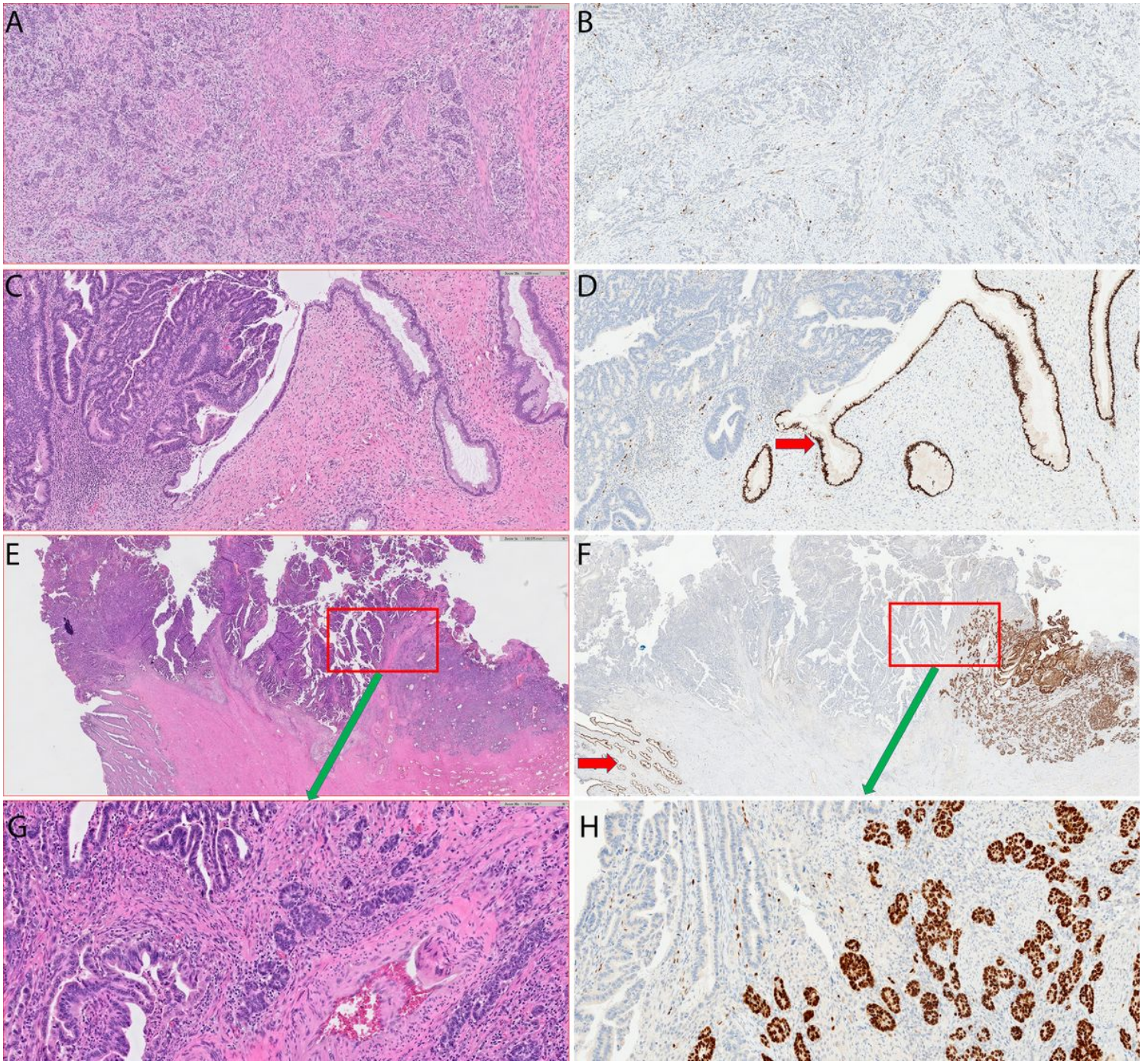

Figure 5

SOX17 expression in cervical carcinomas. SOX17 immunostain showed negative staining in cervical squamous cell carcinoma (A, B) and one endocervical adenocarcinoma (C, D); but focal positive nuclear staining in another endocervical adenocarcinoma (E, F, G, H). A, C, E and G: H&E staining; B, D F and H: SOX17 immunostain. A-D: 100x; E, F: 10x, G, H: 200x. Note: SOX17 is positive in normal endocervical glands indicated by red arrows (D and F). Green arrows indicate the areas in red rectangles with high magnification.

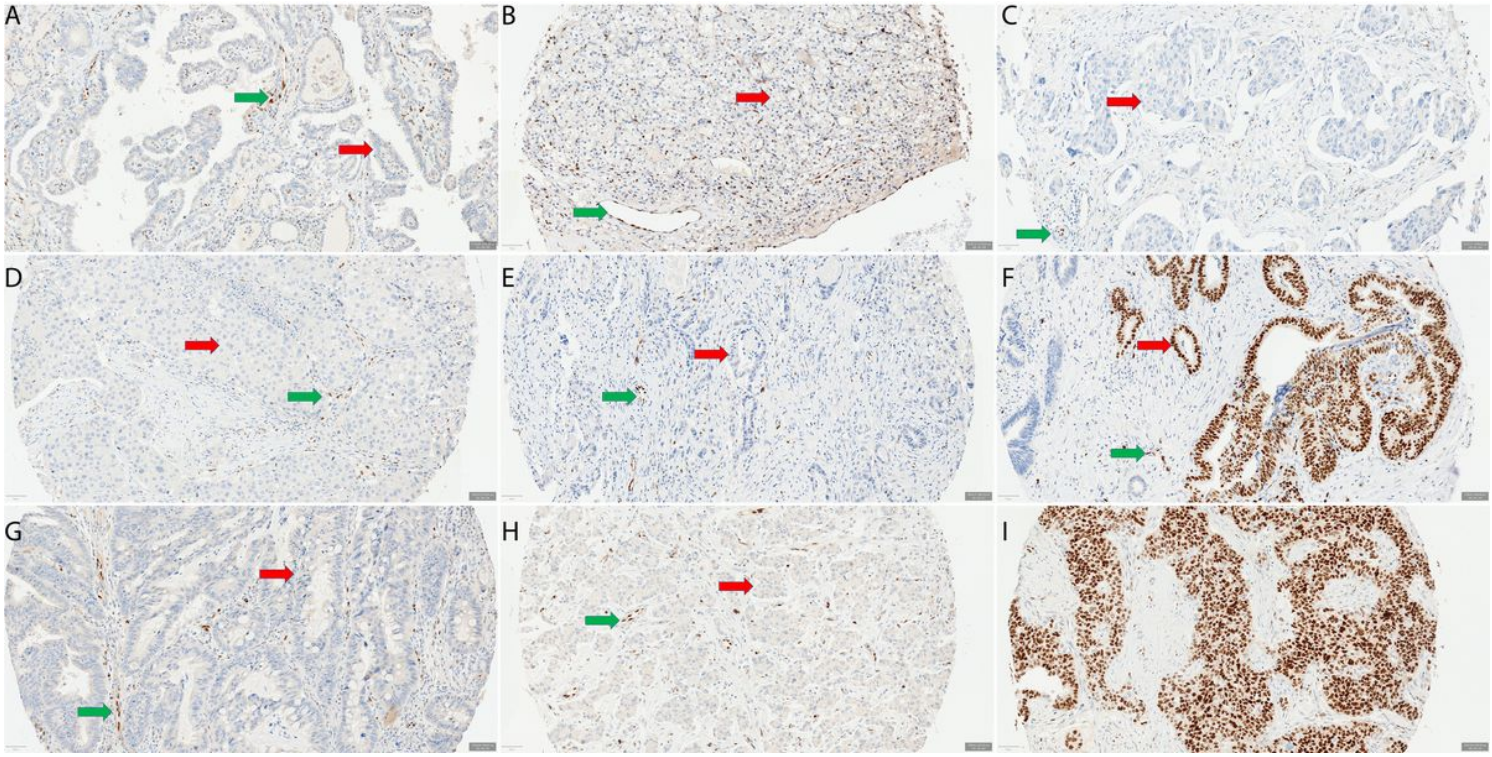

Figure 6

SOX17 expression in non-gynecologic tumors. SOX17 immunostain showed negative staining in papillary thyroid carcinoma (A), clear cell renal cell carcinoma (B), bladder high grade urothelial carcinoma (C), breast invasive ductal carcinoma (D), one cholangiocarcinoma (E), colonic adenocarcinoma (G), and one hepatocellular carcinoma (H), but showed positive staining in another cholangiocarcinoma (F) and another hepatocellular carcinoma (I). 200x. The red arrows indicate tumor cells, and the green arrows indicate blood vessels.

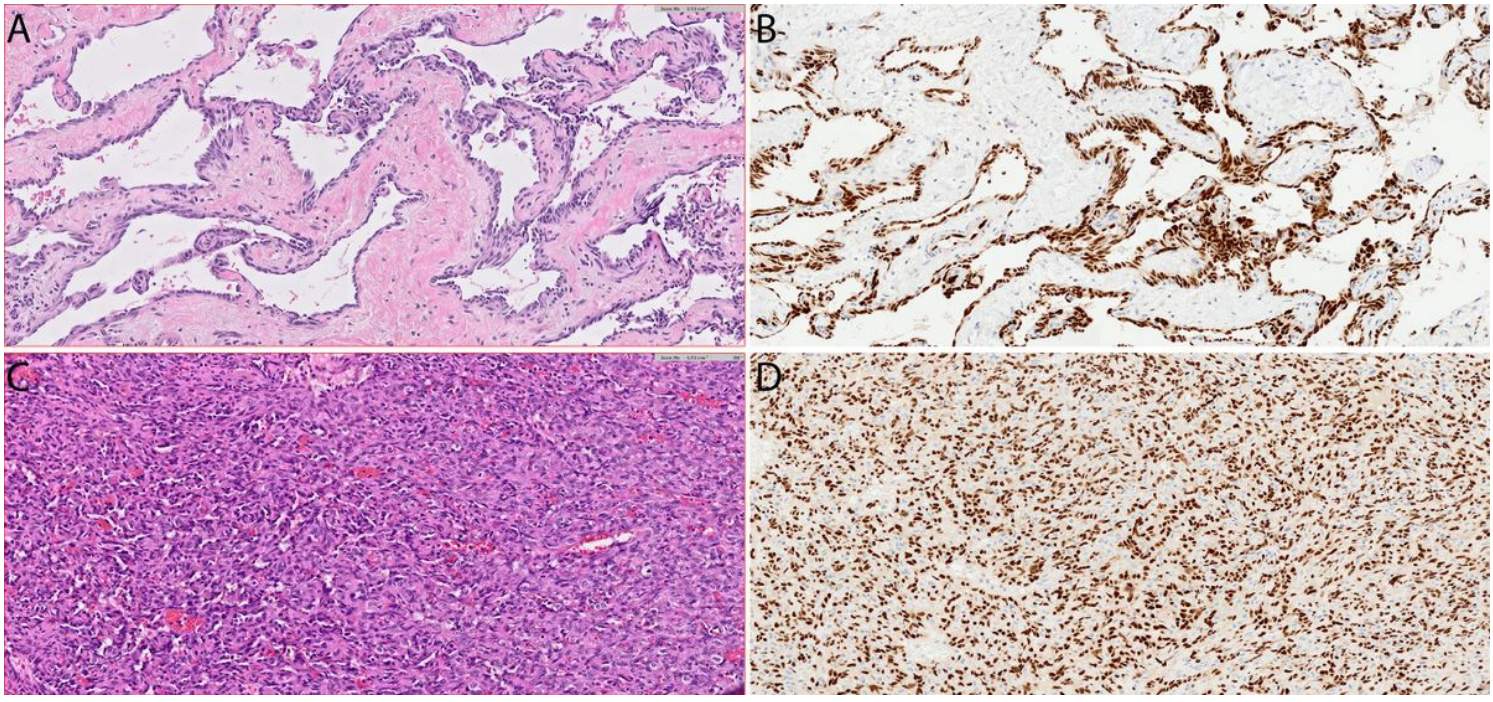

Figure 7

SOX17 expression in angiosarcomas. SOX17 immunostain showed positive nuclear staining in both well-differentiated angiosarcoma (A, B) and poorly differentiated angiosarcoma (C, D). A and C: H&E staining; B and D: SOX17 immunostain. 200x.