

Expression of the sortilin receptor (SORT1) in healthy and tumor tissues

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Introduction

- ▶ Sortilin (SORT1), or neurotensin receptor-3, is a scavenger receptor in the Vacuolar Protein Sorting 10 protein (Vps10p) family.
- ▶ SORT1 is involved in the rapid transport of molecules across the cell membrane with an internalization half-life of ≤4 min of its ligands (neurotensin and progranulin).¹ SORT1 is thus an ideal candidate for the internalization of peptide-drug conjugates (PDCs).
- ▶ The role of SORT1 in cancer is being investigated; it is associated with progression, invasion and more aggressive disease. The PDC TH1902 has been shown to exert its anti-cancer effects in triple-negative breast cancer (TNBC), ovarian and endometrial cancers.²⁻⁵
- ▶ The pattern and prevalence of SORT1 expression in different healthy and cancer tissues is still not well understood, but it has been shown to be highly expressed in some cancers such as breast and ovarian.⁶⁻⁸
- ▶ The goal of this study was to **gain better understanding of the expression of SORT1 in healthy tissues and multiple cancer types.**

Materials and Methods

- ▶ Screening of healthy and cancer tissue microarrays (TMAs) was undertaken using a qualified immunohistochemistry (IHC) method.
- ▶ IHC staining for SORT1 was performed using the primary antibody ab188586 (Abcam) for the detection in formalin-fixed, paraffin-embedded (FFPE) human tissues. Nuclei are counterstained using hematoxylin (blue stain) to assess cell and tissue morphology.
- ▶ Assay testing utilized the TechMate IHC platform (Roche Diagnostics)
- ▶ List of TMAs screened:

Tumor Indication	Biomax ID	No. Cores/ TMA	No. Cores/ Indication	Tumor Indication	Biomax ID	No. Cores/ TMA	No. Cores/ Indication
Breast Cancer	BC08013d	72	189 non-TNBC	Pancreatic Cancer	PA601	60	169 35 normal
	BR1008b	100	180 TNBC		PA483e	48	
	BRM961a	96	28 normal		PA961f	96	
	BR1301	130	1 other condition	Melanoma	ME551	55	169 14 normal
Ovarian Cancer	OV802b	80	240 20 normal		ME481e	48	
	BC11115d	100			ME804b	80	
	OV808a	80	Colon Cancer		BC001134b	150	260 various tumors
CO702d	69	193 26 normal		BC001157a	72		
CO807	80			FDA800b	72		
CO701a	70	96 19 normal		Multi-Tumor			34 normal
UT801a	80						
Endometrial Cancer	BC09012b	63	28 other conditions	Multi-Normal	BN1021	102	102 normal

Total cores screened: 1,803
Total tumor cores screened: 1,496
Total normal or adjacent tissues screened: 278
Total other conditions tissues screened: 29

▶ Scoring method (H-score)

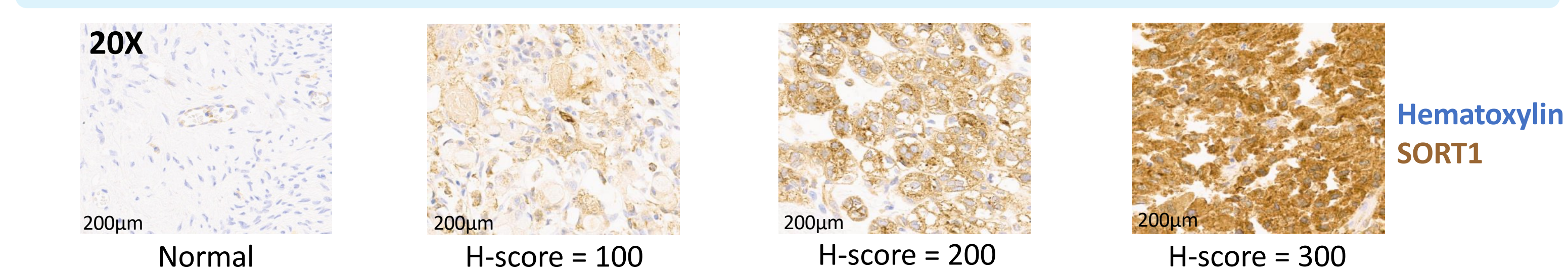
The H-Score is calculated by summing the percentage of cells with intensity of expression staining multiplied by their corresponding differential intensity on a four-point semi-quantitative scale (0, 1+, 2+, 3+). Thus, scores range from 0 to 300.

$$\text{H-Score} = [(\% \text{ at } <1) \times 0] + [(\% \text{ at } 1+) \times 1] + [(\% \text{ at } 2+) \times 2] + [(\% \text{ at } 3+) \times 3]$$

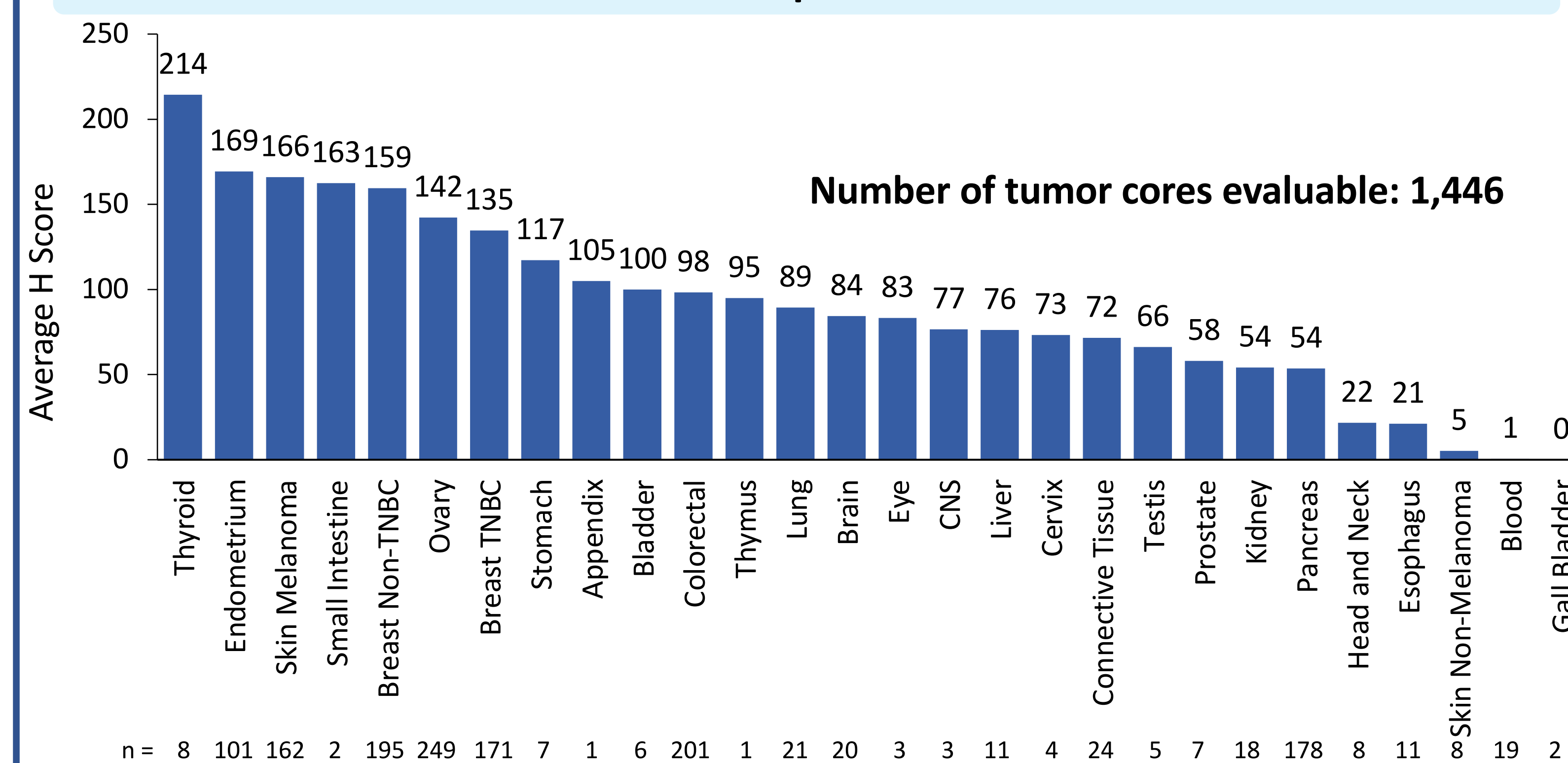
Note: The H-score is an accurate way of describing reactivity in a homogenous tissue like cancer. Due to the heterogeneity of cells in normal tissue (i.e. presence of multiple cell types), it was not possible to attribute an H-score representative of the tissue core. A descriptive approach was taken to identify the cell type and its staining intensity in normal tissues.

Results

A. Example of Differential Staining in Ovarian Cancer



B. Pan Tumor SORT1 Expression in Human Cancers

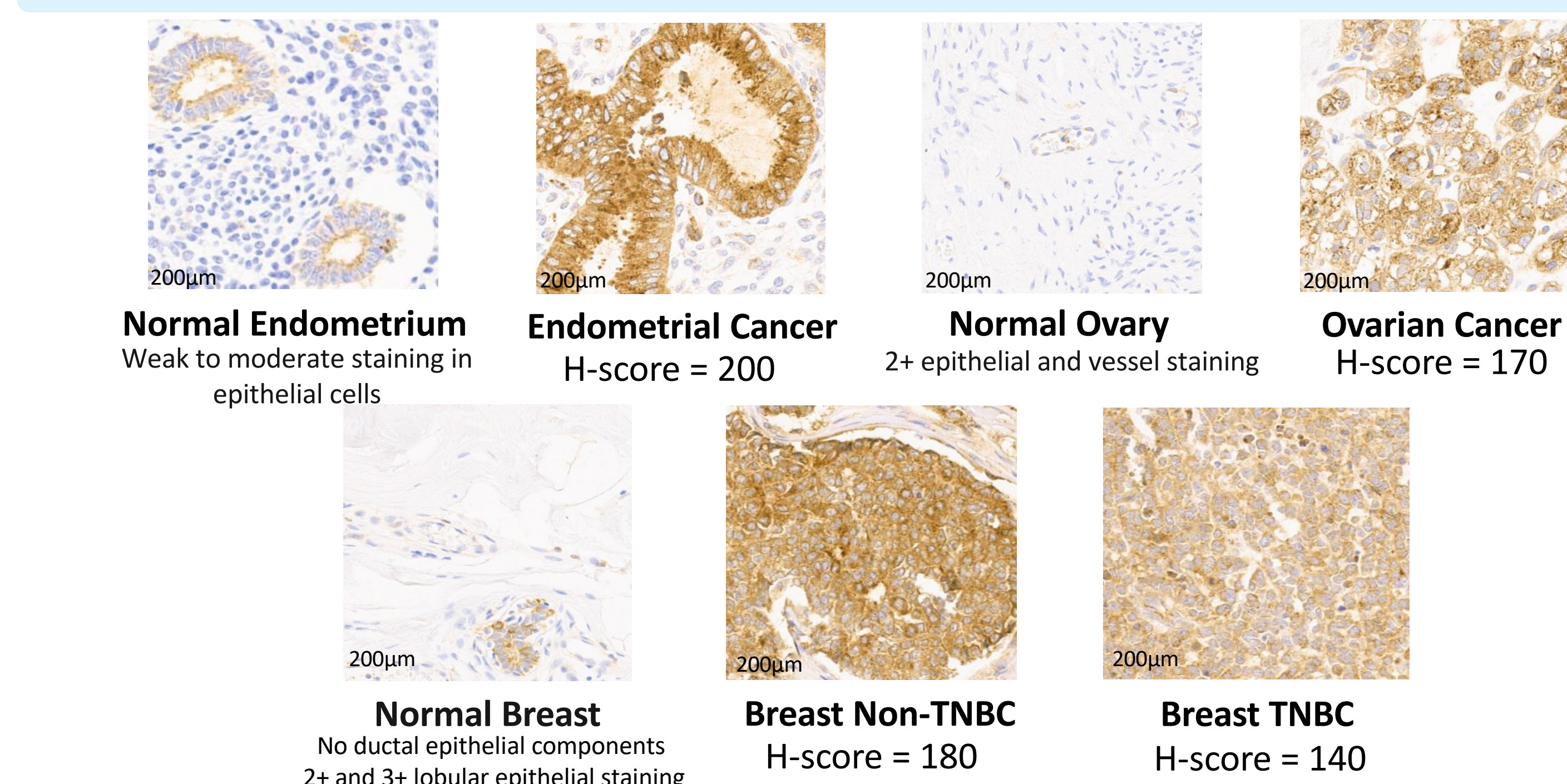


C. Breakdown of SORT1 Reactivity in Tumor Types By H-Score

Breakdown of SORT1 reactivity was analyzed for tumor types with n ≥50 (total of n = 1,257 in this sub-analysis).

Cancer	No. of Evaluable Cases	H-Score 0 to <100		H-Score 100 to <200		H-Score 200 to 300		% of Indication H-score ≥100	Average H-Score
		No. of Cases	% of Indication	No. of Cases	% of Indication	No. of Cases	% of Indication		
Endometrial	101	15	15	42	42	44	44	86	169
Melanoma	162	19	12	87	54	56	35	89	166
Breast Non-TNBC	195	24	12	101	52	70	36	88	159
Breast TNBC	171	51	30	77	45	43	25	70	135
Ovarian	249	63	25	118	47	68	27	74	142
Colorectal	201	92	46	85	42	24	12	54	98
Pancreatic	178	131	74	38	21	9	5	26	54

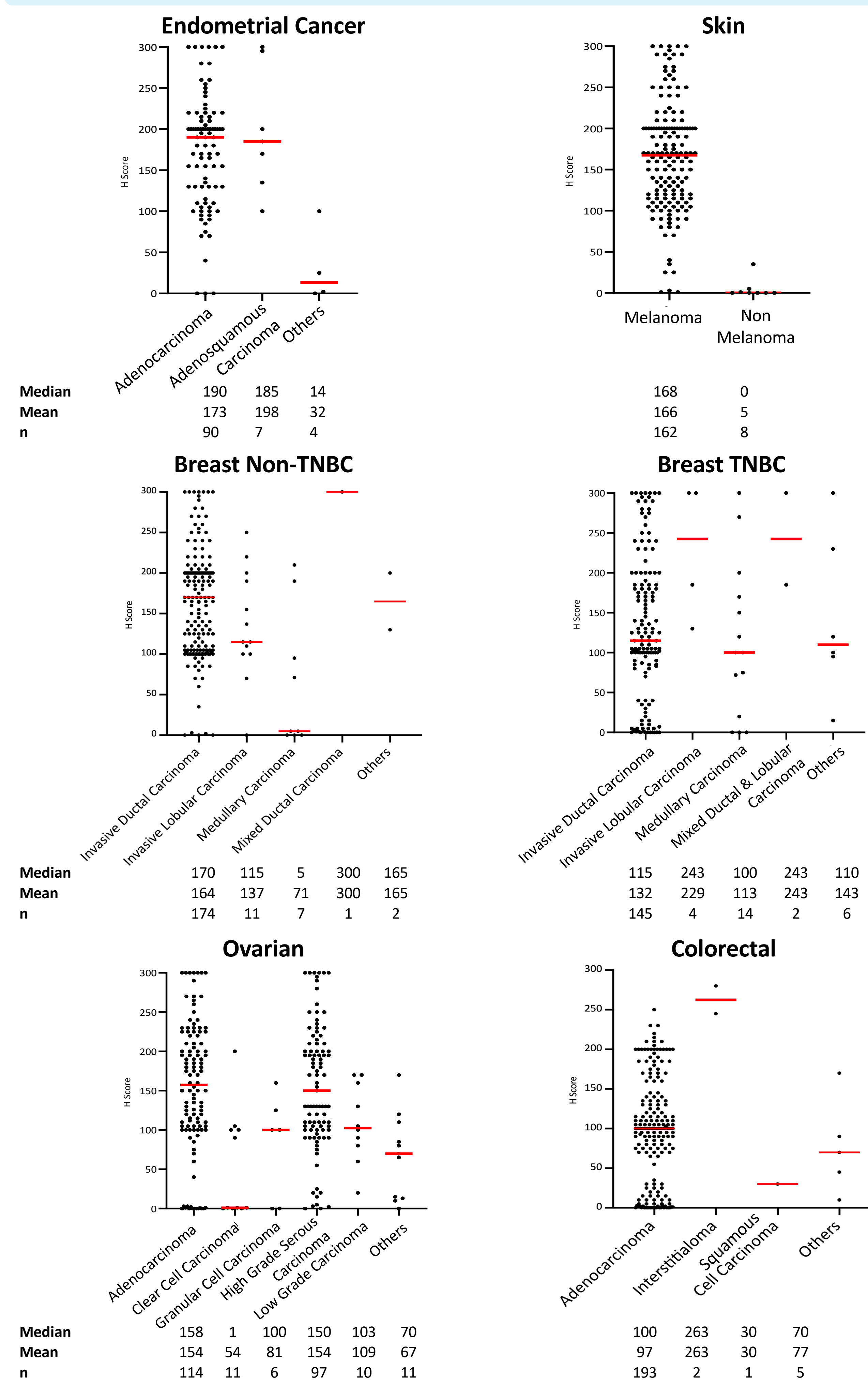
D. SORT1 Expression in Normal vs. Tumor Tissues



Interestingly, SORT1 staining was either negative (null) or low for most healthy tissues including lung, stomach, liver, ovary, prostate, lymph node, esophagus, small intestine, cervix, skin, spleen, bone marrow and thymus. Some healthy tissues had moderate or strong staining in >10% of cells, i.e. colonic mucosa, rectal epithelium, pancreatic islets and vessels, breast lobules, testicular spermatids and Sertoli cells, kidney tubules and cerebral neuronal cells and astrocytes.

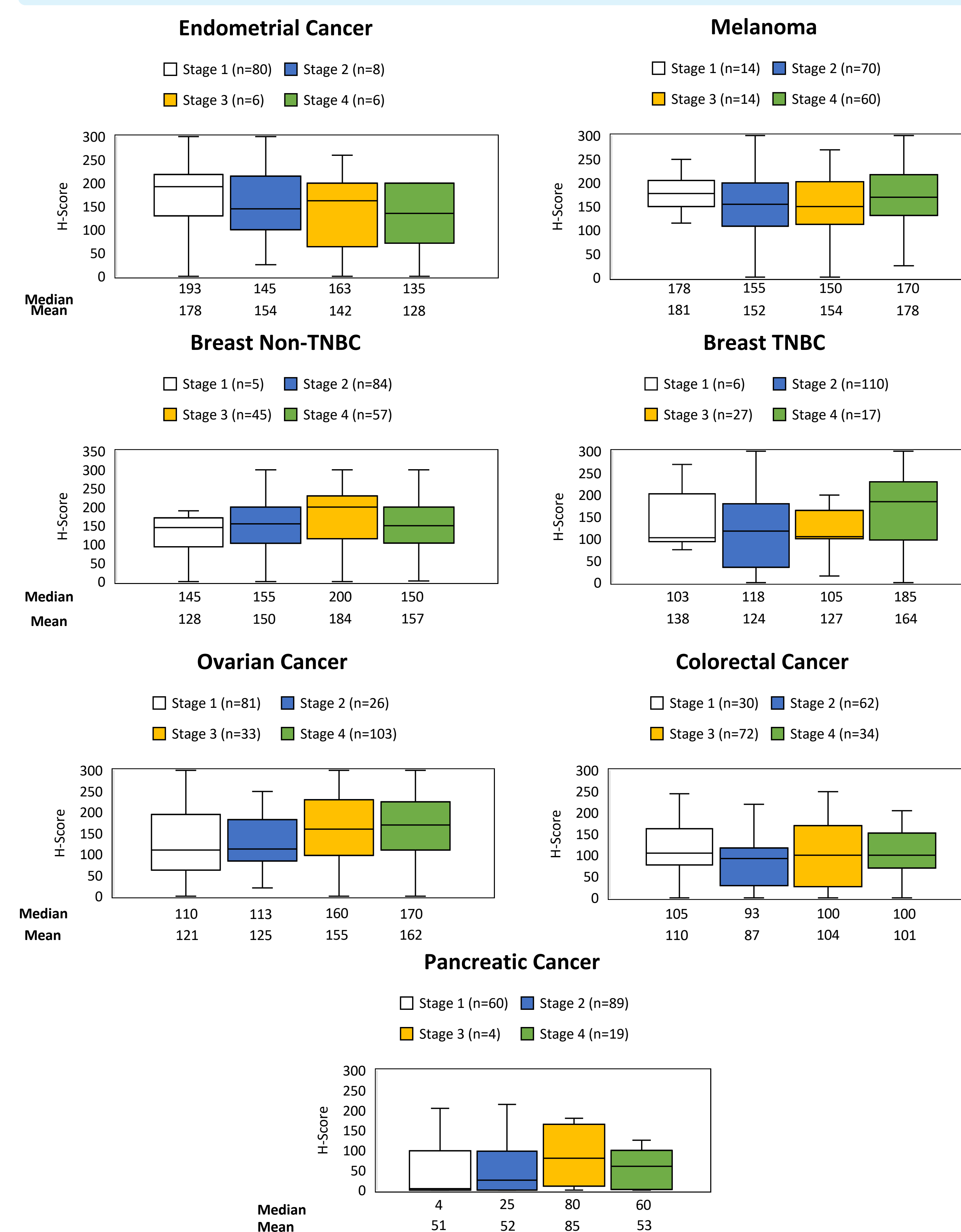
Results Cont'd

E. Sub analysis of SORT1 Expression in Different Pathological Sub-Types



Results Cont'd

F. Sub-Analysis of SORT1 Expression in Different Cancer Stages



Conclusion

- ▶ SORT1 is more highly expressed in many cancers compared to normal tissues, and high expression is maintained throughout the progression from stages 1 to 4.
- ▶ Expression of SORT1 is null or low in many normal tissues, e.g. lung, stomach, liver, ovary, prostate, lymph node, esophagus, small intestine, cervix, skin, spleen, bone marrow and thymus. This allows for a more personalized approach for anti-cancer drug delivery, with the potential to reduce toxicity.
- ▶ This data will be used to support the ongoing preclinical and clinical programs of the Theratechnologies SORT1+ Technology™ platform. A first in human study of a novel peptide-drug conjugate, TH1902 (clinicaltrials.gov: NCT04706962) is ongoing.
- ▶ This is the first assessment of SORT1 expression across a variety of TMA's representing multiple tumor types. Further TMAs will be evaluated using the same method to increase the sample size and broaden the tumor types evaluated (e.g. prostate, SCLC, thyroid, etc.).