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Sialic acids in gynecological cancer development and progression: Impact on diagnosis and treatment

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Abstract

Gynecological cancers are in the top 10 of most common cancers in women. Survival and outcome are strongly related to the stage at diagnosis. Therefore, early diagnosis is essential in reducing morbidity and mortality. The high mortality rate of gynecological cancers can mainly be attributed to ovarian cancer (OC). OC is commonly diagnosed at an advanced stage due to a lack of proper screening tools allowing early detection. Endometrial cancer (EC) on the contrary, is mostly diagnosed at an early stage and has, in general, better outcomes. The incidence of nonendometrioid EC has increased in the last decade, displaying a shared tumor biology with OC and consequently significantly worse outcome. New approaches allowing detection of gynecological cancers in an early stage are therefore desired. Recent studies on cancer biology have shown the relevance of altered glycosylation in the occurrence and progression of cancer. The aberrant expression of sialic acid, a specific carbohydrate terminating glycoproteins and glycolipids on the cell-surface, is frequently correlated with malignancy. We aimed to determine the current understanding of sialic acid function in different gynecological cancers to identify the gaps in knowledge and its potential use for new diagnostic and therapeutic avenues. Therefore we performed a review on current literature focusing on studies where sialylation was linked to gynecological cancers. The identified studies showed elevated levels of sialic acid in serum, tissue and sialylated antigens in most patients with gynecological cancers, underlining its potential for diagnosis.

KEYWORDS
biomarker, diagnosis, gynecological cancer, prognosis, sialic acid

Abbreviations: αHER2, alpha human epidermal growth factor receptor 2; CA125, cancer antigen 125; CA125IA, cancer antigen 125 immunoassay; EC, endometrial cancer; HGSOC, high-grade serous ovarian cancer; IL-6/-8, interleukin-6/-8; KO, knockout; LFIA, lateral flow immunoassay; O_2, dioxygen; OC, ovarian cancer; P-3F-NeuNAc, 5-(acetylamino)-3,5-dideoxy-3-fluoro-D-*erythro*-α-L-manno-2-nonulopyranosonic acid methyl ester 2,4,7,8,9-pentaacetate; PSA, prostate-specific antigen; SA, sialic acid; SHMT1, serine hydroxymethyl transferase 1; Siglecs, sialic acid-binding immunoglobulin-like lectins; S-Lc_4, sialyl-lactotetra 4; sLeA, sialyl-Lewis^A antigen; sLeX, sialyl lewis^X antigen; SNA, *Sambucus nigra* agglutinin; SSEA-1, stage-specific embryonic antigen-4; ST, sialyltransferase; ST3Gal-1/-4, beta-galactoside alpha-2,3-sialyltransferase-1/-4; ST6Gal-1, beta-galactoside alpha-2,6-sialyltransferase 1; sTn, sialyl-Tn antigen; TJA-I, *Trichosanthes japonica* agglutinin.

What's new?

Recent studies have shown the relevance of altered glycosylation in the occurrence and progression of cancer. In this review, the authors found elevated levels of sialic acid in serum and tissue and high levels of sialylated antigens in most patients with gynaecological cancers, underlining the potential of sialic acid for diagnosis. Elevated levels of sialylation were related with tumour growth, poor differentiation, inhibition of apoptosis, and chemoresistance. Taken together, the studies suggest that sialylation levels could be used to discriminate healthy and benign samples from cancer samples and even early and advanced stages in ovarian, cervical, and endometrial cancer.

1 | INTRODUCTION

Gynecological cancers are in the top 10 of most common cancers in women with an annual incidence of 1.3 million cases worldwide in 2018 (Figure 1). Survival and outcome are strongly related to the stage at diagnosis.[2] Although treatment of gynecological cancers is improving, there is substantial burden of treatment-related side effects, which impact patients' physical and psychological quality of life and daily activities.[3-5] The overall high mortality rate of gynecological cancers can mainly be attributed to ovarian cancer (OC), commonly diagnosed at an advanced stage, due to a lack of complaints and screening tools that facilitate early detection. Endometrial cancer (EC), on the contrary, is mostly diagnosed at an early stage and has, in general, a good outcome. In the last decades the incidence of nonendometrioid EC, that have shared tumor biology with OC and worse outcome, has increased substantially.[6,7] Early detection thus plays a pivotal role in reducing cancer related mortality as well as treatment associated morbidity.

Recent studies on cancer biology have shown the relevance of altered glycosylation in the occurrence and progression of cancer. Glycosylation is the attachment of carbohydrates to proteins and lipids carriers that are mostly expressed at the outside of the cellular membrane.[8] These complex carbohydrate structures or sugar chains are called glycans which are often likened to trees as they share a highly branched structure (Figure 2). The lipid or protein carrier serves as the membrane anchor and represents the roots. The following branching string of monosaccharides make up the stem and branches and finally, the outermost monosaccharides constitute the leaves. Glycosylated proteins and

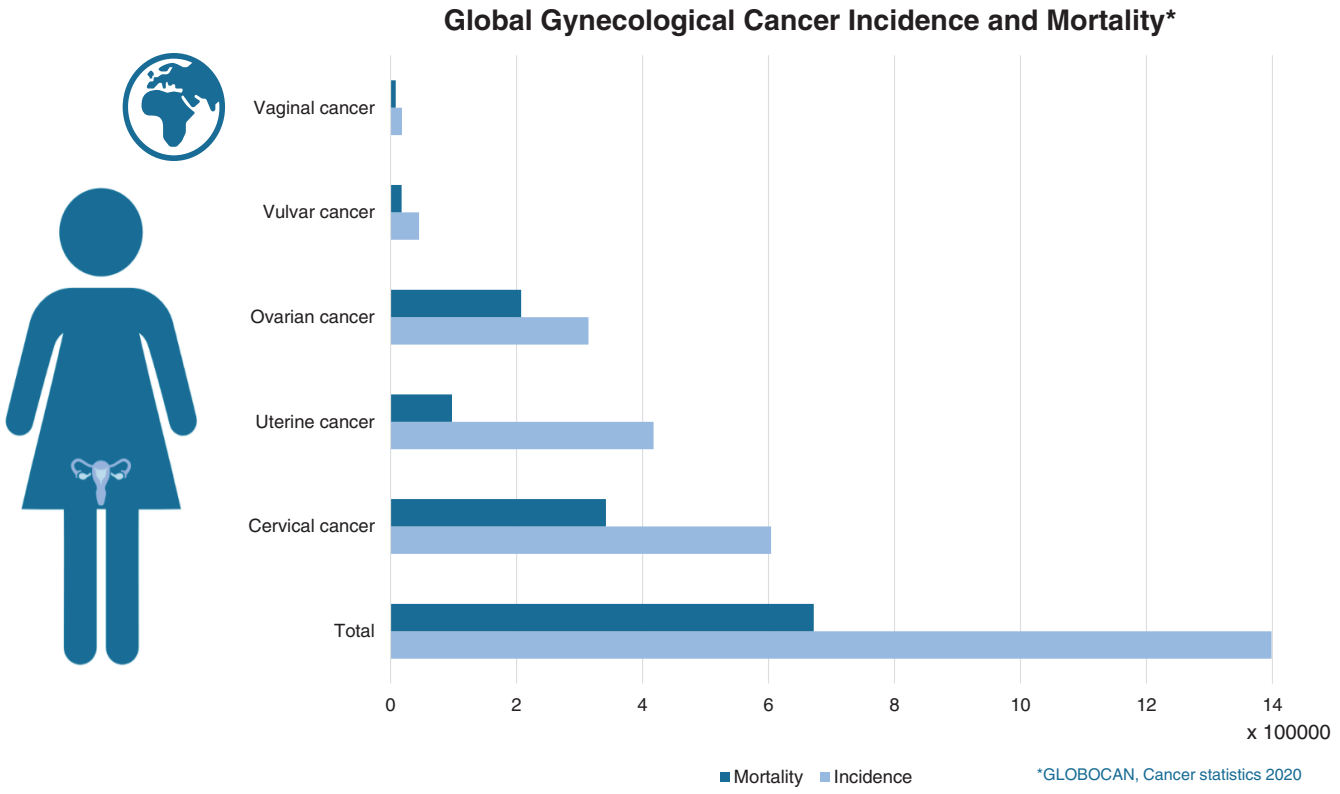

FIGURE 1 Global gynecological cancer incidence and mortality in 2020

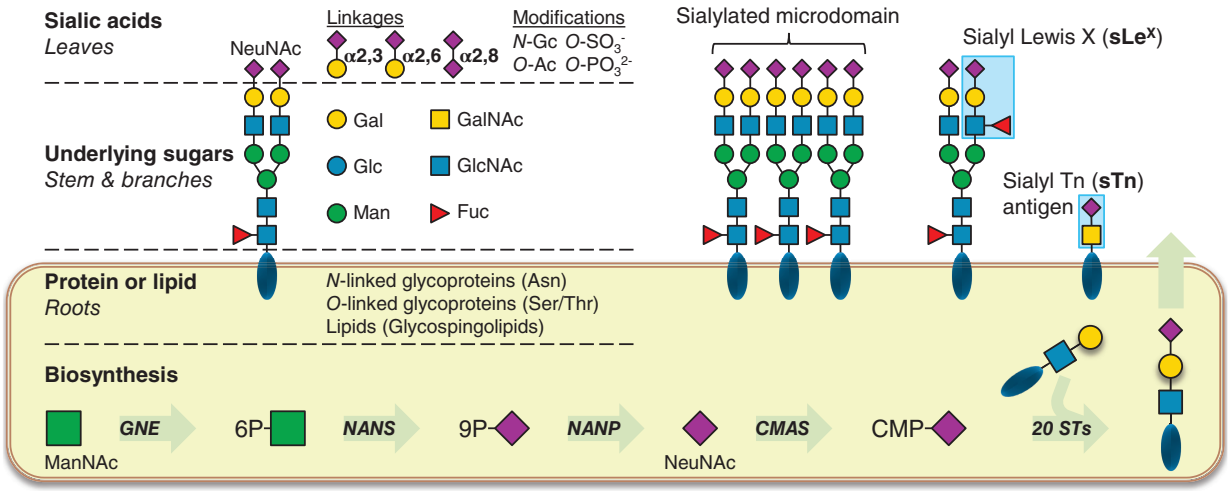

FIGURE 2 Biosynthesis of sialic acid in vertebrate cells and levels of sialoglycan complexity. A large variety of sialylated glycans are formed due to protein or lipid attachment, underlying sugars, linkages and modifications.[11] Ac, acetyl; CMAS, cytidine monophosphate *N*-acetylneuraminic acid synthetase; Fuc, fucose; Gal, galactose; GalNAc, *N*-acetyl galactosamine; Gc, glycolyl; Glc, glucose; GlcNAc, *N*-acetyl glucosamine; GNE, UDP-GlcNAc 2-epimerase/ManNAc kinase; Man, mannose; NANP, *N*-acetylneuraminate 9-phosphate phosphatase; NANS, sialic acid synthase; NeuNAc, *N*-acetylneuraminic acid (sialic acid); STs, sialyltransferases

lipids are involved in several physiological processes, such as cell recognition, cell-cell interaction and communication, migration and adhesion.[10] In particular, the capping monosaccharides that represent the leaves of the glycan tree interact with a variety of receptors. One of the most abundant capping monosaccharides are sialic acids (SAs)[9,11] (Figure 2). Sialic acid (*N*-acetylneuraminic acid) is a carbohydrate present at the surface of mammalian cells and is a part of a family of more than 50 carbohydrates that share this nine-carbon backbone.[11,12] Sialic acid is biosynthesized from *N*-acetyl-mannosamine and transferred to the termini of glycolipids and glycoproteins by a set of 20 different sialyltransferases (STs). The sialic acid residue is added to the underlying sugar via an α2,3-, α2,6- or α2,8-linkage, meaning the C2 position of sialic acid is attached to the C3, C6 or C8 position of another sugar via a α-glycosidic bond. This creates an enormous diversity of sialylated glycans (sialoglycans).[12] Changes in cellular sialoglycan expression are frequently correlated with malignancy, and therefore could be used as diagnostic, and prognostic biomarker.[13] Elevated levels of serum total sialic acid have been found in many cancer patients. Hypersialylation supports tumor cells to grow and metastasize, resulting in a worse prognosis.[14-19] Sialoglycans are recognized by sialic acid specific receptors on immune cells, such as sialic acid-binding immunoglobulin-like lectins (Siglecs). The sialoglycan-Siglec interaction results in suppression of an immune response as sialic acids are considered self-associated molecular patterns. Many studies have demonstrated that (hyper) sialylated tumor cells benefit from this mechanism to evade the immune system.[17,20-26] Furthermore, the negative charge of sialic acids results in enhanced cell-cell adhesion, actomyosin contraction and migration.[27] Removal of sialic acids might therefore be an efficient therapeutic approach in cancer treatment. The proof of principle was studied by Ono et al who demonstrated that direct blockage of overexpressed sialic acid by a thin hydrogel barrier inhibits adhesion, motility and growth of cancer cells and supports apoptosis.[28]

Many studies have explored the relevance of sialic acid in gynecological cancers, of which most focused on OC and to a lesser extent on endometrial and cervical cancer.[29-32] Alterations in sialic acid expression could be supportive for diagnosis or indicative of tumor progression.[33] In OC, aberrant sialylation has been exhibited in early stage tumors, underl

ining its potential as diagnostic biomarker.[34] Within different gynecological cancers, there is some overlap with the histological subtypes of different origins, such as high-grade serous ovarian and endometrial cancer. Mechanistic insights in the histological subtypes may thus be translated to cancers of other origins. At this point, sialic acid is not used as a biomarker or therapeutic target in gynecological cancers. To determine the role of sialic acid in gynecological cancers and identify the gaps relevant for clinical implications, we performed a review on sialylation in gynecological cancers.

2 | METHODS

2.1 | Search strategy

The literature search was performed in the databases PubMed and Medline. Synonyms of sialic acid and sialylation in combination with synonyms of gynecological cancers were used and the summarized findings of articles are shown in Table 1.

2.2 | Study selection

In total, 255 studies published between January 2010 and May 2021 were acquired through the database searches and cross referencing. Searching through Google Scholar did not further supplement the

TABLE 1 Overview of articles about sialic acid or sialylation in relation to cervical, endometrial and ovarian cancer

	Summarized findings of sialic acid analysis				
	Cell lines	mRNA expression	Tissue concentration	Serum concentration	Ascites
Premalignant					
Cervical intraepithelial neoplasia (CIN)	NF	NF	N = 4	N = 1	NF
Gynecological cancers, early stage					
Cervix	NF	NF	NF	NF	NF
Endometrial/uterine	N = 1	NF	NF	N = 1	NF
Ovarian	N = 2	NF	NF	N = 5	NF
Gynecological cancers, late-stage					
Cervix	NF	N = 3	N = 2	NF	NF
Endometrial/uterine	N = 1	NF	N = 2	N = 1	NF
Ovarian	N = 14	N = 5	N = 7	N = 11	N = 3

Note: Articles containing multiple cancer categories are counted multiple times.
Abbreviation: NF, not found.

database searches. After removal of duplicates, 251 articles remained. Based on the abstracts, 130 articles were regarded as eligible. Full-text selection resulted in an additional exclusion of 82 studies resulting in a total of 4

8 studies for the review (Figure S1; Table S1). The following inclusion criteria were specified: focus on sialic acids in relation to cancer diagnosis, progress and tumor behavior. Exclusion criteria were: non-English articles, and nonmalignancy focus. Three independent investigators (A. Y. B., J. F. A. P., J. M. A. P.) selected eligible articles based upon title and abstract. After this first selection, all remaining articles underwent full-text screening and it was decided whether these studies fulfilled the inclusion criteria. In case of disagreement, a fourth investigator (T. J. B.) was consulted for outcome and a final decision.

2.3 | Data analysis

For structuring the selected papers, both the used techniques were described classified into: in vitro and in vivo. The studies were then categorized by study type: cell line, formalin-fixed, paraffin-embedded (FFPE) tissue, xenograft model, genetic, serum and ascites studies. Cell lines, FFPE tissue and genetics were grouped under in vitro, and xenograft models, serum, ascites and extracellular vesicle studies were grouped under in vivo. In addition, the included studies and techniques were summarized for the different gynecological cancers, that is, ovarian cancer, endometrial cancer, cervical cancer and vulvar cancer (Table S1).

3 | RESULTS

Our literature search has identified a large number of studies focused on the impact of sialic acid expression in gynecological cancers. All studies are listed in Table 1, categorized according to study type and cancer stage and with more detail in Table S1. No data were available on the relation between sialic acid and vulvar cancer. The role of sialylation in gynecological cancers were performed on serum, ascites, human cell surface tissue, cancer cell lines and patient derived xenograft models (Figure 3). The main approaches involved measuring and modulation of mRNA levels of sialyltransferases enzymes to establish the diagnostic and therapeutic potential of tumor sialylation. Second, the expression levels and type of sialylated glycans were investigated to assay their diagnostic potential. We categorized the studies according to the gynecological sample studied.

3.1 | In vitro—Cell lines

Most cell line studies focusing on the sialylation of gynecological cancers utilized OC cell lines. Wen et al demonstrated the relation between the level of ST3Gal-1 (beta-galactoside alpha-2,3-sialyltransferase 1) and cancer progression.[31] Advanced stage OC derived cell lines (ES2 and OVCAR-3) expressed significantly increased levels of ST3Gal-1 when compared cell lines derived from early stage mouse ovarian surface epithelial cell line (MOSEC), suggesting that overexpression of ST3Gal-1 is relevant for tumor progression, peritoneal seeding, and distant metastasis.[31] Other studies showed similar results with upregulation of ST3Gal-1 and ST6Gal-1 (beta-galactoside alpha-2,6-sialyltransferase 1) in ovarian cell cancer lines ES2, SK-OV-3 and OVCAR-3.[35-37] The energy demand and oxygen consumption of tumors increase as it grows in size. When the oxygen demand is greater than the oxygen available, the tumor becomes hypoxic. Greville et al analyzed the influence of hypoxia on the *N*-glycosylation profiles of OC cell lines (A2780, PEO1, PEO4). A significant increase in sialylation on secreted *N*-glycans was observed in hypoxic conditions (0.5%-2% O_2), when compared to normal conditions (21% O_2), except for PEO1.[38]

Ovarian epithelial cells transduced with a ST6Gal-1 containing lentiviral vector led to reduced activation of caspases, which are enzymes involved in the process of apoptosis. This ST6Gal-1 mediated inhibition of apoptosis might contribute to resistance to

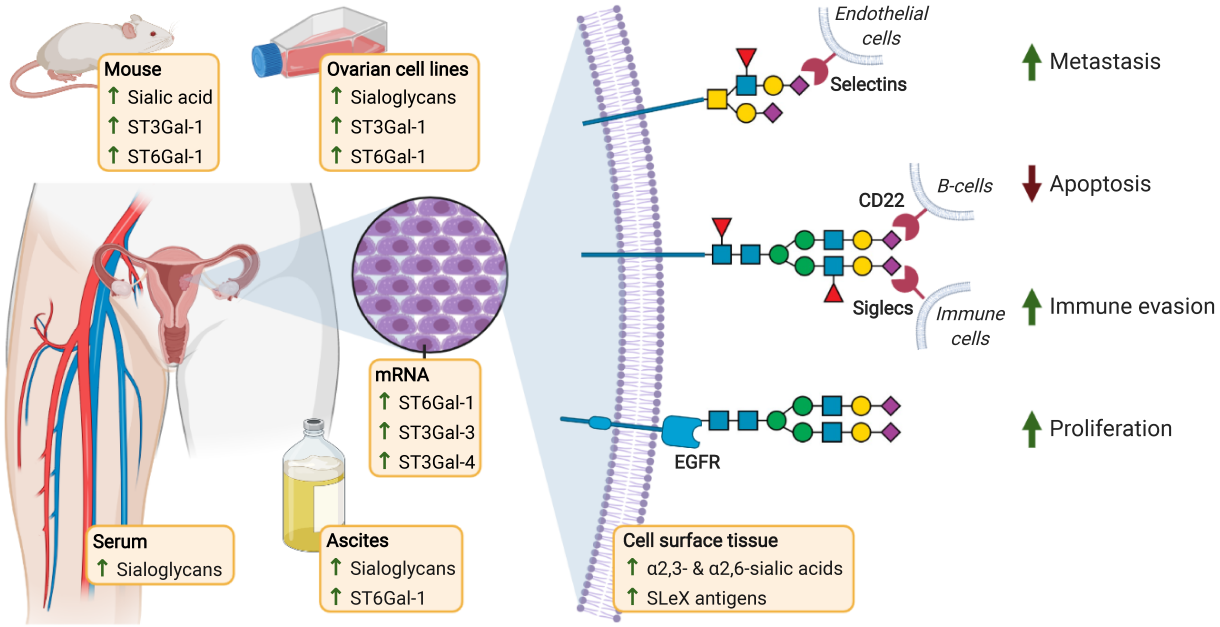

FIGURE 3 Sialic acid analysis in gynecological cancers on mRNA level, in ovarian cell lines, mice, serum, ascites and cell surface tissue and the role of aberrant sialic acid expression on gynecological cancers. Created with BioRender

cisplatin-induced caspase activation.[39] In addition, knockdown of this sialyltransferase decreased the resistance to the cytotoxic anti-cancer drug *paclitaxel*,[37] illustrating the link between ST6Gal-1 upregulation and chemoresistance.[39] Overexpression of ST3Gal-1 in OC cell line A2780 was related to increased cell growth, migration and invasion.[31,37] Additionally, a linear relation between ST3Gal-1 expression and epidermal growth factor receptor signaling in epithelial OC patients was detected.[31,40]

Targeting tumor associated sialoglycans offers the opportunity to develop therapeutics antibodies with reduced off-target effects. The glycolipid stage-specific embryonic antigen-4 (SSEA-4) is stabilized by its terminal sialic acid and is present in the OC cell lines and breast cancer cell lines. Soliman et al found that mouse-human chimeric antibody ch28/11 recognizes this sialic acid of SSEA-4, representing a promising therapeutic avenue for targeting OC.[41]

3.2 | In vivo—Cell lines in mice

The effect of increased ST3Gal-1 expression on resistance to the cytotoxic anticancer drug *paclitaxel* in vitro, was translated to a nude mouse xenograft model by Wu et al, demonstrating the contribution of ST3Gal-1 expression to chemotherapy resistance. Overexpression of ST3Gal-1 in OC cells (A2780) showed increased tumor volumes in mice. ST3Gal-1 overexpression reduces the curative effect of paclitaxel on tumor growth.[37] Comparable results were found in a mouse xenograft model with cervical cancer cells.[42] The level of sialic acid was also influenced by serine hydroxymethyl transferase 1 (SHMT1). Sialic acid metabolite levels were reduced as a result of shRNA-induced knockdown of SHMT1. SHMT1 knockdown in ovarian cell lines COV504 and COV413B inhibited its colony-forming ability. An in vivo study where SHMT1 knocked down OC cell lines were injected in nude mice showed reduced tumor growth and decreased levels of sialic acid. Besides, sialic acid stimulated the expression of pro-oncogenic inflammatory cytokines interleukin-6 and -8 (IL-6 and IL-8). Altogether, this illustrates that SHMT1 controls the expression of pro-oncologic inflammatory cytokines by regulating the cellular levels of sialic acid to stimulate OC tumor growth.[43]

The correlation of hypersialylation with cancer progression and metastasis has led to studies investigating its potential as therapeutic target. To reduce cellular sialylation, a sialyltransferase inhibitor was evaluated on advanced stage serous type epithelial OC.[36] Additionally, the tumor-associated sialyl-Tn antigen (sTn), a truncated *O*-glycan containing a sialic acid, has been used for tumor targeting. Eavarone et al[44] investigated the therapeutic effect of an antibody-drug conjugate targeting sTn in the SK-OV-3 cell line, resulting in a target-specific therapeutic effect.[45] Subsequently, in vivo testing resulted in inhibited cancer cell line growth of patient derived ovarian xenograft models in mice.[44]

3.3 | In vitro—Tissue

The use of sialylated glycans and *N*-glycomic changes were explored as diagnostic biomarkers for OC with enhanced sensitivity and specificity.[46,47] In premalignant and malignant cervical cancer cells, significantly increased α2,3- and α2,6-sialylation levels and a higher percentage of tetrasaccharide sialyl lewis^X antigen (sLeX) expressing cells were observed when compared to normal cervical samples (Figure 3).[48-50] However, contrasting findings were reported by Jin

et al in 2018, where an inverse relationship between the percentage of sialyl-Lewis^A antigen (sLeA) positive cells and their extend of cervical intraepithelial neoplasia was found.[51] Lectin *Sambucus nigra* agglutinin (SNA), which is often used to detect α2,6-sialylation, could not discriminate between normal and cancer epithelial cells from the cervix.[52] In EC, terminal sialic acid levels could be used to predict EC grading by using the lectins *Sambucus sieboldiana* agglutinin, SNA and TJA-I (*Trichosanthes japonica* agglutinin).[53] Pan et al demonstrated a strong correlation between sialylated glycopeptides and α2,3-sialyltransferase 1 expression in tumor tissue of high-grade serous ovarian carcinoma. However, no strong correlation was observed between α2,6-sialyltransferase 1 and sialylated glycopeptides.[54] A study of Zahradnikova et al found five *N*-glycan structures, including sialoglycans, that may be associated with resistance of advanced-stage, high-grade nonmucinous OC to platinum/taxane based chemotherapy in tissue and serum samples.[55]

Barone et al investigated using sialyl-lactotetra (S-Lc$_4$) as a marker for epithelial ovarian tumors. S-Lc$_4$ serves as a marker on the cell surface of undifferentiated human pluripotent stem cells, such as human embryonic stem cells and human induced pluripotent stem cells. The expression of S-Lc$_4$ is rapidly downregulated upon differentiation. S-Lc$_4$ was overexpressed in borderline type and malignant ovarian tumors. The data demonstrated the association of S-Lc$_4$-positivity with disease-free survival. However, the survival time after progress was significantly shorter for patients with S-Lc$_4$ positive tumors compared to S-Lc$_4$ negative. The level of S-Lc$_4$ expression is cancer-related, but the expression of S-Lc$_4$ does not increase over time. Altogether, these results suggest that S-Lc$_4$ could be a potent marker for serous borderline and type 1 tumors.[56]

3.4 | In vitro—Genetics

ST3Gal-1 mRNA levels were compared in tumor tissue from patients with high and low grade OC. In each histopathological cancer type, ST3Gal-1 protein levels were elevated compared with normal tissue.[57] Studies in tissues and cell lines have revealed the relation between sialyltransferase mRNA expression and cancer progression in cervical cancer. The mRNA expression of α2,3-sialyltransferase 4 is transcriptionally regulated using several promotors and was significantly enhanced in cervical carcinoma cell lines (HeLa and SiHa) compared to normal tissue. The lectin blot analysis demonstrated that ST3Gal-4 overexpression enhanced the expression of α2,3-linked sialic acid while diminishing α2,6-linked sialic acid on the membrane proteins of cervical cancer cells.[58] Qi et al showed a link between loss of either the ST3Gal-3 or ST3Gal-6 genes and decreased cell proliferation and colony formation in the HeLa cell line, as opposed to the effect in ST3Gal-4 knockout (KO) cells. The loss of these genes significantly suppressed the phosphorylation levels of extracellular signal-regulated kinase and AKT (serine/threonine kinase), which are involved in cell proliferation and cell survival. Interestingly, the α2,3-sialylation levels of β1 integrin were suppressed in the ST3Gal-4 KO cells, whereas these were increased in the ST3Gal-3 and ST3Gal-6 KO cells. These results indicate that the three α2,3-sialyltransferases had different functions in cell proliferation and cell adhesion.[59]

The mRNA expression levels of ST3Gal-1 and ST6Gal-1 in OC patients were significantly upregulated, while ST3Gal-3, ST3Gal-4 and ST3Gal-6 were downregulated in OC tissues when compared to healthy controls (Figure 3).[30] Furthermore, the endocervical adenocarcinoma cell lines HO-8910 (HeLa derivative) and HO-8910PM (HeLa derivative) expressed increased mRNA levels of ST3Gal-3 and were more frequently resistant to chemotherapy medications cisplatin and paclitaxel when compared to SK-OV-3 cells, with low mRNA levels of α2,3-sialyltransferase. High dose cisplatin could downregulate ST3Gal-3 mRNA expression levels and enhance the number of apoptotic cells in both SK-OV-3 and HO-8910PM cells.[42,60,61] A study of Wichert et al found the correlation between high ST6Gal-1 mRNA levels and lymphovascular invasion and reduced survival.[32]

3.5 | In vivo—Serum

Aberrant glycosylation profiles could be found in the serum of OC patients with different cancer stages.[18,33,34,62,63] The bi- and trisialylated highly-branched glycans were significantly elevated in OC patients' serum, but were barely detectable in healthy controls (Figure 3).[33,62] In contrast, a significant decrease in less branched and sialylated *N*-glycan structures was observed in early and late epithelial OC samples compared to healthy controls.[34] The total sialylation level (α2,3-/α2,6-linked sialic acids) was significantly increased in cancer samples when compared to healthy controls and could be used for differentiating the healthy control, early stages and advanced stages of OC.[18,34] Lin et al observed a higher level of glycosylation and sialylation of IgG glycans in endometrioid EC, in comparison with non-endometrioid subtypes. Patients with early stage tumors (FIGO stage IA) had significantly higher levels of mono-sialylated structures in IgG glycans and total sialylation, in comparison with patients diagnosed with advanced stage (FIGO stage IB-IV). Moreover, the proportion of disialylated IgG glycans also were more abundant in the low-risk patient group, but the difference was not statistically significant. Altogether, patients with well- and moderately differentiated tumors displayed a higher abundance of sialylated structures than patients with poorly differentiated tumors.[64] Reduced levels of sialic acids after chemotherapy implicates its applicability as response biomarker during chemotherapy.[19,63,65] A study of Zhao et al demonstrated that α2,3- and α2,6-linked sialic acid and Lewis type *N*-glycans could discriminate between patients which were responsive or resistant to chemotherapy. Thus combination of chemotherapy with reduction of sialic acid on cancer cell surface could be a potent therapeutic avenue. The drug sensitive patients showed decreased levels of α2,6-sialic glycans when compared to normal controls, while there was significant increased expression of α2,3-sialic acid and Lewis type *N*-glycans found in drug-resistant patients. Therefore, Lewis type *N*-glycans and both sialic acid linkages could have potential utility of chemotherapy response prediction.[66]

Multiple studies of Biskup et al investigated the diagnostic utility of serum glycome profiling by benchmarking it against cancer antigen 125 (CA125), the current biomarker for OC. The study used the value GLYCOV, which indicates the amount of upregulated sialylated glycans in patient's serum. GLYCOV was able to distinguish the early stages of OC and the healthy controls, while CA125 did not. Correspondingly, the receiver operating characteristic curve illustrated the superiority of GLYCOV over CA125 in sensitivity and specificity.[67-69] Furthermore, a study of Pochechueva et al shows that plasma-derived antibodies bind to sialylated glycans including sTn. This presents an alternative to CA125 for differentiating benign controls from high-grade serous ovarian cancer (HGSOC) patients and could function as a diagnostic biomarker.[65,70] Only IgM-isotype anti-glycan antibodies against the sialylated antigens that contained α2,6-linked sialic acid discriminated between control and HGSOC, because the discrimination was lost when α2,6-sTn was replaced by α2,3-sTn.[65,70] In EC, patients with Grade 3 had significantly elevated serum levels of sTn compared to patients with Grade 1 and Grade 2 EC. Additionally, patients with lymph node metastasis exhibited increased serum sTn levels compared to patients without lymph node metastasis.[71] Bayoumy et al described the development of a quantitative lateral flow immunoassay (LFIA) of aberrantly glycosylated CA125 and compared this technique to the conventional CA125 immunoassay (CA125IA). The developed CA125-sTn-LFIA assay showed in EOC and endometriosis samples a specificity of 98% and sensitivity of 72%, while the CA125-IA showed specificity of 98% with a sensitivity of 16%. The superiority of the CIA125-sTn-LFIA test over the conventional CA125 ELISA is linked to the specific and efficient capturing of the sTn motifs of the cancerous isoforms of macromolecular MUC16/CA125, which are associated with EOC.[72] This was confirmed by another study that showed similar results with improved identification of EOC than the conventional CA125-IA.[73] No significant differences in sialylation were found between cervical intraepithelial lesions or cervical cancer samples and controls in an enzyme-linked lectin assay using the SNA lectin.[74]

3.6 | In vivo—Ascites and extracellular vesicles

Changes in the glycome were also detected in ascites, a peritoneal fluid that is produced when malignant tumor cells escape from the primary tumor site into the surrounding abdominal cavity. This fluid promotes cell proliferation and enable tumor cells to enter the circulation and spread to other organs.[75] In OC, Biskup et al show that high-volume ascites contains a significantly increased amount of sialylated structures when compared to low-volume ascites.[75,76] Additionally, a study of Kuzmanov et al demonstrated an overexpression of only the sialyltransferase gene ST6Gal-1 across different ovarian tumor subtypes when compared to fluid from normal and benign ovarian cysts and peritoneal effusions, while other STs genes were unchanged or decreased in ascites fluids from OC patients (Figure 3).[77] Furthermore, the *Maackia amurensis* lectin revealed the enrichment of several sialoglycoproteins with α2,3-linked sialic acid in extracellular vesicles from ovarian carcinoma cells, while the level of SNA binding to α2,6-linked sialic acid in the vesicles was at the same level as the control after incubation with sialidase.[78]

4 | DISCUSSION

To improve the knowledge on the role sialic acid in gynecological cancers, we reviewed the contribution of sialic acid in relation to diagnosis, prognosis and cancer progression. Sialic acid plays an important role in tumor progression, invasion and metastasis in ovarian, endometrial and cervical cancer. Significantly enhanced total sialylation levels in cancer samples were frequently observed in both in vivo and in vitro studies. Similar results were found for sialylated antigens and enhanced mRNA expression of sialyltransferases. Elevated levels of sialylation were related with tumor growth, poor differentiation, inhibition of apoptosis and chemoresistance (Figure 3). Hence, sialylation levels could be used to discriminate healthy or benign from cancer samples and even distinguish early and advanced stages in ovarian, cervical and endometrial cancer.

These findings are consistent with a growing body of literature demonstrate the hypersialylation and increased expression of sialylated antigens in prostate, breast, bladder, and testicular cancer and malignancies in the bone marrow.[79-86] Generally, there were many similarities between gynecological cancers and other cancers, whereas the type of sialyltransferases that are overexpressed varied per cancer type. Using nanotechnology like surface-enhanced Raman spectroscopy, sialic acid has been found in saliva, blood and cancer tissue of breast cancer patients, indicating its potential to be a highly sensitive and specific (noninvasive) biomarker for the screening of breast cancer in women.[87,88] Likewise, biochemical analysis of saliva and serum revealed enhanced levels of different forms of sialic acid in patients with oral cancer when compared to healthy controls. Different studies have pointed out that sialic acid analysis in saliva could be used in early detection of oral cancer.[89-91] Current diagnosis of prostate cancer relies on prostate-specific antigen (PSA) testing and there is a clinical need to identify new biomarkers. Glycan analysis represented a new resource of biomarkers with clinical utility and should be exploited as tool for prostate cancer diagnosis and patient prognosis.[92] A study of Michalakis et al referred to sialic acid as an adjunct in predicting prostate malignancy when PSA values are not clearly defined.[93] Zhang et al confirmed this promising capability of serum sialic acid as a diagnostic and prognostic biomarker for prostate cancer and bone metastasis.[94] Elucidation of the role of sialic acid in gynecological and other cancers illustrate the potential to use sialic acid as a diagnostic and prognostic biomarker.

Various methods have been used to interfere with hypersialylation. Fluorinated sialic acid analog (P-3F-NeuNAc) and its more potent carbamate-based analogs block the biosynthesis of sialic acid and inhibit sialyltransferases.[95,96] P-3F-NeuNAc treatment resulted in reduction of α2,3-/α2,6-linked sialic acids in melanoma cells (B16F10) for several days and impair cell adhesion, diminish migration, prevents

cancer metastasis and reduces tumor growth in vivo. This indicates it to be a potent inhibitor of sialylation and may be used for anticancer therapy development.[97,98] These findings can also be translated to OC with a study of Gupta et al, demonstrating treatment with P-3F-NeuNAc blocked tumor growth and migration in OC.[43] Alternatively an alpha human epidermal growth factor receptor 2 (αHER2) antibody-sialidase conjugate potently and selectively strips sialic acids from breast cancer cells.[99] This work illustrated antibody-sialidases as a platform technology that might be used to target other cancer types as well. Techniques for imaging, detecting and targeting sialic acid on the surface of cancer cells have been reported. For instance, polymeric nanocarriers possess the desirable characteristics to be used as a specific tumor-selective drug delivery system for sialic acid-targeting. However, there are still many challenges to overcome before precise and effective methods are developed to facilitate adequate disease diagnosis, prognosis or controlled antitumor drug delivery in vivo.[100]

Overall, sialic acids play an important role in the most common gynecological cancers and could be relevant as diagnostic, prognostic and predictive biomarkers. The tumor promoting role of sialic acid in gynecological cancers also defines it as a potential therapeutic target. To investigate the applicability of integrating sialic acid analysis in the diagnoses and treatment of gynecological cancers, more in-depth studies are required as specified for the different cancers.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in this study, and data sources and handling of these data are described in the Section 2 and in Table S1. Further information is available from the corresponding author upon request.

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REFERENCES

1. IARC Estimated number of incident cases and deaths worldwide, females, all ages. Retrieved November 15, 2021, from https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=900&key=total&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group[]=0&ages_group[]=17&nb_items=55&group_cancer=0&include_nmsc=0&include_nmsc_other=1&type_multiple=%7B%22inc%22%3Atrue%2C%22mort%22%3Atrue%2C%22prev%22%3Afalse%7D&orientation=horizontal&type_sort=0&type_nb_items=%7B%22top%22%3Atrue%2C%22bottom%22%3Afalse%7D
2. NIH Cancer stat facts: cervical cancer. Retrieved October 9, 2020, from https://seer.cancer.gov/statfacts/html/cervix.html
3. Lind H, Waldenström AC, Dunberger G, et al. Late symptoms in long-term gynaecological cancer survivors after radiation therapy: a population-based cohort study. *Br J Cancer*. 2011;105(6):737-745.
4. Lindgren A, Dunberger G, Enblom A. Experiences of incontinence and pelvic floor muscle training after gynaecologic cancer treatment. *Support Care Cancer*. 2017;25(1):157-166.
5. Tsatsou I, Parpa E, Tsilika E, et al. A systematic review of sexuality and depression of cervical cancer patients. *J Sex Marital Ther*. 2019;45(8):739-754.
6. NIH Corpus and uterus, NOS. Recent trends in SEER age-adjusted incidence rates, 2000–2018. Retrieved October 9, 2020, from https://seer.cancer.gov/explorer/application.html?site=58&data_type=1&graph_type=2&compareBy=race&chk_race_1=1&rate_type=2&hdn_sex=3&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&advopt_display=2
7. Clarke MA, Devesa SS, Harvey SV, Wentzensen N. Hysterectomy-corrected uterine corpus cancer incidence trends and differences in relative survival reveal racial disparities and rising rates of non-endometrioid cancers. *J Clin Oncol*. 2019;37(22):1895-1908.
8. Varki A. Biological roles of glycans. *Glycobiology*. 2017;27(1):3-49.
9. Cohen M, Varki A. The sialome—far more than the sum of its parts. *OMICS*. 2010;14(4):455-464.
10. Kim YJ, Varki A. Perspectives on the significance of altered glycosylation of glycoproteins in cancer. *Glycoconj J*. 1997;14(5):569-576.
11. Varki Ajit, Schnaar Ronald L., Schauer Roland. Sialic acids and other nonulosonic acids. *Essentials of Glycobiology [Internet]*. 3rd ed. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2017.179–195. https://www.ncbi.nlm.nih.gov/books/NBK453082/
12. Büll C, Stoel MA, den Brok MH, Adema GJ. Sialic acids sweeten a tumor's life. *Cancer Res*. 2014;74(12):3199-3204.
13. Varki A, Kannagi R, Toole BP. Glycosylation changes in cancer. In: Varki A, Cummings RD, Esko JD, et al., eds. *Essentials of Glycobiology*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 2009.597–609.
14. Narayanan S. Sialic acid as a tumor marker. *Ann Clin Lab Sci*. 1994;24(4):376-384.
15. Patel PS, Adhvaryu SG, Balar DB, Parikh BJ, Shah PM. Clinical application of serum levels of sialic acid, fucose and seromucoid fraction as tumour markers in human leukemias. *Anticancer Res*. 1994;14(2B):747-751.
16. Schneider F, Kemmner W, Haensch W, et al. Overexpression of sialyltransferase CMP-sialic acid:Galbeta1,3GalNAc-R alpha6-sialyltransferase is related to poor patient survival in human colorectal carcinomas. *Cancer Res*. 2001;61(11):4605-4611.
17. Varki A. Since there are PAMPs and DAMPs, there must be SAMPs? Glycan "self-associated molecular patterns" dampen innate immunity, but pathogens can mimic them. *Glycobiology*. 2011;21(9):1121-1124.
18. Aranganathan S, Senthil K, Nalini N. A case control study of glycoprotein status in ovarian carcinoma. *Clin Biochem*. 2005;38(6):535-539.
19. Thakkar V, Patel P, Prajapati N, Kaur R, Nandave M. Serum levels of glycoproteins are elevated in patients with ovarian cancer. *Indian J Clin Biochem*. 2014;29(3):345-350.
20. Beatson R, Tajadura-Ortega V, Achkova D, et al. The mucin MUC1 modulates the tumor immunological microenvironment through engagement of the lectin Siglec-9. *Nat Immunol*. 2016;17(11):1273-1281.
21. Crocker PR, Paulson JC, Varki A. Siglecs and their roles in the immune system. *Nat Rev Immunol*. 2007;7(4):255-266.
22. Hudak JE, Canham SM, Bertozzi CR. Glycocalyx engineering reveals a Siglec-based mechanism for NK cell immunoevasion. *Nat Chem Biol*. 2014;10(1):69-75.
23. Jandus C, Boligan KF, Chijioke O, et al. Interactions between Siglec-7/9 receptors and ligands influence NK cell-dependent tumor immunosurveillance. *J Clin Invest*. 2014;124(4):1810-1820.

24. Läubli H, Borsig L. Selectins as mediators of lung metastasis. *Cancer Microenviron*. 2010;3(1):97-105.
25. Läubli H, Pearce OM, Schwarz F, et al. Engagement of myelomonocytic Siglecs by tumor-associated ligands modulates the innate immune response to cancer. *Proc Natl Acad Sci U S A*. 2014; 111(39):14211-14216.
26. Lizcano A, Secundino I, Döhrmann S, et al. Erythrocyte sialoglycoproteins engage Siglec-9 on neutrophils to suppress activation. *Blood*. 2017;129(23):3100-3110.
27. Sun H, Zhou Y, Jiang H, Xu Y. Elucidation of functional roles of sialic acids in cancer migration. *Front Oncol*. 2020;10:401.
28. Ono K, Sanada Y, Kimura Y, et al. A thin hydrogel barrier linked onto cell surface sialic acids through covalent bonds induces cancer cell death in vivo. *Biomater Sci*. 2020;8(2):577-585.
29. Schultz MJ, Holdbrooks AT, Chakraborty A, et al. The tumor-associated glycosyltransferase ST6Gal-I regulates stem cell transcription factors and confers a cancer stem cell phenotype. *Cancer Res*. 2016;76(13):3978-3988.
30. Wang PH, Lee WL, Juang CM, et al. Altered mRNA expressions of sialyltransferases in ovarian cancers. *Gynecol Oncol*. 2005;99(3): 631-639.
31. Wen KC, Sung PL, Hsieh SL, et al. α2,3-sialyltransferase type I regulates migration and peritoneal dissemination of ovarian cancer cells. *Oncotarget*. 2017;8(17):29013-29027.
32. Wichert B, Milde-Langosch K, Galatenko V, Schmalfeldt B, Oliveira-Ferrer L. Prognostic role of the sialyltransferase ST6GAL1 in ovarian cancer. *Glycobiology*. 2018;28(11):898-903.
33. Alley WR Jr, Vasseur JA, Goetz JA, et al. N-linked glycan structures and their expressions change in the blood sera of ovarian cancer patients. *J Proteome Res*. 2012;11(4):2282-2300.
34. Dědová T, Braicu EI, Sehouli J, Blanchard V. Sialic acid linkage analysis refines the diagnosis of ovarian cancer. *Front Oncol*. 2019;9:261.
35. Chowdhury SR, Ray U, Chatterjee BP, Roy SS. Targeted apoptosis in ovarian cancer cells through mitochondrial dysfunction in response to *Sambucus nigra* agglutinin. *Cell Death Dis*. 2017;8(5):e2762.
36. Sung PL, Wen KC, Horng HC, et al. The role of α2,3-linked sialylation on clear cell type epithelial ovarian cancer. *Taiwan J Obstet Gynecol*. 2018;57(2):255-263.
37. Wu X, Zhao J, Ruan Y, Sun L, Xu C, Jiang H. Sialyltransferase ST3GAL1 promotes cell migration, invasion, and TGF-β1-induced EMT and confers paclitaxel resistance in ovarian cancer. *Cell Death Dis*. 2018;9(11):1102.
38. Greville G, Llop E, Huang C, et al. Hypoxia alters epigenetic and N-glycosylation profiles of ovarian and breast cancer cell lines in-vitro. *Front Oncol*. 2020;10:1218.
39. Schultz MJ, Swindall AF, Wright JW, Sztul ES, Landen CN, Bellis SL. ST6Gal-I sialyltransferase confers cisplatin resistance in ovarian tumor cells. *J Ovarian Res*. 2013;6(1):25.
40. Britain CM, Holdbrooks AT, Anderson JC, Willey CD, Bellis SL. Sialylation of EGFR by the ST6Gal-I sialyltransferase promotes EGFR activation and resistance to gefitinib-mediated cell death. *J Ovarian Res*. 2018;11(1):12.
41. Soliman C, Chua JX, Vankemmelbeke M, et al. The terminal sialic acid of stage-specific embryonic antigen-4 has a crucial role in binding to a cancer-targeting antibody. *J Biol Chem*. 2020;295(4):1009-1020.
42. Zhang X, Pan C, Zhou L, Cai Z, Zhao S, Yu D. Knockdown of ST6Gal-I increases cisplatin sensitivity in cervical cancer cells. *BMC Cancer*. 2016;16(1):949.
43. Gupta R, Yang Q, Dogra SK, Wajapeyee N. Serine hydroxymethyl transferase 1 stimulates pro-oncogenic cytokine expression through sialic acid to promote ovarian cancer tumor growth and progression. *Oncogene*. 2017;36(28):4014-4024.
44. Eavarone DA, Al-Alem L, Lugovskoy A, et al. Humanized anti-Sialyl-Tn antibodies for the treatment of ovarian carcinoma. *PLoS One*. 2018;13(7):e0201314.
45. Munkley J. The role of Sialyl-Tn in cancer. *Int J Mol Sci*. 2016; 17(3):275.
46. Chen H, Deng Z, Huang C, Wu H, Zhao X, Li Y. Mass spectrometric profiling reveals association of N-glycan patterns with epithelial ovarian cancer progression. *Tumour Biol*. 2017;39(7):10104283 17716249.
47. Ricardo S, Marcos-Silva L, Valente C, Coelho R, Gomes R, David L. Mucins MUC16 and MUC1 are major carriers of SLe(a) and SLe(x) in borderline and malignant serous ovarian tumors. *Virchows Arch*. 2016;468(6):715-722.
48. Jin Y, Kim SC, Kim HJ, Ju W, Kim YH, Kim HJ. Increased sialylation and reduced fucosylation of exfoliated cervical cells are potential markers of carcinogenesis in the cervix. *Clin Chem Lab Med*. 2016; 54(11):1811-1819.
49. López-Morales D, Reyes-Leyva J, Santos-López G, Zenteno E, Vallejo-Ruiz V. Increased expression of sialic acid in cervical biopsies with squamous intraepithelial lesions. *Diagn Pathol*. 2010;5:74.
50. Velázquez-Márquez N, Santos-López G, Jiménez-Aranda L, Reyes-Leyva J, Vallejo-Ruiz V. Sialyl Lewis x expression in cervical scrapes of premalignant lesions. *J Biosci*. 2012;37(6):999-1004.
51. Jin Y, Kim SC, Kim HJ, Ju W, Kim YH, Kim H-J. Use of protein-based biomarkers of exfoliated cervical cells for primary screening of cervical cancer. *Arch Pharm Res*. 2018;41(4):438-449.
52. Tozawa-Ono A, Kubota M, Honma C, et al. Glycan profiling using formalin-fixed, paraffin-embedded tissues: hippeastrum hybrid lectin is a sensitive biomarker for squamous cell carcinoma of the uterine cervix. *J Obstet Gynaecol Res*. 2017;43(8):1326-1334.
53. Nishijima Y, Toyoda M, Yamazaki-Inoue M, et al. Glycan profiling of endometrial cancers using lectin microarray. *Genes Cells*. 2012; 17(10):826-836.
54. Pan J, Hu Y, Sun S, et al. Glycoproteomics-based signatures for tumor subtyping and clinical outcome prediction of high-grade serous ovarian cancer. *Nat Commun*. 2020;11(1):6139.
55. Zahradnikova M, Ihnatova I, Lattova E, et al. N-glycome changes reflecting resistance to platinum-based chemotherapy in ovarian cancer. *J Proteomics*. 2021;230:103964.
56. Barone A, Linder A, Mateoiu C, et al. Evaluation of sialyl-lactotetra as a marker for epithelial ovarian tumors. *Front Oncol*. 2020;10: 561888.
57. Wu J, Xie X, Nie S, Buckanovich RJ, Lubman DM. Altered expression of sialylated glycoproteins in ovarian cancer sera using lectin-based ELISA assay and quantitative glycoproteomics analysis. *J Proteome Res*. 2013;12(7):3342-3352.
58. Wu Y, Chen X, Dong W, et al. ST3Gal IV mediates the growth and proliferation of cervical cancer cells in vitro and in vivo via the Notch/p21/CDKs pathway. *Front Oncol*. 2020;10:540332.
59. Qi F, Isaji T, Duan C, et al. ST3GAL3, ST3GAL4, and ST3GAL6 differ in their regulation of biological functions via the specificities for the α2,3-sialylation of target proteins. *FASEB J*. 2020;34(1): 881-897.
60. Wang X, Zhang Y, Lin H, et al. Alpha2,3-sialyltransferase III knockdown sensitized ovarian cancer cells to cisplatin-induced apoptosis. *Biochem Biophys Res Commun*. 2017;482(4):758-763.
61. Zhang X, Yang X, Chen M, et al. ST3Gal3 confers paclitaxel-mediated chemoresistance in ovarian cancer cells by attenuating caspase-8/3 signaling. *Mol Med Rep*. 2019;20(5):4499-4506.
62. Ruhaak LR, Kim K, Stroble C, et al. Protein-specific differential glycosylation of immunoglobulins in serum of ovarian cancer patients. *J Proteome Res*. 2016;15(3):1002-1010.
63. Shetty V, Hafner J, Shah P, Nickens Z, Philip R. Investigation of ovarian cancer associated sialylation changes in N-linked glycopeptides by quantitative proteomics. *Clin Proteomics*. 2012;9(1):10.
64. Lin S, Wang Y, Wang X, Yan B, Lou W, Di W. Serum immunoglobulin G N-glycome: a potential biomarker in endometrial cancer. *Ann Transl Med*. 2020;8(12):748.

65. Pochechueva T, Chinarev A, Schoetzau A, et al. Blood plasma-derived anti-glycan antibodies to sialylated and sulfated glycans identify ovarian cancer patients. *PLoS One*. 2016;11(10): e0164230.
66. Zhao R, Lin G, Wang Y, et al. Use of the serum glycan state to predict ovarian cancer patients' clinical response to chemotherapy treatment. *J Proteomics*. 2020;223:103752.
67. Biskup K, Braicu EI, Sehouli J, et al. Serum glycome profiling: a biomarker for diagnosis of ovarian cancer. *J Proteome Res*. 2013;12(9): 4056-4063.
68. Biskup K, Braicu EI, Sehouli J, Tauber R, Blanchard V. The serum glycome to discriminate between early-stage epithelial ovarian cancer and benign ovarian diseases. *Dis Markers*. 2014;2014:238197.
69. Li PL, Zhang X, Li TF, et al. Combined detection of sialic acid and hydroxyproline in diagnosis of ovarian cancer and its comparison with human epididymis protein 4 and carbohydrate antigen 125. *Clin Chim Acta*. 2015;439:148-153.
70. Jacob F, Goldstein DR, Bovin NV, et al. Serum antiglycan antibody detection of nonmucinous ovarian cancers by using a printed glycan array. *Int J Cancer*. 2012;130(1):138-146.
71. Hashiguchi Y, Kasai M, Fukuda T, Ichimura T, Yasui T, Sumi T. Serum sialyl-Tn (STN) as a tumor marker in patients with endometrial cancer. *Pathol Oncol Res*. 2016;22(3):501-504.
72. Bayoumy S, Hyytiä H, Leivo J, et al. Glycovariant-based lateral flow immunoassay to detect ovarian cancer-associated serum CA125. *Commun Biol*. 2020;3(1):460.
73. Salminen L, Nadeem N, Rolfsen AL, et al. Exploratory analysis of CA125-MGL and -STn glycoforms in the differential diagnostics of pelvic masses. *J Appl Lab Med*. 2020;5(2):263-272.
74. Jin Y, Kim SC, Kim HJ, Ju W, Kim YH, Kim HJ. A lectin-based diagnostic system using circulating antibodies to detect cervical intraepithelial neoplasia and cervical cancer. *Glycobiology*. 2016;26(1): 100-107.
75. Miyamoto S, Ruhaak LR, Stroble C, et al. Glycoproteomic analysis of malignant ovarian cancer ascites fluid identifies unusual glycopeptides. *J Proteome Res*. 2016;15(9):3358-3376.
76. Biskup K, Braicu EI, Sehouli J, Tauber R, Blanchard V. The ascites N-glycome of epithelial ovarian cancer patients. *J Proteomics*. 2017; 157:33-39.
77. Kuzmanov U, Musrap N, Kosanam H, et al. Glycoproteomic identification of potential glycoprotein biomarkers in ovarian cancer proximal fluids. *Clin Chem Lab Med*. 2013;51(7):1467-1476.
78. Gomes J, Gomes-Alves P, Carvalho SB, et al. Extracellular vesicles from ovarian carcinoma cells display specific glycosignatures. *Biomolecules*. 2015;5(3):1741-1761.
79. Bai R, Luan X, Zhang Y, Robbe-Masselot C, Brockhausen I, Gao Y. The expression and functional analysis of the sialyl-T antigen in prostate cancer. *Glycoconj J*. 2020;37(4):423-433.
80. Cheng J, Wang R, Zhong G, et al. ST6GAL2 downregulation inhibits cell adhesion and invasion and is associated with improved patient survival in breast cancer. *Onco Targets Ther*. 2020;13:903-914.
81. Jin F, Wang F. The physiological and pathological roles and applications of sialyl Lewis x, a common carbohydrate ligand of the three selectins. *Glycoconj J*. 2020;37(2):277-291.
82. Marini M, Tani A, Manetti M, Sgambati E. Characterization and distribution of sialic acids in human testicular seminoma. *Acta Histochem*. 2020;122(3):151532.
83. Mehta KA, Patel KA, Pandya SJ, Patel PS. Aberrant sialylation plays a significant role in oral squamous cell carcinoma progression. *J Oral Pathol Med*. 2020;49(3):253-259.
84. Nagasundaram M, Horstkorte R, Gnanapragassam VS. Sialic acid metabolic engineering of breast cancer cells interferes with adhesion and migration. *Molecules*. 2020;25(11).2632.
85. Natoni A, Bohara R, Pandit A, O'Dwyer M. Targeted approaches to inhibit sialylation of multiple myeloma in the bone marrow microenvironment. *Front Bioeng Biotechnol*. 2019;7:252.
86. Ouyang S, Liu JH, Ni Z, Ding GF, Wang QZ. Downregulation of ST3GAL5 is associated with muscle invasion, high grade and a poor prognosis in patients with bladder cancer. *Oncol Lett*. 2020;20(1): 828-840.
87. Hernández-Arteaga AC, de Jesús Zermeño-Nava J, Martínez-Martínez MU, et al. Determination of salivary sialic acid through nanotechnology: a useful biomarker for the screening of breast cancer. *Arch Med Res*. 2019;50(3):105-110.
88. Oztürk LK, Emekli-Alturfan E, Kaşikci E, Demir G, Yarat A. Salivary total sialic acid levels increase in breast cancer patients: a preliminary study. *Med Chem*. 2011;7(5):443-447.
89. Jacob TV, Ramesh M, Murali S, Ramesh K, Sanjay PR, Abraham P. A non-invasive study to estimate and compare salivary sialic acid level as tumor marker in patients with pre-cancer and oral cancer. *J Cancer Res Ther*. 2016;12(2):634-639.
90. Achalli S, Madi M, Babu SG, Shetty SR, Kumari S, Bhat S. Sialic acid as a biomarker of oral potentially malignant disorders and oral cancer. *Indian J Dent Res*. 2017;28(4):395-399.
91. Krishnan K, Balasundaram S. Evaluation of total and lipid bound sialic acid in serum in oral leukoplakia. *J Clin Diagn Res*. 2017;11(3): ZC25-ZC27.
92. Scott E, Munkley J. Glycans as biomarkers in prostate cancer. *Int J Mol Sci*. 2019;20(6).1389.
93. Michalakis K, Ilias I, Triantafyllou A, et al. Detection of prostate cancer by sialic acid level in patients with non-diagnostic levels of prostate-specific antigen. *Maturitas*. 2012;73(4):325-330.
94. Zhang C, Yan L, Song H, et al. Elevated serum sialic acid levels predict prostate cancer as well as bone metastases. *J Cancer*. 2019; 10(2):449-457.
95. Heise T, Pijnenborg JFA, Büll C, et al. Potent metabolic sialylation inhibitors based on C-5-modified fluorinated sialic acids. *J Med Chem*. 2019;62(2):1014-1021.
96. Rillahan CD, Antonopoulos A, Lefort CT, et al. Global metabolic inhibitors of sialyl- and fucosyltransferases remodel the glycome. *Nat Chem Biol*. 2012;8(7):661-668.
97. Büll C, Boltje TJ, Wassink M, et al. Targeting aberrant sialylation in cancer cells using a fluorinated sialic acid analog impairs adhesion, migration, and in vivo tumor growth. *Mol Cancer Ther*. 2013;12(10): 1935-1946.
98. Büll C, Boltje TJ, van Dinther EA, et al. Targeted delivery of a sialic acid-blocking glycomimetic to cancer cells inhibits metastatic spread. *ACS Nano*. 2015;9(1):733-745.
99. Gray MA, Stanczak MA, Mantuano NR, et al. Targeted glycan degradation potentiates the anticancer immune response in vivo. *Nat Chem Biol*. 2020;16(12):1376-1384.
100. Xiong Y, Li M, Lu Q, Qing G, Sun T. Sialic acid-targeted biointerface materials and bio-applications. *Polymers*. 2017;9(7).249.

SUPPORTING INFORMATION

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