VGLL3 AND VEGETABLES: A LITERATURE REVIEW OF GENE NETWORKS, NUTRITION, AND STRATEGY FOR SEX BIASED CANCER PREVENTION

By

Hazel Tiglao Salunga

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Basic Medical Science – Master of Science

2024

ABSTRACT

Sex-biased inflammatory differences are exhibited in autoimmune disease by various genetic markers, however one genetic marker that stands above the rest is a molecule known as vestigial-like family member 3 (VGLL3). VGLL3 has been shown to be important for myogenic lineage development, adipocyte differentiation, maturity in Atlantic salmon, inflammatory pathways, and more recently, as a female-biased signature in autoimmune disease. Whether VGLL3 plays a similar role in cancer is still unknown. Here, we reviewed VGLL3's role in reproductive malignancies, specifically breast, ovarian, and cervical cancer. VGLL3 is extensively tied to the risk, development, and progression in these cancers, and despite the widespread mechanisms, there is an opportunity to deepen that understanding for precision nutrition and cancer prevention. Cervical cancer remains a fully preventable disease and these findings are novel in the specificity and intricacy of disease, as well as potential ability to prevent and treat cancer in a sex-conscious manner. The long-term benefits of prevention lessen the emotional, physical, and economic burden of disease.

TABLE OF CONTENTS

Introduction

An individual's sex plays a significant role in the incidence, prevalence, and course of immunoinflammatory disease (Demyanets 2012). Sex-specific molecular mechanisms of inflammation have been elegantly delineated in the context of autoimmune disease (Liang 2017). Significant differences related to the X-chromosome are explained by evolutionary processes such as X-inactivation, sexual antagonism, and hemizygous exposure (Libert 2019). More subtle differences are accounted for by the intersection of genes, signaling pathways and molecules. Vestigial family member 3 (VGLL3) is a unique molecule akin to sex-biased inflammatory implications in autoimmunity and metabolism. Newer research illuminates its multifaceted role in the development and progression of cancer such as soft tissue sarcomas, ovarian cancer, breast, prostate, gastric, and perineuriomas revealing its complex associations with oncogenes and tumor suppressor genes. Although various oncogenic and tumor suppressor errors give rise to reproductive cancers it is unknown whether a specific sex-biased marker such as VGLL3, and its downstream players could potentially play a key role in female reproductive cancer development. Recent studies, however, indicate VGLL3's multi dependent role in ovarian (Cody 2009, Gambaro 2013) breast (Hori 2020, 2022, Takakura 2021, Ma 2022, Kawamura 2022), and cervical (Ding 2020) suggesting a cancer-type dependent function of VGLL3 in tumorigenesis which may potentially align with its sex-biased signature in autoimmune disease, but the mechanisms have remained elusive. Determining a sex-biased signature in cancer is critical to investigate because as some studies point out, there *is* a higher cancer risk in women compared to men in the context of p53 mutations (Hwang 2003). Currently, VGLL3's role in malignant breast cancer has been studied extensively, whereas only one article exists on its relationship to cervical cancer, highlighting deficits in the body of knowledge. Cervical cancer ranks highly as a preventable

disease, and its natural sequence, from contracting human papillomavirus, to the progression of cervical intraepithelial neoplasia 1 through 3 has been found to respond to nutrient mediated changes (Chih 2013). Considering VGLL3's uniquely sex-biased role in autoimmune disease, this literature review reveals its other roles associated with female reproductive malignancies and provides insight from which a female-biased gene could be targeted for nutrient-mediated prevention strategies, and ultimately the ability to approach cancer therapeutics in a sex-conscious manner. This proposed strategy is multi-fold, first identifying the molecular mechanisms of female biased disease, second, identifying nutrition-mediated opportunities for database creation, and third recognizing an opportunity for a sustainable strategy creation. Instinctively, sex, nutrition, and health are intertwined and should serve as a deliberate focal point of intervention.

Chapter 1: Early work on VGLL3

1.1 VGLL3 and its initial roles

There are currently less than 100 published journal articles surrounding VGLL3, when the key term "VGLL3" is searched on PubMed. Early work surrounding vestigial protein is related to VITO-1 (a scalloped interaction domain containing protein) and activation of muscle specific genes (Mielcarek 2009). Vestigial-like genes were also discovered in *Drosophila*, Xenopus, and mammals, where four VGLL1-4 have been described in mammals (Faucheux 2010). Subsequent research revealed its role in soft tissue sarcomas (Helias-Rodziewicz 2010), testis steroidogenesis (McDowell 2012), adipocyte differentiation (Halperin 2013) and even salmon maturation (Ayllon 2015) before the advent of VGLL3 related work and sex-specific markers and cancer. Of note, VGLL3 has a diverse contributing role in many systems and its identification as a sex-specific molecule has the potential to reveal critical biological differences between females and males and the future for therapeutics.

1.2 VGLL3 and sex-specific markers

VGLL3's female-biased molecular signature is first noted in female skin keratinocytes and autoimmune disease (Liang 2017) as well as its role in metabolic homeostasis (Pagenkopf 2020). The work of Liang et al revealed VGLL3's strong female biased expression that acts on molecular networks related to susceptibility in lupus, scleroderma, and Sjogren's syndrome in women (Liang 2017). Mechanistically, VGLL3 regulates B-cell activating factors, (*BAFF/TNFSF13B*) which plays an important role in cytokine response to certain cell types such as skin, monocytes, and salivary glands (Liang 2017). It has been found in abundance in female skin combined with greater localization in the nucleus, which demonstrates its tendency in female biased regulation in transcription (Billi 2019). As skin is a protective barrier serving as

the first line of defense, it is a sensitive indicator of immune function (Pagenkopf 2020). During the initial inflammatory process of rheumatoid arthritis, damage to the mucosa may signal the creation of antibodies known as anti-citrullinated peptides (ACPAs) (Billi 2019). Overexpression of VGLL3 in a transgenic mouse model was created and found sufficient to recapitulate the inflammatory processes of cutaneous lupus in female skin.

Furthermore, sexual dimorphism is best understood on a molecular level demonstrated by extensive transcriptomic data in humans (Li 2017 and Gershoni 2017). Regarding metabolism, one crucial difference between sexes is the requirement to protect and feed a developing embryo. Pagenkopf et al examined and determined how increased levels of VGLL3 in females provide aid during this metabolic challenge. This data is interesting because lower levels of VGLL3 are seemingly protective or suggestive of less risk of autoimmune disease formation and progression. The explanation for this is *nutritional deficiency* (Pagenkopf 2019). During starved states, the chromatin landscape of VGLL3 is remodeled and impacted by induction of interferon alpha (IFN-a); specifically, driving upregulation of interleukin-17 (IL-17C) and restricting IL-1 signaling, reserving basal defense, and preventing systemic inflammation. With VGLL3 at the intersection of autoimmune disease susceptibility and presentation, it serves as a good starting point to consider for other inflammatory states such as cancer.

Chapter 2: Sex-determination in cancer

Like autoimmune disease, sex plays a significant role in the effect of cancer incidence, prognosis, and treatment. Despite known importance, specific differences between females and males are not prioritized for cancer treatment plans, which in turn impact the overall course of the disease (Lopes-Ramos 2020). Sex-biased differences are rarely considered in examination, prevention, and treatment strategies which ultimately undermine sex as a biological variable in medical and research settings. Among influential differences to consider are genetic predisposition, anatomy, physiology, body composition, pharmacokinetics, pharmacodynamics and overall metabolism, response, and toxicity (Özdemir 2018). This is important because sex differences can dramatically influence cancer outcomes.

In recent work, two databases, Gene Expression Omnibus (GEO) and Cancer Genome Atlas (TCGA) have granted unprecedented insight into the comprehensive characterization of molecular differences between female and male patients and related mechanisms across a broad range of human cancer types (Yuan 2016). Specifically, multi-omic data encompassing gene expression signatures, transcription factor motifs, somatic mutations, chromatin accessibility, copy number alterations, and methylation provide crucial insight for developing key prevention and treatment strategies amongst sexes and even account for chromosomal abnormalities (Lopes-Ramos 2020). Beyond reproductive tract cancers, further utilization of a database known as, surveillance epidemiology and end results (SEER) programs and Weighted Gene Co-expression Network Analysis (WGCNA), demonstrated apparent differences and disparities across multiple types of cancer which vary between sex, age, and race. Here the data shows that females tend to face lower incidence rates and mortality compared to males. Common cancers encountered by males include those in the urogenital tract, GI tract, and various systems including

hematological, neurological, and epidermis. Females have been shown to have better survival rates, but face increased risk for thyroid, cranial nerve, gallbladder, anus, anal canal, and anorectal cancers (Lopes-Ramos 2020). Sex-biased gene networks may account for the divergent experiences of female and male presentation and experience of disease. VGLL3's molecular signature and role is a meaningful starting point to determine whether it serves as a signature in cancer and may best be accounted for when reviewing ovarian, breast, and cervical cancer in the literature.

Chapter 3: VGLL3 and reproductive cancer

Early work determining VGLL3's role with reproductive cancer focused on tumor suppressor effects in ovarian cancer, the Hippo pathway in breast, and microRNA (miRNA) cervical cancer. Prior to Liang et al in 2017, VGLL3's sex-biased signature was not recognized purely for its role in other inflammatory states. As the knowledge of VGLL3 grows, it may be worthwhile to consider examining VGLL3 to better understand its significance in certain cancer occurrences between males and females. In cancer research, significant sex differences exist as Hwang et al discovered, including a higher cancer risk in women compared to men in the context of p53 mutations.

In the current literature regarding VGLL3 and cancer, there is no overlap between mechanistic pathways, and no clear regard for sex-biased disease signatures which demonstrate the unique and imperative delineation of the transcriptional regulator in these forms of cancer as well as other various forms of cancer.

3.1 Ovarian cancer

The first study conducted on VGLL3, and ovarian cancer was by Cody et al in 2009. Contrasting to a later, and more intentional analysis of sex-biased gene networks in autoimmune disease, VGLL3 was discovered primarily in loss of heterozygosity studies of chromosome 3 related to ovarian cancer. Alfred G. Knudson's cancer two hit hypothesis outlines that most tumor suppressor genes require inactivation of two alleles resulting in the cancer phenotype. Loss of heterozygosity contributes to tumor suppressor gene inactivation because it occurs when there is already a loss of one normal copy of the gene, inactivating the other, which follows Knudson's two hit hypothesis. Cody et al identified a location on chromosome 3 and potential tumor suppressor gene locus where they initially hypothesized that epigenetic inactivation would result

in ovarian cancer. The authors utilized a microcell-mediated chromosome transfer (MMCT) to derive a specific chromosome 3 mutation demonstrating suppression of tumorigenic potential. The study further revealed VGLL3 was not impacted by change in allelic content and instead found to be under expressed, along with zinc binding motif ZNF654 in tumor samples versus normal ovarian surface epithelial (NOSE) cells. This may suggest VGLL3 was not impacted by loss of heterozygosity ascertaining another mode of regulation perhaps through transcriptional modification of genes (Cody 2009). In 2013, Gambaro et al conducted similar chromosome transfer studies of 3p12-q12.1 into OV-30 ovarian cancer cell line haploinsufficient for 3p and lacking VGLL3 expression, further examining the effect of tumorigenic potential and growth in NOSE. In line with Cody et al, loss of VGLL3 expression was observed in tumors where gene and protein expression were significantly reduced in high grade ovarian cancer compared to normal ovarian epithelial cells. These results would later undermine VGLL3 upregulation in tumor-progression models in Haque et al as well as understanding of VGLL3s role in breast cancer.

In more recent work, Hippo was examined due to its known dysregulation reported in various types of cancers (Harvey 2013). Haque et al reviewed Hippo in the context of high-grade serous ovarian carcinoma (HGSOC) and identified key genes which impact clinical outcome and pathophysiology of disease. Haque et al found mRNA expression of associated genes VGLL4, TEAD3, TEAD4, and YAP1 to be elevated in HGSOC and low levels of VGLL3 and TAZ. Contrastingly, in terms of disease progression, VGLL3 expression was determined to be increased in stage III and IV, which are advanced stages of HGSOC. Related to overall survival, increased levels of VGLL3 correlated with lower levels of survival. Increased levels, may, in part be explained by increased RNA stability and efficient post translational processes of mRNA

molecules that lead to unregulated expression of tumor cell components or post-translational modification which stabilizes the protein in question. For further validation of the relationship between tumorigenesis and increased VGLL3, it would be worthwhile to examine VGLL3's role in post translational modification and its effect on mRNA stability and protein expression in various ovarian cancer cell lines (Haque 2023). Overall, VGLL3's significant roles in ovarian cancer cannot be oversimplified as a tumor suppressor and more work is required to determine its specific influence on both tumor suppressor and oncogene pathways. Understanding the specific VGLL3 pathway in ovarian cancer reveals significant details the scientific community should use to further improve nutrient based preventative strategies and future therapeutics for sex-biased autoimmunity and reproductive cancers.

3.2 Breast cancer

VGLL3's role in breast cancer is dynamic and involves various pathways including Hippo (Hori, 2020, Ma 2022), inflammatory interleukin-1 alpha (Takakura 2021), high mobility group AT-hook2 (HMGA2) (Hori 2022), and glycinamide ribonucleotide formyl transferase (GART)(Kawamura).

The Hippo framework involves Yes-associated transcriptional coactivators and PDZ binding motif (YAP/TAZ). VGLL3 is a cofactor for the Tea domain containing transcription factors (TEADs) which promote tissue and tumor development with YAP/TAZ (Hori 2020). Hori et al demonstrated increased levels of VGLL3 promotes upregulation of two Hippo related proteins-large tumor suppressor kinase 2 (2) and angiomotin-like 2 (AMOTL2) (Hori 2020), where LATS2 promotes cytoplasmic retention and protein degradation of YAP/TAZ (Hao 2008). Previous work demonstrated one mammalian vestigial like factor, VGLL4, competes with co-activator YAP for binding to TEADs and building on this concept, Hori et al concluded members

of VGLL family, specifically VGLL3 may promote the inactivation of YAP/TAZ to enhance binding of itself which may explain increased gene expression and proliferation in malignant breast cancer. Additional work done by Ma et al uncovered a significant mechanism related to LATS-YAP-TEAD-VGLL3 in estrogen receptor positive breast cancer. The authors' work confirmed VGLL3 does in fact compete with YAP/TAZ transcriptional cofactors, and when VGLL3 is bound to TEAD, and augments transcriptional silencing via nuclear receptor co-repressor 2 (NCOR2) and silencing mediator for retinoid or thyroid-hormone receptors (SMRT. In conclusion, it can influence transcription for estrogen receptor- alpha dependent breast cancer growth and cellular proliferation via stimulation or inhibition of expression of downstream players. The authors nuance this by speculating, TEAD remains inactive when complexed with VGLL1/4 and in a repressive state when associated with VGLL2/3.

In addition to Hippo, VGLL3 is associated with an inflammatory signaling pathway. Takakura et al discovered VGLL3 may promote expression and secretion of IL-1a and proved it in two breast cancer cell lines: MDA-MB-231 and MDA-MB-436. Knockdown of VGLL3 significantly reduced IL1a expression and secretion in these cell lines. An extension of this work led to the discovery of VGLL3's role in mesenchymal cell motility. Hori et al (2022) determined VGLL3 promotes epithelial to mesenchymal transition like cell motility by inducing high mobility group AT-hook2 (HMGA2) gene.

The last and unique role VGLL3's plays in cancer are related to purine metabolism. Kawamura et al determined VGLL3 increases dependency on de novo nucleotide synthesis via glycinamide ribonucleotide formyl transferase trifunctional protein (GART) expression in cancer cells. They proved this by demonstrating that highly expressing VGLL3 cancer cell lines they generated (BT549, MDA-MB23, and A549) were sensitive to mycophenolic acid (MPA) and IMP

dehydrogenase which catalyzes GMP synthesis from IMP, downstream of GART (Kawamura 2022). This sensitivity to MPA, a purine nucleotide inhibitor, may prove GART is impacted in VGLL3 high expressed cell lines. Interestingly, this gives recognition to GART as a potential molecular target for treatment of VGLL3 high cancer cell lines.

3.3 Cervical cancer

Currently, only one study exists regarding VGLL3 and cervical cancer, demonstrating opportunity in the research of a female-biased gene signature in this pervasive cancer type. In 2020, authors Ding et al identified microRNA regulation of VGLL3 as a crucial pathway for the progression of cervical cancer. Through the examination of the University of California Santa Cruz Genome Browser, processed data from larger databases including TCGA, International Cancer Genome Consortium, and Therapeutically Applicable Research to Generate Effective Treatments, were extensively reviewed and included in this body of work. Considering cervical cancer may be associated with age (Ding 2020), the authors selected over 300 clinical, RNA seq counts, and microRNA data and divided it into 3 groups, reflecting patient age . Significant findings included differentially expressed mRNAADH7 expression upregulated in patients older than 60 and VGLL3 expression downregulated in the older age groups, suggesting both containing significant roles with cervical cancer survival rate. Compared to the known pathway of VGLL3 in ovarian and breast cancer, this was the first study to indicate VGLL3 is regulated by microRNA, miR-330, and significantly correlated with cervical cancer survival rate, indicating VGLL3 may influence cervical cancer carcinogenesis through regulation of miR330 expression. In cancer, this is paramount because miR-330-3p impacts cancer related processes such as mitosis, cellular migration, tumor invasion, cellular transition, blood vessel formation, and apoptosis (Jafarzadeh 2022). Lastly, Ding et al noted VGLL3 gradually declined with

decreasing patient age suggesting it may be associated with the progression at different age groups.

Compared to the VGLL3 female-biased signature in autoimmune disease demonstrating independence of biological age, VGLL3 in the context of cervical cancer may predict risk across age groups, this is another helpful layer to achieving effective sex-specific treatment through one's lifetime.

Chapter 4: VGLL3 and other inflammatory states

4.1 General inflammation in pregnancy

In addition to cancer, VGLL3 networks remain far reaching into various states of inflammation and increased immune activation, such as pregnancy. Women who experience pregnancy and childbirth face the physiological reality of building a defensible environment for the growth and protection of offspring. During this time, the adaptive immunity (i.e. NK cells, macrophages, and T regulatory cells) as well as circulating antibodies play a crucial role in the implantation of the embryo and development of the placenta. Beyond VGLL3's role in upregulating pro-inflammatory genes, it has a significant role in driving BAFF (Liang 2017), which promotes B-cell expansion, autoantibody production, immune complex deposition, and end-organ damage. BAFF is known to enhance the survival of B-cells in vitro and regulate the peripheral cell population, and its receptor, B-cell activating receptor (BAFF-R) is important for BAFF-mediated survival (NIH 2019). Elevated levels of BAFF have been found in to negatively impact the progression of pregnancy as well as other pathological states of pregnancy (Xu 2019), giving rise to prothrombotic and hypertensive states (Tay 2018, Xu 2019, Wu 2021, van den Hoogen 2022). This finding makes BAFF a promising molecule to investigate in pre, peri, and postpartum states.

In salpingitis and ectopic pregnancy in the fallopian tube, Xu et al discovered statistically significant elevations of BAFF mRNA in whole tissue patient samples undergoing salpingectomy as well as elevated serum levels of BAFF, tumor necrosis-α (TNF-α) and IL-6 in whole blood samples compared to the control group. Another autoimmune challenge in pregnancy is primary antiphospholipid syndrome, characterized by thrombotic events, pregnancy morbidity and presence of specific antibodies known as antiphospholipid antibodies (aPLs) and

adverse pregnancy outcomes (APOs) demonstrated by a significant elevation in BAFF relative to healthy pregnant and healthy nonpregnant controls (Li 2020). In the case of pre-eclampsia (PE), BAFF levels were measured in 19 patients with PE and 10 patients with fetal growth restriction (Tay 2018) and found BAFF levels were higher in women with PE compared to healthy controls, with no significant levels in FGR.

Although an overall increase in antibodies does not fully explain the onset of ectopic pregnancy, prothrombotic, and hypertensive states, understanding the possible outcomes of elevated BAFF, and therefore VGLL3s overall role in pregnancy and immune activity is compelling and important for the accurate screening and prevention of threatening inflammatory states in pregnancy.

Chapter 5: Precision nutrition and cancer

Precision nutrition is "the nutrition or dietary guidance designed to optimize health, facilitate disease prevention, and enhance therapeutic benefit through profiling at the level of the individual" (Maruvada 2020). Additionally, it provides an understanding of the interaction between genes, metabolome, and diet. In recent years, dietary interventions have significantly shaped cancer treatment and impact many characteristics of tumorigenesis including caner growth, development, and therapeutic response (Martinez-Garay 2023). Simply put, an effective way to stave off cancer may in fact be *food.* The Cancer Genome Atlas (TCGA) is a landmark cancer genomic program developed in 2006, molecularly characterizing over 20,000 primary cancers and matched normal samples across 33 cancer types (NIH). With the creation of TCGA, there is greater accessibility to cancer biomarkers and the potential to build a reliable understanding of the impact of nutrients in the cancer epigenome. This knowledge may bridge the gap between cancer and nutrient research, especially as the field continues to grow. Gynecological cancers specifically, ovarian, breast, and cervical share a related genetic marker-VGLL3. Whether VGLL3's sex-specific network is significant in these cancers remain to be answered. Furthermore, it is known nutrition serves as a beneficial starting point to prevent and lessen disease burden in cancer, especially in the case of cervical cancer. For the purposes of this review, cervical cancer will be analyzed.

Cervical cancer is known to develop and progress through HPV infection, cervical intraepithelial neoplasia to cervical cancer (Koshiyama 2019). Current scientific evidence focuses on the relationship between nutrition and HPV (Letafati 2023), HPV and squamous intraepithelial lesions (SIL) as well the varying nutrient impacts on the stages (CIN1-CIN3) leading to cervical cancer (Koshiyama 2019). In 2020, the World Health Organization focused its efforts in creating

processes to eliminate cervical cancer (Kakotin 2023) while accounting for social circumstance, and personal/cultural/structural and economic barriers hindering access to health services (WHO 2022). The outcome of the efforts became known as the "90-70-90" project, where specific goals must be met by 2030 to be on the path toward cervical cancer elimination (WHO 2022). The project outlines that countries must have 90% of girls fully vaccinated with HPV vaccine by age 15, 70% of women screened at the age of 35 and again at 45, and 90% of women identified with cervical disease to receive treatment (WHO 2022).

Knowing prevention strategies for CIN 1-3 as well as cervical cancer are crucial in the prevention of the disease happening in the first place. Radiotherapy, chemotherapy, interventional therapy, and radical hysterectomy are other treatment forms (Biewenga 2011, Kumar 2015). However, factors such as lymphatic metastasis, postoperative recurrence, and other toxic side effects from treatment all have an adverse effect on therapeutic outcomes (Li 2019) and, therefore, it is necessary to determine effective prevention strategies to decrease patient burden of disease.

In the case of HPV and SIL, a diet rich with vegetables are associated with a 54% decreased HPV persistence (Sedjo 2002) and higher papaya consumption reduced SIL risk (Siegel 2010). Risk for developing CIN1 was associated with serum levels of Vitamin A (Yeo 2000) and Vitamin D (Vahedpoor 2017). In one clinic-based study, Yeo et al investigated a population of Southwest American Indian women, a group known to have higher rates of preinvasive cervical lesions and determined those with lower levels of serum retinol (Vitamin A), had increased chances of progressing to CIN1 compared to women with high serum levels of retinol. This suggests retinol may be protective in HPV to CIN1 progression. Additionally, in a study with 29 patients who took a high dose of Vitamin D (50,000 IU) every 2 weeks for 6 months, exhibited

lower insulin metabolism marker levels and improved levels of biomarkers of inflammation and oxidative stress (Vahedpoor 2017). Overall, these results demonstrate a diet rich in vegetables, Vitamin A and Vitamin D may decrease risk in HPV persistence as well as progression to CIN 1.

In a population based cervical cancer screening in China, Feng et al determined that dietary intake of onion vegetables, legumes, nuts, and meat is associated with reduced risk of CIN2 and may be protective against CIN2. Progression of HPV infection into invasive cervical cancer such as CIN 3 can take many decades. Protective factors for CIN 3 include regular dietary intake of dark-green and deep, yellow-colored vegetables, including fruits and vegetables rich in B-carotene. Tomita et al investigated the additive effect of low intake of dark green and deep, yellow-colored vegetables, smoking, and developing CIN 3. They found lower serum and micronutrient concentrations in subjects positive for CIN 3 compared to controls, suggesting dark green and deep colored vegetable consumption could be protective (Tomita 2010).

These findings shed light on valuable considerations for precision nutrition. Female biased genetic marker VGLL3 has been reviewed in the context of reproductive malignancies and offers insight on what pathways are impactful during disease. Data focused on precision nutrition for cervical cancer, although still largely epidemiological, offers awareness of nutrient specific effects. Currently, there are no universally accepted biomarker classification schemes that close the gap between nutrient effects on cancer pathways. To further understand sex-biased disease and precision nutrition, it may be important to define if VGLL3 is a useful female biased maker for precision nutrition research.

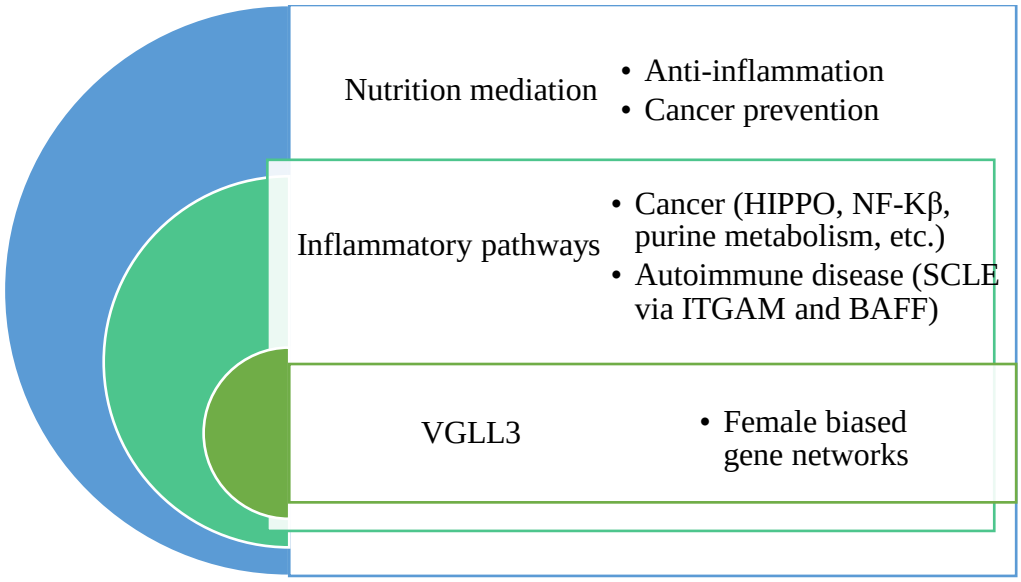

Figure 1. Summary of far-reaching effects of VGLL3 female biased gene networks.

Conclusion

In 2017, Liang et al provided unprecedented insight in VGLL3's female-biased gene network and risk for autoimmune disease. Following these findings, VGLL3 has been found to be extensively tied to reproductive cancer via several significant pathways. This review specifically examined its role in ovarian, breast, and cervical cancer. Determining VGLL3's sex-biased role in another inflammatory state such as cancer is novel and may allow for the prevention and treatment of cancer in a sex-conscious manner. Furthermore, deeply understanding molecular pathways of disease allows for closing the gap between the onset of cancer and preventative nutrition. One specific example is the cervical cancer profile. With cervical cancer impacting many countries worldwide despite ample ability to prevent disease, utilizing nutrition may be one way to combat the disease. Much epidemiological literature exists on various nutrients such as Vitamin A, Vitamin D, and B-carotene serving as preventative and protective components for each stage of disease (HPV infection, progression to SIL, and CIN 1-3). However, how these nutrients directly impact mechanisms of disease is still unknown. This literature review uncovers a crucial starting point for this kind of work. Long term benefits may lower emotional, physical, and economic burdens of disease.

Considering advancing research technologies, the discovery of sex-biased molecular signatures is a significant starting point for precision medicine. Starting with transcriptome analysis, AI may have the potential to combine information with cancer type, stage, nutrition genomics, molecular diagnostics, and develop dietary regimens aimed at targeting specific cancer while maintaining patient-centric needs (Figure 1).

For future studies, a series of things need to be carefully considered: Firstly, VGLL3 needs to be evaluated as a significant sex-specific contributor to reproductive cancers including breast,

ovarian, and cervical, comparing its mechanism to male reproductive cancers such as prostate cancer. Secondly, studies surrounding beneficial nutrients such as Vitamin A, D, beta-carotene, and specific dark and light vegetables should reflect the direct mechanism related to sex-specific gene networks such as VGLL3, instead of general inflammatory pathways. The results for precision nutrition should be validated using experimental methods instead epidemiological data (although it still has many strengths) as epidemiological data may sometimes demonstrate correlative and not causative data. Lastly, preventative nutrition should not be the only source of therapy but should be respected as a powerful tool and be used as a primary strategy in conjunction with other therapies based on patient needs.

BIBLIOGRAPHY

1. Halperin DS, Pan C, Lusis AJ, Tontonoz P. Vestigial-like 3 is an inhibitor of adipocyte differentiation. J Lipid Res. 2013 Feb;54(2):473-81. doi: 10.1194/jlr.M032755. Epub 2012 Nov 13. PMID: 23152581; PMCID: PMC3541706.

2. Ayllon F, Kjærner-Semb E, Furmanek T, Wennevik V, Solberg MF, Dahle G, Taranger GL, Glover KA, Almén MS, Rubin CJ, Edvardsen RB, Wargelius A. The vgll3 Locus Controls Age at Maturity in Wild and Domesticated Atlantic Salmon (Salmo salar L.) Males. PLoS Genet. 2015 Nov 9;11(11):e1005628. doi: 10.1371/journal.pgen.1005628. PMID: 26551894; PMCID: PMC4638356.

3. Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. Nat Rev Immunol. 2010 Aug;10(8):594-604. doi: 10.1038/nri2815. PMID: 20651746.

4. Hwang SJ, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. Am J Hum Genet. 2003 Apr;72(4):975-83. doi: 10.1086/374567. Epub 2003 Feb 27. PMID: 12610779; PMCID: PMC1180359.

5. Demyanets S, Wojta J. Sex differences in effects and use of anti-inflammatory drugs. Handb Exp Pharmacol. 2012;(214):443-72. doi: 10.1007/978-3-642-30726-3_20. PMID: 23027462.4.

6. Pagenkopf A, Liang Y. Immunometabolic function of the transcription cofactor VGLL3 provides an evolutionary rationale for sexual dimorphism in autoimmunity. FEBS Lett. 2020 Oct;594(20):3371-3383. doi: 10.1002/1873-3468.13911. Epub 2020 Sep 4. PMID: 32803756; PMCID: PMC7722229.

7. Özdemir BC, Csajka C, Dotto GP, Wagner AD. Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology. J Clin Oncol. 2018 Sep 10;36(26):2680-2683. doi: 10.1200/JCO.2018.78.3290. Epub 2018 Jul 13. PMID: 30004815.

8. Clocchiatti A, Cora E, Zhang Y, Dotto GP. Sexual dimorphism in cancer. Nat Rev Cancer. 2016 May;16(5):330-9. doi: 10.1038/nrc.2016.30. Epub 2016 Apr 15. PMID: 27079803.

9. Mielcarek M, Piotrowska I, Schneider A, Gunther S, Braun T. VITO-2 a new SID domain protein, is expressed in the myogenic lineage during early mouse embryonic development. Gene Expression Patterns. 2009 March; 9(3):129-137. doi: https://doi.org/10.1016/j.gep.2008.12.002

10. Faucheux C, Naye F, Tréguer K, Fédou S, Thiébaud P, Théze N. Vestigial like gene family expression in Xenopus: common and divergent features with other vertebrates. Int J Dev Biol. 2010;54(8-9):1375-82. doi: 10.1387/ijdb.103080cf. PMID: 20712000.

11. Hélias-Rodzewicz Z, Pérot G, Chibon F, Ferreira C, Lagarde P, Terrier P, Coindre JM, Aurias A. YAP1 and VGLL3, encoding two cofactors of TEAD transcription factors, are amplified and overexpressed in a subset of soft tissue sarcomas. Genes Chromosomes Cancer. 2010 Dec;49(12):1161-71. doi: 10.1002/gcc.20825. PMID: 20842732.

12. McDowell EN, Kisielewski AE, Pike JW, Franco HL, Yao HH, Johnson KJ. A transcriptome-wide screen for mRNAs enriched in fetal Leydig cells: CRHR1 agonism stimulates rat and mouse fetal testis steroidogenesis. PLoS One. 2012;7(10):e47359. doi: 10.1371/journal.pone.0047359. Epub 2012 Oct 25. PMID: 23133512; PMCID: PMC3484991.

13. Li B, Qing T, Zhu J, Wen Z, Yu Y, Fukumura R, Zheng Y, Gondo Y, Shi L. A Comprehensive Mouse Transcriptomic BodyMap across 17 Tissues by RNA-seq. Sci Rep. 2017 Jun 23;7(1):4200. doi: 10.1038/s41598-017-04520-z. PMID: 28646208; PMCID: PMC5482823.

14. Gershoni M, Pietrokovski S. The landscape of sex-differential transcriptome and its consequent selection in human adults. BMC Biol. 2017 Feb 7;15(1):7. doi: 10.1186/s12915-017-0352-z. PMID: 28173793; PMCID: PMC5297171.

15. Liang Y, Tsoi LC, Xing X, Beamer MA, Swindell WR, Sarkar MK, Berthier CC, Stuart PE, Harms PW, Nair RP, Elder JT, Voorhees JJ, Kahlenberg JM, Gudjonsson JE. A gene network regulated by the transcription factor VGLL3 as a promoter of sex-biased autoimmune diseases. Nat Immunol. 2017 Feb;18(2):152-160. doi: 10.1038/ni.3643. Epub 2016 Dec 19. PMID: 27992404; PMCID: PMC5289297.

16. Billi AC, Gharaee-Kermani M, Fullmer J, Tsoi LC, Hill BD, Gruszka D, Ludwig J, Xing X, Estadt S, Wolf SJ, Rizvi SM, Berthier CC, Hodgin JB, Beamer MA, Sarkar MK, Liang Y, Uppala R, Shao S, Zeng C, Harms PW, Verhaegen ME, Voorhees JJ, Wen F, Ward NL, Dlugosz AA, Kahlenberg JM, Gudjonsson JE. The female-biased factor VGLL3 drives cutaneous and systemic autoimmunity. JCI Insight. 2019 Apr 18;4(8):e127291. doi: 10.1172/jci.insight.127291. PMID: 30996136; PMCID: PMC6538382.

17. Ramírez A, Bravo A, Jorcano JL, Vidal M. Sequences 5' of the bovine keratin 5 gene direct tissue- and cell-type-specific expression of a lacZ gene in adult development. Differentiation. 1994 Nov;58(1):53-64. doi: 10.1046/j.1432-0436.1994.5810053. x. PMID: 7532601.

18. Yuan Y, Liu L, Chen H, Wang Y, Xu Y, Mao H, Li J, Mills GB, Shu Y, Li L, Liang H. Comprehensive Characterization of Molecular Differences in Cancer between Male and Female Patients. Cancer Cell. 2016 May 9;29(5):711-722. doi: 10.1016/j.ccell.2016.04.001. PMID: 27165743; PMCID: PMC4864951.

19. Chih HJ, Lee AH, Colville L, Binns CW, Xu D. A review of dietary prevention of human papillomavirus-related infection of the cervix and cervical intraepithelial neoplasia. Nutr Cancer. 2013;65(3):317-28. doi: 10.1080/01635581.2013.757630. PMID: 23530631.

20. WHO. *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem.* World Health Organization; Geneva, Switzerland: 2020. 56p

21. Lopes-Ramos CM, Quackenbush J, DeMeo DL. Genome-Wide Sex and Gender Differences in Cancer. Front Oncol. 2020 Nov 23; 10:597788. doi: 10.3389/fonc.2020.597788. PMID: 33330090; PMCID: PMC7719817.

22. Cody NA, Shen Z, Ripeau JS, Provencher DM, Mes-Masson AM, Chevrette M, Tonin PN. Characterization of the 3p12.3-pcen region associated with tumor suppression in a novel ovarian cancer cell line model genetically modified by chromosome 3 fragment transfer. Mol Carcinog. 2009 Dec;48(12):1077-92. doi: 10.1002/mc.20535. PMID: 19347865.

23. Gambaro K, Quinn MC, Wojnarowicz PM, Arcand SL, de Ladurantaye M, Barrès V, Ripeau JS, Killary AM, Davis EC, Lavoie J, Provencher DM, Mes-Masson AM, Chevrette M, Tonin PN. VGLL3 expression is associated with a tumor suppressor phenotype in epithelial ovarian cancer. Mol Oncol. 2013 Jun;7(3):513-30. doi: 10.1016/j.molonc.2012.12.006. Epub 2013 Jan 16. PMID: 23415753; PMCID: PMC5528482.

24. Harvey KF, Zhang X, Thomas DM. The Hippo pathway and human cancer. Nat Rev Cancer. 2013 Apr;13(4):246-57. doi: 10.1038/nrc3458. Epub 2013 Mar 7. PMID: 23467301.

25. Haque R, Lee J, Chung JY, Shin HY, Kim H, Kim JH, Yun JW, Kang ES. VGLL3 expression is associated with macrophage infiltration and predicts poor prognosis in epithelial ovarian cancer. Front Oncol. 2023 Jun 5; 13:1152991. doi: 10.3389/fonc.2023.1152991. PMID: 37342190; PMCID: PMC10277618.

26. Hori N, Okada K, Takakura Y, Takano H, Yamaguchi N, Yamaguchi N. Vestigial-like family member 3 (VGLL3), a cofactor for TEAD transcription factors, promotes cancer cell proliferation by activating the Hippo pathway. J Biol Chem. 2020 Jun 26;295(26):8798-8807. doi: 10.1074/jbc.RA120.012781. Epub 2020 May 8. PMID: 32385107; PMCID: PMC7324512.

27. Ma S, Tang T, Probst G, Konradi A, Jin C, Li F, Gutkind JS, Fu XD, Guan KL. Transcriptional repression of estrogen receptor alpha by YAP reveals the Hippo pathway as a therapeutic target for ER+ breast cancer. Nat Commun. 2022 Feb 25;13(1):1061. doi: 10.1038/s41467-022-28691-0. PMID: 35217640; PMCID: PMC8881512.

28. Takakura Y, Hori N, Terada N, Machida M, Yamaguchi N, Takano H, Yamaguchi N. VGLL3 activates inflammatory responses by inducing interleukin-1α secretion. FASEB J. 2021 Nov;35(11):e21996. doi: 10.1096/fj.202100679RR. PMID: 34679187.

29. Hori N, Takakura Y, Sugino A, Iwasawa S, Nomizo K, Yamaguchi N, Takano H, Yamaguchi N. Vestigial-like family member 3 stimulates cell motility by inducing high-mobility group AT-hook 2 expression in cancer cells. J Cell Mol Med. 2022

May;26(9):2686-2697. doi: 10.1111/jcmm.17279. Epub 2022 Apr 2. PMID: 35366053; PMCID: PMC9077286.

30. Kawamura T, Takehora Y, Hori N, Takakura Y, Yamaguchi N, Takano H, Yamaguchi N. VGLL3 increases the dependency of cancer cells on de novo nucleotide synthesis through GART expression. J Cell Biochem. 2022 Jun;123(6):1064-1076. doi: 10.1002/jcb.30251. Epub 2022 Apr 17. PMID: 35434822.

31. Ding S, Huang X, Zhu J, Xu B, Xu L, Gu D, Zhang W. ADH7, miR-3065 and LINC01133 are associated with cervical cancer progression in different age groups. Oncol Lett. 2020 Mar;19(3):2326-2338. doi: 10.3892/ol.2020.11348. Epub 2020 Jan 24. PMID: 32194732; PMCID: PMC7039144.

32. Jafarzadeh A, Paknahad MH, Nemati M, Jafarzadeh S, Mahjoubin-Tehran M, Rajabi A, Shojaie L, Mirzaei H. Dysregulated expression and functions of microRNA-330 in cancers: A potential therapeutic target. Biomed Pharmacother. 2022 Feb;146:112600. doi: 10.1016/j.biopha.2021.112600. Epub 2021 Dec 27. PMID: 34968919.

33. Jiao S, Wang H, Shi Z, Dong A, Zhang W, Song X, He F, Wang Y, Zhang Z, Wang W, Wang X, Guo T, Li P, Zhao Y, Ji H, Zhang L, Zhou Z. A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. Cancer Cell. 2014 Feb 10;25(2):166-80. doi: 10.1016/j.ccr.2014.01.010. PMID: 24525233.

34. Hao Y, Chun A, Cheung K, Rashidi B, Yang X. Tumor suppressor LATS1 is a negative regulator of oncogene YAP. J Biol Chem. 2008 Feb 29;283(9):5496-509. doi: 10.1074/jbc.M709037200. Epub 2007 Dec 24. PMID: 18158288.

35. Giuliano AR, Siegel EM, Roe DJ, Ferreira S, Baggio ML, Galan L, Duarte-Franco E, Villa LL, Rohan TE, Marshall JR, Franco EL; Ludwig-McGill HPV Natural History Study. Dietary intake and risk of persistent human papillomavirus (HPV) infection: the Ludwig-McGill HPV Natural History Study. J Infect Dis. 2003 Nov 15;188(10):1508-16. doi: 10.1086/379197. Epub 2003 Nov 3. PMID: 14624376.

36. Giuliano AR, Nyitray AG, Kreimer AR, Pierce Campbell CM, Goodman MT, Sudenga SL, Monsonego J, Franceschi S. EUROGIN 2014 roadmap: differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection. Int J Cancer. 2015 Jun 15;136(12):2752-60. doi: 10.1002/ijc.29082. Epub 2014 Jul 26. PMID: 25043222; PMCID: PMC4297584.

37. Kronzer VL, Bridges SL Jr, Davis JM 3rd. Why women have more autoimmune diseases than men: An evolutionary perspective. Evol Appl. 2020 Dec 1;14(3):629-633. doi: 10.1111/eva.13167. PMID: 33767739; PMCID: PMC7980266

38. TNFRSF13C TNF receptor superfamily member 13C [*Homo sapiens* (human)] [Internet]. Bethesda (MD). National Library of Medicine (US), National Center for Biotechnology

Information; 2023- [cited 2023 10 05]. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=115650

39. Xu J, Luo X, Qu S, Yang G, Shen N. B cell activation factor (BAFF) induces inflammation in the human fallopian tube leading to tubal pregnancy. BMC Pregnancy Childbirth. 2019 May 14;19(1):169. doi: 10.1186/s12884-019-2324-5. PMID: 31088412; PMCID: PMC6518762.

40. Wu Y, Xin M, Han Q, Wang J, Yin X, He J, Yin C. Extensive serum biomarker analysis in the prethrombotic state of recurrent spontaneous abortion. J Cell Mol Med. 2021 Jul;25(14):6679-6694. doi: 10.1111/jcmm.16671. Epub 2021 Jun 16. PMID: 34132454; PMCID: PMC8278118.

41. van den Hoogen LL, Bisoendial RJ. B-Cells and BAFF in Primary Antiphospholipid Syndrome, Targets for Therapy? J Clin Med. 2022 Dec 20;12(1):18. doi: 10.3390/jcm12010018. PMID: 36614819; PMCID: PMC9821657.

42. Tay J, Costanzi A, Basello K, Piuri G, Ferrazzi E, Speciani AF, Lees CC. Maternal Serum B Cell activating factor in hypertensive and normotensive pregnancies. Pregnancy Hypertens. 2018 Jul;13:58-61. doi: 10.1016/j.preghy.2018.05.001. Epub 2018 May 3. PMID: 30177072.

43. Maruvada P, Lampe JW, Wishart DS, Barupal D, Chester DN, Dodd D, Djoumbou-Feunang Y, Dorrestein PC, Dragsted LO, Draper J, Duffy LC, Dwyer JT, Emenaker NJ, Fiehn O, Gerszten RE, B Hu F, Karp RW, Klurfeld DM, Laughlin MR, Little AR, Lynch CJ, Moore SC, Nicastro HL, O'Brien DM, Ordovás JM, Osganian SK, Playdon M, Prentice R, Raftery D, Reisdorph N, Roche HM, Ross SA, Sang S, Scalbert A, Srinivas PR, Zeisel SH. Perspective: Dietary Biomarkers of Intake and Exposure-Exploration with Omics Approaches. Adv Nutr. 2020 Mar 1;11(2):200-215. doi: 10.1093/advances/nmz075. Erratum in: Adv Nutr. 2020 Mar 1;11(2):468. PMID: 31386148; PMCID: PMC7442414.

44. Martínez-Garay C, Djouder N. Dietary interventions and precision nutrition in cancer therapy. Trends Mol Med. 2023 Jul;29(7):489-511. doi: 10.1016/j.molmed.2023.04.004. Epub 2023 May 30. PMID: 37263858.

45. Milner JA. Incorporating basic nutrition science into health interventions for cancer prevention. J Nutr. 2003 Nov;133(11 Suppl 1):3820S-3826S. doi: 10.1093/jn/133.11.3820S. PMID: 14608120.

46. Zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer. 2002 May;2(5):342-50. doi: 10.1038/nrc798. PMID: 12044010.

47. Biewenga P, van der Velden J, Mol BW, Stalpers LJ, Schilthuis MS, van der Steeg JW, Burger MP, Buist MR. Prognostic model for survival in patients with early stage cervical

cancer. Cancer. 2011 Feb 15;117(4):768-76. doi: 10.1002/cncr.25658. Epub 2010 Oct 4. PMID: 20922801.

48. Kumar L, Pramanik R, Kumar S, Bhatla N, Malik S. Neoadjuvant chemotherapy in gynaecological cancers - Implications for staging. Best Pract Res Clin Obstet Gynaecol. 2015 Aug;29(6):790-801. doi: 10.1016/j.bpobgyn.2015.02.008. Epub 2015 Mar 6. PMID: 25840650.

49. Li N, Guo X, Liu L, Wang L, Cheng R. Molecular mechanism of miR-204 regulates proliferation, apoptosis and autophagy of cervical cancer cells by targeting ATF2. Artif Cells Nanomed Biotechnol. 2019 Dec;47(1):2529-2535. doi: 10.1080/21691401.2019.1628038. PMID: 31204513.

50. Feng, C.Y., Lin, M., Lakhaney, D., Sun, H.K., Dai, X.B., Zhao, F.H., Qiao, Y.L. The association between dietary intake and cervical intraepithelial neoplasia grade 2 or higher among women in a high-risk rural area of China. *Arch. Gynecol. Obstet.* **2011**, *284*, 973–980.

51. Vahedpoor Z, Jamilian M, Bahmani F, Aghadavod E, Karamali M, Kashanian M, Asemi Z. Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia: a Randomized, Double-Blind, Placebo-Controlled Trial. Horm Cancer. 2017 Feb;8(1):58-67. doi: 10.1007/s12672-016-0278-x. Epub 2017 Jan 3. PMID: 28050798; PMCID: PMC10355858.

52. Tomita LY, Roteli-Martins CM, Villa LL, Franco EL, Cardoso MA; BRINCA Study Team. Associations of dietary dark-green and deep-yellow vegetables and fruits with cervical intraepithelial neoplasia: modification by smoking. Br J Nutr. 2011 Mar;105(6):928-37. doi: 10.1017/S0007114510004447. Epub 2010 Nov 24. PMID: 21092390.

53. Sedjo RL, Roe DJ, Abrahamsen M, Harris RB, Craft N, Baldwin S, Giuliano AR. Vitamin A, carotenoids, and risk of persistent oncogenic human papillomavirus infection. Cancer Epidemiol Biomarkers Prev. 2002 Sep;11(9):876-84. PMID: 12223432.

54. Koshiyama M. The Effects of the Dietary and Nutrient Intake on Gynecologic Cancers. Healthcare (Basel). 2019 Jul 7;7(3):88. doi: 10.3390/healthcare7030088. PMID: 31284691; PMCID: PMC6787610.

55. Letafati A, Sakhavarz T, Khosravinia MM, Ardekani OS, Sadeghifar S, Norouzi M, Naseri M, Ghaziasadi A, Jazayeri SM. Exploring the correlation between progression of human papillomavirus infection towards carcinogenesis and nutrition. Microb Pathog. 2023 Oct;183:106302. doi: 10.1016/j.micpath.2023.106302. Epub 2023 Aug 9. PMID: 37567326.

56. Giuliano AR, Siegel EM, Roe DJ, Ferreira S, Baggio ML, Galan L, Duarte-Franco E, Villa LL, Rohan TE, Marshall JR, Franco EL; Ludwig-McGill HPV Natural History Study. Dietary intake and risk of persistent human papillomavirus (HPV) infection: the Ludwig-

McGill HPV Natural History Study. J Infect Dis. 2003 Nov 15;188(10):1508-16. doi: 10.1086/379197. Epub 2003 Nov 3. PMID: 14624376.

57. Yeo ASS, Schiff MA, Montoya G, Masuk, Mary, Van Asselt-King L, Becker T M. Serum Micronutrients and Cervical Dysplasia in Southwestern American Indian Woman. *Nutrition and Cancer*. 2000; 38:2, 141-150. Doi:10.1207/S15327914NC382_1

58. Ono A, Koshiyama M, Nakagawa M, Watanabe Y, Ikuta E, Seki K, Oowaki M. The Preventive Effect of Dietary Antioxidants on Cervical Cancer Development. Medicina (Kaunas). 2020 Nov 10;56(11):604. doi: 10.3390/medicina56110604. PMID: 33182663; PMCID: PMC7698010.

59. Guo L, Zhu H, Lin C, Che J, Tian X, Han S, Zhao H, Zhu Y, Mao D. Associations between antioxidant vitamins and the risk of invasive cervical cancer in Chinese women: A case-control study. Sci Rep. 2015 Sep 4;5:13607. doi: 10.1038/srep13607. PMID: 26337940; PMCID: PMC4559762.

60. Siegel EM, Salemi JL, Villa LL, Ferenczy A, Franco EL, Giuliano AR. Dietary consumption of antioxidant nutrients and risk of incident cervical intraepithelial neoplasia. Gynecol Oncol. 2010 Sep;118(3):289-94. doi: 10.1016/j.ygyno.2010.05.022. Epub 2010 Jun 18. PMID: 20691333; PMCID: PMC3691953.

61. Chan CT, Lieu M, Sobey CG, Drummond GR, Vinh A. Diagnosing and Treating Hypertensive Disorders of Pregnancy? The Answer May Now Be Less BAFF-ling. Hypertension. 2017 Nov;70(5):884-886. doi: 10.1161/HYPERTENSIONAHA.117.09849. Epub 2017 Sep 18. PMID: 28923900.

62. Li XY, Duan HJ, Liu XY, Deng XL. Change of serum B-cell activating factor level in patients with positive antiphospholipid antibodies and previous adverse pregnancy outcomes and its significance. Chin Med J (Engl). 2020 Oct 5;133(19):2287-2294. doi: 10.1097/CM9.0000000000000948. PMID: 32842014; PMCID: PMC7546878.