RESEARCH PAPER

Sex as a Biological Determinant of the Warburg Effect: A Narrative Review of Hormonal, Chromosomal, and Epigenetic Mechanisms in Cancer

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ABSTRACT

Background and Rationale

Sex differences in cancer incidence, progression, and mortality are well documented across multiple cancer types, yet the molecular mechanisms driving these disparities remain incompletely characterised. A central but underexplored question is whether the Warburg effect the metabolic hallmark of cancer involving preferential aerobic glycolysis, operates differently in male and female tumours, and if so, why.

Objective

This narrative review examines the molecular basis of sexual dimorphism in the Warburg effect across multiple cancer types, integrating evidence from sex hormone signalling, sex chromosome-linked gene regulation, epigenetic mechanisms, and interactions with the tumour microenvironment.

Key Findings

Four interconnected biological layers underlie sex-biased cancer metabolism. First, androgen receptor signalling functions as a near-universal pro-glycolytic driver in male-predominant cancers — directly transactivating GLUT1, HK2, and LDHA while estrogen receptor signalling exerts a more context-dependent, dual regulatory role, alternating between glycolytic promotion and oxidative redirection depending on glucose availability. Second, sex chromosome gene dosage establishes a hardwired metabolic asymmetry: females benefit from biallelic expression of the X-linked tumour suppressor KDM6A, which acts as an epigenetic brake on glycolytic chromatin remodelling, while males carry Y-linked genes such as KDM5D that promote immune evasion and metastasis, compounded by the metabolic instability caused by age-associated loss of the Y chromosome. Third, sex-biased epigenetic regulation, operating through histone modifications, X-inactivation escape, and metabolite-driven chromatin feedback, directly controls glycolytic gene accessibility in a sex-dependent manner. Fourth, the tumour microenvironment reflects and amplifies these differences through sex-specific patterns of immune cell metabolism, cancer-associated fibroblast behaviour, and adipose tissue distribution. Cancer-type analyses across breast, prostate, bladder, glioma, hepatocellular carcinoma, colorectal, and lung cancers confirm that these mechanisms are tissue-specific and cannot be reduced to a single male-biased rule.

Conclusions and Implications

Sex is a fundamental determinant of the Warburg effect at every level of biological organisation. Incorporating sexual dimorphism into metabolic cancer research from preclinical modelling to biomarker development and clinical trial design is essential for advancing precision oncology. Therapeutic strategies targeting aerobic glycolysis must account for the distinct hormonal, chromosomal, and epigenetic contexts that govern metabolic reprogramming in male and female tumors.

Keywords: Warburg effect, sex differences, cancer metabolism, androgen receptor, estrogen receptor, sex chromosomes, KDM6A, epigenetic regulation, tumour microenvironment, aerobic glycolysis, sexual dimorphism.

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INTRODUCTION

Sexual dimorphism in cancer is one of the most intriguing phenomena in oncology that has consistently been observed without any mechanistic explanation. There is epidemiological evidence that not only is there a higher incidence of cancer in males over a wide age range and across a very broad spectrum of tumour types, there is also a higher likelihood of death (1,2)(3). For cancers in which there is a clear sex difference, the male to female ratio is between 1.26:1 (haematological malignancies) and 4.86:1 (cancers of the bladder, colon, skin, liver and brain) (1,2). In addition to incidence and mortality, the distribution of metastases, presence of prognostic biomarkers, and sensitivity to different treatment options, have also been described as differences between men and women in patients with various types of tumours (4–6). Despite all this evidence, sex differences were absent from cancer research, how drugs are developed and from the design of clinical trials. Such a discrepancy partly stems from the deficiencies in understanding the various biological pathways that lead to sexual dimorphism, which have been historically focused mainly on circulating sex hormones as key (and perhaps sole) regulators of cancer-related outcomes in men and women. A more complete schema is required, which can incorporate the entire array of molecular factors responsible for biological sex differences in malignancy. One key part of this bigger picture is the metabolic reprogramming of subsequent oncodifferentiation. This is coupled to subsequent oncodifferentiation or metabolic reprogramming, as a central part of this bigger picture. Malignant transformation is characterised by a dramatic shift in metabolism from oxidative phosphorylation to aerobic glycolysis (the so-called Warburg effect) (7). But it has become clear over the last few years that this metabolic rewiring does not happen evenly in both sexes. On the contrary, differences between males and females at the basic inductive level of different types of cells dramatically contribute to the degree, control and therapeutic outcomes of the Warburg effect in cancer (8). The molecular basis of these kinds of metabolic differences between the sexes, therefore, has great potential for the creation of more accurate and technology-based approaches in cancer therapy. In this review, the molecular mechanisms that explain why the Warburg effect exists as a 'sex difference' in cancer. In particular, this review examines the contributions of sex hormones, sex chromosome-linked genes, epigenetic regulation and major signalling pathways in defining sex specific cancer metabolism, their significance and translational relevance, and the importance of increasing this dimension of cancer biology into the limelight.

METHODOLOGY

Review Design:

This study was conducted as a narrative review. This design was chosen deliberately over a systematic review because the objective was to synthesise mechanistic molecular evidence across heterogeneous study types, including cell line experiments, animal models, omics datasets, and clinical observations, rather than to pool quantitative outcomes from homogeneous trials. A systematic review or meta-analysis would not be appropriate for this scope.

Literature Search

A structured search was conducted across PubMed/MEDLINE, Scopus, and Google Scholar without date restriction, with a final search update in April 2026. The following search term categories were used in combination:

- *Sex differences / sexual dimorphism / biological sex* combined with *cancer / oncology / malignancy*
- *Warburg effect / aerobic glycolysis / cancer metabolism* combined with *sex hormones / estrogen / androgen / testosterone / dihydrotestosterone*
- *Androgen receptor / estrogen receptor / GPER* combined with *glycolysis / metabolic reprogramming / HIF-1α / PI3K/AKT/mTOR*
- *X chromosome / Y chromosome / KDM6A / KDM5D / loss of Y chromosome* combined with *cancer / tumour suppressor / epigenetics*
- *Tumour microenvironment / cancer-associated fibroblasts / tumour-associated macrophages / adipose tissue* combined with *sex / glycolysis / lactate*
- Cancer-type-specific searches: *breast cancer, prostate cancer, bladder cancer, glioma, hepatocellular carcinoma, colorectal cancer, lung cancer* combined with *sex differences / Warburg / metabolism*

Inclusion Criteria

- Original research articles, preclinical studies, omics analyses (genomic, transcriptomic, proteomic, metabolomic), and prior narrative or systematic reviews addressing sex differences in cancer metabolism
- Studies reporting molecular mechanisms linking sex hormones, sex chromosomes, or epigenetic regulators to glycolytic reprogramming
- Cancer-type-specific studies reporting sex-stratified metabolic, genetic, or clinical outcomes

Exclusion Criteria

- Studies exclusively examining reproductive cancers without reference to broader metabolic mechanisms

- Articles focused solely on cancer epidemiology without molecular mechanistic data
- Non-peer-reviewed sources, conference abstracts without full-text data, and editorials without primary evidence

Source Selection and Data Extraction

Articles were screened by title and abstract for relevance. Full texts were retrieved for all candidate articles. Evidence was organized thematically across four mechanistic domains: (1) sex hormone signalling and glycolysis, (2) sex chromosome-linked gene regulation, (3) epigenetic control of the Warburg effect, and (4) tumour microenvironment interactions. Cancer-type-specific evidence was reviewed separately and integrated into the thematic synthesis.

Limitations Acknowledged

This review does not claim to provide exhaustive coverage of all published literature on sex differences in cancer. As a narrative review, study selection involved judgment-based prioritisation of mechanistic depth over bibliographic completeness. The majority of evidence reviewed derives from cell line and animal models, which constrains direct clinical translation. Sex-stratified clinical trial data remain sparse across most cancer types addressed**.**

The Warburg Effect: Background and Molecular Basis

Warburg effect is the term used for the metabolic phenomenon that cancer cells take up and make the maximum amount of lactic acid per amount of glucose they take up, despite the presence of sufficient amounts of oxygen and fully functional mitochondria. This apparently counterintuitive choice seemed at first to be simply a sign of underlying mitochondrial respiratory damage (9,10), and was first reported by Otto H. Warburg in the early 1920s. This understanding was then challenged and, in most cases, refuted since functional cytochrome and preserved oxidative phosphorylation (OXPHOS) function was shown in the overwhelming majority of tumour cells (11,12), indicating that the metabolic shift toward aerobic glycolysis is the result of active oncogenic reprogramming and not caused by impaired mitochondrial function. It is through a network of master regulatory signals that this reprogramming is controlled at the molecular level. A central axis of glycolytic flux resides in the PI3K/Akt/mTOR signalling axis, which is activated by a wide range of oncogenic signals such as growth factor signalling, hypoxia (reduced oxygen), oncogene activation (c-MYC and RAS), and loss of tumour suppressor activity (loss of PTEN, p53 or VHL) (13,14). Key to this "reprogrammed" state is the upregulation of a particular form of the enzyme pyruvate kinase, called PKM2. In contrast to its fully active forms, PKM2 is largely in a nearly inactive dimeric conformation, limiting the final step in glycolysis. The enzymatic bottleneck results in excess glycolytic intermediates that are temporised for anabolic biosynthetic pathways, such as nucleotide biosynthesis through the pentose phosphate pathway, lipid biosynthesis and production of non-essential amino acids, which help accommodate increased need for biomass synthesis and rapid proliferation characteristic of malignant cells (13,14). Together it is, therefore, more appropriately viewed not as a metabolic defect, but as a whole new programme which cancer cells choose to adopt to achieve a wide-ranging proliferative benefit not just in the accumulation of ATP, but rather their range of anabolic needs associated with tumour growth.

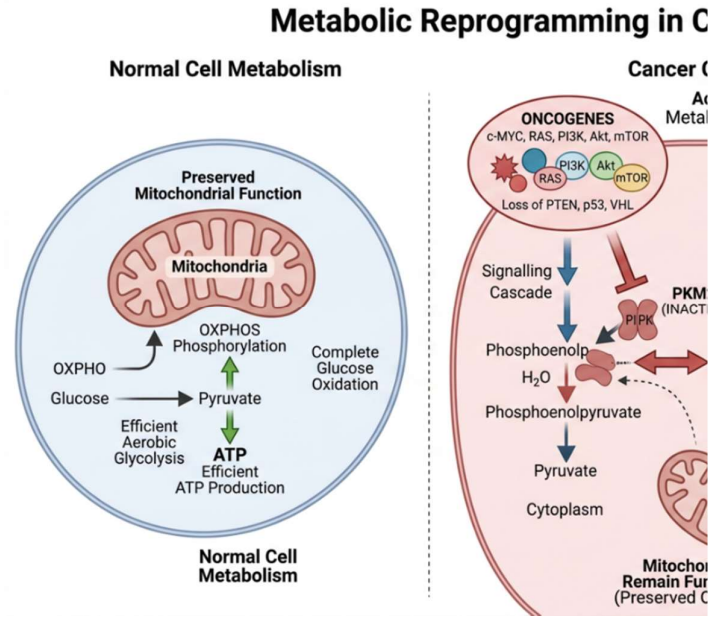


Figure 1: Metabolic Reprogramming in Cancer Cells: Shift from Oxidative Phosphorylation to Aerobic Glycolysis

4. SEX HORMONES AND THE WARBURG EFFECT

4.1 Estrogen and Glucose Metabolism in Cancer

The strong impact of estrogen, mainly 17β-estradiol (E2), on cellular metabolism occurs via both genomic and non-genomic mechanisms through the estrogen receptors (ERα and ERβ). ER α signalling favours a complex metabolic phenotype in hormone-responsive breast cancer: although estrogen can activate glucose uptake under certain conditions, it can also induce mitochondrial biogenesis and OXPHOS efficiency, thereby restricting the Warburg shift (15). Experiments in breast cancer cells (MCF-7) have shown that E2 treatment also causes the uptake of the GLUT1 and GLUT3 expression, which is involved in enhanced glucose uptake. At the same time, ERα activates the transcription of genes associated with TCA cycle enzymes, as well as induces mitochondrial oxidative activity, establishing a metabolic stress between glycolysis and OXPHOS. The relative levels of ERα

versus Erβ expression in estrogen-responsive cancers also seem to influence the net glycolytic production because Erβ has been linked to lower glycolysis and tumour suppression metabolic activity (15–18). This interaction is essential, with estrogen having the potential to regulate the pyruvate dehydrogenase activity between increasing the production of glycolysis in the presence of plentiful glucose or supporting oxidative phosphorylation when glucose is scarce (19). In terms of mechanism, E2 and ER can both prevent and induce several metabolic reprogramming responses according to glucose availability: stimulating glycolysis and inhibiting the TCA cycle upon glucose abundance in the extracellular environment and stimulating the TCA cycle and inhibiting glycolysis upon glucose deficiency in the extracellular environment in accordance with cell energy needs (20). Nevertheless, since the stimulation of the ER beta has been associated with augmented metabolic processes and control of mammosphere enlargement in HER2 + breast cancer stem cells, the detailed bioenergetic impacts of ER-PR crosstalk on metabolic processes should be examined in further studies (21). Even though the optimum role of estrogen in the body is to increase the glycolysis and oxidative phosphorylation to sustain the high energetic and biomass requirements of proliferating breast cancer cells, the bioenergetic mechanisms of the endocrine-resistant breast cancer cells to estrogen or anti-estrogens are still unclear (22,23). This metabolic complexity highlights why it is difficult to inhibit individual metabolic pathways since the mechanisms against therapeutic drugs can often entail metabolic restructuring e.g. the boosting of glycolysis in response to drug therapy (24,25). The hyper-estrogen states, which are the results of obesity or exposure to exogenous hormones in endometrial cancer, promote increased GLUT expression coupled with mTOR stimulation and aerobic glycolysis contributing to the obesity-cancer metabolic relationship, which disproportionately affects women (26). The non-genomic signalling induced by membrane bound estrogen receptor GPER (GPR30) via EGFR transactivation, cAMP/PKA and PI3K/AKT causes a stimulation of glycolytic flux without any nuclear transcription. The equilibrium ratio between the ER-nuclear and GPER-mediated signalling, therefore, defines the inclusive estrogen-glycolysis associations in a tumour-type-focused issue (27,28)

4.2 Role of Androgen Signalling in Sex-Biased Warburg Metabolism

Androgens, particularly testosterone and its more potent derivative dihydrotestosterone (DHT), signal primarily through the androgen receptor (AR), a nuclear transcription factor. In prostate cancer, androgen signalling is a well-established driver of glycolytic reprogramming; AR directly regulates transcription of GLUT1, LDHA, and several pentose phosphate pathway enzymes, enhancing glucose uptake and aerobic glycolysis (29). AR has been identified as a direct transcriptional activator of HK2 in prostate cancer cells, linking androgen signalling to the rate-limiting step of glycolysis (30). Furthermore, AR promotes the expression of fatty acid synthase (FASN) and the pentose phosphate pathway, redirecting glycolytic intermediates toward biosynthetic anabolism to support rapid cellular proliferation (29,31). Androgen deprivation therapy (ADT), a cornerstone of advanced prostate cancer management, partially reverses glycolytic reprogramming but may paradoxically trigger compensatory OXPHOS upregulation and metabolic plasticity contributing to castration resistance (31). Beyond prostate cancer, AR signalling has been documented to upregulate glycolysis in hepatocellular carcinoma (HCC), where male sex is a major risk factor and AR promotes glycolytic gene expression in concert with HIF-1α(32). In bladder cancer, AR mediates increased glucose consumption and lactate secretion, partially accounting for the higher incidence and worse prognosis seen in males (33). The widespread expression of AR in numerous cancer types and its ubiquitous pro-glycolytic transcriptional activity thus represent a major mechanism of sex-biased Warburg effect (34)

4.3 Transcriptional Mediators Linking Sex Hormones to the Warburg Phenotype

c-MYC, a pleiotropic oncogenic transcription factor and master regulator of glycolytic gene expression, represents a critical convergence point for both androgen and oestrogen signalling in cancer metabolism. Androgen receptor activation in prostate cancer sustains c-MYC transcriptional activity, and AR blockade consistently produces negative enrichment of MYC target gene signatures alongside downregulation of HK2 and LDHA, establishing AR–MYC as a functional axis governing the rate-limiting steps of glycolysis (35) In oestrogen receptor-positive breast cancer, ERα similarly engages c-MYC to promote glucose transporter expression and glycolytic flux, whereas triple-negative breast cancer, which lacks hormonal receptor input, frequently acquires MYC amplification as a compensatory mechanism to sustain equivalent glycolytic drive (36). The sex hormone–MYC axis, therefore, represents a mechanistic bridge through which hormonal context dictates the amplitude of the Warburg phenotype across cancer types (37).

The peroxisome proliferator-activated receptor (PPAR) family, particularly PPARγ and PPARα, constitutes another metabolic node subject to sex hormone modulation. PPARγ, which promotes lipogenic programmes and indirectly supports anabolic glycolysis by diverting glycolytic intermediates toward lipid biosynthesis, is co-activated by oestrogen signalling in hormone-

responsive cancers; ERα and PPARγ share transcriptional co-activators and jointly upregulate fatty acid synthase (FASN) expression, linking oestrogen to de novo lipogenesis (38). In contrast, androgen signalling in prostate cancer suppresses PPARα-mediated fatty acid oxidation under castration-sensitive conditions, shifting carbon flux toward glycolysis and lipid storage rather than oxidative catabolism, a balance that inverts during castration resistance (39). Sex-specific differences in PPAR isoform activity thus represent a hormonally regulated mechanism through which glycolytic intermediates are partitioned between energy production and biosynthetic anabolism (40)
The oestrogen-related receptor alpha (ERRα), an orphan nuclear receptor that structurally resembles ERα but responds to metabolic rather than hormonal ligands, functions as a further integrative node linking sex hormone signalling to mitochondrial and glycolytic reprogramming. ERRα transcriptionally activates genes encoding glycolytic enzymes, OXPHOS components, and TCA cycle intermediates, and its activity is repressed by the PGC1α–ERRα axis in prostate cancer, where androgen signalling positively feeds back through AMPK to induce PGC1α, creating a metabolic circuit with tumour-suppressive properties through MYC downregulation (40) Conversely, oestrogen-driven activation of ERα can competitively suppress ERRα-mediated mitochondrial biogenesis, biasing cancer cells toward aerobic glycolysis and away from oxidative metabolism(41). The interplay between ligand-activated sex hormone receptors and the orphan ERRα thus constitutes a finely balanced hormonal–metabolic rheostat whose dysregulation contributes to sex-biased Warburg reprogramming in cancer (37)

4.4 Sex Hormone Cross-Talk with Key Metabolic Signalling Nodes

Sex hormones are not passive bystanders in cancer metabolism they actively rewire the core signalling architecture that drives the Warburg effect. The Warburg effect is governed by the PI3K/Akt/mTOR axis acting in concert with transcription factors HIF-1α, p53, and c-Myc to regulate key glycolytic enzymes, including PKM2 and PDK1 (42). These nodes have receptors for sex hormones that converge directly on them. In estrogen receptor-positive (ER+) breast cancer, expression of PKM2 is found to be very high in Aromatase inhibitor-resistant (AI-R) cells compared to sensitive cells, activation of aerobic glycolysis is responsible for the resistance, and silencing of PKM2 reduces glycolytic activity and increases sensitivity towards AIs, revealing the direct link between epigenetic control and both ER+ and AI expression, along with ER+ and AI sensitivity (43). A mitochondria-localised ERα isoform, ERα-LBD, which lacks canonical activation function and DNA-binding domains, contributes to the development of fulvestrant resistance in breast cancer cells by supporting increased glycolysis, mitochondrial respiration and stem-like properties (44). This suggests that the rewiring that occurs under estrogen action precedes classic nuclear transcription and calls for the relevance of cytoplasmic and mitochondrial pools of ERalpha as direct mediators of the Warburg effect. The androgen receptor (AR) undergoes a unique metabolic pathway that is significant in prostate cancer. Androgens hijack the AMPK–PGC-1α pathway to enhance the metabolism of prostate cancer cells by up-regulating their rates of glycolysis, glucose oxidation, and fatty acid oxidation, which leads to higher ATP levels and the growth of mitochondria (45). Consequently, there is a reciprocal feedback loop: AMPK activation is shown to decrease AR transcriptional activity and nuclear localisation of AR, indicating that AR activation inhibits AR, and vice versa (46). Aerobic glycolysis is even more complicated in castration-resistant prostate cancer (CRPC): advanced CRPC, NEPC and double-negative prostate cancer all share the Warburg effect, indicating the aerobic glycolysis phenotype as the ultimate AMPK–mTOR metabolic endpoint, irrespective of its dependence on AR. Concurrently, under AR inhibition, there is a clear inhibitory relationship between AR and PI3K/Akt, which leads to the increased activity of the PI3K/Akt pathway in cells and their survival, thus accounting for the frequent exhausted efficacy of AR-targeted monotherapy (47). Taken together, sex hormone receptors ERα, ERβ, GPER, and AR do not simply regulate proliferation; they sit upstream of the PI3K/Akt/mTOR–HIF-1α–c-Myc–AMPK network that determines whether a tumour cell commits to aerobic glycolysis, and endocrine therapy resistance is, in large part, a story of metabolic escape through these same interconnected nodes.

5. SEX CHROMOSOME-LINKED REGULATION OF CANCER METABOLISM

Sex chromosome genes establish a fundamental metabolic dimorphism that precedes hormonal influence, beginning as early as fertilisation (48). This genetic baseline dictates how cells utilise nutrients, with males generally exhibiting a higher reliance on glycolytic pathways, a characteristic often amplified in the Warburg effect during oncogenesis (48–50). The Warburg effect, or aerobic glycolysis, involves the preferential use of glycolysis over oxidative phosphorylation even in the presence of oxygen, a shift that is more pronounced in male-derived tumour cells (50,51).

5.1 X- Linked Metabolic Genes and X-Inactivation Escape

The X chromosome contains several metabolic regulators and epigenetic modifiers that escape X-inactivation in females, providing a "double dose" of certain tumour suppressors such as *KDM6A*. This gene demethylates H3K27me3 to restrict tumour growth, a protective mechanism that is inherently

reduced in males who possess only a single X chromosome (49,50). Consequently, the lack of a second X chromosome copy in males may contribute to a more permissive environment for metabolic reprogramming toward a glycolytic phenotype (48,49). In cancers such as lower-grade gliomas, these sex-specific genetic profiles directly correlate with the intensity of the Warburg effect (50). Males often show significant overexpression of glycolytic genes, which is inversely tied to survival rates, highlighting how sex chromosome genes drive metabolic phenotypes that favor aggressive tumour progression (48)(50). Early developmental differences persist into adulthood, where males utilise carbohydrates more heavily, potentially priming them for the metabolic shifts seen in cancer (48) (52).

This dimorphism extends to the tumour microenvironment (TME), where sex-linked differences in immune response and nutrient availability further shape the metabolic shift toward aerobic glycolysis (48,49,53). The interplay between X-linked epigenetic modifiers and metabolic enzymes creates a distinct oncogenic landscape for each sex, where metabolites themselves can act as epigenetic cofactors to reinforce glycolytic phenotypes (48,54).

5.2. Y-Linked Genes and Tumour Progression

In many aspects, there are specific genes on the Y chromosome that directly promote tumour progression, via epigenetic regulation of the physical and immunological properties of the cell (48,49). In combination with male cancer, KDM5D is a Y-linked histone demethylase that plays an important role in malignancy (49,50). KDM5D alters the epigenetics, giving rise to a tumour niche which facilitates the growth and survival of the tumour (48,49). One of the most important epigenetic roles of KDM5D in moving genes is related to cell-cell adhesion and immune recognition genes (49,50). Turn off adhesion homing genes, tumour cells develop increased invasive/metastatic potential and lose adhesion. At the same time, suppression of genes involved in immunity enables the tumour to evade the host immune system which contributes greatly to the prognosis of the disease in males. The Y chromosome itself does not contain just KDM5D, but also has other genes that interact with metabolic and signalling pathways for supporting the quick proliferation of cells. These sex-linked factors act on the cancer and thus give general ‘sex' programming, which means male-derived cancers grow more aggressively (48,49). This genetic predisposition works outside of the influence of circulating hormones and could be a risk factor for certain aggressive cancer phenotypes (48).

5.3. Loss of Y Chromosome and Cancer Risk

A loss of the Y chromosome (LOY) in somatic cells is a previously documented aging phenomenon linked to the development of many non-reproductive cancers (48,49). LOY is caused by alterations in several specific regulatory genes, such as DDX3Y, EIF1AY, KDM5D, RPS4Y1, UTY and ZFY, that play a crucial role in the regulation of normal cellular homeostasis (49,50). These genes are missing, creating critical omissions in biological checks, which create larger metabolic instability and oncogenic potential (48,49).

These genes that are removed from the Y chromosome are especially important for cell cycle regulation (48). Many genes (such as UTY and ZFY) participate in the regulation of the precision and timing of cell division, and their absence leads to the disruption of cell cycle control, permitting cells to multiply in an uncontrolled way, as in cancer (48,49). This dysregulation frequently accompanies a switch to an increased glycolytic flux, with the loss of regulatory control in the maintenance of this oxidative metabolism (48,50).

Additionally, LOY is highly associated with a decrease in the body's ability to remove precancerous cells (48). Depletion of genes like EIF1AY and DDX3Y is expected to affect protein synthesis and RNA helicase activity vital for strong cellular stress responses (49,50). The more these protective mechanisms are compromised, the more the potential for malignant transformation exists, especially in tissues with a high metabolic load that might be stimulated to Malignant Hyperplasia, favourable sites (48,49).

5.4 Comparative Analysis of Cancer Mechanisms in Males and Females

The comparative landscape of cancer biology reveals that sex is a primary determinant of metabolic and genetic behaviour in tumors described in Table 1. Males generally face a higher incidence and more aggressive progression in many non-reproductive cancers, a trend driven by the inherent glycolytic bias of XY cells and the absence of protective X-linked suppressors like *KDM6A*. The presence of Y-linked genes further exacerbates this by promoting immune evasion and metastasis through epigenetic remodelling (48,49).

Females, conversely, benefit from a more balanced metabolic profile and the protective effects of estrogen in specific contexts, such as the browning of white adipose tissue and the partitioning of fatty acids toward ketone bodies (55). However, this advantage is context-dependent; in certain cancers, estrogen can promote the Warburg effect to enhance tumour survival (49,50). The "double dose" of X-linked genes that escape inactivation provides an additional layer of tumour suppression that is largely absent in males (48,49).

Understanding these dimorphic mechanisms is essential for the development of sex-stratified therapies (48,56). While males may require interventions that specifically target glycolytic enzymes or restore the functions lost through LOY,

female patients might benefit more from therapies that modulate estrogen signalling or target the unique vulnerabilities of their more oxidative metabolic state (48,49,53).

Metric	Male (XY)	Female (XX)	References
Metabolic Bias	Glycolytic / Warburg Effect dominance	Oxidative / Balanced metabolism	(48,50)
Key Genetic Driver	Y-linked *KDM5D* (Repression of adhesion)	X-linked *KDM6A* (Tumour suppression)	(48–50)
Hormonal Influence	Testosterone-driven signaling	Estrogen-modulated (GPER/HIF1A)	(49,53,55)
Cancer Risk Factor	Loss of Y Chromosome (LOY)	X-inactivation escape / Double Dose	(48,49)
Survival Outcome	Generally lower in non-reproductive cancers	Generally higher due to protective factors	(48,53,55)

6. Sex-Biased Epigenetic Regulation of the Warburg Effect

The epigenetic landscape is fundamentally different between males and females and directly affects the reprogramming of cancer cells' metabolism. The following review from 2024 helped delineate sex differences in cancer as being epigenetic in nature, based on the imprinting, X complement, X inactivation and genes that escape from X inactivation (57). One key mechanism for this imbalance is the 'escape from X inactivation tumour suppressor' (EXITS) genes. Females are biallelic for KDM6A (UTX) (X chromosome, histone H3K27 demethylase), and this has been shown to act as a brake on glycolytic reprogramming, especially in bladder cancer (57–59). In males, loss of the hemizygous copy of KDM6A removes this brake, opening up chromatin at metabolic gene loci and thus predisposing a more aggressive Warburg phenotype. Glioma evidence supports this: X-linked glycolytic genes that drive tumour growth, such as phosphoglycerate kinase (PGK), have been linked to sex differences in tumour growth, which start from embryogenesis (60). This ends up in a metabolic bias that is encoded on the chromosomes, and this metabolic predisposition is epigenetically transmitted to males, irrespective of the cancer type. This bias is further accentuated by sex hormones, that are upstream regulators of the epigenetic machinery involved in the regulation of glycolysis. Pyruvate dehydrogenase (PDH) activity during glucose replete conditions is suppressed by estrogen (ER) in breast cancer via ERα and ERβ signalling pathways, possibly through AMPK pathways and inhibiting the entry of pyruvate into the TCA cycle. This effect is exacerbated under hypoxia, where ERα-associated glycolysis is co-regulated by HIF-1α, and which further influences the molecular landscape of the chromatin remodelling machinery as a result of altering the activity of other epigenetic modifying enzymes, such as histone demethylases, including JMJD2B (61). From the male perspective, the risk for cancer and degree of aggressiveness in metabolic phenotypes is increased by androgens (62). The transcription of glycolytic genes via HIF-1α further promotes ATP-dependent drug efflux and downregulates drug import, particularly in glycolysis-heavy aggressive breast cancer types (63). Other hormone / epigenetic links add detail to this. The miR-let-7a/PKM2/LDHA regulatory axis regulated by ER status, directly regulates glycolytic flux, and PKM2 and LDHA are epigenetic-metabolic effectors that are directly affected by ER status (64). In addition, the expression of both LDHA and LDHB is modulated by binding of the orphan nuclear receptor known as estrogen-related receptor alpha (ERRα) to promoter regions of both genes and direct regulation of the activity of both lactate dehydrogenases by ERRα is evident in thyroid tumours, and this interaction forms one example of the epigenetic effects exerted by sex hormones on expression of glycolytic enzyme genes, far from limited to reproductive cancers (65). Importantly, a one-way relationship is not the only one. Aerobic glycolysis directly impacts the chromatin structure via the synthesis and consumption of key metabolic intermediates, such as acetylCoA, alpha-ketoglutarate and NAD^+; all of which are substrates or cofactors for histone acetyltransferases and demethylases, which in turn promote epigenetic reprogramming (66). This loop was further reiterated in a paper published in 2024 in Annual Reviews, which concluded that the metabolic and genetic mechanisms that trigger the Warburg effect are themselves subject to feedback into the regulation of the epigenetic reprogramming and dedifferentiation mechanisms, which are sex-specific (67). These converging layers also shape immunity: sex-biased epigenetic differences in gene expression, cellular senescence, and metabolism affect anti-tumour immune responses, with incomplete X inactivation potentially enhancing immune activity in females (68). While androgens broadly associate with higher cancer risk and mortality in males, estrogen appears protective in several cancer contexts. This hormone-epigenome-metabolism axis remains incompletely characterised for most non-reproductive cancers. Taken together, sex-biased epigenetic regulation of the Warburg effect is a multi-layered problem, chromosomal dosage, hormone-driven chromatin remodelling, and metabolite-dependent feedback each operating in parallel, with each layer representing a distinct and largely underexplored therapeutic window.

7. Sexual Dimorphism in The Tumor Microenvironment and Metabolic Interactions

7.1 Immune Cell Metabolism and Sex Differences

The tumour microenvironment (TME) is a complex ecosystem of cancer cells, immune cells, stromal cells, and extracellular matrix components, all engaged in extensive metabolic cross-talk. In addition to cancer cells, the TME encompasses a wide range of stromal, innate, and adaptive immune cells whose cooperation and competition support

tumour proliferation, progression, metastasis, and immune evasion, with cellular heterogeneity driving metabolic heterogeneity depending on cell states, location, and nutrient availability (69). Sex differences in immune cell composition, activity, and metabolism profoundly influence this metabolic milieu. Activated immune cells can switch to glycolysis to meet increased energy demands; however, malignant cells outcompete immune cells for glucose and oxygen uptake, and the increased production of lactate creates a hypoxic and acidotic TME that weakens immune cell activation and polarizes cellular responses towards immune anergy (70).

Insufficient glucose in the TME impairs T cell anti-tumor activity, and low-glycemic tumour microenvironments have been found to decrease T cell viability, associated with low expression of EZH2 and decreased glycolytic function (71), The more vigorous immune responses characteristic of females may provide greater resistance to these immunosuppressive metabolic conditions, contributing to relatively better outcomes in female cancer patients. Conversely, the male-biased Warburg effect generates a more lactate-rich, immunosuppressive TME, a pattern directly demonstrated in melanoma, where higher LDH-A expression in male melanoma cells leads to significantly greater lactate secretion, enrichment of pro-tumoral regulatory T cells (Tregs), and a concurrent decrease in the number and cytotoxic activity of anti-tumour $CD8^+$ T cells (72).

Tumour-associated macrophages (TAMs) also show sex-biased metabolic phenotypes. Estrogen has been shown to shift macrophage polarization toward the M1 anti-tumor phenotype (73). By contrast, androgen receptor signaling enhances macrophage-driven promotion of cancer progression in breast cancer, and in prostate cancer, androgen stimulation mediates metastasis through STAT3 activation and upregulation of inflammatory cytokines including TREM-1, CCL2, and CXCL8 (74). These sex hormone effects on TAM metabolic phenotype further contribute to a sexually dimorphic cancer metabolic microenvironment.

7.2 Cancer-Associated Fibroblasts and Metabolic Symbiosis

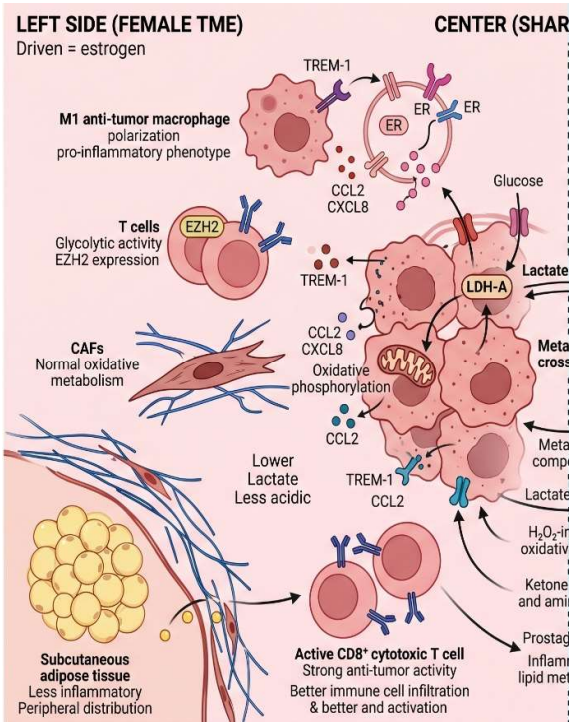
Cancer-associated fibroblasts (CAFs) are crucial components of the TME that undergo significant phenotypic changes and metabolic reprogramming, profoundly impacting tumor growth through bidirectional crosstalk with tumour cells, promoting cancer cell survival, proliferation, invasion, and immune evasion (75). A subset of CAFs undergoes the 'reverse Warburg effect,' in which they perform aerobic glycolysis and secrete lactate and pyruvate that are subsequently oxidised by cancer cells. In this dual-chamber model, cancer cells secrete hydrogen peroxide into the TME to induce oxidative stress in neighbouring stromal cells, causing CAFs to undergo aerobic glycolysis and produce high-energy fuels such as pyruvate and ketone bodies that power cancer cell proliferation (76).

In breast cancer, HIF-1 has been identified as the key molecular driver of the reverse Warburg effect in CAFs, and targeting HIF-1 as part of a TME-centred therapeutic strategy may prove beneficial by addressing this metabolic reprogramming (77). This HIF-1-driven mechanism is likely modulated by sex, as estrogen exposure in breast stroma directly alters fibroblast metabolic phenotype and secretory profile, while in prostate cancer, androgen signalling in CAFs promotes secretion of metabolic substrates including ketone bodies and amino acids that fuel androgen-resistant cancer cell metabolism creating a sex-specific metabolic symbiosis between stroma and tumour cells.

7.3 Adipose Tissue and Sex-Specific Metabolic Fuel Supply

Adipose tissue is an increasingly recognised metabolically active component of the TME, particularly in breast, ovarian, and prostate cancers. Visceral adipose tissue (VAT) has been linked to increased amounts of tumour-promoting metabolites, including free arachidonic acid, phospholipases, prostaglandin synthesis-related enzymes, and inflammation-related lipid metabolites compared to subcutaneous adipose tissue. VAT adipocytes are also lipolytically more active and contribute more to plasma free fatty acid levels, particularly in obese individuals, with worse clinical outcomes observed in patients with colon, oesophageal, and renal cancers (78).

The distinct fat distribution between sexes directly shapes this dynamic. Men possess nearly 30% more visceral fat than women, and visceral fat adipocytes are generally larger, hyperlipolytic, insulin-resistant, and molecularly distinct from subcutaneous adipocytes, with venous blood from VAT circulating directly to the liver via the portal vein, amplifying its metabolic impact on tumour-adjacent tissues. Visceral adiposity in males nurtures a pro-carcinogenic microenvironment through the release of pro-inflammatory adipokines, increased free fatty acids and glycerol, promoting lipid peroxidation, and myeloid-derived suppressor cell infiltration, collectively increasing cancer initiation risk (79). In contrast, females carry proportionally greater subcutaneous fat, which has a less pro-inflammatory lipid profile and weaker direct connection to visceral tumor microenvironments. Sex steroid hormones modulate visceral versus subcutaneous lipid accumulation, with males and postmenopausal women more prone to abdominal obesity and its associated pro-inflammatory lipid signatures (80). These sex-specific differences in adipose distribution and function thus contribute a distinct, hormonally regulated metabolic fuel supply that shapes tumour growth and immune function in a sex-dependent manner.



Sex-Specific Metabolic Reprogramming in the Tumor Microenvironment

8. SEX- DIMORPHIC WARBURG EFFECT IN SPECIFIC CANCER TYPES

8.1 Breast Cancer

Breast cancer provides some of the clearest evidence for sex hormone-driven metabolic dimorphism. Estrogen receptor status directly determines glycolytic intensity: estrogen receptor-negative (ER−) breast cancers show elevated glycolytic and glycogenolytic intermediates consistent with an enhanced Warburg effect compared to ER+ tumours, alongside higher levels of oncometabolite 2-hydroxyglutarate and the immunomodulatory tryptophan metabolite kynurenine (81) This metabolic divergence reflects hormonal control of glycolytic programming: breast cancer tissue shows a simultaneous increase in AMPK protein expression alongside glucose utilisation, favouring glycolysis and the pentose phosphate pathway, with specific features of glycolysis and glycogen metabolism differing between normal-weight and overweight/obese premenopausal women (82). Estrogen itself exerts a dual regulatory role depending on glucose availability stimulating glycolysis when glucose is abundant and redirecting metabolism toward the TCA cycle when glucose is scarce, creating a hormonally gated metabolic switch that is absent in male-pattern cancers driven by androgen receptor signalling. Furthermore, estrogen-related receptors (ERRs) act as co-factors of HIF-1α and enhance HIF-dependent transcription of glycolytic genes under hypoxia, while also stimulating glycolysis under normoxia (83) placing ERRs as a direct bridge between sex hormone biology and the Warburg phenotype in breast tissue.

8.2 Prostate Cancer

Prostate cancer occupies a biologically unique metabolic position among male-predominant cancers. Unlike most tumours, primary prostate cancer does not initially exhibit the Warburg effect. Malignant transformation involves a conversion from energy-inefficient glycolytic secretory epithelial cells to energy-efficient oxidative cancer cells, the reverse of the metabolic switch seen in most other cancer types (84). However, this changes with disease progression. The androgen receptor transcriptionally regulates the mitochondrial pyruvate carrier, linking cytosolic with mitochondrial metabolism; elevated expression of this carrier in primary prostate cancer is associated with poor clinical outcomes, while reduced LDHB expression through promoter methylation further drives the Warburg shift in advanced disease (85). Androgen deprivation therapy partially reverses this glycolytic reprogramming but paradoxically triggers compensatory oxidative phosphorylation, contributing to castration resistance, demonstrating that the AR-Warburg axis is not static but dynamically reconfigured under therapeutic pressure. Expression of lipid metabolism enzymes, including ATP-lyase, CPT-1a, SCD, SREBP, ACC-1, and FAS are associated with androgen receptor activity in prostate cancer, supporting the evidence that manipulation of lipid metabolism could serve to counter prostate cancer progression (86)

8.3 Bladder Cancer

Bladder cancer is among the most sex-biased of all non-reproductive cancers. Bladder cancer incidence is approximately four times higher in males than in females, and in experimental models of bladder carcinogenesis, male mice are over 13 times more likely than female mice to develop the disease (87). This disparity is mechanistically linked to androgen receptor activity and its downstream metabolic consequences. Distinct characteristics of the male and female immune systems, differences in circulating hormone levels and hormone receptor expression, and different genetic and epigenetic alterations are major biological factors contributing to disparate incidence rates and outcomes for male and female bladder cancer patients.[8] Specifically, androgen receptor expression in bladder cancer cells is associated with chemoresistance, and in AR-positive bladder cancer cells excess androgen decreases sensitivity to cisplatin, whereas AR-negative cells are significantly more sensitive (88) indicating that androgen-driven metabolic reprogramming toward glycolysis directly shapes therapy resistance in this sex-biased cancer. The X-linked tumour suppressor KDM6A, which escapes X inactivation in females and breaks glycolytic chromatin remodelling, is hemizygously lost in

males, further amplifying the male-biased Warburg phenotype in bladder cancer.

8.4 Glioma and Glioblastoma

Brain tumours provide direct transcriptomic and metabolomic evidence for sex-dimorphic glycolysis. Using lower-grade glioma transcriptome data from The Cancer Genome Atlas (TCGA), male-specific decreased survival resulting from glycolytic gene overexpression was identified, with patients in the high-glycolytic group showing significant differences in key genomic alterations, including 1p/19q codeletion, CIC, EGFR, NF1, PTEN, FUBP1, and IDH mutations, compared to the low-glycolytic group (89). Critically, glycolytic stratification predicted poor prognosis in males independently of grade, histology, and mutation status but not in females, confirming that glycolytic gene expression is a male-specific survival determinant in glioma. At the protein level, integrative proteomic and phosphoproteomic characterisation of glioblastoma uncovered sex-specific protein abundance and phosphorylation activities, including EGFR activation in males and SPP1 hyperphosphorylation in female patients, with female GBM patients showing higher MGMT promoter methylation and more favourable clinical outcomes (90). Metabolically, male and female glioblastoma differ not only in glycolysis but in broader nutrient utilization males exhibit greater glutamine uptake, pointing to a male-biased reliance on amino acid catabolism to fuel biosynthesis alongside aerobic glycolysis.

8.5 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is among the most sex-biased cancers globally. HCC incidence is 2 to 3 times higher in men than in women, depending on region, and the liver is a sexually dysmorphic organ that is extremely susceptible to interactions with estrogens and androgens, with sex hormones acting to modulate HCC risk, aggressiveness, and response to treatment (91). At the molecular level, sex-stratified differential expression analysis of HCC tumours revealed that while both sexes show activation of apoptosis and cell cycle pathways, males show enrichment of PI3K, PI3K/AKT, FGFR, EGFR, and IL-2 signalling pathways, while females show PPAR pathway enrichment (92) directly implicating the PI3K/AKT/mTOR axis, a master driver of glycolytic reprogramming, as a male-dominant oncogenic mechanism in liver cancer. Additionally, elevated HCC risk from glucose impairment was observed in men only, with sex-specific associations between metabolic factors and HCC risk, suggesting that glycemic dysregulation is a male-predominant driver of hepatocarcinogenesis (93)

8.6 Colorectal Cancer

Colorectal cancer (CRC) demonstrates that sex-dimorphic metabolism varies not only by cancer type but by tumor location within the same organ. Metabolomics analysis of patient colon tumours revealed sex-specific metabolic sub phenotypes dependent on anatomic location, with tumors from women with right-sided colon cancer showing a nutrient-deplete phenotype with enhanced energy production to fuel asparagine synthesis and amino acid uptake, while metabolites in the glycolysis pathway, pentose phosphate pathway, carnitine shuttle, and methionine metabolism all showed sex-related differences (94). This is consistent with the broader protective role of estrogen in CRC: estrogens appear to confer protection against CRC progression whereas androgens have been linked to increased risk, and estrogen receptor beta (ERβ) can attenuate CRC development through its effects on colon crypt proliferation and macrophage infiltration (95). The circadian system may also contribute, with polymorphisms in CLOCK sequence and miRNA-regulated clock-genes associated with longer overall survival in females with metastatic CRC compared to males (96).

8.7 Lung Cancer

Lung cancer presents a more complex and counterintuitive pattern of sex-dimorphic metabolism. Gene set enrichment analysis in lung adenocarcinoma (LUAD) discovered gene sets annotated as androgen response, glycolysis, Myc targets, fatty acid metabolism, and unfolded protein response as being significantly enriched in females over males (97). a finding that challenges the assumption that the Warburg effect is uniformly male-biased across all cancer types. This may reflect the biology of never-smoker lung cancer, which disproportionately affects women: approximately 15% of lung cancer develops in never-smoking women compared to 5–10% in men in North America (98). Female-specific EGFR mutation-positive lung cancers, the dominant molecular subtype in never-smoker women, may engage distinct glycolytic programs compared to tobacco-driven, male-predominant squamous cell carcinomas. This underscores that sex-dimorphic Warburg biology is tissue-specific and context-dependent, and cannot be reduced to a simple male-biased rule across all cancer types.

9. THERAPEUTIC IMPLICATIONS OF SEXUAL DIMORPHISM IN THE WARBURG EFFECT

9.1 Sex- Stratified Metabolic Targeting

The recognition that the Warburg effect is sexually dimorphic has profound implications for anti-cancer metabolic therapies. Agents targeting glycolytic enzymes, including 2-deoxy-D-glucose (2-DG), LDHA inhibitors, and HK2 inhibitors, may exhibit differential efficacy in male versus female patients depending on the degree of glycolytic dependence.[137] Preclinical studies suggest that male-derived cancer cell lines and xenografts are generally more sensitive to glycolytic blockade than female-derived models, consistent with a higher

degree of glycolytic dependence in male tumours (99). PFKFB3 inhibitors, which lower F2,6BP levels and reduce PFK1 activity, represent another class of glycolytic targeting agents with potential sex-specific efficacy (100). Similarly, MCT inhibitors targeting lactate transport may be more effective in androgen-driven male cancers with high lactate secretion (101). Clinical trials of metabolic agents should stratify patients by sex and analyse sex as a biological variable to identify differential responses (102).

9.2 HIF-1α as a Sex-Informed Therapeutic Target

HIF-1α inhibitors have been pursued as anti-cancer agents given the central role of HIF-1α in driving the Warburg effect (103). Given that HIF-1α regulation differs between sexes—with estrogen having complex activating and inhibitory interactions with HIF-1α and androgens generally stabilising HIF-1α sex may be a critical determinant of HIF-1α inhibitor efficacy. Developing sex-stratified strategies for HIF-1α targeting, possibly in combination with anti-hormonal agents, represents a rational therapeutic approach (104).

9.3 Combination of Hormone Therapy with Metabolic Interventions

The mechanistic links between sex hormone signalling and metabolic reprogramming suggest that combining hormone-directed therapies with metabolic inhibitors could yield synergistic effects (105) Preclinical studies in prostate cancer have demonstrated that androgen deprivation sensitises CRPC cells to glycolytic inhibitors, as ADT-mediated AR suppression partially restores OXPHOS dependence. In breast cancer, combining anti-estrogen therapy with mTOR inhibitors, which also suppress glycolysis, has shown clinical benefit in luminal cancers, though metabolic mechanisms have not been fully explored in the context of sex biology (106,107)

9.4 Metabolic Imaging and Biomarkers

18F-FDG PET imaging, which measures glucose uptake, is widely used in cancer staging and response assessment. Sex-specific differences in FDG avidity, related to dimorphic glycolytic activity, can affect the sensitivity and specificity of PET imaging in different cancer types (108). Sex should be considered as a variable when interpreting PET metabolic data and establishing standardised uptake value (SUV) thresholds (109). Emerging metabolic biomarkers, including circulating lactate, pyruvate, and metabolomics profiles, show sex-specific patterns that could serve as non-invasive measures of the sex-dimorphic Warburg effect (110).

10. Discussion

This narrative review aims to collate emerging evidence that sexual dimorphism is a fundamental, mechanistically sound determinant of the Warburg effect in cancer, through four mutually overlapping layers of study: sex hormones signaling, sex chromosome-related gene dosage, epigenetic modulation, and metabolism of tumour microenvironment. Combined, these results strongly support the notion that sex is not simply a demographic variable but a genuine biological factor that impacts the amplitude, control and therapeutic implications of aerobic glycolysis in most cancers.

Perhaps the most-documented aspect of this dimorphism occurs at the level of glycolytic reprogramming, a process for which sex hormones play an important part but which has not been fully understood. AR directly transactivates GLUT1, HK2 and LDHA in prostate cancer (29, 30), it enhances glycolytic flux in hepatocellular carcinoma (HCC) in a cooperative fashion with HIF-1α (32), and it promotes glycolytic flux and lactate production in human bladder cancer cells (33). More than anything else, the AR–glycolysis axis is a dynamic process. While partially reversing glycolytic reprogramming, A.D.T. also exerts compensatory oxidative phosphorylation and metabolic flexibility that lead to castration resistance (31, 45), and certain metabolism data indicate that metabolism of cells or tumors can be suppressed for a short period by using an AR-targeted therapy alone, which is not always enough and that frequently induces metabolism back into glycolytic mode (47), given the reciprocal binding inhibition between AR and the PI3K/Akt pathway. Overall, these observations indicate that therapeutic interventions for male predominant cancer should consider the feedback–regulatory dynamic between the AR and the metabolic axis, instead of the assumption that there exists a linear impact of hormonal suppression on metabolic quiescence.

The progesterone-dependent and estrogen-activated signaling of metabolism is also highly complex and fundamentally distinct. The dual role of ERα is to promote glycolysis during glucose sufficiency, but direct carbon flux to the TCA cycle during glucose deprivation (20), suggesting an evolutionarily conserved metabolic flexibility that apparently has no androgen-driven equivalent. In the context of cancer, it is these hormones that mediate the Warburg switch, and indeed they have been demonstrated to be physiologically relevant in breast cancer as ER-negative tumours always have higher glycolytic activity compared to ER-positive tumours, along with increased oncometabolite production (81). It then becomes even more complicated because there is also a non-genomic contribution of membrane-bound GPER which involves transactivation of EGFR and activation of PI3K/AKT signaling bestowed by the binding of the anti-hormones (27, 28), bypassing the canonical anti-hormonal strategies. This increased role for the ERα isoform in a metabolically powerful manner (both in promoting increased glycolysis and

resistance to fulvestrant, (44)) only shares the ER's metabolic effects with nucleus binding ERs, a role not targeted by existing endocrine therapies.

The transcriptional mediators linking sex hormones to the Warburg phenotype — c-MYC, the PPAR family, and ERRα — reveal a network architecture in which hormonal context determines the amplitude, rather than the presence or absence, of glycolytic reprogramming. The AR–MYC functional axis governing HK2 and LDHA in prostate cancer (35) and the analogous ERα–MYC engagement in ER-positive breast cancer (36) suggest that c-MYC functions as a shared convergence node through which profoundly different hormonal inputs produce convergent metabolic outputs. Therapeutic implications follow directly: because c-MYC integrates signals from both AR and ERα, MYC-targeted interventions might theoretically address glycolytic reprogramming in a sex-agnostic manner, whereas upstream hormone receptor-directed agents will inevitably produce sex-divergent metabolic effects depending on whether AR or ERα is the dominant upstream driver.

The sex chromosome-linked layer of metabolic dimorphism is arguably the most underappreciated, yet in some respects the most fundamental, because it operates independently of and prior to hormonal influence, beginning from fertilisation (48). The haploinsufficiency of KDM6A in males — a consequence of the single X chromosome and absent in females, who benefit from biallelic expression via X-inactivation escape — removes a key epigenetic brake on glycolytic chromatin remodelling, a mechanism that has been most rigorously demonstrated in bladder cancer (57–59) but likely contributes to the male-biased Warburg phenotype across multiple cancer types. The glioma data from TCGA are particularly compelling: glycolytic gene overexpression predicted poor survival in male patients independently of grade, histology, and mutation status, but showed no equivalent prognostic signal in females (89), suggesting that the chromosomally encoded glycolytic bias has independent clinical relevance beyond what can be explained by hormonal differences alone. Conversely, Y-linked genes, particularly KDM5D, contribute to the male-biased oncogenic landscape through epigenetic repression of cell-cell adhesion and immune recognition genes (49, 50), while loss of Y chromosome in somatic cells — an age-associated phenomenon affecting DDX3Y, EIF1AY, KDM5D, RPS4Y1, UTY, and ZFY — disrupts cell cycle checkpoints and amplifies glycolytic flux by removing regulatory oversight of oxidative metabolism (48, 49). These chromosomal mechanisms constitute a hardwired metabolic asymmetry that precedes and constrains the hormonal effects described above.

The epigenetic regulation of the Warburg effect adds a further dimension by providing the mechanistic bridge through which sex chromosomes and sex hormones converge on chromatin to modulate glycolytic gene expression. The bidirectional relationship between aerobic glycolysis and epigenetic state — in which glycolytic intermediates including acetyl-CoA, alpha-ketoglutarate, and NAD^+ serve as substrates and cofactors for histone-modifying enzymes, allowing metabolic flux to directly reconfigure chromatin (66, 67) — creates a self-reinforcing loop that may help explain why male-biased glycolytic phenotypes, once established, are so difficult to reverse therapeutically. The JMJD2B histone demethylase axis co-regulated by ERα and HIF-1α under hypoxia (61) exemplifies this principle: estrogen signalling does not merely regulate transcription factor binding but actively remodels the epigenetic landscape in a manner that determines which metabolic gene programmes are accessible, making epigenetic state a sex-dependent variable in cancer metabolism. Equally noteworthy is the miR-let-7a/PKM2/LDHA axis modulated by ER status (64), which illustrates that post-transcriptional regulation of glycolytic enzymes is itself hormonally gated, adding another layer of sex-specific control below the level of transcription.

The tumour microenvironment emerges from this review as a critical site of sex-dimorphic metabolic interaction that is frequently overlooked in reductive cell-autonomous analyses of cancer metabolism. The male-biased Warburg effect generates a more lactate-rich, immunosuppressive microenvironment, directly demonstrated in melanoma where higher LDH-A expression in male tumour cells increases lactate secretion, enriches pro-tumoral regulatory T cells, and depletes cytotoxic $CD8^+$ T cells (72). This immunometabolic axis creates a second mechanism through which glycolytic bias translates into poorer male survival outcomes beyond the direct tumour cell-intrinsic effects of aerobic glycolysis. The sex-biased polarisation of tumour-associated macrophages — with estrogen favouring anti-tumoral M1 phenotypes (73) and androgen receptor signalling in macrophages promoting cancer progression via STAT3 and inflammatory cytokine pathways (74) — suggests that the immune component of the TME is itself a hormonally regulated contributor to sex-dimorphic cancer outcomes. The reverse Warburg effect in cancer-associated fibroblasts, whereby HIF-1-driven CAF glycolysis provides metabolic substrates for cancer cell proliferation (76, 77), is further modulated by sex, as estrogen alters breast stromal fibroblast metabolism and androgen signalling in prostate cancer CAFs promotes secretion of ketone bodies and amino acids that fuel castration-resistant cell

metabolism. Finally, the greater visceral adiposity of males, with its higher lipolytic activity, pro-inflammatory adipokine secretion, and direct hepatic portal connection (79), provides a hormonally regulated, sex-specific metabolic fuel supply that shapes tumour growth in a manner that subcutaneous fat distribution in females does not replicate.

Cancer-type-specific analyses reinforce both the breadth and the tissue-specificity of these mechanisms. Prostate cancer's atypical metabolic trajectory — initially exhibiting a reversal of the Warburg phenotype, with malignant transformation involving a shift toward oxidative metabolism before reverting to aerobic glycolysis in advanced and castration-resistant disease (84, 85) — illustrates that the AR–Warburg axis is dynamically reconfigured under therapeutic pressure and cannot be treated as a static target. Bladder cancer's four-fold male excess and 13-fold difference in experimental carcinogenesis models (87) represent perhaps the most extreme example of sex-biased cancer incidence, mechanistically anchored in the coincidence of AR-driven glycolytic reprogramming and hemizygous KDM6A loss. Glioma and hepatocellular carcinoma provide further evidence that PI3K/AKT/mTOR-driven glycolytic reprogramming is a male-dominant oncogenic mechanism (89, 92, 93), while lung adenocarcinoma's female-enriched glycolytic gene expression (97) — likely reflecting the distinct biology of EGFR-mutant, never-smoker lung cancer — illustrates that the assumption of uniform male-biased Warburg dominance does not hold across all tissue contexts. Colorectal cancer's sex-dimorphic metabolic subphenotypes varying by tumour location (94), and the protective role of ERβ in attenuating CRC development (95), further demonstrate that sex-biology effects on the Warburg phenotype are anatomically and molecularly contextualised rather than global.

Several important limitations of the current evidence base deserve acknowledgement. First, the majority of mechanistic studies reviewed here were conducted in cell lines and preclinical models that may not fully recapitulate the hormonal milieu and chromosomal complexity of human tumours in vivo. Second, many studies have not systematically co-varied sex, hormone receptor status, and epigenetic context, making it difficult to disentangle the independent and interactive contributions of each layer. Third, the therapeutic implications drawn from preclinical observations — including the differential sensitivity of male- and female-derived cancer models to glycolytic blockade (99), MCT inhibitors (101), and HIF-1α inhibitors (103, 104) — require prospective validation in sex-stratified clinical trials before they can be translated into practice. Fourth, the non-reproductive cancer contexts in which sex-dimorphic metabolic effects are most prominent (lung, bladder, glioma, liver, colorectal) remain understudied relative to the breast and prostate cancer literature, and the hormone-epigenome-metabolism axis is incompletely characterised for most of these cancer types. Fifth, the interaction between biological sex and gender-associated behavioural factors — including differential exposure to metabolic risk factors such as obesity and physical inactivity — has not been fully disentangled from intrinsic biological mechanisms in epidemiological data.

Future research priorities emerging from this synthesis include systematic sex-stratified multi-omics profiling of glycolytic pathway activity across cancer types, the development of sex-informed metabolic biomarker frameworks for clinical staging and therapeutic monitoring, and the rational design of combination strategies pairing anti-hormonal agents with glycolytic inhibitors based on the mechanistic links delineated here. The emerging recognition that metabolic imaging with ^{18}F-FDG PET is itself subject to sex-specific variation in standardised uptake values (108, 109) has immediate implications for the standardisation of imaging-based metabolic assessments in oncological practice. Circulating metabolomics profiles showing sex-specific patterns in lactate, pyruvate, and related metabolites (110) may ultimately provide accessible non-invasive surrogates of the sex-dimorphic Warburg phenotype amenable to routine clinical monitoring.

Conclusion

The convergence of evidence across sex hormone biology, sex chromosome genetics, epigenetic regulation, and tumour microenvironment biology establishes that sex is a fundamental determinant of the Warburg effect in cancer at every level of biological organisation. The male-biased glycolytic phenotype, chromosomally hardwired through KDM6A haploinsufficiency and amplified by androgen receptor-driven transcriptional programmes, generates a metabolic and immunological microenvironment that is fundamentally distinct from the more metabolically flexible, hormonally gated landscape of female-pattern cancers. Realising the full potential of cancer metabolic therapy will require that sex be elevated from a variable to be adjusted for into an active design principle in preclinical modelling, biomarker development, and clinical trial stratification. Truly personalised precision oncology must incorporate sexual dimorphism in the Warburg effect as a core biological consideration.

Abbreviations

^{18}F-FDG PET	Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography
2-DG	2-Deoxy-D-Glucose
ACC-1	Acetyl-CoA Carboxylase 1

^{18}F-FDG PET	Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography
Acetyl-CoA	Acetyl Coenzyme A
ADT	Androgen Deprivation Therapy
AI-R	Aromatase Inhibitor-Resistant
Alpha-KG	Alpha-Ketoglutarate
AMPK	AMP-Activated Protein Kinase
AR	Androgen Receptor
ATP	Adenosine Triphosphate
CAFs	Cancer-Associated Fibroblasts
cAMP/PKA	Cyclic Adenosine Monophosphate / Protein Kinase A
c-MYC	Cellular Myelocytomatosis Oncogene
CCL2	C-C Motif Chemokine Ligand 2
CD8+ T cells	Cytotoxic T Lymphocytes
CIC	Capicua Transcriptional Repressor
CPT-1a	Carnitine Palmitoyl Transferase 1a
CRC	Colorectal Cancer
CRPC	Castration-Resistant Prostate Cancer
CXCL8	C-X-C Motif Chemokine Ligand 8
DDX3Y	DEAD-Box Helicase 3 Y-Linked
DHT	Dihydrotestosterone
E2	17β-Estradiol
EGFR	Epidermal Growth Factor Receptor
EIF1AY	Eukaryotic Translation Initiation Factor 1A Y-Linked
ER	Estrogen Receptor
ER+ / ER−	Estrogen Receptor-Positive / Negative
ERα / ERβ	Estrogen Receptor Alpha / Beta
ERα-LBD	Estrogen Receptor Alpha Ligand-Binding Domain (Isoform)
ERRα	Estrogen-Related Receptor Alpha
EXITS	Escape from X Inactivation Tumour Suppressor
EZH2	Enhancer of Zeste Homolog 2
^{18}F-FDG PET	Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography
F2,6BP	Fructose-2,6-Bisphosphate
FAS / FASN	Fatty Acid Synthase
FGFR	Fibroblast Growth Factor Receptor
FUBP1	Far Upstream Element Binding Protein 1
GBM	Glioblastoma Multiforme
GLUT1 / GLUT3	Glucose Transporter 1 / 3
GPER (GPR30)	G Protein-Coupled Estrogen Receptor
H3K27me3	Trimethylation of Histone H3 at Lysine 27
HCC	Hepatocellular Carcinoma
HER2+	Human Epidermal Growth Factor Receptor 2-Positive
HIF-1α	Hypoxia-Inducible Factor 1-Alpha
HK2	Hexokinase 2
IDH	Isocitrate Dehydrogenase
IL-2	Interleukin-2
JMJD2B	Jumonji Domain-Containing Protein 2B
KDM5D	Lysine Demethylase 5D
KDM6A (UTX)	Lysine Demethylase 6A
LDHA / LDHB	Lactate Dehydrogenase A / B
LOY	Loss of Y Chromosome
LUAD	Lung Adenocarcinoma
MCT	Monocarboxylate Transporter
MGMT	O^6-Methylguanine-DNA Methyltransferase
miR-let-7a	MicroRNA Let-7a
mTOR	Mechanistic Target of Rapamycin
NAD^+	Nicotinamide Adenine Dinucleotide
NEPC	Neuroendocrine Prostate Cancer
NF1	Neurofibromatosis Type 1
OXPHOS	Oxidative Phosphorylation
PDH	Pyruvate Dehydrogenase
PDK1	Pyruvate Dehydrogenase Kinase 1
PFK1	Phosphofructokinase 1
PFKFB3 / PFKFB4	6-Phosphofructo-2-Kinase/Fructose-2,6-Bisphosphatase 3 / 4

^{18}F-FDG PET	Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
PGK	Phosphoglycerate Kinase
PI3K	Phosphoinositide 3-Kinase
PI3K/AKT/mTOR	Phosphoinositide 3-Kinase / Protein Kinase B / Mechanistic Target of Rapamycin
PKM2	Pyruvate Kinase M2 Isoform
PPAR / PPARα / PPARγ	Peroxisome Proliferator-Activated Receptor / Alpha / Gamma
PR	Progesterone Receptor
PTEN	Phosphatase and Tensin Homolog
Ras	Rat Sarcoma Viral Oncogene
RPS4Y1	Ribosomal Protein S4 Y-Linked 1
SCD	Stearoyl-CoA Desaturase
SPP1	Secreted Phosphoprotein 1
SREBP	Sterol Regulatory Element Binding Protein
STAT3	Signal Transducer and Activator of Transcription 3
SUV	Standardised Uptake Value
TAMs	Tumour-Associated Macrophages
TCA Cycle	Tricarboxylic Acid Cycle
TCGA	The Cancer Genome Atlas
TME	Tumour Microenvironment
TREM-1	Triggering Receptor Expressed on Myeloid Cells 1
Tregs	Regulatory T Cells
UTY	Ubiquitously Transcribed Tetratricopeptide Repeat Containing Y-Linked
VAT	Visceral Adipose Tissue
VHL	Von Hippel-Lindau
ZFY	Zinc Finger Y-Linked

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