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Sex differences in cancer and immunotherapy outcomes: the role of androgen receptor

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Across the wide range of clinical conditions, there exists a sex imbalance where biological females are more prone to autoimmune diseases and males to some cancers. These discrepancies are the combinatory consequence of lifestyle and environmental factors such as smoking, alcohol consumption, obesity, and oncogenic viruses, as well as other intrinsic biological traits including sex chromosomes and sex hormones. While the emergence of immuno-oncology (I/O) has revolutionised cancer care, the efficacy across multiple cancers may be limited because of a complex, dynamic interplay between the tumour and its microenvironment (TME). Indeed, sex and gender can also influence the varying effectiveness of I/O. Androgen receptor (AR) plays an important role in tumorigenesis and in shaping the TME. Here, we lay out the epidemiological context of sex disparity in cancer and then review the current literature on how AR signalling contributes to such observation via altered tumour development and immunology. We offer insights into AR-mediated immunosuppressive mechanisms, with the hope of translating preclinical and clinical evidence in gender oncology into improved outcomes in personalised, I/O-based cancer care.

KEYWORDS

sex, immunotherapy, androgen receptor, tumour microenvironment, gender oncology

1 Introduction

Differences in biological and sociocultural patterns between males and females have led to notable contrast in the characteristics of cancer pathophysiology. Research has revealed sex disparities in cancer incidence and prognosis, which are influenced by sex chromosomes and sex hormones, as well as distinct lifestyles, dietary habits, and environmental exposures (1). Since 2014, the National Institutes of Health have urged scientists to incorporate sex as a biological variable in their study design, aiming to reduce sex-related research biases (2). We now know that sex hormones play a crucial role in the initiation, progression, and treatment

outcomes of cancer. Extensive studies are available on the crucial role of oestrogen and its pathways in the onset and progression of tumours, sometimes notwithstanding the oestrogen receptor (ER) status (3). On the other hand, the role of androgens and their signalling pathways on different cancers is less understood, except in prostate cancer. Emerging evidence on how androgen receptor (AR) affects tumour immunology has once again emphasised the significance of sex difference in response to antitumor therapies (4), prompting further investigation into this intriguing area.

This review collates current knowledge of the connection between biological sex and cancer epidemiology, the interplay between environmental and hormonal factors, AR and cancer sexual dimorphism, as well as the effect of AR on cancer immunology, before suggesting how AR contributes to immunotherapy resistance. Nevertheless, it is necessary to remain cognisant of how human *genders* - sociocultural constructs of the characteristics of men and women - exert significant influence on the lifestyles and exposures experienced by the two *biological sexes*, together shaping the apparent differences in immunotherapy response between males and females.

2 Epidemiology

Recent studies have shown that females tend to have more potent immune functions than males (5), and their overly robust immune system can paradoxically be a double-edged sword that leads to increased occurrence of immune dysregulation (6–8). Therefore, sex has always been an important risk factor for certain infections (6), autoimmune disorders (9), cardiovascular diseases (10) and so on. However, whether certain cancers affect more males than females (or vice versa) remains a contentious topic (11, 12). Based on the GLOBOCAN2020 database (13) regarding the top 10 cancers by incidence and mortality (Figures 1A, B), we can observe that besides the more sex-specific cancers (breast, cervix, prostate), there are 6 male-dominant cancers (bladder, colorectal, liver, lung, oesophagus, stomach) and 1 female-dominant cancer (thyroid) (Figures 1C, D).

Expectably, breast cancer occupies the foremost position in the incidence of cancers in females, accounting for 24.5% of new cancer cases, far more than colorectal cancer (CRC) at 9.4% (Figure 2A). Thyroid cancer (TC) is the only non-reproductive-related cancer that is female-dominant, with a male/female incidence ratio of 0.31 (Figure 1D). Importantly, however, when males do get TC, the male sex seems to be an independent negative indicator of TC prognosis. Data from Canada reveals that men with well-differentiated TC have a higher risk of recurrence than women, with a hazard ratio (HR) of 2.72 (15).

Compared with females, many of the common cancers occur more frequently in men (Figure 2B). Bladder cancer exhibits a notable sex disparity in incidence and mortality (Figure 1D), while females with non-muscle invasive bladder cancer have a higher risk of recurrence than males (16). This could potentially explain why the male/female mortality ratio is lower than the incidence ratio in

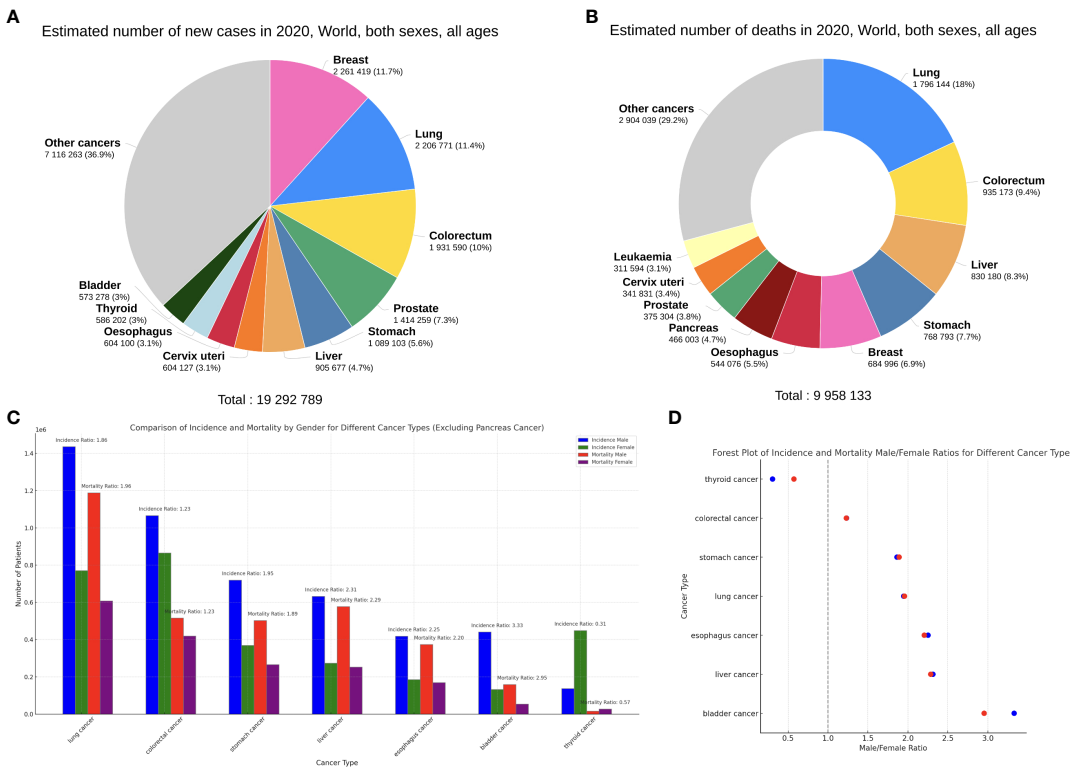

FIGURE 1
(A, B) Top 10 most common cancers worldwide (all ages and sexes) by incidence **(A)** and mortality **(B)**, plotted on the Global Cancer Observatory (GCO) platform (14). **(C)** The incidence and mortality of the 7 sex-neutral cancers in the top 10, females versus males. **(D)** Male/Female ratios of incidence (blue) and mortality (red) of the 7 cancers. Data from GLOBOCAN2020.

bladder cancer. Liver cancer is another male-dominant cancer, ranking third in mortality globally (17). With a male/female incidence and mortality ratio of 2.31 and 2.29 (Figure 1D), the sex disparity is even more pronounced in East Asia (18). Other gastrointestinal tumours, including gastric, oesophageal, and colorectal cancers, also show higher incidence and mortality rates in males, consistent with the trends reported in literature (19–21). Lung cancer is also a male-dominant cancer; yet sex difference in lung cancer incidence is more pronounced within individual subtypes, with a greater male predominance in squamous cell carcinoma (17) and a notable East Asian female predominance in EGFR-mutated adenocarcinoma, the mechanisms of which are still not well understood (22). Notably, recent studies have reported a reversal of the sex disparity in lung cancer, where its incidence has become higher amongst young and middle-aged females (23) with more estimated new cases (17).

Notable sex disparities also exist in cancers with lower incidence rates. For instance, nasopharyngeal carcinoma (NPC) has a strong male predominance amongst Asian cancers, where the male/female incidence ratio ranges from 2:1 to 3:1 (24). Sexual dimorphism also exists in melanoma biology (3), with a male/female incidence ratio in melanoma ranging from 2:1 to 3:1 as well (25). Melanoma in males tends to be more aggressive, while female patients show better prognosis and longer survival (26–28).

3 Non-AR-related factors contributing to sex disparities in cancer incidence

3.1 Modifiable factors

As demonstrated earlier, males generally have higher incidence and mortality rates than females for bladder, colorectal, liver, lung, oesophagus, and stomach cancers (29). These sex disparities cannot solely be explained by the biological sex; lifestyle and environmental exposures are indispensable as well. In the UK, excluding sex-specific cancer types, modifiable risk factors account for 36.4% of male cancer cases and 25.6% of female cases. Tobacco smoking alone contributed to 15% of preventable cancer cases in the UK in 2015 and represents the highest proportion of preventable cancer cases in the US and Australia (30). Male and female smokers are 23 and 13 times more likely to develop lung cancer compared to non-smokers, respectively (31). Chronic alcohol consumption is also strongly linked to various cancers, with dose-response relationships seen in multiple epidemiological studies for liver, colorectal and upper aerodigestive tract cancers (32–34). Subgroup analyses in people with alcohol use disorders have shown that females have a higher risk of developing cancers compared to men (OR=1.767) (35). Additionally, consuming the same amount of alcohol leads to a greater increase in absolute lifetime cancer risk for women (1.4%) compared to men (1%), although these higher cancer rates in women may be attributed to breast cancer (36).

Obesity represents a major public health challenge, with approximately 55% of cancers in females and 24% in males in the USA considered obesity related. Importantly, 42% of new cases of overweight and obesity related cancers are gynaecological and breast cancers. This implies a stronger correlation between high body-mass index (BMI) and female cancers, highlighting the role of aromatase and oestrogen in gynaecological and breast cancer development (37). Non-sex specific cancers have a higher incidence in males, particularly oesophageal (male to female ratio of adenocarcinoma 4.4, squamous cell carcinoma 2.7) and colorectal cancers (38, 39). Obesity also plays a role in the tumorigenesis of these cancers, possibly involving chronic inflammation and systemic insulin and adipokine dysregulation (40, 41) that raise the incidence of metabolic syndrome (including metabolic dysfunction-associated steatotic liver disease, MASLD) particularly in males (42).

Globally, oncogenic viruses contribute to approximately 10% of all malignancies, although this varies between higher and lower income countries (43). The population attributable fractions are higher in females than males, primarily due to the inclusion of sex-specific cancers. Causative agents include human papillomaviruses (HPV), hepatitis B/C viruses (HBV/HCV), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV) (30). HPV^{+}

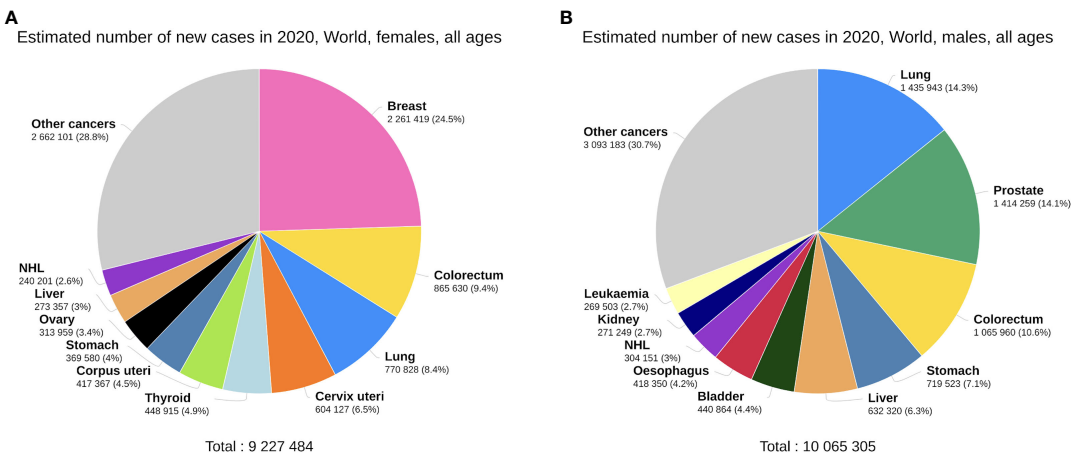

FIGURE 2
Top 10 most common cancers worldwide by incidence, females **(A)** versus males **(B)**, plotted on the GCO platform (14). Data from GLOBOCAN 2020.

head and neck squamous cell carcinoma (HNSCC) (44), EBV-driven NPC (24), as well as HBV/HCV-driven hepatocellular carcinoma (HCC) (45) all show a strong male predominance.

3.2 Sex chromosomes

Sex chromosome differences may also contribute to variations in cancer incidence. Females have XX and males have XY sex chromosome combinations, while intersex individuals such as those with Turner's or Klinefelter's syndrome have chromosomal patterns deviating from the typical configurations. In XX individuals, some pseudoautosomal genes can escape X-chromosome inactivation (XCI) providing a "buffering" effect against allele mutations. Incomplete XCI occurs in 23% of X chromosome genes (46). Thus, a single allele mutation leads to complete alteration of gene function in males, as opposed to a heterozygous alteration in females. This serves as a safeguard, preserving tissue function in the presence of mutations. Many of these genes, including *ATRX*, *KDM5C, KDM6A*, and *MAGEC3*, have tumour suppressor functions. Additionally, mutated alleles on the inactive X chromosome are typically expressed at lower levels or not expressed at all, mitigating their impact on cellular function (47). In females, the selective proliferation of specific mosaic subpopulations exhibiting preferential expression of one X chromosome can lead to skewed XCI (48). This can confer advantageous immunomodulation against cancer – a protective mechanism not available to males who obligatorily express the same mutated maternal X-linked gene.

X-linked genes, including *HUWE1*, *FLNA* and *MED12*, can directly modulate *TP53* expression. This association may render males at a higher risk of p53 dysfunction. Females exhibit a higher incidence of non-expressed mutations among p53-associated X-linked genes. Bioinformatic analyses in 12 non-reproductive cancers have shown that in females, less than half of these exome mutations were transcribed into mRNA, whereas the majority underwent mRNA transcription in males (49). These findings suggest tumour suppressor effects of the X chromosome.

Loss of Y chromosome (LOY) has been implicated in the pathogenesis of lung cancer, renal tumours and up to 40% of bladder cancer (50–52). In muscle invasive bladder cancer, patients exhibiting low Y chromosome gene expression of *KDM5D*, *KDM6C*, *TBL1Y* and *ZFY* demonstrate worse prognosis (52). Mosaic LOY in peripheral leukocytes is also associated with solid tumour incidence. Extreme downregulation of Y is linked to increased cancer risk and resistance against EGFR tyrosine kinase inhibitors (53), which may also impact immunotherapy response downstream. Loss of the entire X chromosome(s) has been documented in early-stage astrocytoma, neuroblastoma and medulloblastoma (54–56).

3.3 Oestrogen and ER

The link between oestrogen or ER and non-reproductive cancers is unclear. At the molecular level, oestrogen and ER affect PD-1 signalling, Wnt/β-catenin pathways and the Ras/MAPK pathway, amongst many other aspects of cancer biology (57–62).

Circulating E1 (oestrone) and E2 (oestradiol) levels were found to have no statistically significant relationship with colon cancer in a cohort of 1000 postmenopausal women (62). However, a 2015 meta-analysis revealed a reduced ratio of ERβ expression in CRC compared to the normal mucosa (OR=0.216), associated with poorer overall and disease-free survival (63). Conversely, exogenous oestrogen reduces the risk of CRC by 37% as demonstrated by the landmark Women's Health Initiative study (64). *In vitro*, ERβ was shown to modify the hypoxic response by downregulating HIF-1α, VEGFA and PDGF (65).

Oestrogen plays a complex role in the liver. It has been implicated in various liver pathologies like fibrosis and fatty liver disease, but its role in HCC remains unclear. In a cohort of 275 men, higher total E2 is associated with increased HCC risk (OR=1.58) (66). A recent cohort study shows a survival advantage for female HCC patients over males in perimenopausal and early-menopausal ages but not in postmenopausal women, possibly due to declining endogenous oestrogen production (67). However, female patients in phase III trials for immune checkpoint inhibitors (ICI) for HCC are found to have worse overall survival (OS) than males (68). Whether this discrepancy can be attributed to oestrogen is unclear. Studies exploring the use of tamoxifen in HCC have yielded mixed results, with some showing prolonged survival but larger studies finding no significant association (69–71).

In lung cancer, oestrogen appears to have a protective effect. A meta-analysis of female lung cancer cases demonstrates that higher levels of sex steroid hormone exposure, both endogenous and exogenous, reduce lung cancer risk by 10% (72), yet the role of ERα or ERβ is unclear. Some studies suggest that ERα is associated with worse prognosis in non-small cell lung cancer (NSCLC) (73), while others find no significant effect. Some meta-analyses indicate an association between ERβ and better prognosis in NSCLC (73, 74), while others consider it an unreliable prognostic marker (75, 76) depending on the methods employed, such as uni- vs multivariate analysis, bioinformatics, or immunohistochemistry (IHC) analysis. Finally, female reproductive factors like breastfeeding are associated with a decreased risk of oesophageal and gastric adenocarcinoma, though parity, menstruation, and the use of hormone replacement therapy have no association (77). Interestingly, the use of tamoxifen, a selective oestrogen receptor modulator (SERM), is associated with an increased risk of gastric adenocarcinoma (78) as well as endometrial cancer. The tissue-specific agonist/antagonist role of SERMs like tamoxifen reflects the complex role of the oestrogen-ER signalling axis in tumorigenesis.

4 Androgens, AR, and tumour pathophysiology

4.1 Androgens and non-reproductive cancers

Androgens include testosterone, dihydrotestosterone (DHT), and dehydroepiandrosterone (DHEA), among others. Testosterone produced by the testes plays a pivotal role in initiating the development of masculine traits, hence exists in higher levels in

males and lower in females. Androgen deficiencies in males can result in the development of feminine traits (79), while increased androgen production in females can lead to a shift from feminine to masculine traits and also be associated with polycystic ovarian syndrome (PCOS) (80). Their biological functions are executed by binding with AR and activating intracellular AR signalling downstream. Besides prostate cancer, the role of androgens in tumorigenesis is less studied compared to oestrogen. Higher concentrations of testosterone are associated with increased risk of liver cancer, particularly in men, while higher levels of DHEA, the adrenal precursor, are associated with a 53% decrease in risk (66, 81). Higher circulating testosterone is associated with a decreased risk of CRC in men, but this is not shown in women (81). The association between testosterone and oesophageal cancer is unclear, with varying degrees of significance across studies (81, 82). Gastric, pancreatic and bladder cancers are also shown to have no significant association with testosterone levels (81). Interestingly, androgen deprivation therapy (ADT) using finasteride has shown improved survival in patients with non-muscle invasive bladder cancer, suggesting a potential strategy to reduce bladder cancer incidence and recurrence (83).

4.2 Overview of AR

AR is a member of the nuclear receptor superfamily acting as a ligand-dependent transcription factor (84). Consisting of eight exons, the AR gene is located on the X chromosome. It comprises a ligand-binding domain (LBD), a DNA-binding domain (DBD), and an N-terminal domain (NTD). In the unbound state, AR forms a complex with co-chaperones, heat shock proteins, and cytoskeletal proteins in the cytoplasm. Ligand binding induces conformational changes, receptor dimerization, and translocation to the cell nucleus. The NTD influences transcriptional activity, while the DBD allows binding to and recognition of androgen response elements (AREs) on target genes where it serves to induce or repress gene expression through binding to chromatin at *cis* AREs (85). AR can also modulate post-translational modifications by phosphorylation, methylation, or ubiquitination (86, 87) (Figure 3). While AR exerts effects mostly in sex hormone-dependent tissues, such as the prostate, testes, ovaries, and endometrium (88, 89), it is also widely expressed in kidneys, liver, urinary bladder, as well as the cardiovascular, immune, musculoskeletal and nervous systems (88, 90–94). It is also noted that membrane androgen receptors (mARs), such as ZIP9 and GPRC6A, are a group of G protein-coupled receptors that directly alter cellular signalling upon androgen stimulation, also known as the non-genomic pathway (95, 96) (Figure 3). While studies have demonstrated the implications of mARs on prostate cancer, they are beyond the scope of this review.

A report of teenagers developing hepatocellular carcinoma due to excess androgen intake have spurred interest in the effect of androgen and AR on cancer (97, 98). In 1980, an article published in *The Lancet* highlighted the association between elevated levels of free testosterone in males and an increased risk of melanoma (99). While multiple observations support the hypothesis that excess androgens may be tumorigenic (100), a definitive mechanistic explanation is still lacking, which necessitates our summary of current knowledge below.

4.3 AR and tumour development/progression

AR signalling is the primary driver of castration resistant prostate cancer (CRPC) (101). Enzalutamide, an AR antagonist, competes with androgens to bind to AR and blocks nuclear ARE binding, thereby inhibiting downstream transcriptional activity (102) and enabling antitumor effect (103). AR and ER exhibit similarities as nuclear receptors, allowing substantial signalling crosstalk (Figure 3) (104). In ER+ breast cancer, AR competes with ER for oestrogen response elements (EREs) and inhibits ER activity, playing a tumour-suppressive role especially in premenopausal patients (105). However, AR may promote cancer progression in certain ER– breast cancers. A study indicated that the luminal AR (LAR) subtype accounts for 15% of triple-negative breast cancer and AR is an attractive therapeutic target (106). Higher AR expression and corresponding aggressive phenotypes are observed predominantly in tissue samples from African American women, with a strong interaction between AR and JAK-STAT signalling (107). Another study shows that *PIK3CA* is highly mutated in the LAR subtype, where PI3K inhibitors can reduce LAR cell proliferation (108). Salivary duct carcinoma (SDC), a male-dominant cancer, is a rare, aggressive malignancy also characterised by high AR expression, ranging from 70% to 97.8% (109–111). Recent studies have found that the occurrence of SDC is closely related to the AR signalling pathway (112), sharing similar molecular profiles with high-grade breast ductal carcinoma and apocrine breast cancer (113). AR-V7, an AR splicing variant, accounts for over 50% of AR in SDC and plays a crucial role in the resistance and progression in CRPC (114). Other studies have reported that *FOXA1* mutations are present in 10% of SDC cases, resulting in drug resistance and tumour progression also via the AR pathway (113).

With its homolog crucial for primary sex determination in *C. elegans* (115), FOXA1 is a key transcription factor necessary for AR and ER activities in prostate and breast cancers (116). AR driven transcription in molecular apocrine breast cancer is mediated by FOXA1 (117). In prostate cancer, *FOXA1* exhibits a high mutation rate, thereby affecting AR transcription (118). Elevated levels of FOXA1 have been associated with poor prognosis in prostate cancer. FOXA1 function in AR signalling and its impact on prostate cancer differs markedly from its role in ER signalling and breast cancer progression (119). A study published in 2012 highlights the significance of FOXA1 and FOXA2 in sexual dimorphism in liver cancer, noting that modulation of these factors can reverse the observed gender differences (120). Other *FOX* family genes are also crucial in regulating the PI3K-AKT-mTOR pathway. FOXO3a, a PI3K/AKT downstream substrate, can induce AR expression as a positive regulator (121). FOXO1, a downstream effector of AR, can also lead to AR hyperactivation in prostate cancer with PTEN loss, independent of androgen binding (122).

The crosstalk between AR and other signalling pathways has also been reported (123, 124). With a strong association between

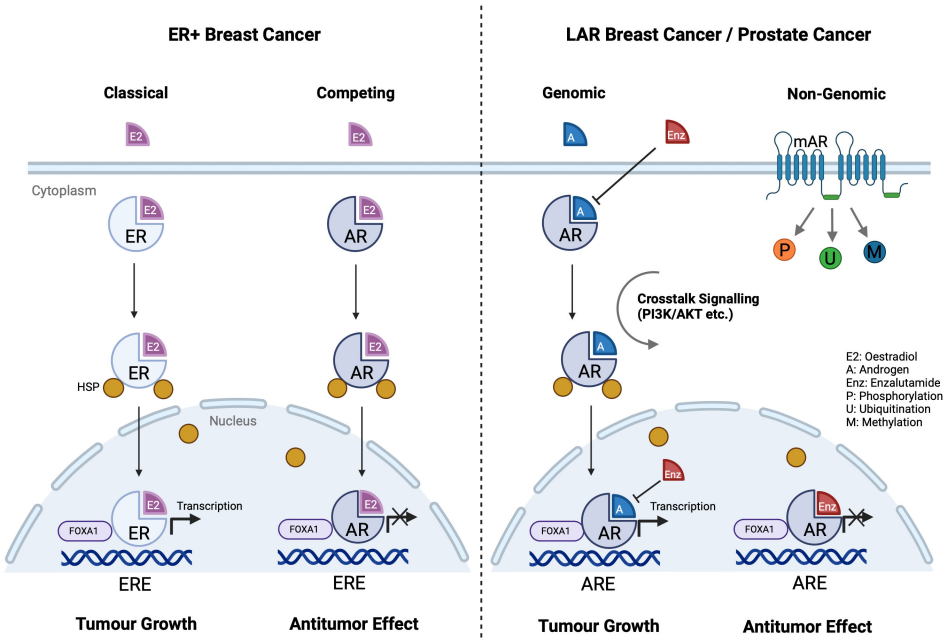

FIGURE 3
AR and ER signalling pathways in different cancer cells. ER and AR share similar structures, and they compete in each other's signalling pathways. In ER+ breast cancer cells, AR substitutes ER on ERE and stops downstream transcription, eliciting an antitumor effect. ER and AR also share the same co-activator FOXA1 on ERE. In LAR breast cancer and prostate cancer, enzalutamide competes with androgen to stop AR activation. (Created with BioRender.com).

nuclear AR expression and Wnt/β-catenin signalling in bladder cancer, ADT has shown great therapeutic potential (124). Moreover, TCF1 and AR have overlapping binding sites on β-catenin (125). β-catenin translocates into the nucleus and interacts with TCF1 and lymphoid enhancer factor, activating the transcription of target genes. TCF1 is required for the self-renewal of stem-like CD8+ T cells in response to viral or tumour antigens, preserving heightened responses to checkpoint blockade immunotherapy (126). This implies not only a causal relationship between AR signalling and tumour progression via β-catenin pathways, but also a connection between AR and antitumor immune responses (more in Section 5.2). In addition, androgens can also influence the effectiveness of BRAF-targeted therapy in melanoma. AR expression is elevated in BRAF-resistant melanoma. Inhibition of both the AR and BRAF/MEK pathways counteracts resistance and hence improves cytotoxicity (127). Intriguingly, blocking AR not only inhibits the proliferation of BRAF-resistant cells, but also enhances the infiltration of CD8+ T cells and promotes cancer cell apoptosis (128). This prompts further investigation on how AR affects immune responses, and targeting AR may offer new combination therapies for cancer treatment.

5 AR and cancer immunotherapy

5.1 Sex difference in clinical trial outcomes

There are several meta-analyses evaluating the comparative efficacy of immuno-oncology (I/O) on various cancers across genders (Table 1). A 2018 meta-analysis summarises 20 clinical trials involving ICIs across various cancer types, with a total of 11,351 participants (129). These trials predominantly focus on melanoma (32%) and NSCLC (31%). The meta-analysis reveals significant sex differences in clinical outcomes, where females experience lower response rates than males. However, the significant heterogeneity calls for analysis specific to individual cancer types and treatments. In 2019, the same team conducted another meta-analysis of chemotherapy and I/O for advanced lung cancer; this time with opposite conclusions compared to a year ago (130). Women with advanced lung cancer seem to derive a larger benefit from the addition of chemotherapy to anti-PD-1/PD-L1 compared with men. Another meta-analysis on NSCLC patients receiving combination chemo-immunotherapy first-line also concludes that females show a more significant improvement in OS and progression-free survival (PFS) (132). These findings highlight the potential impact of gender on the effectiveness of both targeted and combination of chemo-immunotherapies in NSCLC.

In 2020, a meta-analysis on NSCLC includes 13 studies with monotherapy and 5 with combination regimens (KEYNOTE 010/024 with pembrolizumab versus chemotherapy and CHECKMATE 017/026/057 with nivolumab versus chemotherapy), a total of 1028 female and 1435 male patients (131). The result confirms that EGFR wild-type patients could benefit from immunotherapy monotherapy (HR=0.77; $p<0.001$) while those of mutant types experienced no survival benefit (HR=1.11; $p=0.54$). While EGFR mutations are more likely to occur in females (134), there is no apparent efficacy-sex association overall (131). Therefore, to explore

TABLE 1 Summary of meta-analyses evaluating the efficacy of I/O interventions across males and females on different cancers.

Cancer Type	# Patients	Year	Reference	Comparative Arms	Summary of Findings
Advanced solid tumours • 32% melanoma • 31% NSCLC	11,351	2018	Conforti et al (129)	ICI compared with others	Females show lower response rates
Advanced NSCLC/ SCLC Advanced NSCLC	4,923 3,974	2019	Conforti et al (130)	ICI + chemotherapy VS chemotherapy ICI alone OR ICI + chemotherapy	Females benefit more from the ICI + chemotherapy combination
Advanced solid tumours	10,664	2020	Wei et al (131)	13 ICI-alone regimens 5 ICI-based combinations	EGFR mutations are more likely to occur in females No sex difference for ICI monotherapy benefits Females benefit more from ICI-based combinations
Advanced/ recurrent NSCLC	5,830	2022	Takada et al (132)	ICI + non-ICI VS non-ICI	Females show greater benefit in OS and PFS when receiving combined chemoimmunotherapy
Advanced HCC	5,169	2023	Balcar et al (68)	ICI alone OR ICI-based combinations	Females show smaller (pooled) OS benefit from ICI- based therapy Comparable outcomes for Atezo/Bev (on a real-world cohort of 840 patients)
mRCC mUC	4,206 (mRCC) 2,240 (mUC)	2023	Yanagisawa et al (133)	ICI-based combination VS TKI ICI-based combination VS chemotherapy	PFS and OS benefit seen in first-line ICI-based combination; no difference between the sexes OS benefit seen in first-line ICI-based combination; no difference between the sexes

mRCC, metastatic renal cell carcinoma; mUC, metastatic urothelial carcinoma.

the effect of AR in I/O efficacy, confounding factors such as mutations will need to be properly controlled and stratified.

There are no sex differences in the superior OS benefits from first-line ICI-based combination therapies in metastatic renal cell carcinoma (RCC) or metastatic urothelial carcinoma (UC) (133). In locally advanced RCC, however, adjuvant I/O monotherapy reduces recurrence risk in female patients (HR=0.71, 95% CI 0.55–0.93) but not in male patients (133). On the other hand, males with muscle-invasive bladder cancer have better DFS on adjuvant I/O compared to females (133). A meta-analysis on HCC shows single-agent I/O exhibits less OS benefit in females than males. On the other hand, combination atezolizumab-bevacizumab (Atezo/Bev) – a first-line standard of care for advanced HCC – yields comparable efficacy between males and females in a real-world cohort (68). Nevertheless, these studies did not conduct stratified analysis based on AR expression, which may have overlooked the importance of AR in sex disparity.

Other phase III trials in advanced urothelial, hepato-pancreato-biliary and upper or lower gastrointestinal tract cancers have also been individually screened for outcome differences in patients treated with ICI based on sex or AR levels (135–145). However, none of these trials made explicit analysis on how sex or AR affects the outcomes in these cancers. Importantly, though, one study on 23,296 patients enrolled in SWOG trials shows a 49% increased risk of adverse events (AE) in females receiving I/O, especially of haematological AEs (146, 147). It is hoped that more prospective studies on the relationship between sex, AR expression and I/O efficacy and AEs can be carried out to further explore the role of AR signalling in cancer immunology and immunotherapy.

5.2 AR and cancer immunology

While previous sections have attempted to address how genetic, environmental, and hormonal effects lead to distinct tumorigenesis and disease progression patterns between males and females, studies over the past decade have emerged to explain how AR within the tumour microenvironment (TME) conspire to this process and alter patient response to treatments such as ICIs. This section summarises the effect of AR signalling in different TME cell types, laying the foundation for subsequent discussion on another dimension of I/O resistance (Figure 4).

Although AR signalling plays a key role in tumour immunosuppression, it is important to note the caveat when interpreting preclinical studies involving AR and biological sex. Cells harvested from male subjects have long been exposed to androgens and AR signalling. Hence, when manipulating AR-related pathways, male cells may behave very differently compared with female cells. Consequently, when designing and analysing clinical trials for I/O and antiandrogen combination, it is indispensable to include stratification based on biological sex, along with other variables such as circulating androgens, AR mutation/ amplification/IHC status, and PD-L1 scoring.

5.2.1 AR signalling in lymphocytes

In murine models of CRC and melanoma, male mice have more aggressive tumours which seemingly depend on $CD8^+$ TILs (4, 148). AR signalling inhibits CD8 T cell stemness by regulating the epigenetic programme of T cell differentiation (4), while reducing IFNγ secretion via USP18 which inhibits NF-κB activation (148). This causes male TILs to be more terminally exhausted

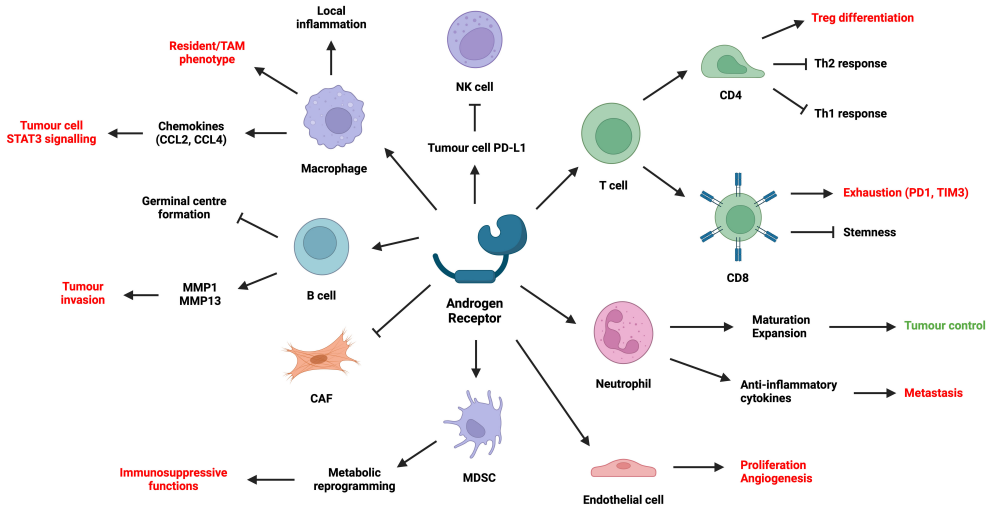

FIGURE 4
Summary of the effect of AR on different cell types in the TME. (Created with BioRender.com).

(PD1$^+$TIM3$^+$) with a loss of stem-cell like state (TCF1$^-$). Surgical castration in combination with ICI improves tumour control. These results correlate well with CRC and melanoma patient data, where AR positively correlates with PD1 and TIM3 expression in CD8$^+$ TILs. In addition, AR signalling transactivates *Tcf7*-centred regulons and directly results in the exhaustion of TCF1$^+$ progenitor CD8$^+$ T cells in murine bladder cancer (149). CD8$^+$-specific *Ar*-KO or systemic use of enzalutamide reduces tumour burden, while combining castration with ICI improves tumour control. These processes do not seem to depend on sex chromosomes, but more on androgen exposure and AR signalling.

Evidence is clear that AR signalling in male CD4$^+$ T cells suppresses Th1 and Th2 responses and favour T_{regs}. AR signalling stabilises *Foxp3*$^+$ T_{regs} during allergen challenge in males (150), possibly via a functional ARE within the *Foxp3* locus (151). Androgens also reduce the differentiation towards Th2 (150) and suppress Th2 functions in males (152), a consequence of AR binding to *Dusp2*. Androgen exposure also reduces Th1 differentiation by inhibiting IL-12 signalling (153). Pan-T cell *Ar*-KO renders severe airway inflammation in male mice during allergen exposure (150, 152).

One recent study has shown that while there are more NK cells in males, they often exhibit reduced cytotoxicity and tumour control (154). Such effect depends on both epigenetic factors (e.g. UTX) on the X chromosome (154) and the effect of sex hormones on tumour cell PD-L1 expression (155, 156). Specifically, high-dose androgen treatment on prostate cancer cells upregulates circFKBP5, which increases their PD-L1 expression and hence NK suppression (155). On the other hand, antiandrogens on bladder cancer cells reduce PD-L1 expression via ADAR2, which in turn increases NK cell cytotoxicity (156). Sorafenib treatment on HCC cell lines also enhances NK cell killing by reducing AR expression, leading to increased IL-12A secretion and NK activation. Further research is needed on the direct effects of AR signalling on NK cells.

There are limited findings on how AR signalling impacts B cell function. Androgens partially facilitate B cell migration away from the follicle centre via CCL21-GPR174 interaction, which prevents germinal centre formation (157). B cell proliferation and IgE synthesis are increased either by reducing circulating androgens (158) or by AR knockout (159), yet these effects do not enhance airway inflammation in allergen challenge (158). In another study, IL-8 increases AR expression on B cells, which promotes bladder cancer cell invasion by upregulating B cell expression of MMP1 and MMP13 (160).

5.2.2 AR signalling in macrophages, DCs, and MDSCs

The direct role of AR signalling on myeloid cell phenotype and function remains a contentious area of research. Androgens upregulate TREM1-associated signalling pathways in THP-1 and induce resident-like phenotypes, promoting prostate cancer cell migration and proliferation (161). Enzalutamide reduces immunosuppressive tumour associated macrophages (TAMs) in prostate cancer patients (161). Nevertheless, while AR signalling in macrophages can increase prostate tumorigenesis via increased CCL4 (162) and consequent STAT3 activation, blocking AR in TAMs or prostate cancer cells may actually promote metastasis via CCL2/STAT3-mediated macrophage recruitment (163). Furthermore, in atherosclerosis (164) and wounds (165), AR signalling promotes local inflammation by enhancing TNFα expression, monocyte differentiation and chemotaxis (166), as well as foam cell formation via altered lipid metabolism. AR signalling in alveolar macrophages also promotes M2 macrophage-mediated eosinophilic inflammation, increasing lung damage in asthma mouse models (167). Hence, the role of AR signalling in macrophages depends not only on its direct effects, but also on the local tissue and disease contexts.

Though analysis has shown that ADT may lead to increased infiltration of myeloid-derived suppressor cells (MDSCs) into the TME (168, 169), there have been few studies looking at the direct effect of AR signalling on MDSCs or dendritic cells (DCs). B16 and 4T1 implantation results in higher tumour burden in female mice that is correlated with a higher plasmacytoid DC infiltration and

less MDSCs compared with male mice (170). Functions of these tumour-associated DCs could depend on FOXO3-regulated AR/ER expression (170). In another seminal study, AR knockout or antagonism on MDSCs facilitate MC-38 tumour progression in mice, resulting from pAMPK-mediated metabolic reprogramming (171). Increased glycolysis and decreased mitochondrial respiration led to immunosuppressive MDSC phenotype (171), which has well been established (172).

5.2.3 AR signalling in neutrophils

Research has shown that androgens promote neutrophil maturation and expansion in the bone marrow, as well as subsequent chemotaxis towards foci of injury or malignancy (173–175). AR-KO mice are often neutropenic and susceptible to acute bacterial infection (176). Male mice castrated prior to melanoma implantation also show impaired neutrophil maturation and function, with elevated metastatic burden that can be ameliorated by rescue testosterone replacement (174). Conversely, women with PCOS and insulin resistance often show increased circulating androgens associated with raised neutrophil count (177). Interestingly, in another study, ADT suppresses neutrophil cytotoxicity via increased TGFβ-RI (178), which is also seen in prostate cancer patients receiving ADT (174). High dose androgens or TGFβ-RI inhibition rescue AR-mediated neutrophil suppression and restore its anti-tumour effects (178).

However, androgen-sensitised neutrophils can also exhibit reduced bactericidal functions or cytotoxicity, hence promoting tumour progression. This phenotype is accompanied by high expression of anti-inflammatory cytokines such as IL-10 (175). For instance, AR signalling promotes hepatic neutrophil accumulation and contribute to MC-38 and B16 liver metastases (LM) (173). Antagonising neutrophil AR signalling axis significantly mitigates LM. Two other studies show tumour infiltrating neutrophils promote AR expression in bladder cancer and RCC cells, which increases their metastatic potential (179, 180). Therefore, systemic administration of antiandrogens often shows equivocal effects on neutrophil-mediated tumour control.

5.2.4 AR signalling in CAFs and endothelial cells

Several studies have demonstrated the important role of AR in preventing fibroblasts from differentiating into CAFs in skin cancers (181, 182) and prostate cancer (183–186). Low AR levels in prostate cancer stroma is associated with poorer patient survival. AR inhibits ANKRD1 (181) and LMO2 (183) expression, both of which are activators of CAF-related gene signatures. AR downregulation or deactivation leads to transition from normal fibroblasts to CAFs, enhancing tumorigenesis, tumour cell stemness and invasion via ECM remodelling and increased MMP expression (186), as well as increased expression of cytokines including IL-6, IL-8, IL-11, CCL2, IFNγ and M-CSF, all of which are also known to induce an immunosuppressive TME (182–185).

Further studies are anticipated on the effects of AR signalling in tumour endothelium and angiogenesis (187). While AR signalling in prostate cancer and RCC cells is known to upregulate angiogenic cytokines including VEGF and CXCL5 (188–190), AR signalling on endothelial cells themselves can also directly increase proliferation (191). AR-deficient or AR-antagonised endothelial cells show reduced angiogenic capacity and failure to activate eNOS (192, 193). How these findings may translate into tangible clinical intervention remains to be elucidated.

5.3 Mechanisms of AR and I/O resistance

Patient scRNA-seq and murine models have suggested that an increased AR signalling may predict I/O resistance, resulting from downregulation of IFNγ and upregulation of $CD8^+$ T cell exhaustion programmes. Indeed, as previous sections have shown, a recurrent *in vivo* finding is that castration or T cell-specific AR knockout can improve I/O response in male mice, while antiandrogens rescue I/O response and tumour control in androgen-exposed females. While it is natural to test I/O-antiandrogen combinations in the clinical setting, I/O nevertheless fails to synergise with AR antagonists in metastatic CRPC after all, as evident in the IMbassador250 trial (194). Why is this?

One explanation, as discussed earlier, is that male $CD8^+$ T cells have experienced long-term androgen exposure, predisposing them towards exhausted phenotypes during tumour progression, irrespective of subsequent AR signalling manipulation. In preclinical studies, castration or cell-specific AR knockout is almost always performed *before* tumour inoculation and I/O treatment. The dynamics of interaction between malignant cells and the TME may well be different from research involving antiandrogens. It reminds us that the sequence of I/O versus AR signalling manipulation is crucial to an optimised patient response.

Another hypothesis is that AR antagonists suppress anti-tumour immunity independently of AR. One study has shown that AR antagonists inhibit initial T cell priming via an off-target effect on GABA-A (195). Even if T cell exhaustion may be reduced with antiandrogen treatment, the initial neoantigen presentation and infiltration into the tumours can also be compromised, cancelling out the beneficial effect of AR antagonist on checkpoint inhibition. Indeed, another study also shows increased monocytic MDSC infiltration, decreased CD8+ TIL number and increased PD-L1 expression in enzalutamide-treated murine Myc-CaP tumours (168). When these tumour cells acquire enzalutamide resistance, they upregulate PD-L1 expression and possess an increased capacity to skew myeloid cells towards MDSCs and M2 macrophages (168, 195), further suppressing T cell function. Strikingly, another study shows a signalling crosstalk between AR and the glucocorticoid receptor (GR) (196). AR inhibition upregulates GR while high-dose steroids confer enzalutamide resistance to a prostate cancer model (196). This finding necessitates a more thorough understanding of the escape mechanisms of tumour cells when treated with combined I/O and antiandrogen (101).

Also importantly, as evident in previous sections, AR signalling exhibits heterogeneous effects on different TME cell types, resulting in equivocal efficacy when combining I/O with systemic antiandrogen administration. While AR on lymphocytes (T, B, NK) negatively regulates their cytotoxic functions in general, AR on macrophages and neutrophils regulate their functions in a sequence-dependent manner. Specifically, AR promotes the proliferation, maturation and

infiltration of macrophages and neutrophils into the tissues. However, it subsequently renders these cells anti-inflammatory in the TME. AR inhibition also enhances the immunosuppressive functions of DCs and MDSCs. Furthermore, increasing evidence has shown that AR prevents fibroblast differentiation towards CAFs and regulates endothelial cell proliferation. Therefore, there is much unknown as to how systemic AR inhibition on a heterogenous TME affect immunotherapy efficacy. Interestingly, a recent analysis of NSCLC exosome and transcriptome datasets show significant enrichment of DCs and T cells as well as a T cell dysfunction phenotype in the TME of female patients, while the male patients generally possess a T cell excluded TME (197). These findings are highly consistent with the effects of AR signalling on TME cell types as described earlier, demonstrating the key role of AR in regulating tumour immunology and I/O response. Future combinatory I/O with AR modulation will require delicate consideration into the individual tumour characteristics.

Specifically in prostate cancer, preclinical studies have shown, as discussed above, how blocking AR signalling can in fact compromise T cell priming or activation (195), upregulate CCL2/STAT3-mediated macrophage recruitment (163), reduce neutrophil maturation or expansion (174), promote CAF accumulation (184), and increasing tumour cell expression of GR (196), all of which may negate the benefits of checkpoint blockade in these patients (198). Future combinatory trials in advanced prostate cancer will need to select patients early in their disease progression, and give careful thoughts on both the checkpoint (PD-1, PD-L1, CTLA4, TIGIT, etc.) to be targeted, as well as the timing of I/O relative to AR inhibition (198, 199).

6 Concluding remarks

The perceived sexual dimorphism in cancer epidemiology is the consequence of a myriad of factors, including socioeconomic and cultural disparities (200), environmental exposures, sex chromosomes, sex hormones, as well as sex hormone receptors such as AR. Indeed, gender oncology is emerging as an important aspect of personalised medicine that recognises and addresses such differences in cancer incidence and therapeutic responses (147). While research has elucidated the role of AR in tumour development and progression, studies have often overlooked the impact of AR signalling on the TME and I/O outcomes. We have shown that AR plays heterogeneous roles in individual TME cell types, sometimes independent of androgens, which potentially explains the equivocal efficacy of antiandrogen and I/O combination so far. It is hoped that future clinical studies on cancers could disaggregate outcomes by sex and stratify androgen/AR level more frequently, hence providing further evidence for antiandrogen and I/O combination or personalised I/O tailored to sex and androgen/AR status. Translational studies on AR modulation of the TME can help design better trials of I/O-based gender oncology with AR as a potential biomarker. By doing so we may optimise treatment strategies and improve individualised patient outcomes.

Author contributions

JZ: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing. QW: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing. AT: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. CL: Data curation, Visualization, Writing – original draft, Writing – review & editing. HT: Conceptualization, Resources, Supervision, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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