Unveiling sex differences in pancreatic ductal adenocarcinoma: Current evidence and future directions (Review)

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Abstract. Pancreatic ductal adenocarcinoma (PDAC) is the seventh leading cause of cancer-related death worldwide in both men and women. While sex-specific differences are increasingly recognized as critical determinants of health and disease, particularly in oncology, they remain markedly underexplored in PDAC. Emerging evidence suggests that sex differences influence numerous aspects of PDAC, including treatment response and prognosis. This knowledge gap represents a notable barrier to the development of effective, personalized therapeutic strategies for both sexes. The present review provides a comprehensive overview of the current knowledge on sex-based differences in PDAC, encompassing epidemiology, risk factors, chemotherapy pharmacokinetics and toxicity, prognosis, therapeutic response, immune interactions, tumor microenvironment, tumor microbiota and molecular biomarkers.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies, characterized by late-stage diagnosis, limited therapeutic options and poor prognosis. Despite advancements in oncology, the 5-year survival rate remains dismal at ~13% (1). While substantial research has focused on genetic and environmental risk factors, molecular changes and novel treatment options for PDAC, the influence of biological sex on disease incidence, progression and treatment response remains insufficiently understood.

Sex- and gender-specific factors are increasingly recognized as important determinants of disease susceptibility, progression, and treatment outcomes. Sex refers to biological attributes, while gender encompasses socially constructed roles and behaviors (2). Both biological and sociocultural components of sex and gender can profoundly influence healthcare delivery from prevention and screening to diagnosis and therapy, highlighting the need for more individualized sex- and gender-specific approaches (3,4). Despite recent efforts, women remain underrepresented in clinical studies, often due to inclusion biases related to fertility concerns and hormonal variability (5). In oncology, these disparities remain insufficiently addressed, hindering progress toward truly personalized and effective treatment strategies (6). How sex-specific factors shape disease biology and outcomes is particularly evident in colorectal cancer. Although it affects both sexes, women over the age of 65 have higher mortality rates and a lower 5-year survival rate compared with age-matched men (7).

This survival disadvantage may, at least in part, be related to the higher likelihood of women developing right-sided colon cancer, which is often associated with more aggressive tumor phenotypes, and to their greater susceptibility to treatment-related toxicity (7,8). These findings underscore the clinical relevance of sex-based differences in cancer biology and outcomes and highlight opportunities to develop strategies that optimize treatment based on sex-specific factors.

By contrast, sex-specific differences in PDAC remain poorly studied, resulting in limited evidence for sex-based variations in pathophysiology and a lack of precision medicine approaches tailored to both men and women. The present review summarizes current evidence on the epidemiological, biological and clinical aspects of sex differences in PDAC. By identifying key disparities, the present review aims to highlight the need for sex-specific strategies in prevention, diagnosis and treatment, which could advance personalized and effective care, while offering approaches to improve the integration of these variables into basic and clinical research.

2. Epidemiology

PDAC displays a slightly higher incidence in men than in women, with 269,709 vs. 241,283 respective new cases reported in 2022, ranking it as the 15th and 16th most common cancer in men and women, respectively (9). Globally, PDAC incidence rates are rising, with a disproportionately steeper increase observed in women. Between 1975 and 2016, incidence rates increased annually by 1.1% in women compared with 0.38% in men, highlighting a growing burden of PDAC among women (10). The highest incidence rates are reported in highly developed regions, likely due to lifestyle and environmental factors, with Western Europe currently exhibiting the highest lifetime risk of PDAC (11).

Notably, the incidence and mortality of PDAC peak at different ages between sexes: In men, the highest number of cases and deaths occurs between ages 65-69 years, whereas in women, it peaks between ages 75-79 years (12). Of particular concern is the rising incidence of PDAC among women <40 years, who now show higher rates compared with age-matched men (13,14). A study by Cavazzani *et al* (13) reported the greatest increase in PDAC incidence among women aged 18-26 years, with an average annual percentage change (AAPC) of 9.37% [95% confidence interval (CI), 7.36-11.41%; P<0.0001], compared with an AAPC of 4.43% in men of the same age group. Survival rates remain poor for both sexes, with a 5-year survival of ~13% (1). While the age-standardized mortality rate is higher in men overall, this varies by age group. The most pronounced sex difference in relative survival is observed in patients <44 years, with survival rates of 24.37% in women vs. 18.03% in men. However, this difference diminishes with age, and survival rates become comparable in individuals >65 years (4.68% in women vs. 4.44% in men) (15).

PDAC represents a growing global public health challenge. The disproportionately steeper rise in incidence among women, particularly at younger ages, highlights the urgent need for sex-specific strategies in prevention, early detection, and treatment.

3. Risk factors

Multiple risk factors for PDAC have been well established, including tobacco smoking, alcohol consumption, obesity, diabetes mellitus, chronic pancreatitis, and genetic predisposition (14). However, sex-based differences are often overlooked. This section provides an overview of sex-specific variations in non-genetic PDAC risk factors.

Cigarette smoking. Cigarette smoking is a well-documented risk factor for PDAC, with a reported OR of 1.77 (95% CI, 1.38-2.26) for current smokers compared with never smokers, and a dose- and duration-dependent increase in risk (16). However, evidence regarding sex differences in smoking-related PDAC risk remains conflicting. A large meta-analysis found no significant difference in smoking-related PDAC risk between men and women (16). By contrast, a multiethnic cohort study involving 192,035 participants reported a notably higher risk in women who began smoking before age 20 years, with a 71% increased PDAC risk [hazard ratio (HR), 1.71; 95% CI, 1.14-2.57], compared with a 49% increase in men (HR, 1.49; 95% CI, 1.03-2.15) (17). These findings are supported by data from the International Pancreatic Cancer Case-Control Consortium, which reported a particularly elevated risk among female smokers <65 years of age (18). Although smoking cessation significantly reduces PDAC risk, the benefit appears to be less pronounced in women. A pooled analysis from Japan found that female former smokers remained at elevated risk, whereas the risk normalized in men after quitting (19,20).

These findings suggest that smoking may pose a particularly strong and persistent risk for younger women, even when cessation occurs later in life. Thus, although smoking is a well-established PDAC risk factor, sex- and age-related differences, are not yet firmly supported and warrant further high-quality prospective research. Key studies reporting sex-specific differences in smoking-related PDAC risk are summarized in Table I.

Body mass index (BMI) and obesity. Obesity is recognized as a modifiable risk factor for PDAC, with growing evidence suggesting that women may be particularly vulnerable to obesity-related risk (20). A study reported that women with a BMI ≥40 had more than double the risk of PDAC [relative risk (RR), 2.76; 95% CI, 1.74-4.36] (21). A pooled analysis from the PanScan Consortium further emphasized that central adiposity, measured by the waist-to-hip ratio, is more strongly associated with PDAC risk in women than in men (22). This finding suggests that fat distribution may play a more critical role in PDAC risk among women. An additional study indicated that components of metabolic syndrome, defined as abdominal obesity, diabetes, hypertension and dyslipidemia, increase PDAC risk more significantly in women (23). Conversely, obesity during early adulthood appears to be more closely associated with PDAC mortality in men, highlighting the potential influence of both timing and age of weight gain (24).

Table II provides an overview of sex-specific effects of overweight and obesity on PDAC risk. In summary, multiple large, prospective cohort and pooled analyses support that obesity, particularly central or severe obesity, confers a greater PDAC risk in women than in men, although age and timing

Table I. Comparative summary of studies on smoking and pancreatic ductal adenocarcinoma risk by sex.

First author, year	Number of patients	Study design	Results	P-value	Evidence level[a]	(Refs.)
Gram *et al*, 2023	1,936	Prospective cohort study, followed participants aged 45-75 years for a mean of 19.2 years	Current smoker: ♀ HR, 1.49 (95% CI, 1.24 1.79) ♂ HR, 1.48 (95% CI, 1.22-1.79) Early smoking: ♀ HR, 1.71 (95% CI, 1.14-2.57) ♂ HR, 1.49 (95% CI, 1.03-2.15)	N/A for interaction by sex N/A for interaction by sex	B	(17)
Bosetti *et al*, 2012	6,507 cases/12, 890 controls	Pooled case-control (PanC4 Consortium)	Current smoker (15 to <25 cigarettes/day): ♀ OR, 2.60 (95% CI, 1.74-3.90) ♂ OR, 1.92 (95% CI, 1.55-2.38) High consumption (≥25 cigarettes/day): ♀ OR, 3.84 (95% CI, 2.73-5.42) ♂ OR, 2.92 (95% CI, 2.01-4.23)	0.195 0.286	B	(18)
Koyanagi *et al*, 2019	354,154	Pooled analysis of 10 prospective population-based cohort studies in Japan	Current smoker (compared with never smokers): ♀ HR, 1.81 (95% CI, 1.43-2.30) ♂ HR, 1.59 (95% CI, 1.32-1.91) Former smoker (compared with never smokers): ♀ HR, 1.77 (95% CI, 1.19-2.62) ♂ HR, 1.10 (95% CI, 0.89-1.36) Risk per 10 pack-years (compared with never smokers): ♀ HR, 1.06 (95% CI, 0.92-1.22) ♂ HR, 1.06 (95% CI, 1.03-1.10)	N/A for interaction by sex N/A for interaction by sex N/A for interaction by sex	A	(19)

[a]Evidence levels (A-C): A, high evidence: Randomized large, controlled trials, systematic reviews or meta-analyses, large prospective cohort studies, consistent results across multiple independent study groups or reproducible preclinical data with low risk of bias; B, moderate evidence: Non-randomized or small cohort studies, single RCTs, or preclinical data with some methodological limitations; and C, low evidence: Exploratory or descriptive studies (such as *in vitro* studies and case reports) with high bias risk or lacking controls. HR, hazard ratio; OR, odds ratio; CI, confidence interval; N/A, not available.

of weight gain may modify this relationship. Further research should clarify the underlying sex-specific metabolic and hormonal factors driving this vulnerability.

Diabetes mellitus. The association between diabetes mellitus and PDAC appears to be largely independent of sex. While a study has reported a higher prevalence of PDAC among male diabetic patients (25), others found no statistically significant difference in overall PDAC risk between men and women (25-28). Although sex alone may not significantly modify PDAC risk in diabetic patients, lifestyle factors and comorbidity patterns, which often differ by sex, may still influence overall risk and should be considered in prevention strategies (26-28).

Alcohol. Heavy alcohol consumption (defined as ≥9 drinks per day) is associated with an increased risk of PDAC, particularly in men (29). Several large studies and pooled analyses have shown that the association between heavy alcohol intake and PDAC is more pronounced in men than in women (29-31). However, this apparent sex difference may partly reflect a statistical limitation: Female heavy drinkers are often under-represented in study cohorts, limiting the ability to accurately assess risk in women (31). Nonetheless, a pooled analysis of 14 prospective cohort studies (n=2,187 PDAC cases) found a statistically significant association between alcohol intake ≥30 g/day and PDAC in women (RR, 1.41; 95% CI, 1.07-1.85) (30). At even higher intake levels, the risk was more substantial in men. Notably, the study could not assess the impact of very high alcohol intake in women due to the small number of female participants consuming ≥45 g/day (30). In regions with higher socioeconomic status, a growing trend of alcohol consumption has been observed among young women (32). If this trend continues, alcohol may become an

Table II. Comparative summary of studies on obesity and PDAC risk by sex.

First author, year	Number of patients	Study design	Results	P-value	Evidence level[a]	(Refs.)
Genkinger *et al*, 2015	1,096,492	Pooled analysis of 20 prospective cohort studies from the NCI BMI and Mortality Cohort Consortium	Waist circumference (per 10 cm): ♀ HR, 1.09 (95% CI, 1.03-1.15) ♂ HR, 1.08 (95% CI, 1.02-1.15) Waist-to-hip ratio: ♀ HR, 1.10 (95% CI, 1.01-1.21) ♂ HR, 1.12 (95% CI, 1.02-1.23) BMI in early adulthood (per 5 kg/m^2): ♀ HR, 1.11 (95% CI, 1.03-1.21) ♂ HR, 1.25 (95% CI, 1.15-1.35)	0.86 0.80 0.04	A	(24)
Arslan *et al*, 2010	2,170 PDAC cases/2,209 matched controls	Pooled nested case-control study (Pancreatic Cancer Cohort Consortium-PanScan)	PDAC risk and body composition BMI: ♀ OR, 1.34 (95% CI, 1.05-1.70) ♂ OR, 1.33 (95% CI, 1.04-1.69) Waist-to-hip-ratio: ♀ OR, 1.87 (95% CI, 1.31-2.69) ♂ N/A, not significant	N/A for interaction by sex N/A for interaction by sex	A	(22)
Calle *et al*, 2003	900,053	Prospective cohort study (Cancer Prevention Study II), Follow-up 16 years	PDAC mortality by BMI BMI, 25.0-29.9 kg/m^2: ♀ RR, 1.11 (95% CI, 1.00-1.24) ♂ RR, 1.13 (95% CI, 1.03-1.25) BMI, 30.0-34.9 kg/m^2: ♀ RR, 1.28 (95% CI, 1.07-1.52) ♂ RR, 1.41 (95% CI, 1.19-1.66) BMI, ≥40.0 kg/m^2: ♀ RR, 2.76 (95% CI, 1.74-4.36) ♂ RR, 1.49 (95% CI, 0.99-2.22)	N/A for interaction by sex N/A for interaction by sex N/A for interaction by sex	A	(21)
Johansen *et al*, 2010	577,315/862 PDAC cases	Pooled prospective cohort study from the Metabolic Syndrome and Cancer Project (Me-Can)	PDAC risk and metabolic syndrome [sex-specific results (z-score-based HRs)] BMI: ♀ 0.92, (95% CI, 0.79-1.07) ♂ 0.90, (95% CI, 0.80-1.02) Mid-blood pressure: ♀ 1.34, (95% CI, 1.08-1.66) ♂ 1.15, (95% CI, 0.97-1.35) Glucose: ♀ 1.98, (95% CI, 1.41-2.76) ♂ 1.37, (95% CI, 1.01-1.85) Cholesterol: ♀ 1.16, (95% CI, 0.96-1.41) ♂ 0.81, (95% CI, 0.69-0.95)	 0.45 0.06 0.02 0.08	A	(23)
Jiao *et al*, 2010	952,494/2,639 PDAC cases	Pooled analysis of 7 prospective cohorts (US, Finland and China). Mean follow-up of 6.9 years	PDAC risk and BMI BMI (per 5 kg/m^2 increment): ♀ RR, 1.12 (95% CI, 1.05-1.19) ♂ RR, 1.06 (95% CI, 0.99-1.13) BMI, 30.0-34.9 kg/m^2: ♀ RR, 1.34 (95% CI, 1.11-1.64) ♂ RR, 1.11 (95% CI, 0.95-1.30)	 N/A for interaction by sex N/A for interaction by sex	A	(20)

[a]Evidence levels (A-C): A, high evidence: Randomized large, controlled trials, systematic reviews or meta-analyses, large prospective cohort studies, consistent results across multiple independent study groups or reproducible preclinical data with low risk of bias; B, moderate evidence: Non-randomized or small cohort studies, single RCTs or preclinical data with some methodological limitations; and C, low evidence: Exploratory or descriptive studies (such as *in vitro* studies and case reports) with high bias risk or lacking controls. HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; N/A, not available; PDAC, pancreatic ductal adenocarcinoma; BMI, body mass index.

important contributor to an increased PDAC incidence among women in the coming years.

Chronic pancreatitis (CP). CP significantly increases the risk of PDAC, with a reported 16- to 22-fold elevation, particularly within the first 2 years following a CP diagnosis (33,34). CP is more commonly diagnosed in men, who also tend to develop the disease at a younger age compared with women (33). This male predominance is largely attributed to higher rates of alcohol consumption and smoking (33,35). However, to date and to the best of our knowledge, no significant sex-based differences have been observed in the magnitude of PDAC risk among patients with CP (33-35).

Hormonal factors. There is growing evidence suggesting that female sex hormones may exert a protective effect against the development of PDAC. However, studies examining hormone-related exposures have yielded conflicting results (Table III). A recent systematic review and meta-analysis of 21 observational studies involving 7,700 PDAC cases adds important context: Ever-use of oral contraceptives (OCs) was associated with a modest but statistically significant reduction in PDAC risk (RR, 0.85; 95% CI, 0.73-0.98) (36). This inverse association was particularly evident in high-quality studies and European cohorts, while no clear effect emerged in studies from Asia or America (36). Notably, no dose-response relationship was observed, as PDAC risk did not vary by duration of OC use (36). Despite notable heterogeneity, the meta-analysis supports a potential protective role of exogenous estrogen.

In this context, findings from individual studies illustrate the variability across hormone-related exposures. Several studies investigating exogenous hormone therapy (HRT) reported reduced PDAC risk: A Swedish cohort study of 17,035 women linked high estrogen levels and HRT use to lower PDAC risk (37), and another large cohort likewise found a protective association with estrogen therapy (38). However, these results were not replicated in an American cohort of 37,459 women, in which HRT showed no association with PDAC risk (39).

Studies assessing endogenous estrogen exposure show similar inconsistency. In the American cohort, later menopause was related to a lower PDAC risk and a significant inverse relationship was observed between age at menopause and risk, suggesting a protective effect of longer endogenous estrogen exposure (39). However, a separate case-control study reported the opposite: An increased PDAC risk was associated with later menopause (40). To date and to the best of our knowledge, no consistent association has been observed between PDAC risk and other reproductive factors such as parity (number of children) or breastfeeding (37-39,41). In conclusion, current data suggest that higher lifetime estrogen exposure may reduce PDAC risk, though results are inconsistent and often lose significance after adjustment, indicating potential residual confounding or differences in population characteristics, hormone formulations or follow-up duration. Overall, evidence is moderately strong but lacks consistency and mechanistic clarity. While estrogen may have a protective role, current data are insufficient to confirm causality, warranting further research integrating hormonal and genetic markers.

4. Pharmacokinetics and toxicity of chemotherapy

Chemotherapeutic drugs are commonly prescribed at standardized doses based on body weight or body surface area, although therapeutic efficacy is more closely related to circulating drug concentrations than to the administered dose (6). As a result, interindividual variations in drug metabolism can lead to suboptimal outcomes, including reduced efficacy or increased toxicity (6). Pharmacokinetics and pharmacodynamics differ between the sexes, yet this is often overlooked in clinical dosing strategies. Factors such as higher body fat percentage in women (42), greater renal function in men (6), and differences in muscle mass, total body water, cardiac output, and liver perfusion (4) all influence drug distribution and metabolism. A recent systematic review identified significant sex-specific pharmacokinetic differences for several drugs, including 5-fluorouracil (5-FU) and paclitaxel, both of which are integral components of standard PDAC treatment regimens (4,43). 5-FU, a key drug in the FOLFIRINOX regimen (leucovorin, 5-FU, irinotecan, and oxaliplatin) (43), is cleared >20% more rapidly in men than in women. Consequently, equivalent dosing may lead to increased toxicity in women and a potential risk of underdosing in men (44). Notably, this sex difference in clearance remains significant even after adjusting for age and dose (45). The difference may be partially explained by sex-specific variation in the activity of dihydropyrimidine dehydrogenase, the primary enzyme responsible for metabolizing 5-FU (45). In addition, genetic variants of methylenetetrahydrofolate reductase, an enzyme that influences 5-FU cytotoxicity, have demonstrated sex-dependent effects, suggesting that female patients may require lower 5-FU doses to avoid toxicity (42). In line with these findings, a study on colorectal cancer has shown that women experience a significantly higher rate of side effects from 5-FU-based therapies, both in the adjuvant and metastatic settings (4). In the treatment of colorectal cancer, increased toxicity has been reported not only in combination regimens but also with 5-FU monotherapy (4).

Sex-related pharmacokinetic differences for oxaliplatin are inconsistent. While a study has reported a 40% lower clearance in women (46), another found no significant sex-based differences (47). Data on irinotecan are similarly mixed. Certain studies suggest that women may have lower clearance, reduced volume of distribution and decreased bioavailability, potentially influencing both efficacy and toxicity (48,49). However, another investigation attributed this variability primarily to liver function, with minimal differences attributable to sex (50). Although 5-FU, irinotecan, and oxaliplatin are administered in combination in PDAC treatment, the interactions and cumulative pharmacokinetic effects of these drugs remain poorly understood. Although pharmacokinetic findings imply differing toxicity risks, few studies have systematically evaluated chemotherapy-related adverse events in PDAC by sex. Existing data are often limited by small sample sizes or single-center designs. Some report higher toxicity rates in women, such as constipation, hand-foot syndrome and epigastric pain (51), and an increased incidence of febrile neutropenia and agranulocytosis during FOLFIRINOX treatment (52). Others, including a prospective Korean study, found no significant overall differences but noted more frequent dose

Table III. Comparative summary of studies on female hormonal determinants and PDAC risk.

First author/s, year	Number of patients	Study design	Results	P-value	Evidence level[a]	(Refs.)
Ilic *et al*, 2021	21 studies (10 case-control + 11 cohort), 7,700 PDAC cases	Systematic review and meta-analysis (Europe, America and Asia)	Ever use of OCs: RR, 0.85 (95% CI, 0.73-0.98)	0.03	A	(36)
			No dose-response relationship for duration: <1 year: RR, 1.08 (95% CI, 0.91-1.29) <5 years: RR, 1.07 (95% CI, 0.95-1.19) 5-10 years: RR, 1.08 (95% CI, 0.93-1.26)	>0.05 for all		
Andersson *et al*, 2018	17,035/110 PDAC cases	Prospective population-based cohort study (Sweden)	Age at menarche (continuous): HR, 1.17 (95% CI, 1.04-1.32)	0.008	B	(37)
			Ever use of any HRT: HR, 0.48 (95% CI, 0.23-1.00)	0.049		
			Estrogen-only HRT: HR, 0.22 (95% CI, 0.05-0.90)	0.035		
			Ever use of OC: HR, 0.68 (95% CI, 0.44-1.06)	0.091		
			Parity, breastfeeding and menopause timing: HR, ~1.00	>0.05 for all		
Lee *et al*, 2013	118,164/323 PDAC cases	Prospective cohort study (USA)	Estrogen-only HRT, current use: HR, 0.59 (95% CI, 0.42-0.84)	0.003	A	(38)
			Estrogen HRT ≥20 years: HR, 0.55 (95% CI, 0.33-0.91)	0.036		
			OC use ≥10 years: HR, 1.72 (95% CI, 1.19-2.49)	0.014		
			High dose OC use ≥10 years: HR, 2.08 (95% CI, 1.05-4.12)	0.024		
			Age at menarche, parity, menopause and breastfeeding HR, ~1.00	>0.05 for all		
Prizment *et al*, 2006	37,459/228 PDAC cases	Prospective population-based cohort study (USA)	Age at menopause ≥55 vs. <45 years: HR, 0.35 (95% CI, 0.18-0.68)	0.005	B	(39)
			Age at menopause (continuous, 5-year increase): HR, 0.81 (95% CI, 0.72-0.91)	0.001		
			Ever use of any HRT: HR, 1.07 (95% CI, 0.82-1.40)	0.606		
			Ever use of OC: HR, 0.90 (95% CI, 0.62-1.30)	0.566		
			Parity, menarche and age at first birth HR, ~1.00	>0.05 for all		
Duell and Holly, 2005	241 PDAC cases/818 controls	Population-based case-control study (USA)	Age at menopause ≥55 vs. <45 years: OR, 1.9 (95% CI, 1.2-2.8)	0.003	B	(40)
			Estrogen-only HRT: HR, 0.84 (95% CI, 0.62-1.1)	>0.05		
			Ever use of OC:	>0.05		

Table III. Continued.

First author/s, year	Number of patients	Study design	Results	P-value	Evidence level[a]	(Refs.)
Stevens *et al*, 2009	995,1957/1,182 PDAC cases	Prospective cohort study (UK)	HR, 0.95 (95% CI, 0.65-1.4) Parity (ever vs. never): RR, 0.88 (95% CI, 0.79-0.98) Age at menarche, age at birth, age at menopause, breastfeeding and number of children	0.01 >0.05 for all	A	(41)

[a]Evidence levels (A-C): A, high evidence: Randomized large, controlled trials, systematic reviews or meta-analyses, large prospective cohort studies, consistent results across multiple independent study groups or reproducible preclinical data with low risk of bias; B, moderate evidence: Non-randomized or small cohort studies, single RCTs, or preclinical data with some methodological limitations; and C, low evidence: Exploratory or descriptive studies (such as *in vitro* studies and case reports) with high bias risk or lacking controls. HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; N/A, not available; PDAC, pancreatic ductal adenocarcinoma; HRT, hormone replacement therapy; OC, oral contraceptive.

reductions among female patients (53), suggesting lower tolerance or heightened susceptibility to toxicity.

Gemcitabine, either as a monotherapy or in combination with nab-paclitaxel, is another well-established PDAC treatment regimen for PDAC. To date and to the best of our knowledge, no clinical evidence supports a sex-specific difference in gemcitabine pharmacokinetics (54,55). While sex has been shown to influence the clearance and toxicity of solvent-based paclitaxel (56,57), this effect is not observed with nab-paclitaxel, which displays no sex-related differences in elimination (58), suggesting a distinct pharmacological mechanism.

In summary, pharmacokinetic studies of 5-FU, irinotecan and oxaliplatin suggest that standardized dosing does not adequately account for sex-specific variability, with men at risk of potential underdosing and women at higher risk of toxicity. Major PDAC trials rarely stratify adverse events by sex, underscoring the need for comprehensive, sex-disaggregated toxicity analyses. Addressing this through novel therapy concepts is essential to optimize therapeutic efficacy, minimize adverse events and advance sex-sensitive treatment strategies in pancreatic cancer.

5. Prognosis and therapy response

Few studies, albeit with large populations, have explored sex differences in treatment allocation and prognostic outcomes in PDAC. Notably, the Dutch Pancreatic Cancer Group conducted two large retrospective studies analyzing sex-based differences in tumor characteristics, treatment decisions, and survival outcomes in both stage I-III and metastatic PDAC cohorts, each including >6,000 patients (59,60). In both cohorts, female patients were older, had worse performance status but fewer comorbidities and were less likely to receive systemic chemotherapy compared with male patients. The primary reason for this disparity was a higher preference among women for best supportive care across all disease stages. No sex-based difference was observed in the likelihood of undergoing surgical resection in resectable PDAC, except among women aged ≥80 years, who were less frequently offered surgery (59,60). By contrast, two additional studies reported a lower likelihood of curative treatment planning for female patients. The first was a preliminary analysis of 100 patients from the Chemotherapy, Host Response and Molecular dynamics in Periampullary cancer (CHAMP) study, which includes both pancreatic and periampullary adenocarcinomas. The second was a nationwide Swedish cohort study of 5,677 patients with periampullary tumors, which similarly reported that fewer women were planned for curative treatment (61,62). However, in the Swedish cohort, this difference disappeared after adjustment for age and tumor location, unlike in the CHAMP study. This discrepancy may be explained by the inclusion of other periampullary tumors, such as duodenal adenocarcinomas, which have different surgical and prognostic profiles and may influence treatment decisions. The largest study to date, conducted by the American College of Surgeons and including 22,993 patients, identified male sex as a risk factor for major morbidity following pancreaticoduodenectomy (63). These findings highlight that sex disparities in treatment outcomes are not unequivocal and must be interpreted with caution. Most available studies are retrospective and heterogeneous in design, with varying inclusion criteria, treatment eras and adjustment for confounders, which limits the strength of causal inference. Observed associations between sex and prognosis in PDAC likely reflect the interplay of multiple factors, including age, performance status, comorbidities, socioeconomic status, access to specialized care and patient preferences, rather than biological sex alone. Few studies have stratified analyses or applied sensitivity models to disentangle these sociocultural and clinical variables from intrinsic biological differences. Nevertheless, several studies have identified female sex as an independent prognostic factor for improved overall survival (OS) in PDAC (59,60,64). Large cohort studies have reported a statistically significant increase, or at least a trend toward, increased OS in women, even after adjusting for confounders. However, in the end, only two studies have directly examined

sex differences in response to FOLFIRINOX. A small cohort study by Hohla *et al* (65), which included 49 patients with unresectable PDAC, found a significantly higher disease control rate in female patients treated with FOLFIRINOX compared with males. Similarly, the PRODIGE 4/ACCORD 11 randomized trial observed a trend toward longer median OS in female patients with metastatic disease receiving FOLFIRINOX, although this did not reach statistical significance (64). These findings again raise important questions about whether differences in chemotherapy toxicity and metabolism contribute to improved survival outcomes in women, underscoring the need for prospective studies with sex-stratified analyses and standardized reporting to improve the assessment of the biological vs. sociocultural determinants of treatment response in PDAC (3).

6. Immune response and the tumor microenvironment (TME)

Sex-based biological differences, particularly within the immune system, are well recognized across multiple diseases, including cancer (66-68). Generally, women exhibit stronger innate and adaptive immune responses, which has been linked to a higher prevalence of autoimmune disorders in women (66,67). The immune differences in men and women are regulated by both gonadal hormones, primarily estrogen and androgens and genetic mechanisms (66,69). Notably, stronger interferon signaling in women may result from two key mechanisms: i) Estrogen-mediated immune activation; and ii) X chromosome-linked differences. Estrogen enhances interferon production through Toll-like receptor 7 (TLR7) activation (70,71), and since TLR7 is encoded on the X chromosome, its expression and downstream immune responses are amplified in women (72). In addition, T and B cells in women demonstrate enhanced signaling and antibody responses to infections and vaccinations (67,73), which may contribute to more effective tumor immune surveillance. Estrogen further shapes the TME by modulating T cell activation and immune checkpoint expression (67,68,74). Across several cancer entities, the TMEs in women tend to display stronger immune activation than those of men (68,75).

In PDAC, the TME is a key contributor to immune evasion and poor prognosis; it is typically characterized by scarce cytotoxic T cell infiltration, abundant regulatory T cells and a dense, fibrotic stroma, which are features that also limit the response to immunotherapy (76,77). As a result, checkpoint inhibitors have shown limited efficacy in PDAC due to the inherently immunosuppressive nature of the tumor (78). Nevertheless, emerging evidence indicates that sex differences do influence immune pathways and the TME in PDAC. For example, He *et al* (79) identified a typically immunosuppressive subpopulation of formyl peptide receptor 2 (+) M2 macrophages that is specifically enriched in PDAC lesions from female patients. These tumor associated macrophages (TAMs), induced by estrogen, were associated with T cell exhaustion, reduced immune cell infiltration and poorer survival in women, suggesting a sex-specific immunosuppressive mechanism. In contrast to these findings, a recent study reported that female patients with PDAC exhibit higher levels of stromal biomarkers and increased tumor stiffness, both of which were associated with longer survival (80). The researchers further showed that estrogen signaling shapes the TME by driving cancer-associated fibroblasts toward a more tumor-suppressive phenotype (80). However, these estrogen-related effects were mediated not by systemic hormones but by locally produced estrogens within the tumor tissue and therefore do not fully explain the survival differences observed between women and men (80). In another study investigating patients with treatment-naive PDAC, women exhibited elevated circulating levels of C-X-C motif chemokine ligand (CXCL)9, IL-1β, IL-6, IL-10 and IL-13, supporting the notion of enhanced systemic immune activation in women (81).

Sex differences may also impact immune responses to chemotherapy. In a recent study by van Eijck *et al* (82), female sex was an independent prognostic factor for 5-year OS in patients with localized PDAC treated with neoadjuvant gemcitabine-based chemotherapy followed by surgery (43% OS in females vs. 22% in males). Notably, after neoadjuvant therapy, the TME in female patients showed fewer immunosuppressive M2 macrophages ($CD163^{+}MRC1$) and a distinct transcriptomic profile with higher expression of *CXCL10* and *CXCL11* and lower levels of *CCL2* and *IL-34*, suggesting an enhanced antitumor immune response (82). Although data on sex differences in immune responses in PDAC remain limited and potentially confounded by complex interactions among hormones, drugs and genetics, current evidence suggests that women may exhibit a more immunosuppressive TME characterized by a higher abundance of estrogen-influenced immunosuppressive macrophages, contrary to the expected higher immune activation in women. Notably, gemcitabine appears to induce greater macrophage plasticity in women, indicating a potential pathway for immune activation. Together, these observations highlight that sex and sex hormones uniquely shape immune activity in the TME and modulate responses to chemotherapy. Fig. 1 summarizes sex-related hormonal and genetic differences in PDAC, highlighting the distinct roles of estrogens and androgens in shaping tumor biology, immune responses and the TME in women and men. Although immune-targeted therapies have shown limited success in PDAC, emerging approaches such as neoantigen vaccination show promise and may enhance immune-based treatment strategies (83). Accounting for sex-specific immune regulation will therefore be critical as immunotherapies for PDAC continue to advance.

7. Tumor microbiota

Research on tumor microbiota has provided compelling insights into its role in modulating the TME (84) and shaping systemic immune responses, thereby influencing various diseases (85). In PDAC, the intratumoral microbiota significantly impacts prognosis and therapeutic efficacy, most notably by altering the TME (86), influencing tumor phenotype (87), and degrading chemotherapeutic agents such as gemcitabine (88,89). However, the influence of sex on the tumor microbiota remains unclear. To date, few studies have assessed bacterial species distribution by sex in patients with PDAC and none have reported significant differences (86,90). This is further supported by comparable rates of bacterial colonization in tumor tissue across sexes (91), as well as a

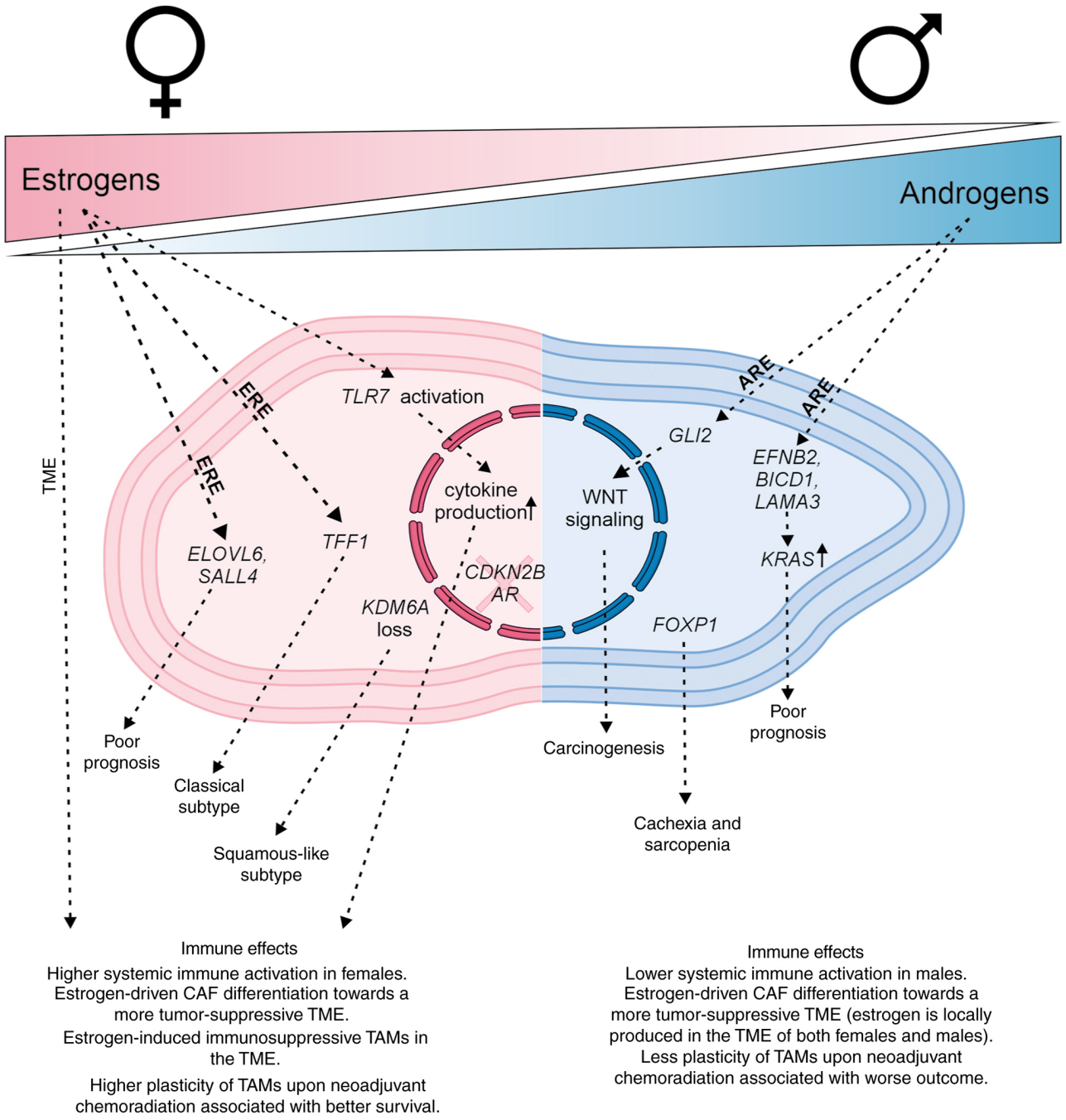

Figure 1. Overview of sex-related hormonal and genetic differences for PDAC. Estrogens significantly shape immune functions, including innate immune responsiveness through TLRs and the regulation of cytokine production. In PDAC, estrogens influence transcriptional subtypes and further modulate the TME by promoting the differentiation of CAFs toward a more tumor-suppressive phenotype. Conversely, estrogens can also affect TAMs, driving them toward a more immunosuppressive state. Notably, TAMs in women show greater plasticity following neoadjuvant chemoradiation with gemcitabine, which is associated with improved survival. By contrast, androgens are linked to carcinogenesis and cachexia. Notably, the effects of estrogens are not restricted to women; men can also produce estrogen locally within the tumor tissue, similarly promoting CAF differentiation toward a more tumor-suppressive TME. PDAC, pancreatic ductal adenocarcinoma; TME, tissue microenvironment; ERE, estrogen response element; ARE, androgen response element; AR, androgen receptor; TAM, tumor-associated macrophage; CAF, cancer-associated fibroblasts; TLR, Toll-like receptor; CDKN2B, cyclin-dependent kinase inhibitor 2B; TFF1, trefoil factor 1; KDM6A, lysine demethylase 6A; GLI2, zinc finger protein 2; EFNB2, ephrin B2; BICD1, bicaudal D cargo adaptor 1; LAMA3, laminin α3; ELOVL6, elongation-of-very-long-chain-fatty acids 6; SALL4, Sal-like protein 4.

similar prevalence of intratumoral gram-negative bacteria in male and female patients (89). Although it should be noted that none of the studies chose the investigation of sex-specific differences as their primary endpoint.

Nonetheless, sex-specific differences in the oral and gut microbiota have been reported in patients with PDAC compared with healthy controls (92). These differences are also evident in murine models, where a recent study identified increased abundance of *Ligilactobacillus* and *Acetatifactor* in female mice with PDAC (93). While intriguing, the implications of these findings for immune modulation or tumor progression remain unclear. Further illustrating the role of microbiota in therapy, antibiotic administration has been shown to enhance gemcitabine efficacy in advanced PDAC (94), although this

effect was not associated with patient sex. While current evidence does not show consistent sex-based differences in the tumor microbiota of PDAC, emerging findings in gut and oral microbiomes, as well as in preclinical models, underscore the need for further investigation. Understanding how sex may modulate the microbiome-immune-tumor axis could open new avenues for personalized therapeutic strategies.

8. Biomarkers and genetics

Serum Biomarkers. The most commonly used biomarker for PDAC is carbohydrate antigen 19-9 (CA19-9), although its specificity and sensitivity remain limited (95). Few studies have examined sex-specific differences and results are inconsistent. A study reported more men (77.3%) with elevated CA19-9 serum levels than women (66.7%) (96), although the clinical significance of this difference remains unclear. However, several novel biomarkers that are not used in clinical practice have shown sex-based differences in expression patterns. For example, tissue inhibitor of metalloproteinase 1 (TIMP1) has been shown to be associated with liver metastases and poorer survival specifically in male patients, a finding supported by mouse models showing earlier metastasis with higher TIMP1 levels in males (97). In addition, thymidine kinase (TK) levels have been reported to be higher in men: In one study, 21 men vs. 9 women had TK levels above the median, while low TK levels showed no sex difference (98). Moreover, the serum marker adiponectin has been shown to be associated with shorter survival in female patients only (99). These findings indicate that certain biomarkers may have sex-specific prognostic value, although none are currently used in clinical routine, to the best of our knowledge. While some sex-related differences have been reported, most data remain exploratory and lack consistent validation. The continued absence of reliable biomarkers in PDAC remains a major challenge for early detection and personalized therapy, underscoring the need for large, well-designed studies that systematically incorporate sex as a biological variable.

Genetic alterations. The four major driver mutations in PDAC affecting *KRAS, CDKN2A*, *TP53* and *SMAD4* occur at similar frequencies in both male and female patients (100,101). However, other tumor-related genes show sex-specific mutation patterns; for example, alterations in *CDKN2B* and the androgen receptor (*AR*) gene are more frequently observed in female patients (100). Additionally, AR and estrogen receptor binding sites in promoter regions contribute to distinct sex-specific gene expression patterns in PDAC (102). A study found that among all upregulated genes in male PDAC samples, 24 contained androgen response elements (AREs), including *EFNB2*, *BICD1* and *LAMA3*, which strongly correlate with *KRAS* expression, as well as *GLI2*, a key transcription factor involved in carcinogenesis. These ARE-regulated genes in men are enriched in tumor-related pathways, such as axon guidance and extracellular matrix components, and are associated with poorer survival. By contrast, among all genes upregulated in female PDAC samples compared with normal tissue, only 3 genes, *ELOVL6*, *SALL4* and *TFF1*, are upregulated by estrogen response elements. Overall, this suggests that AR-driven transcription plays a more dominant and functionally relevant role in male PDAC biology (102), while these sex-specific molecular effects do not appear to be linked to differential activity in the estrogen or pregnenolone pathways (103). Furthermore, no sex-specific differences were described for single nucleotide polymorphisms (SNPs) of DNA repair genes (104), although other SNPs had sex-specific effects. For instance, the leptin receptor SNP rs11585329 is associated with improved survival in men (99), while the APC I1307K variant correlates with improved outcomes in women (74). While these findings expand our understanding of sex-specific genomic features in PDAC, most evidence is derived from retrospective or database-driven analyses with limited functional validation. Linking these alterations to biological function and therapeutic vulnerability will be crucial to translate genomic sex differences into clinical relevance.

Transcriptional and epigenetic regulation. Notably, the expression of certain transcription factors contributes to sex-specific differences in tumor biology. For example, the transcription factor Kaiso has been linked to increased tumor invasiveness and poorer prognosis in male patients (105). Additionally, the transcription factors FoxP1 and activin have been associated with the development of cachexia and sarcopenia, which appear to affect male patients with PDAC more severely (106,107). However, findings on sex-specific molecular tumor subtypes based on transcription profiles remain inconsistent. Some studies suggest a higher prevalence of the more aggressive quasi-mesenchymal or basal-like subtypes in men with resected PDAC, potentially explaining poorer outcomes (108,109). By contrast, other studies report no significant sex-based differences in gene expression signatures used to predict treatment response to gemcitabine and FOLFIRINOX (110,111). In the realm of epigenetics, evidence indicates that loss of the histone demethylase, lysine demethylase 6A (KDM6A), induces a squamous-like, metastatic PDAC subtype specifically in female patients (112). In mouse models, male Kdm6a-knockouts retained cancer protection through UTY, a Y-chromosome-encoded homolog of Kdm6a, suggesting a sex-specific regulation of chromatin remodeling (112). Hence, current evidence on transcriptional and epigenetic regulation indicate a potential impact of sex-differences, although data are scarce. Moreover, variable study designs and limited validation contribute to conflicting results. More specific approaches focusing on sex-differences will be essential to clarify whether currently described data represent true biological mechanisms or context-dependent findings.

Histopathology and tissue biomarkers. Thus far and to the best of our knowledge, there is no evidence that histopathological features, such as gland formation, stromal density or entosis differ significantly between male and female patients with PDAC (113-115). Similarly, the expression of multiple diagnostic tissue biomarkers for PDAC, including CK7, mucin-1 and SMAD4, does not show any sex-related variation in histopathological examinations (Table IV). Due to retrospective analyses, these results must be interpreted with caution. Up to now, to the best of our knowledge, no clinically validated sex-specific biomarkers for PDAC exist. Future studies incorporating sex as a biological variable, particularly through multi-omics approaches, are essential to uncover novel, personalized biomarkers in PDAC.

Table IV. Current evidence on biomarkers in pancreatic ductal adenocarcinoma: Sex-specific differences.

First author, year	Marker	Number of patients	Clinical situation	Detection method	Results	Evidence level[a]	(Refs.)
Song *et al*, 2022	CK7	55	Resected	IHC	No significant sex difference	B	(116)
Xiong *et al*, 2022	CK8	176	Resected	mRNA expression	No significant sex difference	B	(117)
Qian *et al*, 2022	MUC1	420	Resected	IHC	No significant sex difference	B	(118)
Ermiah *et al*, 2022	CEA	123	Resected and advanced	Electrochemiluminescence immunoassay	No significant sex difference	B	(119)
Ermiah *et al*, 2022	CA19-9	123	Resected and advanced	Electrochemiluminescence immunoassay	No significant sex difference	B	(119)
Qian *et al*, 2022	MUC5AC	407	Resected	IHC	No significant sex difference	B	(118)
Sumiyoshi *et al*, 2024	CA19-9/DUPAN2	521	Resected	Serum level	No significant sex difference	B	(120)
Liang *et al*, 2017	CA 125/ MUC16	160	Resected	mRNA expression	No significant sex difference	B	(121)
Liang *et al*, 2017	CA125/ MUC16	110	Resected	IHC	No significant sex difference	B	(121)
Xiao *et al*, 2014	CDX2	61	Resected	IHC	No significant sex difference	B	(122)
Amal *et al*, 2024	SMAD4	60	Resected and advanced	IHC	No significant sex difference	B	(123)
Amal *et al*, 2024	S100P	60	Resected and advanced	IHC	No significant sex difference	B	(123)

[a]Evidence levels (A-C): A, high evidence: Randomized large, controlled trials, systematic reviews or meta-analyses, large prospective cohort studies, consistent results across multiple independent study groups or reproducible preclinical data with low risk of bias; B, moderate evidence: Non-randomized or small cohort studies, single RCTs, or preclinical data with some methodological limitations; and C, low evidence: Exploratory or descriptive studies (such as *in vitro* studies and case reports) with high bias risk or lacking controls. CK7/8, cytokeratin 7/8; MUC1/5AC/16, mucin-1/5AC/16; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; DUPAN2, duke pancreatic monoclonal antigen type 2; CA125, cancer antigen 125; CDX2, caudal-related homeobox 2; SMAD4, mothers against decapentaplegic homolog 4; S100P, S100 calcium-binding protein P; IHC, immunohistochemistry.

9. Discussion and future perspectives

PDAC exhibits clear sex-based differences across multiple dimensions, including incidence, risk factors, tumor biology, immune response and treatment outcomes. While men have historically shown higher incidence and mortality rates, the burden of disease is rising disproportionately in women, particularly in younger women, underscoring the importance of sex-specific research. Rising pancreatic cancer rates in young women likely result from a combination of sex-based biological vulnerability and gender-related behavioral patterns. Biologically, women appear more susceptible to the carcinogenic effects of obesity, central fat distribution and early-life smoking. Socially and behaviorally, earlier smoking initiation, rising obesity rates and increasing risky alcohol consumption intensify exposure to these factors. These combined dynamics highlight the need for targeted, sex- and gender-specific risk-prevention strategies.

Biological sex influences not only disease susceptibility but also chemotherapy pharmacokinetics, toxicity profiles, immune responses, and potentially tumor progression pathways. Women often experience greater treatment-related toxicity, while men may face subtherapeutic dosing, indicating that standardized treatment regimens may inadequately account for sex-based variability. In this context, existing therapeutic drug-monitoring approaches for agents such as 5-FU and irinotecan represent an important but underused opportunity; when applied consistently, these tools could facilitate more precise dose optimization for both sexes and help mitigate sex-related differences in exposure and toxicity. In addition, gender and sociocultural factors influence how cancer treatment is received and tolerated, yet they remain largely unaddressed in research and clinical practice. Despite accumulating evidence, most large clinical trials and translational studies still fail to stratify or analyze outcomes by sex, leaving a critical gap in our ability to personalize therapy.

To advance toward precision medicine in PDAC, sex must be systematically incorporated as a biological variable at every stage of research and clinical development. For

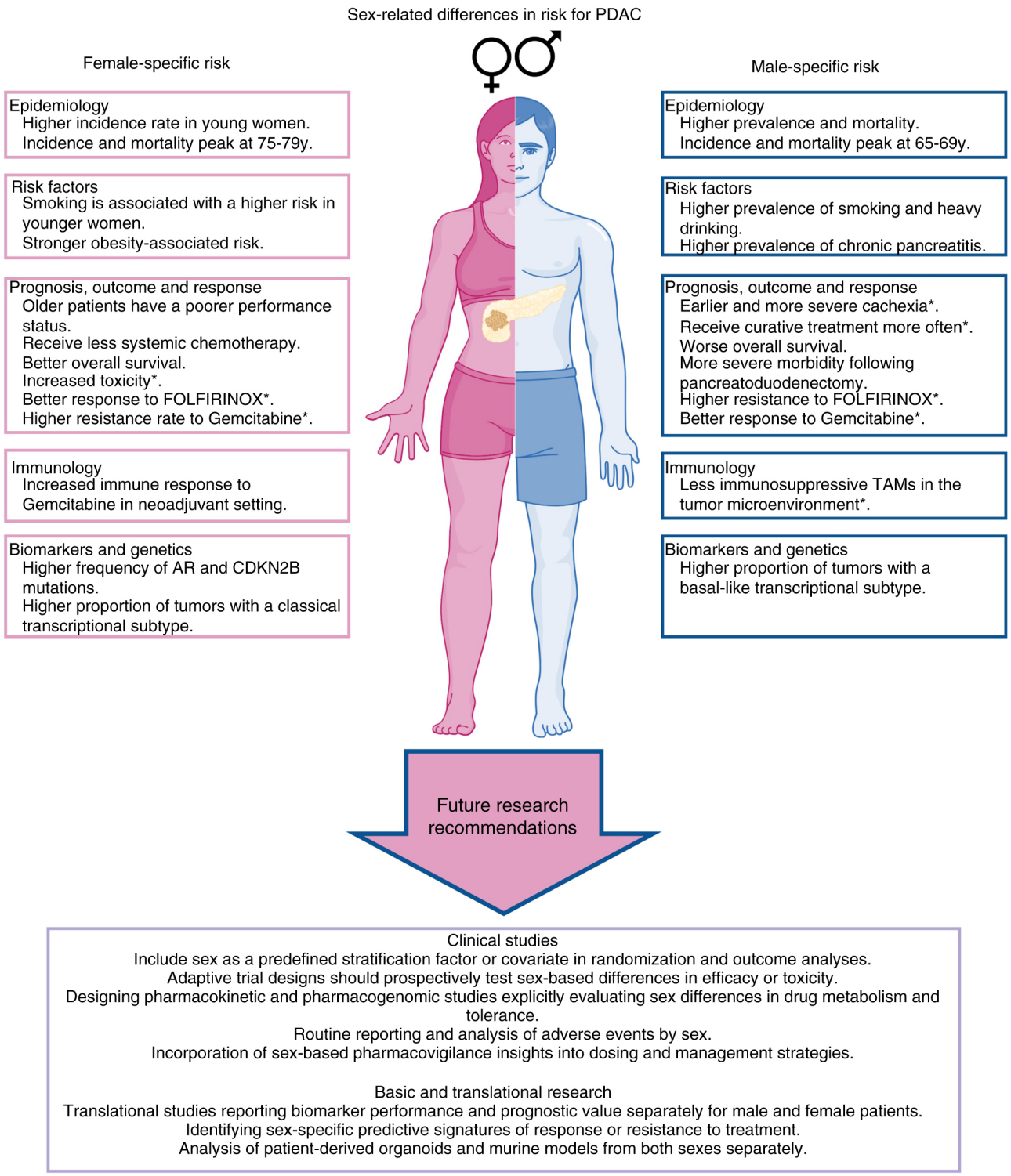

Figure 2. Structured overview of sex-related differences in PDAC. The left panel summarizes aspects associated with female patients, including epidemiological patterns, relevant risk factors, prognostic considerations, immune-related features and molecular characteristics. The right panel presents the corresponding male-associated domains, following the same thematic categories for direct comparison. The lower section synthesizes overarching implications for future research, highlighting the need to integrate sex as a biological variable in study design and translational investigations. *trends have been shown, but further studies are needed. PDAC, pancreatic ductal adenocarcinoma; TAM, tumor-associated macrophage; AR, androgen receptor; CDKN2B, cyclin-dependent kinase inhibitor 2B.

instance, future PDAC trials should include sex as a predefined stratification factor or covariate in randomization and outcome analyses, ensuring adequate statistical power for sex-specific endpoints. Adaptive trial designs could prospectively test sex-based differences in efficacy or toxicity. Pharmacokinetic and pharmacogenomic studies should explicitly evaluate sex differences in drug metabolism, immune response, tolerance and exposure-response associations to guide individualized dosing strategies. Furthermore, translational studies should report biomarker performance and prognostic value separately for men and women, to identify sex-specific predictive signatures of response or resistance. Finally, in preclinical models,

the development of sex-balanced patient-derived organoids and murine models should be considered for dissecting sex-dependent mechanisms and therapeutic vulnerabilities (Fig. 2).

It should be acknowledged that current evidence is largely derived from retrospective analyses with heterogeneous methodologies and limited adjustment for confounders. Nevertheless, the present review highlights that sex-stratified data remain underreported in PDAC trials, and that preclinical systems rarely account for hormonal or chromosomal sex effects. Addressing these limitations will require coordinated efforts to standardize sex reporting, design prospective studies with balanced enrollment and integrate multi-omic datasets to unravel biological from sociocultural determinants of outcome. In conclusion, addressing sex disparities in PDAC is not merely a scientific objective but a prerequisite for equitable precision oncology. Incorporating sex-based insights into risk assessment, biomarker discovery and therapeutic design will be essential to optimize treatment efficacy and minimize toxicity, ultimately moving toward more personalized and effective care for all patients with PDAC.

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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References

1. American Cancer Society. Cancer Facts & Figures 2025. American Cancer Society, Atlanta, 2025.
2. Kaufman MR, Eschliman EL and Karver TS: Differentiating sex and gender in health research to achieve gender equity. Bull World Health Organ 101: 666-671, 2023.
3. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, De Vries GJ, Epperson CN, Govindan R, Klein SL, *et al*: Sex and gender: Modifiers of health, disease, and medicine. Lancet 396: 565-582, 2020.
4. Delahousse J, Wagner AD, Borchmann S, Adjei AA, Haanen J, Burgers F, Letsch A, Quaas A, Oertelt-Prigione S, Özdemir BC, *et al*: Sex differences in the pharmacokinetics of anticancer drugs: A systematic review. ESMO Open 9: 104002, 2024.
5. Sosinsky AZ, Rich-Edwards JW, Wiley A, Wright K, Spagnolo PA and Joffe H: Enrollment of female participants in United States drug and device phase 1-3 clinical trials between 2016 and 2019. Contemp Clin Trials 115: 106718, 2022.
6. Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, Csajka C, Coukos G, Dafni U, Dotto GP, Ducreux M, *et al*: Gender medicine and oncology: Report and consensus of an ESMO workshop. Ann Oncol 30: 1914-1924, 2019.
7. Kim SE, Paik HY, Yoon H, Lee JE, Kim N and Sung MK: Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol 21: 5167-5175, 2015.
8. Abdel-Rahman O: Impact of sex on chemotherapy toxicity and efficacy among patients with metastatic colorectal cancer: Pooled analysis of 5 randomized trials. Clin Colorectal Cancer 18: 110-115 e2, 2019.
9. Ferlay JEM, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I and Bray F: Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer, Lyon. Available from: https://gco.iarc.who.int/today2024.
10. Khalaf N, El-Serag HB, Abrams HR and Thrift AP: Burden of pancreatic cancer: From epidemiology to practice. Clin Gastroenterol Hepatol 19: 876-884, 2021.
11. Wang S, Zheng R, Li J, Zeng H, Li L, Chen R, Sun K, Han B, Bray F, Wei W and He J: Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: A population-based systematic analysis of GLOBOCAN. Lancet Gastroenterol Hepatol 9: 229-237, 2024.
12. GBD 2017 Pancreatic Cancer Collaborators: The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of disease study 2017. Lancet Gastroenterol Hepatol 4: 934-947, 2019.
13. Cavazzani A, Angelini C, Gregori D and Cardone L: Cancer incidence (2000-2020) among individuals under 35: An emerging sex disparity in oncology. BMC Med 22: 363, 2024.
14. Huang J, Lok V, Ngai CH, Zhang L, Yuan J, Lao XQ, Ng K, Chong C, Zheng ZJ and Wong MCS: Worldwide Burden of, risk factors for, and trends in pancreatic cancer. Gastroenterology 160: 744-754, 2021.
15. ECIS-European Cancer Information System. 2025. Available from: https://ecis.jrc.ec.europa.eu/explorer.php.
16. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, Canzian F, Steplowski E, Arslan AA, Gross M, *et al*: Cigarette smoking and pancreatic cancer: A pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 170: 403-413, 2009.
17. Gram IT, Park SY, Wilkens LR, Le Marchand L and Setiawan VW: Smoking and pancreatic cancer: A sex-specific analysis in the Multiethnic Cohort study. Cancer Causes Control 34: 89-100, 2023.

18. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, *et al*: Cigarette smoking and pancreatic cancer: An analysis from the International pancreatic cancer case-control consortium (Panc4). Ann Oncol 23: 1880-1888, 2012.
19. Koyanagi YN, Ito H, Matsuo K, Sugawara Y, Hidaka A, Sawada N, Wada K, Nagata C, Tamakoshi A, Lin Y, *et al*: Smoking and pancreatic cancer incidence: A pooled analysis of 10 population-based cohort studies in Japan. Cancer Epidemiol Biomarkers Prev 28: 1370-1378, 2019.
20. Jiao L, Berrington de Gonzalez A, Hartge P, Pfeiffer RM, Park Y, Freedman DM, Gail MH, Alavanja MC, Albanes D, Beane Freeman LE, *et al*: Body mass index, effect modifiers, and risk of pancreatic cancer: A pooled study of seven prospective cohorts. Cancer Causes Control 21: 1305-1314, 2010.
21. Calle EE, Rodriguez C, Walker-Thurmond K and Thun MJ: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348: 1625-1638, 2003.
22. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, Fuchs CS, Gross MD, Jacobs EJ, Lacroix AZ, *et al*: Anthropometric measures, body mass index, and pancreatic cancer: A pooled analysis from the pancreatic cancer cohort consortium (PanScan). Arch Intern Med 170: 791-802, 2010.
23. Johansen D, Stocks T, Jonsson H, Lindkvist B, Bjorge T, Concin H, Almquist M, Häggström C, Engeland A, Ulmer H, *et al*: Metabolic factors and the risk of pancreatic cancer: A prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and cancer project. Cancer Epidemiol Biomarkers Prev 19: 2307-2317, 2010.
24. Genkinger JM, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena JW, Giles GG, Hartge P, Singh PN, Stolzenberg-Solomon RZ, *et al*: Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol 26: 2257-2266, 2015.
25. Mao Y, Tao M, Jia X, Xu H, Chen K, Tang H and Li D: Effect of diabetes mellitus on survival in patients with pancreatic cancer: A systematic review and meta-analysis. Sci Rep 5: 17102, 2015.
26. Mellenthin C, Balaban VD, Dugic A and Cullati S: Risk factors for pancreatic cancer in patients with new-onset diabetes: A systematic review and meta-analysis. Cancers (Basel) 14: 4684, 2022.
27. Song S, Wang B, Zhang X, Hao L, Hu X, Li Z and Sun S: Long-term diabetes mellitus is associated with an increased risk of pancreatic cancer: A meta-analysis. PLoS One 10: e0134321, 2015.
28. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F and Woodward M: Type-II diabetes and pancreatic cancer: A meta-analysis of 36 studies. Br J Cancer 92: 2076-2083, 2005.
29. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, Bosetti C, Li D, Gallinger S, Miller AB, *et al*: Alcohol consumption and pancreatic cancer: A pooled analysis in the International pancreatic cancer case-control consortium (PanC4). Ann Oncol 23: 374-382, 2012.
30. Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, van den Brandt PA, English DR, Freudenheim JL, Fuchs CS, Giles GG, *et al*: Alcohol intake and pancreatic cancer risk: A pooled analysis of fourteen cohort studies. Cancer Epidemiol Biomarkers Prev 18: 765-776, 2009.
31. Jiao L, Silverman DT, Schairer C, Thiebaut AC, Hollenbeck AR, Leitzmann MF, Schatzkin A and Stolzenberg-Solomon RZ: Alcohol use and risk of pancreatic cancer: The NIH-AARP Diet and Health Study. Am J Epidemiol 169: 1043-1051, 2009.
32. Arab JP, Dunn W, Im G and Singal AK: Changing landscape of alcohol-associated liver disease in younger individuals, women, and ethnic minorities. Liver Int 44: 1537-1547, 2024.
33. Santos R, Coleman HG, Cairnduff V and Kunzmann AT: Clinical prediction models for pancreatic cancer in general and at-risk populations: A systematic review. Am J Gastroenterol 118: 26-40, 2023.
34. Gandhi S, de la Fuente J, Murad MH and Majumder S: Chronic pancreatitis is a risk factor for pancreatic cancer, and incidence increases with duration of disease: A systematic review and meta-analysis. Clin Transl Gastroenterol 13: e00463, 2022.
35. Kirkegard J, Mortensen FV and Cronin-Fenton D: Chronic pancreatitis and pancreatic cancer risk: A systematic review and meta-analysis. Am J Gastroenterol 112: 1366-1372, 2017.
36. Ilic M, Milicic B and Ilic I: Association between oral contraceptive use and pancreatic cancer risk: A systematic review and meta-analysis. World J Gastroenterol 27: 2643-2656, 2021.
37. Andersson G, Borgquist S and Jirstrom K: Hormonal factors and pancreatic cancer risk in women: The Malmo diet and cancer study. Int J Cancer 143: 52-62, 2018.
38. Lee E, Horn-Ross PL, Rull RP, Neuhausen SL, Anton-Culver H, Ursin G, Henderson KD and Bernstein L: Reproductive factors, exogenous hormones, and pancreatic cancer risk in the CTS. Am J Epidemiol 178: 1403-1413, 2013.
39. Prizment AE, Anderson KE, Hong CP and Folsom AR: Pancreatic cancer incidence in relation to female reproductive factors: Iowa women's health study. JOP 8: 16-27, 2007.
40. Duell EJ and Holly EA: Reproductive and menstrual risk factors for pancreatic cancer: A population-based study of San Francisco Bay Area women. Am J Epidemiol 161: 741-747, 2005.
41. Stevens RJ, Roddam AW, Green J, Pirie K, Bull D, Reeves GK and Beral V; Million Women Study Collaborators: Reproductive history and pancreatic cancer incidence and mortality in a cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev 18: 1457-1460, 2009.
42. Ioannou C, Ragia G, Balgkouranidou I, Xenidis N, Amarantidis K, Koukaki T, Biziota E, Kakolyris S and Manolopoulos VG: MTHFR c.665C>T guided fluoropyrimidine therapy in cancer: Gender-dependent effect on dose requirements. Drug Metab Pers Ther 37: 323-327, 2022.
43. Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, Hackert T, Golan T, Prager G, Haustermans K, *et al*: Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 34: 987-1002, 2023.
44. Mueller F, Buchel B, Koberle D, Schurch S, Pfister B, Krahenbuhl S, Froehlich TK, Largiader CR and Joerger M: Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: Results from a prospective population pharmacokinetic study. Cancer Chemother Pharmacol 71: 361-370, 2013.
45. Milano G, Etienne MC, Cassuto-Viguier E, Thyss A, Santini J, Frenay M, Renee N, Schneider M and Demard F: Influence of sex and age on fluorouracil clearance. J Clin Oncol 10: 1171-1175, 1992.
46. Bastian G, Barrail A and Urien S: Population pharmacokinetics of oxaliplatin in patients with metastatic cancer. Anticancer Drugs 14: 817-824, 2003.
47. Nikanjam M, Stewart CF, Takimoto CH, Synold TW, Beaty O, Fouladi M and Capparelli EV: Population pharmacokinetic analysis of oxaliplatin in adults and children identifies important covariates for dosing. Cancer Chemother Pharmacol 75: 495-503, 2015.
48. Klein CE, Gupta E, Reid JM, Atherton PJ, Sloan JA, Pitot HC, Ratain MJ and Kastrissios H: Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. Clin Pharmacol Ther 72: 638-647, 2002.
49. Berg AK, Buckner JC, Galanis E, Jaeckle KA, Ames MM and Reid JM: Quantification of the impact of enzyme-inducing antiepileptic drugs on irinotecan pharmacokinetics and SN-38 exposure. J Clin Pharmacol 55: 1303-1312, 2015.
50. Chabot GG, Abigerges D, Catimel G, Culine S, de Forni M, Extra JM, Mahjoubi M, Hérait P, Armand JP, Bugat R, *et al*: Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. Ann Oncol 6: 141-151, 1995.
51. De Francia S, Mancardi D, Berchialla P, Armando T, Storto S, Allegra S, Soave G, Racca S, Chiara F, Carnovale J, *et al*: Gender-specific side effects of chemotherapy in pancreatic cancer patients. Can J Physiol Pharmacol 100: 371-377, 2022.
52. Kim J, Ji E, Jung K, Jung IH, Park J, Lee JC, Kim JW, Hwang JH and Kim J: Gender differences in patients with metastatic pancreatic cancer who received FOLFIRINOX. J Pers Med 11: 83, 2021.
53. Keum J, Lee HS, Kang H, Jo JH, Chung MJ, Park JY, Park SW, Song SY and Bang S: Single-center risk factor analysis for FOLFIRINOX associated febrile neutropenia in patients with pancreatic cancer. Cancer Chemother Pharmacol 85: 651-659, 2020.
54. Sugiyama E, Kaniwa N, Kim SR, Hasegawa R, Saito Y, Ueno H, Okusaka T, Ikeda M, Morizane C, Kondo S, *et al*: Population pharmacokinetics of gemcitabine and its metabolite in Japanese cancer patients: Impact of genetic polymorphisms. Clin Pharmacokinet 49: 549-558, 2010.
55. Jiang X, Galettis P, Links M, Mitchell PL and McLachlan AJ: Population pharmacokinetics of gemcitabine and its metabolite in patients with cancer: Effect of oxaliplatin and infusion rate. Br J Clin Pharmacol 65: 326-333, 2008.
56. Lim HS, Bae KS, Jung JA, Noh YH, Hwang AK, Jo YW, Hong YS, Kim K, Lee JL, Park SJ, *et al*: Predicting the efficacy of an oral paclitaxel formulation (DHP107) through modeling and simulation. Clin Ther 37: 402-417, 2015.

57. Joerger M, Kraff S, Huitema AD, Feiss G, Moritz B, Schellens JH, Beijnen JH and Jaehde U: Evaluation of a pharmacology-driven dosing algorithm of 3-weekly paclitaxel using therapeutic drug monitoring: A pharmacokinetic-pharmacodynamic simulation study. Clin Pharmacokinet 51: 607-617, 2012.
58. Chen N, Li Y, Ye Y, Palmisano M, Chopra R and Zhou S: Pharmacokinetics and pharmacodynamics of nab-paclitaxel in patients with solid tumors: Disposition kinetics and pharmacology distinct from solvent-based paclitaxel. J Clin Pharmacol 54: 1097-1107, 2014.
59. Pijnappel EN, Schuurman M, Wagner AD, de Vos-Geelen J, van der Geest LGM, de Groot JB, Koerkamp BG, de Hingh IHJT, Homs MYV, Creemers GJ, *et al*: Sex, gender and age differences in treatment allocation and survival of patients with metastatic pancreatic cancer: A nationwide study. Front Oncol 12: 839779, 2022.
60. Gehrels AM, Wagner AD, Besselink MG, Verhoeven RHA, van Eijck CHJ, van Laarhoven HWM, Wilmink JW and van der Geest LG; Dutch Pancreatic Cancer Group: Gender differences in tumor characteristics, treatment allocation and survival in stage I-III pancreatic cancer: A nationwide study. Eur J Cancer 206: 114117, 2024.
61. Olsson Hau S, Williamsson C, Andersson B, Eberhard J and Jirstrom K: Sex and gender differences in treatment intention, quality of life and performance status in the first 100 patients with periampullary cancer enrolled in the CHAMP study. BMC Cancer 23: 334, 2023.
62. Williamsson C, Rystedt J and Andersson B: An analysis of gender differences in treatment and outcome of periampullary tumours in Sweden-A national cohort study. HPB (Oxford) 23: 847-853, 2021.
63. Pastrana Del Valle J, Mahvi DA, Fairweather M, Wang J, Clancy TE, Ashley SW, Urman RD, Whang EE and Gold JS: Associations of gender, race, and ethnicity with disparities in short-term adverse outcomes after pancreatic resection for cancer. J Surg Oncol 125: 646-657, 2022.
64. Lambert A, Jarlier M, Gourgou Bourgade S and Conroy T: Response to FOLFIRINOX by gender in patients with metastatic pancreatic cancer: Results from the PRODIGE 4/ACCORD 11 randomized trial. PLoS One 12: e0183288, 2017.
65. Hohla F, Hopfinger G, Romeder F, Rinnerthaler G, Bezan A, Stattner S, Hauser-Kronberger C, Ulmer H and Greil R: Female gender may predict response to FOLFIRINOX in patients with unresectable pancreatic cancer: A single institution retrospective review. Int J Oncol 44: 319-326, 2014.
66. Dunn SE, Perry WA and Klein SL: Mechanisms and consequences of sex differences in immune responses. Nat Rev Nephrol 20: 37-55, 2024.
67. Klein SL and Flanagan KL: Sex differences in immune responses. Nat Rev Immunol 16: 626-638, 2016.
68. Ye Y, Jing Y, Li L, Mills GB, Diao L, Liu H and Han L: Sex-associated molecular differences for cancer immunotherapy. Nat Commun 11: 1779, 2020.
69. Weinstein Y, Ran S and Segal S: Sex-associated differences in the regulation of immune responses controlled by the MHC of the mouse. J Immunol 132: 656-661, 1984.
70. Griesbeck M, Ziegler S, Laffont S, Smith N, Chauveau L, Tomezsko P, Sharei A, Kourjian G, Porichis F, Hart M, *et al*: Sex differences in plasmacytoid dendritic cell levels of IRF5 drive higher IFN-α production in women. J Immunol 195: 5327-5336, 2015.
71. Webb K, Peckham H, Radziszewska A, Menon M, Oliveri P, Simpson F, Deakin CT, Lee S, Ciurtin C, Butler G, *et al*: Sex and pubertal differences in the type 1 interferon pathway associate with both X chromosome number and serum sex hormone concentration. Front Immunol 9: 3167, 2019.
72. Hagen SH, Henseling F, Hennesen J, Savel H, Delahaye S, Richert L, Ziegler SM and Altfeld M: Heterogeneous escape from x chromosome inactivation results in sex differences in type I IFN responses at the single human pDC level. Cell Rep 33: 108485, 2020.
73. Umlauf BJ, Haralambieva IH, Ovsyannikova IG, Kennedy RB, Pankratz VS, Jacobson RM and Poland GA: Associations between demographic variables and multiple measles-specific innate and cell-mediated immune responses after measles vaccination. Viral Immunol 25: 29-36, 2012.
74. Abramenko N, Vellieux F, Vesela K, Kejik Z, Hajduch J, Masarik M, Babula P, Hoskovec D, Pacák K, Martásek P, *et al*: Investigation of the potential effects of estrogen receptor modulators on immune checkpoint molecules. Sci Rep 14: 3043, 2024.
75. Han J, Yang Y, Li X, Wu J, Sheng Y, Qiu J, Wang Q, Li J, He Y, Cheng L and Zhang Y: Pan-cancer analysis reveals sex-specific signatures in the tumor microenvironment. Mol Oncol 16: 2153-2173, 2022.
76. Ho WJ, Jaffee EM and Zheng L: The tumour microenvironment in pancreatic cancer-clinical challenges and opportunities. Nat Rev Clin Oncol 17: 527-540, 2020.
77. Clark CE, Hingorani SR, Mick R, Combs C, Tuveson DA and Vonderheide RH: Dynamics of the immune reaction to pancreatic cancer from inception to invasion. Cancer Res 67: 9518-9527, 2007.
78. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, *et al*: Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366: 2455-2465, 2012.
79. He F, Tay AHM, Calandigary A, Malki E, Suzuki S, Liu T, Wang Q, Fernández-Moro C, Kaisso M, Olofsson-Sahl P, *et al*: FPR2 shapes an immune-excluded pancreatic tumor microenvironment and drives T-cell exhaustion in a sex-dependent manner. Cancer Res 83: 1628-1645, 2023.
80. Manoukian P, van Schie DM, van Schelt AS, Wassenaar NPM, Dings MPG, Lansbergen MF, Waasdorp C, Leite de Oliveira R, Wickenhagen WV, Heijboer AC, *et al*: Estrogen production in pancreatic cancer shapes a tumor suppressive stromal microenvironment. Cancer Res: Nov 19, 2025 (Epub ahead of print).
81. Ahmed A, Kohler S, Klotz R, Giese N, Hackert T, Springfeld C, Jäger D and Halama N: Sex differences in the systemic and local immune response of pancreatic cancer patients. Cancers (Basel) 15: 1815, 2023.
82. van Eijck CWF, Mustafa DAM, Vadgama D, de Miranda NFCC, Groot Koerkamp B, van Tienhoven G, van der Burg SH, Malats N and van Eijck CHJ; Dutch Pancreatic Cancer Group (DPCG): Enhanced antitumour immunity following neoadjuvant chemoradiotherapy mediates a favourable prognosis in women with resected pancreatic cancer. Gut 73: 311-324, 2024.
83. Sethna Z, Guasp P, Reiche C, Milighetti M, Ceglia N, Patterson E, Lihm J, Payne G, Lyudovyk O, Rojas LA, *et al*: RNA neoantigen vaccines prime long-lived CD8(+) T cells in pancreatic cancer. Nature 639: 1042-1051, 2025.
84. Li Y, Chang RB, Stone ML, Delman D, Markowitz K, Xue Y, Coho H, Herrera VM, Li JH, Zhang L, *et al*: Multimodal immune phenotyping reveals microbial-T cell interactions that shape pancreatic cancer. Cell Rep Med 5: 101397, 2024.
85. Andrews MC, Duong CPM, Gopalakrishnan V, Iebba V, Chen WS, Derosa L, Khan MAW, Cogdill AP, White MG, Wong MC, *et al*: Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. Nat Med 27: 1432-1441, 2021.
86. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, Quesada P, Sahin I, Chandra V, San Lucas A, *et al*: Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell 178: 795-806 e12, 2019.
87. Guo W, Zhang Y, Guo S, Mei Z, Liao H, Dong H, Wu K, Ye H, Zhang Y, Zhu Y, *et al*: Tumor microbiome contributes to an aggressive phenotype in the basal-like subtype of pancreatic cancer. Commun Biol 4: 1019, 2021.
88. Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y, Geller LT, Rotter-Maskowitz A, Weiser R, Mallel G, Gigi E, *et al*: The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science 368: 973-980, 2020.
89. Guenther M, Gil L, Surendran SA, Palm MA, Heinemann V, von Bergwelt-Baildon M, Mayerle J, Engel J, Werner J, Boeck S and Ormanns S: Bacterial lipopolysaccharide as a negative predictor of adjuvant gemcitabine efficacy in pancreatic cancer. JNCI Cancer Spectr 6: pkac039, 2022.
90. Stein-Thoeringer CK, Renz BW, De Castilhos J, von Ehrlich-Treuenstatt V, Wirth U, Tschaidse T, Hofmann FO, Koch DT, Beirith I, Ormanns S, *et al*: Microbiome dysbiosis with enterococcus presence in the upper gastrointestinal tract is a risk factor for mortality in patients undergoing surgery for pancreatic cancer. Ann Surg 281: 615-623, 2025.
91. Nalluri H, Jensen E and Staley C: Role of biliary stent and neoadjuvant chemotherapy in the pancreatic tumor microbiome. BMC Microbiol 21: 280, 2021.
92. Khan ZA, Ghorbani M, Heffinger L, Damdimopoulos A, Moro CF, Björnstedt M, Löhr JM, Heuchel R, Chen MS and Sarhan D: Genderized gut and oral microbiome shifts: Uncovering sex-specific dysbiosis in pancreatic cancer. bioRxiv: Oct 3, 2024 (Epub ahead of print). doi: https://doi.org/10.1101/2024.10.02.616338.

93. Kaune T, Griesmann H, Theuerkorn K, Hammerle M, Laumen H, Krug S, Plumeier I, Kahl S, Junca H, Gustavo Dos Anjos Borges L, *et al*: Gender-specific changes of the gut microbiome correlate with tumor development in murine models of pancreatic cancer. iScience 26: 106841, 2023.
94. Fulop DJ, Zylberberg HM, Wu YL, Aronson A, Labiner AJ, Wisnivesky J, Cohen DJ, Sigel KM and Lucas AL: Association of Antibiotic receipt with survival among patients with metastatic pancreatic ductal adenocarcinoma receiving chemotherapy. JAMA Netw Open 6: e234254, 2023.
95. O'Neill RS and Stoita A: Biomarkers in the diagnosis of pancreatic cancer: Are we closer to finding the golden ticket? World J Gastroenterol 27: 4045-4087, 2021.
96. Balaban DV, Marin FS, Manucu G, Zoican A, Ciochina M, Mina V, Patoni C, Vladut C, Bucurica S, Costache RS, *et al*: Clinical characteristics and outcomes in carbohydrate antigen 19-9 negative pancreatic cancer. World J Clin Oncol 13: 630-640, 2022.
97. Hermann CD, Schoeps B, Eckfeld C, Munkhbaatar E, Kniep L, Prokopchuk O, Wirges N, Steiger K, Häußler D, Knolle P, *et al*: TIMP1 expression underlies sex disparity in liver metastasis and survival in pancreatic cancer. J Exp Med 218: e20210911, 2021.
98. Asplund E, Bergqvist M, Krook M and Lohr JM: Plasma thymidine kinase activity as a prognostic biomarker in pancreatic ductal adenocarcinoma: A single-center prospective study. Scand J Gastroenterol 58: 1044-1048, 2023.
99. Babic A, Wang QL, Lee AA, Yuan C, Rifai N, Luo J, Tabung FK, Shadyab AH, Wactawski-Wende J, Saquib N, *et al*: Sex-specific associations between adiponectin and leptin signaling and pancreatic cancer survival. Cancer Epidemiol Biomarkers Prev 32: 1458-1469, 2023.
100. Zhang X, Mao T, Zhang B, Xu H, Cui J, Jiao F, Chen D, Wang Y, Hu J, Xia Q, *et al*: Characterization of the genomic landscape in large-scale Chinese patients with pancreatic cancer. EBioMedicine 77: 103897, 2022.
101. Boeck S, Jung A, Laubender RP, Neumann J, Egg R, Goritschan C, Vehling-Kaiser U, Winkelmann C, Fischer von Weikersthal L, Clemens MR, *et al*: EGFR pathway biomarkers in erlotinib-treated patients with advanced pancreatic cancer: Translational results from the randomised, crossover phase 3 trial AIO-PK0104. Br J Cancer 108: 469-476, 2013.
102. Ramezankhani R, Ghavidel AA, Rashidi S, Rojhannezhad M, Abolkheir HR, Mirhosseini M, Taleahmad S and Vosough M: Gender-related differentially expressed genes in pancreatic cancer: Possible culprits or accomplices? Front Genet 13: 966941, 2022.
103. Peduzzi G, Archibugi L, Katzke V, Gentiluomo M, Capurso G, Milanetto AC, Gazouli M, Goetz M, Brenner H, Vermeulen RCH, *et al*: Common variability in oestrogen-related genes and pancreatic ductal adenocarcinoma risk in women. Sci Rep 12: 18100, 2022.
104. Li D, Suzuki H, Liu B, Morris J, Liu J, Okazaki T, Li Y, Chang P and Abbruzzese JL: DNA repair gene polymorphisms and risk of pancreatic cancer. Clin Cancer Res 15: 740-746, 2009.
105. Jones J, Mukherjee A, Karanam B, Davis M, Jaynes J, Reams RR, Dean-Colomb W and Yates C: African Americans with pancreatic ductal adenocarcinoma exhibit gender differences in Kaiso expression. Cancer Lett 380: 513-522, 2016.
106. Schonk MM, Ducharme JB, Neyroud D, Nosacka RL, Tucker HO, Judge SM and Judge AR: Myofiber-specific FoxP1 knockout protects against pancreatic cancer-induced muscle wasting in male but not female mice. bioRxiv: Sep 21, 2024 (Epub ahead of print).
107. Zhong X, Narasimhan A, Silverman LM, Young AR, Shahda S, Liu S, Wan J, Liu Y, Koniaris LG and Zimmers TA: Sex specificity of pancreatic cancer cachexia phenotypes, mechanisms, and treatment in mice and humans: Role of Activin. J Cachexia Sarcopenia Muscle 13: 2146-2161, 2022.
108. Muckenhuber A, Berger AK, Schlitter AM, Steiger K, Konukiewitz B, Trumpp A, Eils R, Werner J, Friess H, Esposito I, *et al*: Pancreatic ductal adenocarcinoma subtyping using the biomarkers hepatocyte nuclear Factor-1A and cytokeratin-81 correlates with outcome and treatment response. Clin Cancer Res 24: 351-359, 2018.
109. Guenther M, Surendran SA, Steinke LM, Liou I, Palm MA, Heinemann V, Haas M, Boeck S and Ormanns S: The prognostic, predictive and clinicopathological implications of KRT81/HNF1A- and GATA6-Based transcriptional subtyping in pancreatic cancer. Biomolecules 15: 426, 2025.
110. Nicolle R, Bachet JB, Harle A, Iovanna J, Hammel P, Rebours V, Turpin A, Ben Abdelghani M, Wei A, Mitry E, *et al*: Prediction of adjuvant gemcitabine sensitivity in resectable pancreatic adenocarcinoma using the GemPred RNA signature: An ancillary study of the PRODIGE-24/CCTG PA6 clinical trial. J Clin Oncol 42: 1067-1076, 2024.
111. Fraunhoffer N, Hammel P, Conroy T, Nicolle R, Bachet JB, Harle A, Rebours V, Turpin A, Ben Abdelghani M, Mitry E, *et al*: Development and validation of AI-assisted transcriptomic signatures to personalize adjuvant chemotherapy in patients with pancreatic ductal adenocarcinoma. Ann Oncol 35: 780-791, 2024.
112. Andricovich J, Perkail S, Kai Y, Casasanta N, Peng W and Tzatsos A: Loss of KDM6A activates super-enhancers to induce gender-specific squamous-like pancreatic cancer and confers sensitivity to BET inhibitors. Cancer Cell 33: 512-526 e8, 2018.
113. Kouchi Y, Takano S, Harada-Kagitani S, Shinomiya Y, Yogi N, Sakamoto T, Mishima T, Fugo K, Kambe M, Nagai Y, *et al*: Complex glandular pattern is an aggressive morphology that predicts poor prognosis of pancreatic ductal adenocarcinoma. Ann Diagn Pathol 64: 152110, 2023.
114. Grochowski P, Grosser B, Sommer F, Probst A, Waidhauser J, Schenkirsch G, Reitsam NG and Märkl B: The concept of stroma areactive invasion front areas (SARIFA) as a new prognostic biomarker for lipid-driven cancers holds true in pancreatic ductal adenocarcinoma. BMC Cancer 24: 768, 2024.
115. Hayashi A, Yavas A, McIntyre CA, Ho YJ, Erakky A, Wong W, Varghese AM, Melchor JP, Overholtzer M, O'Reilly EM, *et al*: Genetic and clinical correlates of entosis in pancreatic ductal adenocarcinoma. Mod Pathol 33: 1822-1831, 2020.
116. Song J, Ruze R, Chen Y, Xu R, Yin X, Wang C, Xu Q and Zhao Y: Construction of a novel model based on cell-in-cell-related genes and validation of KRT7 as a biomarker for predicting survival and immune microenvironment in pancreatic cancer. BMC Cancer 22: 894, 2022.
117. Xiong F, Guo T, Wang X, Wu G, Liu W, Wang Q, Wang B and Chen Y: Keratin 8 is an inflammation-induced and prognosis-related marker for pancreatic adenocarcinoma. Dis Markers 2022: 8159537, 2022.
118. Qian Y, Gong Y, Liu Y, Chen Y, Wang R, Dai Z, Zou X, Tasiheng Y, Luo G, Lin X, *et al*: Atypical mucin expression predicts worse overall survival in resectable pancreatic ductal adenocarcinoma. J Immunol Res 2022: 7353572, 2022.
119. Ermiah E, Eddfair M, Abdulrahman O, Elfagieh M, Jebriel A, Al-Sharif M, Assidi M and Buhmeida A: Prognostic value of serum CEA and CA19-9 levels in pancreatic ductal adenocarcinoma. Mol Clin Oncol 17: 126, 2022.
120. Sumiyoshi T, Uemura K, Shintakuya R, Okada K, Baba K, Harada T, Serikawa M, Ishii Y, Nakamura S, Arihiro K, *et al*: Clinical utility of the combined use of CA19-9 and DUPAN-2 in pancreatic adenocarcinoma. Ann Surg Oncol 31: 4665-4672, 2024.
121. Liang C, Qin Y, Zhang B, Ji S, Shi S, Xu W, Liu J, Xiang J, Liang D, Hu Q, *et al*: Oncogenic KRAS targets MUC16/CA125 in pancreatic ductal adenocarcinoma. Mol Cancer Res 15: 201-212, 2017.
122. Xiao W, Hong H, Awadallah A, Zhou L and Xin W: Utilization of CDX2 expression in diagnosing pancreatic ductal adenocarcinoma and predicting prognosis. PLoS One 9: e86853, 2014.
123. Amal AM, Ahmed MSM, Hareedy AAM, Khattab HMH and Mahmoud EK: The utility of SMAD4 and S100P as diagnostic immunohistochemical markers for pancreatic ductal adenocarcinomas in egyptian patients. J Microsc Ultrastruct: Jun 25, 2024 (Epub ahead of print). doi: 10.4103/jmau.jmau_71_23.

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