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Sex-Specific Mechanisms at the Interface of Hemostasis and Vascular Biology

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Background

- Cancer-associated VTE is a leading cause of morbidity and mortality in oncology patients.
- Sex hormones — estrogens, progesterone, and androgens — modulate coagulation, fibrinolysis, and platelet function.
- Hormone-sensitive cancers (breast, ovarian, endometrial, prostate) present unique thrombotic risk profiles.
- Current thromboprophylaxis guidelines do not fully account for hormonal context or sex-specific pathways.
- Understanding sex-specific hemostatic mechanisms may enable more targeted VTE prevention.

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Sex-Specific Hormonal Effects on Hemostasis

How sex hormones modulate coagulation and thrombotic risk

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Estrogens: Pleiotropic Prothrombotic Effects

Mechanism of Action

- Act via nuclear ERα, ERβ and membrane G-protein–coupled receptors
- Influence vasodilation, vascular remodeling & myocardial hypertrophy
- Increase hepatic synthesis of procoagulant factors
- Reduce natural anticoagulant activity
- Shift hemostatic balance → hypercoagulability

High-Estrogen Clinical States

- Pregnancy
- Oral contraceptive use
- Postmenopausal hormone replacement therapy
- Tamoxifen (SERM): partial agonist on hepatic coagulation pathways → ↑ VTE risk
- Aromatase inhibitors: reduce estrogen → different risk profile

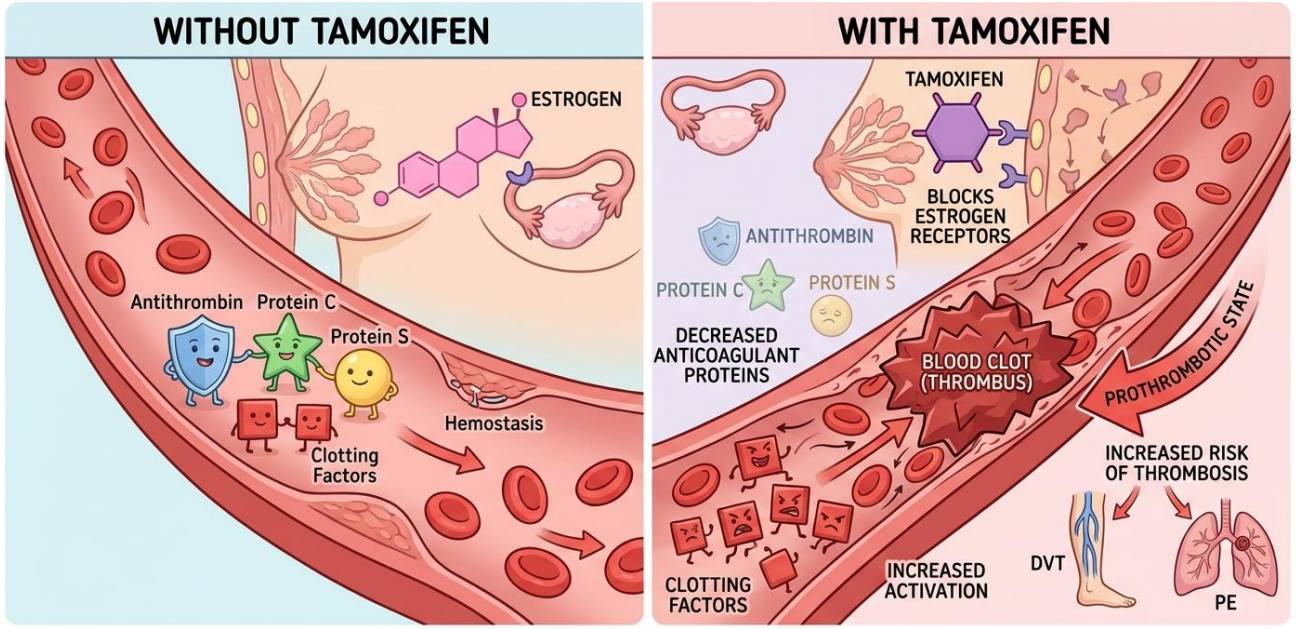
Okwuosa TM et al., Circ Genom Precis Med 2021;14: e000082

Prothrombotic Effect of Tamoxifen

Reduction of Natural Anticoagulants: Tamoxifen lowers the circulating levels of **Antithrombin, Protein C**, and **Protein S**,

Increased Clotting Factor Activity: It promotes a pro-coagulant environment by increasing the levels of Factor IX and enhancing thrombin generation.

Elevated Clinical Risk: These biochemical changes lead to a clinically significant increase - approximately **2–3 times** – VTE risk



TAMOXIFEN, a selective estrogen receptor modulator (SERM), reduces natural anticoagulants and activates clotting factors, leading to an increased risk of blood clots (prothrombotic effect).

Endocrine Therapy: Tamoxifen vs Aromatase Inhibitors

Tamoxifen (SERM)

- Partial estrogen agonist on hepatic tissue
- ↑ Thrombin generation
- ↓ Sensitivity to endogenous anticoagulants
- 2–3× higher VTE risk vs controls
- Annual incidence ~0.5–1% postmenopausal
- Risk amplified when combined with surgery or CDK4/6 inhibitors

Aromatase Inhibitors (AI)

- Suppress systemic estrogen levels
- No pro-thrombotic changes in hemostatic biomarkers
- VTE risk comparable to placebo in major trials
- May shift risk toward adverse cardiovascular outcomes (arterial)
- Preferred for VTE-prone patients on endocrine therapy

Progesterone & Testosterone: Nuanced Roles

Progesterone

- Minimal direct effects on coagulation pathways
- Often considered hemostatic neutral
- Clinical relevance mainly in combination with estrogen

Testosterone

- Overall low thrombotic risk in general use
- Meta-analysis: OR 1.41 (95% CI 0.96–2.07) — not significant
- Large case-crossover study: ~2-fold ↑ VTE in 6-month hazard period *Walker RF, JAMA Intern Med. 2020*

⚑ Key Clinical Message

A potential short-term increase in thrombotic risk following initiation of testosterone therapy supports the need for close clinical monitoring during early treatment phases — even in men without confirmed hypogonadism.

Nordstrom SM, Weiss EJ. Expert Rev Hematol 2008; 1:3-8; .Barcellona D, Grandone E, Marongiu F. Blood Transfus 2024; 22:46-54.

Breast Cancer: Hormone Dependence & Thrombotic Risk

The most common cause of CAT in women

Breast Cancer: Epidemiology & VTE Risk

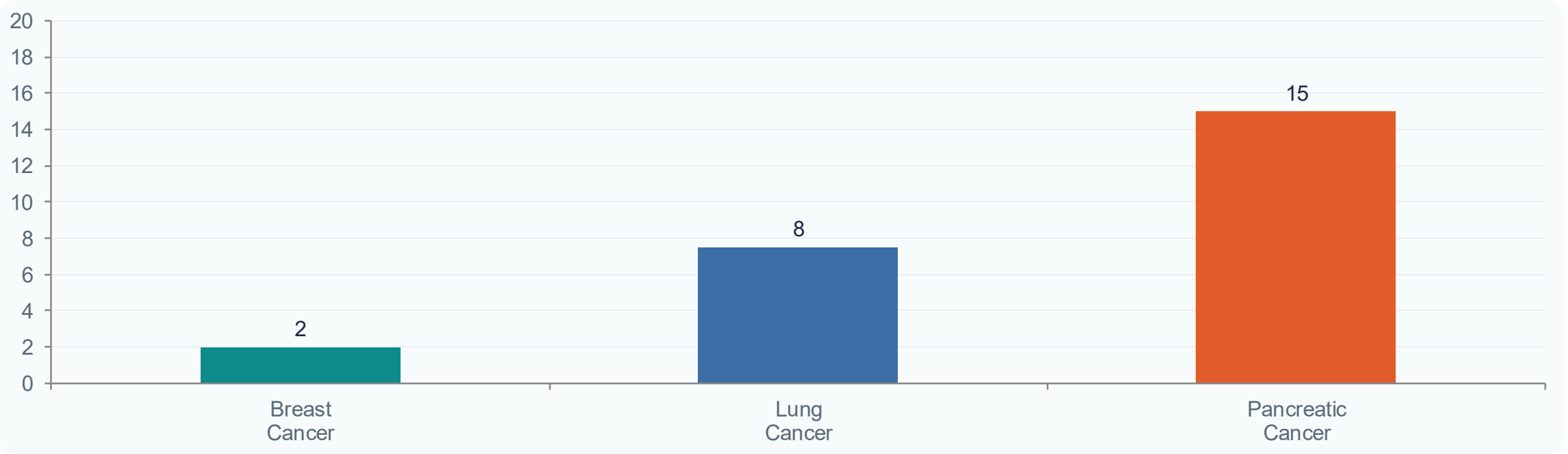
~70%
ER+/PR+ tumors

1–3%
Cumulative VTE incidence

2–3×
Higher risk age ≥70 yrs

#1
Cause of CAT in women

Risk Modifiers — Comparative VTE Incidence by Tumor Type



Łukasiewicz S, et al. Cancers (Basel) 2021; Horsted F, et al.PLoS Med 2012;9; . Razouki ZA, et al. Support Care Cancer 2022;30:8589-8597.

Breast Cancer: Treatment-Related VTE Risk Modifiers

Surgery	**0.2–1.2%**	30-day incidence; up to 3–4× with complex reconstruction or >3h procedures
Chemotherapy	**2–7×**	VTE rate 2–5% in first year; risk persists months after completion
Tamoxifen (SERM)	**2–3×**	Annual incidence ~0.5–1% in postmenopausal women; hepatic agonist effects
CDK4/6 Inhibitors	**2–8%**	2–5% in trials; up to 8% in real-world settings — potential underestimation
Metastatic disease	**6×**	Progressive systemic coagulation activation and tumor-burden inflammation

Gynecological Cancers: Ovarian & Endometrial

Hormonal dependence and thrombotic vulnerability

Ovarian Cancer: Among the Most Thrombogenic Solid Tumors

11–27%
Overall VTE incidence

55%
VTE within 3 months (RIETE)

7.29
Recurrence/100 pt-yrs on AC

Key Drivers of Thrombogenicity

- Clear cell carcinoma: 2.5–4× higher risk vs other subtypes
- ↑ Tissue Factor (TF) expression + cancer procoagulant
- NETs (neutrophil extracellular traps) activation
- Advanced stage, high grade, ascites (peritoneal carcinomatosis)
- Anatomical compression → unusual-site thrombosis
- Platinum-based chemotherapy → ~7× ↑ VTE risk
- Cytoreductive surgery + HIPEC → CAT in ~5.6% of patients

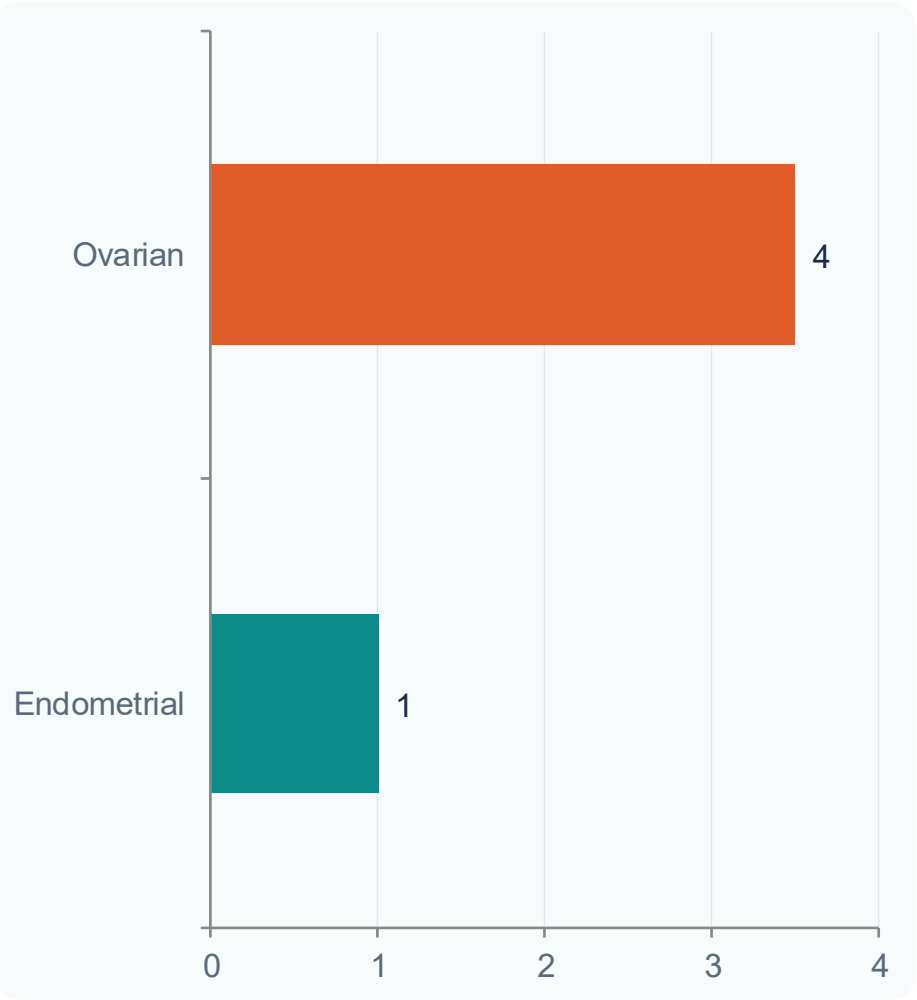
RIETE Registry Findings

- Ovarian cancer: 55% develop VTE within 3 months
- Breast cancer: only 19% within 3 months
- Highest VTE recurrence rate under anticoagulation
  (Sebastián OG, et al.*Res Pract Thromb Haemost. 2025)*
- Targeted therapies (anti-VEGF, PARP inhibitors) → mild–moderate ↑ thrombotic risk

Endometrial Cancer: Estrogen, Obesity & Surgical Risk

- VTE risk strongly linked to prolonged exposure to unopposed estrogen
- Obesity amplifies risk 2–3× via chronic inflammation and elevated PAI-1 levels
- VTE incidence after surgery: 2–4% without thromboprophylaxis
- Substantially higher than <1% after breast surgery
- Extended postoperative thromboprophylaxis recommended: up to 28 days
- Particularly after extensive pelvic procedures and lymphadenectomy
- Risk is ~3–4× lower than ovarian cancer but higher than breast cancer

Relative VTE Risk by Gynecologic Cancer



Prostate Cancer: Androgen Deprivation & Thrombosis

A sex-specific prothrombotic phenotype in men

ADT: Clinical Evidence & Risk Progression

1.5–2.5×

Overall VTE risk vs unexposed

2.52

Excess risk — Year 1 (95%CI 1.54–4.12)

4.05

Excess risk — Year 2 (95%CI 2.51–6.55)

Key Findings from Population-Based Studies

- Study period 1997–2013: 11,242 anti-androgen monotherapy, GnRH agonists, 1,091 combined androgen blockade, 3,789 orchiectomy
- Excess thromboembolic risk increases with treatment duration and is highest in men switching ADT regimens
- Risk already evident within Year 1 → synergistic interaction of acute hormonal withdrawal, cancer pro-thrombotic factors, and metabolic alterations
- Newer agents (abiraterone, enzalutamide) have not emerged as major independent VTE drivers — but longer-term surveillance is warranted

Androgen Deprivation Therapy (ADT): Thrombotic Mechanisms

Metabolic Changes

Visceral adiposity, insulin resistance, dyslipidemia, sarcopenia — all established VTE contributors

Endothelial Dysfunction

↓ Nitric oxide bioavailability, ↑ oxidative stress, ↑ adhesion molecules → platelet–endothelium interactions

Pro-inflammatory Milieu

↑ IL-6, TNF-α, CRP → amplification of TF expression and thrombin generation

Hemostatic Imbalance

↑ Fibrinogen, impaired fibrinolysis → state of hypercoagulability

Breast vs Prostate Cancer: Contrasting Thrombotic Mechanisms

Women — Breast Cancer

- Estrogenic signaling directly affects hemostasis
- Endocrine therapy = dominant long-term VTE driver
- Direct hepatic effects on coagulation factor synthesis
- Tamoxifen → ↑ thrombin generation
- AIs → cardiovascular / arterial shift
- CDK4/6 inhibitors add VTE risk on top of endocrine therapy

Men — Prostate Cancer

- Androgen deprivation → distinct prothrombotic phenotype
- Mediated largely through metabolic and vascular pathways
- NOT via direct hepatic coagulation factor synthesis
- Metabolic: adiposity, insulin resistance, dyslipidemia
- Vascular: endothelial dysfunction, ↑ adhesion molecules
- Risk accumulates with treatment duration and regimen switching

CAT Pathophysiology: Convergent Mechanisms

Tumor Biology

TF & cancer procoagulant expression
NETs activation
Cancer-derived inflammatory cytokines (IL-6, TNF-α)

Endocrine Therapy

SERM hepatic agonist effects
ADT metabolic derangements
Endothelial dysfunction
Fibrinogen ↑, fibrinolysis ↓

Treatment-Related

Chemotherapy endothelial injury
Surgery & anesthesia
Central venous catheters
Venous stasis / immobility

Patient Factors

Age, obesity, comorbidities (DM, CVD)
Prior VTE history
Mobility limitations

Disease Extent

Stage, nodal involvement, metastases
Histological subtype
Tumor burden & ascites

Sex & Hormonal Environment

Type, level, duration of hormone exposure
Menopausal status
Exogenous hormone use

Sex Differences: Clinical Implications

Tailoring care to the hormonal and biological profile

Conclusions

01 Hormones exert profound, sex-specific effects on cancer biology, hemostasis, and vascular function

02 Estrogens promote prothrombotic states via hepatic coagulation pathways; androgen deprivation acts through metabolic/vascular mechanisms

03 VTE risk varies markedly across cancers: ovarian > endometrial > prostate > breast; each with distinct drivers

04 Sex-specific differences demand risk-adapted thromboprophylaxis accounting for tumor type, hormonal environment, and treatment modality

05 As survival improves in hormone-sensitive cancers, optimizing VTE prevention without increasing bleeding risk is a critical component of personalized oncologic care

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