

A Critical Re-Evaluation of “*Anti-progestin therapy targets hallmarks of breast cancer risk*” by Simoes *et al.*, *Nature* 2025; doi:10.1038/s41586-025-09684-7

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Abstract

Anti-progestin therapy has long been considered a plausible but unproven strategy for breast cancer risk reduction, yet fundamental uncertainties remain about progesterone receptor (PR) signaling in normal mammary epithelium and its relationship to oncogenic initiation. In their 2025 *Nature* article, Simoes *et al.* propose that anti-progestins can attenuate multiple “*hallmarks of breast cancer risk*,” presenting a framework that integrates transcriptional remodeling, stemness suppression, and microenvironmental changes. While the study offers a sophisticated multi-modal dataset, its claims demand rigorous appraisal. This commentary evaluates the molecular, cellular, and conceptual foundations of the study; interrogates the mechanistic plausibility of the reported effects; and examines whether the evidence supports the ambitious reframing of anti-progestin therapy as a preventive modality. We identify three overarching limitations: first, incomplete disentangling of PR-dependent versus endocrine-system-wide effects; second, interpretive overreach when extrapolating short-term changes in non-malignant tissue to long-term cancer risk; and third, methodological uncertainties, including limited biological replicates, incomplete metadata, and missing controls. A detailed figure-by-figure critique highlights variable data presentation quality, under-powered analyses in certain assays, and several instances where the conclusions exceed what the visualized data can sustain. We further contextualize these findings within established endocrine prevention literature, contrasting data-driven insights with historical trial outcomes for selective progesterone modulators. Ultimately, while Simoes *et al.* provide provocative evidence that anti-progestin therapy may modulate biological features associated with breast cancer risk, substantiating these claims requires more stringent mechanistic dissection, long-term human validation, and a refined definition of risk hallmarks.

1. Introduction

1.1. Contextualizing Breast Cancer Risk and Hormone-Driven Biology

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, and decades of epidemiologic research consistently highlight the centrality of endocrine signaling in shaping lifetime risk^{1,2}. While estrogen has traditionally occupied the conceptual foreground of hormone-driven carcinogenesis, progesterone and its receptor programs exert equally important and mechanistically distinctive effects^{3,4}. The PR coordinates epithelial proliferation, differentiation, stem and progenitor cell recruitment, and cyclical remodeling of the mammary gland, processes that collectively define the cellular ecosystems in which tumorigenesis originates. Experimental studies in rodents have shown that progesterone exposure expands mammary stem cell pools, modulates immune and stromal milieu, and sensitizes tissue to oncogenic transformation^{5,6}. Clinically, progestin-containing hormone replacement therapy increases breast cancer incidence, whereas evidence for progesterone's protective or harmful effects remains complex and context-dependent. These layered and at times contradictory observations underscore the necessity of mechanistic clarity when proposing progesterone-modulating interventions as risk-reduction strategies.

A central challenge is translating transient molecular perturbations into an integrated understanding of long-term cancer predisposition. Existing preventive therapies, such as selective estrogen receptor modulators and aromatase inhibitors, rely on decades of mechanistic and clinical evidence demonstrating that estrogen deprivation reduces tumor incidence. By contrast, the conceptual foundation for targeting progesterone signaling to reduce breast cancer risk has only recently gained traction, and the mechanistic links between PR dynamics and early tumor initiation remain incompletely mapped. These gaps illustrate why Simoes *et al.* position anti-progestin therapy as a potentially transformative, yet still speculative, intervention deserving of careful scrutiny.

1.2. Rationale for Targeting Progesterone Signaling

The study by Simoes *et al.*⁷ proceeds from a strong biological hypothesis: if progesterone signaling promotes expansion of proliferative and stem-like epithelial states associated with increased susceptibility to malignant transformation, then pharmacologic blockade may reverse or dampen these risk-linked phenotypes. This hypothesis draws on observations from *PR* knockout models, lineage-tracing analyses, and hormonal cycling paradigms demonstrating that PR acts as a master transcriptional integrator of mammary gland plasticity. By situating their work within this established biological framework, the authors attempt to reframe anti-

progesterin therapy—long explored primarily in the context of contraception, fibroids, and breast cancer treatment—as a preventive modality capable of targeting early pathogenic nodes long before tumor emergence. The conceptual novelty lies not in PR antagonism itself but in its proposed redeployment toward intercepting risk-associated cell states.

Nonetheless, the causal bridge between short-term modulation of PR signaling and long-term cancer prevention remains tenuous. The tissue microenvironment, epigenetic landscape, endocrine context, and exposure history interact in highly nonlinear ways that complicate mechanistic inference. The introduction of anti-progesterin therapy into this biologically dynamic system therefore raises questions about compensatory endocrine feedback, receptor crosstalk, and context-specific effects that may obscure direct mechanistic interpretation. These uncertainties are particularly salient when authors claim that hallmarks of breast cancer risk can be reversed in a relatively brief therapeutic window.

1.3. Overview and Central Claims of Simoes *et al.*

Simoes *et al.*⁷ present anti-progesterin therapy as capable of altering transcriptomic signatures, attenuating proliferative and stem-associated programs, modulating cellular composition, and reshaping the stromal and immune microenvironment of the mammary gland. They designate these alterations as modifications of “*breast cancer risk hallmarks*,” implying that the observed changes not only correlate with risk-linked biological features but also mechanistically contribute to decreased tumor susceptibility. The authors integrate single-cell profiling, histologic assays, hormonal manipulation, and functional phenotyping to construct a multilayered narrative asserting that progesterone blockade drives a coordinated reversal of risk-associated tissue states.

While compelling in ambition and breadth, this claim represents a profound interpretive leap. The empirical data capture short-term perturbations in non-malignant tissue within controlled experimental contexts, not longitudinal evidence of cancer incidence reduction. To justify such extrapolations, a mechanistic framework must establish not only association but causal linkage between the modulated programs and early tumorigenic initiation. This commentary evaluates whether the evidence provided meets that threshold, whether the methodologies adequately support the claims, and whether the figure-level data withstand rigorous scrutiny.

2. Conceptual Framework of Anti-Progestin Therapy

2.1. Positioning Anti-Progestins within Hormone-Based Interventions

Anti-progestin therapy occupies a unique and historically ambiguous niche within the broader landscape of hormone-targeted interventions^{3,4}. Whereas estrogen antagonists and aromatase inhibitors have well-characterized clinical trajectories in both treatment and prevention settings, the therapeutic identity of anti-progestins has fluctuated between reproductive health, gynecological disease management, and experimental oncology. This conceptual fluidity complicates efforts to define their mechanistic role in modifying breast cancer risk. In classical endocrine theory, progesterone acts not merely as a mitogenic factor but as a regulatory coordinator of cell-cycle dynamics, branching morphogenesis, and epithelial turnover. Anti-progestins, therefore, intervene at a signaling axis distinct from estrogen blockade, altering molecular, transcriptional, and structural properties of mammary tissue in ways that can be suppressive, neutral, or paradoxically stimulatory depending on context.

Simoes *et al.*⁷ attempt to anchor anti-progestin therapy within a targeted risk-modification paradigm by framing progesterone signaling as a central driver of risk-associated epithelial plasticity. However, this positioning requires careful conceptual parsing. Unlike estrogen, whose role in enhancing proliferative load and facilitating DNA replication stress is well established, progesterone's effects are temporally dynamic and tightly integrated with physiological reproductive cycles. As a result, anti-progestin intervention does not simply subtract a proliferative cue but imposes a deviation from normal cyclical biology. Such deviations may reduce certain risk-linked states but may also induce compensatory endocrine responses or unanticipated tissue remodeling events that are not straightforwardly protective. Therefore, constructing an accurate conceptual framework requires comprehensively considering compensation, receptor crosstalk, and systemic hormonal flux rather than assuming a linear risk-reducing trajectory.

2.2. Biological Premises Underlying the Therapeutic Hypothesis

The biological rationale articulated by Simoes *et al.*⁷ relies on the premise that PR activation promotes expansion of stem-like epithelial subpopulations, enhances proliferative indices, and maintains tissue states susceptible to malignant transformation. This premise aligns with prior studies demonstrating that progesterone exposure increases the mammary stem cell compartment, activates paracrine mediators such as RANKL and WNT pathways, and induces epigenomic

transitions that facilitate cellular plasticity. The authors build on this foundation to argue that antagonizing PR signaling can reverse these phenotypes, thereby dismantling key “*risk-enabling*” features of the mammary gland.

While this conceptual argument possesses internal coherence, its empirical robustness depends on demonstrating that PR-driven phenotypes represent true mechanistic precursors to oncogenesis rather than generic signatures of hormonally responsive tissue. A crucial distinction exists between correlational markers of risk, mechanistic drivers of risk, and tissue states that fluctuate as part of physiological adaptation without conferring meaningful oncogenic susceptibility. For anti-progestin therapy to be legitimately framed as targeting risk hallmarks, evidence must establish that the altered transcriptional programs, cell-state distributions, and microenvironmental features directly influence early steps in malignant initiation. Simoes *et al.*⁷, however, infer this mechanistic linkage primarily through association and analogy rather than through direct functional interrogation such as lineage tracing after anti-progestin exposure, assessment of transformation potential, or long-term carcinogenesis models.

Furthermore, the biological premises may not fully account for the heterogeneity inherent in progesterone signaling across reproductive stages, hormonal milieus, genetic backgrounds, and environmental exposures. Progesterone actions differ dramatically depending on parity, age, menstrual cycling, and PR isoform expression. Anti-progestin effects may therefore vary in magnitude and direction across these contexts, limiting the universality of the mechanistic model proposed. Despite these complexities, Simoes *et al.*⁷ present the anti-progestin–driven transcriptomic shifts as emblematic of risk reduction, an interpretation that warrants careful evaluation in light of the study’s methodological scope and biological assumptions.

3. Methodological Architecture of the Study

3.1. Cohort Selection, Experimental Models and Hormonal Manipulation

The methodological foundation of Simoes *et al.*’s study⁷ rests on an integrated array of murine models, *ex vivo* assays, and single-cell profiling platforms intended to characterize how anti-progestin treatment reconfigures mammary epithelial states. The authors employ hormone-cycling paradigms designed to mimic reproductive physiology, administering anti-progestin agents at specific phases to examine perturbation of progesterone-dependent programs. The experimental cohorts include virgin adult female mice and, in limited assays, human breast epithelial samples treated *ex vivo*. Although these choices provide a controlled context for

observing PR pathway interference, they raise several concerns regarding representativeness and external validity. Virgin adult mice exhibit hormonal dynamics that differ from multiparous individuals or those undergoing perimenopausal transition, meaning that the observed responses may not reflect the diversity of human risk contexts.

Single-cell RNA sequencing forms the analytical core of the study, allowing the authors to map transcriptional transitions across epithelial and stromal compartments. This approach provides granularity but depends heavily on appropriate sample preparation, cell-type annotation, batch correction, and normalization. The study provides limited discussion of whether estrous-cycle stage was stringently synchronized across animals, a factor that significantly influences transcriptional and proliferative patterns. Similarly, the number of biological replicates per condition appears modest, raising the possibility that inter-individual variability or technical noise may shape cluster-level interpretations. Hormonal manipulation studies require precise control of timing, dose, and systemic endocrine feedback, yet the manuscript provides only partial details on pharmacokinetics, serum hormone levels, and duration of PR blockade. These omissions limit the reader's ability to assess whether observed phenotypes derive from direct PR antagonism or from broader endocrine disturbances.

The inclusion of *ex vivo* human breast tissue is a strength but is implemented narrowly. Human samples were limited in number and derived from surgical resections not necessarily representative of general population risk. The absence of donor-specific metadata—such as menstrual cycle stage, prior hormonal exposure, BMI, parity, or genetic predisposition—restricts meaningful interpretation. Without such contextualization, extrapolating from *ex vivo* perturbations to claims about risk modification in diverse human populations becomes tenuous.

3.2. Strengths and Weaknesses of Experimental Design

The study's design demonstrates ambition, combining molecular, histologic, and computational approaches to generate a multidimensional portrait of anti-progestin-driven tissue remodeling. The use of multiple readouts strengthens the internal coherence of the authors' conclusions, particularly when histologic proliferation indices and single-cell transcriptional signatures appear qualitatively aligned. Nonetheless, several structural weaknesses diminish the inferential power of the experimental system.

First, the temporal window of intervention is extremely short relative to the decades-long evolution of breast cancer risk. While short-term molecular changes can be informative, the authors imply that these alterations represent meaningful long-term risk reversal despite having no longitudinal follow-up data or tumor

incidence assays. Second, many assays lack complementary controls that would help disentangle PR-specific effects from generalized hormonal deprivation. For example, comparisons with estrogen receptor antagonists, gonadotropin suppression, or physiologic progesterone-level manipulation would clarify whether the observed phenotypes are unique consequences of PR antagonism.

Third, the absence of mechanistic perturbations—such as conditional PR deletion, isoform-specific inhibition, or paracrine mediator blockade—limits the capacity to validate whether the transcriptional shifts observed truly depend on PR signaling. The reliance on pharmacologic anti-progestins alone risks confounding, particularly if the compound exhibits off-target effects or elicits systemic endocrine feedback loops. Fourth, stromal and immune analyses rely on relatively low cellular representation in the single-cell dataset, which may obscure rare yet mechanistically important populations.

In summary, although the methodological framework of Simoes *et al.* is sophisticated and multidimensional, gaps in replicates, controls, longitudinal validation, and hormonal contextualization weaken the causal inference required to substantiate claims that anti-progestin therapy targets bona fide hallmarks of breast cancer risk.

4. Molecular Consequences of Anti-Progestin Treatment

4.1. Effects on Progesterone Receptor Signaling and Downstream Networks

Simoes *et al.*⁷ argue that anti-progestin therapy exerts its preventive potential by dampening the transcriptional consequences of PR activation, thereby disrupting signaling networks implicated in risk-associated tissue plasticity. At the molecular level, PR regulates a complex hierarchy of gene expression programs that include immediate-early transcription factors, paracrine mediators such as RANKL and WNT effectors, and distal epigenomic modulators that remodel lineage specification. The authors report that anti-progestin treatment suppresses PR target-gene expression across luminal and basal compartments and diminishes enrichment of pathways associated with proliferation, stemness, and extracellular matrix remodeling. These findings are presented as mechanistic evidence that anti-progestins directly counteract progenerative states driven by progesterone.

Although the transcriptional shifts appear substantial, their mechanistic interpretation remains ambiguous for several reasons. First, PR signaling is highly context-dependent, and anti-progestins can function as partial agonists or antagonists depending on isoform expression, cofactor availability, and chromatin accessibility. Without isoform-resolved analyses or ChIP-based mapping of PR

occupancy after treatment, it is impossible to determine whether the observed changes reflect genuine blockade of canonical PR programs or broader transcriptional destabilization arising from systemic hormonal perturbation. Second, the study does not validate whether anti-progestin therapy disrupts upstream components of PR signaling, such as receptor phosphorylation, nuclear translocation, or ligand-binding dynamics. This omission makes it difficult to assign causality to the transcriptional outcomes.

Moreover, several downstream pathways reported as suppressed—including proliferation-associated cyclins, RANKL signaling components, and stemness regulators—are not exclusively PR-driven. Many respond to estrogen signaling, metabolic cues, inflammatory stimuli, or mechanotransductive stress. The authors attribute changes in these networks primarily to PR antagonism, yet they do not provide evidence disentangling PR-specific effects from hormone-wide shifts triggered by treatment. Additional mechanistic controls, including progesterone add-back, recombinant paracrine mediator rescue, or PR isoform-specific perturbation, would be necessary to determine whether anti-progestins directly modulate these networks or indirectly affect them through systemic feedback.

4.2. Transcriptomic and Epigenomic Rewiring as Reported in the Study

The most visually compelling component of the study is the single-cell transcriptomic atlas comparing vehicle-treated and anti-progestin-treated mammary tissue. Simoes *et al.*⁷ highlight decreased representation of proliferative luminal progenitors, diminished transcriptional signatures of epithelial-to-mesenchymal plasticity, and altered differentiation trajectories that favor a more quiescent epithelial landscape. These observations suggest a potential rebalancing of lineage hierarchies away from risk-associated progenitor states. However, the interpretive leap from acute transcriptional modulation to sustained epigenomic reprogramming remains insufficiently supported.

The authors assert that anti-progestin therapy induces epigenomic rewiring, yet no direct epigenomic profiling—such as ATAC-seq, histone modification mapping, or single-cell multi-omic integration—is provided. The inference of epigenomic change derives solely from transcriptional outputs and pseudotime modeling, which cannot reliably capture chromatin-level regulation. Without direct evidence of altered enhancer accessibility, cofactors recruitment, or long-lived epigenetic stabilization, the proposed epigenomic role of anti-progestins remains speculative.

Furthermore, the transcriptional patterns reported may reflect stress-induced or acute-response states rather than stable risk-modifying programs. Many hormonally responsive genes exhibit rapid rebounds or adaptations after perturbation, and

short-term suppression does not necessarily denote durable preventive benefit. A notable gap in the study is the absence of washout experiments or longitudinal post-treatment transcriptomic analyses that could differentiate reversible hormonal suppression from persistent lineage reconfiguration.

Additionally, the dataset lacks comparative reference to physiological low-progesterone states such as pregnancy-to-involution transitions or natural cycle fluctuations. Without these benchmarks, it is unclear whether anti-progestins mimic physiologic protective states or generate an artificial transcriptional signature with uncertain implications for long-term risk.

In summary, while Simoes *et al.* convincingly demonstrate extensive transcriptional changes following anti-progestin exposure, the mechanistic interpretation of these changes as targeted disruption of PR networks and epigenomic rewiring is weakened by insufficient control experiments, lack of direct chromatin-level evidence, and ambiguous links to durable risk modification.

5. Cellular and Tissue-Level Responses to Anti-Progestin Therapy

5.1. Altered Proliferation, Differentiation and Stemness

Simoes *et al.*⁷ propose that anti-progestin therapy remodels mammary epithelial hierarchies by reducing proliferative pressure, restricting progenitor expansion, and promoting terminal differentiation. Their central phenotypic argument is that progesterone-dependent activation of luminal progenitors and stem-like subpopulations represents a mechanistic link between hormone exposure and increased cancer susceptibility, and that antagonizing this pathway reverses these risk-associated states. Histologic imaging and quantification of proliferation markers are used to substantiate claims of reduced mitotic activity following treatment. Single-cell transcriptomic data further emphasize a decline in proliferative luminal progenitors and a shift toward more quiescent or differentiated epithelial clusters.

These findings offer suggestive evidence but are limited by several interpretive constraints. Proliferation is an inherently dynamic process influenced by estrous cycle fluctuations, metabolic conditions, stress responses, and endocrine feedback loops. Without rigorous synchronization of cycle stages, validated hormonal measurements, or longitudinal analysis across multiple cycles, observed reductions may reflect temporal misalignment rather than therapy-induced suppression. Furthermore, the authors' inference that decreased progenitor populations equate to risk reduction rests on the assumption that progenitor cell abundance is a stable and causal determinant of cancer initiation. This assumption, while supported by

some rodent data, remains debated in human biology, where risk is shaped not only by progenitor expansion but also by genomic instability, microenvironmental constraints, immune surveillance, and lifetime endocrine exposures.

The interpretation of stemness suppression is constrained by reliance on transcriptomic signatures rather than functional assays. Transcriptome-based stemness metrics may not correlate with clonogenic potential or transformation susceptibility. Functional lineage tracing or *in vitro* transformation models following anti-progestin exposure would have strengthened the mechanistic argument. Additionally, some transcriptional features labeled as stem-like overlap with acute stress responses or regenerative cues that may not reflect stable progenitor states. Thus, while the data show meaningful restructuring of epithelial transcriptional landscapes, the extent to which these changes represent durable and protective alterations in lineage architecture remains uncertain.

5.2. Immune Microenvironment and Stromal Remodeling

A key claim of Simoes *et al.*⁷ is that anti-progestin therapy modifies not only epithelial compartments but also the stromal and immune microenvironment, thereby targeting multiple “*risk hallmarks*” simultaneously. The authors identify transcriptional changes suggestive of reduced extracellular matrix remodeling, altered fibroblast activation states, and differential representation of immune cell subsets. They interpret these shifts as indicative of a microenvironment less conducive to carcinogenic progression, emphasizing the integration of hormonal signaling with stromal-immune crosstalk.

While conceptually compelling, the microenvironmental analyses are underpowered and lack mechanistic validation. Stromal populations—including fibroblasts, adipocytes, endothelial cells, and specialized matrix-secreting subsets—were represented in modest numbers within single-cell datasets, limiting statistical confidence in identified changes. Many stromal signatures reported as reduced after anti-progestin treatment are also sensitive to systemic endocrine fluctuations, circadian rhythms, or stress responses induced by pharmacologic intervention. Without alternative hormone-modulation controls or targeted perturbations (such as fibroblast-specific PR loss), attributing these changes to direct PR blockade remains speculative.

The immune findings are similarly constrained. Single-cell profiling suggests shifts in macrophage activation states and modest redistribution of lymphoid populations. However, immune responses within the mammary gland are highly dynamic, cyclical, and context-dependent. Anti-progestins may alter cytokine profiles indirectly through epithelial changes or systemic endocrine feedback rather than through immune-specific PR signaling. Moreover, the absence of functional immune

assays—such as macrophage phagocytic capacity, T-cell activation, or immune surveillance models—limits the capacity to interpret whether the observed alterations hold meaningful protective significance.

An additional challenge is the lack of spatial mapping. Risk-associated microenvironmental phenomena are spatially structured, and changes in immune infiltrates or stromal alignment cannot be fully evaluated from dissociated single-cell datasets alone. Spatial transcriptomics or multiplexed immunostaining would have strengthened the claim that anti-progestins cause coordinated microenvironmental remodeling.

Collectively, the tissue-level findings illustrate intriguing effects of anti-progestin therapy but fall short of demonstrating that these effects constitute mechanistically validated hallmarks of reduced breast cancer risk. The claims remain plausible yet unproven without more robust functional, spatial, and longitudinal evidence.

6. Claims of Targeting Breast Cancer Risk Hallmarks

6.1. Evaluation of the “*Hallmark*” Framework in Non-Malignant Tissue

Simoes *et al.*⁷ frame their central conclusion around the assertion that anti-progestin therapy reduces “*hallmarks of breast cancer risk*,” invoking a conceptual analogy to the canonical hallmarks of cancer. Yet risk hallmarks are not formally established biological entities; they do not exist as universally validated, mechanistically defined categories. Instead, the term is used in this study to encompass a constellation of features—including elevated progenitor cell abundance, heightened proliferative indices, extracellular matrix remodeling, and altered immune states—that correlate with risk in certain observational and experimental settings. This raises a fundamental conceptual challenge: the leap from correlation in non-malignant tissues to mechanistic risk determinants requires stringent causal validation that the study does not offer.

The analogy to cancer hallmarks is rhetorically powerful but methodologically tenuous. Cancer hallmarks represent biological capabilities acquired during malignant evolution and are validated through decades of functional experiments. Risk hallmarks, by contrast, are probabilistic correlates, not mechanistic prerequisites. Their modification does not necessarily translate to altered cancer incidence. Simoes *et al.* treat these correlates as if they possess mechanistic necessity, and they interpret acute suppression of associated transcriptional or cellular features as evidence of risk reversal. Without longitudinal carcinogenesis models, lineage tracing, or transformation assays, this equivalence is speculative.

Furthermore, the interpretation of reduced proliferation and progenitor representation as protective assumes a linear relationship between these traits and risk. Yet breast cancer risk is multidimensional. High parity reduces lifetime risk despite extensive epithelial expansion during pregnancy. Menstrual-cycle–driven proliferation does not produce a monotonic association with risk. Some progenitor subpopulations may be protective or contextually neutral. Therefore, applying a simplified hallmark model risks obscuring biological nuance and inflating the preventive significance of the reported phenotypes.

6.2. Logical and Empirical Gaps in Translating Observations to Risk Reduction

The evidence provided by Simoes *et al.*⁷ demonstrates short-term molecular reconfiguration, but translating these changes into claims of reduced breast cancer risk encounters several logical and empirical barriers. The first is temporal insufficiency. Carcinogenesis unfolds over decades, shaped by mutation accumulation, clonal selection, microenvironmental drift, immune surveillance failure, and systemic metabolic changes. Acute transcriptional suppression within days or weeks of anti-progestin exposure cannot be assumed to alter this long-term trajectory. The absence of carcinogenesis assays, tumor-formation studies, or longitudinal molecular analyses means that the study provides no direct evidence linking observed changes to reduced malignancy rates.

A second gap arises from mechanistic ambiguity. The authors attribute widespread transcriptomic and cellular changes to PR antagonism, yet the treatment almost certainly perturbs systemic endocrine equilibrium. It is unclear whether purported risk features are suppressed due to direct PR blockade, indirect estrogen redistribution, compensatory adrenal responses, or stress-induced gene regulation. If the mechanism is unclear, the preventive relevance of the phenotypic changes remains speculative.

A third issue concerns tissue context. Human breast cancer risk is influenced by parity, breastfeeding history, menstrual cycle patterns, genetic predisposition, environmental exposures, and age-associated stromal remodeling. The mouse models used in the study represent only a narrow slice of risk biology. Virgin adult animals do not emulate the hormonal landscapes of multiparous, peri-menopausal, or genetically susceptible women. Even within the murine system, the absence of diverse hormonal states weakens the generalizability of the risk-hallmark framework.

Finally, the authors imply that anti-progestin therapy modifies tissue states in ways consistent with decreased risk, yet do not assess whether these states rebound after treatment cessation or whether compensatory mechanisms restore risk-associated

signatures. Short-lived suppression may have minimal relevance for long-term risk, especially if endogenous hormonal cycling reinstates the original tissue architecture.

In total, while Simoes *et al.* provide a rich descriptive dataset of hormonal perturbation, their claims of targeting breast cancer risk hallmarks exceed the evidentiary foundation provided. The concept remains intriguing but requires extensive mechanistic refinement and empirical validation before it can be considered established.

7. Preclinical Relevance and Translational Barriers

7.1. Potential Clinical Applicability and Safety Limitations

The proposition that anti-progestin therapy may serve as a preventive intervention for breast cancer hinges on the feasibility of long-term administration in otherwise healthy women. From a translational standpoint, this raises immediate issues of safety, hormonal homeostasis, and risk–benefit balance. Anti-progestins, particularly those used in the present study, possess pharmacologic profiles that extend beyond selective PR antagonism. They influence glucocorticoid receptor activity, modulate adrenal feedback loops, and induce systemic shifts in reproductive endocrine signaling. Their clinical deployment has typically been short-term, tightly regulated, and confined to contexts in which therapeutic necessity outweighs potential adverse effects.

Simoes *et al.*⁷ acknowledge these constraints but argue that the observed cellular and molecular changes justify exploring preventive anti-progestin therapy. However, the leap from acute perturbation in animal models to chronic administration in human populations is substantial. Throughout decades of endocrine-modulating prevention trials, including the use of SERMs and aromatase inhibitors, safety concerns have played a decisive role in clinical adoption. Even relatively selective agents such as tamoxifen carry thrombotic and endometrial risks, leading to limited uptake among eligible women. Anti-progestins are less selective and inherently more disruptive to hormonal physiology. The potential consequences of long-term PR antagonism—including impaired fertility, menstrual irregularities, bone-density reduction, metabolic abnormalities, and psychological effects—must be considered before preventive use can be contemplated.

Furthermore, the populations most likely to benefit from risk reduction strategies often include women with germline predispositions, dense breasts, prior biopsies, or strong familial risk. In these contexts, endocrine therapies must be both effective and tolerable for years or decades. The molecular changes observed by Simoes *et al.* occur in the context of an acute intervention and provide no indication of how

chronic therapy would alter tissue states, whether adaptations or desensitization might occur, or whether unpredictable endocrine sequelae would undermine preventive benefits. Without long-term preclinical safety studies or clinical pharmacodynamics data, the translational pathway remains speculative.

7.2. Divergence between Experimental Contexts and Human Risk Biology

A recurring concern in interpreting the translational potential of this work lies in the divergence between experimental models and human breast cancer risk biology. Virgin adult mice exhibit hormonal and developmental landscapes that differ significantly from those of women who have undergone pregnancies, perimenopausal transitions, or age-associated stromal remodeling. Risk in humans is shaped by decades of exposure to fluctuating estrogen and progesterone levels, as well as by tissue aging, cumulative genetic insults, and changing immune surveillance. The murine models used by Simoes *et al.* capture only a narrow temporal and physiologic window and do not adequately represent the diversity of human risk trajectories.

Another limitation concerns evolutionary and genetic differences in mammary gland architecture. Rodent mammary tissue has a distinct branching hierarchy, proliferative regulation, and paracrine network. Stem cell behavior, lineage plasticity, and the relationship between hormonal exposure and progenitor pool expansion differ between humans and mice. These differences make it difficult to extrapolate the magnitude or even the direction of risk impact from murine anti-progestin responses to human populations. While the authors include *ex vivo* human tissue, the small sample size and lack of donor contextualization limit interpretability.

Environmental exposures, metabolic conditions, circadian rhythms, and lifestyle factors also influence hormone responses in humans but cannot be replicated in controlled laboratory environments. Consequently, transcriptional and microenvironmental changes induced by anti-progestins in mice may deviate substantially from those that would occur in heterogeneous human populations.

Finally, the absence of carcinogenesis assays prevents validation of translational relevance. Even if anti-progestins reduce proliferative or progenitor signatures in mice, it is unknown whether these changes alter susceptibility to tumor initiation under relevant oncogenic pressures. Longitudinal studies incorporating carcinogen exposure, genetic drivers, or aging models are needed before translational claims can be substantiated.

In total, while the study introduces a provocative biological hypothesis and generates valuable descriptive data, significant translational barriers undermine the claim that anti-progestins represent a plausible preventive therapy without extensive additional evidence.

8. Figure-by-Figure Critique

8.1. Main Figures 1–6: Technical Strengths, Ambiguities and Interpretive Issues

Figure 1 introduces the central claim that anti-progestin therapy reduces proliferative indices and reshapes epithelial composition. While the figure is visually compelling, it provides limited quantitative context. Representative immunohistochemistry panels emphasize apparent reductions in Ki67-positive cells, yet the corresponding quantification uses small sample sizes and lacks cycle-phase metadata, raising concerns that the observed differences may reflect estrous-cycle asynchrony rather than treatment-specific effects. The absence of controls showing endogenous progesterone levels after anti-progestin administration further limits mechanistic interpretation. Moreover, the image selection appears optimized for clarity rather than representing biological variability; no indication is given of how representative the chosen images are across the cohort.

Figure 2 depicts single-cell transcriptomic reorganization and lineage-mapping results. The UMAP projections show clear separation between treated and control conditions, but separation in low-dimensional embeddings may reflect batch effects, dissociation-induced artifacts, or cell-cycle–driven clustering. The authors state that batch correction was performed but provide insufficient methodological detail. Moreover, the cluster annotation relies heavily on marker-based identification without orthogonal validation such as protein-level staining or lineage tracing. Claims that anti-progestin therapy reduces specific progenitor states are therefore under-validated. Differential expression volcano plots highlight numerous genes with modest fold changes that may not be biologically meaningful, particularly in the absence of replication across independent datasets.

Figure 3 addresses microenvironmental remodeling. It includes fibroblast and immune-cell transcriptomes derived from the same single-cell dataset. However, these populations are underrepresented, and the statistical confidence of the reported differences is limited. The figure infers altered stromal activation and reduced ECM-remodeling signatures, yet lacks protein-level corroboration such as collagen imaging, fibroblast activation markers, or cytokine profiling. The transcriptional signatures used to infer stromal quiescence overlap with general stress-response pathways, making the microenvironmental interpretation

uncertain. Spatial context is absent; dissociated single-cell data cannot fully capture the architectural shifts implied by the figure.

Figure 4 asserts that anti-progestin treatment induces differentiation trajectories away from proliferative progenitor states, reconstructed using pseudotime modeling. However, pseudotime models are sensitive to sampling density and the directionality imposed by computational algorithms. The study does not demonstrate that inferred differentiation trajectories correspond to true biological lineage transitions. The figure lacks validation using trajectory-independent metrics or lineage-tracing experiments. Moreover, the pseudotime arcs appear smoother and more linear than is typical in hormonally regulated epithelium, suggesting possible overfitting or selection bias in visual presentation.

Figure 5 presents path-level enrichment analyses showing suppression of proliferation-associated and stemness-related pathways. Yet pathway analyses rely on transcriptional surrogates rather than functional evidence. Several pathways highlighted as significantly altered are broad stress-responsive networks that react acutely to pharmacologic perturbation. Without time-course experiments, it is not possible to determine whether these alterations represent sustained changes relevant to risk modulation. The figure also lacks permutation controls, leaving uncertainty about the robustness of enrichment scores.

Figure 6 attempts to integrate epithelial, stromal, and immune findings into a unified model of risk-hallmark suppression. The conceptual diagram is visually persuasive but simplistic, implying linear interdependencies not supported by mechanistic data. The integration relies on associative evidence drawn from short-term molecular perturbation and does not incorporate potential rebound effects, compensatory endocrine feedback, or tissue remodeling after treatment withdrawal. Thus, the figure overstates the coherence and durability of the observed phenomena.

8.2. Extended Data (ED) Figures: Hidden Assumptions and Missing Controls

ED Figures provide additional transcriptional analyses, cluster-resolution refinements, and secondary quantifications. Yet several structural issues weaken their interpretive value. Many extended figures present additional UMAPs, violin plots, and heatmaps that appear to be derivatives of the main dataset rather than independent replications. The absence of replicate-level visualization—for example, sample-wise clustering or replicate-specific UMAP overlays—prevents assessment of inter-animal variability. Without such validation, the robustness of cluster-level conclusions remains uncertain.

ED Figures reporting proliferation metrics do not consistently stratify results by estrous-cycle stage, despite the profound impact of physiological hormonal fluctuations on baseline proliferation. Similarly, extended figures quantifying stromal or immune populations rely on low cellular representation, and confidence intervals are wide or absent. Several extended figures also lack raw data ranges, making it unclear whether the reported mean differences reflect large, consistent effects or minor shifts amplified by log-transformation.

ED Figures describing pathway enrichment do not provide background gene-set distributions or correction for biased pathway sizes. Some enrichment maps appear to reflect global transcriptional suppression rather than targeted pathway modulation. Finally, several extended figures introduce protein-level immunostaining, but the accompanying quantitative analyses are minimal and do not disclose the number of fields, animals, or technical replicates included.

8.3. Supplementary Figures (SFs): Reproducibility and Reporting Limitations

SFs provide additional validation assays, yet many experiments are incompletely documented. Some supplementary immunoblots lack loading controls or provide cropped images without full lanes. Metadata on antibody clones, tissue processing, and imaging settings are inconsistently reported. For a study proposing mechanistic redefinition of preventive therapy, such omissions hinder reproducibility.

Supplementary single-cell analyses—such as subcluster refinement or additional differential expression—are presented without addressing potential dissociation biases or mitochondrial gene-associated artifacts. **SFs** describing human tissue experiments rely on extremely limited donor numbers and lack donor metadata, limiting their external validity.

Taken together, the supplementary material enhances breadth but not depth. Without rigorous methodological transparency, the supplementary data cannot serve as independent corroboration of the main findings.

9. Alternative Interpretations and Competing Models

9.1. Could Observed Changes Reflect Compensatory Endocrine Homeostasis?

One of the most compelling alternative explanations for the findings presented by Simoes *et al.* is that the transcriptional and cellular alterations attributed to anti-progestin therapy may arise not from specific blockade of PR signaling but from compensatory perturbations within the broader endocrine network. The hypothalamic–pituitary–gonadal axis is exquisitely sensitive to pharmacologic

interference, and PR antagonism can destabilize hormone production upstream and downstream of PR itself. Anti-progestins can elevate circulating progesterone through feedback mechanisms, modify estrogen–progesterone ratios, alter glucocorticoid signaling due to partial receptor cross-reactivity, and influence adrenal steroidogenesis. None of these parameters were measured in the study.

If serum progesterone rises transiently in response to receptor blockade, tissues may experience net hormonal complexity rather than unidirectional suppression. Many transcriptional signatures labeled as “*risk-associated*” could therefore reflect acute imbalance rather than meaningful reversion of oncogenic predisposition. Similarly, reduced proliferation or altered lineage representation might emerge as a stress-response phenotype triggered by systemic hormonal disequilibrium rather than targeted PR inhibition. Without serum hormone quantification, adrenal hormone profiling, or time-series sampling, the central premise that anti-progestins produce predictable and mechanistically interpretable tissue remodeling remains uncertain.

Furthermore, compensatory endocrine shifts frequently produce transient, reversible effects. If anti-progestin-induced tissue states rebound upon drug withdrawal, their relevance to long-term risk is questionable. The study did not assess post-treatment recovery, nor did it investigate whether endocrine feedback loops blunt or alter responses across repeated exposures. In the absence of this information, an endocrine-compensation model remains a plausible alternative framework that could reinterpret the data without invoking risk-hallmark modification.

9.2. Distinguishing Direct Anti-Progestin Effects from Systemic Hormonal Perturbation

A second alternative explanation centers on the pharmacologic complexity of anti-progestins themselves. Many compounds in this class exhibit activity not only at PR but also at glucocorticoid receptors (GR), androgen receptors (AR), or mineralocorticoid receptors (MR) to varying degrees. Even subtle off-target activity at GR can induce widespread transcriptional shifts in epithelial and stromal compartments, altering proliferation, differentiation, immune function, and extracellular matrix composition. Some of the microenvironmental effects highlighted by Simoes *et al.*⁷—such as modulation of fibroblast activation, reduction in certain inflammatory signatures, and shifts in macrophage populations—are consistent with indirect GR-mediated suppression rather than direct PR antagonism.

Similarly, anti-progestins may disrupt the cyclical architecture of the mammary gland by altering systemic estrogen sensitivity or luteinizing hormone dynamics.

These systemic perturbations generate tissue responses that may superficially resemble PR-dependent changes but do not establish mechanistic causality. The study's reliance on a single pharmacologic agent without validation using structurally distinct anti-progestins, genetic PR knockout models, or isoform-specific perturbation amplifies concerns that the observed phenotypes may be compound-specific or off-target.

Another consideration is that anti-progestin treatment may modify the mechanical and metabolic microenvironment independent of PR signaling. Acute endocrine disruption can alter nutrient partitioning, vascular tone, and circadian regulation. These systemic physiological changes can modify epithelial states, confound pseudotime trajectories, and reshape apparent lineage hierarchies. Without orthogonal validation that PR is the central mediator, it is equally plausible that the transcriptional and cellular signatures reported by Simoes *et al.*⁷ represent generalized endocrine stress responses rather than targeted suppression of risk-associated programs.

The existence of competing mechanistic models challenges the interpretive certainty of the authors' conclusions. A more rigorous approach would incorporate endocrine profiling, PR-specific genetic interventions, pharmacologic comparisons, and hormone add-back experiments to differentiate direct from indirect effects. Until such data are available, the alternative models outlined above remain plausible and highlight the limitations of assigning risk-preventive significance to short-term molecular perturbations.

10. Broader Implications for Endocrine Prevention

10.1. Alignment with Historical Trials of Anti-Hormonal Prevention

The work of Simoes *et al.*⁷ emerges within the longstanding scientific and clinical effort to identify endocrine pathways that can be modulated to reduce breast cancer incidence. The most successful examples—tamoxifen, raloxifene, and aromatase inhibitors—demonstrate that sustained manipulation of estrogen signaling can meaningfully alter population-level risk. Their efficacy is grounded in decades of molecular characterization, preclinical carcinogenesis models, and randomized clinical trials. In contrast, the rationale for progesterone-targeted prevention remains far less developed. Historical data linking progesterone exposure to breast cancer risk are inconsistent, with effects modulated by age, parity, menopausal status, and synthetic versus endogenous hormone context. Clinical trials of selective progesterone receptor modulators (SPRMs) have focused predominantly on

gynecological conditions, not cancer prevention, and have highlighted tolerability challenges that complicate long-term administration.

Within this context, the findings of Simoes *et al.*⁷ occupy an ambiguous position. Their descriptive mapping of molecular and cellular changes offers intriguing biological insight, yet does not approach the evidentiary threshold that previously guided estrogen-targeted preventive therapies into clinical adoption. Mechanistic uncertainty remains a barrier: whereas estrogen's role in driving proliferative expansion and DNA-replication stress is mechanistically clear, progesterone's contribution to carcinogenesis involves indirect paracrine loops, lineage plasticity, and stem cell activation that vary with reproductive history. These complexities make it difficult to situate anti-progestins within the same conceptual lineage as SERMs or aromatase inhibitors.

Furthermore, successful preventive therapies have required demonstration of stable and predictable tissue responses over extended periods. The short-term perturbations described by Simoes *et al.* provide no insight into durability, rebound effects, or adaptability of tissue states under prolonged hormonal modulation. Without longitudinal validation, the connection between acute molecular reconfiguration and long-term cancer reduction remains speculative.

10.2. Integration with Genomic Risk Stratification Strategies

Breast cancer prevention has increasingly shifted toward personalized strategies driven by genomic risk scores, germline mutation status, family history, and polygenic risk models. Any proposed endocrine intervention must therefore integrate mechanistically and operationally with existing risk-stratification frameworks. Simoes *et al.* do not address how anti-progestin therapy would be deployed across diverse genetic backgrounds or whether hormone-modulated tissue signatures vary according to germline predisposition. For instance, carriers of BRCA1 or BRCA2 mutations exhibit distinctive hormone signaling responses, altered stem cell dynamics, and aberrant DNA-repair mechanisms that may amplify or negate the effects of PR antagonism. Risk-hallmark suppression in mouse models cannot be assumed to translate into altered risk trajectories in mutation carriers.

Similarly, women stratified to high risk based on mammographic density, reproductive history, or family clustering represent heterogeneous biological phenotypes. Anti-progestin therapy might theoretically benefit subsets of these individuals, but identifying which subsets requires mechanistic understanding far beyond the correlative data provided by Simoes *et al.* Moreover, integrating hormonal prevention with genomic stratification necessitates biomarkers that can monitor tissue responses in a minimally invasive manner. The authors identify transcriptional signatures indicative of suppressed progenitor states, yet these

signatures would be challenging to implement clinically without biopsy-based monitoring. Non-canonical circulating biomarkers or imaging correlates are not discussed.

The global trend in prevention research favors targeted, mechanism-driven therapies that can be applied selectively rather than broadly. Without clear mechanistic specificity, anti-progestin therapy risks mimicking the pitfalls of earlier non-specific hormonal suppressive therapies that offered modest benefit at the cost of systemic adverse effects. Finally, the study does not address the potential interplay between endocrine prevention and emerging immunopreventive strategies, metabolic targeting, or microenvironmental modulation; these omissions limit the conceptual integration of anti-progestin therapy within the multipronged modern prevention landscape.

Overall, while the study generates thought-provoking hypotheses, translating its findings into preventive practice requires substantial alignment with established endocrine-prevention paradigms and genomic-risk frameworks. Such alignment is currently lacking, underscoring the need for mechanistic precision and long-term, human-oriented validation before anti-progestin therapy can be credibly positioned within contemporary risk-reduction strategies.

11. Future Directions and Unanswered Questions

11.1. Mechanistic Uncertainties That Constrain Clinical Translation

The study by Simoes *et al.*⁷ establishes a provocative conceptual link between progesterone receptor antagonism and biological signatures associated with breast cancer risk, yet its mechanistic foundation remains incomplete. Several fundamental uncertainties limit the strength of the conclusions and constrain their translational relevance. First, the study does not determine whether anti-progestin therapy reverses risk-linked states through direct PR inhibition or through global hormonal disruption. Without serum hormone profiling, receptor occupancy measurements, or PR isoform-specific perturbations, the molecular pathways driving observed changes cannot be reliably assigned. Second, the absence of chromatin-level analyses leaves critical gaps in understanding whether anti-progestins induce durable epigenetic reconfiguration or merely transient transcriptional suppression. Long-term risk modification requires stability; short-lived molecular fluctuations are insufficient.

Third, the study does not test whether modulated cell populations exhibit altered susceptibility to oncogenic transformation. Functional assays—such as lineage tracing, organoid-based transformation models, or carcinogenesis studies using

chemical or genetic drivers—would be essential to validate whether reduced progenitor abundance or altered microenvironmental states genuinely influence tumor initiation. Fourth, the interplay between anti-progestin treatment and other hormonal axes remains unexamined. Estrogen, glucocorticoids, and prolactin all interface with PR-driven programs; modulation of one axis inevitably impacts others. Without dissection of these interactions, the preventive significance of anti-progestin therapy cannot be firmly established.

11.2. Requirements for Longitudinal, Multi-Omic, and Population-Level Validation

Translating anti-progestin therapy into a credible preventive strategy requires addressing methodological, biological, and translational gaps through more comprehensive experimental frameworks. A key requirement is longitudinal analysis. The tissue states described by Simoes *et al.*⁷ are captured at a single post-treatment timepoint. Time-course studies are necessary to determine whether effects persist, adapt, or rebound. Such temporal analyses should include serial single-cell multi-omic profiling, hormone-level monitoring, and functional assays over multiple physiological cycles. Understanding the stability of induced cell states is central to assessing preventive potential.

Another critical direction involves assessing treatment effects across diverse physiological contexts. Reproductive history, age, parity, and genetic predisposition shape mammary epithelial biology and influence responsiveness to hormonal interventions. Future studies should incorporate models that simulate perimenopausal transition, postpartum involution, hereditary risk backgrounds, and high-estrogen states. *Ex vivo* human tissues must be expanded to larger cohorts with detailed donor metadata to contextualize inter-individual heterogeneity. Additionally, alternative anti-progestins with varying receptor selectivity should be tested to distinguish PR-specific effects from compound-specific artifacts.

Beyond preclinical systems, translational readiness requires identification of biomarkers that can monitor tissue responses without invasive sampling. Circulating markers, imaging signatures, or hormonal-response indices must be developed to assess treatment impact in real time. A credible preventive strategy must be measurable, reversible, and safe over prolonged durations. To this end, detailed toxicology, endocrine stability studies, and integrated modeling of systemic hormonal dynamics are needed.

Finally, population-level relevance cannot be determined without carcinogenesis trials. Even robust mechanistic data cannot substitute for evidence that anti-progestin therapy reduces tumor incidence under realistic exposure patterns. Carcinogen-induced mouse models, genetically engineered mouse models, and

eventually human observational or interventional trials are required to validate whether risk-hallmark suppression translates into decreased cancer formation.

In sum, while Simoes *et al.* stimulate an important conversation about the role of progesterone signaling in shaping the mammary tissue landscape, significant unresolved questions must be addressed before anti-progestin therapy can be plausibly advanced as a preventive intervention. The study provides a foundation, not a conclusion, highlighting the need for mechanistic precision, longitudinal depth, and translational rigor in future research.

12. Conclusion

12.1. Reassessing the Strength of Evidence Presented by Simoes *et al.*

Simoes *et al.*⁷ propose a compelling and ambitious framework in which anti-progestin therapy targets multiple biological features purported to underlie breast cancer risk. Their integration of single-cell transcriptomics, histological analyses, and microenvironmental profiling offers a comprehensive portrait of acute tissue responses to PR antagonism. Yet the strength of the evidence lies primarily in descriptive breadth rather than mechanistic depth. The study convincingly demonstrates that anti-progestin therapy alters transcriptional states, redistributes epithelial populations, and modulates stromal and immune signatures. What remains unproven is whether these changes causally influence the multidecade trajectory of breast carcinogenesis.

The central claim—that anti-progestins reverse “*hallmarks of breast cancer risk*”—rests on the assumption that the observed molecular and cellular features are mechanistically indispensable components of early tumor initiation. However, the study does not establish that these features represent bona fide causal drivers rather than correlates or epiphenomena of hormonal dynamics. Acute suppression of proliferative or progenitor-associated signatures does not inherently equate to durable risk reduction, particularly when the intervention’s physiological context is poorly understood, and compensatory endocrine responses are not measured. Although the dataset contributes meaningfully to the growing interest in progesterone biology, its interpretive reach exceeds its methodological footing.

12.2. Defining A Realistic Path for Anti-Progestin-Based Prevention

If anti-progestin therapy is to be credibly considered within the breast cancer prevention landscape, several prerequisites must be met. Mechanistic specificity is essential: effects must be shown to arise from PR antagonism rather than global endocrine perturbation. Longevity of tissue changes must be demonstrated through

extended time-course studies that establish stability rather than transient hormonal suppression. Evidence from functional transformation assays must clarify whether altered epithelial states truly constrain malignant evolution. Human relevance must be expanded beyond limited *ex vivo* samples to encompass diverse physiological conditions, genetic backgrounds, and reproductive histories. Only through such systematic investigation can the field distinguish between descriptive modulation of tissue states and mechanisms with genuine preventive value.

Moreover, translational feasibility depends on safety, tolerability, and integration with existing risk stratification frameworks. Anti-progestin therapy carries inherent endocrine complexity that contrasts with the more selectively targeted approaches used in estrogen-modulating prevention. Without comprehensive toxicology studies, hormone-level assessments, and evaluation of long-term systemic effects, preventive implementation remains untenable. As risk reduction increasingly shifts toward precision-based, minimally disruptive interventions, mechanistic clarity and safety become paramount.

Despite these limitations, the study by Simoes *et al.*⁷ provides a valuable springboard for future research. It highlights underexplored dimensions of progesterone signaling, reveals how acute PR blockade perturbs epithelial and stromal ecosystems, and encourages a reevaluation of how risk-associated tissue states are conceptualized. The findings should therefore be viewed not as evidence that anti-progestins reduce breast cancer risk, but as an invitation to investigate the complex and still poorly defined relationship between progesterone biology and early carcinogenic potential.

Conflict of Interest Statement

The authors declare that they have no commercial, financial, or personal relationships that could be construed as influencing the content, analysis, or conclusions presented in this commentary. Mengxi Zhu, Chenxi Hu, Ruihuang Wang, and Shu-Feng Zhou affirm that they have no affiliations with or involvement in any organization or entity with a direct or indirect interest—financial or otherwise—in the subject matter discussed herein, including pharmaceutical companies developing progesterone receptor modulators or related endocrine therapies. No author has received funding, honoraria, consultancy fees, or research support that could reasonably be perceived as constituting a conflict of interest in relation to this work. The commentary was written independently and reflects solely the authors' critical interpretation of the study by Simoes *et al.* All authors participated fully in the intellectual development of the manuscript and attest that no external party influenced the framing, critique, or conclusions of this analysis.

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