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PERSPECTIVE

TARGETING PROGESTERONE SIGNALING FOR BREAST CANCER PREVENTION

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ABSTRACT: Effective strategies for primary prevention of breast cancer in premenopausal women remain limited, largely due to the modest tolerability and uptake of existing endocrine interventions. In our recent study, we demonstrate that short-term antagonism of progesterone receptor (PR) signaling targets multiple biological determinants of breast cancer risk, including epithelial progenitor activity, extracellular matrix remodeling and tissue mechanics. In this Perspective, we reflect on the conceptual and translational implications of these findings. We discuss how progesterone-driven endocrine-mechanical feedback loops shape increased risk tissue states and how their pharmacological disruption enables coordinated attenuation of epithelial and stromal susceptibility. We further consider the integration of multi-omics profiling and imaging biomarkers as a framework for prevention trials. PR antagonism may represent a promising foundation for biomarker-guided risk-reduction approaches in younger women and highlight broader opportunities for targeting tissue architecture in cancer prevention.

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Impact statement: Progesterone receptor antagonism targets drivers of breast cancer risk across epithelial and stromal tissue compartments, establishing a new approach to prevention in younger women.

Key words: *Breast cancer prevention; progesterone receptor antagonists; mammographic density; extracellular matrix remodeling.*

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INTRODUCTION

Breast cancer remains the leading cause of cancer-related mortality among women worldwide and continues to represent a major public health challenge, particularly for younger individuals at increased genetic or familial risk (1). Although substantial advances have been made in early detection and treatment, effective strategies for primary prevention in premenopausal women remain limited. Most established preventive interventions have focused on modulation of estrogen signaling, approaches that are often associated with poor tolerability, long treatment durations and limited uptake (2). In this context, our recent work proposes an alternative framework for breast cancer prevention based on targeted inhibition of progesterone receptor (PR) signaling (3).

PROGESTERONE AND BREAST CANCER RISK

Progesterone has long been recognized as a central regulator of mammary gland development, coordinating cyclical epithelial expansion and differentiation across the menstrual cycle. Experimental studies in both murine and human systems have demonstrated that progesterone drives proliferation of stem and progenitor cell populations, resulting in increased ductal branching and tissue complexity.

These effects are mediated predominantly through paracrine signaling from PR-positive luminal mature cells to PR-negative luminal progenitors, a population increasingly implicated as a likely cell of origin for aggressive breast cancer subtypes. Epidemiological data further support this biological model, linking exposure to exogenous progestins, through hormonal contraception or hormone replacement therapy, to increased breast cancer incidence. The relative contribution of each progesterone receptor isoform (PR-A and PR-B) to these effects remains incompletely understood. In addition, crosstalk with other steroid hormone receptors, including estrogen, androgen and glucocorticoid receptors, may further influence epithelial and stromal responses to progesterone signaling.

THE BC-APPS1 CLINICAL STUDY

Guided by the progesterone mechanistic insights, we designed the Breast Cancer-Anti-Progestin Prevention Study 1 (BC-APPS1) to interrogate the impact of PR antagonism on normal breast tissue biology *in vivo*. By integrating paired tissue sampling with multi-omics profiling, functional assays and advanced imaging, our study moves beyond conventional pharmacological trials and establishes a comprehensive experimental paradigm for early-phase cancer prevention research. This approach demonstrates how molecular and cellular profiling can be embedded within clinical studies to generate mechanistic understanding alongside translational relevance. As with many early window-of-opportunity studies, the trial involved a limited number of participants and relatively short exposure to treatment. Consequently, the biological effects observed should be interpreted as early mechanistic signals rather than evidence of long-term clinical benefit, and the generalizability of these findings across populations with diverse ethnic and genetic backgrounds remains to be determined. Short-term window studies in other tissues could similarly deconvolute causal pathways before large-scale clinical trials are undertaken.

EFFECTS OF PR ANTAGONISM ON BREAST TISSUE

A central contribution of the study is the demonstration that short-term treatment with the PR antagonist ulipristal acetate, selected because of its well-characterized pharmacological profile and its prior clinical use, induces consistent suppression of epithelial proliferation and luminal progenitor activity. Selective targeting of luminal progenitors in the premenopausal breast is of particular relevance given their susceptibility to oncogenic transformation and accumulation of genomic instability.

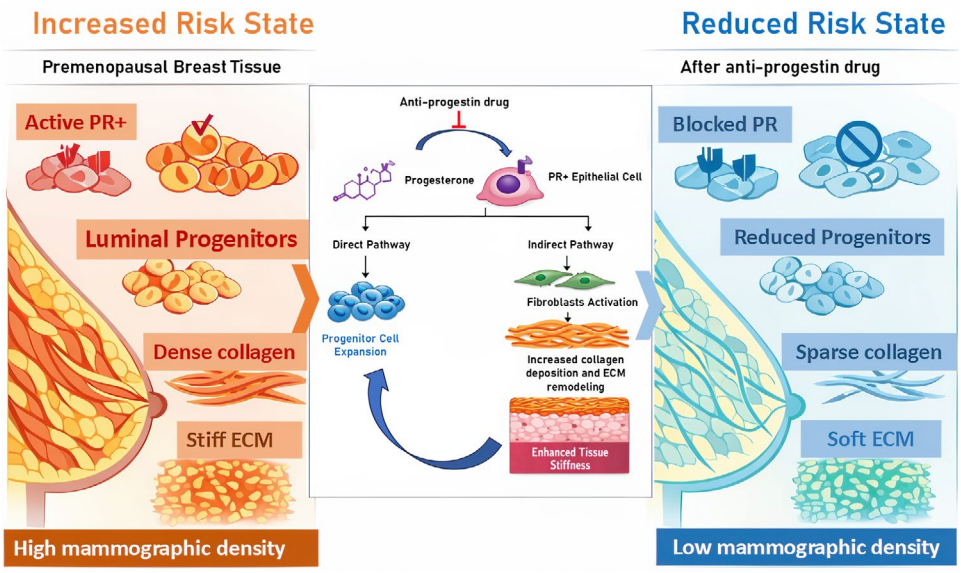

Figure 1. *Progesterone receptor antagonism disrupts endocrine–mechanical feedback in the premenopausal breast, leading to reduced luminal progenitor cell activity, decreased collagen organization and lower tissue stiffness. The schematic breast panels illustrate the tissue-level effects associated with anti-progestin therapy, including reductions in mammographic density, extracellular matrix remodeling and collagen deposition, consistent with a less stiff and mechanically active tissue microenvironment.*

Beyond its effects on epithelial compartments, the study reveals a profound influence of PR antagonism on the stromal microenvironment, thereby broadening the functional scope of PR biology (**Figure 1**). Integrated transcriptomic and proteomic analyses identify coordinated downregulation of extracellular matrix (ECM) components, most notably collagens I, IV and VI. These molecular changes are accompanied by reduced collagen fiber alignment and decreased tissue stiffness, as demonstrated by histological analysis and biomechanical measurements. Together, these findings establish progesterone signaling as a regulator not only of cellular behavior but also of tissue architecture and mechanical properties. This raises the possibility that PR activity functions upstream of mechano-transduction pathways, positioning endocrine signaling as a modulator of physical forces that shape oncogenic susceptibility. However, further mechanistic studies will be required to dissect how endocrine signaling interfaces with mechanotransduction pathways.

Of note, collagen VI emerged as an important element of the luminal progenitor niche. Imaging mass cytometry revealed a spatial association between collagen VI-rich regions and SOX9-positive luminal progenitor cells, providing evidence that biochemical and biomechanical cues converge within defined microenvironments to sustain high-risk cellular states. Complementary *in vitro* experiments further demonstrated that stiffness-induced progenitor activation can be antagonized by anti-progestins, reinforcing the proposed mechanistic model. Future work should determine whether collagen VI deposition precedes progenitor expansion or is instead a downstream consequence of progenitor activation. Collectively, these findings support a conceptual shift in how breast cancer risk is understood. Rather than being driven solely by cumulative genetic damage or isolated proliferative signals, risk emerges as a property of dynamic tissue ecosystems shaped by hormonal, stromal and mechanical interactions. Progesterone signaling appears to operate within a positive feedback loop, in which hormone-responsive epithelial cells stimulate fibroblast-mediated matrix deposition, increasing tissue stiffness and amplifying progenitor responsiveness. PR antagonism disrupts this circuit, leading to coordinated attenuation of both epithelial and stromal risk determinants. This system-level perspective warrants quantitative modelling of endocrine-mechanical feedback loops to define thresholds beyond which tissue states become self-sustaining or, conversely, reversible.

IMAGING CORRELATES AND RISK BIOMARKERS

The integration of molecular, histological and imaging data further enhances the translational relevance of the study. The observed reduction in fibroglandular volume on magnetic resonance imaging provides a clinically accessible correlation of underlying biological remodeling. Mammographic density is among the strongest established risk factors for breast cancer, yet remains largely untargeted in preventive strategies. By demonstrating that PR antagonism can modulate this parameter, the study establishes a direct link between molecular intervention and population-level risk markers. However, these findings are based on surrogate tissue and imaging markers and therefore do not directly demonstrate a reduction in breast cancer incidence. A key next step will be to assess whether density reduction persists after treatment cessation and whether imaging could serve as a surrogate endpoint in prevention trials.

Particularly noteworthy is the stronger effect of anti-progestin therapy on breast tissue in women with high mammographic density, suggesting that baseline density may serve as a predictive biomarker of response to anti-progestin therapy, although this requires validation in larger studies. Such stratification could enable more precise prevention strategies, targeting intervention to individuals most likely to derive meaningful risk reduction. As density reporting becomes increasingly routine, imaging could guide individualized risk-reduction strategies, potentially reducing overtreatment while ensuring that high-risk individuals receive targeted intervention. This approach aligns with broader trends in precision medicine and underscores the importance of integrating biological and imaging-based profiling into preventive frameworks.

FUTURE DIRECTIONS FOR PR ANTAGONISTS

If validated in larger and longer-term studies, PR antagonism could represent a new class of pharmacological prevention for premenopausal women at elevated risk. Nevertheless, such strategies would likely require repeated or prolonged treatment, making careful evaluation of safety in hormone-sensitive tissues essential. The societal implications of this possibility are substantial. Preventive options for younger women are currently limited, with surgical risk reduction and

Table 1. *Future directions for progesterone receptor antagonism in breast cancer prevention.*

DOMAIN	KEY QUESTIONS	FUTURE RESEARCH DIRECTIONS
Long-term efficacy	Are short-term biological changes durable?	Longitudinal prevention trials with extended follow-up
Safety	What are the systemic effects of prolonged PR antagonism?	Evaluation of endocrine, metabolic and reproductive safety
Mechanisms	How do endocrine-mechanical feedback loops operate at the molecular level?	Integrated spatial multi-omics and mechanobiology studies
Downstream progesterone targets	Which PR-regulated pathways could be therapeutically targeted beyond PR antagonism?	Investigation of downstream effectors such as RANKL (denosumab), CXCL13, Wnt4, and extracellular matrix regulators including collagens
Biomarkers	Can imaging markers predict response?	Validation of mammographic density and fibroglandular volume as predictive biomarkers
Population diversity	Do responses vary across genetic or ethnic backgrounds?	Inclusion of diverse cohorts and stratified analyses
Prevention strategies	How should PR antagonists be administered?	Intermittent or cyclic dosing regimens aligned with hormonal cycles

long-term endocrine therapies posing significant physical and psychological burdens. The repositioning of PR antagonists for cancer prevention therefore warrants ethical and regulatory consideration, particularly with respect to long-term safety, fertility, acceptability and equitable access (**Table 1**). In this context, intermittent or cyclic dosing strategies aligned with endogenous hormonal rhythms merit exploration as potentially more physiological prevention regimens.

DISCUSSION AND CONCLUSIONS

There are several additional considerations that merit discussion. One concerns the concept of mechanical memory. ECM organization and tissue stiffness can persist long after hormonal cues change, influencing cellular behavior over extended timescales. This raises the possibility that short-term PR antagonism may induce durable protective states by reprogramming the mechanical niche. Future studies should explore whether such interventions confer long-lasting resistance to oncogenic transformation. Experimental models incorporating washout periods could directly test the durability of these mechanically imprinted states. A second implication lies in the identification of endocrine-mechanical feedback loops as drivers of cancer risk. Interrupting these self-reinforcing circuits pharmacologically represents a novel preventive paradigm, targeting not only molecular drivers but also the tissue architecture that sustain them. This concept may have relevance beyond breast cancer, particularly in fibrosis-associated malignancies or tissues where hormonal signaling and mechanical stress intersect. Finally, the potential psychosocial impact of biological risk reduction warrants consideration. Demonstrable reductions in mammographic density and tissue-based risk markers may alleviate cancer-related anxiety in high-risk individuals. Integrating biological prevention with measures of psychological well-being could represent an important dimension of future prevention trials. Such longitudinal cohorts, combining patient-reported outcomes with molecular endpoints, may also enable the development of predictive models of individual risk trajectories, thereby supporting adaptive use of PR antagonists in response to evolving tissue states rather than fixed schedules. Future prevention studies could integrate patient-reported outcomes alongside molecular and imaging markers to better understand how biological risk modulation influences patient perception and decision-making. Moreover, if PR antagonists were to be implemented as preventive interventions, issues of cost, access and regulatory approval would also need to be addressed to ensure equitable availability across different healthcare systems, including low- and middle-income countries.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of interest

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Authors' contributions

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Publications ethics

Plagiarism

The article provides a perspective of a study, with accurate citations.

Data falsification and fabrication

The writing and contents of the article are entirely developed by the authors. The authors used an artificial intelligence tool to assist in the creation of **Figure 1**.

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