2026 Volume: 02 Issue: 04 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

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UTERINE FIBROIDS

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Article Received: 24 February 2026
Article Revised: 14 March 2026
Published on: 03 April 2026

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DOI: https://doi-doi.org/101555/ijrpa.3643

ABSTRACT

Uterine fibroids (leiomyomas) are the most common benign neoplasms in women, representing a monumental clinical and public health challenge. As a medical student, I am confronted with a stark paradox: these tumors are ubiquitous, affecting up to 70-80% of women, yet our understanding of their precise etiology and our ability to offer long-term, non-invasive, fertility-preserving treatments remain frustratingly limited. This article aims to dissect the intricate tapestry of fibroid pathogenesis, moving beyond a simple hormonal narrative to explore the cutting-edge science that defines them. We will examine the compelling evidence that positions these tumors as disorders of myometrial stem cells, reprogrammed by developmental insults and driven by mutually exclusive genomic drivers, most notably MED12 mutations. We will map the complex signaling networks—from the classic estrogen and progesterone pathways to the critical roles of the extracellular matrix, mechanotransduction, and defective DNA repair—that orchestrate tumor growth and symptomology. Finally, we will analyze the current therapeutic landscape, from surgical standards to emerging molecularly targeted therapies, emphasizing the urgent need for personalized medicine approaches that address the specific molecular subtype of a patient's disease.

1. INTRODUCTION: The Weight of a Common Tumor

The first time I saw a uterus studded with fibroids in the pathology lab, I was struck by its sheer size and distorted architecture. The benign growths had transformed a small, pear-shaped organ into a large, irregular mass. This visual was a powerful reminder that "benign" is not synonymous with "benign in its impact." Uterine fibroids are the primary indication for hysterectomy worldwide, a major cause of reproductive dysfunction including infertility and recurrent pregnancy loss, and a source of chronic morbidity from menorrhagia, anemia, and

pelvic pain. The annual economic burden in the United States alone is estimated at $34 billion, accounting for hospitalizations, surgeries, and lost work productivity (1). This burden is not distributed equally; it disproportionately affects Black women, who experience a three-fold higher incidence, earlier onset, and more severe symptoms (2). This disparity is a call to action, demanding that we look beyond simple biology and consider the complex interplay of genetics, environment, and social determinants of health.

The goal of this review is to synthesize the current state of knowledge, highlighting the paradigm shifts that are reshaping our understanding of fibroids. We have moved from viewing them as simple, hormone-driven growths to recognizing them as complex, genetically heterogeneous neoplasms with a developmental origin. This new understanding is the foundation upon which future, more effective therapies will be built.

2. Epidemiology and Risk Factors: A Multifactorial Puzzle

Understanding who develops fibroids and why is the first step in prevention. The epidemiological landscape is complex, with a web of risk and protective factors.

2.1. The Central Role of Race and Ethnicity

The most significant and consistently replicated risk factor is race. Black women have a cumulative incidence of 80-90% by age 50, compared to 40-70% in White women (2). The reasons are multifactorial:

- Genetic Susceptibility: Genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) that confer increased risk, some of which are more prevalent in women of African descent (3).
- Hormonal Milieu: Some studies suggest Black women may have higher circulating levels of estradiol and lower levels of sex hormone-binding globulin (SHBG), leading to greater estrogen bioavailability (4).
- Vitamin D Deficiency: The risk is compounded by a high prevalence of vitamin D deficiency in Black women due to skin pigmentation reducing vitamin D synthesis. Vitamin D is a potent anti-proliferative and pro-apoptotic agent in fibroid cells (5).
- Psychosocial Stress: The Black Women's Health Study has shown a positive association between self-reported experiences of racial discrimination and the incidence of fibroids (6). The proposed mechanism involves chronic stress-induced dysregulation of the

hypothalamic-pituitary-adrenal (HPA) axis, leading to altered cortisol and catecholamine levels, which in turn can influence ovarian steroidogenesis and promote inflammation (7).

2.2. Reproductive and Hormonal Factors

- Age: Fibroids are rare before menarche, increase in prevalence throughout the reproductive years, peak in the perimenopause, and typically regress after menopause. This pattern underscores their hormone dependency.
- Parity: A robust inverse relationship exists. Each full-term pregnancy reduces risk by 10-20% (8). The protective effect is hypothesized to result from the prolonged anovulation, progesterone-driven differentiation of stem cells, and dramatic uterine remodeling that occurs postpartum.
- Oral Contraceptives: The relationship is nuanced. Some studies show a reduced risk with current use, while early use (at a young age) has been associated with a slightly increased risk in some cohorts (9).

2.3. Metabolic and Lifestyle Factors

- Obesity: A one-unit increase in BMI is associated with a 2-6% increase in fibroid risk (10). Adipose tissue is a major site of aromatase activity, converting androstenedione to estrone. Furthermore, obesity is associated with chronic low-grade inflammation and insulin resistance, both of which can promote fibroid growth.
- Diet: A diet rich in red meat and ham is associated with increased risk, while high intake of green vegetables, fruits, and fish is protective (11). Citrus fruits, in particular, have been linked to reduced risk, possibly due to their flavonoid content.
- Alcohol Consumption: Alcohol, especially beer, is a consistent risk factor, possibly by increasing circulating sex hormone levels and causing direct DNA damage via its metabolite, acetaldehyde (12).

2.4. Environmental Exposures: The Developmental Origins of Disease

This is a critical and evolving area. Endocrine-disrupting chemicals (EDCs) like phthalates, bisphenol A (BPA), and the legacy pollutant diethylstilbestrol (DES) are of particular concern.

- Developmental Reprogramming: The Eker rat model (which carries a Tsc-2 mutation) has been instrumental in showing that neonatal exposure to DES can increase the penetrance of fibroid development from 60% to 100% (13). This exposure occurs during a critical window of myometrial development and targets myometrial stem cells (MMSCs), altering their epigenetic landscape and making them more susceptible to transformation later in life.
- Epigenetic Mechanisms: These early-life exposures induce lasting changes, including DNA methylation alterations and histone modifications (e.g., decreased H3K27me3 via EZH2 dysregulation) in MMSCs, effectively "priming" them for future tumorigenesis upon exposure to reproductive hormones (14).

3. The Cellular and Molecular Basis of Fibroids

3.1. The Stem Cell Model of Origin

The current paradigm posits that fibroids are clonal tumors arising from a single transformed myometrial stem cell. MMSCs have been isolated from human myometrium and characterized by markers such as CD34, CD49b, and CD44 (15). Critically, MED12 mutations have been identified specifically in the stem cell fraction of fibroids but not in adjacent normal myometrium, confirming that the driver mutation occurs at the level of the stem/progenitor cell (16). These tumor-initiating cells (TICs) then give rise to the heterogeneous cell populations within a fibroid, including smooth muscle cells and a large population of collagen-producing tumor-associated fibroblasts (TAFs) (17).

3.2. Driver Mutations: The Genomic Landscape

The application of next-generation sequencing has revealed that fibroids can be genetically stratified into at least four major, mutually exclusive subtypes based on their primary driver mutation. This has revolutionized our understanding, proving that fibroids are not a single disease but a family of diseases with a common clinical phenotype.

Driver Mutation Prevalence Key Molecular Consequence Clinical Associations

MED12 45-90% Disruption of CDK8/19 kinase activity, leading to aberrant Mediator complex function and altered transcription of key growth and differentiation genes (18). Smaller tumors, multiple tumors, subserosal location. Positive correlation with increased tumor-associated fibroblasts (TAFs) (17).

HMGA2 8-10% Overexpression due to chromosomal rearrangements (e.g., t(12;14)). Alters chromatin structure and activates PLAG1, a proto-oncogene (19). Larger, solitary tumors often with a distinct gene expression profile.

FH ~1.6% Loss of fumarate hydratase leads to fumarate accumulation. This inhibits prolyl hydroxylases, stabilizing HIF1α and driving a pseudo-hypoxic state. Alters cellular metabolism (20). Often part of Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome when germline.

COL4A5/COL4A6 ~2% Deletions at 22q13.1 leading to fusion transcripts. The mechanism is less clear but leads to overexpression of nearby genes like IRS4 (insulin receptor substrate 4) (21). Rare subtype; clinical significance still being elucidated.

3.3. Key Signaling Pathways and the Tumor Microenvironment

Once the driver mutation is established, a complex network of signaling pathways promotes tumor growth.

3.3.1. The Steroid Hormone Axis: A Revised View

While estrogen was long considered the primary driver, the focus has shifted to progesterone.

- Estrogen's Role: Estrogen upregulates the expression of progesterone receptors (PRs) in fibroid cells, priming them for progesterone action. It also promotes the proliferation of the TAF population within the tumor (17).
- Progesterone's Role: Progesterone is now understood as the key mitogenic factor. Binding to its receptor (PR-A and PR-B) drives the expression of growth factors like EGF, TGF-β, and anti-apoptotic factors. This explains why Selective Progesterone Receptor Modulators (SPRMs) are so effective in reducing fibroid size and bleeding (22).

3.3.2. The Extracellular Matrix (ECM) and Mechanotransduction

A hallmark of fibroids is the excessive accumulation of a disorganized, stiff ECM, rich in collagen types I and III, fibronectin, and proteoglycans (23).

- Consequences of Stiffness: This increased stiffness is not just a structural feature; it is a driver of disease. Cells sense this physical force through integrins and focal adhesions, activating the mechanotransduction pathways YAP/TAZ and β-catenin (24). These

pathways then promote further cell proliferation, survival, and ECM production, creating a self-perpetuating fibrotic loop.

- The ECM as a Reservoir: The ECM acts as a reservoir for growth factors like TGF-β and activin-A, releasing them and prolonging their signaling. Targeting the ECM directly, for instance with collagenase injections, is a novel therapeutic strategy aimed at breaking this vicious cycle (25).

3.3.3. DNA Damage and Repair

Emerging evidence points to a role for genomic instability in fibroid pathogenesis. Fibroids exhibit lower expression of key DNA repair genes like BRCA1, RAD51, and ATM compared to adjacent normal myometrium (26). This reduced repair capacity may make myometrial cells more susceptible to the accumulation of driver mutations, especially in the face of cyclical DNA damage induced by menstruation and the oxidative stress associated with fluctuating hormone levels.

4. Current Treatment Paradigms and Their Limitations

The treatment of fibroids is guided by the patient's symptoms, fibroid characteristics, and reproductive goals. The options range from watchful waiting to major surgery.

- Medical Management:
- GnRH Agonists: (e.g., leuprolide) induce a hypoestrogenic state, shrinking fibroids by 30-50%. However, they are limited by significant menopausal side effects and a "rebound growth" upon cessation, restricting use to short-term (e.g., pre-surgical).
- Selective Progesterone Receptor Modulators (SPRMs): (e.g., ulipristal acetate) represent a major advance. By blocking the proliferative effects of progesterone while maintaining some estrogenic action, they effectively control bleeding and induce fibroid shrinkage with a better side-effect profile than GnRH agonists (27). However, concerns about rare but serious liver injury have led to restrictions on their use in some regions.
- Tranexamic Acid & NSAIDs: These are used to manage heavy menstrual bleeding but do not affect fibroid size.
- Interventional and Surgical Procedures:
- Uterine Artery Embolization (UAE): A minimally invasive procedure that blocks the blood supply to fibroids, causing ischemic necrosis and shrinkage. Effective for bulk-

related symptoms, but generally not recommended for patients desiring future fertility due to potential effects on ovarian reserve and endometrial function.

- Myomectomy: The gold-standard surgical treatment for patients who wish to preserve fertility. It involves the surgical removal of fibroids, leaving the uterus intact. However, fibroids recur in a significant proportion of patients (up to 50%).
- Hysterectomy: The only definitive cure. It is the most common surgical treatment but eliminates fertility and has long-term implications even when the ovaries are preserved.

5. Emerging Therapies and the Future of Precision Medicine

The detailed molecular understanding of fibroids is paving the way for targeted therapies.

- Targeting the Mediator Kinase Module: Since MED12 mutations disrupt CDK8/19 kinase activity, these kinases are a potential therapeutic target. Preclinical studies with small-molecule CDK8/19 inhibitors are showing promise in suppressing the growth of fibroid cells (28). This would be the first targeted therapy for the majority of fibroid patients.
- Modulating the ECM: As discussed, the ECM is a key driver of pathology. Phase I clinical trials have shown that direct injection of a collagenase enzyme (from Clostridium histolyticum) into fibroids is safe and reduces tissue stiffness, offering a novel approach to shrinking tumors by degrading the pathological matrix (25).
- Vitamin D Therapy: Given the strong association between vitamin D deficiency and fibroids, vitamin D supplementation is being investigated as a low-risk, non-invasive chemopreventive and therapeutic option. Laboratory studies show vitamin D can reduce fibroid cell proliferation, promote apoptosis, and reduce ECM production (5).
- Epigenetic Therapies: As developmental EDC exposure reprograms the epigenome of MMSCs, drugs that reverse these epigenetic marks (e.g., HDAC inhibitors, EZH2 inhibitors) are being explored as a potential way to prevent fibroid initiation or progression (14).

6. CONCLUSION: A CALL FOR A NEW APPROACH

As a medical student, studying uterine fibroids is a lesson in complexity. It is a disease where a common driver mutation like MED12 sits at the center of a web that includes a patient's race, their grandmother's environmental exposures, their own hormonal milieu, and the physical stiffness of their own tissue.

The future of fibroid care lies in moving away from a one-size-fits-all approach. We are entering an era of precision gynecology, where a patient's treatment will be guided by the molecular fingerprint of her fibroids. Is it MED12-mutant? Is it driven by the ECM? Is it an FH-deficient subtype? Answering these questions will allow us to choose the right drug, the right procedure, or the right preventative strategy for the right patient.

This shift is not just an academic exercise; it is a moral and clinical imperative for the millions of women who have long been told to "live with" a disease that we are now finally beginning to truly understand.

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