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Review Article

# Epidemiology and Genetic Molecular Mechanisms involved in Fibroids

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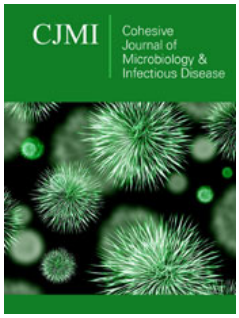


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## Introduction

Uterine fibroids are benign mesenchymal proliferations. They vary widely in the uterus and develop at the expense of smooth muscle and are often separated from the myometrium by a pseudocapsule associated with connective tissue condensation Audebert [1]. Often asymptomatic, they are associated with significant morbidity and constitute a real public health problem. The cost of management is excessively expensive, and the only treatment considered effective is surgery. Fibroids are, in fact, the most common indication of gynecological surgery in the United States and represent 600,000 hysterectomies and 60,000 myomectomies a year [2,3]. Total costs (including lost productivity and morbidities) associated with surgical and nonsurgical treatment are estimated to be between $6 billion and $35 billion annually [4]. Despite the large-scale medical and financial burden posed by uterine fibroids, the functional roles of the various factors and genes involved in their etiology and growth remain unclear. This shows a great need to undertake a study that would evaluate the epidemiological, clinical, and molecular features of uterine fibroids.

## Uterine Fibroids: Epidemiology and Risk Factors

### Epidemiology

#### Age

The presence of fibroids is definitely very important from 40 years. Studies by Buttram et al. [5] have shown that uterine fibroids affect 20 to 25% of women in reproductive activity and nearly 40% of women over 40 years of age. According to Okolo [6], fibroids affect millions of women worldwide and in 60% of cases occur in women aged 45 years.

#### Age at Menarche

Women with an early age of menarche have a higher risk of developing myomas [6,7]. Several studies have demonstrated an association between early onset of first menses and a risk of developing uterine fibroids [7,8]. Women who have had their mumps early have a higher risk of having multiple uterine fibroids (RR=2.31, CI=1.50-3.59). It is expected that late menopause increases the risk of myoma onset due to prolonged exposure to gonadal steroids. However, the epidemiological data on this subject are still insufficient [9].

#### Race

There are several significant differences in the pathobiology of fibroids between different ethnic groups. African American women develop the disease at a higher frequency and with symptoms associated with more severe uterine fibroids. Hispanic women have an intermediate disease profile and Caucasian women are the least severely affected ethnic group [10-13]. Marsh et al. [14] conducting a prospective pilot study of young black and caucasian women (18-30 years old) with uterine fibroids demonstrated a 3-fold higher prevalence in black women compared to caucasian women (26% vs. 7%). Studies by Baird et al. [11], looking at the single or multiple aspect of uterine fibroids, found that 73% of African American women

had multiple fibroids, while only 45% of Caucasian women had this phenotype.

**Family history**

In a study conducted by Vikhlyaeva et al. [15], with a level of evidence 2, a familial predisposition was reported in uterine fibroids. They show that fibroids are 2.2 times more common when, in the first-degree family, there are women with fibroids (97 families, 97 patients and 118 family members). The risk is 1.94 for sisters and 2.12 for girls.

**Socio-economic factors, education and stress**

Lumbiganon et al. [16] on their population found a positive association between professional life and fibroids, education and fibroids (respectively RR 1.6 (1.21-2.27) and RR 3.46 (2.22-5.41) for patients who have more than 7 years of study.

## Risk Factors

### Weight

In all studies, a positively significant association was found between obesity and fibroid growth. Marshall et al. [17] publishes a moderate RR. This risk is positively associated with weight gain since age 18 and is not related to Body Mass Index (BMI) at age 18. Lumbiganon [16] found a RR of 1.46 (1.19-1.78) for a BMI between 25-29. Sato et al. [18] draw attention to the distribution of fats and uterine fibroids. They classified 100 sick patients and 200 controls in BMI < or ≥ 24.0 and fat percentage < or ≥ 30%. There were no fibroids in muscular patients (BMI <24.0 and percent fat <30%).

## Reproductive Factors

The inverse association between myoma and parity is known Wise [19]. Wise's [19] study of African American women has shown that the time elapsed since the most recent birth is positively related to the risk of myomas in parous women. This observation may be explained by non-hormonal causes, such as postpartum tissue changes during the uterine involution process [19]. The cause is an increase in exposure to menstrual cycles during the life of a nulliparous woman, without interruption of pregnancy and lactation.

### Diet

Recently, Wise [19] published the results on the relationship between dietary fat intake and myoma risk in African-American women, confirming an increased risk associated with the consumption of omega-3 fatty acids long chain, especially marine fatty acids. Dark-fleshed fish was the main source of marine fatty acids in this study. They validated that a diet rich in fruits and vegetables reduced the risk of myoma, especially that rich in fruits.

### Oral contraceptive

The relationship between oral contraceptives and myomas has been largely elucidated. Published studies show a reduction or absence of risk between the use of oral contraceptive combined with the appearance of myomas Berisavac [20]. One study has shown that oral contraception may play a role in the development of uterine fibroids. Others have found no association between the occurrence of fibroids and the use of contraception Parazzini [21].

### Vitamin D

Vitamin D is important for protection against several aspects of malignant tumor formation, including regulation of cell cycle proteins, angiogenesis, and inflammation Mocellin [22]. Hypovitamin D is suggested as a potential risk in myoma formation.

## Genetic and Molecular Mechanisms involved in Fibroids

### Genetic Findings

The occurrence of uterine fibroids can be attributed to several causes including hormonal disorder, early menopause, and physiological and genetic factors.

### Med12

Mutations of the MED12 gene have been demonstrated for the first time by Mäkinen et al. [23] in cases of uterine fibroids. These studies showed a mutation frequency of this gene of 70% with 64.4% of the mutations found in exon 2. Studies conducted by Perot et al. [24] showing a mutation frequency of 66.6%, the work of Bertsch et al. [25] indicating a frequency of mutations of 74.7%, those of Halder et al. [26] with a mutation frequency of 64.3% and those of Kénémé et al. [27] with a frequency of 88.89%.

### High mobility groups

High Mobility Groups (HMG) are non-histone proteins associated with chromatin. They are also DNA binding proteins that can induce conformational changes, thus indirectly regulating transcription by influencing access to other proteins [27,28]. In a study by Dal Cin et al. [28] of women undergoing hysterectomy, 48.5% of the fibroids analyzed were found to have strong expression of HMGI-Y and HMGI-C, which are important elements in the regulation of the function and structure of chromatin [28].

### CYP17A

CYP17α polymorphism has been investigated in uterine fibroids in populations with high ethnic diversity such as South Africa, Brazil, and the Caribbean [29,30]. In South Africa, Amant et al. [30] reported a strong association between uterine fibroids and the presence of the A2 mutant allele. The work of Alleyne [31], based on the allelic distribution of CYP17α, showed a predominance of the homozygous A1/A1 genotype with a frequency of 52% followed by the heterozygous A1/A2 genotype with a frequency of 41%; A2/A2 genotype constituting only 6% of cases. In Brazil, however, no association was noted between uterine fibroids and the presence of the mutant A2 allele.

### Cytogenetic findings

Despite their mild nature, 40-50% of fibroids contain chromosomal abnormalities [31-37]. The latter automatically implies that there are at least two or more pathogenic mechanisms responsible for the formation of fibroids since 50% of leiomyomas have a normal karyotype.

### Translocation T (12; 14) (Q14-15; Q23-24)

About 200 different chromosomal abnormalities have been described in leiomyomas, but there are a few that have been reported by several researchers to be prevalent Sandberg [38]. About 20% of karyotypically abnormal leiomyomas contain a translocation between chromosomes 12 and 14 (t (12; 14) (q15; q24)).

### Del7q22q32, Cut-like homeobox 1

Translocations of the long arm of chromosome 7 occur in about 17% of karyotypically abnormal leiomyomas Sandberg [38], and the loss of heterozygosity of 7q22, most likely involving homeobox Cut-like 1 (CUX1), occurs in about 10-35% of unselected cases of human fibroids [38-44].

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