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The Epidemiology and Genetics of Uterine Leiomyoma

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Uterine leiomyomas (fibroids) are the most common benign neoplasms in premenopausal women, which confer significant morbidity during the reproductive years and represent a significant public health issue. The incidence of fibroids has been associated with African-American race, early onset of menarche, early parity, and environmental/dietary exposures. These sex steroid-responsive uterine tumors are characterized by de novo transformation of the myometrium into fibroids via excessive formation of the extracellular matrix (ECM). Cytogenic anomalies, mutations in mediator complex subunit 12 (MED 12), and aberrant DNA methylation/demethylation have been observed, but have not been reported as direct mediators of fibroid development. Recent advances in epigenetics have implied a functional role of G protein-coupled receptor 10 (GPR10) overexpression and irregular microRNA expression in the pathobiology of fibroids that require future investigation. Herein, the impact of epidemiologic and genetic factors on the incidence and development of fibroids is reviewed.

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Introduction

Human leiomyomata (fibroids) are benign smooth muscle tumors of the uterus, which represent the most common neoplasms in women of reproductive age, and have a lifetime incidence of approximately 70% in the general population [1]. Approximately 20–40% of women with fibroids report significant symptoms and seek gynecologic care [1]. The most common clinical symptoms include abnormal uterine bleeding, dysmenorrhea, pelvic pain, infertility, and recurrent pregnancy loss; fibroids remain the leading indication for hysterectomy in the United States [2]. This disorder constitutes a major public health concern resulting in a significant degree of morbidity in premenopausal women with an estimated annual societal cost of approximately $5.9–34.4 billion (USD) in the United States [2].

These estrogen- and progesterone-dependent uterine tumors are clonal in origin and are typically diagnosed following menarche [3,4]. The most commonly accepted molecular mechanism of disease development is the transformation of myometrial smooth muscle (comprising the majority of uterine muscle mass) fibroblasts and the formation of dysfunctional extracellular matrix (ECM) [5]. However, the specific functional role of genetic mediators in cellular transformation, proliferation, apoptosis, neovascularization, and cellular hypertrophy has been difficult to characterize with certainty [5]. Most importantly, transforming growth factor beta (TGF-β) and its cognate receptor (TGF-βR) have been implicated by several investigators as critical mediators of cell signaling contributing to the genesis of uterine fibroids [5,6]. The intrinsic biological functions of TGF-β, including cellular hypertrophy and ECM turnover, are central to various fibrotic disorders, potentially including uterine leiomyoma [5]. Recently, investigators have provided additional insight into the possible roles (independent and synergistic) of several other molecules, including RE1-suppressing transcription factor (REST), G protein receptor 10 (GPR10), and matrix metalloproteinases (MMPs); alteration of several genes (e.g., *MED12*, *HMGA2, CYP1A1,* and *CYP1B1*), proto-oncogenes (e.g., p27 and p53), and related signaling pathways (e.g., PI3K-AKT-MTOR); and epigenetic etiologies such as histone modification, DNA demethylation, and aberrant microRNA (miRNA) expression [7–11].

Despite the first formal description of fibroids in the 16th century, the influence of genetic and epigenetic mediators in the pathobiology of this disorder remains unclear. The interplay of population health and genomics, demographics, environmental exposure, and genetics with the development of uterine fibroids warrants comprehensive examination. In this review, we will discuss contemporary epidemiologic and genetic topics pertinent to the pathogenesis of uterine leiomyomata.

Epidemiology

Prevalence

Prior to the mid-1990s, the majority of prevalence data for uterine fibroids were based on a small number of European case series that described findings from the histologic examination of surgical specimens [12–14]. Unfortunately, these studies did not provide an accurate estimate of the true prevalence of disease as they did not account for women who were asymptomatic or symptomatic and did not undergo surgical treatment. In the late 1990s, the Nurses' Health Study (NHS), a prospective cohort of >95,000 premenopausal women, reported that the annual rate of new annual fibroid diagnosis was approximately 12.8 per 1000 woman years [15]. Subsequently, the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study reported that >80% of African-American (AA) and 70% of Caucasian women developed fibroids by 50 years of age [16,17]. Racial/ethnic disparity of uterine fibroids has been a consistent observation by several independent investigators and is one of the most consistent epidemiologic characteristic of uterine fibroids. Additional risk factors such as age of menarche, parity, environmental exposure, and dietary/lifestyle habits have been delineated over the past decade, and have prompted an analysis of the effect of “nature versus nurture” on the development of this gynecologic disorder.

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