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Estrogens and uterine fibroids: an integrated view

Hadeel N. Alsudairi[*] ⓘ, **Alanoud T. Alrasheed**[*] ⓘ, **Volodymyr Dvornyk** ⓘ

College of Science and General Studies, Alfaisal University,
P.O.Box 50927, Riyadh, 11533, Kingdom of Saudi Arabia
Corresponding author: Volodymyr Dvornyk (vdvornyk@alfaisal.edu)

Abstract
Background: Uterine fibroids or uterine leiomyomata (UL) are common benign tumors of the uterine myometrium affecting a significant proportion of women at reproductive age. UL is a disease with complex etiology determined by many genetic and environmental factors. Estrogen is widely acknowledged as one of the main factors contributing to the risk and pathogenesis of UL. **The aim of the study:** To summarize available literature data about the estrogen-related environmental factors, genes and metabolic pathways, which may play a role in the disease. **Materials and methods:** The PubMed, Scopus, and Web of Science literature databases were searched for relevant articles using such keywords as "uterine fibroids", "uterine leiomyoma", "estrogen", "gene", "association", "expression", "epigenetic" in various combinations. **Results:** Estrogen contributes to the risk and pathophysiology of UL in multiple ways. Apart from the well-known effect of estrogen on expression of many genes mediated by estrogen receptors, it increases sensitivity of myometrium to progesterone and thus influences expression of the progesterone-controlled genes. On the other hand, the data about association of various estrogen-related genes with UL are largely inconsistent and inconclusive. **Conclusion:** The observed heterogeneity of UL apparently results from the diversity of mechanisms contributing to the disease. This makes identification of the causative genetic variants challenging and prompts for further studies of this problem.
Keywords: uterine fibroids; estrogen; pathogenesis; genetics; epigenetics; transcriptomics

[*] Contributed equally

Introduction. In eutherian mammals, the uterus facilitates the development of the embryo and the fetus and is necessary for reproduction. The uterus is derived from the Mullerian embryonic ducts and is divided into the inner endometrium and the outer myometrium. The inner endometrium is composed of luminal epithelium, glandular epithelium and endometrial stroma, while the myometrium is formed by smooth muscles. The most common benign pelvic neoplasms that occur in the myometrium smooth muscle layer of the uterus with a prevalence rate of 20-40% in women within their fertile years are uterine fibroids also known as uterine leiomyomata (UL). They are surprisingly very common; approximately 70% of women may develop these fibroids before menopause and 15 to 30% of these women experience serious symptoms [1]. The symptoms of this disease may include excessive menstrual bleeding, abdominal pain, pregnancy complications, pelvic pain, dysmenorrhea, menorrhagia, anemia, urinary incontinence, preterm labor, and infertility in certain instances [2]. UF bear a significant economic burden: the annual direct and indirect costs for the USA alone were estimated at $5.9-34.4 billion [3]. UL is a complex disease and like other multifactorial diseases is determined by many environmental and genetic factors. There is ample evidence that female sex hormones, particularly estrogen, play an important role in pathogenesis of the disease [4]. This review considers estrogen-related factors and mechanisms, which may be involved in the development of UL.

Estrogens and risk for UL

Estrogen has been implicated in pathophysiology of UL due to its pronounced effect on expression of various genes involved in control of cell growth and apoptosis [5, 6]. The elevated level of estrogen in UL patients may result from two sources. The first is estrogen in the bloodstream, while the second is estrogen synthesized in the fibroid tissue through conversion of androgens by aromatase [7, 8]. The latter seems to be particularly important for development of UL as the expression of aromatase was not observed in healthy myometrium [7]. Moreover, this source of estrogen is sufficient for maintaining the growth of the fibroid tissue even without supply of estrogen from other sources [8].

In addition to endogenous estrogen, another risk factor for UL is exposure to various exogenous estrogen-like chemicals. In addition to mimicking effect of natural estrogens, exogenous estrogens may bind to respective hormone receptors and detrimentally affect hormone synthesis and metabolism. One of the common consequences of the exogenous estrogen-like chemicals exposure is precocious puberty [9]. Prenatal exposure to diethylstilbestrol (DES), a synthetic non-steroid estrogen analog, was reported to promote hyper responsiveness to normal levels of estrogen hormone and confer a higher risk of UL [10, 11]. DES was the first synthetic estrogen developed in 1930s and prescribed to pregnant women to prevent miscarriage and to relieve morning sickness. Daughters of DES exposed moms developed adenocarcinomas, uterine structural variation, and were at higher risk of premature labor, ectopic pregnancy, and UL [12, 13]. In addition to DES, environmental phenolic estrogens such as BPA, octylphenol and nonylphenol can be involved in the UL pathogenesis. BPA is a synthetic estrogen used for manufacturing plastic goods and resins that are widely used in food packaging.

Estrogen-regulated gene expression in UL

Estrogen contributes to the growth of UL through several mechanisms. On the one hand, it increases responsiveness of the cell to progesterone [14], which in turn up-regulates the expression of proliferating cell nuclear antigen (*PCNA*) and epidermal growth factor (*EGF*) [15]. On the other hand, estrogen affects the expression of various growth factors and apoptosis-related genes. Importantly, this effect can be either inducing or repressing. Specifically, increased expression on the UL tissue was reported for several estrogen-regulated genes, such as type I and III collagen, connexin 43 gap junction protein, parathyroid hormone-related peptide, IGF-I and its receptor, and progesterone receptor (PR)

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[5]. Similar effect was documented for vascular endothelial growth factor (*VEGF*), a gene contributing to angiogenesis [16], insulin-like growth factor-I (*IGF-I*) and other genes potentially involved in the IGF-I signaling pathway [17, 18], genes involved in IGF-IR/MAPK signaling [18], and several growth factors [19, 20]. Contrastingly, estrogen reduced levels of actin-A and myostatin mRNA levels in the human myometrium [21], two growth factors, which inhibit myometrial cell growth.

Since UL is an estrogen-dependent disease, two primary estrogen receptor genes (*ESR1* and *ESR2*) have been among the main targets of gene expression studies of UL. Wang et al. [22] determined that the level of the *ESR1* expression was elevated in the UL cells as compared to the surrounding normal myometrium, and so was it as compared to *ESR2*. 1,25-dihydroxyvitamin D3 significantly downregulated the expression of *ESR1* and two progesterone receptors [23]. Similar effect on the *ESR1* expression was documented after treatment of UL with a gonadotropin-releasing hormone analogue (GnRHa) [22]. The responsiveness of the UL myometrium to estrogen was suggested to be determined by the ratio of the *ESR1* to *ESR2* expression; it was higher in the cells with the predominant *ESR1* expression [24].

The integrated analysis of several UL microarray studies determined twelve estrogen-regulated genes in the ovariectomized rat model treated with estrogen [25]. These genes belong to various metabolic pathways contributing to cell survival and tumor growth. Specifically, estrogen upregulated the anti-apoptotic *PCP4* gene and inhibited the expression of growth inhibitory receptors *PTGER3* and *TGFBR2*. Furthermore, estrogen might counteract PPARγ signaling, which is thought to inhibit fibroid growth and survival [25].

One more mechanism of the estrogen stimulating effect on the UL growth was described by Luo et al. [26] who determined that estrogen activated stromal fibroblasts, which,

in turn, promoted proliferation of fibroid cells.

Association of estrogen-related genes with UL

Given the acknowledged link between estrogen and UL, attempts have been made to determine association between estrogen metabolism-related genes and UL. However, the number of the respective studies is limited. Their results are summarized in Table.

The most commonly analyzed genes were *COMT*, *ESR1*, and *ESR2*. Allele C of the *ESR1* PvuII polymorphism was reported to confer approximately a two-fold higher risk for UL [27]. The strong association of five *ESR2* gene polymorphisms with UL was documented in the Indian population [28]. Two common polymorphisms of the *COMT* gene, IVS1+2329C>T and Val158Met, Ile462Val and Gly45Asp loci in *CYP1A1* and Ala119Ser locus of *CYP1B1* were also suggested as risk factors for UL [29-31]. However, the results of the candidate genes association studies are largely inconclusive and quite limited, so that further more extensive studies are necessary.

The earlier GWAS meta-analysis by Rafnar et al. [32] suggested at least two main genetic pathways contributing to the development of UL: tumorigenesis- and hormone-related, respectively. The GWAS meta-analysis of 35,474 cases and 267,505 controls of European ancestry identified eight novel and confirmed 21 previously reported loci for UL [33]. Among these, several loci were related to estrogen and progesterone signaling, namely *ESR1*, *FSHB*, *GREB1*, *WNT2*, and *WNT4* (Table 1). A transethnic GWAS meta-analysis of Europeans and African-Americans in the sample of 21,804 cases and 205,525 controls supported the previous finding for *WNT4* [34]. Finally, the most recent GWAS of the Japanese population confirmed *GREB1* and *WNT4* as candidate genes for UL in this ethnicity [35] (Table 1). However, the results of the GWAS were somewhat inconsistent, which suggests that the genetic basis of the disease is apparently more complex and involve other genes and intergenic interactions not determined by the analyses utilized.

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Table

Data on associations of estrogen-related genes with UL

Candidate gene	Polymorphism	Total sample size	Ethnicity	P	References
Candidate gene association studies					
CCDC57	rs4247357	43	Barbadian	0.75	[43]
	rs150468462			0.63	
	rs6502087			0.92	
COMT	rs4680(Val158Met)	2,749	Multiethnic	0.04	[30]†
		972	Multiethnic	NS*	
		600	Chinese	<0.05	[31]
	rs3087869			<0.05	
	(IVS1+2329C>T)				
	rs165774			NS	
	rs165599			NS	
CYP1A1	rs1048943(Ile462Val)	160	Egyptian	0.08	[29]
		600	Chinese	<0.05	[31]
	rs4646421			NS	
	rs4646422(Gly45Asp)			<0.05	
CYP1B1	rs1056837(Asp449Glu)	40	Barbadian	0.003	[43]
	rs1056836(Leu432Val)	37	Barbadian	0.86	[44]
	rs1056827(Ala119Ser)	600	Chinese	<0.05	[31]
	rs1056836(Leu432Val)			<0.05	
	rs1056837(Asp449Glu)			NS	
CYP17A1	rs743572	105	Taiwan	0.017	[45]
ESR1	rs9340799 (XbaI)	213	Turkish	0.5447	[46]
		216	Chinese	0.00005	[47]
	rs2234693(PvuII)	213	Turkish	0.6225	[46]
		216	Chinese	0.00005	[47]
		125	Caucasian	0.906	[48]
		429	Multiethnic	<0.05	[49]
		105	Chinese	0.017	[45]
	rs9322331	125	Brazilian	0.325	[50]
	rs17847075	125	Brazilian	0.586	
ESR2	-13950T/C	296	Indian	0.48	[51]
	rs1256049	300	Chinese	NS	[52]
		300	Indian	0.001	[28]
	rs2987983	101	Caucasian	0.439	[53]
	rs3020450			0.830	
		300	Indian	0.001	[28]
	rs3020449	101	Caucasian	0.974	[53]
		300	Indian	0.001	[28]
	rs3020450				
	rs1271572				
	rs1256049				
	rs4986938				
GPR30	rs3808350	111	Turkish	0.017	[54]
	rs3808351			0.08	
	rs11544331			0.346	
PGR	rs10895068 (+331G/A)	296	Indian	0.0023	[51]
	PROGINS	213	Turkish	0.0584	[46]
		1,848	Multiethnic	NS	[55]†
Genome-wide association studies					
ESR1	rs58415480	302,979	Caucasian	1.9×10^{-54}	[33]†
FSHB	rs11031006			5.7×10^{-15}	
WNT2	rs2270206			4.6×10^{-08}	
GREB1	rs35417544			2.3×10^{-19}	
	rs12479436		Japanese	9.5×10^{-19}	[35]
WNT4	rs7412010	302,979	Caucasian	2.4×10^{-29}	[33]†
	rs10917151	227,329	Multiethnic	1.76×10^{-24}	[34]†
	rs3820282	3,483	Japanese	3.5×10^{-35}	[35]

Note: * NS, not significant; † meta-analysis.

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Obesity, estrogen, and risk of UL

Obesity is one of the phenotypes associated with UL. BMI, waist circumference, hip circumference, waist-height ratio, body fat content and body fat percentage are all positively correlated with the development of uterine fibroids [36]. Visceral fat was shown to act as hormone-active tissues, thus by increasing the production of inflammatory mediators, can ultimately lead to UL. The extra-peritoneal fat thickness independently correlates with the development of uterine fibroids (P<0.0001) [37]. The results of this study suggested that the visceral fat area (VFA) was a risk factor for UL. This risk elevated with the increase in the VFA, which in turn correlated with the UL size even though the correlation was relatively weak [37].

A recent meta-analysis further confirmed an increased risk for UL in women with a higher body mass index (BMI) [38]. The observed effect of obesity is apparently explained by the role of the fat tissue in the production of estrone and estradiol from the androgen precursors and the respective increase in the level of circulating estrogen [39]. On the other hand, some data suggested that the effect of higher estrogen level might be opposite for a risk of incident and recurrent UL: it increases the former and decreases the latter [40].

Estrogen-related epigenetic factors

Various epigenetic mechanisms have been implicated in the development of UL [41]. A genome-wide methylation analysis identified 478 genes, which were hypomethylated and 1,014, which were hypermethylated in UL as compared to the surrounding myometrium [42]. Among these, 22 genes, which manifested both aberrant methylation and expression, possessed the consensus sequences of the ER response element and thus were targeted by estrogen. These estrogen-regulated genes contribute to various processes important for pathophysiology of UL, such as extracellular matrix expansion and apoptosis.

Conclusion. Estrogen influences a risk and pathogenesis of UL through multiple mechanisms. This contributes to the heterogeneity of this neoplasm and makes identification of the causative genetic variants challenging.

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Conflict of interests

The authors have no conflict of interest to declare.

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Information about the authors
Hadeel N. Alsudairi, Undergraduate Student at the Department of Life Sciences, College of Science and General Studies, Alfaisal University, Riyadh, Kingdom of Saudi Arabia, E-mail: halsudairi@alfaisal.edu, ORCID: https://orcid.org/0000-0002-5802-4326.
Alanoud T. Alrasheed, Undergraduate Student at the Department of Life Sciences, College of Science and General Studies, Alfaisal University, Riyadh, Kingdom of Saudi Arabia, E-mail: atalrasheed@alfaisal.edu, ORCID: https://orcid.org/0000-0002-1709-3835.
Volodymyr Dvornyk, PhD, Associate Professor at the Department of Life Sciences, College of Science and General Studies, Alfaisal University, Riyadh, Kingdom of Saudi Arabia, E-mail: vdvornyk@alfaisal.edu, ORCID: https://orcid.org/0000-0002-2535-103X.