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Histological and Molecular Study of HOXA11 Gene in Endometrial Carcinoma

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ABSTRACT

Background & Objective: Endometrial carcinoma (EC) is one of the most common cancers and the fourth most common cancer affecting females, mostly affecting postmenopausal women. EC originates from the endometrium and is further sub-divided into two types that are estrogen dependent; type 1 and type 2 with different gene expression patterns.

Materials & Methods: This research was carried out between December 2021 and August 2022 in the Laboratories of the College of Science/Department of Biology and the other local lab and PCR was employed to establish HOXA11 presence. The aims of the study were to reveal the histological alterations in malignant and benign tumors and normal endometrium and to examine the relationship between HOXA11 levels and clinicopathological parameters including stage, grade, muscle and lymph node invasion, and histological type.

Results: The mean HOXA11 expression values were compared in cancer, benign, and control endometrial patients' groups. The mean HOXA11 expression level was the lowest in endometrial cancer patients; they had a mean of 0. 24±0. 03, those with benign endometrial tumors had the second lowest with a mean of 0. 94±0. 06, while the control patients had the highest mean expression with 1. 00±0. 07. The comparison of the HOXA11 expression between the endometrial cancer patients and the control group showed a statistically significant difference (P-value >0. 001), thus underlining its diagnostic value. Also, there was a significant difference in the HOXA11 expression means between patients with benign tumors and control patients (P-value = 0. 021). As for HOXA11, the mean expression was relatively lower in the patients with benign endometrial tumors, 0. 94±0. 06 as compared to the control group 1. 00±0. 07. In addition, the mean HOXA11 expression in endometrial cancer patients was 0. 24±0. 03 which was significantly (P-value >0. 001) less than that in benign endometrial tumor patients.

Conclusion: These results stress the importance of HOXA11 expression as a diagnostic marker and its possible application in differential diagnosis between endometrial cancer and benign neoplasms and normal tissues.

Keywords: Endometrial Cancer, Polymerase Chain Reaction, HOXA11, Benign

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Introduction

Endometrial cancer is the sixth most common malignancy in women, and it is known to be a disease among postmenopausal women, but there is a rising in the number of endometrial cancers among premenopausal women **(1)**. Endometrial cancer (EC) is arising in the inner epithelial lining of the uterus. In 2020, the age-standardized incidence and mortality rate were 8.7 and 1.8 per 100 00

0 population, respectively **(2)**. Typically, two types of endometrial cancer are distinguished, with type I accounting for the majority of all EC cases. Type I includes the endometrioid EC, which has a good prognosis and is estrogen-dependent. In contrast, type II includes non-endometrioid EC and high-grade EC with poor prognosis **(3)**. Uterine fibroids (UFs), also known as leiomyomas or myomas. Endometrial polyps are a common gynecological disease, they are composed of epithelial (glandular) and stromal (fibroblastic) elements admixed with blood vessels **(4)**. *HOXA11* is a member of the HOX family of genes comprised of four clusters, namely HOX A, HOX B, HOX C, and HOX D. *HOXA11* is expressed in both epithelium and stroma in the adult uterus and appears to be regulated by ovarian steroids and contribute to endometrial tumorigenesis, which encodes a transcription factor, is involved in proliferation,

differentiation, and embryologic development of the endometrium **(5)**.

Methods

2.1 Samples collection

This study included 45 samples of tissues were collected from endometrial tumor patients, **(6)** samples were taken from patients diagnosed as EC with age ranged between 27 and 80 years, while the rest 20 were recorded as a benign tumor with age range between 23 and 58 years and 10 samples no cancers tissues ranged from 31 to 53 years were diagnosed as hormonal imbalance. All samples of patients were collected from Al-Zahraa and AL-Karama Teaching Hospitals in Wasit Province, and from Private Laboratory (BioTech) AL-Kut Province. This lab study was carried out in the Laboratories of the College of Science/ Department of Biology and in a local lab during the period between December 2021 and August 2022.

2.2 Handling and Immediate Processing:

Upon retrieval, tissue samples were promptly immersed in 10% buffered formalin to ensure optimal fixation. Care was taken to mark the orientation of resected samples, especially in the case of larger specimens. Orientation markers, using sutures or dyes, helped in maintaining the histological context and facilitated accurate pathological interpretation later on.

2.3 Tissue Fixation

Ensuring the preservation of cellular and tissue architecture is pivotal for accurate histopathological assessment. The fixation process stabilizes tissue components, preventing post-sampling degradation.

2.4 Molecular studies of HOXA11 gene in tumor endometrial

Total RNA was extracted from tissue samples by using an RNA extraction protocol (GENEzol™ TriRNA Pure Kit, cat# GZX100/ D100) and done according to company instructions as following steps:

2.4.1 Deparaffinization

1. Five sections of 8 nm per 1.5- ml were transferred to Eppendorf tube and solubilized the paraffin twice with 1 mL of xylene for 5 mm at room temperature, then centrifuged at high-speed m a micro centrifuge for 10 mm and the pellet was saved after each time.
2. Samples were washed with 1 mL of absolute ethanol for 10 min and once with ethanol 95%, then centrifuged in a micro centrifuge for 10 min and the pellet was saved after each time
3. Tissues were air-dry the with tubes open m a thermoblock at 37°C for approx 30 min.
4. Proteinase K was added to a final concentration of 6 mg/mL (43 µL of 20 mg/mL proteinase K every 100 µL of digestion solution).
5. Incubate overnight at 45°C with swirling.
6. Micro pestles were used to homogenize digested tissues.

2.4.2 RNA extraction

1. 400 µl of DR Buffer and 4 µl of ß-mercaptoethanol were added to the tissue sample and then the sample was homogenized with a Tissue micro pestle, then tissue samples thoroughly.
2. Ground tissue was transferred to a 1.5 ml micro centrifuge tube and 400 µl of DR Buffer and 4 µl of ß-mercaptoethanol were added. Shear the tissue by passing the lysate through a 20-G needle syringe 10 times.
3. Samples were incubating lysate at room temperature for 5 minutes, then centrifuged at 16,000 x g for 2 minutes. After that GD Column was placed in a 2 ml Collection Tube then supernatant was transferred to the GD Column, and centrifuged at 16,000 x g for 1 minute.
4. Flow past the GD Column membrane following centrifugation, increase the centrifuge time until it passes completely. Save the flow-through in the 2 ml Collection Tube for RNA Purification.
5. GD Column was placed in a new 2 ml Collection Tube and stored at room temperature (15-25ºC).
6. Elution Buffer (50 µl per sample) was heated to 60ºC

2.4.3 RNA Purification

1. 0.8 volume of absolute ethanol was added to the flow-through in the 2 ml Collection Tube and mix well by pipetting, then sample was transferred to the RB Column in a 2 ml Collection Tube and centrifuged at 16,000 x g for 1minute.
2. RB Column was placed the in a new 2 ml Collection Tube and 400 µl of RW1 Buffer into was added to the RB Column and centrifuge at 16,000 x g for 30 seconds. Discard the flow-through and place the RB Column back in the 2 ml Collection Tube. Add 600 µl of RPE Buffer (make sure ethanol was added) into the RB Column, centrifuged at 16,000 x g for 30 seconds.
3. Discard the flow-through and place the RB Column back in the 2 ml Collection Tube. Add 600 µl of RPE Buffer, and centrifuge at

14-16,000 x g for 30 seconds. Discard the flow-through and place the RB Column back in the 2 ml Collection Tube. Centrifuge at 16,000 x g for 3 minutes to dry the column matrix.

4. RB Column, then placed in a clean 1.5 ml micro centrifuge tube (RNase-free). And 50 µl of RNase-free Water into the center of the column matrix and was left stand for at 3, and centrifuge at 16,000 x g for 1minute to elute the purified RNA.

2.4.4 Reverse Transcription

Reverse Transcription is carried out with the SuperScript First-Strand Synthesis System for RT-PCR (cDNA). The following procedure is based on Invitrogen's protocol.

1. The RNA/Primer Mixture in each tube was prepared as shown in Table (1):

Table 1. The components of RNA/Primer Mixture (cDNA) Prepare

Component	Volume (µL)
Total RNA	**5 µg**
random primer (0.1 µg/µl)	**1 µl**
2X reaction mix	**10 µl**
Enzyme mix	**1 µl**
RNAase Free water	**3 µl**
Total volume	**20 µl**

2. A reaction master mixture was prepared for each reaction as shown in Table (2):

Table 2. Thermocycler Program

Item	Step 1	Step 2	Step 3	Step 4
Temperature (°C)	25	42	85	4
Time	10 min	15 min	5 Min	∞

3. The tubes were incubated at 25°C for 10 min as the first step.

4. Then tubes were incubated at 42°C for 15 min, heated at 85°C for 5 min, and then chilled on 4°C

5. cDNA was stored at -20°C until use for real-time PCR.

2.4.5 Molecular detection for HOXA11 gene

2.4.5.1 Primers dilution

The stock primers solutions (100 pmole/1µl) were prepared by adding NUECLASE FREE water in exact volumes as required by the manufacturer company.

In order to achieve a final concentration of 10 pmoles/1µl, stock solutions for each primer were diluted with NUECLASE FREE water using a 1:9 ratio. Both forward and reverse primers were added in volumes of 1µl (10 pmole/1µl).

It is shown in Table (5).

Table 3. Primers sequences of *HOXA11* gene

Primer	Sequence (5'-3')	Product size (bp)
HOX11 F	TGCCAAGTTGTACTTACTACGTC	
HOX11 R	GTTGGAGGAGTAGGAGTATGTA	
GAPDH F	TGCACCACCAACTGCTTAG	
GAPDH R	CAGGCAGGGATGATGTTC	

2.4.5.2 PCR working reaction

Components of PCR reaction and mixing amounts were shown in Table (4).

Table 4. PCR components.

Component	Component of one sample
Sibergreen mastermix	12 µl
Forward primer	1 µM
Reverse primer	1 µM
cDNA template	5 ng/µl
Nuclease free water	1
Final volume	20

2.4.5.3 The PCR programs of *HOXA11* gene

A.PCR Programs of *HOXA11* gene

The PCR reaction was carried out as shown in Table (5) and Figure (1).

Table 5. PCR Programs of HOXA11 gene

Steps	Temperature	Time	No. Of cycles
Initial denaturation	95 ℃	10 min	1 cycle
Denaturation	95 ℃	30 sec	40 cycles
Annealing	60℃°	40sec	
Extension	72 ℃	30sec	
Final extension	25 ℃	30sec	1 cycle
Holding	4 ℃	Forever	-

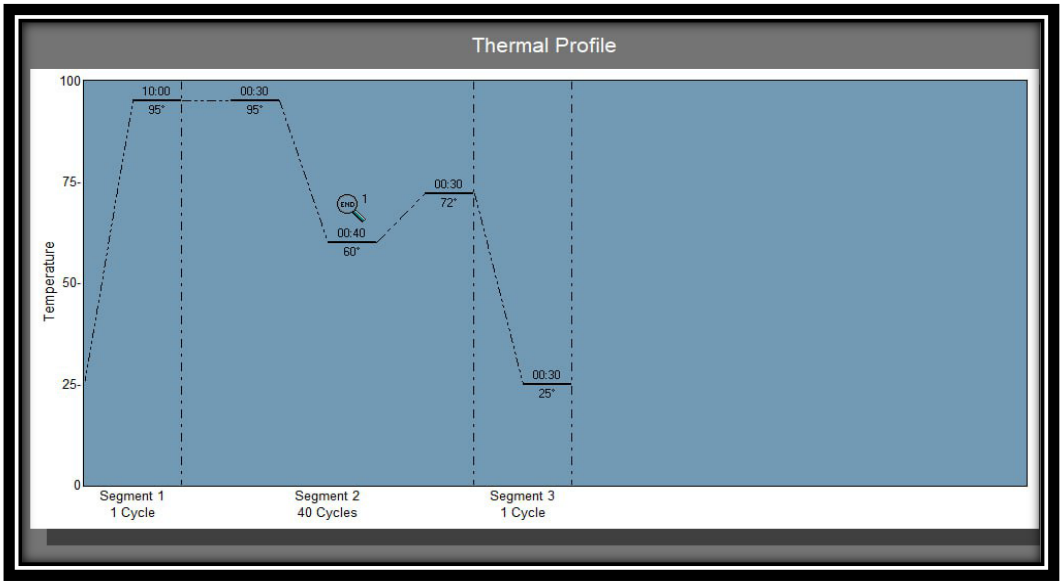


Figure 1. PCR Programs of HOXA11 gene

2.5 Statistical analysis

Data were entered and analyzed using the software program Statistical Package for Social Sciences (SPSS) version 26. All numerical variables were represented by means (a measure of central tendency) and standard deviation (a measure of dispersion) while categorical variables were presented by frequencies and percentages. Histograms and bar charts were also used to present variables. Independent sample t-test and one-way ANOVA test were used to assess the mean differences of numerical continuous variables accordingly. Fisher's Exact Test was used to assess the association between two categorical variables instead of the chi-square test (more than 20% of the expected cells were less than 5). A *P*-value equal to or less than 0.05 was considered significant.

Results

3.1.1 Distribution of endometrium patients according to aging group

This study investigated the age distribution of a sample of endometrium patients, encompassing a total of 45 individuals. The mean age of the sample was 46.29 years, with a standard deviation of 12.26 years. The age range varied from 23 to 80 years, and patients were categorized into four age groups: 20-34 years (20% of cases), 35-49 years (35.6% of cases), 50-64 years (37.8% of cases), and 65-80 years (6.7% of cases). The distribution is visually represented in Figure 2, with age intervals displayed.

Group 3 (50-64 years) had the greatest endometrial patient incidence rate (37.8%), followed by group 2 (35-49 years) with 35.6%. These findings imply that endometrial disorders are more common in women over 40. Under 40, endometrial disorders are not a major concern, according to the study. The lack of corpus luteum during perimenopause causes discontinuous ovulation and a drop in progesterone levels. Unhindered endogenous estrogen stimulation of the endometrium may cause endometrial hyperplasia and cancers. **(7)**. This result is agreed with the result of **(8)** who indicated that the age ranges at diagnosis were as follows: 6% less than 40 years, 6% (41–50) years, 25% (51–60) years, 42% (61–70) years and 21% over (70) years. Moreover, **(9)** reported that the mean age of diagnosis among the premenopausal group is (44.9+7.5) years old, which is significantly younger as compared to the postmenopausal group at (62.3 + 6.5) years.

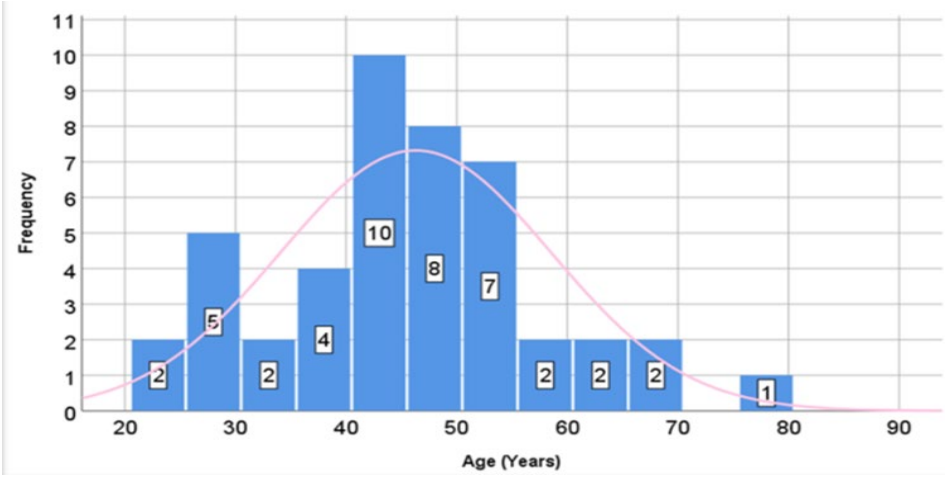


Figure 2. Histogram of the age distribution for 45 samples with endometrial patients with age interval.

3.1.2 Distribution of age according to endometrium histopathology diagnosis among 45 patients.

This study shows diagnostic distribution for 45 endometrial samples.15 (33.3%) patients with endometrial tumor cancer (malignant tumors), 20 (44.4%) with benign tumors, and 10 (22.2%) with no endometrial alterations and hormonal imbalance as a control group.

This study determined mean age and standard deviation in endometrial samples. Table 6 shows that 55.60±10.60 patients had endometrial cancer tumors, 40.70±12.40 had benign tumors, and 43.50±5.96 had endometrium control.

Table 6. Distribution of age according to endometrium histopathology diagnosis among 45 patients.

Histopathology Diagnosis	Frequency	Percentage	Mean age	S.D	P-value
Endometrial cancer tumors	15	33.3%	55.60	12.40	0.001
Endometrial benign tumors	20	44.4%	40.70	10.60	
Endometrium control (Hormonal imbalance)	10	22.2%	43.50	5.96	
Total	45	100%			

These results showed significant difference (P-value=0.001) between the three diagnosed groups of patients regarding age. Patients with endometrial cancer were with a higher mean age (55.60±12.40) when compared with benign conditions were with a mean age of (40.70±10.60) and with control group conditions were with a mean age of (43.50±5.96). This result in concordant with result **(10)** found that the mean age of the studied patients with endometrial cancer was (61.9 ±11.4) years, the maximum age of the patients was 78 years and the minimum age was 35 years and the most common age group of patients was 56-65 years and explain the age group of (56-65) years was the highest (36.1%), followed by the age group of (66-75) years was (26.2%), with a mean age group of 61.92 ±11.47 (35-78) years. Also, this result is agreed with **(11)** suggest that age ≥ 50 years old is a high-risk factor for the development of EC. This may due to increase in estrogen levels in the body caused by various reasons continuously stimulates the proliferation of endometrial tissue and long-term estrogen exposure of the endometrium and the lack of progesterone antagonism **(9)**.

Malignant

3.1.3 Distribution of malignant endometrium patients according to histopathological type

Four histological types were determined in the endometrium cancer patients. 11(73.3%) patients of them were endometrioid adenocarcinoma, 1(6.7%) patients had serous endometrial adenocarcinoma, 2(13.3%) patients with Villoglandular Adenocarcinoma and 1(6.7%) patients with Malignant Mixed Mullerian Tumor (Table 7).

Table 7. Distribution of malignant endometrial patients according to histopathological type

Histotype	Frequency	Percentage
Endometrioid Adenocarcinoma	11	73.3%
Serous Endometrial Adenocarcinoma	1	6.7%
Villoglandular Adenocarcinoma	2	13.3%
Malignant Mixed Mullerian Tumor	1	6.7%

According to histological nature, most malignant endometrial tumor patients have Endometrioid Adenocarcinoma. There were 73.3% cases and 13.3% of Villoglandular Adenocarcinoma. One patient (6.7%) had serous endometrial adenocarcinoma and malignant mixed Mullerian tumor. This result in concordant with result **(12)** found that Endometrioid adenocarcinomas (EEC) are the most frequent subtype and more common (≅ 80%) and EEC is very aggressive carcinomas compared with other types the less common clinically aggressive. Also, clear that Serous Endometrial Adenocarcinoma represents ∼10% of all endometrial cancer diagnoses, it accounts for up to 39% of endometrial cancer related deaths **(13)**.

3.1.4 Association between age group and histotype of malignant endometrial tumor patients

This study included 27–80-year-old malignant endometrial tumor patients. The lowest age was 27 and the highest 80. Malignant endometrial tumor patients were divided into four age groups **(1-4)** separated by 15 years. The first age category was 20–34, the last 65–80. Malignant endometrial age group estimates showed 1 case (100%) in age group 1 (20-34) was Villoglandular Adenocarcinoma, 2 cases (100%) in age group 2 (35-49) were Endometrioid, 8 cases (88.9%) were Endometrioid, 1 case (11.1%) was Villoglandular, and 1 case (33.3%) was Endometrioid.

Table 8. Association between age group and histotype of malignant endometrial tumor patients.

Age category (years)	Histotype				P-value
	Endometrioid	Serous Endometrial Adenocarcinoma	Villoglandular Adenocarcinoma	Malignant Mixed Mullerian Tumor	
20-34	0(0%)	0(0%)	1(100%)	0(0%)	0.110
35-49	2(100%)	0(0%)	0(0%)	0(0%)	
50-64	8(88.9%)	0(0%)	1(11.1%)	0(0%)	
65-80	1(33.3%)	1(33.3%)	0(0%)	1(33.3%)	

This table demonstrates no age-related cancer histotype difference (P=0.110). All patients under 35 had Villoglandular Adenocarcinoma. Only two 35-49-year-olds had Endometrioid Adenocarcinoma. Result **(13)** found that age at diagnosis was found to be statistically different across histologic categories (p=0:02) with endometrioid type tumors presenting on average at a younger age (mean = 68:5) years than other subtypes. In addition, **(14)** showed that the mean age of patients was 55 years (range 45-74) for group 1 and was 56ys (range 43-75) for group2. Also, **(14)** explained that the mean age of the patients was 56 years (25–77 years), Endometrioid carcinoma was the commonest histological type (136 patients, 88%). Other histological cell types were clear cell carcinoma **(14)** 9%patients, papillary serous carcinoma **(3)** 1.9%patients, and adenosquamous carcinoma **(2)** 1.2% patients.

3.1.5 Frequency distribution of the endometrial cancer patients according to grading

In this study involved 15 endometrium cancer patients is divided into three grades, grade I was appeared in 12 (80.0%) of patients, grade II found in 2 (13.3%) of patients while grade III was presented in 1 (6.7%) of patients (Table 9).

Table 9. Frequency distribution of the endometrial cancer patients according to grading

Grade	Frequency	Percentage
G1	12	80.0%
G2	2	13.3%
G3	1	6.7%
Total	15	100%

Table 9 shows that 80% of patients in this research had a grade I endometrial cancer, 13.3% had grade II, and 6.7% had grade III. Grade I patients are more common than grade II and grade III individuals, possibly due to early diagnosis and treatment for abnormal uterine hemorrhage. This result matches **(15)** that endometrial cancer had 15 grade I tumors (33.33%), 23 grade II tumors (51.11%), and 7 grade III tumors (15.56%). Furthermore, **(14)** observed that preoperative abnormal tissue grading showed that 73.3 percent of patients were grade 1, 20% were grade 2, and 6.7% were grade 3 for both groups. The postoperative results showed some changes: 60% of patients were grade 1, 33.3% were grade 2, and 6.7% were grade 3. In group 2, 66.7% were grade 1, 20% were grade 2, and 13.3% were grade 3.

3.1.6 Frequency distribution of the endometrial cancer patients according to staging.

In this study, it was found that endometrium cancer patients are divided into three stages, stage I was appeared in 14(93.3%) of patients, stage II found in 1(6.7%) of patients while stage III found in 0(0%) of patients Table (10).

Table 10. Frequency distribution of the endometrial cancer patients according to staging.

Stage	Frequency	Percentage
I	14	93.3%
II	1	6.7%
III	0	0%
Total	15	100%

Results of Table (10) According to the staging fraction of cancer cases, most patients (93.3%) were in stage I, 1 (6.7%) were in stage II, and none were in stage III. This matches result **(8)**, which identified 37.7% stage II and 31.1% stage III patients. Additionally, **(10)** demonstrated that the Premenopause subgroup (126) staging showed that 90(71.4%) of patients were stage 1, 18(14.3%) were stage 2, 15(11.9%) were stage 3, and 2(1.6%) were stage 4. Postmenopause subgroup (155) findings showed some changes: 133 (72.9%) patients were stage 1, 18 (11.6%) were stage 2, 14 (9.0%) were stage 3, and 4 (2.6%) were stage 4.

3.6 Frequency distribution of muscle invasiveness among 15 patients diagnosed with malignant endometrial cancer

Endometrium cancer is either invasive or non-invasive muscles. In this study, it was found that 3(20%) of patients suffering from muscles invasiveness endometrium cancer, and other 12 (80%) of them presented with non-invasive Figure (3).

The results of this Figure (3) showed that the proportion of absent muscle invasion in endometrium cancer patients is higher compared with present invasion muscle. Invasiveness was present in about 80% while invasion muscle was present in about 20% of patients who were diagnosed with endometrial cancer in this study. Results of Moreover, **(16)** explain that the none muscular invasion was 101 (98.06%) of 103 cases with premenopausal EC and was 101(89.38%) of 113 cases with postmenopausal EC, whereas the muscular invasion was 2 (1.94%) of 103 cases and was 12 (10.62%) of 113 cases with postmenopausal EC with P(value= 0.079) in both cases. Moreover, **(17)** explains that in (EC) depth of myometrial invasion none or <50% was 50 (65.8%) cases and in myometrial invasion ≥ 50% was 26 (34.2%) cases.

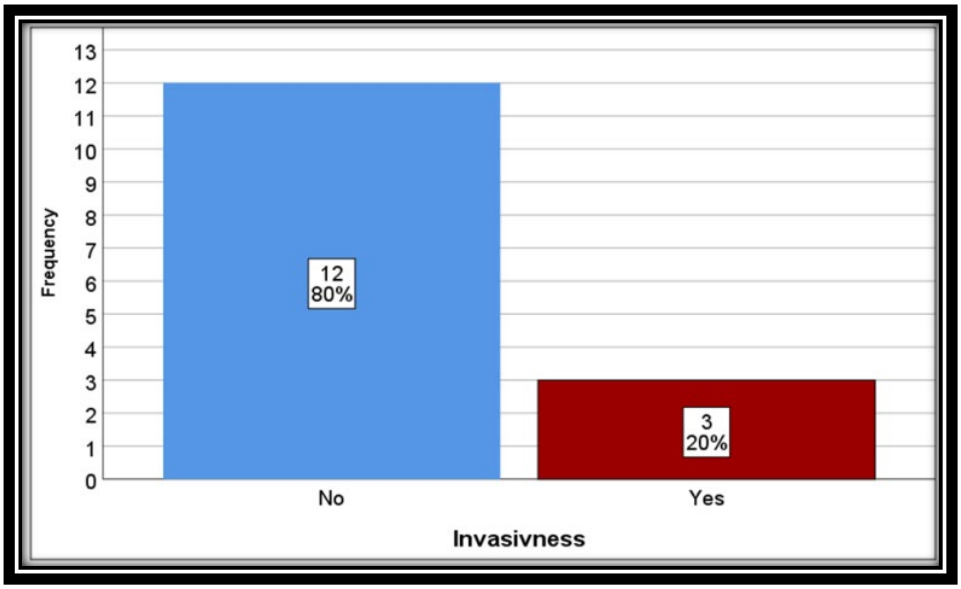


Figure 3. **Frequency distribution of muscle invasiveness among 15 patients diagnosed with malignant endometrial cancer.**

3.1.7 Frequency distribution of the lymph node involvement among 15 patients diagnosed with malignant endometrial cancer

Endometrium cancer is either invasive or non-invasive lymph node. In this study, it was found that 15 (100%) of patients suffering from lymph node invasiveness endometrium cancer, and other 0 (0.0%) of them presented with non-invasive Table (11).

Table 11. **Frequency distribution of the lymph node involvement among 15 patients diagnosed with malignant endometrial cancer**

Variable	Yes Number (%)	No Number (%)
Lymph node involvement	15(100%)	0(0%)

Table (11) demonstrated that endometrial cancer patients have more lymph node invasion than those without. Results of **(16)** show that none lymphatic metastasis was 102 (99.035%) of 103 premenopausal EC cases and 101 (89.38%) of 113 postmenopausal EC cases, while muscular invasion was 1 (0.97%) and 12 (10.62%) of 113 cases, with P (value= 0.003) in both cases. According to lymph node invasion was present in 26 (34.2%) EC patients and missing in 50 (65.8%). However, **(6)** found 20% (13 out of 63) and 14% (13 out of 92) lymph node metastases in high-grade and low-grade illness, respectively.

3.1. 8: Association between age group and histotype of the benign endometrial tumor.

In this research, benign individuals aged 20–64 were included. The minimum age was 20; maximum 64. The benign patients were divided into three age groups **(1-3)** separated by 15 years. The first age group was 20–34, the last 50–64. Estimation of benign age group showed that 0(0.0%) cases with polyp, 7(100%) cases with leiomyoma in age group 1(20-34), 4(57.1%) cases with polyp, 3(42.9%) in age group 2(35-49), 4(66.7%) and 2(33.3%) in age group 3 (19-50), Table (12).

Table 12. **Association between age group and histotype of the benign endometrial tumor.**

Age category (years)	Histotype		P-value
	Polyp endometrial	Leiomyoma endometrium	
20-34	0(0%)	7(100%)	0.028
35-49	4(57.1%)	3(42.9%)	
50-64	4(66.7%)	2(33.3%)	

This study found a significant connection between benign tumor histotype and age (P=0.028). Leiomyoma was identified in all 20-34-year-olds (100%) and polyp 4 in 66.7% of those over 50. According to **(18)**, benign

endometrial polyps were found in 5 age groups **(1-5)** with a 10-year interval. The study found that endometrial polyps were most common in groups younger than 60, with 60% of cases in 30-40, 47% in 41-50, 36% in 51-60, and 0% in 61-70 and >70 (P-value<0.0001).

3.2 Histological Structure

3.2. Microscopical Structure of Endometrial Tissues

3.2.1.1 Microscopical Structure of Endometrial control

The histological examination of endometrial control tissues using H&E stain revealed two distinct zones. The basal layer, situated next to the myometrium, exhibited a highly cellular lamina propria and the deep basal ends of uterine glands. In contrast, the superficial functional layer, or functionalism, displayed a spongier and less cellular lamina propria, enriched in ground substance. This layer included most of the length of the glands and the surface epithelium, undergoing changes during menstrual cycles. However, the basal layer remained relatively unchanged, characterized by a single layer of columnar epithelium atop the stroma. The stroma, a connective tissue layer, varied in thickness based on hormonal influences. Simple tubular glands extended from the endometrial surface to the base of the stroma, which also featured a rich blood supply from the spiral arteries (Figure 4). These findings align with a previous study **(19)**, which identified two sublayers of the endometrium: the basal layer connecting to the myometrium and the functional layer facing the uterine cavity.

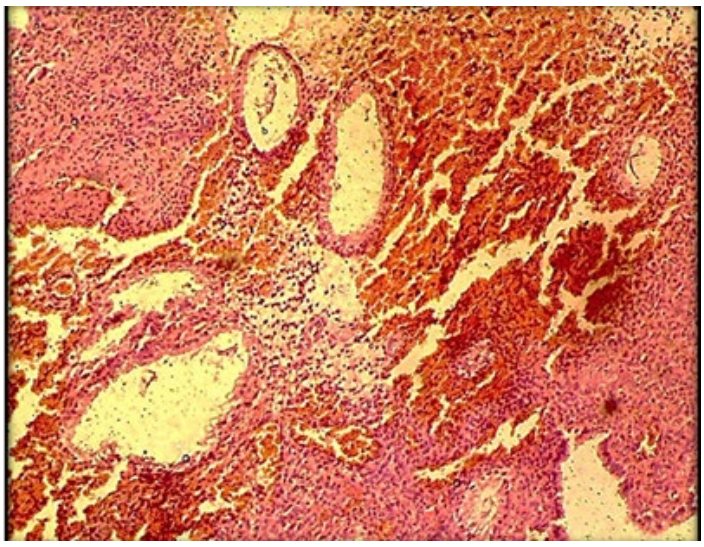


Figure 4. Endometrial control tissues with H&E stain (4X).

3.2.1.2 Microscopical Structure of Endometrial Malignant

H&E staining of endometrial malignant samples showed that the inner epithelial lining of the uterus is where endometrial cancer originates. Friable, hemorrhagic spherical, polypoid expansile masses indicate localized illness. Diffuse endometrial involvement may cause an indurated surface without exophytes. There may be necrosis and bleeding. Grossly, myometrial invasion foci are well-defined gray-white patches lighter than the surrounding myometrium. Extension from the surface lesion is usual. Endometrial cancer has multiple histopathological subtypes:

A- Endometrioid Adenocarcinoma

H&E staining of well-differentiated endometrioid adenocarcinoma tissues showed proliferation of complex glandular architecture mitosis branching lined tall columnar epithelial cells with moderate atypical nuclear changes (Figure 5).Produces small, round back-to-back glands without intervening stroma, budding, papillae, and cribriforming in grade 1 lesions, uniform and oval to cylindrical nuclei with minimal atypia and small discrete nucleoli, cellular axes perpendicular to the basement membrane, and stratification may or may not be present. These results were consistent with **(20)**, findings that endometrioid adenocarcinoma cells grow in patterns similar to normal endometrium, with many new glands formed from columnar epithelium with abnormal nuclei and very close glands without stromal tissue.

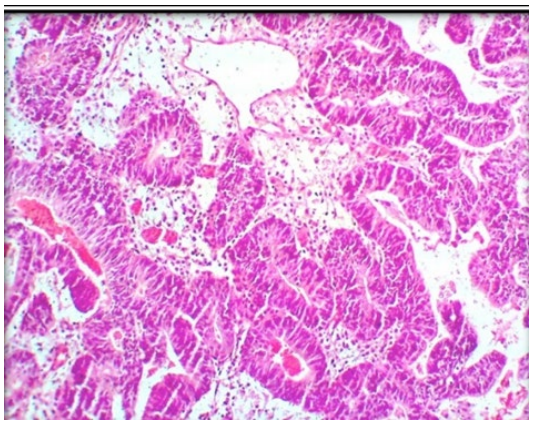


Figure 5. A well-differentiated endometrioid adenocarcinoma (10X).

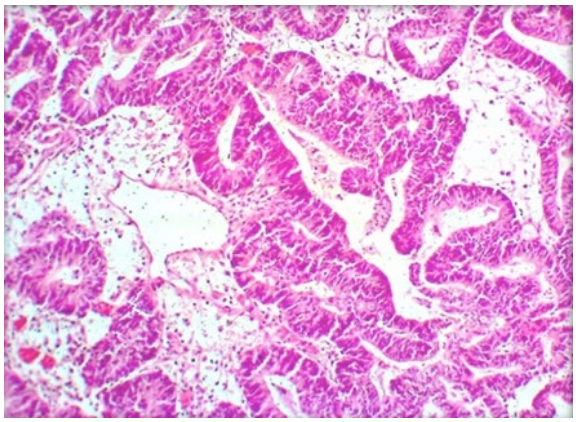


Figure 6. A well-differentiated endometrioid adenocarcinoma with grade I. Note the absence of intervening stroma between the irregularly shaped glands. Nuclei demonstrate only mild pleomorphism (10X).

B- Villoglandular Adenocarcinoma

Villoglandular (Papillary) Adenocarcinoma tissue sections stained with H&E showed increased endometrial tissue volume, closely packed glands, and a 3:1 gland-to-stroma ratio. Some sections showed cystic dilatation with papillary-like projection, tall columnar cells, enlarged round nucleoli, and moderate atypia Figure 7 Villoglandular carcinoma has a papillary architecture with fragile fibrovascular stalks bordered by cuboidal to columnar cells, low cellular stratification, and unclear nucleoli (Figure 8). This trait matched the finding of **(21)**.

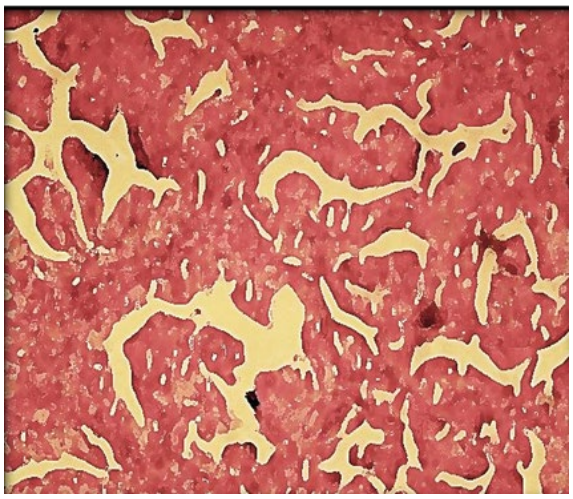


Figure 7. Villoglandular (Papillary) Adenocarcinoma tissue with H&E stain (10X).

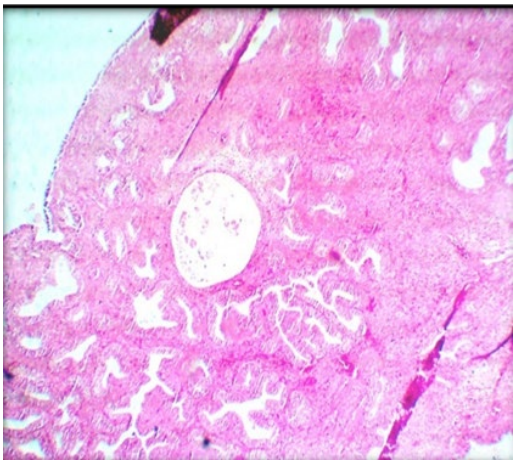


Figure 8. Villoglandular (Papillary) Adenocarcinoma tissue with H&E stain (4X).

C. Serous Carcinoma

The histological examination of sections of in Serous Carcinoma tissue with H&E stain was appeared serous carcinoma revealed infiltrative growth of atypical endometrial with significant areas of typical solid epithelial growth, associated with intervening extensive areas of necrosis and hemorrhage, the growth forming trabeculae and complex papillary configuration lined by pleomorphic cellular and nuclear features, these tumors have a predilection for peritoneal spread, similar to primary ovarian serous adenocarcinoma. A papillary configuration is frequently present histologically, but these lesions may grow in a solid or acinar pattern.Papillae, when present, have fibrovascular cores that are lined by pleomorphic, hyperchromatic nuclei with eosinophilic macronucleoli (nuclear grade 3).Not infrequently, large, bizarre nuclei, often multinucleated, are observed. Cellular stratification and tufting or budding are frequently found (Fig. 9). Also, **(21)** described that tumor cells can appear discohesive, nuclei are typically high grade with pleomorphism, hyperchromasia, prominent nucleoli and frequent mitotic figures (including atypical mitotic figures), can be confined to an endometrial polyp as a small surface proliferation or completely effacing the polyp, background endometrium, if present, is often atrophic and not graded into low and high grade as done in the ovary but by default is a high grade carcinoma.

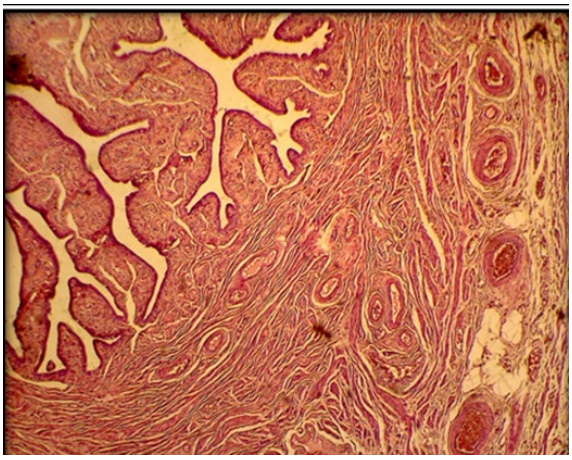


Figure 9. Serous Carcinoma with grade II and stage II tissue with H&E stain (4X).

3.2.1.3 Microscopical Structure of Endometrial Benign

A-Endometrial polyp

The histological examination of sections of benign endometrium tissues with H&E stain was appeared as cyclical endometrium, often secretory in type, reflecting the fact that an abundant secretory endometrium may have a polypoid appearance. Often, the gynecologist is not aware of the presence of a polyp. In such instances, fragments of polyp are often admixed with fragments of non-polypoid endometrium, making the diagnosis difficult, as the features can be subtle. On examination under low power, the initial clue to the presence of a polyp is often the admixture of fragments of a normal cyclical endometrium and fragments that are morphologically different, the stroma is generally more fibrous than in the surrounding endometrium. Other morphological features commonly found in polyps include collections of thick-wall stromal blood vessels, glandular architectural abnormality (often in the form of dilated glands with unusual shapes and focal crowding) and various epithelial metaplasias. The glands within a polyp often show proliferative activity, even when the surrounding endometrium does not (Figur10). This result was identical to the result of **(4)** found that the polyp are composed of benign-appearing epithelial (glandular) and stromal (fibroblastic) elements admixed with blood vessels, with variable ratios of the epithelial vs.

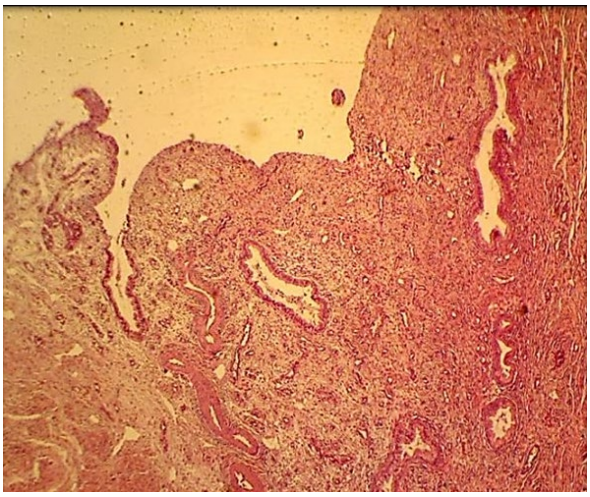


Figure 10. Endometrial polyp tissue with H&E stain (4X).

B-Leiomyoma endometrium

The histological examination of sections of leiomyoma endometrium tissue with H&E stain was appeared as noncancerous arising from uterine smooth muscle cells bundles and having middle typical nuclear changes and fibroblasts, they contain a large amount of extracellular matrix (including collagen, proteoglycan, fibronectin) and are surrounded by a thin pseudocapsule of areolar tissue and compressed muscle fibers (Figure 11 & 12). This result was identical to the result of **(15)** found that through microscopic histopathological examination pertaining to endometrial glandular and stromal changes, myometrial and leiomyomatous histopathological changes in terms of secondary changes, variants, nuclear atypia, mitosis, and coagulative necrosis.

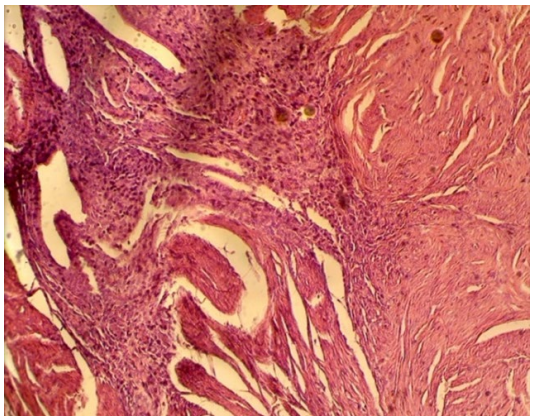


Figure 11. Endometrial polyp tissue with H&E stain (10X).

3.3 Expression of *HOXA11* in endometrium

3.3.1 HOXA11 gene expression for the three groups with endometrial patients

This Figure11 (3.32) indicated *HOXA11* expression in endometrial cancer and benign tumors patients in comparison with the control group. Expression the means of *HOXA11* (0.24±0.03) was reported in 15 cases of endometrial cancer of out of 45 endometrial patients, (0.94±0.06) in 20 cases of endometrial benign of out of 45 endometrial patients, (1.00±0.07) in 10 cases of endometrial control of out of 45 endometrial patients (Figure 12).

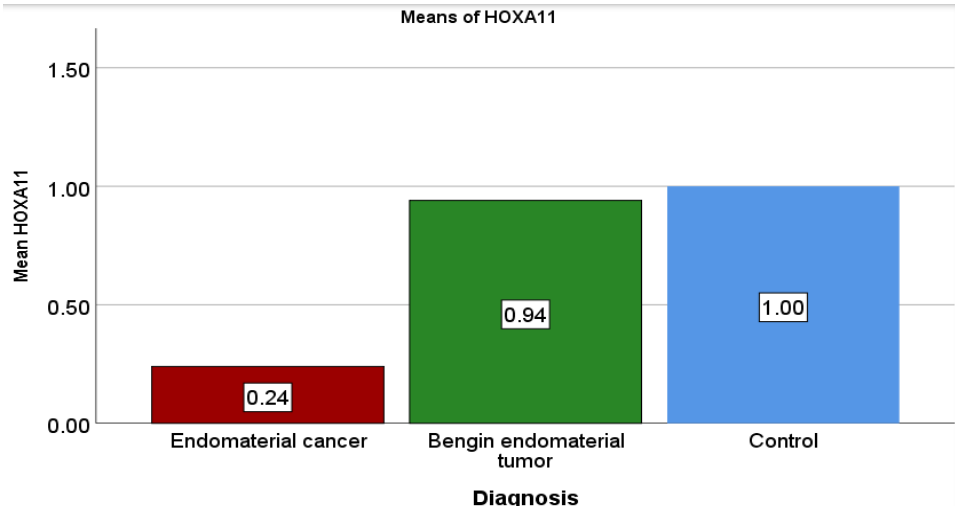


Figure 12. Means of HOXA11 gene expression for the three groups with endometrial patients.

These results showed the expression of the means *HOXA11* of three groups (cancer, benign and control) of endometrial patients. Patients with endometrial cancer had the lowest value mean (0.24±0.03) among the three groups, followed by the mean expression *HOXA11*in endometrial benign (0.94±0.06) and the higher value mean expression *HOXA11* for patients with endometrial control (1.00±0.07). Results of **(16)** showed that Low *HOXA11* expression may promote the proliferation, migration, invasion of endometrial cancer cells, and increase their resistance to cisplatin through activating PTEN/AKT pathway and showed that *HOXA11* expression was significantly down-regulated in endometrial cancer tissue samples, the overexpression of *HOXA11* promoted the apoptosis, but inhibited the proliferation, migration and invasion of endometrial cancer cells.

3.3.2 Mean difference in HOXA11 gene expression between endometrial cancer tumor and control patients.

Table (13) indicated the means expression *HOXA11*of endometrial cancer patients in comparison with the control group. The mean expression of *HOXA11* (0.24±0.03) was recorded with Standard deviation (0.03) in endometrial cancer patients and the mean expression of *HOXA11* (1.00±0.07) was recorded with Standard deviation (0.07) in endometrial control patients group Table (13).

Table 13. Mean difference in HOXA11 gene expression between endometrial cancer and control sample.

Group	Mean	Standard deviation	P-value
Endometrial cancer	0.24	0.03	<0.001
Control	1.00	0.07	

These results show a significant difference (P-value<0.001) was also seen in the means of *HOXA11* expression between patients with endometrial cancer and the control. Results showed that the methylation of *HOXA11* promoter has shown to decrease the mRNA level of *HOXA11*.Also, **(17)** explain that low *HOXA11*

expression enhanced the proliferation, migration, invasion, and cisplatin resistance of endometrial cancer cells, indicating that *HOXA11*, if down regulated, is a tumor-promoting factor.

3.3.3 Mean difference in HOXA11 gene expression between endometrial benign tumor and control patients.

Table (14) indicated the means expression *HOXA11* of endometrial benign patients in comparison with the control group. The mean expression *HOXA11* (0.94±0.06) was recorded with Standard deviation (0.06) in endometrial benign patients and the mean expression *HOXA11* (1.00±0.07) was recorded with Standard deviation (0.07) in endometrial control patients group.

Table 14. Mean difference in HOXA11 gene expression between endometrial benign tumor and control patients.

Group	Mean	Standard deviation	P-value
Endometrial benign tumor	0.94	0.06	0.021
Control	1.00	0.07	

These results regarding the values means of *HOXA11* expression and show a significant difference (P-value=0.021) was also seen in the means of *HOXA11* expression between patients with benign tumor and the control patients. Those patients with endometrial benign tumors had a lower value mean *HOXA11* expression (0.94±0.06) than the control group patients (1.00±0.07). Results of **(39)** showed that the possible mechanisms linking polyps to infertility are the release of chemicals or mechanical interference that may affect sperm motility or embryo implantation, and shown that inflammatory markers, glycodelin, and aromatase are increased in patients with endometrial polyps and levels of *HOXA-11*, which are responsible for endometrial receptivity, are decreased. Moreover, **(22)** found that Lower HOXA11 mRNA levels were observed in mid-secretory endometrial biopsies from women in the infertile group when compared to fertile controls; however, the difference failed to show statistical significance. Decreased HOXA11 expressions have been reported in the presence of submucosal leiomyomas.

3.3.4 Mean difference in HOXA11 gene expression between endometrial cancer and benign endometrial tumor patients.

Table 15 **(17)** indicates the means expression *HOXA11* of endometrial cancer tumor patients in comparison with endometrial benign tumor patients. The mean expression of *HOXA11* (0.24±0.03) was recorded with Standard deviation (0.03) in endometrial cancer patients and the mean expression of *HOXA11* (0.94±0.06) was recorded with Standard deviation (0.06) in endometrial benign patients.

These results regarding the values mean of *HOXA11* expression with endometrial cancer tumor patients (0.24±0.03) was also significantly (P-value <0.001) lower than the mean of *HOXA11* expression with benign endometrial tumor patients.

Table 15. Mean difference in HOXA11 gene expression between endometrial cancer and benign endometrial tumor patients.

Group	Mean	Standard deviation	P-value
Endometrial cancer	0.24	0.03	<0.001
Endometrial benign tumor	0.94	0.06	

Discussion

The lack of corpus luteum during perimenopause causes discontinuous ovulation and a drop in progesterone levels. Unhindered endogenous estrogen stimulation of the endometrium may cause endometrial hyperplasia and cancers. **(7)**. This result is agreed with the result of (8) who indicated that the age ranges at diagnosis were as follows: 6% less than 40 years, 6% (41–50) years, 25% (51–60) years, 42% (61–70) years and 21% over (70) years. Moreover, **(9)** reported that the mean age of diagnosis among the premenopausal group is (44.9+7.5) years old, which is significantly younger as compared to the postmenopausal group at (62.3 + 6.5) years.

This result in concordant with result **(10)** found that the mean age of the studied patients with endometrial cancer was (61.9 ±11.4) years, the maximum age of the patients was 78 years and the minimum age was 35 years and the most common age group of patients was 56-65 years and explain the age group of (56-65) years was the highest (36.1%), followed by the age group of (66-75) years was (26.2%), with a mean age group of 61.92 ±11.47 (35-78) years. Also, this result is agreed with (11) suggest that age ≥ 50 years old is a high-risk factor for the development of EC. This may due to increase in estrogen levels in the body caused by various reasons continuously stimulates the proliferation of

endometrial tissue and long-term estrogen exposure of the endometrium and the lack of progesterone antagonism **(9)**.

This result in concordant with result **(12)** found that Endometrioid adenocarcinomas (EEC) are the most frequent subtype and more common (≅ 80%) and EEC is very aggressive carcinomas compared with other types the less common clinically aggressive. Also, clear that Serous Endometrial Adenocarcinoma represents ~10% of all endometrial cancer diagnoses, it accounts for up to 39% of endometrial cancer related deaths **(13)**.

In addition, **(14)** showed that the mean age of patients was 55 years (range 45-74) for group 1 and was 56ys (range 43-75) for group2. Also, **(14)** explained that the mean age of the patients was 56 years (25–77 years), Endometrioid carcinoma was the commonest histological type (136 patients, 88%). Other histological cell types were clear cell carcinoma **(14)** 9%patients, papillary serous carcinoma **(3)**1.9%patients, and adenosquamous carcinoma **(2)** 1.2% patients.

This result matches **(15)** that endometrial cancer had 15 grade I tumors (33.33%), 23 grade II tumors (51.11%), and 7 grade III tumors (15.56%). Furthermore, **(14)** observed that preoperative abnormal tissue grading showed that 73.3 percent of patients were grade 1, 20% were grade 2, and 6.7% were grade 3 for both groups. The postoperative results showed some changes: 60% of patients were grade 1, 33.3% were grade 2, and 6.7% were grade 3. In group 2, 66.7% were grade 1, 20% were grade 2, and 13.3% were grade 3.

This matches result **(8)**, which identified 37.7% stage II and 31.1% stage III patients. Additionally, **(10)** demonstrated that the Premenopause subgroup (126) staging showed that 90(71.4%) of patients were stage 1, 18(14.3%) were stage 2, 15(11.9%) were stage 3, and 2(1.6%) were stage 4. Postmenopause subgroup (155) findings showed some changes: 133 (72.9%) patients were stage 1, 18 (11.6%) were stage 2, 14 (9.0%) were stage 3, and 4 (2.6%) were stage 4.

Results of Moreover, **(16)** explain that the none muscular invasion was 101 (98.06%) of 103 cases with premenopausal EC and was 101(89.38%) of 113 cases with postmenopausal EC, whereas the muscular invasion was 2 (1.94%) of 103 cases and was 12 (10.62%) of 113 cases with postmenopausal EC with (P-value= 0.079) in both cases. Moreover, **(17)** explains that in (EC) depth of myometrial invasion none or <50% was 50 (65.8%) cases and in myometrial invasion ≥ 50% was 26 (34.2%) cases.

Results of **(16)** show that none lymphatic metastasis was 102 (99.035%) of 103 premenopausal EC cases and 101 (89.38%) of 113 postmenopausal EC cases, while muscular invasion was 1 (0.97%) and 12 (10.62%) of 113 cases, with P (value= 0.003) in both cases. According to lymph node invasion was present in 26 (34.2%) EC patients and missing in 50 (65.8%). However, **(6)** found 20% (13 out of 63) and 14% (13 out of 92) lymph node metastases in high-grade and low-grade illness, respectively.

According to **(18)**, benign endometrial polyps were found in 5 age groups **(1-5)** with a 10-year interval. The study found that endometrial polyps were most common in groups younger than 60, with 60% of cases in 30-40, 47% in 41-50, 36% in 51-60, and 0% in 61-70 and >70 (P-value<0.0001).These findings align with a previous study **(19)**, which identified two sublayers of the endometrium: the basal layer connecting to the myometrium and the functional layer facing the uterine cavity.These results were consistent with **(20)**, findings that endometrioid adenocarcinoma cells grow in patterns similar to normal endometrium, with many new glands formed from columnar epithelium with abnormal nuclei and very close glands without stromal tissue. Also, **(22)** described that tumor cells can appear discohesive, nuclei are typically high grade with pleomorphism, hyperchromasia, prominent nucleoli and frequent mitotic figures (including atypical mitotic figures), can be confined to an endometrial polyp as a small surface proliferation or completely effacing the polyp, background endometrium, if present, is often atrophic and not graded into low and high grade as done in the ovary but by default is a high grade carcinoma. This result was identical to the result of **(4)** found that the polyp are composed of benign-appearing epithelial (glandular) and stromal (fibroblastic) elements admixed with blood vessels, with variable ratios of the epithelial vs. This result was identical to the result of **(16)** found that through microscopic histopathological examination pertaining to endometrial glandular and stromal changes, myometrial and leiomyomatous histopathological changes in terms of secondary changes, variants, nuclear atypia, mitosis, and coagulative necrosis. Results of **(17)** showed that Low HOXA11 expression may promote the proliferation, migration, invasion of endometrial cancer cells, and increase their resistance to cisplatin through activating PTEN/AKT pathway and showed that HOXA11 expression was significantly down-regulated in endometrial cancer tissue samples, the overexpression of HOXA11 promoted the apoptosis, but inhibited the proliferation, migration and invasion of endometrial cancer cells. Also, **(18)** explain that low HOXA11 expression enhanced the proliferation, migration, invasion, and cisplatin resistance of endometrial cancer cells, indicating that HOXA11, if down regulated, is a tumor-promoting factor. Results of (39) showed that the possible mechanisms linking polyps to infertility are the release of chemicals or mechanical interference that may affect sperm motility or embryo implantation, and shown that inflammatory markers, glycodelin, and aromatase are increased in patients with endometrial polyps and levels of HOXA-11, which are responsible for endometrial receptivity, are decreased. Moreover, **(23)** found that Lower HOXA11 mRNA levels were

observed in mid-secretory endometrial biopsies from women in the infertile group when compared to fertile controls; however, the difference failed to show statistical significance. Decreased HOXA11 expressions have been reported in the presence of submucosal leiomyomas.

Results of **(47)** evaluated that the expression levels of *HOXA11* in the eutopic endometrium (EU) was significantly lower in women with peritoneal endometriosis compared to the control group participants (P <0.05) and cleared expressed *HOXA11* at significantly lower levels in the eutopic endometrium (EU) than in the ectopic endometrium (EC), that is, in women with peritoneal endometriosis (P<0.05) in women with endometriosis. Moreover, **(22)** showed that expressions of each gene were evaluated using real-time reverse transcriptase polymerase chain reaction (RT-PCR), a trend toward decreased endometrial *HOXA-11*, was detected in both SM submucosal leiomyomas (SM), and Intramural leiomyomas (IM) groups before myomectomy when compared to both fertile group and septate uterus, and the differences failed to show statistical significance. After myomectomy of IM, we have detected (9.0-fold) increase in endometrial *HOXA-11* mRNA expression, this increase in endometrial *HOXA-11*mRNA expression was significant.

Conclusion

In this study, we endeavored to understand the differential gene expression patterns of *HOXA11* across varying states of endometrial tissue health, namely, endometrial cancer (EC), benign tumors, and normal controls. Our results have provided compelling insights into the potential roles these genes play in colorectal tumorigenesis and disease progression.

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Authors' Contribution

Each author participated in data analysis, drafting, and revising of the manuscript, and consented to assume responsibility for all aspects of this project.

Conflict of Interest

The authors declared no conflicts of interest.

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