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Original Research

The effect of age on prediction of concurrent endometrial cancer in patients with atypical endometrial hyperplasia

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Summary

Purpose: To evaluate the effect of age on prediction of concurrent endometrial cancer (EC) in patients with atypical endometrial hyperplasia (AEH). *Materials and Methods:* Medical data of 176 patients who were diagnosed with atypical endometrial hyperplasia and underwent surgical treatment enrolled the study group. Clinicopathological features, preoperative and postoperative information were collected. The age distrubition for patients with atypical endometrial hyperplasia and endometrial cancer were examined and stratified according to five-year age increments. *Results:* Concurrent endometrial cancer was detected in 35(19.8%) patients. atypical endometrial hyperplasia and lower grade hyperplasia (simple or complex) was found in 82(46.5%) and 27(15.3%) patients, respectively. Endometrial cancer was most frequently seen in 51-60 age group. Endometrial cancer in final pathology significantly increased (p = 0,0005) after the age of 53 with sensitivity of 65.52% and 76.67%. *Conclusion:* Endometrial cancer increases significantly after the age of 53 in patients with atypical endometrial hyperplasia. Based on this study it is recommended that clinicians shoud be aware of this knowledge while informing patients and planning treatment.

Key words: Age; Atypical endometrial hyperplasia (AEH); Endometrial cancer (EC).

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries [1]. The main risk factors for endometrial carcinoma are over expression of estrogen without adequate opposition by progestin, tamoxifen therapy, age, obesity, nulliparity, diabetes mellitus, familial syndromes and hypertension [2, 3]. There are two histological types of EC. Type I tumors comprise approximately 80% of endometrial carcinomas. These tumors typically have a favourable prognosis, are estrogen-dependent, and may be preceded by atypical endometrial hyperplasia (simple atypical hyperplasia, complex atypical hyperplasia), and intraepithelial neoplasm (atypical and/or simple-complex endometrial hyperplasia) [5]. Type II tumors account for 10- 20% of endometrial carcinomas. These tumors are often high-grade, have a poor prognosis, and not obviously associated with estrogen stimulation [5]. A precursor lesion is rarely identified [6]. Age is an important risk factor for EC. The mean age of EC patient is approximately 62 years [1, 2]. Most of the patients with EC are diagnosed above the age of 50 years [2, 3].

Endometrial hyperplasia is characterized by a proliferation of endometrial glands with irregular size and shape. There is an increase in the endometrial gland-to-stroma ratio [7]. Endometrial hyperplasia is divided into four groups according to 1994 WHO classification system. These are simple hyperplasia (SH), complex hyperplasia (CH), complex atypical hyperplasia (CAH), and simple atypical hyperplasia (SAH) [8, 9]. The WHO system has widely used this classification [8]. Women with atypical endometrial hyperplasia (AEH) may have coexistent endometrial carcinoma (EC) or may progress to carcinoma [9]. Patients with AEH are usually diagnosed in the premenopausal period [10]. Many previous studies have shown that postoperative EC detection rate varies between 10-59 % in patients with AEH [11-14].

To the best of the authour's our knowledge there are limited number of studies evaluating the distribution of AEH according to age groups and their association with EC. Moreover, there is lack of literature evaluating cut-off age for concurrent EC in patients with AEH. From this point of view, the authors hypothesized that increased age has a significant effect on the detection of EC in patients with AEH.

Materials and Methods

The medical data of 336 patients who were diagnosed with AEH by endometrial biopsy between the years 2007-to 2018 were evaluated retrospectively. Sixty of these patients had underwent medical treatment, 56 of them had suspicion of EC, and 44 patients had lack of medical data. Patients with suspected EC in preoperative endometrial biopsy, and patients with lack of medical data and who preferred medical progestin treatment for AEH were excluded from the study. One-hundred-seventy-six patients who underwent surgical treatment were included in the study. The study was conducted at university clinic and was approved by the medical ethics committee with the number 2018/295.

Clinicopathological features of the patients including age, gravida, parity, body mass index (BMI), and systemic

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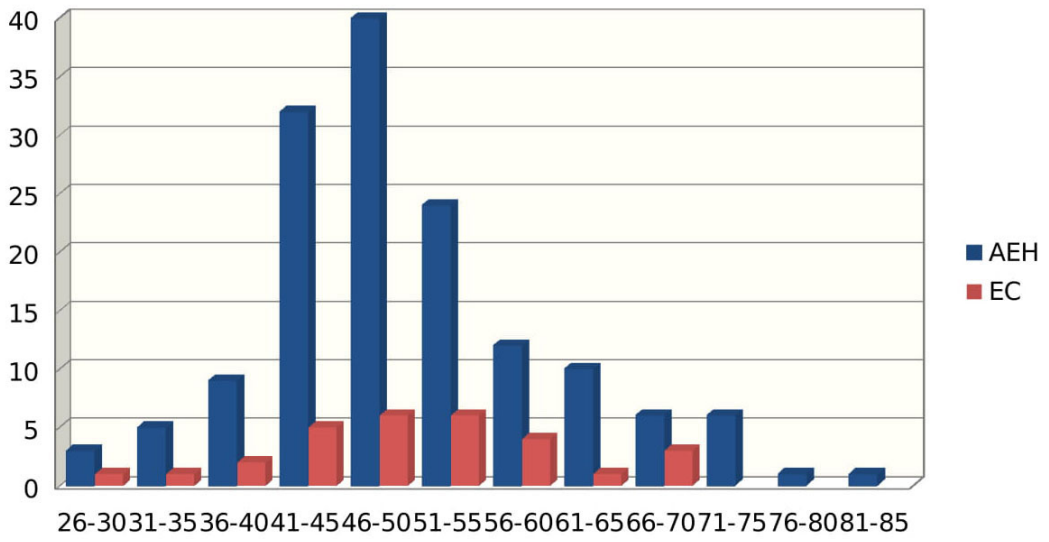

Figure 1. — Preoperative distribution of patients diagnosed as AEH and postoperative distribution of patients diagnosed as EC according to age groups. AEH: atypical endometrial hyperplasia, EC: endometrial cancer

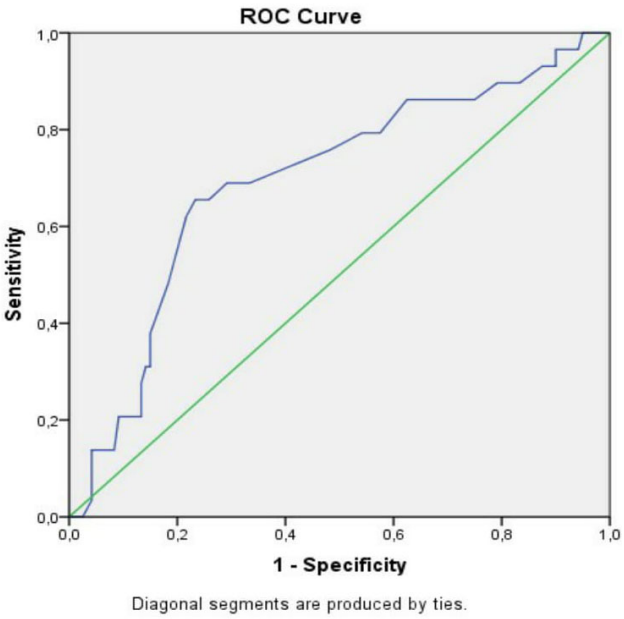

Figure 2. — ROC CURVE; The effect of age cariable on determination of endometrial cancer

diseases were evaluated. The age distrubition for patients with atypical endometrial hyperplasia and EC were examined and stratified according to five-year age increments. Endometrial biopsy procedures were performed in an outpatient setting with a pipelle and a 4-mm Karman cannula in patients with cervical patency. During the procedure, paracervical block was applied with 5-ml, 2% lidocaine. Patients who underwent cervical dilatation were treated with mild sedation in the operating room with 50 mg aldolan and 10 mg midazolam intravenously. Cervical dilatation was performed with 4-mm Hegar dilator and sampling with Karman cannula. Pathology specimens were examined by a pathologist specialized in gynecologic oncology. All patients who were diagnosed with AEH were informed about medical and surgical treatments. Consent was obtained from the patients for surgical treatment. Total hysterectomy and/or bilateral salpingo-oophorectomy was performed via laparotomy or laparoscopy according to the clinical features of the patients. The specimens were examined by the same pathologist and postoperative histopathological results were compared with preoperative diagnosis.

Table 1. — *Characteristic features (mean value) all patients n:176*

Gravidy (n)	2.82	Premenopausal n (%)	106 (%60.2)
Parity (n)	2.21	Postmenopausal n (%)	70 (%39.7)
Abortus (n)	0.71	DM n (%)	25 (%14.2)
Age (years) mean	50.4	HT n (%)	55 (%31.2)
BMI (kg/m^2)	32.67	Hypothyroidism n (%)	16 (%9.09)
Ca125 (IU/ml)*	16.56		

*BMI: body mass index, CA125: cancer antigen 125. *Normal range: 0-35 IU/mL, DM:diabetes mellitus, HT: hypertension*

Data was analyzed using SPSS 21 package program. Summary values of quantitative data are shown as mean or median (Q1-Q3). Summary values of qualitative variables are shown as frequency and percentage. The normal distribution of quantitative variables was investigated by Shapiro Wilk test. Quantitative comparisons of two groups were performed by Mann Whitney test. The recommended cut-off value for age was obtained by ROC curve analysis. Results with $p < 0.05$ were considered significant.

Table 2. — *Preoperative and postoperative diagnoses*

Preop diagnose \ Postop diagnose	No hyper-plasia	SH	SAH	CH	CAH	EC
SAH (n:37)	8	5	21	-	1	2
CAH (n:139)	24	5	5	17	55	33
Total (n:176)	32 (%18.1)	10 (%5.6)	26 (%14.7)	17 (%9.6)	56 (%31.8)	35 (%19.8)

SH: Simple hyperplasia, SAH: Simple atypic hyperplasia, CH: Complex hyperplasia, CAH: Complex atypic hyperplasia, EC: Endometrial cancer

Table 3. — *Characteristics of patients defined as AEH and EC according to final pathology . (median distribution features)*

	AEH (n:82)	EC (n:35)	*p*
Gravidy n (SD)	2 (1-4)	3 (2-4)	0.441
Parity n (SD)	2 (1-3)	2 (2-3)	0.17
Abortus n (SD)	0 (0-1)	0 (0-1)	0.53
Age years (SD)	48 (42-53)	55 (48-61)	**0.002**
BMI (kg/m^2)	30.5 (29-35)	34 (29-37)	0.59
Ca125 (IU/ml)*	12 (9-15)	13 (8-16)	0.863
Premenopausal n (%)	55 (67.07%)	11 (31%)	**0.032**
Postmenopausal n (%)	27 (32.9%)	24 (68%)	**0.029**

*BMI: body mass index, CA125: cancer antigen 125, *Normal range: 0-35 IU/mL, AEH: atypic endometrial hyperplasia, EC: Endometrial cancer*

Results

A total of 176 patients who were diagnosed as AEH with preoperative endometrial biopsy and underwent surgical treatment were included in this study. Preoperative diagnosis was CAH and SAH in 139 (78.9%) and 37 (21.02%) patients, respectively. The mean age of the patients was 50.4 years. Out of the total patients 106 (60.2%) premenopausal and 70 (39.7%) were postmenopausal. Eighty-six patients (48.8%) had a systemic disease. Demographic and clinical characteristics of the patients including age, gravida, parity, abortus, body mass index (BMI), Ca-125 level, menopausal status, and systemic disease are shown in Table 1. When patients were examined according to final pathology, they were categorized as no hyperplasia, simple hyperplasia, simple atypical hyperplasia, complex hyperplasia, complex atypical hyperplasia, and EC. Of the study group, final pathology revealed EC in 35 (19.8%) patients. Preoperative diagnosis of SAH and CAH was found to be more advanced in 3/37 (8.1%) and 33/139 (23.7%) patients, respectively. Comparison of pre- and postoperative diagnosis are shown Table 2.

According to final histopathological results when patients were classified as only AEH group (n = 82) and EC group (n = 35), premenapausal patients constituted 67.07% (n = 55) and 31% (n = 11) in patients with only AEH and EC, respectively, whereas postmenapausal patients composed of 32.9% (n = 27) and 68% (n = 24) in patients with only AEH and EC, respectively. Median age was significantly higher in patients with EC (p = 0.002). Patients characteristics according to their final pathology are shown in Table 3.

When patients are stratified according to five-year age increments, AEH was mostly diagnosed between 46-50 years age group (n = 49, 27.8%). Based on the final histopathological results EC was mostly diagnosed in 51-55, 56-60 years age groups (n = 8, 22.8% in each group). Age stratification, preoperative pathology, and patients diagnosed as EC are shown in Table 4 and Figure 1. According to the FIGO 2009 staging system EC Stage IA, Stage IB, and Stage II were diagnosed in 27 (77.1%), 4 (11.4%), and 4 (11.4%) patients, respectively. Eight (22.8%) patients underwent staging surgery due to local advanced disease.

Using the uni-multi variant tests for age, odds ratio (OR) for EC was 1.060 (1.018-1.103, 95% CL, Sig. 0.005). Using the ROC curve test for prediction of the concurent EC were found in the 53-year group. After the age of 53 EC probability in final pathology significantly increased (p = 0,0005), with sensitivity of 65.52% and 76.67% (Table 5, and Figure 2).

Discussion

In this study, the authors evaluated the distribution of the patients who were diagnosed as AEH and EC according to the age groups and found that EC probability increases significantly after the age of 53 in patients with AEH. There are very few studies examining AEH and EC according to distribution of age groups [10, 14, 15]. Reed *et al.* reported that the 60-64-year-old group is the peak age of patients with both AEH and EC [11]. In this study, AEH and EC were most commonly detected between 46-50 and 51-60 year age group, respectively. There are several reasons why the results of Reed *et al.* study are different from the present study. AEH and EC incidence rates may vary between countries and races [10, 11, 14, 16]. In addition, no information was presented regarding postmenopausal hormonal therapy and obesity in Reed *et al.* study. In this study [10], patients between 1985 and 2003 were evaluated and postmenopausal hormone therapy was widely used during this period. Obesity rates vary depending on the level of development among countries. The difference between this study and the present study may be attributed to these reasons. Another incidence from Asia reported that AEH and EC was most commonly detected between 46-50 and 51-60-year age groups, respectively [15]. The results of

Table 4. — *Preoperative distribution of patients diagnosed as AEH and postoperative distribution of patients diagnosed as EC accordingto age groups.*

Diagnosis Age groups													
	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80	81-85	total
AEH frequency	3	6	11	39	49	29	14	11	6	6	1	1	n:176
AEH Percent%	1.7	3.4	6.2	**22.1**	**27.8**	**16.4**	7.9	6.2	3.4	3.4	0.5	0.5	100
EC Frequency	-	1	1	2	6	8	8	5	1	3	-	-	n:35
EC percent%	-	2.8	2.8	5.7	**17.1**	**22.8**	**22.8**	**14.2**	2.8	8.5	-	-	100

AEH: atypic endometrial hyperplasia, EC:Endometrial cancer

Table 5. — *Roc curve; The effect of age variable on determination of endometrial cancer*

Area under the ROC curve	0.695
Significance level p (Area = 0.5)	0.0005
Associated criterion	> 53
Sensivitiy	65.52
Spescivity	76.67

the present study seems compatible with this study. Antonsen SL *et al.* reported the peak age range of AEH was 45-49 years and the peak age range of EC was 70-74 years and, EC increased over 50 years of age [14]. Many studies in the literature presented that increased age is an independent risk factor for AEH and EC [1-7, 9, 11-14,16]. In the present study, odds ratio (OR) for EC was found to be 1.060 (1.018-1.103, 95% CL, sig. 0.005) in accordance with the literature. The present authors found a seven-year difference between mean ages of AEH and EC (48 and 55 years).

Many studies in the literature revealed the relationship between the presence of concurent EC and AEH in postmenopausal period [11-13]. The finding that differentiates this study from the other studies is that the concurrent EC increased after the age of 53 years, with 65.52% sensitivity and 76.67% specificity in patients with AEH. The current authors have previously reported the mean menapausal age range to be 47-50 years in Anatolia region [17]. Therefore, with many other risk factors, 53-years-olds may allow time for EC to develop. Concurrent EC detection rate in the literature was very wide (10-59%) [11-21] and in the present study, the authors found a concurrent EC detection rate as 19.8% in patients with AEH consistent with many studies [16-19]. The differences between these studies and present work can be attributed to various reasons including demographic characteristics, the number of patients in the study, the average age, the number of patients who received hormonal therapy after menopause, and BMI. In addition, difficulty in the pathologic diagnosis of EH and EC may also help explain the differences between studies [6, 12, 22].

The present study has some restrictive aspects. Firstly, the present study was designed retrospectively. Due to the nature of this study, some patient's characteristics could not be evaluated that could be a risk factor for AEH and EC, as postmenopausal hormonal therapy, familial history of cancer, and tamoxifen use. Secondly, study included patients with AEH who underwent surgical treatment. Therefore, the data of some patients with AEH who received only medical treatment are missing. This situation is negative aspect of this study.

As a result, risk factors must be well-evaluated in order to prevent deficiency or over-treatment in patients with AEH. It should be kept in mind that patients with AEH are more likely to be seen in the premenopausal period and patients with EC are more likely to be seen in the postmenopausal period. In conclusion, EC probability increases significantly after the age of 53 in patients with AEH and clinicians shoud be aware of this knowledge while informing patients and planning treatment.

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Conflict of interest

The authors declare that they have no conflict of interest.

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