Journal of Cytology & Histology
ISSN: 2157-7099

Osogami et al., J Cytol Histol 2016, 7:1
DOI: 10.4172/2157-7099.1000386

Research Article Open Access

Preoperative Cervical Cytology and E-Cadherin Expression in Endometrial Cancer

Osogami H, Tanaka R*, Suzuki T, Tamate M, Habata S, Sugio A, Matsuura M, Iwasaki M and Saito T

Department of Obstetrics and Gynecology, Sapporo Medical University School of Medicine, Sapporo, Japan

Abstract

Objective: It is reported that cervical cytology is a significant factor related to stage, tumor grade, nodal metastasis, recurrence and survival rate in endometrial cancer. Moreover, reduced expression of the cell adhesion molecule E-cadherin is associated with higher tumor grade and metastasis in endometrial cancer. The objective of this study is to evaluate the relationship between the results of cytological assessment of glandular cells in cervical cytology before surgery, prognostic factors, and E-cadherin expression in endometrial cancer.

Methods: Between 2004 and 2011, 263 patients with endometrial cancer at all stages were treated with hysterectomy. We reviewed preoperative cervical smears and assigned each to one of three categories: (1) Negative, (2) Atypical glandular cells (AGC), and (3) Adenocarcinoma (AC). The relationship of these cytology, prognostic factors, and E-cadherin expression was evaluated.

Results: Statistical significance in overall survival was shown for preoperative cervical cytology, age, surgical stage, histological type, tumor grade, myometrial invasion, cervical involvement, lymph node metastasis except peritoneal cytology. Patients with AC cytology were more likely than those with normal cervical cytology to have a higher International Federation of Gynecology and Obstetrics (FIGO) stage, poorer histopathology, higher tumor grade, deeper myometrial invasion, higher incidence of cervical involvement, and higher prevalence of lymph node metastasis. In addition, AC and AGC cytology appeared to be associated with a poorer prognosis and to have lower E-cadherin expression than negative cytology.

Conclusions: Cervical cytology may be a guide to prognosis in endometrial cancer, and E-cadherin expression may correlate with appearances of abnormal endometrial cells.

Keywords: Cytology; E-cadherin; Endometrial cancer; Prognosis

Introduction

Endometrial cancer is the most frequently diagnosed gynecological malignancy in the United States, with an estimated 43,470 new cases diagnosed in 2010 [1]. In Japan, endometrial cancer is currently the fourth most common gynecologic malignancy, with an estimated incidence of 6,665 new cases in 2010 [2]. Notably, however, the Japan Society of Obstetrics and Gynecology (JSOG) reported that endometrial cancer increased from 976 cases in 1983 to 4267 in 2005 and 6113 in 2009, and accounted for about half of all cases of malignant uterine disease [3]. The estimated 5-year overall survival for early-stage endometrial carcinoma is 82% but decreases remarkably to 67% for regional disease and 16% for distant disease. Although the majority of patients (approximately 83%) are diagnosed as having stage I or II disease, those with advanced-stage endometrial carcinoma have poor prognosis [4]. The treatment of endometrial cancer is primarily based on surgery, consisting of hysterectomy and bilateral salpingo-oophorectomy. There is no worldwide consensus whether pelvic and/or para-aortic lymphadenectomy should be performed as part of the staging procedure [5,6]. For endometrial cancer patients, the expensiveness of surgery depends on the presence of risk factors for metastatic disease, like high tumor grade, deep myometrial invasion, and cervical involvement [6]. However, preoperative assessment of these factors remains a challenge. Therefore, to predict prognosis in patients with endometrial cancer before surgery is important to evaluate the indications of therapies appropriately.

The Papanicolaou cervicovaginal test (Pap test) was designed to screen for squamous pathology of the cervix. In that regard, it has been a resounding success for decades. Often, moreover, atypical endometrial cells are also present incidentally on Pap tests. This provides cytopathologists with an opportunity to examine these cells in specimens obtained for other reasons, sometimes raising suspicion of significant abnormalities of the endometrium that otherwise may have gone undetected. Atypical glandular cells (AGC) represent a diagnostic category with features suggestive of adenocarcinoma but which are not sufficient for a definitive diagnosis in the Bethesda System (TBS) 2001 [7]. It has been reported that 3 - 32% of patients diagnosed with AGC have endometrial cancer, moreover the reported rates of AC cytology among patients with endometrial cancer range from 11% to 31% [8-11]. Pap test himself noted long ago that the vaginal smear method is not as accurate for diagnosing carcinoma of the fundus as it is for diagnosing carcinoma of the cervix [12]. Nevertheless, cervical cytology is a significant factor related to stage, tumor grade, nodal metastasis, recurrence and survival rate in endometrial cancer [10,11,13].

E-cadherin is one of the caretakers of the epithelial phenotype and is responsible for stable cell-cell contacts and adherens junctions. There is a direct correlation between lack of E-cadherin and loss of the epithelial phenotype [14]. Previous studies showed that reduced expression of

***Corresponding author:** Tanaka R, Department of Obstetrics and Gynecology, Sapporo Medical University School of Medicine, South 1 West 16, Chuo-ku, Sapporo, 060-8543 Japan, Tel: +81-11-611-2111; Fax: +81-11-614-0860; E-mail: rtanaka@sapmed.ac.jp

Received November 03, 2015; **Accepted** January 03, 2016; **Published** January 05, 2016.

Citation: Osogami H, Tanaka R, Suzuki T, Tamate M, Habata S, et al. (2016) Preoperative Cervical Cytology and E-Cadherin Expression in Endometrial Cancer. J Cytol Histol 7: 386. doi:10.4172/2157-7099.1000386

the cell adhesion molecule E-cadherin is associated with higher tumor grade and metastasis in endometrial cancer [15].

The objective of this study is to evaluate the relationship between the results of cytological assessment of glandular cells in cervical cytology before surgery, prognostic factors, and E-cadherin expression in endometrial cancer.

Materials and Methods

Specimens

Between January 2004 and December 2011, 263 patients with endometrial carcinoma at all stages were treated with hysterectomy in Sapporo Medical University. None of these patients had received any form of tumor-specific therapy before surgical excision. Before surgical treatment, cervical specimens were collected from all patients, and cervical cytology was examined. We reviewed these cervical smears and assigned each to one of three categories: (1) Negative, (2) Atypical glandular cells (AGC), and (3) Adenocarcinoma (AC).

Immunofluorescence

The cells collected from cervix were fixed with cold acetone on the slides. The fixed tissue cells were pre-incubated with a blocking solution (PBS containing 5% skimmed milk) for 30 min at room temperature incubated with anti-E-cadherin (Clone No., HECD-1; Takara) diluted 1:500 for 2 h, and washed in PBS. FITC-conjugated anti-mouse immunogloblin diluted 1:200 in PBS was then added (Dakopatts, Copenhagen, Denmark) and the slides were incubated for 1 h. After incubation with secondary antibodies, the slides were washed in PBS, mounted in fluorescent mounting medium (Dakopatts) and examined by immunofluorescent microscopy (Nikon, Tokyo).

Tissue samples

One hundred eighteen specimens of these patients with endometrial adenocarcinoma were selected for immunohistochemistry. The specimens were formalin-fixed, paraffin-embedded and then cut into 1- to 2-μm-thick sections for H&E and immunohistochemical staining.

Immunohistochemistry

Tissue sections for immunohistochemistry were deparaffinized in xylene for 10 minutes, fixed in 100% ethanol for 5 minutes, and then rehydrated through a graded ethanol series. Thereafter, heat-induced epitope antigen retrieval was accomplished by immersing the sections in Target Retrieval Solution (Dako) and heating them at 100°C for 20 minutes using microwave irradiation. The sections were then incubated in Peroxidase-Blocking Solution for 10 minutes to quench endogenous peroxide activity, after which they were washed twice with phosphate-buffered saline (PBS) and incubated with the primary antibody for 40 minutes at room temperature. The primary antibodies used were rabbit anti-E-cadherin (1:400 dilution; 24E10, Cell Signaling). The sections were then rinsed twice with PBS, incubated with the corresponding secondary antibody for 30 minutes at room temperature, washed again with PBS, and incubated for 5 minutes with Dab + Substrate Buffer (Dako). Finally, the slides were counterstained with 10% hematoxylin and photographed using a microscope equipped with a digital camera. Cells positive for anti-E-cadherin antibody displayed brownish granules on their membrane.

Immunohistochemical evaluation

Two independent observers (HO and RT) blinded to the clinical outcome evaluated E-cadherin staining using a semiquantitative formula: intensity score × proportion (0.0-1.0). The intensity score was defined as follows: negative staining (0), faint staining (1), moderate staining (2), and strong staining (3). In brief, the calculation formula is (0 × proportion + 1 × proportion + 2 × proportion + 3 × proportion), and the total score ranges from 0 to 3.0.

Statistical analysis

The clinical characteristics of the study population were summarized using descriptive statistics. Correlations between the cervical cytology, patient age, histologic parameters and E-cadherin staining were assessed using the t test or ^{2} test. Multivariate logistic regression analysis was performed to determine clinical factors associated with AC. Survival rates were estimated by Kaplan-Meier analysis. The log-rank test was used to compare survival curves. All statistical tests were performed using SPSS version 20.0 software (Tokyo, Japan), and 2-tailed p values <0.05 were considered statistically significant.

Results

The mean age of the patients was 59.5 years, with a range of 30 to 87 years. Examination of the cervical cytology revealed that of the 263 patients with endometrial carcinoma, 136 (51.7%) were Negative, 64 (24.3%) had AGC, and 63 (24.0%) had AC; 188 cases (71.5%) were surgical stage I, 28 (10.6%) were stage II, 37 (14.1%) were stage III, and 10 (3.8%) were stage IV. Histologic subtypes included 245 (93.2%) endometrioid adenocarcinomas (108 International Federation of Gynecology and Obstetrics (FIGO) grade 1, 93 grade 2 and 44 grade 3), 9 serous adenocarcinomas, and 9 others; 177 patients (67.3%) had less than 50% myometrial invasion, 86 (32.7%) had greater than 50%, 45 (17.1%) had cervical involvement, and 16 (6.1%) had positive peritoneal cytology. Pelvic or para-aortic lymphadenectomy was performed on all stage I-III patients and on 4 of the 10 stage IV patients. 27 (10.5%) of the 257 patients receiving lymphadenectomy showed pelvic or para-aortic lymph node metastasis. Univariate analysis of the value of various clinicopathological factors including preoperative cervical cytology in relation to overall survival is shown in Table 1. Table 1 contains exact

	N=263	HR* (95% CI)	p value
Cervical cytology			
Negative	136	1.000	
AGC	64	2.648 (1.044-6.715)	0.040
AC	63	5.280 (2.295-12.150)	<0.001
Age			
<50 years	46	1.000	
≧50 years	217	7.400 (1.014-54.016)	0.048
Stage			
I, II	216	1.000	
III, IV	47	12.689 (6.330-25.437)	<0.001
Histological type			
Endometrioid	245	1.000	
Others	18	9.375 (4.732-18.571)	<0.001
(containing serous)			
Grade			
G1,2	201	1.000	
G3	44	3.336 (1.443-7.712)	0.026
Myometrial invasion			
< 50%	177	1.000	
≧ 50%	86	9.397 (4.115-21.459)	<0.001
Cervical involvement			
Negative	218	1.000	
Positive	45	4.707 (2.435-9.100)	<0.001
Lymph node metastasis			

Negative	230	1.000	
Positive	27	16.880 (8.327-34.216)	<0.001
Peritoneal cytology			
Negative	247	1.000	
Positive	16	2.168 (0.767-6.133)	N.S†
* Hazard Ratio † not significant			

Table 1: Univariate analysis of cervical cytology and prognostic factors in overall survival.

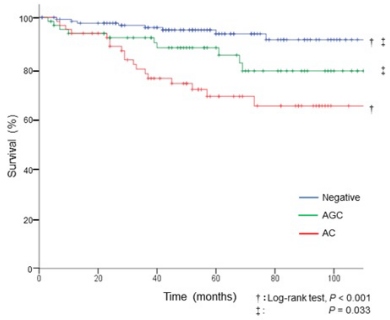

Figure 1: Kaplan-Meier analysis of overall survival for patients with each cervical cytology. Overall survival was significantly longer in Negative than AC ($p < 0.001$) and AGC ($p = 0.033$) using Log-rank test

	Cervical cytology			
Clinicopathologic Findings (N (%))	**Negative 136(51.7)**	**AGC 64(24.3)**	**AC 63(24.0)**	**p value (Negative vs AC)**
Age				
<50 years	25(54.3)	12(26.1)	9(19.6)	
≧50 years	111(51.2)	52(24.0)	54(24.9)	N.S. †
Stage				
I, II	120(55.6)	56(25.9)	40(18.5)	
III, IV	16(34.0)	8(17.0)	23(48.9)	<0.001
Histological type				
Endometrioid	132(53.9)	60(24.5)	53(21.6)	
Serous	2(22.2)	1(11.1)	6(66.7)	
Others	2(22.2)	3(33.3)	4(44.4)	0.003
Grade				
G1,2	117(58.2)	45(22.4)	39(19.4)	0.016 ‡
G3	15(34.1)	15(34.1)	14(31.8)	0.011
Myometrial invasion				
>50%	101(57.1)	43(24.3)	33(18.6)	
≧50%	35(40.7)	21(24.4)	30(34.9)	0.004
Cervical involvement				
Negative	123(56.4)	54(24.8)	41(18.8)	
Positive	13(28.8)	10(22.2)	22(48.9)	<0.001
Lymph node metastasis				
Negative	125(54.3)	58(25.3)	47(20.4)	
Positive	8(29.6)	4(14.8)	15(55.6)	0.001
Peritoneal cytology				
Negative	130(52.6)	61(23.5)	56(22.7)	
Positive	6(37.5)	3(18.8)	7(43.8)	N.S. †
†; Not significant, ‡; Negative vs. AGC				
Multivariate logistic regression analysis				
	OR	(95% CI)	p value	
Stage (III, IV vs. I, II)	4.496	(2.012-10.049)	<0.001	
Cervical involvement	4.148	(1.839-9.353)	<0.001	

Table 2: Relationship between preoperative cervical cytology and clinicopathologic findings.

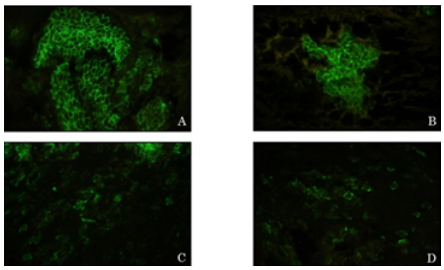

Figure 2: (A) Negative-Localization of E-cadherin is along plasma membrane. (B) AGC: E-cadherin appeared to be diffusely distributed along the cell-cell contacts. (C,D). AC: E-cadherin was diffused into cytoplasm and E-cadherin expression was decreased. (Representative images of immunostaining for E-cadherin (green); ×200)

values of Hazard ratio (HR) results from proportional hazard regression, together with exact values of designated probablility and 95% concfidence interval (CI). Statistical significance in overall survival was shown for preoperative cervical cytology, age, surgical stage, histological type, tumor grade, myometrial invasion, cervical involvement, lymph node metastasis except peritoneal cytology in this study.

Figure 1 shows Kaplan-Meier analysis of overall for patients with each cervical cytology (Negative, AGC, or AC). Overall survival was significantly longer in Negative than AC ($p < 0.001$) and AGC ($p = 0.033$) using Log-rank test.

Table 2 summarizes the results of the preoperative cervical cytology (Negative, AGC, and AC with Pap smears) and clinicopathologic findings. No significant correlation was found between the patients' age and Pap smear findings. Of the 216 patients with FIGO stage I or II, 120 (55.6%) had Negative cytology and 40 (18.5%) had AC, whereas among the 47 patients with FIGO stage III or IV, 16 (34.0%) were Negative and 23 (48.9%) had AC ($p < 0.001$). Of the 245 patients with endometrioid type disease, 132 (53.9%) were Negative and 53 (21.6%) had AC, whereas among the 18 patients with non-endometrioid type disease, 4 (22.2%) were Negative and 10 (55.6%) had AC ($p = 0.003$). Of the 201 patients with Grade 1 or 2 endometrioid type, 45 (22.4%) had AGC and 39 (19.4%) had AC, whereas among the 44 patients with Grade 3, 15 (34.1%) had AGC ($p = 0.016$) and 14 (31.8%) had AC ($p = 0.011$). Of the 177 patients with less than 50% myometrial invasion, 101 (57.1%) were Negative and 33 (18.6%) had AC, whereas among the 86 patients with deeper myometrial invasion, 35 (40.7%) were Negative and 30 (34.9%) had AC ($p = 0.004$). Of the 218 patients without cervical involvement, 123 (56.4%) were Negative and 41 (18.8%) had AC, whereas among the 45 patients with cervical involvement, 13 (28.8%) were Negative and 22 (48.9%) had AC ($p < 0.001$). Of the 230 patients without lymph node metastasis, 125 (54.3%) were Negative and 47 (20.4%) had AC, whereas among the 27 patients with metastasis, 8 (29.6%) were Negative and 15 (55.6%) had AC ($p = 0.001$). No significant association was found between the cervical cytological findings and the patients' age or peritoneal cytological findings. On multivariate analysis, the only significant variable associated with AC were stage (OR = 4.496, 95%CI: 2.012-10.049) and cervical involvement (OR = 4.148, 95%CI: 1.839-9.353). There was no association with age, histological type grade, myometrial invasion, lymph node metastasis, or peritoneal cytology.

Figure 2 showed that Localization of E-cadherin is along plasma membrane in Negative (Figure 2A), however E-cadherin-specific fluorescenece appeared to be diffusely distributed along the cell-cell contacts in AGC (Figure 2B), moreover E-cadherin was diffused into cytoplasm and E-cadherin expression was decreased in AC (Figures 2C and 2D).

	Cervical cytology			
Expression score	**Negative N=53**	**AGC N=32**	**AC N=29**	**p value**
E-Cadherin				
0.00 - 0.19	15	9	13	
0.20 - 0.99	12	17	9	
1.00 - 3.00	26	6	7	
Average	0.926	0.594	0.497	0.008† 0.015‡
T-test was performed. †: Negative vs AC ‡: Negative vs AGC-EM				

Table 3: Relationship between preoperative cervical cytology and E-cadherin expression.

In addition, Table 3 summarizes the relationship between the cervical cytology and immunohistochemical detection of E-cadherin in region of endometrial carcinoma (Figure 2). Expression score of E-cadherin immunohistochemistry was each 0.926, 0.594 and 0.497 in Negative, AGC and AC and the score of AC and AGC was significantly high compared with Negative ($p = 0.008$ and 0.015).

Discussion

Among patients with endometrial cancer, the reported rates of negative cervical cytology range from 41% to 56%, while those for AC range from 11% to 31% [8-11]. Among the patients in the present study, 51.7% showed negative cervical cytology and 24.0% showed AC. The 2001 Bethesda System terminology has incorporated changes to the reporting of glandular abnormalities to better reflect current knowledge and understanding of glandular neoplasia in cervical cytology, improve communication among laboratories and clinicians, and thereby facilitate appropriate management of patients. The Bethesda interpretation of Atypical glandular cells defines an increased level of risk, as opposed to a specific neoplastic precursor entity [7]. In most studies which investigated relation between cervical cytology and prognostic factor in endometrial cancer, cervical cytology is classified as Normal or Abnormal. However, we used an AGC cytology category quoted from TBS 2001 in this study. Overall survival was significantly longer and Expression score of E-cadherin immunohistochemistry was significantly higher in Negative than AGC. In addition, more patients with Grade 1 or 2 has AGC compared with AC. These suggest that AGC should be distinguished from Negative or AC when prognosis of endometrial cancer is investigated.

Many studies have focused on the potential for cervical cytology to serve as a predictor of clinical parameters for endometrial cancer [11]. As compared to patients with negative preoperative cervical cytology, those with positive cervical cytology tend to be older [16] and have a higher FIGO stage [8,10, 17,18], poorer histopathology [8,18], higher tumor grade [8,10,17,19], deeper myometrial tumor invasion [8,10], higher incidence of cervical involvement [8,18-20] and extrauterine spread, including positive peritoneal washing [10,21] and lymph node metastasis [8,18]. Our study similarly demonstrated that patients with AC were more likely than Negative to have poorer prognostic indicators, including a higher FIGO stage, poorer histopathology, higher tumor grade, deeper myometrial invasion, higher incidence of cervical involvement, and higher prevalence of lymph node metastasis except patient's age and positive peritoneal washing. In addition, AC cytology appears to be associated with a poorer prognosis than negative cytology ($p < 0.001$).

Prognosis in endometrial cancer is associated with clinical or pathological features, cell morphology, protein expression, and genetic alterations. For endometrial cancer, inactivating mutations in PTEN and activating mutations in KRAS and PIK3CA have been reported to occur in 30-50, 10-30, and 30- 40% of endometrial cancers, respectively [22]. Furthermore, mutations or over expressions of genes involved in these pathways have been associated with invasion metastasis, and prognosis of a variety of cancers, including endometrial cancer [23]. The PI3K/PTEN/AKT/mTOR pathway further interacts with the estrogen receptor at multiple levels, supporting potential crosstalk between estrogens and the PI3K pathway [24,25]. The RAS/RAF/MEK pathway is involved in a variety of essential tumorigenic functions including angiogenesis, cell cycle regulation, proliferation, and survival [26]. Cell-cell adhesion participates in histogenesis and plays a critical role in the establishment and maintenance of cell polarity and cell society. Reduced cell-cell adhesiveness allows cancer cells to disobey the social order, resulting in destruction of the histologic structure, the morphologic hallmark of malignant tumors. In cancers in vivo, particularly the diffuse type, tumor cells are dissociated throughout the entire tumor mass, lose their cell polarity, and infiltrate the stroma in a scattered manner [27]. Consistent with this concept, immunohistochemical studies have revealed that decreased E-cadherin expression is associated with tumor differentiation and progression in endometrial carcinoma [28]. This study showed that in endometrial cells collected from the cervix, localization of E-cadherin was along plasma membrane in Negative, was diffusely distributed along the cell-cell contacts in AGC, and E-cadherin was diffused into cytoplasm and E-cadherin expression was decreased in AC.

We previously reported that HEC-1A cells (moderately differentiated endometrioid cancer cells) show weaker cell adhesion and are more invasive than Ishikawa cells (well-differentiated endometrioid cancer cells) in 3D co-cultures of endometrial cancer cells and fibroblasts with human collagen sponges [29]. Moreover, our previous study showed that decreased expression of E-cadherin in endometrioid adenocarcinoma was associated with tumor dedifferentiation and myometrial invasion, and hypermethylation in the promoter region of the E-cadherin gene was correlated with tumor progression, tumor dedifferentiation, and the depth of myometrial invation [30]. Cellular changes resulting in a more mesenchymal-like state driven by a pathological Epithelial-mesenchymal transition (EMT) program in tumors are thought to play a significant role in carcinoma progression and are associated with a poor prognosis. The central target of EMT signaling pathways is repression of E-cadherin expression, which represents an important molecular change affecting tumor progression and metastasis [31]. In the present study, we detected the significant difference between Negative and AGC or AC with respect to E-cadherin immunohistochemistry, therefore suggest that E-cadherin is related with cytological findings in endometrial cancer.

In summary, we found that

1. Patients with AGC or AC cytology was significantly poorer prognosis than Negative.
2. AC cytology is associated with several prognostic factors and AGC is associated with tumor grade.
3. E-cadherin expression is weaker in patients with AGC and AC cytology than Negative. We reported the association between cervical cytology and E-cadherin expression, however these results may indicate only small proportion because E-cadherin concerns various parts in endometrial cancer.

References

1. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics. CA Cancer J Clin 60: 277-300.

2. Nakamura K, Kodama J, Hongo A, Hiramatsu Y (2012) Role of emmprin in endometrial cancer. BMC Cancer 12: 191.
3. Banno K, Nogami Y, Kisu I, Yanokura M, Umene K, et al. (2013) Candidate biomarkers for genetic and clinicopathological diagnosis of endometrial cancer. Int J Mol Sci 14: 12123-12137.
4. Sato N, Takagi K, Suzuki T, Miki Y, Tanaka S, et al. (2014) Immunolocalization of corticotropin-releasing hormone (CRH) and its receptors (CRHR1 and CRHR2) in human endometrial carcinoma: CRHR1 as a potent prognostic factor. Int J Gynecol Cancer 24: 1549-1557.
5. Mariani A, El-Nashar SA, Dowdy SC (2010) Lymphadenectomy in endometrial cancer: which is the right question? Int J Gynecol Cancer 20: S52-54.
6. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): A randomised study. Lancet 373: 125-136.
7. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, et al. (2002) The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 287: 2114-2119.
8. Fukuda K, Mori M, Uchiyama M, Iwai K, Iwasaka T, et al. (1999) Preoperative cervical cytology in endometrial carcinoma and its clinicopathologic relevance. Gynecol Oncol 72: 273-277.
9. Gu M, Shi W, Barakat RR, Thaler HT, Saigo PE (2001) Pap smears in women with endometrial carcinoma. Acta Cytol 45: 555-560.
10. DuBeshter B, Deuel C, Gillis S, Glantz C, Angel C, et al. (2003) Endometrial cancer: the potential role of cervical cytology in current surgical staging. Obstet Gynecol 101: 445-450.
11. Thrall M, Kjeldahl K, Gulbahce HE, Pambuccian SE (2007) Liquid-based Papanicolaou test (SurePath) interpretations before histologic diagnosis of endometrial hyperplasias and carcinomas: study of 272 cases classified by the 2001 Bethesda system. Cancer 111: 217-223.
12. Papanicolaou GN, Traut HF (1943) Diagnosis of Uterine Cancer by the Vaginal Smear. New York, The Commonwealth Fund.
13. Brown AK, Gillis S, Deuel C, Angel C, Glantz C, et al. (2005) Abnormal cervical cytology: a risk factor for endometrial cancer recurrence. Int J Gynecol Cancer 15: 517-522.
14. Hipp S, Walch A, Schuster T, Hofler H, Becker KF (2008) Precise measurement of the E-cadherin repressor Snail in formalin-fixed endometrial carcinoma using protein lysate microarrays. Clin Exp Metastasis 25: 679-683.
15. Blechschmidt K, Kremmer E, Hollweck R, Mylonas I, Hofler H, et al. (2007) The E-cadherin repressor snail plays a role in tumor progression of endometrioid adenocarcinomas. Diagn Mol Pathol 16: 222-228.
16. Cherkis RC, Patten SF, Dickinson JC, Dekanich AS (1987) Significance of atypical endometrial cells detected by cervical cytology. Obstet Gynecol 69: 786-789.
17. Schneider ML, Wortmann M, Weigel A (1986) Influence of the histologic and cytologic grade and the clinical and postsurgical stage on the rate of endometrial carcinoma detection by cervical cytology. Acta Cytol 30: 616-622.
18. Larson DM, Johnson KK, Reyes CN, Broste SK (1994) Prognostic significance of malignant cervical cytology in patients with endometrial cancer. Obstet Gynecol 84: 399-403.
19. Lozowski MS, Mishriki Y, Solitare GB (1986) Factors determining the degree of endometrial exfoliation and their diagnostic implications in endometrial adenocarcinoma. Acta Cytol 30: 623-627.
20. Zuna RE, Erroll M (1996) Utility of the cervical cytologic smear in assessing endocervical involvement by endometrial carcinoma. Acta Cytol 1996: 40: 878-884.
21. Turner DA, Gershenson DM, Atkinson N, Sneige N, Wharton AT (1989) The prognostic significance of peritoneal cytology for stage I endometrial cancer. Obstet Gynecol 74: 775-780.
22. Yuan TL, Cantley LC (2008) PI3K pathway alterations in cancer: variations on a theme. Oncogene 27: 5497-5510.
23. Wang LE, Ma H, Hale KS, Yin M, Meyer LA, et al. (2012) Roles of genetic variants in the PI3K and RAS/RAF pathways in susceptibility to endometrial cancer and clinical outcomes. Journal of cancer research and clinical oncology 138: 377-385.
24. Kirkegaard T, Witton CJ, McGlynn LM, Tovey SM, Dunne B, et al. (2005) AKT activation predicts outcome in breast cancer patients treated with tamoxifen. The Journal of pathology 207: 139-146.
25. Antico-Arciuch VG, Dima M, Liao XH, Refetoff S, Di Cristofano A (2010) Cross-talk between PI3K and estrogen in the mouse thyroid predisposes to the development of follicular carcinomas with a higher incidence in females. Oncogene 29: 5678-5686.
26. Montagut C, Settleman J (2009) Targeting the RAF-MEK-ERK pathway in cancer therapy. Cancer lett 283: 125-134.
27. Hirohashi S (1998) Inactivation of the E-cadherin-mediated cell adhesion system in human cancers. Am J Pathol 153: 333-339.
28. Sakuragi N, Nishiya M, Ikeda K, Ohkouch T, Furth EE, et al. (1994) Decreased E-cadherin expression in endometrial carcinoma is associated with tumor dedifferentiation and deep myometrial invasion. Gynecol Oncol 53: 183-189.
29. Tanaka R, Saito T, Ashihara K, Nishimura M, Mizumoto H, et al. (2003) Three-dimensional coculture of endometrial cancer cells and fibroblasts in human placenta derived collagen sponges and expression matrix metalloproteinases in these cells. Gynecol Oncol 90: 297-304.
30. Saito T, Nishimura M, Yamasaki H, Kudo R (2003) Hypermethylation in promoter region of E-cadherin gene is associated with tumor dedifferention and myometrial invasion in endometrial carcinoma. Cancer 97: 1002-1009.
31. Cheng Y, Zhou Y, Jiang W, Yang X, Zhu J, et al. (2012) Significance of E-cadherin, beta-catenin, and vimentin expression as postoperative prognosis indicators in cervical squamous cell carcinoma. Hum Pathol 43: 1213-20.