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Pap Test – With or Without Vaginal Smear?

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A B S T R A C T

The aim of this study was to evaluate medical and economic justification of vaginal smears as a part of primary screening for cervical carcinoma and its precursors. Study included 245.048 participants whose VCE (vaginal, cervical, endocervical) smears were examined at Department of clinical cytology of University Hospital Center Osijek from 2003 till 2008. There were 12.639 (5.2%) abnormal findings, and they were divided into three groups: abnormal cells found only in vaginal smear (V), abnormal cells found in vaginal and in at least one other smear (V+) and abnormal cells not found in vaginal smear (C/E). These three groups were analysed in respect to cytological differential diagnosis and age of participants. It was estimated how many women could be additionally included in the screening, if vaginal smear would be included in the Pap test only after 50 years of age. In 6.9% of cytologically diagnosed lesions abnormal cells were found exclusively in vaginal smears (0.35% of all findings). As for squamous cell lesions, 91.2% were mild lesions (ASC and LSIL). Invasive squamous cell carcinoma was not diagnosed exclusively by vaginal smear in either woman under 50 years of age, while in women over 50 years of age it was diagnosed in 2.3% of cases. Exclusively by vaginal smear was diagnosed 3.9% of all AGC and 6.3% of adenocarcinoma, while in 85.0% of glandular epithelium lesions abnormal cells were not found in vaginal smears. Two thirds of adenocarcinoma diagnosed exclusively by vaginal smears were endometrial adenocarcinoma, but that is only 10.3% of all endometrial carcinoma diagnosed by Pap test. Obtained results show that taking of vaginal smears along with cervical and endocervical smears as a part of primary screening for cervical carcinoma and its precursors in women under 50 years of age is not justifiable, since vaginal smear only has a role in detection of endometrial carcinoma that are extremely rare in younger age groups. If vaginal smear would be taken only in women over 50 years of age, additional 37.7% of women under 50, or 25.1% women over 50 years of age could be included in the screening.

Key words: *cervical screening, Pap test, cervical/vaginal smear*

Introduction

In vaginal smear Papanicolaou accidentally discovered cells of cervical carcinoma and established new diagnostic method for detection of cervical carcinoma in early, asymptomatic and curable stage[1–3], and it is after discovery and publication of this revolutionary understanding that vaginal smear became accepted as a screening method for detection of premalignant and malignant changes in asymptomatic women. However, already in the first years of application of this method, it was determined that samples obtained directly from cervix using wooden spatula[4] were more efficient and easier to analyse than vaginal smears[5], and later endocervical canal sample was included in routine practice[6]. Beside this historical significance, vaginal smear is valuable for hormone status evaluation and detection of infections, and in peri- and postmenopausal women for identification of carcinoma cells from endometrium, tubes, ovaries and cervix, incidence of which is significantly increasing after 50 years of age.

Experience shows that vaginal smear analysis is time-consuming because this is a part of smear with the most prominent degenerative changes of the cells and with the highest number of inflammatory cells and microorganisms. In contrast, it contains relatively small number of cervical cells, among which is hard to find early preinva-

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sive lesions. Since more than 90% of neoplastic changes of cervix develop in transformation zone[7], sample taken directly from cervix contains numerous abnormal cells, including those located deeper that do not desquamate spontaneously. Current practice is that LBC Pap test contains only cervical and endocervical sample taken in one act or separately with two different instruments.

Conventional Pap test has been conducted in Croatia from the middle of the last century, and it includes samples taken from posterior fornix of vagina (vaginal), from ectocervix (cervical) and from endocervical canal (endocervical smear). However, large number of Pap tests with insufficient number of educated cytotechnologists justifies idea of possible exclusion of vaginal sample.

The aim of this study was to evaluate medical and economic justifiability of vaginal smear as a part of primary screening.

Materials and Methods

The study included 245.048 participants whose VCE (vaginal, cervical and endocervical) smears were examined as a part of primary screening at Department for clinical cytology of University Hospital Center Osijek from 2003 till 2008. Vaginal and cervical samples were taken using wooden spatula[4], while endocervical samples were taken using cotton swab or a brush, and were all smeared on to one slide. Smears were examined by four cytotechnologists, which daily examine on average 45 VCE smears smeared onto one slide. Results were classified in concordance with Croatian modification of Bethesda 2001 classification[8,9], but in data processing diagnoses dysplasia media, dysplasia gravis, carcinoma *in situ* and carcinoma *in situ* with possible initial invasion were observed as one – HSIL. Atypical squamous cell (ASC) diagnosis comprised three diagnoses: atypical squamous cells – undefined significance, atypical squamous cells – heavy squamous intraepithelial lesion (HSIL) can not be excluded and atypical squamous cells – invasive lesion can not be excluded. In data processing of glandular epithelium lesions, atypical glandular cell (AGC) group was observed as a whole, although Croatian modification[9] of Bethesda classification recognises three categories in this group – cases of probable reactive, intraepithelial or invasive lesions. AGC group and adenocarcinoma were divided according to origin of colum- nar cells into endocervical, endometrial, extrauterine and undefined origin.

Abnormal findings were divided into three groups: ones where abnormal cells were found only in vaginal smear (V), ones where abnormal cells were found in vaginal and in at least one other smear (V+) and ones where abnormal cells were not found in vaginal smear (C/E). These three groups were analysed in respect to cytological differential diagnosis and age of participants.

It was determined how many women could existing cytological team additionally include in the screening, if vaginal smear should be included in Pap test only after 50 years of age. Significance of difference was tested at 95% level[10].

Results

Out of 245,048 examined smears, 12,639 (5.2%) were abnormal. Exclusively in vaginal smear, abnormal cells were found in 870 smears, which make 6.9% of all abnormal results (i.e. 0.35% of all results). In combination of vaginal smear and one other smear, abnormal cells were found in 3,170 (25.1%) smears, and in 8,599 samples (68%) abnormal cells were not found in vaginal smear (Table 1).

Exclusively by vaginal smear it was discovered 7.2% of squamous lesions (14.2% of ASC, 7.4% of LSIL, 2.7% of HSIL and 1.7% of invasive squamous carcinoma), while in 66.2% of lesions abnormal cells were not found in vaginal smear (65.4% of ASC, 70.3% of LSIL, 57.9% of HSIL and 7.8% of invasive squamous carcinoma). In 26.6% of lesions abnormal cells were found both in vaginal and cervical/endocervical smears (Table 2).

Exclusively by vaginal smear it was discovered 4.2% of glandular lesions (3.9% of AGC and 6.3% of adenocarcinoma), while in 85.0% of lesions abnormal cells were not found in vaginal smear (87.6% of AGC, 56.3% of AIS

TABLE 1
EPITHELIAL CELL ABNORMALITY *PER* SMEAR (N=12.639)

		Smears			Total
		V	V+	C/E	
Abnormal cells	Squamous cell lesions	819	3014	7526	11359
		7.2%	26.5%	66.3%	100%
	Glandular cell lesions	51	132	1036	1219
		4.2%	10.8%	85%	100%
	Squamous + Glandular cell lesions	0	24	37	61
		0%	39.3%	60.7%	100%
Total		870	3170	8599	12639
		6.9%	25.1%	68%	100%

V – vaginal smear, V+ – vaginal and at least one other smear, C/E – cervical and/or endocervical smear

TABLE 2
ABNORMAL SQUAMOUS CELL FINDINGS *PER* SMEAR (N=11.420)

		Smears			Total
		V	V+	C/E	
Abnormal squamous cells	ASC	213	307	981	1501
		14.2%	20.5%	65.4%	100%
		26%	10.1%	13%	13.1%
	LSIL	535	1622	5097	7254
		7.4%	22.4%	70.3%	100%
		65.2%	53.4%	67.4%	63.5%
	HSIL	70	1003	1477	2550
		2.7%	39.3%	57.9%	100%
		8.5%	33%	19.5%	22.3%
	Squamous cell carcinoma	2	104	9	115
		1.7%	90.4%	7.8%	100%
		0.2%	3.4%	0.1%	1%
Total		820	3036	7564	11420
		7.2%	26.6%	66.2%	100%
		100%	100%	100%	100%

V – vaginal smear, V+ – vaginal and at least one other smear, C/E – cervical and/or endocervical smear, ASC – abnormal squamous cells, LSIL – low risk squamous intraepithelial lesion, HSIL – high risk squamous intraepithelial lesion

TABLE 3
ABNORMAL COLUMNAR CELL FINDINGS *PER* SMEAR (N=1.280)

		Smears			Total
		V	V+	C/E	
AGC	Endocervical	28	57	984	1069
		2.6%	5.3%	92%	100%
	Endometrial	18	39	59	116
		15.5%	33.6%	50.9%	100%
	Undefined origin	1	5	8	14
		7.1%	35.7%	57.1%	100%
	Extrauterine	0	1	0	1
		0%	100%	0%	100%
	Total	47	102	1051	1200
		3.9%	8.5%	87.6%	100%
AIS	Endocervical	0	7	9	16
		0%	43.8%	56.3%	100%
Adeno**c**arcinoma	Endocervical	0	13	3	16
		0%	81.3%	18.8%	100%
	Endometrial	3	21	5	29
		10.3%	72.4%	17.2%	100%
	Undefined origin	1	12	4	17
		5.9%	70.6%	23.5%	100%
	Extrauterine	0	1	1	2
		0%	50%	50%	100%
	Total	4	47	13	64
		6.3%	73.4%	20.3%	100%

V – vaginal smear, V+ – vaginal and at least one other smear, C/E – cervical and/or endocervical smear

TABLE 4
ABNORMAL CELL FINDINGS OF THE GRAVEST LESIONS *PER* SMEAR WITH RESPECT TO AGE OF PARTICIPANTS (N=179)

		Smears			Total
		V	V+	C/E	
Squamous cell carcinoma	Under 50 years of age	0	22	6	28
		0%	78.6%	21.4%	100%
	Over 50 years of age	2	82	3	87
		2.3%	94.3%	3.4%	100%
	Total	2	104	9	115
		1.7%	90.4%	7.8%	100%
Adenocarcinoma	Under 50 years of age	0	3	6	9
		0%	33.3%	6.67%	100%
	Over 50 years of age	4	39	12	55
		7.3%	70.9%	21.8%	100%
	Total	4	42	18	64
		6.3%	65.6%	28.1%	100%

V – vaginal smear, V+ – vaginal and at least one other smear, C/E – cervical and/or endocervical smear

TABLE 5
ABNORMAL CELL FINDINGS WITH RESPECT TO AGE OF PARTICIPANTS (N=12.639)

		Smears			Total
		V	V+	C/E	
Age	Under 50 years of age	711	2673	7468	10852
		6.6%	24.6%	68.8%	100%
	Over 50 years of age	159	497	1131	1787
		8.9%	27.8%	63.3%	100%
Total		870	3170	8599	12639
		6.9%	25.1%	68%	100%

V – vaginal smear, V+ – vaginal and at least one other smear, C/E – cervical and/or endocervical smear

and 20.3% of adenocarcinoma). In 10.8% of lesions abnormal cells were found both in vaginal and cervical/endocervical smears. Out of 6.3% of adenocarcinoma diagnosed exclusively by vaginal smear, 75% was endometrial adenocarcinoma. However, out of all endometrial adenocarcinoma, exclusively by vaginal smear was diagnosed only 10.3% (Tables 1 and 3).

Medium age of participants with squamous cell carcinoma was 59,6 years, and of ones with adenocarcinoma it was 66.6 years. There was neither one participant under 50 years of age with invasive squamous carcinoma or adenocarcinoma that were diagnosed exclusively by vaginal smear, while squamous cell carcinoma was diagnosed exclusively by vaginal smear in 2.3%, and adenocarcinoma in 7.3% of participants over 50 years of age (Table 4).

Dividing participants in two groups, regardless of grade and type of lesion (squamous or glandular), exclusively by vaginal smear was diagnosed 6.6% of lesions in participants under 50 years of age, and 8.9% of lesions in participants over 50 years of age (Table 5). There was statistically significant difference in finding of abnormal cells by vaginal smear among participants under and over 50 years of age ($z=-3.629$, $p=1.42*10^{-4}$).

Discussion and Conclusion

Value of vaginal sample as a part of conventional Pap test is best illustrated by the type of lesion and the age in which abnormal cells are found exclusively in vaginal smear.

In 6.9% of cytologically diagnosed lesions abnormal cells were found exclusively in vaginal smear. As for squamous cell lesions, 91.2% were mild lesions (ASC and LSIL) (Table 2), which in respect to their biological behaviour have high probability of spontaneous regression and/or possibility of later detection. As for invasive squamous cell carcinoma, abnormal cells were found exclusively in vaginal smear in 1.7% of women, but they were all over 50 years of age. As for cytological diagnosis HSIL, abnormal cells were found exclusively in vaginal smear in 2.7% of women, and those lesions would not have been discovered if vaginal smear had been excluded. However, possibility of incorrect sampling of vaginal smear, where

in one act a smear of posterior fornix and exocervix has been done, can not be excluded.

Exclusively by vaginal smear has been detected overall 4.2% of glandular lesions (3.9% of AGC and 6.3% of adenocarcinoma), while in 85.0% of lesions abnormal cells were not found in vaginal smear. Since neither one adenocarcinoma of endocervical origin nor adenocarcinoma *in situ* (AIS) was detected in vaginal smear, vaginal smear has a role in detecting glandular epithelium lesions of endometrial origin. Out of all endometrial carcinoma that were detected by Pap test, abnormal cells were found exclusively in vaginal smear in 10.3% of them, and since average age of participants with endometrial carcinoma in our study was almost 67 (none of the participants was under 50 years of age), if we should not had taken vaginal smear to women under 50 years of age, we would not have missed neither one endometrial carcinoma.

Richart and Vaillant already determined that for women in reproductive age that have extremely low prevalence of endometrial carcinoma and high prevalence of cervical neoplasia samples should be taken by techniques that provide direct samples from cervix[11].

Similar results obtained Pajtler et al.[12,13], who also pointed out clinical and economic unjustifiability of taking vaginal smears to women under 50 years of age.

From all said can be concluded that taking vaginal smear along with cervical and endocervical smears as a part of primary screening for cervical carcinoma and its precursors to women under 50 years of age is not justifiable, since vaginal smear only has a role in detection of endometrial carcinoma that are extremely rare in younger age groups.

In respect to age structure, 75.4% of examined population was under, and 24.6% was over 50 years of age. If vaginal smear should be taken only to women over 50 years of age, then to 185,109 women only CE smear would be taken, and CVE smear would be taken to 60,299 women. At the same time and with the same staff additional 92,554 CE smears (37.7%) to women under 50 years of age, or 61,703 VCE smears (25.1%) to women over 50 years of age could be examined without significant screening quality reduction. Our cytotechnologists examine 45 smears daily during 7.5 working hours. Considering the age structure of our patients, they would daily spend 112 minutes less for the same amount of samples. Average time of waiting for Pap test results in Croatia is 25 days, and the longest is 90 days. Therefore, exclusion of vaginal smear in patients under 50 years of age would reduce average time of waiting for Pap test results to 18.8 days, and the longest time of waiting to 67.7 days.

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PAPA TEST – SA ILI BEZ VAGINALNOG RAZMAZA?

SAŽETAK

Cilj ove studije bio je procijeniti medicinsku i ekonomsku opravdanost uzimanja vaginalnog razmaza u sklopu primarnog probira cervikalnog karcinoma i njegovih prekursora. U studiju je uključeno 245.408 ispitanica čiji su VCE (vaginalni, cervikalni, endocervikalni) razmazi bili pregledani na Odjelu za kliničku citologiju Kliničkog bolničkog centra Osijek od 2003. do 2008. godine. Abnormalnih je nalaza bilo 12.639 (5,2%), a podijeljeni su u tri skupine: abnormalne stanice nađene samo u vaginalnom razmazu (V), abnormalne stanice nađene u vaginalnom i bar u još jednom razmazu (V+) i abnormalne stanice nisu nađene u vaginalnom razmazu (C/E). Te su tri skupine analizirane u odnosu

na citološku diferencijalnu dijagnozu i životnu dob ispitanica. Procijenjeno je koliko bi se žena moglo dodatno obuhvatiti probirom ukoliko bi se vaginalni razmaz uključio u PAPA test tek nakon pedesete godine života. U 6,9% citološki dijagnosticiranih lezija abnormalne su stanice nađene isključivo u vaginalnim razmazima (0,35% svih nalaza). Kod lezija pločastog epitela u 91,2% slučajeva radilo se o lakšim lezijama (ASC i LSIL). Invazivni pločasti karcinom isključivo vaginalnim razmazom nije dijagnosticiran niti u jedne žene mlađe od 50 godina, dok je u žena starijih od 50 godina dijagnosticiran u 2,3% slučajeva. Isključivo vaginalnim razmazom otkriveno je 3,9% svih AGC i 6,3% adenokarcinoma, dok kod 85,0% lezija žljezdanog epitela abnormalne stanice nisu nađene u vaginalnim razmazima. Dvije trećine adenokarcinoma dijagnosticiranih isključivo vaginalnim razmazom čini adenokarcinom endometrija, no to je samo 10,3% svih PAPA testom dijagnosticiranih endometralnih karcinoma. Iz navedenih se rezultata može zaključiti da ženama mlađim od pedeset godina nema opravdanja uz cervikalni i endocervikalni uzeti i vaginalni razmaz u sklopu primarnog probira cervikalnog karcinoma i njegovih prekursora, budući da vaginalni razmaz ima ulogu jedino u detekciji endometralnih karcinoma koji su u mlađim dobnim skupinama izuzetno rijetki. Ukoliko bi se vaginalni razmaz uzimao samo ženama starijim od 50 godina moglo bi se dodatno pregledati još 37,7% žena mlađih od 50 godina, ili 25,1% žena starijih od 50 godina.