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The hr-HPV based cervical cancer screening: results of a four-years experience in a single screening center of Italy

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Summary

Purpose of Investigation: The study was performed to evaluate four years of experience (2012-2015) in high risk-human papillomavirus (hr-HPV) testing in the cervical cancer screening in Latina (Italy). *Materials and Methods:* The hr-HPV as primary test is performed only on women aged 35-64, followed by a Pap test as triage, while women aged 25-34 are invited to perform only a Pap test. *Results*: Women resulted positive to hr-HPV test and positive to Pap test were 5.6% and 4.1%, respectively. Among women aged 25-34, the hr-HPV test was used as triage for women with atypical squamous cells of undetermined significance (ASCUS) and 69.9% resulted positive to the test. The positive predictive value (PPV) for high cervical intraepithelial lesions (HSIL) was higher in women aged 35-64 (9.9% *vs.* 6.9%), while the detection rate (DR) for HSIL was higher in young women (2.4‰ *vs.* 1.2‰). The authors found that 52.5% of women with hr-HPV+/Pap test resulted with hr-HPV+ at one-year recall and the DR for HSIL lesions of this population was very low (0.27‰). *Discussion*: The present data confirms that the application of hr-HPV test showed elevated performance in cervical cancer screening and that the application of hr-HPV test in managing ASCUS leads to a decreased use of inappropriate colposcopies. Finally, it may be useful to extend the period of follow-up for women hr-HPV+/Pap test to reduce unnecessary colposcopies.

Key words: Human papillomavirus; Cervical cancer; Screening; hr-HPV test; Pap test.

Introduction

The knowledge on the etiological role of high-grade human papillomavirus (hr-HPV) has caused a radical change in the cervical cancer prevention program by introducing hr-HPV test instead of Pap test as a primary test in the screening program [1, 2]. In Italy there is an organized national program for the prevention of cervical cancer in women aged 25-64 with a three-year protocol. The Italian Association of Cervical Screening program guidelines (GISCi) recommends to perform to research hr-HPV with clinical validated molecular test as primary screening test in women aged 35-64 [3]. Moreover, it is also recommended to perform Pap test as triage in women resulting positive to hr-HPV test (hr-HPV+) and to repeat the hr-HPV test after one year in women hr-HPV+ with negative cytology (Pap test-) [3]. In this manner, a sensitive test is combined with a specific test [4]. All women resulted hr-HPV+ and successively positive to Pap test atypical squamous cells of undetermined significance (ASCUS+) or worse and women with hr-HPV+ at one-year recall are referred to colposcopy. While women resulting negative to hr-HPV test (hr-HPV-) at baseline or at one-year recall are advised to repeat the test after three years [3]. It is a different matter for women aged 25-34 who are invited to perform the Pap test as primary test; the rationale is that in young women, the hr-HPV test leads to an over-diagnosis and an increase of unnecessary treatment of regressive cervical lesions [5, 6].

In women aged 25-35 the hr-HPV test is used as triage for the management of women with diagnosis of ASCUS+, and if they result hr-HPV+, they are referred to colposcopy as well as women with diagnosis of low-grade squamous intraepithelial lesion (LSIL+) or worse at baseline. On the contrary, if they result negative to hr-HPV test, they are then referred to the next round after three years as well as women resulting negative to the Pap test at baseline [3]. Although the new screening program is actually grounded on solid evidence and in-deep evaluations, this change required an update in the monitoring of the screening programs annually through the indicators' estimate based on standard references. Some important indicators, such as referral rate (RR) to colposcopy and the total detection rate, have to calculate including the events at one-year recall; therefore, it is necessary to diversify the timing of data collection [7-9].

In the screening centre of Latina (Italy) the authors applied the GISCi guidelines from April 2012 and in this study they evaluate the effect of this screening program after four years (2012-2015) through the calculation of indicators to provide information and to compare these to standard references.

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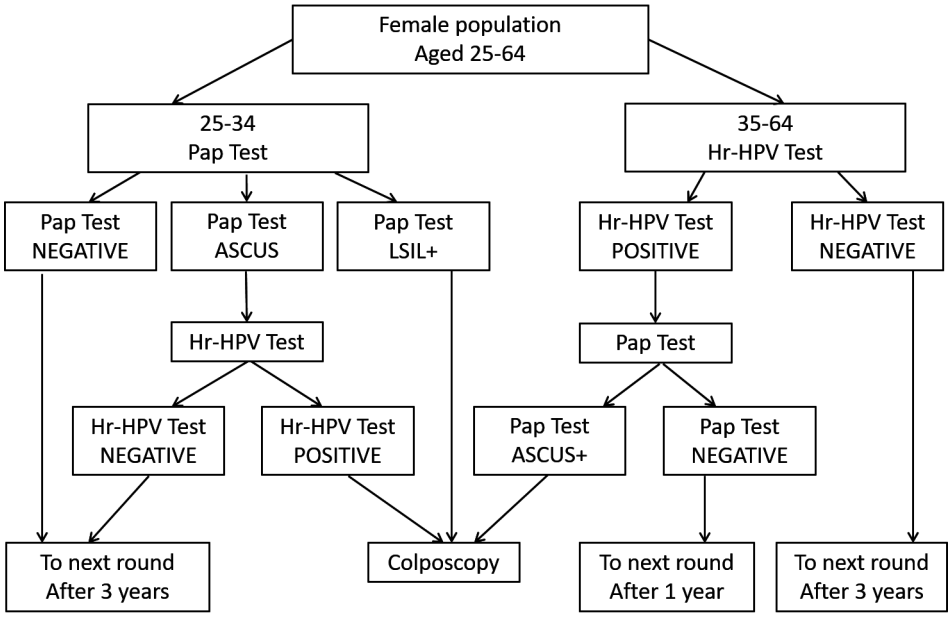

Figure 1. — Algorithm of the cervical cancer screening program in Latina district.

Materials and Methods

The Pathology Unit of ICOT hospital, Department of Medical-Surgical Sciences and Bio-Technologies, Sapienza University of Rome and Screening Unit of Latina, have been running an organized cervical-screening in the Latina district since April 2012. The program is geared towards the entire female population, aged 25-64, and resident in the Latina district. The target female population is represented by about 156,000 women and about 30% is invited annually over three years (three years around time). Women aged 25-34 and 35-64 are invited by mail to perform a Pap test and the hr-HPV test as a primary test respectively. The screening algorithm is described in Figure 1. Cytological diagnosis is reported according to Bethesda System [10] evaluated by one cytologist and two pathologists. The colposcopy is performed by two gynaecologists of the screening unit and the biopsies are read by two pathologists and women with diagnosis of CIN2+ (high grade of cervical intraepithelial neoplasia or worse) were referred to excisional treatment.

The cervical cell samples were obtained by using a cytobrush and were placed in PreservCyt solution; liquid-based cytology was performed by using the Sure Path system. One slide per woman was prepared according to the supplier's instructions.

Exfoliated cervical cells were collected using a cytobrush and eluted in the Sample Transport Medium (STM). Cervical specimens were denatured to disrupt the virus and release the target DNA. The RNA probes were diluted in a probe diluent and once loaded all the samples, calibrators, controls and reagents, the hybridization phase began according to supplier's instructions. The chemiluminescent reaction was measured by luminometer and the emitted light was measured as Relative Light Unit (RLU). For each reaction three negative controls, three positive controls, one quality control for low-risk HPV (lr-HPV), and one quality control for hr-HPV were used . Samples that showed a RLU $\geq$ 1 pg/ml were considered positive.

Results

From 2012 to 2015 191,090 women (48,101 aged 25-34 and 142,989 aged 35-64) were invited and 30% (57,398/191,090) was screened; particularly, participation was 19.2% (9,241/48,101) and 33.7% (48,157/142,989) for women aged 25-34 and 35-64 years, respectively (Table 1). The 4.1% (378/9,241) women aged 25-34, that performed Pap test as the primary test, resulted positive to Pap test with diagnosis of ASCUS or worse (ASCUS+). The most frequent diagnostic category was LSIL (55.3%, 209/378), followed by ASCUS (36.5%, 138/378), HSIL (4.8%, 18/378) and atypical squamous cell, high-grade not excluded (ASCH, 3.2%, 12/378). Every year LSIL was the most frequent diagnostic category except in 2012 (Table 2). Only the 0.4% (35/9,241) was the proportion of inadequate Pap test. Two women with ASCUS (2/138, 1.4%) were missing and they did not undergo the hr-HPV test and the 69.9% (95/136) of women with diagnosis of ASCUS resulted positive to the hr-HPV test that was used as triage. Women that did not show cytological alteration (95.9%, 8,863/9,241) and women resulted ASCUS+/hr-HPV- (30%, 41/136) were advised to repeat the test after three years. The authors performed 48,157 hr-HPV tests as a primary test in women aged between 35-64, with an average of 5.6% (2,677/48,157) test positivity. Nonetheless it was necessary to repeat the hr-HPV test. Among women that resulted positive to hr-HPV test, the 77% (2,054/2,677) resulted negative to Pap test used as a triage test with a RR at one year of 4.3% (2,054/48,157); on the contrary, 617 women resulted positive to Pap test (ASCUS+, 617/2,677; 23%) (Table 1). The most frequent diagnostic category was LSIL (75.4%, 463/614), followed by ASCUS (13.5%, 83/614), HSIL (7.8%, 48/614), and ASCH (3.2%, 20/614). The authors found a strong decrease in ASCUS category from 2012 to 2015 (25.4% al 6%) and only in 2013 two squamous carcino-

Table 1. — *Results of the screening test performance of the HPV screening program.*

	2012		2013		2014		2015		Overall	Indicators
Women invited										
aged 25-34	11484		14013		11811		10793		48,101	
aged 35-64	11378		48910		39570		43131		142,989	
Overall	22862		62923		51381		53924		191,090	
Women examined		%		%		%		%	%	Acceptable standard value*
Aged 25-34	678/11484	5.9	3564/14013	25.4	2842/11811	24.1	2157/10793	20	19.2	
Aged 35-64	4752/11378	41.8	16216/48910	33.2	14276/39570	36.1	12913/43131	29.9	33.7	≥ 50%
Overall	5430/22862	23.8	19780/62923	31.4	17118/51381	33.3	15070/53924	27.9	30	
Proportion of positive hr-HPV test		%		%		%		%	%	Reference range**
Aged 35-64	240/4752	5.1	852/16216	5.3	842/14276	5.9	743/12913	5.8	5.6	4-8%
Proportion of positive Pap test		%		%		%		%	%	Reference range**
Aged 25-34	23/678	3.4	147/3564	4.1	84/2842	3	124/2157	5.7	4.1	1-4.4%
Aged 35-64 (Amon hr-HPV+)	67/240	27.9	181/852	21.2	167/842	19.8	202/743	27.2	23	Critical threshold ≥ 30%*
Referral rate at 1-year		%		%		%		%	%	
Aged 35-64	171/4752	3.6	667/16216	4.1	675/14276	4.7	541/12913	4.2	4.3	
Referral rate to colposcopy		%		%		%			%	Standard reference
Aged 25-34	21/678	3.1	140/3564	3.9	72/2842	2.5	101/2157	4.7	3.6	value^ 4%
Aged 35-64	67/4752	1.4	181/16216	1.1	167/14276	1.2	202/12913	1.6	1.3	National
Overall	88/5430	1.6	321/19780	1.6	239/17118	1.4	303/15070	2	1.7	average^^
									2.4%	
Compliance with referral to colposcopy		%		%		%		%	%	Standard reference value*
Aged 25-34	20/21	95.2	134/140	95.7	71/72	98.6	94/101	93.1	95.5	
Aged 35-64	62/67	92.5	172/181	95	160/167	95.8	194/202	96	95.2	95%
Overall	82/88	93.2	306/321	95.3	231/239	96.7	288/303	95	95.3	
PPV for CIN2+		%		%		%		%	%	Standard
Aged 25-34	3/20	15	9/134	6.7	4/71	5.6	6/94	6.4	6.9	reference value^ 9%
Aged 35-64	6/62	9.7	19/172	11	11/160	6.9	22/194	11.3	9.9	Reference
Overall	9/82	11	28/306	9.2	15/231	6.5	28/288	9.7	8.8	range* 15-38%
Detection rate for CIN2+		‰		‰		‰		‰	‰	Standard
Aged 25-34	3/678	4.4	9/3564	2.5	4/2842	1.4	6/2157	2.78	2.4	reference value^ 2.4‰
Aged 35-64	6/4752	1.3	19/16216	1.2	11/14276	0.8	22/12913	1.7	1.2	National
Overall	9/5430	1.7	28/19780	1.4	15/17118	0.9	28/15070	1.9	1.4	average^^ 4.2‰

**[11] **[11, 14] ^[5, 6] ^^[8].*

mas (CA) (0.3%, 2/614) were found (Table 2). The RR to colposcopy was higher in women aged 25-34 (3.6%, 334/9,241) than women aged 35-64 (1.3%, 617/48,157), while the compliance with referral to colposcopy was the same in the two groups of women (95.3%), and between them only the 31.3% (100/319) and 35.8% (211/588) of women aged 25-34 and 35-64, respectively, showed a normal feature of the cervix (Table 1). The other women, during colposcopy, underwent to biopsy of area with abnormal feature of the cervix to perform a histological diagnosis. CIN1 was the histological diagnosis most frequently observed both in women aged 25-34 (74.4%, 163/219) and in women aged 35-64 (75.6%, 285/377), while the second histological category most frequently observed was CIN3 (5.5%, 12/219) in women aged 25-34 and CIN2 (8.5%, 32/377) in women aged 35-64. Moreover, both in 2014 and in 2015 only one case of invasive squamous carcinoma was observed (Table 3). Regarding parameters considered as indicators of the accuracy of the cervical cancer screening, the present data showed that the positive predictive value (PPV) for CIN2+ was higher in women aged 35-64 (9.9%, 58/588) than women aged 25-34 (6.9%, 22/319); on the contrary, the detection rate) for CIN2+ was higher in women aged

Table 2. — *Results of cytological diagnosis.*

		ASCUS	LSIL	ASCH	HSIL	CA
2012						
	Aged 25-34	11 (47.8%)	9 (39.1%)	0	3 (13%)	0
	Aged 35-64	17 (25.4%)	42 (62.7%)	1 (1.5%)	7 (10.4%)	0
2013						
	Aged 25-34	44 (29.9%)	93 (63.3%)	4 (2.7%)	6 (4.1%)	0
	Aged 35-64	42 (23.2%)	118 (65.1%)	5 (2.8%)	14 (7.7%)	2 (1.1%)
2014						
	Aged 25-34	34 (40.5%)	44 (52.4%)	2 (2.4%)	4 (4.8%)	0
	Aged 35-64	12 (7.2%)	134 (80.2%)	9 (5.4%)	11 (6.6%)	0
2015						
	Aged 25-34	49 (39.5%)	63 (50.8%)	6 (4.8%)	5 (4%)	0
	Aged 35-64	12 (6%)	169 (83.7%)	5 (2.5%)	16 (7.9%)	0
Overall						
	Aged 25-34	138 (36.5%)	209 (55.3%)	12 (3.2%)	18 (4.8%)	0
	Aged 35-64	83 (13.5%)	463 (75.4%)	20 (3.2%)	48 (7.8%)	0

Table 3. — *Results of histological diagnosis.*

		CIN1	CIN2	CIN3	CA
2012					
	Aged 25-34	11 (61.1%)	1 (5.6%)	2 (11.1%)	0
	Aged 35-64	43 (84.3%)	1 (2%)	5 (9.8%)	0
2013					
	Aged 25-34	75 (80.6%)	3 (3.2%)	6 (6.5%)	0
	Aged 35-64	92 (74.2%)	8 (6.5%)	11 (8.9%)	0
2014					
	Aged 25-34	33 (82.5%)	1 (2.5%)	3 (7.5%)	0
	Aged 35-64	61 (76.3%)	8 (10%)	2 (2.5%)	1 (1.2%)
2015					
	Aged 25-34	44 (64.7%)	5 (7.4%)	1 (1.5%)	0
	Aged 35-64	89 (73%)	15 (12.3%)	6 (4.9%)	1 (0.8%)
Overall					
	Aged 25-34	163 (88.1%)	10 (5.4%)	12 (6.5%)	0
	Aged 35-64	285 (83.1%)	32 (9.3%)	24 (7%)	2 (0.6%)

25-34 (2.4‰, 22/9,241) than in women aged 35-64 (1.2‰, 58/48157, Table 1). After one year 2,054 women hr-HPV+/PapTest- at baseline, aged 35-64, were invited to perform hr-HPV test and were screened 58.6% (1,203/2,054). The 52.5% (631/1,203) resulted positive to molecular test and the compliance with referral to colposcopy was of 95.1% (600/631) and 345 women (57.5%) showed a normal feature of the cervix (Table 4). Instead, among the other women undergoing colposcopy, the authors found that CIN1 was the more representative histological category (191/237, 80.6%), followed by CIN2 (12/237, 5%), that was found only in 2013 and 2014, and CIN3 (1/237, 0.4%) that was found only in 2013 (Table 5). Overall, the PPV for CIN2+ at one-year recall in women aged 35-64 hr-HPV+/PapTest- at baseline was 2.2%, while the DR was 0.27‰ (Table 4).

Discussion

This study presents the results of the first four years of cervical cancer screening program organized by Local Health Unit of Latina (Italy), since April 2012. The participation to the screening program is a key parameter to evaluate the effect and the efficiency of the program and, given that this parameter is affected by the adhesion to spontaneous Pap test outside the screening program, standard reference values are not proposed, but a percentage of ≥ 50% is considered as acceptable standard value [11]. In the present study, the authors found that the adhesion was higher in women aged 35-64 than in 25-34 (33.7% *vs.* 19.2%); this data, even if it is encouraging because the introduction of a new molecular test has not worried the women, these values however are lower than the national average (43%) [12] and this suggests the necessity to inform and mainly involve the women of the district. Nevertheless, this value is slightly

Table 4. — *Results of HPV screening program in women aged 35-64 at one-year recall.*

	2012		2013		2014		2015		Overall	Indicators
		%		%		%		%	%	Standard reference or Reference range*
Women invited	171/171	100	667/667	100	675/675	100	541/541	100	100	
Women examined	102/171	59.6	308/667	46.2	588/675	87.1	205/541	37.9	58.6	> 80%
Proportion of positive hr-HPV test	50/102	49	164/308	53.2	312/588	53.1	105/205	51.2	52.5	50-60%
Compliance with referral to colposcopy	50/50	100	160/164	97.6	302/312	96.8	88/105	83.8	95.1	≥ 80%
PPV for CIN2+	0/50	0	7/160	4.4	6/302	2	0/88	0 2.2		
Detection rate for CIN2+	0/4752	‰ 0	7/16216	‰ 0.4	6/14276	‰ 0.4	0/12913	‰ 0	‰ 0.3	

*[11].

Table 5. — *Results of histological diagnosis in women aged 35-64 at one-year recall.*

	CIN1	CIN2	CIN3	CA
2012	2 (100%)	0	0	0
2013	60 (76.9)	6 (7.7%)	1 (1.3%)	0
2014	99 (83.9)	6 (5.1%)	0	0
2015	30 (76.9)	0	0	0
Overall	191 (93.6%)	12 (3.5%)	1 (0.3%)	

higher to the regional adhesion of women that underwent Pap test as primary test (30% *vs.* 29.3%) [13]. The hr-HPV positive rate is consistent with the reference aged range of the New Technologies for Cervical Cancer (NTCC) Italian study in women aged 35-64 (4-8%) [11, 14] and with the national average (6.1%) [12]. Regarding the cytological triage, the present authors found that the Pap test positive rate was consistent with the reference range of the previous survey (20-55%) even if slightly lower than the critical threshold (≥ 30%) [11]. The most representative cytological category was the LSIL confirming that this is the most frequent category between women positive to hr-HPV test [11]. An interesting aspect was the decrease of ASCUS that the authors observed in this study period; this category may be confused with other types of alterations that cause morphological changes such as those caused by an HPV infection [15]. This decrease in ASCUS diagnosis is probably due to the gained experience of the operators involved in cytological triage; this is an extremely important data because it determined a decrease of colposcopies probably unnecessary for women with minor lesions that often regress spontaneously [16].

In young women (25-34), the Pap test positive rate (ASCUS+, 4.1%), used as a primary test, was equal to the value observed in NTCC study performed on women of the same age (4.1%) [5, 6]. However, in NTCC study the most frequently represented category was ASCUS, but with a value below the limits set by the GISCi guidelines (< 5%) [5], while in the present study the authors observed that the most frequently diagnosed category was LSIL (2.3%). Moreover, through the hr-HPV test used as triage of ASCUS category, the present authors showed that 69.9% of women with diagnosis of ASCUS were infected with the hr-HPV, and this value was higher than NTCC study that included the ASCUS+ category (60.6%) [17]. These data confirm that the ASCUS triage using hr-HPV test can help the operators in the management of women aged 25-34 with diagnosis of ASCUS in order to avoid unnecessary colposcopies [18]. Indeed, the RR to colposcopy of the ASCUS category (1.0%) was lower than the RR to colposcopy referred to the total population of women aged 25-34 (3.6%, 334/9,241) and this value is equal to NTCC study (4%) [5, 6]. Moreover, the PPV for CIN2+, a measure of the specificity of the test, referred only to the ASCUS category was 8.4%, while the value referred to the total population of young women was 6.9% and this value is lower than NTCC study (9%) [5, 6]. The DR of CIN2+ referring to the only ASCUS category was lower than the value referred to the total population of women aged 25-34 (0.96‰ *vs.* 2.4‰) and this last value was coherent with the NTCC study [5, 6]. Regarding women aged 35-64, the present authors found that the RR to colposcopy (1.3%, 617/48,157) was lower than the national average (2.4%) [8], but with a percentage of adhesion equal to standard reference value (95%) [11]. The PPV value of CIN2+, in the first experimental project showed values between 15% and 38% while it showed much lower PPV values in women hr-HPV+/ Pap test+ (5-7%) [11]. In the present study, the PPV value (9.9%) was like the national average (10.7%) [12]. Generally, the DR for CIN2+ in the screening program that used hr-HPV test as a primary test was always equal or higher to the DR for CIN2+ of the screening program that used PapTest as a primary test [11]; in this study, the DR value was lower than the national average (4.2‰) [12]. However, this value should be calculated considering the age of women undergoing the hr-HPV test and to the different periods in which the screening programs were commenced; in-

deed, in Latina the screening program began earlier than others and so the difference could be due to this aspect. In the evaluation of the management of hr-HPV+/Pap test- women aged 35-64 at one-year recall, the present authors observed that the compliance to one-year recall was lower than the adequate standard reference (> 80%). Compared to the population screening at baseline, in the group of women hr-HPV+/Pap test- at the one-year-recall, the present authors found a higher percentage of cases hr-HPV+ (52.5% *vs.* 5.6%) and this value is coherent with the range of the previous study (50-60%) [11]; moreover, the present authors detected only a small number of high-grade lesions (5.5%). Indeed, the contribution rate for the detection of CIN2+ in the group hr-HPV+/Pap test at the one-year recall was much less than expected (0.27‰). The one-year recall resulted in an increase of unnecessary colposcopies negatively affecting the PPV for CIN2+ (2.2%) although the HPV clearance value (50%) was coherent with the literature [19]. Hence, it may be useful to modify the follow-up period to repeat the hr-HPV test in women aged 35-64 hr-HPV+/Pap test- at baseline to increase the clearance rate although lengthening the follow up period could affect the compliance to colposcopy [20]. In conclusion, based on the results obtained, the present authors believe that they must invest more in cervical screening program to recruit a greater number of women on the district. However, the data showed an acceptable clinical performance of the screening program for the prevention of cervical cancer in Latina with the use of hr-HPV test as a primary test, in terms of PPV and DR of the CIN2 + lesions. Particularly, this study confirms that the employment of hr-HPV test in the management of ASCUS can help the operators confirm a cytological abnormality caused by an HPV infection and to avoid unnecessary colposcopies in women aged 25-34. Moreover, the low number of CIN2 + lesions identified in women hr-HPV+/Pap test-aged 35-64 recalled at one-year suggests extending the recall period to avoid unnecessary and expensive colposcopies.

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