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Short Communication

HPV triage for low grade (L-SIL) cytology is appropriate for women over 35 in mass cervical cancer screening using liquid based cytology

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ABSTRACT

In the experimental arm of a randomised trial, women were tested both for liquid-based cytology and human papillomavirus (HPV) DNA and referred for colposcopy if cytology was ASCUS (atypical cells of undetermined significance) or more severe. We considered those with ASCUS (757) or LSIL (low-grade squamous intraepithelial lesions) (485) and a valid HPV test who received colposcopy. We computed sensitivity, specificity and ROC

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curves with different values of relative light units (RLU, that are related to viral load) as cut off, using cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) at blind histology review as the endpoint.

The area under the receiver operating characteristic (ROC) curve was significantly less among women aged 25–34 years than in those older, both considering ASCUS/AGUS (atypical glandular cells of undetermined significance) ($p = 0.0355$) and LSIL ($p = 0.0009$). At age 35–60 the curves for ASCUS and LSIL were similar, while at age 25–34 the area under the curve for LSIL was significantly less than for ASCUS ($p = 0.0084$). With LSIL cytology, specificity of Hybrid Capture 2 with 2 RLU cut-off was 35.0% (95%CI 28.4–42.1) at age 25–34 and 64.5% (95%CI 58.3–70.3) at age 35–60.

In conclusion, triaging by HPV testing performed better in women aged over 35 years than those younger. For older women, HPV triaging should also be considered for managing those with LSIL cytology.

1. Introduction

There is clear evidence that, for selecting women with atypical cells of undetermined significance (ASCUS) cytology to be referred for colposcopy (triaging), testing for oncogenic human papillomavirus (HPV) types is more sensitive and specific than repeat cytology.[1–3] Its application in women with ASCUS cytology also dramatically reduces the number of colposcopies without loss in sensitivity compared to direct referral for colposcopy.[2] The situation is more complex for low-grade squamous intraepithelial lesions (LSIL) cytology.[4] The ALTS study, where the mean age of women with LSIL was 24.9 years, found that 83% of these women were HPV positive, suggesting limited utility.[5]

We used data from the experimental arm of a large randomised controlled trial, the New Technologies for Cervical Cancer screening (NTCC) study,[6,7] to estimate the effect of applying the HPV test for managing women with ASCUS and LSIL cytology. In this study the proportion of HPV positive women among women aged 25–34 years (45% in presence of ASCUS and 72% in presence of LSIL)[7] was just slightly lower than that observed in the ALTS study. However, it was much lower in women aged 35–60 years (24% in presence of ASCUS and 42% in presence of LSIL).[6] Therefore HPV prevalence decreased with increasing age in women with ASCUS and LSIL as we had observed in normal women.[6–8]

2. Patients and methods

Methods applied in the first phase of the NTCC study are described in detail elsewhere.[6,7] Briefly, after providing written informed consent, women aged 25–60 years attending for a new screening round in nine Italian organised screening programmes were randomly assigned to two arms (conventional and experimental). The study was approved by the local ethical committees of participating centres. The RCT registration number is ISRCTN81678807. For the present analysis we only considered women assigned to the experimental arm. They had a cervical cell sample taken by plastic Ayre's spatula and cytobrush. Cells were put in PreservCyt® solution (Thin Prep, Cytic Corporation, Boxborough, MA, USA) and used for liquid-based cytology preparation and HPV testing.

Liquid-based cytology was performed by the Thin-Prep® system. Slides were read without knowledge of HPV results in 14 local laboratories participating in regular screening programs. Cytology was classified according to the Bethesda 1991 system (TBS1991) except that the ASCUS diagnoses were not further qualified as favouring a reactive or premalignant/malignant process. Participating laboratories routinely applied quality assurance procedures, as in most Italian organised screening programmes.[9]

HPV DNA testing was performed, blind to cytology, in seven laboratories, using Hybrid Capture 2 (HC2, Digene Corporation, Gaithersburg, MD, USA). Only the high-risk group of probes, designed to detect HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68, was used. HC2 results were expressed as the ratio of each specimen's light emission compared to the average of three concurrently tested controls, each containing 1 pg/ml HPV DNA. This ratio is denoted as relative light units (RLU). Therefore, RLU can be considered as a proxy of viral load relative to 1 pg/ml.

Women with ASCUS or more severe cytology were referred to colposcopy. Colposcopists had access to patient's notes, both for cytology and HPV. Suspicious areas were biopsied.

The primary endpoint was histology-confirmed cervical intraepithelial neoplasia grade 2 or more severe or cervical cancer (CIN2+) detected during the recruitment phase. Operationally, we included lesions detected within 1 year from referral to colposcopy. Histology was independently reviewed, blinded to HPV test and cytology results, as previously described.[6]

We computed sensitivity and specificity of HPV testing for histology-confirmed CIN2 or more severe lesions (CIN2+) separately among women with ASCUS or atypical glandular cells of undetermined significance (AGUS) and with LSIL cytology and among two age groups (25–34 and 35–60). For each group we also computed the receiver operating characteristic (ROC) curves using different log-RLU values as cut-off. With RLU being a ratio, its distribution is strongly skewed and we used log-RLU in order to normalise it. We computed the area under each curve, as an overall measure of test accuracy.

3. Results

22,708 eligible women were assigned to the experimental arm. Overall, 815 women were found to have cytology of ASCUS/AGUS and 527 to have LSIL cytology. For further analyses we considered only those who had valid HPV test and had actually performed a colposcopy (757 women with ASCUS/AGUS cytology and 485 with LSIL). Among women with LSIL cytology 22/219 (10.0%) had histologically confirmed CIN2+ detected in the age group 25–34 versus 10/266 (3.8%) in the 35–60 year age group. The corresponding figures among women with ASCUS/AGUS cytology were 14/516 (2.7%) and 12/241 (5.0%) respectively. Remarkably, the positive predictive value (PPV) of the LSIL category for CIN2+ was much higher with conventional cytology (women from the conventional arm, otherwise not considered here): 14.3% (15/105) at age 25–34 and 10.3% (16/156) at age 35–60.

Fig. 1 presents the ROC curves for HPV testing in predicting histology-confirmed CIN2+. The area under the curve was significantly less among women aged 25–34 years than in the older group, both for women with ASCUS/AGUS ($p = 0.0355$) and LSIL ($p = 0.0009$), the loss being larger in the latter case. In the age group 35–60 the curves for ASCUS/AGUS and LSIL were very similar ($p = 0.62$), while in the age group 25–34 the area under the ROC curve for LSIL women was significantly less than that for ASCUS/AGUS women ($p = 0.0084$).

Sensitivity and specificity of HPV testing with different cut-off for CIN2+ by age and cytology are reported in Tables 1 and 2. Sensitivity was high in all groups with a cutoff of 1 or 2 RLU and remained always over 80% with a cut-off of 20 RLU. Specificity was relatively high for a triage situation among ASCUS/AGUS women aged 35 or more, and was intermediate among LSIL women in the same age group and in ASCUS women aged 25–34. However, it was very low among women aged less than 35 years with LSIL cytology, even with a cut-off of 20 RLU.

The number of women with CIN3+ was limited but the pattern was similar to that for CIN2+ (Tables 1 and 2), and there was a significant difference between the areas under the ROC curves when comparing ASCUS/AGUS to LSIL among women 25–34 ($p = 0.0019$) and when comparing the two age groups among LSIL women ($p < 0.0001$).

4. Discussion

In our study, all ASCUS+ women were referred for colposcopy and compliance was good. This allowed accurate estimates of the sensitivity and specificity of HPV without problems of verification bias. In addition, the primary end point, histology confirmed CIN2+, was determined by a review blinded to HPV test and cytology results. The study was population-based and nested in routine organised screening activity in a low-risk population and nearly 80% of eligible women were enrolled.[6,7]

Our results confirm the low specificity of HPV testing for triaging women with LSIL in the age group 25–34. However they show that HPV triaging performs better in older than in younger women and that reasonable specificity was also reached in women over age 35 when triaging LSIL. A cut-off of 2 RLU improved specificity with little loss of sensitivity.

In the ALTS study, where conventional cytology was used, 74.7% of women with LSIL aged 29+ were HC2 positive versus 84.8% in all ages.[10] The older group was, however, substantially younger than our group 35–60: in the ALTS study 17.6% of women with LSIL were 30 or older and only 3.3% were 40 or older.[5,10] In the HART study[11] a clear age dependency was present, although with higher levels of positivity than in NTCC: 87.0% (40/46) of women with mild dyskaryosis aged 30–35 were HC2 positive versus 65.8% (50/76) aged 35–60, further reduced to 59.0% (23/39) among women aged 40–60 (J. Cuzick, personal communication). This could depend on national criteria of interpretation of cytology or, more plausibly, on the fact that conventional cytology was used in HART.

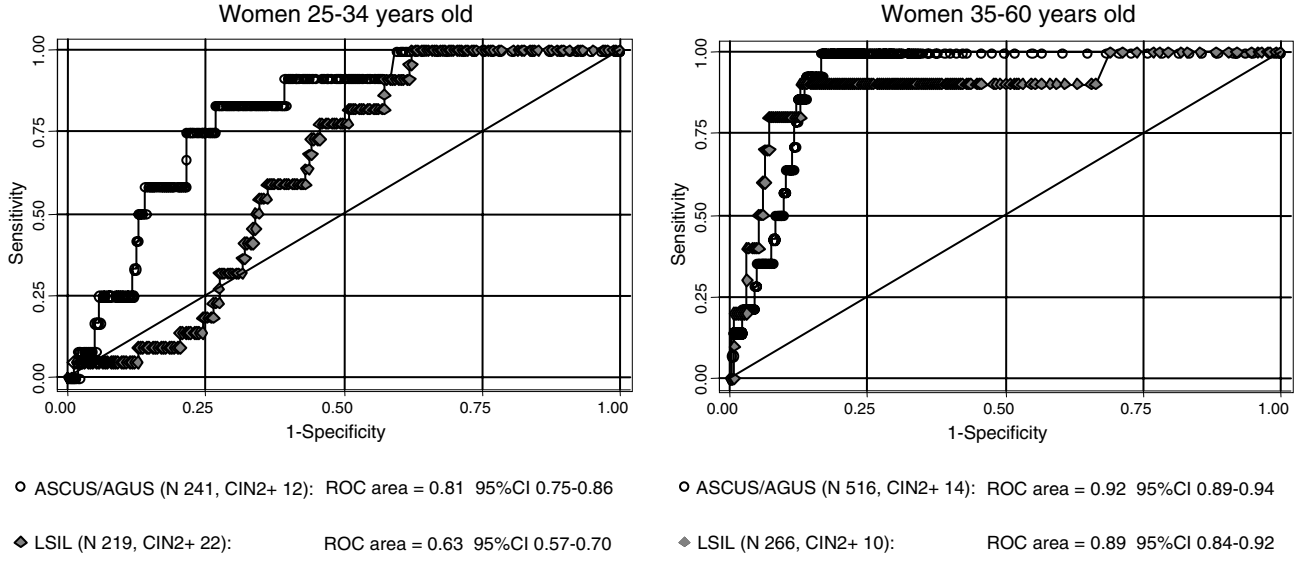

Fig. 1 – Receiver operating characteristic (ROC) curves for Hybrid Capture 2 testing at different log(RLU) of women with ASCUS/AGUS and LSIL cytology to detect CIN2+ by age group.

Table 1 – Sensitivity (95%CI) of HPV testing at different cut-off to detect histologically confirmed CIN among women with ASCUS and LSIL cytology

	Cut-off					
	1 RLU	2 RLU	4 RLU	10 RLU	20 RLU	
Endpoint: CIN2+						Total women with CIN2+
ASCUS/AGUS	92% (62–100)	92% (62–100)	83% (52–98)	83% (52–98)	83% (52–98)	12
Age 25–34	*N* = 11	*N* = 11	*N* = 10	*N* = 10	*N* = 10	
ASCUS/AGUS	100% (77–100)	100% (77–100)	93% (66–100)	86% (57–98)	64% (35–87)	14
Age 35–60	*N* = 14	*N* = 14	*N* = 13	*N* = 12	*N* = 9	
LSIL	100% (85–100)	100% (85–100)	100% (85–100)	91% (71–99)	91% (71–99)	22
Age 25–34	*N* = 22	*N* = 22	*N* = 22	N=20	N=20	
LSIL	90% (56–100)	90% (56–100)	90% (56–100)	90% (56–100)	90% (56–100)	10
Age 35–60	*N* = 9	*N* = 9	*N* = 9	*N* = 9	*N* = 9	
Endpoint: CIN3+						Total women with CIN3+
ASCUS/AGUS	86% (42–100)	86% (42–100)	86% (42–100)	86% (42–100)	86% (42–100)	7
Age 25–34	*N* = 6	*N* = 6	*N* = 6	*N* = 6	*N* = 6	
ASCUS/AGUS	100% (54–100)	100% (54–100)	100% (54–100)	100% (54–100)	67% (22–96)	6
Age 35–60	*N* = 6	*N* = 6	*N* = 6	*N* = 6	*N* = 4	
LSIL	100% (16–100)	100% (16–100)	100% (16–100)	100% (16–100)	100% (16–100)	2
Age 25–34	*N* = 2	*N* = 2	*N* = 2	N=2	*N* = 2	
LSIL	100% (54–100)	100% (54–100)	100% (54–100)	100% (54–100)	100% (54–100)	6
Age 35–60	*N* = 6	*N* = 6	*N* = 6	*N* = 6	*N* = 6	

In each cell *N* is the number of CIN2+ or CIN3+ detected by the HPV test at the relevant cut-off.
ASCUS: Atypical squamous cells of undetermined significance; AGUS: Atypical glandular cells of undetermined significance; CI: Confidence interval; CIN2+: Cervical intraepithelial neoplasia grade 2 or more severe; CIN3+: Cervical intraepithelial neoplasia grade 3 or more severe; HPV: Human papillomavirus; LSIL:Low grade squamous intraepithelial lesion; RLU: Relative light units.

Table 2 – Specificity (95%CI) of HPV testing at different cut-off to detect histologically confirmed CIN among women with ASCUS and LSIL cytology

	Cut-off					
	1 RLU	2 RLU	4 RLU	10 RLU	20 RLU	
Endpoint: CIN2+						Total women with CIN2+
ASCUS/ AGUS	57% (50–63)	60% (54–67)	63% (56–69)	67% (60–73)	73% (66–78)	229
Age 25–34	*N* = 130	*N* = 138	*N* = 143	*N* = 153	*N* = 166	
ASCUS/AGUS	77% (73–81)	83% (79–86)	85% (82–88)	88% (85–90)	89% (86–91)	502
Age 35–60	*N* = 388	*N* = 414	*N* = 427	*N* = 440	*N* = 445	
LSIL	32% (25–39)	35% (28–42)	37% (30–44)	39% (32–46)	42% (35–49)	197
Age 25–34	*N* = 62	*N* = 69	*N* = 73	*N* = 76	*N* = 82	
LSIL	61% (55–67)	65% (58–70)	67% (61–73)	69% (63–74)	71% (65–76)	256
Age 35–60	*N* = 157	*N* = 165	*N* = 172	*N* = 176	*N* = 181	
Endpoint: CIN3+						Total women without CIN3+
ASCUS/AGUS	56% (49–62)	59% (52–65)	62% (55–68)	66% (59–72)	71% (65–77)	234
Age 25–34	*N* = 130	*N* = 138	*N* = 144	*N* = 154	*N* = 167	
ASCUS/AGUS	76% (72–80)	81% (78–85)	84% (80–87)	87% (83–90)	88% (85–91)	510
Age 35–60	*N* = 388	*N* = 414	*N* = 428	*N* = 442	*N* = 448	
LSIL	29% (23–35)	32% (26–38)	34% (27–40)	36% (30–43)	39% (32–46)	217
Age 25–34	*N* = 62	*N* = 69	*N* = 73	*N* = 78	*N* = 84	
LSIL	61% (55–67)	64% (58–70)	67% (61–72)	68% (62–74)	70%(64–76)	260
Age 35–60	*N* = 158	*N* = 166	*N* = 173	*N* = 177	*N* = 182	

In each cell *N* is the number of women without CIN2+ or CIN3+ classified as negative by the HPV test at the relevant cut-off.
ASCUS: Atypical squamous cells of undetermined significance; AGUS: Atypical glandular cells of undetermined significance; CI: Confidence interval; CIN2+: Cervical intraepithelial neoplasia grade 2 or more severe; CIN3+: Cervical intraepithelial neoplasia grade 3 or more severe; HPV: Human papillomavirus; LSIL:Low grade squamous intraepithelial lesion; RLU: Relative light units.

Indeed the PPV of LSIL for CIN2+ in the conventional arm of NTCC (10.3%), where conventional cytology was employed, was similar to that for mild dyskaryosis in HART[11] (10.7% among women 30–60), while it was much lower in the NTCC experimental arm (3.8%), where LBC was used. In the ARTISTIC study,[12] where LBC was used, 54.2% of women with mild dyskaryosis aged 30–64 were HC2 positive. Also in a series of LBC samples tested by GP5+/GP6+ PCR 60% of women younger

than 30 years with LSIL and 44% of those aged 30+ had at least one of 13 high-risk types detected.[13]

Better specificity of HPV testing for ASCUS triage has been observed with increasing age.[9,14,15]

The number of CIN2+ lesions in some groups was limited, resulting in wide confidence intervals for sensitivity. However HPV testing has been shown to have high sensitivity independently of the concomitant cytology and this does not seem to be age-dependent.[16]

In conclusion, NTCC results suggest that HPV triaging for LSIL cytology should not be applied in younger women while at higher ages, especially when liquid based cytology is used; it substantially reduces referral rates compared to universal referral and should be considered as an option.

Conflict of interest statement

Jack Cuzick is a member of the speaker's bureau for Digene Corp. and his institution has research funding from Roche Diagnostics for a different study. Francesca Carozzi is the principal investigator of a grant to his institution from Roche Molecular System. Massimo Confortini is the principal investigator of a grant to his institution from Menarini Diagnostics. Both these grants are for studies different from the present one. None of the other authors have any conflict of interest to declare.

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