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Age-Specific Patterns of Unsatisfactory Results for Conventional Pap Smears and Liquid-Based Cytology: Data from Two Randomized Clinical Trials

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Abstract

Objective—To investigate the rate of unsatisfactory cervical cell samples in liquid-based (LBC) versus conventional cytology (CC) by age.

Design—randomised clinical trials.

Setting—population-based cervical cancer screening in the Netherlands and Italy

Population and sample—asymptomatic women invited for screening enrolled in two randomised trials: NETHCON (Netherlands ThinPrep vs. Conventional Cytology, 39,010 CC, 46,064 LBC) and NTCC (New Technologies in Cervical Cancer Screening, 22,771 CC, 22,403 LBC).

Methods—Comparison of categorical variables using Pearson's chi2 test, logistic regression and trend tests.

Main outcomes—proportion of unsatisfactory samples, ratio LBC versus CC, variation by 5-year group.

Trial Registration

NTCC: Current Controlled Trials ISRCTN81678807.

NETHCON: trialregister.nl Identifier: NTR1032

Disclosure of interest:

For NTCC: MC is the principal recipient of a grant to the Scientific Institute for Cancer Prevention of Tuscany Region from Menarini Diagnostics. This grant is for another study.

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Contribution of authorship:

PC: study design of current paper, statistical analysis, writing of the manuscript;

GR, MA: study design of current paper, critical review of manuscript, statistical analysis;

JB, MC, PK, AP, AGS: laboratory analyses, organisation of the trials, critical review of manuscript;

JB & PK: PI of NETHCON; GR: PI of NTCC.

Ethical approval:

The NTCC study was approved by the local research ethics committees of the participating centers. Ethical approval was obtained by the Dutch Ministry of Health, Welfare, and Sport for the NETHCON trial.

Results—In NETHCON, a lower percentage of LBC samples were called unsatisfactory compared to CC (0.33% vs. 1.11%). There was no significant trend in unsatisfactory results by age group for conventional cytology ($p_{\text{trend}} = 0.54$) but there was a trend towards an increasing percentage of unsatisfactory results with increasing age for LBC ($p_{\text{trend}} < 0.001$). In NTCC, a lower percentage of LBC samples were called unsatisfactory compared to conventional cytology (2.59% vs. 4.10%). There was a decrease in the unsatisfactory results by age group with conventional cytology ($p_{\text{trend}} < 0.001$) and with LBC ($p_{\text{trend}} = 0.01$), although the latter trend was due just to the 55–60 years age group ($p_{\text{trend}} = 0.62$ when excluding this group).

Conclusions—The clinical trial in which the results were collected and the cytologic method used were the most important determinants of unsatisfactory cytology. In all situations, the proportion of unsatisfactory samples was lower in LBC compared to CC. The effects of age depended on the criteria used to define unsatisfactory results.

Keywords

cervical cancer screening; liquid-based cytology; conventional cytology; Pap smear; specimen adequacy

Introduction

Cervical cytology has been the mainstay of cervical cancer screening and prevention programmes since the mid-20th century. In many programs, the conventional cytology (Pap smears) have given way to liquid-based cytology (LBC), such as ThinPrepTM (Hologic, Bedford, MA, USA) and SurePathTM (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Despite the rapid adoption of LBC as the preferred cytologic method in the US, a recent meta-analysis¹ and two randomized controlled trials^{2,3} have concluded that LBC provides no appreciable gains in clinical accuracy over conventional cytology in the detection of precancerous lesions and cancer. One distinct advantage of LBC over conventional cytology is fewer unsatisfactory results, which is primarily due to obscuration by inflammation or blood or due to inappropriate spread or fixation of cells⁴. LBC preparations can also be interpreted more quickly and residual material can be used easily for ancillary molecular testing⁴.

The determinants of unsatisfactory cytology results, aside from the cytologic method, are not well described. Anecdotal, increasing age, especially after menopause, might contribute to the occurrence of unsatisfactory cytology results because of tissue atrophy in the non-estrogenic state following reduced ovarian function. A recent study conducted in the US found that women who had unsatisfactory cytology results were older, menopausal, and/or post-hysterectomy than those who did not have an unsatisfactory result⁵.

Few studies have been reported on the possible impact of cytologic method and age on the occurrence of unsatisfactory results. Two recently completed clinical trials conducted in the Netherlands³ and in Italy², randomizing women to LBC or conventional cytology, provide an opportunity to describe and evaluate age-specific fractions of unsatisfactory results by cytologic method without bias.

Methods

NETHCON (**N**etherlands **T**hinPrep vs. **C**onventional Cytology) was a cluster-randomized clinical trial of consenting women aged 30 to 60 years living in the Netherlands to compare liquid and conventional cytology for detection of histologically-confirmed cervical intraepithelial neoplasia. The trial has been previously described in detail^{3,6}. Briefly, the trial enrolment was from April of 2003 through July of 2006. Five hundred women younger

than 30 years, not eligible for the screening program, were randomized as well and included in the current study. Specimens for both cytologic methods were collected using the Rovers Cervex-Brush (Rovers Medical Devices BV, Oss, the Netherlands)⁷. Cervical specimens for conventional cytology were processed by spreading the cells onto a glass slide and fixing cells within a few minutes. Cervical specimens for ThinPrep were eluted into the PreservCyt buffer and slides were made from the cell suspension using the ThinPrep 3000 Processor. The CISOE-A system⁸ was used for cytologic reporting. Both cytology preparations were evaluated by 2 pathology labs located in Nijmegen and Eindhoven (East-Netherlands).

Criteria for specimen adequacy for conventional slides were based on Bethesda 2001 criteria⁹ and were semi-quantitative by nature. A conventional cytology was considered unsatisfactory when more than 75 percent of the epithelial cells were obscured or could not be well-visualized. Cellularity was assessed semi-quantitatively by counting the number of squamous cells in twenty-five fields using 10-fold magnification with a minimum of 25 well-visualized and preserved squamous cells per field of view for an adequate conventional cytology. For liquid-based cytology, a minimum of 10 fields-of-view with a 40× objective should contain minimal 7 well visualized and preserved squamous cells to achieve a minimum of 5,000 cells per slide. However, when atrophic cellular changes were found, these criteria were applied more liberally, both for conventional as well as for liquid-based cytology.

The NTCC (New Technologies in Cervical Cancer Screening) Trial was a randomized clinical trial of consenting women aged 25 to 60 years living in Italy to compare new screening tests, including human papillomavirus (HPV) DNA testing and LBC, versus the conventional Pap test. The trial has been previously described in detail^{2,10}. Briefly, the trial enrolment was during 2002–3. Women were individually randomized to either conventional cytology or liquid-based cytology and HPV DNA testing. Specimens for both cytologic methods were collected using a plastic Ayre's spatula and a cytobrush. Cervical specimens for conventional cytology were processed by spreading the cells onto a glass slide. Cervical specimens for ThinPrep were eluted into the PreservCyt buffer and slides were made from the cell suspension using the ThinPrep 2000 Processor. The 1991 Bethesda System¹¹, without sub-categorization of atypical squamous cells of undetermined significance, was used for cytologic reporting.

The criteria for specimen adequacy for conventional slides and liquid based-cytology were based on a modified 1991 Bethesda System¹¹ except that the definition "satisfactory for evaluation but limited by" was not considered, which is consistent with the 2001 Bethesda System⁹. The following criteria were applied in order to define unsatisfactory specimens: 1) Scant squamous epithelial component (well-preserved and well visualized epithelial cells spread over less than 10% of the slide surface); 2) obscuring blood, inflammation, thick area, poor fixation, air artefact, and/or contaminant, which precludes interpretation of approximately 75% or more of the epithelial cells, and/or 3) Lack of an endocervical / transformation zone component, except in women with atrophic changes such as post-menopausal women.

Neither study included vaginal vault specimens.

Statistical Methods

We examined the percentage/fraction of unsatisfactory results by five-year age groups and by cytologic method. Both studies enrolled women up to the age of 60 so the oldest age group was 55–60 years. The percentage and binomial 95% confidence interval (95%CI) was calculated for each age-group and cytologic method.

We started with an *a priori* that the two studies would have similar patterns of unsatisfactory results by age and cytologic method such that the two studies could be combined for increased precision. However, in case of inter-study heterogeneity (Cochran's $Q < 0.05$), the proportion of unsatisfactory specimen by age will be presented for each study separately.

To compare the effects of age for a given cytologic method, odds ratios were calculated using the 30–34 year age group as the referent, with two-sided Pearson chi-square tests performed to test for statistical significant differences ($p < 0.05$). To evaluate age-group specific differences by cytologic method, ratios of unsatisfactory results with 95%CI were calculated. A linear effect of age in modifying the method/unsatisfactory odds ratios was estimated and tested as interaction term in an unconditional logistic regression. Generalized linear models were used to estimate the overall impact of study, cytologic preparation, and age.

Results

The unsatisfactory results for both studies are summarized in the Table 1 and plotted in the Figure 1. In NETHCON, 39,010 and 46,064 women underwent conventional cytology and LBC screening, respectively. A lower percentage of LBC samples was called unsatisfactory compared to conventional cytology, 0.33% vs. 1.11%, respectively, for a ratio (LBC to Pap) of unsatisfactory results of 0.30 (95%CI = 0.25–0.36). There was no significant trend in unsatisfactory results by age group for conventional cytology ($p_{\text{trend}} = 0.54$) but there was a trend towards an increasing percentage of unsatisfactory results with increasing age for LBC ($p_{\text{trend}} < 0.001$). Thus, the effect of LBC (vs. Pap) on unsatisfactory results decreased with increasing age ($\beta = 0.037$; $p = 0.0006$), and the LBC/Pap ratio in the proportion of unsatisfactory slides ranged from 0.15 (95% CI = 0.02–1.31) in women aged 25–29 years to 0.50 (95% = 0.37–0.69) in women aged 55–60 years, respectively.

In NTCC (Table 1, Figure 1), 22,771 women underwent conventional cytology screening and 22,403 women underwent LBC. A lower percentage of LBC samples was called unsatisfactory compared to conventional cytology, 2.59% vs. 4.10%, respectively, for a ratio (LBC to Pap) of unsatisfactory results of 0.63 (95%CI = 0.57–0.70). Overall, the cytopathologists participating in the Italian trial were more likely than those in the Dutch trial to call slides as unsatisfactory with either cytologic method ($p < 0.001$). In contrast to NETHCON, there was a decrease in the unsatisfactory results with older age groups using conventional cytology ($p_{\text{trend}} < 0.001$). There was also a decreasing proportion of unsatisfactory slides with older age groups using LBC ($p_{\text{trend}} = 0.01$). However the trend in LBC was due just to the 55–60 years age group ($p_{\text{trend}} = 0.62$ when excluding this group). The age trends with LBC were significantly different between studies when considering all ages ($p_{\text{interaction}} < 0.0001$) but not when excluding the oldest group ($p = 0.44$).

Also in NTCC, a lower percentage of LBC samples were called unsatisfactory compared to the conventional cytology, 2.59% vs. 4.10%, for a ratio (LBC to Pap) of unsatisfactory results of 0.63 (95%CI = 0.57–0.70). This ratio ranged from 0.49 (95% = 0.57–0.70) in women aged 25–29 years to 1.00 (95% = 0.75–1.33) in women aged 45–49 years, respectively. In age groups 50 and older, the ratio slightly decreased but only the ratio for women aged 55–60 years was significantly less than 1. Nevertheless there was an overall significant decreasing effect of LBC with increasing age, although smaller than in the Dutch study ($\beta = 0.018$; $p = 0.002$).

The generalized linear models confirmed these findings. Overall, the proportion of unsatisfactory cytologic results was 4 times less in NETHCON compared to NTCC, and the decrease in unsatisfactory cytology using LBC was greater for NETHCON (odds ratio [OR]

= 0.48, 95% CI = 0.39–0.59) than for NTCC (OR = 0.62, 95% CI = 0.56–0.69). There was a 1.2% and 2.8% decrease in the proportion of unsatisfactory cytology by year of age in NTCC for LBC and conventional cytology, respectively. In NETHCON, there was an 8.8% increase in the proportion of unsatisfactory cytology in women 50 years and older using LBC but there was no relationship between age and the proportion of unsatisfactory cytology for conventional cytology.

Two labs read cytology for NETHCON and 9 labs (6 labs in Turin acted as one lab as they had common quality assurance procedures) read the cytology in NTCC. LBC and conventional slides were assigned to the same cytologists in each lab. The variability in cytology specimen inadequacy by study, laboratory, and method is shown in Table 2. There was significant variation in specimen inadequacy by laboratory in NETHCON ($p < 0.001$) and in NTCC ($p < 0.001$). Notably, the range in variation in specimen inadequacy was less for LBC (NETHCON: 0.33%–0.34%; NTCC: 1.72%–3.84%) compared to conventional cytology (NETHCON: 0.87%–1.28%; NTCC: 1.22%–18.94%). There was also significant statistical interaction between laboratory and cytology method in NETHCON ($p < 0.03$) and in NTCC ($p < 0.001$). In both NETHCON laboratories, LBC showed systematically lower inadequacy rates compared to CC, whereas this was not always the case in the NTCC laboratories.

Discussion

We found significant variation in the percentage of specimen inadequacy between studies. NTCC had a percentage of specimen inadequacy that was approximately 4- to 5-fold higher for the conventional slides and 8- to 10-fold higher for the LBC slides compared to NETHCON. NTCC found the percentage declined with age while NETHCON showed a slight increase with age.

In both studies, the proportion of samples judged as unsatisfactory was significantly lower using LBC than conventional cytology, consistent with the many previous reports⁴. However, the effect of LBC on the unsatisfactory rate was much greater in the Dutch than in the Italian study. The magnitude of the differences observed in NETHCON could partly be due to the differences in the number of cells read by each method (25 fields of a minimum of 25 cells per field for conventional cytology versus a minimum of 5,000 cells for LBC). Relevant differences in the proportion of slides judged as unsatisfactory between countries have already been observed in previous meta-analyses of studies on LBC⁴. In a recent comparison between process results of routine screening programs in Europe¹³, mainly based on conventional cytology, the proportion of women undergoing a repeat screen because of an unsatisfactory conventional cytology varied between 0.2% in Slovenia and 0.8% in the Netherlands to 4.9% in Ireland and 8.0% in England. This suggests that different actual criteria for judging cytology as unsatisfactory are applied in different countries. However, we cannot rule out that the observed differences between studies are simply due to the different sampling devices or the different systems for reporting cytology used in the two studies.

We also observed significant differences in percentage of unsatisfactory cytology specimens between laboratories within each of the two studies in the proportion of slides judged as unsatisfactory and in the effect of the preparation on such proportion. This shows significant variability exists within country in judging slides as unsatisfactory.

We did not observe a consistent effect of age on the proportion of unsatisfactory results in our analysis. For conventional cytology, there was no obvious age trend in NETHCON where there was a marked decrease with age in NTCC. For LBC, there was no apparent

effect with age in either study except in the oldest age group, in which the proportion of unsatisfactory cytology increased in NETHCON (by 88% above the mean inadequate rate for all age groups) and decreased in NTCC (by 37% below the mean inadequate rate for all age groups). Thus, it seems likely that the criteria for judging cytology unsatisfactory may influence the impact of age on the proportion of unsatisfactory results. In general, the reduction of unsatisfactory slides with LBC compared to conventional cytology was greatest in younger women and decreased with increasing age.

Regardless of the cause, the impact of unsatisfactory cytology has important consequences as an unsatisfactory result typically triggers a clinical follow-up to ensure safety^{7,14,15}. Cervical cytology remains an important screening tool for prevention of cervical cancer, and improving quality control of cytology with regards to unsatisfactory results, including the development of global standards, should be made a priority within the cytopathology community.

In conclusion, the cytologic method being used and the cytopathologists reading the slides and/or the criteria employed were the main determinants for the occurrence of unsatisfactory cytology. The impact of age appeared to be minor and to depend primarily on the criteria used to judge an unsatisfactory cytology result.

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Figure 1. Proportion of unsatisfactory cervical cell samples by age and preparation method (conventional cytology versus LBC) in two randomized trials conducted in the Netherlands (above) and Italy (below).

Table 1

Age group specific percentage of unsatisfactory results (%Unsat) and 95% confidence intervals (95%CI) for conventional cytology and liquid-based cytology (LBC) from two randomized clinical trials. Odds ratio (OR) and 95%CI were calculated to examine the effects of age on the fraction of unsatisfactory results, using the 30–34 age group as a reference. Bold type indicates a p value < 0.05. Ratios and 95%CI were calculated to determine the age-group specific differences in the fraction of unsatisfactory results between conventional cytology and LBC.

NETHCON (Dutch)	Conventional Cytology						Liquid-Based Cytology (LBC)						LBC vs. Conventional	
	N	N _{unsat}	%Unsat	95%CI	OR	95%CI	N	N _{unsat}	%Unsat	95%CI	OR	95%CI	Ratio	95%CI
Age Group (Years)														
25–29	238	5	2.10%	0.69%–4.83%	1.9	0.59–4.6	309	1	0.32%	0.01%–1.79%	1.3	0.031–7.8	0.15	0.02–1.31
30–34 (ref)	7,925	90	1.14%	0.91%–1.39%	1.0	----	9,807	25	0.25%	0.17%–0.38%	1.0	----	0.22	0.14–0.35
35–39	5,458	59	1.08%	0.82%–1.39%	0.95	0.67–1.3	6,692	15	0.22%	0.13%–0.37%	0.88	0.41–1.7	0.20	0.12–0.37
40–44	6,915	72	1.04%	0.82%–1.31%	0.92	0.66–1.3	8,430	17	0.20%	0.12%–0.32%	0.79	0.40–1.5	0.19	0.11–0.33
45–49	4,723	44	0.93%	0.68%–1.25%	0.82	0.56–1.2	5,589	21	0.38%	0.23%–0.57%	1.5	0.78–2.7	0.41	0.24–0.68
50–54	5,275	59	1.12%	0.85%–1.44%	0.98	0.70–1.4	5,796	15	0.26%	0.14%–0.43%	1.0	0.50–2.0	0.23	0.13–0.41
55–60	8,476	105	1.24%	1.01%–1.50%	1.1	0.81–1.5	9,441	59	0.62%	0.48%–0.81%	2.5	1.5–4.1	0.50	0.37–0.69
All	39,010	434	1.11%	1.01%–1.22%			46,064	153	0.33%	0.28%–0.39%			0.30	0.25–0.36
NTCC (Italian)	Conventional Cytology						Liquid-Based Cytology (LBC)						LBC vs. Conventional	
	N	N _{unsat}	%Unsat	95%CI	OR	95%CI	N	N _{unsat}	%Unsat	95%CI	OR	95%CI	Ratio	95%CI
Age Group (Years)														
25–29	2,627	147	5.60%	4.75%–6.54%	1.1	0.90–1.4	2,672	74	2.77%	2.18%–3.46%	0.96	0.70–1.3	0.49	0.38–0.65
30–34 (ref)	3,237	160	4.94%	4.22%–5.75%	1.0	----	3,274	94	2.87%	2.33%–3.50%	1.0	----	0.58	0.45–0.75
35–39	4,025	201	4.99%	4.34%–5.71%	1.0	0.81–1.3	3,978	108	2.71%	2.23%–3.27%	0.94	0.71–1.3	0.54	0.43–0.68
40–44	3,880	173	4.46%	3.83%–5.16%	0.90	0.72–1.1	3,804	97	2.55%	2.07%–3.10%	0.89	0.66–1.2	0.57	0.45–0.73
45–49	3,058	92	3.01%	2.43%–3.68%	0.60	0.45–0.78	2,986	90	3.01%	2.43%–3.69%	1.1	0.76–1.4	1.00	0.75–1.33
50–54	3,031	90	2.97%	2.39%–3.64%	0.59	0.45–0.77	2,908	72	2.48%	1.94%–3.11%	0.86	0.62–1.2	0.84	0.61–1.13
55–60	2,913	70	2.40%	1.88%–3.03%	0.47	0.35–0.63	2,781	45	1.62%	1.18%–2.16%	0.56	0.38–0.81	0.68	0.46–0.98
Total	22,771	933	4.10%	3.84%–4.36%			22,403	580	2.59%	2.38%–2.81%			0.63	0.57–0.70

Table 2

Variability in cytology specimen inadequacy by study, method, and clinical center.

	Conventional		LBC		OR	95%CI
	N	%Inadequate	N	%Inadequate		
NETHCON (Dutch)						
Eindhoven	23,269	1.28%	30,372	0.33%	0.26	0.20–0.32
Nijmegen	15,741	0.87%	15,694	0.34%	0.39	0.28–0.53
Total	39,010	1.11%	46,066	0.33%	0.30	0.25–0.36
NTCC (Italian)						
Bologna	1,534	4.50%	1,564	3.84%	0.85	0.58–1.2
Firenze	4,175	1.22%	4,202	2.19%	1.8	1.3–2.6
Imola	1,397	2.86%	1,392	1.72%	0.60	0.34–1.0
Padova	2,058	7.00%	2,031	3.55%	0.49	0.36–0.66
Ravenna	1,632	3.06%	1,567	1.98%	0.64	0.39–1.0
Trento	2,096	3.44%	2,108	3.51%	1.0	0.72–1.4
Torino*	6,879	2.15%	6,549	1.97%	0.91	0.71–1.2
Verona	1,473	18.94%	1,403	2.71%	0.12	0.082–0.17
Viterbo	1,527	5.24%	1,587	3.78%	0.71	0.50–1.0
Total	22,771	4.10%	22,403	2.59%	0.62	0.56–0.69