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Age-specific patterns of unsatisfactory results for conventional Pap smears and liquid-based cytology: data from two randomised clinical trials

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

Design Randomised clinical trials.

Setting Population-based cervical cancer screening in the Netherlands and Italy.

Population Asymptomatic women invited for screening enrolled in two randomised trials: Netherlands ThinPrep® versus conventional cytology (NETHCON; 39 010 CC, 46 064 LBC) and New Technologies in Cervical Cancer Screening (NTCC; 22 771 CC, 22 403 LBC).

Methods Comparison of categorical variables using Pearson's chi-square test, logistic regression and trend tests.

Main outcome measures Proportion of unsatisfactory samples, ratio of LBC versus CC, and variation by 5-year group.

Results In NETHCON, a lower percentage of LBC samples were judged to be unsatisfactory compared with CC samples (0.33 versus 1.11%). There was no significant trend in unsatisfactory results by age group for conventional cytology (P_{trend} = 0.54), but there was a trend towards an increasing percentage of unsatisfactory results with increasing age for LBC (P_{trend} < 0.001). In NTCC, a lower percentage of LBC samples were judged to be unsatisfactory compared with conventional cytology (2.59 versus 4.10%). There was a decrease in the unsatisfactory results by age group with conventional cytology (P_{trend} < 0.001) and with LBC (P_{trend} = 0.01), although the latter trend arose from the 55–60-years age group (P_{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 with CC. The effects of age depended on the criteria used to define unsatisfactory results.

Keywords Cervical cancer screening, conventional cytology, liquid-based cytology, Pap smear, specimen adequacy.

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Introduction

Cervical cytology has been the mainstay of cervical cancer screening and prevention programmes since the mid-20th century. In many programmes, the conventional cytology (Pap smears) have given way to liquid-based cytology (LBC), such as ThinPrep® (Hologic, Bedford, MA, USA) and SurePath® (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Despite the rapid adoption of LBC as the preferred cytologic method in the USA, a recent meta-analysis[1] and two randomised 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 primarily arises because of obscuration by inflammation or blood, or from the inappropriate spread or fixation of cells.[4] LBC preparations can also be interpreted more quickly, and residual material can be used easily for ancillary molecular testing.[4]

The determinants of unsatisfactory cytology results, aside from the cytologic method, are not well described. Anecdotally, increasing age, especially after the 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 USA found that women who had unsatisfactory cytology results were older, menopausal, and/or had undergone a hysterectomy, compared with those who did not have an unsatisfactory result.[5]

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 Netherlands[3] and in Italy,[2] randomising 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

Netherlands ThinPrep® versus conventional cytology (NETHCON) was a cluster-randomised clinical trial of consenting women aged 30–60 years, living in the Netherlands, and was designed to compare liquid and conventional cytology for the detection of histologically confirmed cervical intraepithelial neoplasia. The trial has previously been 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 of age, not eligible for the screening programme, were also randomised 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 system was used for cytologic reporting.[8] Both cytology preparations were evaluated by two pathology labs located in Nijmegen and Eindhoven (East Netherlands).

Criteria for specimen adequacy for conventional slides were based on the Bethesda 2001 criteria,[9] and were semi-quantitative by nature. A conventional cytology was considered unsatisfactory when more than 75% of the epithelial cells were obscured or could not be clearly visualised. Cellularity was assessed semi-quantitatively by counting the number of squamous cells in 25 fields using ten-fold magnification, with a minimum of 25 clearly visualised and preserved squamous cells per field of view for an adequate conventional cytology. For LBC, a minimum of ten fields of view with a 40′ objective should contain a minimum of seven clearly visualised and preserved squamous cells to achieve a minimum of 5000 cells per slide. However, when atrophic cellular changes were found, these criteria were applied more liberally, both for conventional as well as for LBC.

The New Technologies in Cervical Cancer Screening (NTCC) trial was a randomised clinical trial of consenting women aged 25–60 years living in Italy that compared new screening tests, including human papillomavirus (HPV) DNA testing and LBC, with the conventional Pap test. The trial has previously been described in detail.[2,10] Briefly, the trial enrolment was during 2002–2003. Women were individually randomised to either conventional cytology or LBC 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 System,[11] without the subcategorisation of atypical squamous cells of undetermined significance, was used for cytologic reporting.

The criteria for specimen adequacy for conventional slides and LBC were based on a modified 1991 Bethesda System,[11] except that the definition 'satisfactory for evaluation but limited by' was not considered, which is consistent with the 2001 Bethesda System.[9] The following criteria were applied in order to define unsatisfactory specimens: (1) scant squamous epithelial component (well-preserved and clearly visualised 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 the cytologic method. Both studies enrolled women up to the age of 60 years, 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 the case of interstudy heterogeneity (Cochran's $Q < 0.05$), the proportion of unsatisfactory specimens by age will be presented for each study separately.[12]

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

Results

The unsatisfactory results for both studies are summarised in Table 1 and are plotted in 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 with conventional cytology: 0.33 versus 1.11%, respectively, for a ratio (LBC/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 ($P_{trend} = 0.54$), but there was a trend towards an increasing percentage of unsatisfactory results with increasing age for LBC ($P_{trend} < 0.001$). Thus, the effect of LBC (versus 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% CI 0.37–0.69) in women aged 55–60 years, respectively.

In NTCC (Figure 1; Table 1), 22 771 women underwent conventional cytology screening and 22 403 women underwent LBC. Overall, the cytopathologists participating in the Italian trial were more likely than those in the Dutch trial to judge slides to be 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 ($P_{trend} < 0.001$). There was also a decreasing proportion of unsatisfactory slides with older age groups using LBC ($P_{trend} = 0.01$). However, the trend in LBC was only due to the 55–60-year age group ($P_{trend} = 0.62$ when excluding this group). The age trends with LBC were significantly different between studies when considering all ages ($P_{interaction} < 0.0001$), but not when excluding the oldest group ($P = 0.44$).

Also, in NTCC a lower percentage of LBC samples were judged to be unsatisfactory compared with conventional cytology: 2.59 versus 4.10% for a ratio (LBC to CC) of unsatisfactory results of 0.63 (95% CI 0.57–0.70). This ratio ranged from 0.49 (95% CI 0.57–0.70) in women aged 25–29 years to 1.00 (95% CI 0.75–1.33) in women aged 45–49 years, respectively. In age groups of 50 years 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 this was smaller than in the Dutch study ($\beta = 0.018$; $P = 0.002$).

The generalised linear models confirmed these findings. Overall, the proportion of unsatisfactory cytologic results was four times less in NETHCON compared with NTCC, and the decrease in unsatisfactory cytology using LBC was greater for NETHCON (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 aged 50 years and older using LBC, but there was no relationship between age and the proportion of unsatisfactory cytology for conventional cytology.

Two labs performed the cytology for NETHCON and nine labs (six labs in Turin acted as one lab, as they had common quality-assurance procedures) performed 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 with conventional cytology (NETHCON, 0.87–1.28%; NTCC, 1.22–18.94%). There was also significant statistical interaction between laboratory and cytology methodology in NETHCON ($P < 0.03$) and in NTCC ($P < 0.001$). In both NETHCON laboratories, LBC showed systematically lower inadequacy rates compared with 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 between four- and five-fold higher percentage of specimen inadequacy for the conventional slides, and between eight- and ten-fold higher for the LBC slides, compared with NETHCON. NTCC found the percentage declined with age, whereas NETHCON showed a slight increase with age.

Table 1. Age group-specific percentages of unsatisfactory results (%Unsat) and 95% CIs for conventional cytology and LBC from two randomised clinical trials. Odds ratios (ORs) and 95% CIs were calculated to examine the effects of age on the fraction of unsatisfactory results, using the 30–34 years of age group as a reference. Bold type indicates $P < 0.05$. Ratios and 95% CIs were calculated to determine the age-group specific differences in the fraction of unsatisfactory results between conventional cytology and LBC

	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
NETHCON (Dutch)														
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)														
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

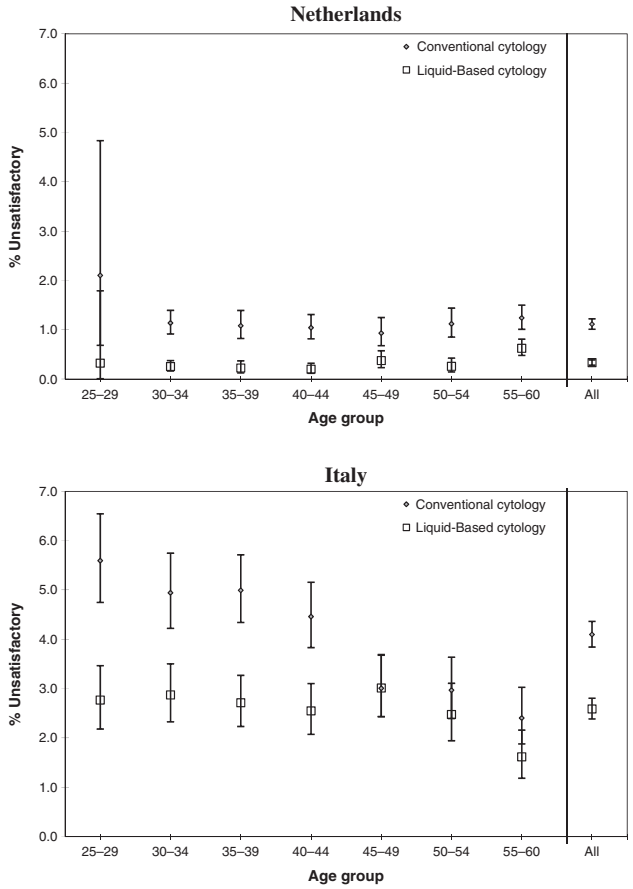

Figure 1. Proportion of unsatisfactory cervical cell samples by age and preparation method (conventional cytology versus LBC) in two randomised trials conducted in the Netherlands (above) and Italy (below).

In both studies, the proportion of samples judged to be unsatisfactory was significantly lower using LBC than conventional cytology, consistent with many previous reports.[4] 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 result from 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 5000 cells for LBC). Relevant differences in the proportion of slides judged as unsatisfactory between countries have already observed in previous meta-analyses of studies on LBC.[4] In a recent comparison between process results of routine screening programmes in Europe,[13] mainly based on conventional cytology, the proportion of women undergoing a repeat screen because of 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 criteria for judging cytology as unsatisfactory are applied in different countries. However, we cannot rule out that the observed differences between studies are simply the result of different sampling devices or different systems for reporting cytology used in the two studies.

We also observed significant differences in 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 proportions. This shows that significant variability exists within each 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, whereas 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 to be unsatisfactory may influence the impact of age on the proportion of unsatisfactory results. In general, the reduction of unsatisfactory slides with LBC compared with 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 the prevention of cervical cancer, and improving the 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.

Disclosure of interests

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Contribution of authorship

PC contributed to the study design of the current paper, the statistical analysis, and the writing of the manuscript.

Table 2. Variability in cytology specimen inadequacy by study, method, and clinical centre

	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

GR and MA contributed to the study design of the current paper, the critical review of the manuscript, and the statistical analysis. JB, MC, PK, AP, and AGS contributed to the laboratory analyses, the organisation of the trials, and the critical review of the manuscript. JB and PK were the principle investigators of the NETHCON trial and GR was the PI of the NTCC trial.

Details of ethics approval

The NTCC study was approved by the local research ethics committees of the participating centres. Ethical approval was obtained by the Dutch Ministry of Health, Welfare, and Sport for the NETHCON trial. Trial registration: NTCC, Current Controlled Trials ISRCTN81678807; NETHCON, trialregister.nl identifier NTR1032.

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