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Switching from Neural Networks (PAPNET) to the Imager (Hologic) for Computer-Assisted Screening

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Key Words
PAPNET neural network scanning · Imager · Computer-assisted screening · Cytoscores · BoonFix

Abstract
Objective: The large set of ThinPrep slides prepared in the Leiden Cytology and Pathology Laboratory is exploited for calculating the impact of the transition from PAPNET neural network scanning to the Imager technology. ***Study Design:*** All cervical samples were suspended and fixed in the coagulant fixative BoonFix. We compared 57,541 ThinPrep slides which were scanned by PAPNET and 64,273 ThinPrep slides processed with the Imager: 99,157 cases originated from the Dutch population screening program of asymptomatic women (screenees) and the remaining 22,657 samples were of symptomatic women. In the PAPNET series, 23% were diagnosed by additional light microscopy; in the Imager method, *all* slides were studied light microscopically. The cytoscores (positive cytology per 1,000 samples) were calculated for normal, atypical squamous cells of undetermined significance (ASC-US), cervical intraepithelial neoplasia (CIN) grades I–II, and for CIN III+. The odds ratios (ORs) for the positive cytoscores were assessed for both the screenees and the symptomatic women. ***Results:*** The cytoscores, per 1,000 cases, for ASC-US varied from 17.77 to 40.59, for CIN I–II from 7.17 to 33.35, and for CIN III+ from 2.81 to 8.8. These 6 cytoscores were higher for symptomatic women than for screenees. We observe significantly elevated ORs for the Imager for ASC-US (1.26 and 1.23), CIN I–II (1.45) and for CIN III+ (1.58 and 1.45). These 3 ORs are higher for screenees than for symptomatic women. ***Conclusion:*** The Imager technology is more efficacious, particularly for handling screenee slides.

Introduction

Computer-assisted screening (CAS) fully profits from the skills of the cytotechnologists (CTs), because they can focus and spend ample time in judging the few microscopic fields selected by the computer. In the Leiden Cytology and Pathology Laboratory, we have used CAS since 1992 [1], and have continued to apply CAS without any interruption until today. In 2007, we switched technologies from PAPNET to Imager. All CTs involved in this transition had several years of experience with CAS PAPNET.

In the first 10 years of PAPNET CAS, 'conventional' smears prepared by the clinician were scanned. However, in 2002 the switch was made to the liquid-based cytology method known as ThinPrep® (Hologic). The ThinPrep processors use a cylinder dispersion technique and a plastic filter membrane to concentrate the cellular material

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Table 1. Cytoscores per 1,000 of 4 cytologic diagnoses of the 2 CAS methods

	Screenees (asymptomatic women)				Indication cases (symptomatic women)			
	Imager		PAPNET		Imager		PAPNET	
	cytoscore	n	cytoscore	n	cytoscore	n	cytoscore	n
Normal	963.10	49,310	972.25	46,627	908.67	11,880	923.09	8,846
ASC-US	22.23	1,138	17.77	852	49.18	643	40.59	389
CIN I–II	10.27	526	7.17	344	33.35	436	30.16	289
CIN III+	4.39	225	2.81	135	8.80	115	6.16	59
Sums	–	51,199	–	47,958	–	13,074	–	9,583

Table 2. ORs and 95% CIs for the screenees and indication cases

	Screenees (asymptomatic women)			Indication cases (symptomatic women)		
	Imager/PAPNET			Imager/PAPNET		
	OR	95% CI	significance[1]	OR	95% CI	significance[1]
ASC-US	1.26	1.15–1.38	yes	1.23	1.08–1.40	yes
CIN I–II	1.45	1.26–1.66	yes	1.12	0.97–1.31	no
CIN III+	1.58	1.27–1.95	yes	1.45	1.06–1.99	yes

[1] CIs that do not include the value 1.0 indicate a statistical significance.

[2]. Finally, the diagnostic material is transferred to the glass slide, ending up in a neat round area with evenly distributed cells. The ThinPrep slides are stained with an almost stoichometric hematoxylin to allow quantification of the DNA. These slides proved to be perfect for the PAPNET neural network scanners, so we could continue our CAS with the superior liquid-based cytology slides. The large set of screening data of ThinPrep slides is exploited for calculating the impact of the transition from PAPNET neural network scanning to the Imager technology.

Materials and Methods

All cervical samples were suspended and fixed in BoonFix and ThinPrep slides were prepared in the Leiden Cytology and Pathology Laboratory. From July 2006 to June 2007, 57,541 ThinPrep slides were scanned by the neural networks of PAPNET. Additional light microscopy was needed in 23% of the PAPNET cases. The remaining cases were diagnosed as within normal limits based on the 128 digital images of the computer screen.

From July 2007 to June 2008, 64,273 ThinPrep slides were scanned with the Imager. In the Imager method, all slides are studied light microscopically, by the 22 selected fields of view with or without additional screening of the computer slide. A slide is only processed by one of these methods.

In total, 99,157 cases originated from the Dutch population screening program of asymptomatic women (screenees). The remaining 22,657 samples were of symptomatic women (indication cases). The cytoscores (positive cytology per 1,000 samples) were calculated for normal, atypical squamous cells of undetermined significance (ASC-US), cervical intraepithelial neoplasia (CIN) grades I–II, and for more severe CIN (CIN III+), for both the screenees and the indication cases.

In the analysis of our data, we focus on the odds ratio (OR) between normal and positive cytoscores. The OR can be strengthened in measuring associations through the calculation of 95% confidence interval (CI) [3].

The OR for ASC-US/normal for screenees between Imager and PAPNET is (1,138/49,310)/(852/46,627), from the counts in table 1. This ratio of ratios is equal to 1.26, and can be found in table 2. The corresponding 95% CI is $\log(CI) = \log(OR) \pm 1.96 \times (1/1{,}138 + 1/49{,}310 + 1/852 + 1/46{,}627)^{0.5}$. With log as the natural logarithm and OR = 1.26, this gives $\log(CI) = 0.234 \pm 0.090$, or from 0.144 to 0.324. Exponentiation gives the CI from $e^{0.144}$ to $e^{0.324}$, or from 1.15 to 1.38 as in table 2. CIs that do not include the value 1.0 indicate a statistical significance.

The population of women in the 2 study periods was static, hence there was no bias that might have influenced the expected prevalence rate.

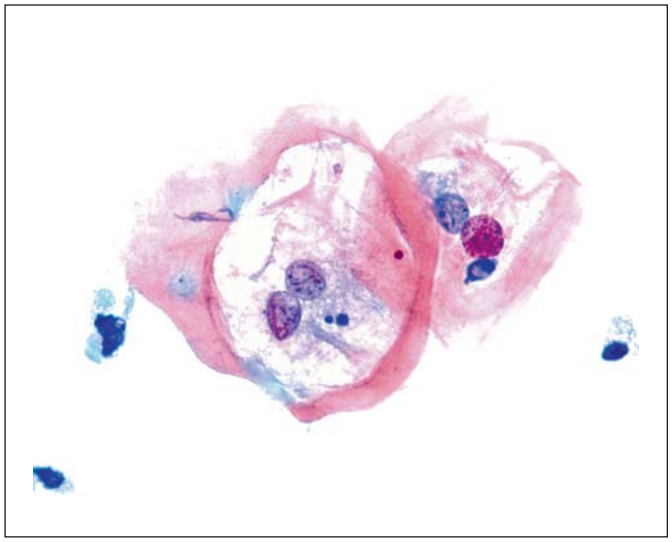

Fig. 1. Koilocytes detected by the Imager.

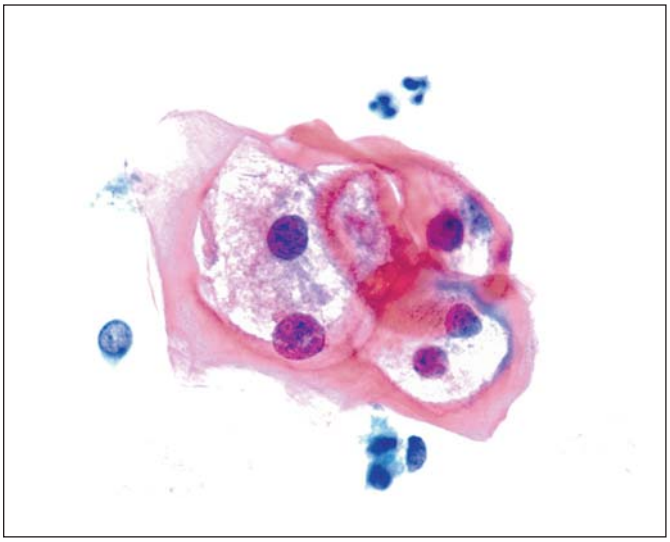

Fig. 2. Koilocytes detected by the Imager.

Results

The cytoscores per 1,000 of 4 cytologic diagnoses of the 2 CAS methods are presented in table 1. Overall, the highest positive cytoscores were those of the Imager indication cases of the study, and the lowest were found in the PAPNET screenee slides. The cytoscores for ASC-US varied from 17.77 to 40.59, for CIN I–II from 7.17 to 33.35, and for CIN III+ from 2.81 to 8.8.

The OR and 95% CI of the cytologic diagnoses of ASC-US, CIN I–II and CIN III+ are presented in table 2. From the 6 ORs, only 1 (CIN I–II indication cases) turns out not to be statistically significant. In the other 5, the superior performance of the Imager is supported by the fact that the ORs are larger than 1.0. In other words, by using the Imager method, more positive cases are detected than by using the PAPNET method.

Discussion

In this paper, we have focused on the cytologic diagnoses of ThinPrep slides processed by 2 methods of CAS and left aside the histologic diagnoses of the women referred to the gynecologist. The histoscore (positive histology per 1,000 women) for CIN III+ was 5.14‰ for screenees and 14.40‰ for indication cases. Thus, also here symptomatic women had higher prevalences. In Dutch studies, it is possible to identify samples taken from asymptomatic women (screenees), which proves to be convenient because the prevalences of positive cytology and histology are much lower than for symptomatic women.

In both CAS systems, there were a few false negatives. Interestingly enough, these false-negative diagnoses proved to be based on observer errors and not machine errors, underlining the importance of the human factor in the 2 totally different methodologies.

In the last decade of the last century, we asked ourselves whether we needed the light microscope after having become efficient in reaching a positive cytologic diagnosis based exclusively on the 128 digital images of the PAPNET computer screen. The BoonFixed digitized abnormal nuclei are visualized in enough detail to warrant a proper diagnosis. Mainly for confirmation we did additional microscopy in 23% of the cases, in 19% because inflammatory patterns were visible on the computer screen.

In our young century, we are back to the microscope using the 22 fields of view selected by the Imager [1]. The microscopic images we come across are, however, of superior quality because we have perfected our liquid-based cytology slides and apply a coagulative fixative, BoonFix, containing polyethylene glycol [4–6]. In our opinion, the thus obtained 3-dimensional light microscopic images are much more informative than the 2-dimensional PAPNET screen views.

Many laboratories have made the switch from manual screening of ThinPrep slides to using the Imager for CAS [7–11]. A Danish laboratory in Odense (also having used PAPNET in the past century) remarked that in all 10 false-negative cases, the abnormal cells had been identified by the scanner, but misinterpreted by the CT [12]. These findings stress the importance of carefulness in the interpretation of the marked fields. Beyond that, the CTs and pathologists should have more confidence in the automated system.

An American laboratory reported that although the Imager finds abnormal cells in most low-grade squamous intraepithelial lesion cases, the system may have limitations in detecting koilocytes in the 22 Imager-selected fields [13]. This is contrary to our experience: koilocytes are excellently detected (fig. 1, 2). Although not evaluated in their study, American CTs reported increased job satisfaction when the switch was made from manual screening to the ThinPrep imaging system in a high-volume metropolitan laboratory.

Note that in the study presented here the slide preparation was identical, and in both methods all positive slides (ASC-US, CIN I–II, and CIN III+) were also seen by a pathologist, who made the final diagnosis light microscopically on a cytology slide in which the abnormal cells were marked by the CT. Nevertheless, we see significantly elevated ORs for the Imager for ASC-US, CIN I–II, and for CIN III+. These 3 ORs were higher for screenees than for symptomatic women. In addition, all CTs involved prefer the Imager for their CAS because they can enjoy the light microscopy of the perfectly preserved and sublimely stained cells.

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