

# Results of the Implementation of Liquid-Based Cytology—SurePath in the Ontario Screening Program

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**BACKGROUND.** The objective of the current study was to evaluate the adequacy and detection rates of SurePath after its implementation in Ontario.

**METHODS.** The detection and adequacy rates of the SurePath liquid-based cytology system (SP-LBC) were calculated for manually reviewed slides of the year 2002. The adequacy and detection rates from this study group were compared with a historical conventional smear (CS) group from the same laboratories during the same period of the previous year.

**RESULTS.** The SP-LBC study group consisted of 352,680 specimens with cytodiagnoses and the CS group included 378,990 specimens. The unsatisfactory rate for SP-LBC (0.24%) was less than that of the CS group (0.58%). The detection rate of atypical squamous cells (ASC+) by the SP-LBC group (4.69%) was greater than that of the CS group (3.81%), as was the detection rate of low-grade squamous intraepithelial lesions (LSIL+; 2.13% vs. 1.50% in the CS group). There was only a trend toward increased detection of high-grade squamous intraepithelial lesions (HSIL+) in the SP-LBC group (0.34%) relative to the CS group (0.31%), because the detection rate for carcinoma by SP-LBC declined.

**CONCLUSIONS.** The implementation of SP-LBC has been followed by better specimen adequacy and detection rates for ASC+, LSIL+, and a trend of increased detection of HSIL+ relative to CS practice. To determine sensitivity rates, a histopathologic database for cervical carcinoma and precancer needs to be established. *Cancer (Cancer Cytopathol)* 2004;102:362-7.

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Gynecologic application of cytologic screening using liquid-based cytology (LBC) has increased in the last few years. Increasing use of LBC has permitted implementation analyses of benefits and costs of this new cytologic technology. Several reports regarding implementation of ThinPrep (Cytec, Boxborough, MA) have been published in the cytologic literature.<sup>1-8</sup> The SurePath LBC (SP-LBC) system for gynecologic screening, previously known as AutoCytePrep or CytoRich (TriPath Imaging, Burlington, NC), has not been used as widely in North America. Many studies of the SP-LBC technique have been conducted in research or small clinical settings,<sup>9-17</sup> but there have been no reports evaluating the performance of the SP-LBC technique after large-scale implementation.

Recent technology assessments of the LBC clinical evidence have concluded that LBC is more sensitive than the conventional Papanicolaou smear, and that there was insufficient evidence to conclude that there are differences in the sensitivities of ThinPrep and SurePath methods.<sup>18,19</sup> There does seem to be a continued need to examine the

merits of the SP-LBC system, approved by the Food and Drug Administration (FDA), because there is a lack of consensus on its merits. The manufacturer claims that the SP-LBC method results in a 64% increase in the detection rate of high-grade squamous intraepithelial lesions (HSIL) and carcinoma.<sup>20</sup> In contrast, a recent clinical, epidemiologic assessment of available literature in this journal by Klinkhamer et al. concluded, "There is insufficient evidence to show that the AutoCytePrep system can contribute to a higher detection rate of cervical abnormalities" in comparison to conventional screening.<sup>21</sup>

Opportunistic cervical screening has been performed in the province of Ontario for more than 4 decades, and the estimated age-standardized incidence rate for cervical carcinoma in 2004 is 7 per 100,000 women.<sup>22</sup> The cervical screening program is still considered to be opportunistic, rather than organized, because the program lacks the legislative authority for the introduction of recruitment, recall, and follow-up of women for Papanicolaou testing or necessary investigation. In 2001, two large Ontario screening laboratories introduced the SP-LBC method. The implementation of SP-LBC methodology in the province has provided an opportunity to analyze adequacy and detection rates of this methodology in cervical screening.

## MATERIALS AND METHODS

The SP-LBC method was introduced in two community laboratory systems during 2001. Each laboratory system consisted of a number of individual laboratory sites, and represented a significant proportion of the overall screening laboratory volume in the province. The majority of cytologic specimens received in these laboratories were retrieved from women during primary screening visits. The implementation of the SP-LBC technique followed the manufacturer's policies and educational program, and was conducted during the latter half of 2001. The current study only used data from the following calendar year (beginning on January 1, 2002) after the period of learning and adjustment. Only data from manually reviewed SP-LBC slides were accepted in the study. No slides were included that underwent FocalPoint (automated) review (TriPath Imaging), or were prepared using other liquid-based methodologies.

The cytology reports from these two laboratory systems were entered into CytoBase, a widely used provincial database. This database is available through a partnership agreement between Cancer Care Ontario (Ontario Cervical Screening Program) and a systems provider—Information Systems for Cytology Etc Corporation (INSCYTE), a private, nonprofit organization formed by several private medical labo-

ratories. In CytoBase, each Papanicolaou test report consists of patient identifiers and demographics, the method of the Papanicolaou test, an adequacy statement, any identified organism, and, finally, a cytodiagnosis using the 1997 Ontario-modified Bethesda System during the time period of the study. In a small percentage of reports registered in CytoBase, a cytodiagnosis is not available if the cytodiagnosis has been omitted in data submission, if only an organism is reported without an accompanying cytodiagnosis, if the birth date is absent, if the test is unsatisfactory, or if the stated age is < 10 years old or > 120 years old.

All manually reviewed SP-LBC slides were identified in CytoBase from the two laboratory systems during the period from January 1, 2002, to December 31, 2002. The historical comparison group consisted of conventional smears (CS) reported by the same laboratory sites in 2001 (before the implementation of LBC). SP-LBC slides from any laboratory site were acceptable only if a historical comparative CS was available in CytoBase for the laboratory site.

The adequacy of Papanicolaou tests was reported using the three categories outlined in the 1991 Bethesda System terminology for reporting of gynecologic cytology—*unsatisfactory*, *satisfactory but limited by...*, and *satisfactory*. For the purposes of the current study, all cytodiagnostic results were tabulated using the 2001 modified Bethesda System for ease of understanding, even though they were originally entered in the 1997 Ontario modified Bethesda System terminology. For each of the two groups, numbers of cytodiagnoses of the seven major epithelial abnormality categories (negative for intraepithelial lesion and malignancy [NILM], atypical squamous cells of uncertain significance [ASCUS], atypical squamous cells [ASC], cannot exclude high-grade squamous intraepithelial lesions [ASC-H], atypical glandular cells [AGC], low-grade squamous intraepithelial lesions [LSIL], high grade intraepithelial lesion [HSIL], and carcinoma) were tabulated. (The 1997 Ontario modified Bethesda System did include the cytodiagnostic category *ASCUS: high-grade squamous intraepithelial lesion cannot be excluded*, which is equivalent to the ASC-H category subsequently defined by the revised Bethesda terminology system in 2001.) The relative prevalence of each diagnostic category also was calculated.

To facilitate comparison of the SP-LBC study group to the historical CS group, the detection rates were analyzed at three cytodiagnostic thresholds: ASC+ (including ASCUS, ASC-H, AGUS, LSIL, HSIL, and carcinoma), LSIL+ (including LSIL, HSIL, and carcinoma), and HSIL+ (HSIL and carcinoma).

For examined parameters, comparisons were carried out using the chi-square statistic.

**TABLE 1**  
**Comparison of Adequacy Rates in the SurePath Study Group versus the Historical Comparison (Conventional) Group<sup>a</sup>**

	SurePath (%)	Conventional (%)
Unsatisfactory	915 (0.24)	2367 (0.58)
Satisfactory but limited by...	72,108 (19.01)	97,430 (24.02)
Satisfactory	306,385 (80.75)	305,859 (75.40)
Total	379,408	405,656

<sup>a</sup> Chi-square statistic = 3551.2890 (*df* = 2; *P* < 0.0001).

## RESULTS

During the study period, CytoBase received 379,408 reports of SP-LBC tests from the 2 laboratory systems. From these reports, 352,680 SP-LBC cytodiagnoses were registered. During the comparable time periods of 2001, 405,656 reports of CS Papanicolaou tests were made by the same laboratories to CytoBase (the historical comparison group). Cytodiagnoses were identified in 378,990 of these reports. In the remaining reports, a definitive cytodiagnosis was not registered within CytoBase for reasons described in the Materials and Methods section.

A comparison of adequacy rates of the SP-LBC study group versus the historical CS group is shown in Table 1. These data show that the unsatisfactory rate (0.24%) for the SP-LBC technique was less than one-half of the historical CS group (0.58%). Similarly, the proportion of tests reported as satisfactory but limited by was less in the SP-LBC study group (19.01%) than in the historical CS group (24.02%). These differences were statistically different as demonstrated by chi-square analysis.

A comparison of detection rates of the SP-LBC study group versus the historical CS group for each of the seven cytodiagnostic categories is shown in Table 2. The proportion of tests reported as NILM by the SP-LBC technique (95.29%) was less than the proportion of tests reported by the historical CS group (96.18%). The proportion of tests reported as ASCUS, ASC-H, LSIL, and HSIL was greater in the SP-LBC study group compared with the historical CS group. In contrast, the proportion of tests reported as AGC or carcinoma in the SP-LBC study group was less than the proportion of tests reported by the historical CS group. All of these differences were statistically significant as demonstrated by chi-square analysis. A chi-square analysis of the SurePath detection rate of HSIL (Table 2) versus all other cytodiagnoses confirmed the significantly increased detection rate of HSIL by SP-LBC as compared with the detection rate of HSIL by the historical CS group (*P* = 0.0182).

Table 3 compares the detection rates of the SP-

LBC and historical CS groups at the three cytodiagnostic thresholds. The detection rate of ASC+ by the SP-LBC study group (4.69%) was greater than that of the historical CS group (3.81%). The increase in the detection rate of ASC+ was largely due to the increased detection of both types of ASC (2.34% in the SP-LBC group vs. 2.07% in the CS group) and LSIL (1.79% in the SP-LBC group vs. 1.19% in the CS group). Similarly, the detection rate for LSIL+ by the SP-LBC study group (2.13%) was greater than that of the historical CS group (1.50%). Both of these differences were statistically significant using chi-square analysis. There was a trend of an increased detection rate for HSIL+ (0.34%) in the SP-LBC study group as compared with the historical CS group (0.31%), but this trend did not reach statistical significance (*P* < .0696). (The significantly increased detection rate of HSIL by SP-LBC compared with the historical CS group was for this single cytodiagnosis category only.)

## DISCUSSION

The current study examined the adequacy and detection rates of the SP-LBC technique from a provincial program cohort of > 350,000 patients. It is the largest study to date of this Papanicolaou test methodology. The study data are derived from multiple laboratories across a large geographic area within a single cervical screening program, which is generally characterized by a well screened, low-risk population. The results and conclusions of a study of this size and nature may provide a more accurate reflection of the potential value of this technique in similar screening programs than in earlier smaller, academic, and clinic-focused studies.

The study had two significant and unavoidable limitations. First, it is a retrospective, observational study conducted after the implementation of a new Papanicolaou test screening tool. The historical comparison (CS) group is drawn from the same laboratories and similar populations during the same period of the year, but is not the preferred randomized, contemporaneous control group. Using a historical comparative group assumes that the prevalence of cytodiagnostic entities is constant over time, which may not necessarily be the case. Although it was recognized that the prevalence rates of cervical disease vary across regions in Ontario, the initial study inquiry of CytoBase did not permit complete stratification by the geographic locale of laboratories within the historical group.<sup>23,24</sup> Further inquiries of CytoBase used a definition of a historical comparative group, which ensured that this historical CS group was aligned to the study group with respect to both the laboratory site and time period of the year. Not all geographic areas

**TABLE 2**  
**Comparison of Detection Rates for Seven Cytodiagnostic Categories: SurePath Study Group versus Historical Comparison (Conventional) Group<sup>a</sup>**

	No. of cases (%)							
	NILM	ASCUS	ASC-H	AGC	LSIL	HSIL	Carcinoma	Total
Conventional	364,555 (96.18)	7499 (1.98)	339 (0.09)	897 (0.24)	4519 (1.19)	1105 (0.29)	76 (0.02)	378,990 <sup>b</sup>
SurePath	336,135 (95.29)	7800 (2.21)	449 (0.13)	782 (0.22)	6330 (1.79)	1136 <sup>c</sup> (0.32)	48 (0.01)	352,680 <sup>b</sup>

NILM: negative intraepithelial lesion and malignancy; ASCUS: atypical squamous cells of undetermined significance; ASC-H: high-grade squamous intraepithelial lesion; AGC: atypical glandular cells; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

<sup>a</sup> Chi-square statistic for entire table = 545.5560 ( $df = 6$ ;  $P < 0.0001$ ).

<sup>b</sup> Totals of cytodiagnostic cases differ from totals of accessioned cases (Table 1) for reasons described in Materials and Methods.

<sup>c</sup> Chi-square statistic for HSIL versus all other cytodiagnoses = 5.5803 ( $df = 1$ ;  $P = 0.0182$ ).

**TABLE 3**  
**Comparison of Detection Rates at Three Cytodiagnostic Thresholds: SurePath Study Group versus Historical Comparison (Conventional) Group**

	SurePath (%)	Conventional (%)	Change
ASC+	16,545 (4.69)	14,435 (3.81)	↑; $P < 0.0001$ , $df = 1$ , chi-square statistic = 350.8013
LSIL+	7514 (2.13)	5700 (1.50)	↑; $P < 0.0001$ , $df = 1$ , chi-square statistic = 404.3850
HSIL+	1184 (0.34)	1181 (0.31)	↑; $P < 0.0696$ , $df = 1$ , chi-square statistic = 3.2925
Total (all cytodiagnoses)	352,680 <sup>a</sup>	378,990 <sup>a</sup>	

ASC: atypical squamous cells; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

<sup>a</sup> Totals of cytodiagnostic cases differ from totals of accessioned cases (Table 1) for reasons described in Materials and Methods.

within the province of Ontario are represented within the study and historical CS groups. The second major deficit in the study is the absence of any histologic follow-up of the cytologic results contained in the provincial database (CytoBase). Consequently, the study lacks any external standard or “truth” and no statement can be made regarding sensitivity. For this reason, the term “detection rate” has been adopted through the study.

Despite these drawbacks, implementation studies with historical comparisons are useful, and may be a final step in the validation process of a new technology. The several large studies of ThinPrep LBC implementations in a variety of clinical settings have, by and large, supported earlier data of improved cytodiagnostic sensitivity.<sup>1–8</sup> In one of these ThinPrep studies, the methodology was similar to that used in the current study, and the detection rate of both LSIL and HSIL was increased compared with the detection rate by CS one year earlier from the same sources.<sup>2</sup>

Only manually screened SP-LBC slides were included in the study group, although FocalPoint automated slide screening was adopted subsequently in one of the laboratory systems during 2002. Consequently, the adequacy and detection rates of the current study reflect manual practice only, and are not influenced or confounded by either full or selective

implementation of FocalPoint screening by the study laboratories. We used data collected in 2002, after a period of adjustment and learning during the 2001 introduction, and results reflect a mature implementation project. The size of the historical comparison group (378,990 CS) is comparable to that of the SP-LBC study group (352,680 slides).

The Ontario Cervical Screening Program has stressed the importance of proper collection technique. The low prevalence of unsatisfactory CS (0.58%) before the implementation of SP-LBC may be a reflection of this emphasis. Nevertheless, a decrease in the proportions of both unsatisfactory and satisfactory but limited by Papanicolaou tests was observed after implementation of SP-LBC (Table 1). This finding confirms numerous reports of improved specimen adequacy using the SP-LBC technique.<sup>9,10,13,15,16</sup>

The SP-LBC study group showed an increase in the detection rates of the major cytodiagnostic categories and a corresponding decrease in the proportion of tests reported as NILM (95.29%) as compared with the historical CS group (96.18%). Significantly, the performance of SP-LBC in the detection of HSIL in the Ontario Cervical Screening Program has exceeded slightly the performance of historical CS. The proportion of tests reported as ASC+ (4.69%) increased from 3.81% in the historical CS group (Table 3). Most of the

increased detection rate of ASC+ in the SP-LBC group was attributable to increased reporting rates of ASCUS (2.21%) and LSIL (1.79%). With respect to LSIL+, the detection rate of the SP-LBC study group (2.13%) was significantly greater than that of the historical CS group (1.50%) (Table 3). Relative to the historical CS group, the SP-LBC demonstrated a > 30% increase in the detection rate for this cytodiagnostic threshold. This finding of an increased detection rate at an LSIL+ threshold for the SP-LBC technique is consistent with other studies. Because histopathologic diagnoses are not available in the database, one cannot conclude that the increased detection rate of either ASC+ or LSIL+ necessarily suggests increased sensitivity for significant disease, and further studies are needed to exclude the possibility of increased nonspecificity after SurePath implementation. Other studies in the literature have indicated that implementation of the SP-LBC technique is not accompanied by an increase in nonspecificity.<sup>11,16</sup>

Although there was a trend toward an increased detection rate of HSIL+ in the SP-LBC study group (0.34%) compared with the historical CS group (0.31%), this trend did not reach statistical significance (Table 3). The lack of a statistically significant improvement in the detection rate of HSIL+ in the SP-LBC group is attributable to the decreased detection rate of carcinoma by the SP-LBC, because improvement in the detection rate of HSIL (alone) by SP-LBC (Table 2) had been demonstrated to be statistically significant (Table 2).

Performance of SP-LBC in the detection of HSIL and HSIL+ has been inconsistent in the literature. Some studies have demonstrated an increased detection rate of HSIL+ relative to the conventional Papanicolaou test,<sup>9,11,16</sup> whereas others have been unable to demonstrate this relative advantage in sensitivity.<sup>13,15,21</sup> Although the increased detection rate of HSIL in the current study was less than the recently FDA-approved manufacturer's claim, it was consistent with a Canadian technology assessment review of SIL detection by LBC.<sup>19</sup> Others have shown that SP-LBC fails to increase HSIL detection rates relative to conventional Papanicolaou tests, but that an SP-LBC cytodiagnosis of LSIL is more likely to yield an HSIL after a biopsy than a conventional Papanicolaou test.<sup>25</sup> Again, the establishment of a histopathologic database is essential to monitor this cytodiagnostic outcome.

The decline in the detection rate of carcinoma (0.01%) relative to the historical CS group (0.02%) is a concern. First, it is important to note that there is no tissue verification of the carcinoma cases in the historical CS group, and one cannot conclude that this historical detection rate represents the actual preva-

lence of invasive carcinoma. Second, it is not possible to determine from the available data whether prevalent carcinoma cases were missed altogether by SP-LBC, or merely placed in another significant cytodiagnostic category, such as HSIL. Recent studies have clearly shown that there is considerable interpretive error (or interobserver variability) in the practice of gynaecologic cytology, and that this variability is influenced by the type of cytologic preparation.<sup>26-28</sup> There is evidence from the College of American Pathologists gynaecology cytology program (PAP) that cytologists experience difficulty in recognizing HSIL and squamous cell carcinoma in LBC of the ThinPrep type, compared with those seen in CS.<sup>29</sup> Participant performance on circulated educational SP-LBC slides in the PAP program indicates that both squamous carcinoma and adenocarcinoma are usually classified as carcinoma, HSIL, or LSIL, and only very rarely misclassified as NILM.<sup>30</sup> It is probable that the decline in the detection rates of carcinoma in the Ontario SP-LBC study group is attributable to recognition of carcinoma cases as HSIL. Such cytodiagnostic classification would still lead to appropriate colposcopic investigation and diagnosis. Nevertheless, further monitoring of this cytodiagnostic category is merited.

The detection rate of ASC-H (0.13%) in the SP-LBC study group is greater than that in the historical CS group (0.09%). Attributing this increase to the implementation of the SP-LBC technique is inappropriate, because the implementation occurred simultaneously with the promulgation of the ASC-H cytodiagnostic category by the 2001 Bethesda terminology system, which may have prompted increased use of this cytodiagnostic category in Ontario, even though it had been available for some time. Any increased use of the ASC-H may have negatively influenced the HSIL detection rate.

The small decrease in the detection rate of AGC in the SP-LBC group (0.22%) in comparison to the historical CS group (0.24%) suggests that there has been no increased nonspecificity within this cytodiagnostic category.

In conclusion, the Ontario implementation of the SP-LBC technique has been followed by superior adequacy and detection rates of ASC+ and LSIL+ in comparison to historical conventional practice, although only a trend of increased detection of HSIL+ could be recognized because the detection rate of carcinoma decreased. After this successful implementation, the screening program now has the capacity to introduce other technologies dependent on the use of SP-LBC. A correlative histopathologic database is required to verify the specificity of SP-LBC.

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