Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: A metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy

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OBJECTIVE: We sought to evaluate the cytologic diagnosis and sample adequacy of the liquid-based cervical cytologic smear (ThinPrep) compared with that of the conventional Papanicolaou smear.

STUDY DESIGN: Prospective studies of ThinPrep and conventional Papanicolaou smears were analyzed for cytologic diagnosis and sample adequacy. Computerized databases, references in published studies, and index reviews published in English were used to identify direct-to-vial and split-sample clinical trials of cervical smears performed by conventional and liquid-based techniques. Only published studies that used the Bethesda system nomenclature with clearly documented outcome data were included. Each trial was assessed for the quality of its method, inclusion and exclusion criteria, adequacy of randomization, sampling protocols, definition of outcome, and statistical analyses.

RESULTS: Twenty-five studies met inclusion criteria for this review. Odds ratios with 95% confidence intervals were calculated for each outcome. Estimates of odds ratios and risk differences for dichotomous outcomes were calculated by use of random and fixed-effects models. Homogeneity was tested across the studies. Results indicate that the ThinPrep test is as good as or superior to the conventional Papanicolaou smear in diagnosing uterine cervical premalignant abnormalities. Also the ThinPrep test provides improved sample adequacy when compared with the conventional Papanicolaou test.

CONCLUSION: The ThinPrep test improved sample adequacy and led to improved diagnosis of low-grade and high-grade squamous intraepithelial lesions. However, there is no difference in the rate of atypical cells of undetermined significance diagnosis between ThinPrep and conventional smear groups. The added cost of ThinPrep cytologic screening and, hence, its cost-effectiveness are not evaluated in this study. (Am J Obstet Gynecol 2001;185:308-17.)

Key words: Thin Prep, Papanicolaou's test, cervical cytology, squamous intraepithelial lesions

Since its formal introduction in the 1940s, the Papanicolaou smear has been a useful tool in screening women for cervical cancer. Detection of precancerous lesions on the cervix has enabled women to receive appropriate treatment, leading to a significant decrease in incidence and mortality rates from invasive cervical cancer in a screened population. In spite of the improvements in women's health care resulting from cervical cancer screening, there remains a population of women in whom the disease develops because of false-negative diagnoses. A false- negative Papanicolaou smear result is defined as "the failure to demonstrate abnormality by Papanicolaou examination in a woman who has disease." The sensitivity of the Papanicolaou smear, which ranges from 50% to 90%, is reflected by the false-negative rate.[1] Proper identification of cervical precancerous lesions relies on several factors, including sample collection, preparation, and examination of exfoliated uterine cervix cells. According to several studies on Papanicolaou smear accuracy, sampling error accounts for most false-negative diagnoses. In addition to the risk of false-negative diagnoses, false-positive diagnoses can lead to confusion in the triage of patients.

With the introduction of liquid-based, thin-layer cytologic screening in the past decade, researchers are attempting to improve diagnostic accuracy. In 1996 the Food and Drug Administration approved the ThinPrep test (Cytyc Corporation, Foxborough, Mass), a fluid-based method of obtaining and preparing cervical cytologic samples for screening. Initial studies with this technique were performed with the ThinPrep Processor Beta model, now replaced by the Food and Drug Administration–approved ThinPrep 2000, which presents 40% more cells[2] and is more automated.[3]

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After thoroughly reviewing the literature, no meta-analysis has been published to date. This systematic overview presents an evaluation of cytologic accuracy and sample adequacy of the ThinPrep test compared with that of the conventional smear.

Material and methods

Data sources. With computerized databases and references from published articles, prospective trials that compared ThinPrep and conventional smears were identified. The computerized databases consisted of MEDLINE, PubMed (National Library of Medicine, Bethesda, Md), and Silver Platter (Silver Platter Information Inc, Norwood, Mass). The searches were conducted for literature published in English between January 1990 and April 2000. Medical subject heading key words included "ThinPrep," "liquid-based cytology," and "Pap smear."

Methods of study selection. Criteria for selection of these studies included prospective trials that evaluated diagnostic cytology according to the Bethesda system nomenclature, as well as adequacy of ThinPrep test compared with that of the conventional smear. Clearly documented data from split-sample and direct-to-vial (case-cohort) studies were assessed. The split-sample method involved obtaining a Papanicolaou smear in a routine fashion, swabbing the glass slide, and then rinsing the residual material into a liquid preservative (PreservCyt, Cleveland, Ohio). The split-sample method was deemed an acceptable means of evaluation, because studies have shown that up to 80% of cells may remain on the sampling device after preparation of the conventional smear. Direct-to-vial studies involved the collection of conventional Papanicolaou smears and ThinPrep specimens separately from the same population base. Publications were evaluated for quality of method, inclusion and exclusion criteria, description of sampling protocols, definition of reported outcomes, and statistical analyses. The search yielded 24 published articles[1,3-24] and one abstract[25] that met inclusion criteria for this metaanalysis.

Forty-nine publications of liquid-based thin-layer cytotechnology were identified (references available on request). Twenty-four were excluded on the basis of use of different thin-layer technology, lack of comparison to conventional smears, and lack of evaluation of specific outcome measures. Twenty-five publications were identified that met inclusion criteria for this review. Eighteen trials were performed in the United States,* one in Canada,[11] one in Japan,[3] two in Australia,[14,16] one in Costa Rica,[2] one in Taiwan,[17] and one in Switzerland.[24] A total of 533,039 women were enrolled in these trials—221,864 in the ThinPrep group and 378,659 in the conventional smear group. A total of 67,484 women were involved in split-sample trials and thus were included in both ThinPrep and conventional smear groups.

*References 1,4-10,12,13,15,18-23, and 25.

Tabulation and integration. Split-sample and direct-to-vial studies were analyzed separately. Both versions of the ThinPrep processor (Beta and ThinPrep 2000) were incorporated and evaluated together, as well as independently. All direct-to-vial studies and 6 of 17 split-sample studies used ThinPrep 2000, whereas the remaining 11 of 17 split-sample trials were performed with the ThinPrep Beta model. Outcomes examined included the following: (1) frequency of diagnoses of atypical cells of undetermined significance, low-grade squamous intraepithelial lesions, and high-grade squamous intraepithelial lesions; and (2) adequacy of sample collection for appropriate evaluation. An adequate smear is defined as one that contains squamous cells, endocervical cells, and possibly metaplastic cells representative of the transformation zone. Unsatisfactory smears or inadequate samples are those described in the studies as limited by components such as poor fixation, scant squamous epithelial component, thick smear, obscuring blood or inflammation, absent endocervical component, or cytolysis.[17]

Because of the small number of atypical glandular cells of undetermined significance diagnoses in various trials,[12,13,18,19,25] some studies included in this metaanalysis combined atypical squamous cells of undetermined significance and atypical glandular cells of undetermined significance into the same category. For the purpose of this metaanalysis, atypical squamous cells of undetermined significance and atypical glandular cells of undetermined significance were also combined into one category—atypical cells of undetermined significance. Only three[18,19,25] of eight direct-to-vial and two[12,13] of the 14 split-sample studies evaluated atypical glandular cells of undetermined significance and atypical squamous cells of undetermined significance independently. The remaining studies were unable to perform a reasonable analysis because of the small number of atypical glandular cells of undetermined significance smears. Although we acknowledge that atypical glandular cells of undetermined significance and atypical squamous cells of undetermined significance are two distinct categories in the Bethesda system, we were unable to analyze them as such in this study, and the inability to separate these data is one of the weaknesses of a metaanalysis.

Statistical analysis. Analysis of the data was performed with the Stata 5.0 (College Station, Tex) statistical software package. The odds ratios (OR) for each outcome and 95% confidence intervals (CI) were calculated in the ThinPrep group and compared with the conventional smear group. Estimates of ORs and risk differences for dichotomous outcomes were calculated by use of random-effects (DerSirmonian and Laird) and fixed-effects (Mantel-Haenszel) models. The differences between results with either method were not substantial, therefore only fixed-effects results are reported. A test of heterogeneity was performed to evaluate the ability to

combine the individual trials (as described by Breslow and Day[26]).

Results

When evaluating the ability of ThinPrep and conventional smears to analyze atypical cells of undetermined significance, there was no difference in the rate of atypical cells of undetermined significance diagnosis between ThinPrep and conventional smears (OR 1.03; 95% CI 0.99, 1.06; Table I). In fact, in split-sample trials, the rate of atypical cells of undetermined significance diagnosis was higher in ThinPrep than in conventional smear when ThinPrep Processor Beta model and ThinPrep 2000 were combined (OR 1.20; 95% CI 1.13, 1.27; Table II). When ThinPrep 2000 alone is compared with conventional smear, there is no difference in the rate of atypical cells of undetermined significance diagnosis (OR 1.05; 95% CI 0.95, 1.16; Table III).

With regard to the diagnosis of the epithelial cell abnormality low-grade squamous intraepithelial lesions, ThinPrep was significantly better than conventional smear. Regarding the cytologic diagnosis of low-grade squamous intraepithelial lesions, ThinPrep was preferred to conventional smear in direct-to-vial studies (OR 2.15; 95% CI 2.05, 2.26; Table IV). In split-sample trials, ThinPrep was favored in both the combined models (OR 1.27; 95% CI 1.21, 1.32; Table V) and the ThinPrep 2000 trials (OR 1.27; 95% CI 1.21, 1.34; Table VI). Similarly, when high-grade squamous intraepithelial lesions were analyzed, ThinPrep was favored over conventional smear in direct-to-vial studies (OR 2.26; 95% CI 2.06, 2.47; Table VII) and in both sets of split-sample trials (OR 1.09; 95% CI 1.00, 1.18; OR 1.14; 95% CI 1.00, 1.29; Tables VIII and IX, respectively).

Our analysis of the pooled data shows that the overall adequacy was significantly improved in the ThinPrep group in all trials—direct-to-vial (OR 2.11; 95% CI 2.07, 2.15), split-sample ThinPrep Processor Beta model + ThinPrep 2000 (OR 1.64; 95% CI 1.53, 1.76), and split-sample ThinPrep 2000 (OR 1.65; 95% CI 1.54, 1.78; Tables X, XI, and XII). As made evident in these tables, the fact that the case-cohort trials used direct rinsing of cervical cells into the liquid medium (rather than secondary placement as seen in split-sample trials) made a significant difference in the percent of specimens considered adequate for evaluation.

Comment

Numerous publications have reported mixed viewpoints regarding the effectiveness of the ThinPrep test in replacing the conventional smear for routine uterine cervical cancer screening. This metaanalysis reveals that ThinPrep appears to be a superior method of evaluating uterine cervix cytologic abnormalities with regard to low-grade and high-grade lesions, as well as a better means of obtaining specimen adequacy for improved evaluation. Our data show that ThinPrep did not reduce the rate of atypical cells of undetermined significance diagnosis.

Neither ThinPrep nor the conventional Papanicolaou test was favored when evaluating atypical squamous lesions, and in part this may be due to lack of division of atypical cells of undetermined significance into atypical glandular and atypical squamous cells of undetermined significance in all of the studies. When analyses specifically separating atypical glandular cells from atypical squamous cells of undetermined significance were evaluated, the number of studies available for atypical glandular cells of undetermined significance evaluation was too small to enable formation of a significant conclusion. Three[18,19,25] of the eight direct-to-vial and two[12,13] of the 14 split-sample studies analyzing atypical cells of undetermined significance separated atypical glandular cells from atypical squamous cells of undetermined significance. For this reason, atypical glandular cells and atypical squamous cells of undetermined significance were combined in all studies included in this systematic review to obtain the power necessary to reach a reasonable conclusion.

Several tables indicate a high heterogeneity when analyzing pooled data. This in part may be due to combining trials evaluating low-risk and high-risk populations, because this can have a significant effect on diagnosis on the basis of the relative incidence of disease. As noted in Tables II, III, V, VI, VIII, IX, XI, and XII, the heterogeneity when isolating testing with the ThinPrep 2000 model from all split-sample studies (Beta model plus ThinPrep 2000) is decreased. Thus, in spite of the heterogeneity of these studies, results regarding the efficacy and adequacy of ThinPrep Papanicolaou tests are still significant.

Earlier studies of ThinPrep technology with the Beta processor, which was not approved by the Food and Drug Administration, demonstrated technical problems and less automation, thus requiring more human intervention, with a possible subsequent decrease in precision because of human error. The ThinPrep 2000 model is the Food and Drug Administration–approved version of thin-layer liquid-based cytologic evaluation of cervical specimens.

One of the significant problems with conventional smears is screening error. Limited transfer of cells from the collecting device to the slide of a conventional smear, as well as faulty interpretation of these smears contributes to a significant number of screening errors. ThinPrep not only improves the amount of cells transferred for evaluation but also presents cells on slides in an automated fashion in a manner that is easier for the cytotechnologist to interpret.

To evaluate cervical cytologic study results in a timely and efficient manner, sufficient specimen adequacy is required. The differences in evaluation of specimen adequacy may be due to several factors, including variation in

Table I. Direct-to-vial comparisons of atypical cells of undetermined significance with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep ACUS*	*(%)*	*Conventional ACUS*	*(%)*	*OR*	*(95% CI)*
Bolick[18]	1998	318/10694	(2.97)	955/39408	(2.42)	1.23	(1.08, 1.40)
Dupree[19]	1998	927/19351	(4.79)	1304/22323	(5.84)	0.81	(0.74, 0.88)
Papillo[20]	1998	204/8541	(2.39)	572/18569	(3.08)	0.77	(0.65, 0.91)
Carpenter[21]	1999	188/2727	(6.89)	625/5000	(12.50)	0.52	(0.44, 0.61)
Diaz-Rosario[22]	1999	2543/56095	(4.53)	3551/74573	(4.76)	0.95	(0.90, 1.00)
Guidos[23]	1999	326/9583	(3.40)	110/5423	(2.03)	1.70	(1.37, 2.12)
Hatch[25]	2000	635/7934	(8.00)	1145/16260	(7.04)	1.15	(1.04, 1.27)
Weintraub[24]	2000	947/39455	(2.40)	1944/129619	(1.50)	1.62	(1.49, 1.75)
	Totals	6088/154380	(3.94)	10206/311175	(3.28)	1.03	(0.99, 1.06)*

Heterogeneity $\chi^2_7 = 272.14$, $P = .000$.
*Pooled odds ratio and 95% confidence interval.

Table II. Split-sample comparisons of atypical cells of undetermined significance with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep ACUS*	*(%)*	*Conventional ACUS*	*(%)*	*OR*	*(95% CI)*
Hutchinson[4]	1991	4/443	(0.90)	3/443	(0.68)	1.34	(0.30, 6.01)
Hutchinson[5]	1992	280/2655	(10.55)	339/2655	(12.77)	0.81	(0.68, 0.95)
Awen[6]	1994	32/1000	(3.20)	33/1000	(3.30)	0.97	(0.59, 1.59)
Wilbur[7]	1994	616/3218	(19.14)	705/3218	(21.91)	0.84	(0.75, 0.95)
Aponte-Cipriani[8]	1995	24/665	(3.61)	24/665	(3.61)	1.00	(0.56, 1.78)
Bur[9]	1995	8/128	(6.25)	8/128	(6.25)	1.00	(0.36, 2.75)
Linder[1]	1995	173/3957	(4.37)	138/3957	(3.49)	1.27	(1.01, 1.59)
Sheets[10]	1995	140/782	(17.90)	153/782	(19.57)	0.90	(0.70, 1.16)
Ferenczy[11]	1996	38/364	(10.44)	25/364	(6.87)	1.58	(0.93, 2.68)
Wilbur[12]	1996	24/259	(9.27)	14/259	(5.41)	1.79	(0.90, 3.54)
Lee[13]	1997	517/6747	(7.66)	529/6747	(7.84)	0.98	(0.86, 1.11)
Corkill[15]	1998	81/1583	(5.12)	59/1583	(3.73)	1.39	(0.99, 1.96)
Hutchinson[2]	1999	650/8636	(7.53)	159/8636	(1.84)	4.34	(3.64, 5.17)
Wang[17]	1999	4/972	(0.41)	15/972	(1.54)	0.26	(0.09, 0.80)
	Totals	2591/31409	(8.25)	2204/31409	(7.02)	1.20	(1.13, 1.27)*

ACUS, Atypical cells of undetermined significance.
Heterogeneity $\chi^2_{13} = 285.82$, $P = .000$.
*Pooled odds ratio and 95% confidence interval.

Table III. Split-sample comparisons of atypical cells of undetermined significance with ThinPrep and conventional Papanicolaou tests with the ThinPrep 2000 processor

Author	*Year*	*ThinPrep ACUS*	*(%)*	*Conventional ACUS*	*(%)*	*OR*	*(95% CI)*
Linder[1]	1995	173/3957	(4.37)	138/3957	(3.49)	1.27	(1.01, 1.59)
Lee[13]	1997	517/6747	(7.66)	529/6747	(7.84)	0.98	(0.86, 1.11)
Corkill[15]	1998	81/1583	(5.12)	59/1583	(3.73)	1.39	(0.99, 1.96)
Wang[17]	1999	4/972	(0.41)	15/972	(1.54)	0.26	(0.09, 0.80)
	Totals	775/13259	(5.85)	741/13259	(5.59)	1.05	(0.95, 1.16)*

ACUS, Atypical cells of undetermined significance.
Heterogeneity $\chi^2_3 = 12.48$, $P = .006$.
*Pooled odds ratio and 95% confidence interval.

sampling devices, sampling techniques, and the use of split-sample specimens. Also not all studies included in this metaanalysis evaluated sample adequacy, thus limiting the overall sample power. The trials included in this study used various types of sampling devices, including broom-type, plastic spatula with or without an endocervical brush, modified wooden Ayer's spatula with or without an endocervical brush, cytobrush, CervexBrush (Rovers Medical Devices, BV, Oss, the Netherlands), Cervibrush Profile Plus (CellPath, West Yorkshire, United Kingdom), and Accellon Combi (Medesign, Dietramszeu-Linden, Germany) cervical biosampler. This varia-

Table IV. Direct-to-vial comparisons of low-grade squamous intraepithelial lesions with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep LSIL*	*(%)*	*Conventional LSIL*	*(%)*	*OR*	*(95% CI)*
Bolick[18]	1998	241/10694	(2.25)	317/39408	(0.80)	2.84	(2.40, 3.37)
Dupree[19]	1998	270/19351	(1.40)	218/22323	(0.98)	1.43	(1.20, 1.72)
Papillo[20]	1998	138/8541	(1.62)	160/18569	(0.86)	1.89	(1.50, 2.38)
Carpenter[21]	1999	188/2727	(6.89)	219/5000	(4.38)	1.62	(1.32, 1.98)
Diaz-Rosario[22]	1999	1520/56095	(2.71)	1178/74573	(1.58)	1.74	(1.61, 1.87)
Guidos[23]	1999	348/9583	(3.63)	53/5423	(0.98)	3.82	(2.85, 5.11)
Hatch[25]	2000	489/7934	(6.16)	471/16260	(2.90)	2.20	(1.93, 2.51)
Weintraub[24]	2000	710/39455	(1.80)	648/129619	(0.50)	3.65	(3.28, 4.06)
	Totals	3904/154380	(2.53)	3264/311175	(1.05)	2.15	(2.05, 2.26)

LSIL, Low-grade squamous intraepithelial neoplasia.
Heterogeneity $\chi^2_7 = 168.45$, $P = .000$.
*Pooled odds ratio and 95% confidence interval.

Table V. Split-sample comparisons of low-grade squamous intraepithelial lesions with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep LSIL*	*(%)*	*Conventional LSIL*	*(%)*	*OR*	*(95% CI)*
Hutchinson[4]	1991	62/443	(14.00)	60/443	(13.54)	1.04	(0.71, 1.52)
Hutchinson[5]	1992	280/2655	(10.55)	238/2655	(8.96)	1.20	(1.00, 1.44)
Awen[6]	1994	15/1000	(1.50)	9/1000	(0.90)	1.68	(0.73, 3.85)
Wilbur[7]	1994	466/3218	(14.48)	404/3218	(12.55)	1.18	(1.02, 1.36)
Aponte-Cipriani[8]	1995	21/665	(3.16)	18/665	(2.71)	1.17	(0.62, 2.22)
Bur[9]	1995	14/128	(10.94)	14/128	(10.94)	1.00	(0.46, 2.19)
Linder[1]	1995	157/3957	(3.97)	91/3957	(2.30)	1.76	(1.35, 2.28)
Sheets[10]	1995	166/782	(21.23)	157/782	(20.08)	1.07	(0.84, 1.37)
Ferenczy[11]	1996	107/364	(29.40)	100/364	(27.47)	1.10	(0.80, 1.52)
Tezuka[3]	1996	51/215	(23.72)	53/215	(24.65)	0.95	(0.61, 1.48)
Wilbur[12]	1996	11/259	(4.25)	13/259	(5.02)	0.84	(0.37, 1.91)
Lee[13]	1997	469/6747	(6.95)	367/6747	(5.44)	1.30	(1.13, 1.50)
Roberts[14]	1997	2384/35560	(6.70)	1963/35560	(5.52)	1.23	(1.16, 1.31)
Corkill[15]	1998	68/1583	(4.30)	29/1583	(1.83)	2.41	(1.55, 3.74)
Hutchinson[2]	1999	295/8636	(3.42)	159/1583	(1.84)	1.89	(1.55, 2.29)
Shield[16]	1999	42/300	(14.00)	40/300	(13.33)	1.06	(0.66, 1.69)
Wang[17]	1999	16/972	(1.65)	11/972	(1.13)	1.46	(0.68, 3.17)
	Totals	4624/67484	(6.85)	3726/67484	(5.52)	1.27	(1.21, 1.32)*

LSIL, Low-grade squamous intraepithelial neoplasia.
Heterogeneity $\chi^2_{16} = 40.05$, $P = .001$.
*Pooled odds ratio and 95% confidence interval.

Table VI. Split-sample comparisons of low-grade squamous intraepithelial lesions with ThinPrep and conventional Papanicolaou tests by use of the ThinPrep 2000 processor

Author	*Year*	*ThinPrep LSIL*	*(%)*	*Conventional LSIL*	*(%)*	*OR*	*(95% CI)*
Linder[1]	1995	157/3957	(3.97)	91/3957	(2.30)	1.76	(1.35, 2.28)
Lee[13]	1997	469/6747	(6.95)	367/6747	(5.44)	1.30	(1.13, 1.50)
Roberts[14]	1997	2384/35560	(6.70)	1963/35560	(5.52)	1.23	(1.16, 1.31)
Corkill[15]	1998	68/1583	(4.30)	29/1583	(1.83)	2.41	(1.55, 3.74)
Shield[16]	1999	42/300	(14.00)	40/300	(13.33)	1.06	(0.66, 1.69)
Wang[17]	1999	16/972	(1.65)	11/972	(1.13)	1.46	(0.68, 3.17)
	Totals	3136/49119	(6.38)	2501/49119	(5.09)	1.27	(1.21, 1.34)*

LSIL, Low-grade squamous intraepithelial neoplasia.
Heterogeneity $\chi^2_5 = 15.79$, $P = .007$.
*Pooled odds ratio and 95% confidence interval.

Table VII. Direct-to-vial comparisons of high-grade squamous intraepithelial lesions with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep HSIL*	*(%)*	*Conventional HSIL*	*(%)*	*OR*	*(95% CI)*
Bolick[18]	1998	70/10694	(0.65)	120/39408	(0.30)	2.16	(1.61, 2.90)
Dupree[19]	1998	54/19351	(0.28)	47/22323	(0.21)	1.33	(0.90, 1.96)
Papillo[20]	1998	60/8541	(0.70)	83/18569	(0.45)	1.58	(1.13, 2.20)
Carpenter[21]	1999	65/2727	(2.38)	94/5000	(1.88)	1.27	(0.93, 1.75)
Diaz-Rosario[22]	1999	291/56095	(0.52)	191/74573	(0.26)	2.03	(1.69, 2.44)
Guidos[23]	1999	100/9583	(1.04)	17/5423	(0.31)	3.35	(2.00, 5.61)
Hatch[25]	2000	257/7934	(3.24)	243/16260	(1.49)	2.21	(1.85, 2.64)
Weintraub[24]	2000	197/39455	(0.50)	130/129619	(0.10)	5.00	(4.00, 6.24)
	Totals	1094/154380	(0.71)	925/311175	(0.30)	2.26	(2.06, 2.47)*

HSIL, High-grade squamous intraepithelial neoplasia.
Heterogeneity $\chi^2_7 = 56.65$, $P = .000$.
*Pooled odds ratio and 95% confidence interval.

Table VIII. Split-sample comparisons of high-grade squamous intraepithelial lesions with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep HSIL*	*(%)*	*Conventional HSIL*	*(%)*	*OR*	*(95% CI)*
Hutchinson[4]	1991	24/443	(5.42)	23/443	(5.19)	1.05	(0.58, 1.88)
Hutchinson[5]	1992	112/2655	(4.22)	103/2655	(3.88)	1.09	(0.83, 1.43)
Awen[6]	1994	3/1000	(0.30)	4/1000	(0.40)	0.75	(0.17, 3.36)
Wilbur[7]	1994	174/3218	(5.41)	161/3218	(5.00)	1.09	(0.87, 1.35)
Aponte-Cipriani[8]	1995	3/665	(0.45)	4/665	(0.60)	0.75	(0.17, 3.36)
Bur[9]	1995	11/128	(8.59)	11/128	(8.59)	1.00	(0.42, 2.40)
Linder[1]	1995	34/3957	(0.86)	25/3957	(0.63)	1.36	(0.81, 2.29)
Sheets[10]	1995	89/782	(11.38)	84/782	(10.74)	1.07	(0.78, 1.46)
Ferenczy[11]	1996	44/364	(12.09)	47/364	(12.91)	0.93	(0.60, 1.44)
Tezuka[3]	1996	61/215	(28.37)	63/215	(29.30)	0.96	(0.63, 1.45)
Wilbur[12]	1996	12/259	(4.63)	10/259	(3.86)	1.21	(0.51, 2.85)
Lee[13]	1997	167/6747	(2.48)	167/6747	(2.48)	1.00	(0.80, 1.24)
Roberts[14]	1997	273/35560	(0.77)	236/35560	(0.66)	1.16	(0.97, 1.38)
Corkill[15]	1998	20/1583	(1.26)	13/1583	(0.82)	1.55	(0.77, 3.12)
Hutchinson[2]	1999	139/8636	(1.61)	133/8636	(1.54)	1.05	(0.82, 1.33)
Shield[16]	1999	8/300	(2.67)	7/300	(2.33)	1.15	(0.41, 3.20)
Wang[17]	1999	40/972	(4.12)	30/972	(3.09)	1.35	(0.83, 2.18)
	Totals	1214/67484	(1.80)	1121/67484	(1.66)	1.09	(1.00, 1.18)*

HSIL, High-grade squamous intraepithelial neoplasia.
Heterogeneity $\chi^2_{16} = 5.11$, $P = .995$.
*Pooled odds ratio and 95% confidence interval.

Table IX. Split-sample comparisons of high-grade squamous intraepithelial lesions with ThinPrep and conventional Papanicolaou tests by use of the ThinPrep 2000 processor

Author	*Year*	*ThinPrep HSIL*	*(%)*	*Conventional HSIL*	*(%)*	*OR*	*(95% CI)*
Linder[1]	1995	34/3957	(0.86)	25/3957	(0.63)	1.36	(0.81, 2.29)
Lee[13]	1997	167/6747	(2.48)	167/6747	(2.48)	1.00	(0.80, 1.24)
Roberts[14]	1997	273/35560	(0.77)	236/35560	(0.66)	1.16	(0.97, 1.38)
Corkill[15]	1998	20/1583	(1.26)	13/1583	(0.82)	1.55	(0.77, 3.12)
Shield[16]	1999	8/300	(2.67)	7/300	(2.33)	1.15	(0.41, 3.20)
Wang[17]	1999	40/972	(4.12)	30/972	(3.09)	1.35	(0.83, 2.18)
	Totals	542/49119	(1.10)	478/49119	(0.97)	1.14	(1.00, 1.29)*

HSIL, High-grade squamous intraepithelial neoplasia.
Heterogeneity $\chi^2_5 = 3.07$, $P = .690$.
*Pooled odds ratio and 95% confidence interval.

Table X. Direct-to-vial comparisons of sample adequacy with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep Satisfactory*	*(%)*	*Conventional Satisfactory*	*(%)*	*OR*	*(95% CI)*
Bolick[18]	1998	9428/10694	(88.16)	31976/39408	(81.14)	1.73	(1.62, 1.85)
Papillo[20]	1998	8013/8574	(93.46)	16039/18613	(86.17)	2.29	(2.08, 2.52)
Carpenter[21]	1999	2433/2727	(89.22)	4000/5000	(80.00)	2.07	(1.80, 2.38)
Diaz-Rosario[22]	1999	45207/56095	(80.59)	58029/74573	(77.82)	1.18	(1.15, 1.22)
Guidos[23]	1999	9470/9583	(98.82)	4198/5423	(77.41)	24.45	(20.10, 29.75)
Weintraub[24]	2000	36567/39864	(91.73)	93896/130381	(72.02)	4.31	(4.15, 4.47)
	Totals	111118/127537	(87.13)	208138/273398	(76.13)	2.11	(2.07, 2.15)*

Heterogeneity $\chi^2_5 = 3763.38$, $P = .0000$.
*Pooled odds ratio and 95% confidence interval.

Table XI. Split-sample comparisons of sample adequacy with ThinPrep and conventional Papanicolaou tests

Author	*Year*	*ThinPrep Satisfactory*	*(%)*	*Conventional Satisfactory*	*(%)*	*OR*	*(95% CI)*
Hutchinson[4]	1991	355/446	(79.60)	328/446	(73.54)	1.40	(1.03, 1.92)
Lee[13]	1997	5656/7223	(78.31)	5101/7223	(70.62)	1.50	(1.39, 1.62)
Shield[16]	1999	36/58	(62.07)	5/58	(8.62)	17.35	(6.01, 50.03)
Wang[17]	1999	873/972	(89.81)	689/972	(70.88)	3.66	(2.85, 4.70)
	Totals	6920/8699	(79.55)	6123/8699	(70.39)	1.64	(1.53, 1.76)*

Heterogeneity $\chi^2_3 = 65.08$, $P = .0000$.
*Pooled odds ratio and 95% confidence interval.

Table XII. Split-sample comparisons of sample adequacy with ThinPrep and conventional Papanicolaou tests by use of the ThinPrep 2000 processor

Author	*Year*	*ThinPrep Satisfactory*	*(%)*	*Conventional Satisfactory*	*(%)*	*OR*	*(95% CI)*
Lee[13]	1997	5656/7223	(78.31)	5101/7223	(70.62)	1.50	(1.39, 1.62)
Shield[16]	1999	36/58	(62.07)	5/58	(8.62)	17.35	(6.01, 50.03)
Wang[17]	1999	873/972	(89.81)	689/972	(70.88)	3.66	(2.85, 4.70)
	Totals	6565/8253	(79.55)	5795/8253	(70.22)	1.65	(1.54, 1.78)*

Heterogeneity $\chi^2_2 = 64.20$, $P = .000$.
*Pooled odds ratio and 95% confidence interval.

tion in devices may contribute to differences in results in the individual trials, because some collection apparatuses may function better than others. A discussion regarding different devices is out of the scope of this analysis. For the purpose of this study, the assumption was made that a good cross-section of tools and techniques was used, thus simulating conventional smear collection worldwide. Split-sample studies may have created a bias against ThinPrep because of a potential lack of transfer of enough cells necessary to make a proper diagnosis, albeit not affecting the overall outcome of this metaanalysis.

Although direct-to-vial studies are unable to directly compare samples from the same patient, they do indicate a statistically significant improvement in the detection of endocervical cells. Linder and Zahniser[1] have demonstrated that ThinPrep reduces the number of samples that are satisfactory but limited by blood, mucus, poor fixation, and inflammatory processes. The improved sample adequacy seen in this metaanalysis is likely the result of its ability to remove blood, debris, and mucus, improve fixation and preservation of cell structure, and ensure uniform sampling, thus likely decreasing the need for repeat Papanicolaou smears because of these factors. To pursue the incidence of false-positive diagnoses and sensitivity issues, further testing with histologic comparisons should be performed. Currently there are few histologic comparisons that are similar enough to evaluate as a metaanalysis.

Concerns regarding the increase in cost for ThinPrep processing compared with conventional smears are valid. A cost analysis reviewed by Sedlacek and Cooper[27] indicates an overall saving in lifetime costs for the diagnosis and treatment of uterine cervix abnormalities with the use of ThinPrep versus the conventional smear. The decrease in overall cost was attributed to reduced number of office visits, as well as fewer treatment and follow-up visits. From our data, this decrease in cost does not appear to be derived from re-

duced diagnoses of atypical cells of undetermined significance but perhaps from improved sampling adequacy. Although these results are encouraging for ThinPrep, more studies need to be performed pertaining to this topic.

The results of this systematic review indicate that ThinPrep is superior to the conventional smear when evaluating most of the outcome variables in this study. Further studies analyzing the histologic correlation of these findings need to be performed to evaluate more definitively the sensitivity and specificity of ThinPrep as a more accurate screening method.

REFERENCES

1. Linder J, Zahniser, D. ThinPrep Papanicolaou testing to reduce false-negative cervical cytology. Arch Pathol Lab Med 1998;122:139-44.
2. Hutchinson ML, Zahniser DJ, Sherman ME, Herrero R, Alfaro M, Bratti MC, et al. Utility of liquid-based cytology for cervical carcinoma screening—results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. Cancer Cytopathol 1999;87:48-53.
3. Tezuka F, Oikawa H, Shuki H, Higashiiwai H. Diagnostic efficacy and validity of the thinprep method in cervical cytology. Acta Cytol 1996;40:513-8.
4. Hutchinson M, Cassin C, Ball H. The efficacy of an automated preparation device for cervical cytology. Am J Clin Pathol 1991;96:300-5.
5. Hutchinson ML, Agarwal P, Denault T, Berger B, Cibas ES. A new look at cervical cytology—ThinPrep multicenter trial results. Acta Cytol 1992;36:499-504.
6. Awen C, Hathway S, Eddy W, Voskuil R, Janes C. Efficacy of ThinPrep preparation of cervical smears: a 1,000-case, investigator-sponsored study. Diagn Cytopathol 1994;11:33-37.
7. Wilbur DC, Cibas ES, Merritt S, James LP, Berger BM, Bonfiglio TA. ThinPrep processor: clinical trials demonstrate an increased detection rate of abnormal cervical cytologic specimens. Am J Clin Pathol 1994;101:209-14.
8. Aponte-Cipriani SL, Teplitz C, Rorat E, Savino A, Jacobs AJ. Cervical smears prepared by an automated device versus the conventional method—a comparative analysis. Acta Cytol 1995;39:623-30.
9. Bur M, Knowles K, Pekow P, Corral O, Donovan J. Comparison of ThinPrep preparations with conventional cervicovaginal smears—practical considerations. Acta Cytol 1995;39:631-42.
10. Sheets E, Constantine N, Dinisco S, Dean B, Cibas ES. Colposcopically directed biopsies provide a basis for comparing the accuracy of ThinPrep and Papanicolaou smears. J Gynecol Tech 1995;1:27-34.
11. Ferenczy A, Robitaille J, Franco E, Arseneau J, Richart RM, Wright TC. Conventional cervical cytologic smears vs. ThinPrep smears—a paired comparison study on cervical cytology. Acta Cytol 1996;40:1136-42.
12. Wilbur D, Dubeshter B, Angel C, Atkison K. Use of thin-layer preparations for gynecologic smears with emphasis on the cytomorphology of high-grade intraepithelial lesions and carcinomas. Diagn Cytopathol 1996;14:201-11.
13. Lee KR, Ashfaq R, Birdsong GG, Corkill ME, McIntosh KM, Inhorn SL. Comparison of conventional Papanicolaou smears and a fluid-based, thin-layer system for cervical cancer screening. Obstet Gynecol 1997;90:278-84.
14. Roberts JM, Gurley AM, Thurloe JK, Bowditch R, Laverty CR. Evaluation of the ThinPrep Pap test as an adjunct to the conventional Pap smear. Med J Aust 1997;167:466-9.
15. Corkill M, Knapp D, Hutchinson M. Improved accuracy for cervical cytology with the ThinPrep method and the endocervical brush-spatula collector procedure. J Lower Genital Tract Dis 1998;2:12-6.
16. Shield P, Nolan G, Phillips G, Cummings M. Improving cervical cytology screening in a remote high risk population. Med J Aust 1999;170:255-8.
17. Wang T, Chen H, Yang Y, Tsou M. Comparison of fluid-based, thin-layer processing and conventional Papanicolaou methods for uterine cervical cytology. J Formos Med Assoc 1999;98:500-5.
18. Bolick D, Hellman D. Laboratory implementation and efficacy assessment of the ThinPrep cervical cancer screening system. Acta Cytol 1998;42:209-13.
19. Dupree WB, Suprun HZ, Beckwith DG, Shane JJ, Lucente V. The promise and risk of a new technology: The Lehigh Valley Hospital's experience with liquid-based cervical cytology. Cancer Cytopathol 1998;84:202-6.
20. Papillo J, Zarka M, St. John T. Evaluation of the ThinPrep Pap test in clinical practice—a seven-month, 16,314-case experience in Northern Vermont. Acta Cytol 1998;42:203-8.
21. Carpenter A, Davey D. ThinPrep Pap test—performance and biopsy follow-up in a university hospital. Cancer Cytopathol 1999;87:105-12.
22. Diaz-Rosario L, Kabawat S. Performance of a fluid-based, thin-layer Papanicolaou smear method in the clinical setting of an independent laboratory and an outpatient screening population in New England. Arch Pathol Lab Med 1999;123:817-21.
23. Guidos B, Selvaggi S. Use of the ThinPrep Pap test in clinical practice. Diagn Cytopathol 1999;20:70-3.
24. Weintraub J, Morabia A. Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer. Diagn Cytopathol 2000;22:52-9.
25. Hatch K. Multisite clinical outcome trial to evaluate performance of the ThinPrep Pap test. Obstet Gynecol 2000;95(Suppl):51S.
26. Breslow N, Day N. Statistical methods in cancer research: the analysis of case control studies. Lyons, France: IARC Scientific Publications. 1980.
27. Sedlacek T, Cooper A. Cervical cancer screening: what is cost-effectiveness? Journal of Lower Genital Tract Disease 1999;3 S1-7.

Discussion

Dr Barbara Moore, Roanoke, Va. This article makes a significant contribution to the field of gynecology by assessing a possible improvement in the conventional Papanicolaou smear, one of the most effective screening tests in medicine. Why does a test that has reduced the incidence of invasive cervical cancer by 70% need improvement? The answer lies in the highly variable sensitivity of the conventional Papanicolaou smear, with multiple studies indicating a high number of false-negative results that are primarily due to sampling error.

ThinPrep technology was initially approved by the Food and Drug Administration in 1991 for nongynecologic indications, and its usefulness had been demonstrated in smear preparation of urine and bronchial cytologic study, as well as fine needle aspirations. In 1996 the Cytyc Corporation received approval to use ThinPrep for cervical cytologic study, and many important advantages over the conventional Papanicolaou smear have been proposed: (1) decreased frequency of atypical squamous and atypical glandular cells of undetermined significance; (2) decreased patient anxiety over diagnoses of atypical squamous or glandular cells of undetermined significance; (3) increased detection of low- and high-grade squamous intraepithelial lesions; (4) decreased inadequate smears because of the filtering out of blood, mucus, and inflammatory cells; (5) decreased overall costs through fewer repeat Papanicolaou smears for inadequate samples, less colposcopy for atypical squamous cells of undetermined significance, and more efficient reading of slides by cytotechnologists; and (6) availability

of human papilloma virus typing, gonorrhea, and chlamydia testing on the original sample without an additional patient visit and examination. Rigorous scientific assessment of these claims is essential to avoid enthusiastic, well-intentioned universal adoption of a new technology with great promise in much the same way that fetal monitoring was embraced.

Dr Bernstein clearly states the purpose of this study was the evaluation of cytologic diagnoses and sample adequacy of ThinPrep smears compared with conventional Papanicolaou smears. The design of the study is sound. Twenty-five prospective studies with clear outcome data comparing the two smear results were selected for the metaanalysis from a collection of 49 studies published in a 10-year period from 1990 to 2000. Those selected represent 7 countries and both low- and high-risk populations. The total sample size is more than 500,000 women, whereas the original data presented by the manufacturer for Food and Drug Administration approval included only 7300 subjects.

The choice of statistical tests was appropriate, with odds ratios used with a 95% confidence interval. Random-effects and fixed-effects models were compared, and a test of heterogeneity was performed to determine whether such varying studies could be analyzed together. Because of differences in ThinPrep collection, the direct-to-vial studies, in which the specimen is placed directly into the liquid medium, were analyzed separately from split-sample studies, in which the cells remaining on the collection device after preparation of the conventional Papanicolaou smear are then placed in the ThinPrep vial.

The statistical results of the metaanalysis support the following results stated in Dr Bernstein's article: (1) Sample adequacy was significantly improved by ThinPrep. (2) ThinPrep did not significantly decrease the number of diagnoses of atypical cells of undetermined significance, as shown by a confidence interval that included 1.00. (3) ThinPrep produced significantly more diagnoses of low-grade squamous intraepithelial lesions. (4) ThinPrep produced significantly more diagnoses of high-grade squamous intraepithelial lesions in the direct-to-vial studies. However, analysis of the split-sample studies does not show this because of a confidence interval that includes 1.00. Thus Dr Bernstein's metaanalysis supports ThinPrep's improved sample adequacy and the increased diagnosis of squamous intraepithelial lesions.

In deciding whether to adopt the ThinPrep smear as an alternative to or replacement for the conventional Papanicolaou smear, it is helpful to review the criteria for a good screening test: high patient acceptability as a result of minimal discomfort, detection of a treatable condition, accuracy, and low cost. ThinPrep and conventional Papanicolaou smears do not differ on these first two criteria. Is the accuracy of ThinPrep equal to or greater than that of conventional Papanicolaou smear? The comparison of cervical cytologic study with histologic study from colposcopic biopsy specimens and endocervical curettage would seem to be the most helpful in determining accuracy.

Finally, the cost-effectiveness of ThinPrep must be evaluated before it can be widely adopted as a superior screening test. More than 50 million Papanicolaou smears are performed annually in the United States alone, with an 8% rate of abnormal findings. This represents a cost of almost $6 billion to detect and treat squamous intraepithelial lesions.[1] Is ThinPrep's increased cost offset by fewer inadequate smears, fewer readings of atypical squamous and glandular cells of undetermined significance, more accurate detection of low- and high-grade squamous intraepithelial lesions allowing earlier treatment, and more efficient cytotechnologist reading? As Dr Bernstein noted, Sedlacek and Cooper's study has shown an overall lifetime cost savings. Clearly, though, additional studies are needed to show whether acceptable cost-effectiveness would be realized with ThinPrep.

What is your rationale for stating that ThinPrep increases the detection of high-grade squamous intraepithelial lesions in split-sample studies when the 95% confidence interval includes 1.00? How many studies in your metaanalysis included histologic correlation with colposcopic biopsy and endocervical curettage? Would a separate analysis of these studies be helpful? With what patient population do you believe ThinPrep technology should be used, in those with prior low- or high-grade squamous intraepithelial lesions, or should it be universally applied?

REFERENCE

1. Sheets EE. Clinical management of abnormal Pap smears. In: Cibas E, Lee K, editors, Recent advances in diagnostic cytology. Boston: Harvard Medical School; 1996. p. 126-9.

Dr Willette LeHew, Norfolk, Va. It is important to be able to culture chlamydia and gonorrhea. This should be available, and it is important because the American College of Obstetrics and Gynecology now recommends that all of our patients between 15 and 25 be tested.

Dr Ira Horowitz, Atlanta, Ga. With respect to the way you obtained a sample with ThinPrep, I gather there are two different set-ups. Were the two different ways of retrieving the sample compared?

Dr Hal Lawrence, Ashville, NC. Recognizing that the purpose of cervical cytologic screening is to prevent invasive cancer and not to wipe out low-grade dysplasia and recognizing that 75% of women in the United States in whom invasive cervical cancer develops have not been screened in 5 years, how can we justify the increased cost of ThinPrep over conventional screening?

Dr JoAnne Pinkerton, Charlottesville, Va. At our institution we are switching to the ThinPrep method, and what is most interesting is the following: Sending sporadic Thin-Prep smears is not helpful. The pathologists really need to switch over and be trained in this to accurately read the samples. It is better to send a large volume rather than just the occasional specimen.

Dr Bernstein (Closing). In terms of clarifying ThinPrep and increased detection of high-grade squamous intraepithelial lesions, the direct-to-vial trials were significantly favored over the split-sample technique. The split-sample technique was used only for study purposes. Currently, only the direct-to-vial method is in commercial use because of its superiority over the split-sample technique. The number of studies including histologic corre-

lation were too few (7 out of 25) to include as part of this metaanalysis.

A cost analysis was not performed in our study, because the pooled data did not include a cost analysis. However, it appears that this test would be cost-effective in a high-risk population if gonorrhea, chlamydia, and human papilloma virus typing can be applied with a single ThinPrep test.

Dr Horowitz asked about sampling methods. Several different techniques and sampling devices were used in the various studies. We assumed they were all adequate in obtaining samples. Unfortunately, the inability to control for certain similarities is one of the weaknesses of a metaanalysis.

The outcome variable of sample adequacy was superior in ThinPrep, which may improve the triage of women with abnormal Papanicolaou smear results. We would still encourage women to undergo regular screening, regardless of the sampling technique conventional or liquid-based cytologic study.