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William E. Lundak
University of Nebraska Medical Center

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A SURVEY OF THE RESULTS OF THE ROUTINE USE OF THE
VAGINAL SMEAR IN THE DETECTION OF UTERINE
CERVICAL CANCER IN PRIVATE PATIENTS

William E. Lundak

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College of Medicine, University of Nebraska

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LIST OF TABLES

Table	Page
I. Results of 15,638 Cytological Examinations	8
II. Subsequent Tissue Diagnosis of 427 Class III Slides	9
III. Results of Tissue Study in Those Women Class IV and Class V	11
IV. Age Specific Prevalence Rates	13
V. Overall Results of 15,638 Cytological Examinations of 10,986 Women	15

LIST OF FIGURES

Figure	Page
1. Age Distribution of Carcinomas of the Cervix	14

TABLE OF CONTENTS

	Page
INTRODUCTION	1
HISTORICAL BACKGROUND	3
GENERAL CONSIDERATIONS OF THE USE OF THE SMEARS . .	4
METHODS OF OBTAINING SMEARS AND STAINING	5
RESULTS OF THE SMEARS	8
GENERAL REMARKS ON THE RESULTS	16
COMPARISON OF THIS SURVEY TO REPRESENTATIVE SURVEYS IN THE LITERATURE	18
SUMMARY	20
CONCLUSIONS	22
BIBLIOGRAPHY	25

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INTRODUCTION

In 1962 some 14,000 women died of cancer of the uterus. This year (1963), of the 35.7 million women between the ages of 35 and 70, about 32,000 will have uterine cancer, 23,000 cancer of the cervix.

The U. S. death rate for uterine cancer has shown a steady decline. In 1940 the age adjusted death rate per 100,000 females was 25.5, by 1959 this figure was 14.0. This decline may be attributed to an extensive public educational program by the American Cancer Society and physicians concerning the "Pap" smear and improved methods in treatment.

The importance of early detection in uterine cancer is reflected in the cure rates. The five year cure rate for the "in-situ" lesions is 100%, while in the stage IV lesions it is 0%. It is therefore apparent that at the present time the best method of attacking the problem of cervical cancer is early detection. Since the early 1940's when the report of Papanicolaou was made on the routine use of vaginal smears in the diagnosis of uterine cancer this method has been used extensively in clinics and hospitals in the United States.¹¹ It is also being used in various foreign medical centers.

The role of the vaginal smear as a screening technique is well established. As more experience is gained in the interpretation of the slides, more reliance is being placed on their diagnostic value.

The purpose of this paper is to present the results of the routine use of the vaginal smear as interpreted by one individual over a six year period from private patients.

HISTORICAL BACKGROUND

Much was contributed to the science of exfoliative cytology by George N. Papanicolaou. The following historical data is from a paper by Dr. Papanicolaou to the Joint Program Committee of the International Union Against Cancer and the American Cancer Institute.²⁰

In 1838, Donne is credited with the earliest reported microscopic examination of body fluids; this was on human colostrum. The first to observe tissue fragments of malignant growths expectorated from the respiratory tract was Wallsche, in 1843.

Pouchet's observations in 1847 are the earliest recorded concerning exfoliative cytology of the female genital tract. These studies were restricted to normal cytology. Between 1847 and Papanicolaou's initial suggestions in 1928, very little was reported concerning exfoliative cytology in diagnosis of uterine cancer. It was not until 1941 that much attention was paid to the initial reports on the diagnostic value of vaginal smears in carcinoma of the uterus. Since 1941, much research and study have been done in this area.

GENERAL CONSIDERATIONS OF THE USE OF THE SMEARS

The slides which were used in this study were obtained from the routine use of the vaginal smear by four specialists in obstetrics and gynecology and approximately twenty-five general physicians. These slides were all read by one of the specialists. The practices represented are those of a general practice in rural areas, and a specialty practice of obstetrics and gynecology in Omaha, Nebraska.

Most of the patients involved are of an average to above average economic status, nearly all of them are white, and there is a fairly equal distribution of rural-urban patients. No estimate of the percentage of Jewish women in these practices can accurately be made.

No slides were obtained on patients less than 18 years old, and a general policy is to obtain smears from all married women regardless of age and all single women over 25 years of age, once a year. Smears are obtained on all new obstetrical patients and are repeated on the routine six-week post partum examination. The years involved in this review are 1957-1963.

METHODS OF OBTAINING SMEARS AND STAINING

The original method of obtaining smears as proposed by Papanicolaou was as follows: A glass pipette equipped with a suction bulb was inserted into the vagina with the bulb depressed. The bulb was then released and the pipette moved from side to side in the vagina as the pipette was withdrawn.¹² A number of different methods have since been devised for obtaining adequate material for cytological study. Aspiration of the vaginal pool, scraping the cervical squamo-columnar junction, aspiration of the endocervical canal, and various combinations of the preceding methods have all been used. There are pros and cons for each method which will not be discussed here.

All of the smears used in this study were obtained by the method devised by Ayre using the wooden "spatula" which he designed. By this method the cervix is visualized by the use of the vaginal speculum which is moistened with running tap water. No lubricant jelly is used as it interferes with proper fixation of the smear. The desired specimens are obtained by scraping the cervical os with the "spatula" at the squamo-columnar junction. The scrapings are then immediately smeared on a glass slide and placed in a Coplin Jar which contains equal parts of ethyl ether and 95% ethyl alcohol. A minimum of 20 minutes must be allowed in this solution to properly fix the slides. The slides are then air dried (which takes only a few moments) and mailed in to be stained and interpreted.

Papanicolaou's method of staining is used but with some

minor modifications.¹³ The change adopted is a reduction of the number of alcohol baths. In staining the slides the major goal is that of obtaining adequate nuclear detail. Several principal stains may be used; EA 50 or EA 36, the choice of which is by personal preference. There is much discussion as to the best type of stain to use; some experts use methylene blue and some use no stain, reading the slides after fixation only.

The basis on which exfoliative cytology is useful in the diagnosis of uterine cancer is the fact that all types of carcinoma of the uterus are exfoliative growths. This means they are constantly shedding superficial cells.¹⁰ An exception to this statement perhaps is adenoma malignum, the origin of which is the gland-bearing mucosa of the endocervix and in the endometrium.

Interpretation and classification of the slides is patterned after the standards as suggested by Papanicolaou and summarized below.

Class

I	Negative	Absence of atypical or abnormal cells.
II	Negative	Atypical cells present but without abnormal features.
III	Suspicious	Cells with abnormal features, suggestive of but not conclusive for malignancy.
IV	Positive	Cells and cell clusters fairly conclusive for malignancy.
V	Positive	Cells and cell clusters conclusive for malignancy.

Generally, a report of anything less than a negative report calls for at least a repeat smear. With positive smears or repeated suspicious smears a cervical biopsy or preferentially a cervical conization is mandatory. The cold knife cone is preferred in suspected in-situ lesions while a punch or wedge biopsy is preferred for lesions which appear grossly invasive. With the increased emphasis on early diagnosis of in-situ lesions more cervical conization procedures are being done than formerly.

RESULTS OF THE SMEARS

The material to be presented in this review is the result of 15,638 cytological examinations on approximately 10,986 patients. Initial classification of these slides is given in Table I. Of the 15,638 cytological examinations, approximately 5,652 of them are repeat examinations. Although it is acknowledged that the number of women who were reexamined after an initial examination might be of some value this was not determined.

Table I. Results of 15,638 Cytological Examinations

Class	Number	% of total
I and II	15,048	96.22
III	489	3.12
IV	81	.51
V	20	.12
		<hr style="width: 100%; border: 0.5px solid black;"/> 99.97

These results show a somewhat higher rate of Class III, IV, and V slides than the results obtained in Southeast Michigan on 16,004 women.¹⁶ It must be noted, however, that considerable bias is present in this study. Perhaps the most important point is that the majority of these patients in the review came to the office with a complaint referable to the genital tract. Many of the patients on whom smears were done were referred to the specialists with some type of lesion. These two facts alone could very

well serve to increase the number of Class III, IV, and V slides significantly.

A breakdown of the results of the slides initially Class III is shown in Table II.

Table II. Subsequent Tissue Diagnosis of 427 Class III Slides

	Number	% of total
Benign lesions (Includes cervicitis, leukoplakia, hydatiform mole, and basal cell hyperplasia)	288	67.45
Endometrial carcinoma	13	3.05
Carcinoma of the cervix		
Invasive	20	4.68
In-situ	17	3.98
Cystadeno carcinoma of the ovary	4	.93
Carcinoma of the vulva	2	.47
Carcinoma of the rectum (Metastatic)	1	.23
No tissue diagnosis	82	19.20
	<u>427</u>	<u>99.99</u>

Of the 489 Class III slides, follow-up was available on 427 women. It must be noted that of these 427 women many of them had repeat smears, the total of which very nearly equals 489. On a few no follow-up was available. No tissue diagnosis was made in 19.20% because of various reasons. A few of these are as follows: (1) The repeat smear was negative, (2) the patient was

six weeks post partum, or (3) the patient just did not return for a repeat examination. The majority of the women who were initially Class III had an ultimate diagnosis of some type of benign lesion, the majority of which was cervicitis. Of the patients who had a tissue specimen submitted for diagnosis, 57 or 16.5% had a subsequent diagnosis of malignancy.

A case follow-up was available on 57 Class IV slides and 19 Class V slides. Here, again, many of these patients had repeat smears and on a few follow-up was not available. The results, therefore, of all 81 Class IV slides and 20 Class V slides were not obtained. In these two classes of slides, tissue studies were done on all of the cases which were reviewed. In general, women who have post menopausal bleeding are assumed to have carcinoma until it is proven otherwise. A negative vaginal smear is not sufficient in these cases to rule out carcinoma. Results of the tissue examinations of the Class IV and V slides are shown in Table III.

Table III. Results of Tissue Study in Those Women Class IV
and Class V

Class IV lesions	No. in 57 cases	Percentage
Adenocarcinoma of Endometrium	5	8.77
Carcinoma of ovaries	3	5.26
Carcinoma of vulva	1	1.73
Carcinoma of vagina	1	1.73
Carcinoma of cervix		
In situ	8	14.03
Invasive	25	43.86
False Positives	<u>14</u>	24.46
	57	
Class V lesions	19 cases	
Adenocarcinoma of Endometrium	3	15.77
Carcinoma of vulva	1	5.26
Metastatic carcinoma of rectum	1	5.26
Carcinoma of cervix		
In situ	3	15.77
Invasive	10	52.63
False Positive	<u>1</u>	5.26
	19	

Perhaps something should be stated concerning the false positive. All of the slides which were labeled false positive for malignancy had some type of benign lesion. The most common was chronic cervicitis. Therefore, in even the Class III slides where nearly 68% of the lesions were benign processes we feel that all cervical lesions which are visualized must be proven to be benign by the physician.

It is of some interest to note the class of slide which immediately preceded the smear in those patients who converted to a suspicious or frankly positive smear. This information was available in 77 patients, and 58 or 75.3% of these patients had Class II smears before converting. This would lead one to consider the idea that perhaps the Class II slides indicate some potentiality that the Class I slides do not. Very similar findings were observed on a much larger group of patients by Dunn and his associates.⁵ Dunn feels that there is some bias in his data, however, in that there is a predominance of older patients in the Class II smear group and that this would partly account for this finding.

There is much discussion in the literature on age specific prevalence rates of the various classes of positive or suspicious slides. This distribution is presented in Table IV.

Table IV. Age Specific Prevalence Rates

Age range	Number	% of total
Class III		
	481 cases	
10-19	1	2.04
20-29	105	21.83
30-39	167	34.72
40-49	87	18.09
50-59	89	18.48
60-69	24	4.98
70-plus	8	1.66
Class IV		
	57 cases	
10-19	0	0
20-29	7	12.28
30-39	10	17.54
40-49	24	42.10
50-59	3	5.26
60-69	10	17.54
70-plus	3	5.26
Class V		
	20 cases	
10-19	0	0
20-29	1	5.00
30-39	3	15.00
40-49	6	30.00
50-59	6	30.00
60-69	3	15.00
70-plus	1	5.00

Table IV clearly demonstrates the peak age for each class as the slides progress from the suspicious to the malignant classifications. This perhaps would be expected since the incidence of atypical cells usually increases as the patients' age increases.

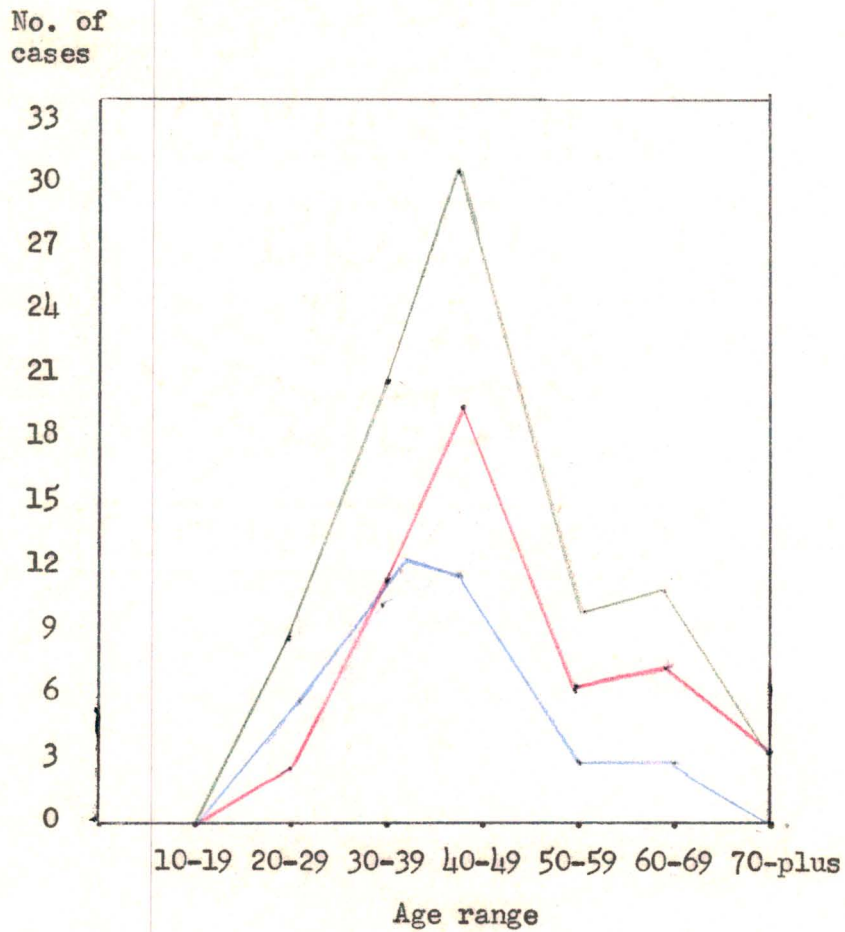


Figure 1. Age Distribution of Carcinomas of the Cervix

Total cases —————
 Invasive —————
 In-situ —————

The results shown in Figure 1 are very similar to those found in all other studies reviewed. The peak range of the in-situ lesions is the 30-39 age group although the total in the 40-49 age group was nearly the same, and the peak incidence of the invasive lesions is the 40-49 age group. This study does represent too small a number of patients, however, to be of true comparative value with those reports studied.

Although parity is no longer considered to have any role in the etiology of carcinoma of the cervix, it did have at one time.⁸ The average parity of the patients with Class III smears is 2.61; Class IV, 2.63; and Class V, 3.5 pregnancies. This particular material is presented for general interest only.

The overall results of the study concerning the malignancies found are summarized in Table V.

Table V. Overall Results of 15,638 Cytological Examinations of 10,986 Women

	No.	% of smear	% of women examined	Rate per 1,000 women
Carcinoma of Endometrium	21	.12	.19	1.9
Carcinoma of cervix	83	.56	.75	7.5
Invasive	55 - 66.2% of total			
In-situ	28 - 33.8% of total			
Carcinoma of vulva and vagina	5	.03	.04	0.4
Carcinoma of ovaries	9	.04	.07	0.7
Carcinoma of rectum	2	.01	.02	0.2

GENERAL REMARKS ON THE RESULTS

This study involved 15,638 cytological examinations on approximately 10,986 patients from 1957 - 1963. These patients are all private patients. The total of 10,986 patients is a rather meticulous approximation that I feel is within 5% of the true value. Administrative difficulties made this approximation a necessity.

The results obtained are very comparable in every respect to similar studies in the literature, and I believe illustrative of findings in similar situations with similar patients. The percentage of findings of cervical cancer is somewhat higher in this study than findings in studies which are total population screening procedures. The majority of patients represented by this data must be considered in a selective population universe for the following reasons: (1) Only selective economic levels are represented in most cases, (2) many of these patients have come to their physician with some type of specific complaint, and (3) the majority of these patients with positive smears are being seen on a consultant basis by the specialists in obstetrics and gynecology.

I feel some criticism of this data could be made in the fact that the exact number of patients involved and the number of repeat slides each patient had done is not known. In addition, follow-up on some of these patients simply was not available. All of these facts affect the figures, but not significantly. Many of these difficulties stem from the fact that approximately 40% of

the information was obtained by writing the referring physicians concerning the patient who is represented by the slide in the specialist's office. Perhaps something should have been done concerning false positive and false negative reports, however, I feel it is very difficult to define a false negative. In no instance in this study was a carcinoma of the cervix represented by other than a Class III, IV, or V slide. There were approximately 15 or .09% of the total number of slides which were false positive. In other studies the number of false positives has ranged from 30% down to zero.

COMPARISON OF THIS SURVEY TO REPRESENTATIVE SURVEYS IN THE LITERATURE

The amount of material in the literature on the subject of carcinoma of the cervix is voluminous. This comparison does not attempt to review this literature but only to present some representative surveys for comparison.

In this study the discovery rate for carcinoma of the cervix was 7.5 per 1,000 women. This compares to a rate of 5.9 per 1,000 women in Southeast Michigan,¹⁶ 6.7 per 1,000 in Shelby County, Tennessee,¹⁶ and 6.3 per 1,000 in Toledo, Ohio.¹⁶ The study in Southeast Michigan was based on 16,004 cytological examinations. The other two studies mentioned are on total population screening studies involving several hundred thousand patients. Approximately 2.53 per 1,000 patients were discovered to have carcinoma in-situ. This compares quite closely to the rate of 2.40 per 1,000 observed on 33,750 women by Dunn.⁵ As noted before, the discovery rate of carcinoma in this review is somewhat higher than others noted but the bias involved here could easily account for this difference. The majority of the patients involved in this study came to their physician with some specific genital tract complaint or were seen on a consultant basis by the specialists in obstetrics and gynecology.

A cervical cancer control program in British Columbia in 1961 involving 17,401 women revealed an average incidence of discovery of carcinoma of 0.9%.² The value here was 1.07%, however, the bias was again involved.

The age specific prevalence rates for carcinoma in-situ in all studies hit a peak in the 30-39 year range, and in the 40-49 year range for invasive carcinoma.⁵ This study is no exception with similar findings.

Dunn and his associates observed that those women with Class II cytology have about 10 times the potentiality in the next year for carcinoma in-situ compared to those previously Class I. We did find in a series of 77 patients who converted from negative to suspicious or positive slides that 75.3% of them were previously Class II.

SUMMARY

This survey represents a review of the routine use of the vaginal smear in private patients over a six year period by a group of specialists in obstetrics and gynecology and general physicians. All of these cytological examinations were interpreted by one of the specialists.

A total of 15,638 cytological examinations were done on approximately 10,986 women. Of these slides, 96.22% were negative; 3.12% were Class III; 0.51% were Class IV; and 0.12% were Class V. As a direct result of the vaginal smears 83 carcinomas of the cervix were discovered. This represents a rate of 7.5 per 1,000 patients examined. Of these 83 patients, 55 or 66.2% were invasive carcinoma and 28 or 33.8% were carcinoma in-situ. This represents rates of 4.97 per 1,000 and 2.53 per 1,000, respectively. The average incidence of discovery of all carcinoma in the study was 1.07%.

A peak incidence of carcinoma in-situ was noted in the 30-39 year age group, and the invasive carcinoma peaked in the 40-49 year age group.

The most common reason for a woman to have a Class III smear was due to some type of cervicitis. Of the Class III smears, 67.45% were due to some type of benign lesion and, as stated above, the most common etiology was cervicitis. Although it is of interest only, the average parity of the Class III slides was 2.61; Class IV, 2.63; and Class V averaged 3.5 pregnancies. One other interesting observation was that of 77 patients who

converted from negative to suspicious or positive slides, 75.3% of them were previously Class II.

A brief comparison of this survey with representative surveys from the literature was made. There were no significant differences in the comparisons. The rate of 7.5 cervical carcinomas per 1,000 patients compared favorable to the rates of 5.9, 6.3, and 6.7 per 1,000 patients in the studies from the literature. The average incidence of the discovery of carcinoma was 0.9% in the literature, 1.07% here. This higher incidence of carcinoma was explained as partially due to the bias represented by the patients in the study.

The peak incidence of the invasive cervical lesions in the literature was the 40-49 year age group; for the in-situ lesions the peak was the 30-39 year age group.

Vaginal smears should be done annually in all women 25 or over, and in all married women once a year also. The frequency at which these examinations must be done is debatable, however, it is generally concluded that the greatest value of the routine vaginal smear is in the detection of in-situ carcinoma of the cervix.

CONCLUSIONS

The purpose of this survey is to review as objectively as possible the results of the routine use of the vaginal smear in private patients seen by a group of general physicians and specialists in obstetrics and gynecology. Secondly, these results were compared briefly to similar surveys from the literature.

No concrete conclusions can be made as to the value of routine use of the vaginal smear since no study was made in this series of the case discovery rate of carcinoma of the cervix prior to the advent of the routine vaginal smear. In our study 7.5 women per 1,000 examined were discovered to have carcinoma of the cervix; 33.8% of these were carcinoma in-situ. This represents the true value of routine vaginal screening. The discovery of far advanced carcinoma is of no value in terms of achieving a cure, however, carcinoma in-situ is a far different situation. These patients are a young group of patients with a peak incidence in the 30-39 year age group. The 5 year cure rate approximates 100%. This is the group which is usually asymptomatic and in which clinical findings are usually absent even though a fatal lesion is present. Large numbers of women who have been examined twice or more show a marked decrease in the numbers of invasive carcinoma discovered in the repeat examinations. From this it may be concluded, I believe, that if all women received regular periodic reexaminations, the mortality rate due to cervical cancer could be reduced to nearly zero.

Comparisons of various surveys have indicated very similar findings in the use of the vaginal smear regardless of the method used to obtain the smear. As noted, we used the method devised by Ayre. From this it may be concluded the method of obtaining the vaginal smear is a matter of personal preference only, and has no bearing on the results.

No conclusions regarding the epidemiology of cervical cancer may be made from this study. I do not think this is possible because of the group of patients represented by the study. In the literature factors related to carcinoma of the cervix are race, early marriage, multiple marriage, extra marital relations, early coitus, frequent coitus without contraceptives and uncircumcised sex partners.

As a general concluding statement I believe that the routine use of the vaginal smear in private practice has great value. Eighty-three cases of carcinoma of the cervix were discovered in this study, approximately 50% of which were not suspected. In carcinoma of the cervix, as with most malignant lesions, early diagnosis offers the only opportunity for effective treatment, and the vaginal smear has been effective as a screening study for cervical carcinoma.

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