A Groundbreaking Work Which Laid the Foundation for Mass Screening in Cervical Cytology in Japan

Robert Y. Osamura

International University of Health and Welfare, Graduate School, Tokyo, and Department of Diagnostic Pathology, Nippon Koukan Hospital, Kawasaki, Japan

Keywords

Cervical cancer · Cervical cytology · Carcinoma in situ · Atypical cells · Cancer staging · Cancer screening

Abstract

This commentary discusses the impact of a milestone article on the accuracy of cervical smears for detecting cancer back in the developmental and transforming era of the cytological detection of atypical and malignant cells. The study served in the establishment of cancer screening in Japan which has contributed greatly in decreasing mortality from cervical cancers.

© 2017 S. Karger AG, Basel

We discuss a milestone paper [1] from the Japanese Society of Clinical Cytology (JSCC) published in *Acta Cytologica*. We consider the article to be important for the following reasons:

1. This was an early, extensive study on the high accuracy of cervical cytology at a cancer hospital.
2. The JSCC was started in 1961 while this study was being carried out.

3. Gynecologists were the founding members of the JSCC and the authors of the paper were contributing gynecologists from the Society.
4. The International Academy of Cytology (IAC) was started in 1957 during this study.

This milestone study [1] stated: “The vaginal aspiration smear was the only test used from 1952 to June 1957. But since July 1957, the scrape smear has been added. The scrape sample was prepared by scraping of the erosive surface in the ectocervix with a cotton swab.”

“The staining method used is Papanicolaou’s EA 36. This study utilized the five-class classification by Papanicolaou. Cases of Class IV and V were considered to be cancer, and cases of Class I and II noncancer, while cases of class III were considered to be false-positive.”

And, regarding surgically resected materials: “Masubuchi divided Stage 0 into three subgroups: Stage 0–A, 0–B, and 0–C. The cases of Stage 0–A show carcinoma in situ-like findings by punch biopsy, but by thorough examination of the removed material no lateral invasion is found, but rather benign characteristics; those of Stage 0–B show typical carcinoma in situ; and those of Stage 0–C are suspected invasive.”

Fig. 1. Dr. Kazumasa Masubuchi and Dr. George Papanicolaou in the early days.

Fig. 2. The mortality rate of uterine/cervical cancer has markedly decreased in Japan.

“The number of carcinomas of the cervix diagnosed from 1952 to 1963 was 2,918, and the number of positive cases (i.e., class IV or Class V) detected by smear was 2,660, so the smear was 91.2% accurate.”

By means of Tables 1–6, the study demonstrated the high accuracy/correct diagnosis rate of smear findings in cancer and non-cancer groups (Table 1) and for cervical cancer staging (stages 0–IV; Table 2), the relationship between the stage of cervical cancer and the smear finding (Table 3), the frequency of class III–V smears in stage 0 (Table 4), the frequency of class III–V smears in “stage I” cervical carcinoma (Table 5), and the histologic findings in non-cancer cases with class III–V smears (Table 6).

Table 7 showed “the result of smear findings in the cases diagnosed atypical epithelium by biopsy during these six and half years” (i.e., July 1957 to December 1963). The authors emphasized that the high rate (54/143 cases, i.e., 37.8%) of atypical epithelium showing class III, IV, or V by smear test is worthy of special attention.

They concluded: “Vaginal smear examinations were adopted as a routine practice in Japan in 1961. From 1961 to 1964 about 20,000 women were cytologically examined at 92 hospitals” (65 cases [0.5%] were diagnosed as carcinoma of the uterus) [1].

This paper emphasized the role of cervical smears in cancer detection in Japan and served as a basis for the subsequent introduction of the cancer screening program.

This Paper and the JSCC

The JSCC is an academic society that promotes scientific research in clinical cytology and cytopathology and the application of research findings in clinical practice. The JSCC’s beginnings date back to 1961. Modern cytological diagnosis began in 1928 with George Papanicolaou [2], whose technique of cervical smears became recognized as an effective method of diagnosing uterine cancer. The Gynecological Cytodiagnosis Discussion Group was formed in Japan in response to the creation of the International Academy of Gynecological Cytology in 1957. In 1961, the latter was renamed the IAC, to include advances in other fields and the former converted to the name JSCC. The study that is the subject of this commentary [1] was conducted during this period of transformation in the field of cytology in Japan (Fig. 1).

The JSCC has been instrumental in the early detection of cancers including cervical, lung, and breast cancers. In the course of the long history of the JSCC, its cervical cancer exams, in particular, have contributed significantly to reducing the fatality rate for uterine/cervical cancer (Fig. 2).

Contributions by Drs. Masubuchi, Tenjin, and Fujii to *Acta Cytologica*

Of 50 contributions to PubMed, Dr. Masubuchi's study group has published a total of 7 papers [1, 3–8] in *Acta Cytologica* ([1] was the first paper he wrote in English); Dr. Tenjin's group a total 4 papers [1, 4, 9, 10]; and Dr. Fujii has contributed 1 [1].

The International Development of Cervical Cancer Detection and Cytology

By the 1960s, cervical cytology screening and the basic concepts of gynecologic cytopathology were fairly well established in the USA. During the 1950s and early 1960s, several famous monographs and atlases were published.

At about this time, numerous articles describing both the cytologic manifestations of cervical carcinoma and its precursors also began to appear in the literature. These excellent publications summarize and illustrate the then-current state of knowledge in this field. They include: Papanicolaou's *Atlas of Exfoliative Cytology* [11] in 1954, Fluhmann's *The Cervix Uteri and Its Diseases* [12] in 1961, Graham's *The Cytologic Diagnosis of Cancer* [13] in 1963, and the first edition of Koss' *Diagnostic Cytology and Its Histologic Bases* [14] in 1961.

Disclosure Statement

The author has nothing to declare regarding this publication.

The Detection of Cervical Cancer at Cancer Institute Hospital in Tokyo from 1952 to 1963

KAZUMASA MASUBUCHI, M.D., YOSHIO TENJIN, M.D.,
JUN-ICHI FUJII, M.D.

Department of Gynecology, Cancer Institute Hospital, Nishi-Sugamo, Toshima-ku Tokyo, Japan

INTRODUCTION

The smear test is used in the Gynecology Department at the Cancer Institute in Tokyo as a screening test for the detection of female genital cancer. It has been applied to all out-patients as a routine method of detection of the disease since 1952.

The following report concerns the result of research from 1952 to 1963.

MATERIALS AND METHODS

The vaginal aspiration smear was the only test used from 1952 to June 1957. But since July 1957, the scrape smear has been added. The scrape sample was prepared by scraping of the erosion surface in the ectocervix with a cotton swab. In cases having little or no change in the ectocervix, the endocervical smear was also taken. For post-menopausal women especially, great importance was placed on the examination of the endocervical scrape smear.

The staining method used is Papanicolaou's EA 36.

This study used the five-class classification by Papanicolaou. Cases of Class IV and V were considered to be cancer, and cases of Class I and II noncancer, while cases of Class III were considered to be false-positive.

After a thorough examination was performed on the removed materials diagnosed as carcinoma in situ, i.e., Stage 0, various gradings were provided according to the pathologic findings. Masubuchi divided Stage 0 into three subgroups: Stage 0-A, 0-B, and 0-C. The cases of Stage 0-A show carcinoma in situ-like findings by punch biopsy, but by thorough examination of the removed material no lateral invasion is found, but rather benign characteristics; those of Stage 0-B show typical carcinoma in situ; and those of Stage 0-C are suspected invasive.

RESULTS

Out of 49,996 patients examined during these 12 years, 3,612 cases (7.2%) were found to be carcinoma, and 46,384 cases were non-cancer.

Presented at the Second International Congress of Exfoliative Cytology, Paris, France, 1965.

As shown in Table 1, 90.4% of the cases diagnosed as cancer yielded positive smears, and 98.7% of the negative cases were correctly diagnosed. Histologic diagnosis by biopsy was adopted for the final determination of the disease.

In Japan, most of female genital cancer is carcinoma of the cervix. Therefore, the main interest of the smear test is cancer of the cervix. The number of carcinoma of the cervix diagnosed from 1952 to 1963 was 2,918, and the number of positive cases (i.e., Class IV or Class V) detected by smear was 2,660, so the smear was 91.2% accurate. As shown in Table 2, the results obtained by combined tests of vaginal aspiration and scrape smear for six and a half years showed higher accuracy in cases in the early stage: 69.6% in Stage 0, 84.9% in Stage I, and 96.4% in Stage II.

Considering the relationship between clinical stages and Papanicolaou's classification in 2,149 cases with cancer of the cervix, as shown in Table 3, 91.5% of all cases are in Class IV and V, 4.7% in Class III, and 3.8% in Classes I and II, that is, false-negative. If Class III is included in cancer cases, the percentage is raised to 96.2%. Therefore, the correct diagnosis was 84.8% in Stage 0, 94.0% in Stage I and 99% in Stages II, III and IV. In Class III, the rate is 15.2% in Stage 0, 9.0% in Stage I and rare in Stages II, III and IV. One cannot disregard the fact that some cases in Stage 0 and early Stage I could be classified as Class III by smear test.

After the three sub-groupings (0-A, 0-B, 0-C) for the cases diagnosed as carcinoma in situ were provided, they were compared with smear findings on the cases from 1960 to 1963. The results of the cases diagnosed as Class III, IV and V are shown in Table 4. In Stage 0-A, 42.9% were Class III, whereas in both Stages 0-B and 0-C only 11.5% were Class III. On the other hand, in Classes IV and V the percentage is as high as 88.5. The cases in Stage I were divided into early invasive and definitely invasive, and the frequency of appearance of Class III in both groups is summarized in Table 5. In the early invasive group, the rate of appearance of Class III was 24.5% and that of Classes IV and V was 75.5%; in the definitely invasive group, the rate of appearance of Class

TABLE 1. *Over-All Results of Smear Findings*
Cancer Institute Hospital, Tokyo (1952-1963)

	1952-June 1957			June 1957-Dec. 1963			Total		
	Number of patients	Correct diagnosis	%	Number of patients	Correct diagnosis	%	Number of patients	Correct diagnosis	%
Cancer	1,389	1,262	90.9	2,223	2,007	90.3	3,612	3,269	90.4
Non-cancer	11,268	10,981	97.5	35,116	34,793	99.1	46,384	45,774	98.7

TABLE 2. *Over-all Results of Smear Findings in Staging of Carcinoma of the Cervix*
(1952-1963)

Stage	1952-June 1957			June 1957-Dec. 1963			Total		
	Number of patients	Correct diagnosis	%	Number of patients	Correct diagnosis	%	Number of patients	Correct diagnosis	%
0	40	20	50.0	184	128	69.6	224	148	66.1
I	153	123	77.4	511	434	84.9	664	557	83.9
II	282	270	95.7	691	666	96.4	973	936	96.2
III	237	230	97.0	684	664	97.1	921	894	97.1
IV	57	50	87.7	79	75	94.9	136	125	91.9
Total	769	693	90.1	2149	1967	91.5	2918	2660	91.2

TABLE 3. *Relation Between Stage of Cancer of the Cervix Uteri and Smear Findings*
Cancer Institute Hospital, Tokyo (July 1957-Dec. 1963)

	Stage 0		Stage I		Stage II		Stage III		Stage IV		Total	%
	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%		
Class IV, V	128	69.6	434	85.0	666	96.4	664	97.1	75	98.6	1967	91.5
Class III	28	15.2	46	9.0	16	2.3	10	1.5	2	0.7	102	4.7
(Class III-IV-V)	156	84.8	480	94.0	682	98.7	674	98.6	77	99.3	2069	96.2
Class I, II	28	15.2	31	6.0	9	1.3	10	1.4	2	0.7	80	3.8
Total	184		511		691		684		79		2149	

TABLE 4. *Frequency of Class III-V Smears in Stage 0*
(1960-1963)

	Class III		Class IV, V		Total
Stage 0-A	6	42.9%	8	57.1%	14
Stage 0-B	3		34		37
Stage 0-C	4	11.5%	20	88.5%	24

III was 8.5%, while in Classes IV and V it was 91.5%.

From July 1957 to 1963, 496 cases were diagnosed by biopsy as nonmalignant, but were placed in Classes III, IV, and V by smear findings. This is only 1.4% of the total 35,116 non-malignant

cases examined during the experimental period (as shown in Table 6). Out of 496 cases, 14.7% were histologically diagnosed as atypical epithelium, but the final decision as to whether the smear test was correct or not should be made after the follow-up study.

TABLE 5. Frequency of Class III, IV, V Smears in "Stage I" Carcinoma of the Cervix (1960-1963)

	Class III	%	Class IV, V	%
Squamous cell carcinoma				
Early invasive	12	24.5	37	75.5
Definite invasive	19	8.5	205	91.5
Adeno-carcinoma	2		10	

TABLE 6. Histologic Findings in Non-Cancer Cases with Class III, IV, V Smears (July 1957-Dec. 1963)

	Class III	Class IV	Class V	Total	%
Atypical epith.	41	15	17	73	14.7
Cervicitis, epidermoid metaplasia	246	43	46	335	67.5
Miscellaneous	72	7	9	88	17.8

Table 7 shows the result of the smear findings in the cases diagnosed atypical epithelium by biopsy during these six and a half years. Out of 143 cases of atypical epithelium, 54 cases (37.8%)

showed Class III, IV or V by smear test. This high rate should be noticed with great attention.

DISCUSSION

Today the final decision of cancer is based on biopsy using histologic criteria. But it is important to follow up the cases in which the smear showed false-positive, not leaving them as erroneous. There were many cases in such a group in which cancer developed later.

SUMMARY

Vaginal smear examinations were adopted as a routine practice in Japan in 1961. From 1961 to 1964 about 20,000 women were cytologically examined at 92 hospitals. There were 65 cases (0.5%) diagnoses of carcinoma of the uterus.

REFERENCES

1. Masubuchi, K.: On early diagnosis of cancer of the cervix uteri. J. Jap. Obst. & Gynec. Soc. (Japanese) 11:567-586, 1959.
2. Masubuchi, K., et al: Detection of the cancer of the cervix uteri by follow-up study. Cancer Clinic (Japanese) 5:505-512, 1959.
3. Masubuchi, K., et al.: On the cytologic diagnosis in cancer of the cervix uteri. Cancer Clinic (Japanese) 5: 599-605, 1959.
4. Masubuchi, K. and Suzuki, T.: The value and the limit of smear test. World of Obstet. & Gynec. (Japanese) 13:948-954, 1961.

TABLE 7. Histologic Abnormal Findings and its Smear Findings (July 1957-Dec. 1963)

Histologic findings	Class I	Class II	Class III	Class IV	Class V	Total
Atypical epith. hyperplasia	59	21	28	15	6	129
Basal-cell hyperplasia	8	1	2	2	1	14
			54	37.8%		

References

1. Masubuchi K, Tenjin Y, Fujii J: The detection of cervical cancer at Cancer Institute Hospital in Tokyo from 1952 to 1963. *Acta Cytol* 1967; 11:32-34.
2. Siang Yong T, Tatsumara Y: George Papanicolaou (1883-1962): discoverer of the Pap smear. *Singapore Med J* 2015;56: 586-587.
3. Masubuchi K: Significance of the role of cytology in population screening of cancers. *Acta Cytol* 1975;19:334-336.
4. Masubuchi K, Kubo H, Tenjin Y, Ono M, Yamazaki M: Follow-up studies by cytology on cancer of the cervix uteri after treatment. *Acta Cytol* 1969;13:323-326.
5. Masubuchi S Jr, Nagai I, Hirata M, Kubo H, Masubuchi K: Cytologic studies of malignant melanoma of the vagina. *Acta Cytol* 1975;19: 527-532.
6. Fujimoto I, Masubuchi S, Miwa H, Fukuda K, Yamaguchi S, Masubuchi K: Psammoma bodies found in cervicovaginal and/or endometrial smears. *Acta Cytol* 1982;26:317-322.
7. Hirai Y, Chen JT, Hamada T, Fujimoto I, Yamauchi K, Hasumi K, Masubuchi K, Sakamoto A: Clinical and cytologic aspects of primary fallopian tube carcinoma. A report of ten cases. *Acta Cytol* 1987;31:834-840.
8. Fujimoto I, Hirai Y, Hasumi K, Masubuchi K, Osamura Y: The value of epithelial membrane antigen in the diagnosis of ovarian tumors. *Acta Cytol* 1990;34:549-554.
9. Tenjin Y, Sugishita T, Yamamoto K: Automated cytoscreening system using 16 mm roll film. *Acta Cytol* 1977;21:276-286.
10. Tenjin Y, Yamamoto K, Sugishita T, Igarashi Y: Basic studies on repair, especially histology, cytology and microspectrophotometry of DNA contents. *Acta Cytol* 1979;23:245-251.
11. Papanicolaou GN (ed): *Atlas of Exfoliative Cytology*. Cambridge, Harvard University Press, 1954.
12. Fluhmann CF (ed): *The Cervix Uteri and Its Diseases*. Philadelphia, W.B. Saunders, 1961.
13. Graham RM (ed): *The Cytologic Diagnosis of Cancer*, ed 2. Philadelphia, W.B. Saunders, 1963.
14. Koss LG, Melamed MR (eds): *Koss' Diagnostic Cytology and Its Histopathologic Bases*. Philadelphia, Lippincott Williams & Wilkins, 1961.