Original article

Usefulness of the Bethesda system for uterine cervical cancer screening in Niigata Prefecture

Kikuo Ikegami, Toshikazu Ikoma, Takao Asai, Yasuo Tsuchiya

Department of Clinical Engineering and Medical Technology, Niigata University of Health and Welfare, Niigata, Japan

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Abstract

Uterine cervical cancer screening using the Bethesda system was put into use in Niigata Prefecture in 2010. However, the effectiveness of the screening using the Bethesda system has not been well evaluated. We aimed to compare the results of smears diagnosed using the Bethesda system in 2010 with the results of smears diagnosed using the Nichibo classification from 1995 through 2009. A total of 337,029 women were screened for cancer. The diagnoses obtained using the Bethesda system (18,449 examinees) were compared with those obtained using the Nichibo classification at the period of 15 years (318,580 examinees). The rate of abnormalities and the detection rate of dysplasia were displayed significant difference between Nichibo classification and Bethesda system ($p<0.05$). However, no significant difference was found in the cancer detection rate between the two classification methods. This finding shows that the Bethesda system is useful for the early detection of dysplasia such as precursor lesions of the uterus and in early treatment.

Introduction

Cytological diagnosis in uterine cervical cancer screening has been carried out using a cytological classification based on the Nichibo classification created by the Japan Association of Obstetricians and Gynecologists in 1978 [1]. The Nichibo classification categorizes disease into 5 stages from Class I to V according to the degree of cellular atypia and describes the typical lesion and handling method for each class [2]. For this reason, the classification was very convenient both for clinicians and cytologists. However, the Nichibo classification had no standardized definition of sample collection method, and of the handling of the cells when they were difficult to diagnose because of small amount of the samples [3]. For this reason, there was a chance to produce a false-negative result in case of insufficient volume of the cells. Furthermore, since human papilloma virus (HPV) infection has been shown to be a risk factor for uterine cervical cancer, the categorization and diagnosis of HPV-infected cells should be clarified [4].

To solve these problems, in 2008, the Japan Association of Obstetricians and Gynecologists formally adopted the cytological-diagnosis narrative form of the Bethesda system and announced the information to gynecologists all over the country [5]. The Bethesda system is a diagnostic system developed by the National Cancer Institute in Bethesda, Maryland, U.S.A., in order to solve the problems in the past class divisions [6,7]. The features of this system

Corresponding author: Kikuo Ikegami
Department of Clinical Engineering and Medical Technology, Niigata University of Health and Welfare, 1398 Shimami-cho, Kita-ku, Niigata City, Niigata, 950-3198, Japan
TEL/FAX: +81-25-257-4409, E-mail: ikegami@nuhw.ac.jp

included the description of presumed pathological change, the judging of specimens as appropriate or inappropriate, and the determination of new criteria for dysplastic cells that are difficult to diagnose [8]. A comparison of the narrative form of the Bethesda system with the Nichibo classification is shown in Table 1. The use of this narrative form is spreading quickly throughout Japan.

In Niigata prefecture, the use of the Bethesda system for uterine cervical cancer screening was begun in 2010. Because the Bethesda system was introduced only recently, its effectiveness has not been sufficiently evaluated yet [9-11]. The purpose of this research was to compare the results of smears performed in uterine cervical cancer screenings diagnosed using the Bethesda system in 2010 with those diagnosed using the Nichibo classification in Niigata Prefecture for 15 years from 1995 to 2008.

Methods

1. Examinees

The uterine cervical cancer screening was carried out in 337,029 women aged 30 years or older from 1995 to 2007 (287,658) or aged 20 years or older from 2008 to 2010 (49,371). The subjects underwent the screening every year between 1995 and 2007, or every other year between 2008 and 2010. The screening was carried out among residents of Niigata Prefecture by the Niigata Health Service Center.

2. Screening findings and statistical procedures

The results of smears of the uterine cervix diagnosed using the Bethesda system in 2010 were compared with those diagnosed using the Nichibo classification from 1995 to 2009. When smears of atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC) were found using the Bethesda system, or smears of class IIIa, IIIb, IV, and V were found using the Nichibo classification, we judged them to be "abnormalities."

The statistical procedures were performed using a software system (IBM SPSS Statistics 20, USA). We used a χ^2-test to reveal the differences in the detection rates of examinees requiring detailed examination, those diagnosed with dysplasia, and those diagnosed with cancer. P

Table 1. Comparison of the Bethesda system and the Nichibo classification

Bethesda system			Nichibo classification	
Classification	Notation	Screening findings[1)]	Classification	Screening findings[1)]
Negative for intraepithelial lesion or malignancy	NILM	Normal	I or II	Normal
Atypical squamous cells of undetermined significance	ASC-US	Abnormal	II	Normal
			IIIa	Abnormal
Atypical squamous cells cannot exclude HSIL	ASC-H	Abnormal	IIIa or IIIb	Abnormal
Low grade squamous intraepithelial lesion	LSIL	Abnormal	IIIa	Abnormal
High grade intraepithelial lesion	HSIL	Abnormal	IIIa or IIIb or IV	Abnormal
Squamous cell carcinoma	SCC	Abnormal	V	Abnormal

1) The following smears were categorized as "abnormal": ASC-US and over by Bethesda system, and class IIIa and over by Nichibo classification

Table 2. Results of cytology by year, and by either Nichibo classification or Bethesda system

Classification	Year	Number of examinees[1)]	Number of abnormalities[2)] (%)	
Nichibo classification	1995	26,131	68	(0.26)
	1996	26,820	42	(0.16)
	1997	25,039	69	(0.28)
	1998	23,495	53	(0.23)
	1999	21,935	55	(0.25)
	2000	22,295	74	(0.33)
	2001	24,014	63	(0.26)
	2002	23,210	83	(0.36)
	2003	24,406	135	(0.55)
	2004	23,450	103	(0.44)
	2005	16,751	88	(0.53)
	2006	16,354	114	(0.70)
	2007	13,758	109	(0.79)
	2008	14,335	132	(0.92)
	2009	16,587	193	(1.16)
Subtotal		318,580	1,381	(0.43) *
Bethesda system	2010	18,449	264	(1.43) *
Total		337,029	1,645	(0.49)

1) Examinees were consisting of initial examinees and re-examinees.
2) The following smears were categorized as “abnormalities”: class IIIa and over by Nichibo classification from 1995 to 2009, and ASC-US and over by Bethesda system in 2010.
*: $p<0.05$

values of less than 0.05 were considered to be statistically significant.

Results

Table 2 shows the results of uterine cervical cancer screening by year from 1995 to 2010. The rates of abnormalities in 2010 and in the past 15 years were 1.43% (264/18,449) and 0.43% (1381/318,580), respectively. The rate of abnormalities was displayed significant difference between Nichibo classification and Bethesda system ($p<0.05$).

Table 3 shows the results of the uterine cervical cancer screening by classification method. Number of examinees having screened as abnormalities were 131 in 2010 and 546 in past 15 years. The detection rate of examinees diagnosed with dysplasia using the Bethesda system was 0.71% (131 examinees) and that found using the Nichibo classification was 0.17% (546 examinees). The detection rate obtained using the Bethesda system was 4.2 times higher than that obtained using the Nichibo classification. The dictation rate of dysplasia of initial examinees is higher than re-examinees in the both of Nichibo classification and Bethesda system ($p<0.025$).

The rate of examinees diagnosed with cancer

Table 3. Results of uterine cervical cancer screening by the two classification methods

Classification		Screening findings: Number of examinees	Screening findings: Number of abnormalities[1] (%)		Clinical diagnosis: Number of dysplasia cases (%)		Clinical diagnosis: Number of cancer cases (%)		
Nichibo classification	Initial examinees	60,215	751	(1.25)	310	(0.51)	167	(0.28)	
	Re-examinees	258,365	630	(0.24)	236	(0.09)	84	(0.03)	
	Total	318,580	1,381	(0.43)	546	(0.17)	251	(0.08)	
Bethesda system	Initial examinees	6,383	168	(2.63)	81	(1.27)	12	(0.19)	
	Re-examinees	12,066	96	(0.80)	50	(0.41)	2	(0.02)	
	Total	18,449	264	(1.43)	131	(0.71)	14	(0.08)	

*1 (Nichibo Re-examinees vs Nichibo Total; Nichibo Total vs Bethesda Initial examinees)
*1 (Nichibo Total vs Bethesda Total)
*2 (Bethesda Initial examinees vs Bethesda Re-examinees)
n.s. (Nichibo Total vs Bethesda Total)

1) The following smears were categorized as "abnormalities": class IIIa and over by Nichibo classification, and ASC-US and over by Bethesda system.
*1: $p<0.025$
*2: $p<0.05$
n.s.: not significant

was 0.08% using the Bethesda system. And no significant difference was found compared with 0.08% in the Nichibo classification.

Discussion

In this study, we found a significant increase in the detection rates of abnormalities or diagnosed with dysplasia in uterine cervical cancer screening using the Bethesda system. However, no significant difference was found in the cancer detection rate between the two classifications.

In the Nichibo classification, examiners working for the Niigata Health Service Center were allowed to determine the degree of HPV-infected cells by themselves. On the other hand, the Bethesda system accepts evidence of the development of uterine cervical cancer by HPV infection. HPV-infected cells were categorized as the LSIL, and difficult cells to judge were categorized as ASC-US. People diagnosed with LSIL and ASC-US were categorized as examinees requiring detailed examination. These two factors seem to have increased the detection rate of examinees requiring detailed examination in the Bethesda system.

The detection rate of examinees diagnosed with dysplasia showing precursor lesions was higher in the Bethesda system than the Nichibo classification. This may simply depend on the increase in the number of examinees requiring detailed examination in the Bethesda system. However, no significant difference was found in the cancer detection rate between the Bethesda system and the Nichibo classification. Furthermore, no significant difference was found in the cancer detection rate between the initial examinees and the re-examinees by the two classification methods.

Women diagnosed as abnormalities by the screening then visit a clinic or a general hospital, and then receive a routine follow-up. Once a woman is diagnosed as dysplasia or more, she does not undergo the cancer screening again. For this reason, there may be no significant difference in the cancer detection rate between the two classification methods. The purpose of the cancer screening is to find precursor lesions early so that effective early treatment can be administered. From this standpoint, the Bethesda system is more valuable than the Nichibo classification in uterine cervical cancer screening.

Some limitations in the present study should be mentioned. We were unable to obtain results for the same samples diagnosed by the Nichibo

classification. Therefore, we were unable to make a direct comparison between results obtained using the Bethesda system and those obtained with the Nichibo classification. By comparing the results diagnosed by the two classifications using the same samples, the usefulness of the Bethesda system may be clarified. The age of the examinees was 30 years and older from 1995 to 2007, and it was 20 years and older in those examined in 2008 and later. To determine whether the differences in the results were influenced by the difference in the age of the examinees, the results obtained in 2010 were compared with those obtained between 2008 and 2009. The mean detection rate of examinees requiring detailed examination was 1.43% (264/18,449) in 2010, while it was 1.05% (325/30,922) in 2008 and 2009. The difference between the 1.43% and 1.05% was a significant difference ($p<0.05$). This result demonstrated the usefulness of the Bethesda system in assessing results obtained from women aged 20 years and older.

In summary, we observed an increase in the detection rates of abnormalities n and in those diagnosed with dysplasia using the Bethesda system in uterine cervical cancer screening. This system can detect precursor lesions of the uterus at an early stage. While our findings require further confirmation using the same samples, we demonstrate the usefulness of the Bethesda system in uterine cervical cancer screening.

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