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Journal	日本口腔検査学会雑誌, 8(1): 33-38
URL	<a href="http://hdl.handle.net/10130/3988">http://hdl.handle.net/10130/3988</a>
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Statistical research

## Clinical statistical study of exfoliative cytology performed during oral cancer screening in Chiba city in the past 11 years

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### Abstract

The purpose of this study was to perform a clinical statistical examination of exfoliative cytology performed during Oral Cancer Individual Screening of the Chiba Dental Association in the past 11 years and to evaluate the results. The results include a total of 3,172 cases where exfoliative cytology was performed during Oral Cancer Individual Screening carried out between 2005 and 2015 at dental clinics of members of the Chiba Dental Association. Characteristics assessed included sex and age. We also included the cell collection sites, clinical diagnoses, later pathological diagnoses and the results of re-cytology about the detailed examinations required (pseudo-positive and positive cases). The number of exfoliative cytology showed a tendency to increase with age and the most frequent age was patients in their 60s. The results of the cytodiagnosis included 3,127 (98.58%) negative cases, 38 (1.20%) pseudo-positive cases and 3 (0.09%) positive cases. Cases of detailed examinations required when a follow-up survey was possible included 10 cases, and 2 of those cases had a diagnosis of oral cancer and 2 had a diagnosis of epithelial dysplasia. The cancer detection rate was 0.06%.

Key words: exfoliative cytology, cancer screening, oral cancer

Received : January 4th 2016 accepted : March 8th 2016

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Introduction

The number of patients with oral cancer has shown a tendency to increase in Japan. There were 2,100 cases of oral cancer in 1975, which increased to 6,900 in 2005 and is expected to increase further to 7,800 in 2015<sup>1)</sup>. In addition, the death rates from oral and pharyngeal cancers has increased from 5.912 per 100,000 population in 2014 to 1.302 per 100,000 in 1975 and 4.500 per 100,000 in 2005<sup>2)</sup>. Chiba city has performed Oral Cancer Group Screening since 1992. Furthermore, the Oral Cancer Individual Screening in dental clinics of dentists who have attended a lecture class began in 2005. The number of cases of individual screening has increased year by year and was 655 in 2015. We perform diagnostic duties of exfoliative cytology in Oral Cancer Individual Screening in Chiba city in cooperation with the Department of Oral and Maxillofacial Surgery, the Tokyo Dental College Chiba Hospital and the Chiba Dental Association. We now report the results of exfoliative cytology screening carried out over the past 11 years.

Material and methods

The subjects consisted of 3,172 cases of exfoliative cytology of patients who had received Oral Cancer Individual Screening in Chiba city between January, 2005 and December, 2015. The criteria include being a citizen of Chiba city and a person who has felt an abnormality in their oral cavity, who has dental caries or periodontal disease, and/or who bites their tongue and buccal mucosa frequently by mistake. Furthermore, subjects who became older than 40 years old and were added by age for inspection after 2011 were included. The Oral Cancer Individual Screening was performed at dental clinics where dentists had attended a lecture class to become a cooperation dentist among members of the Chiba Dental Association. Exfoliative cytology was performed with a history taking, an inspection and a palpation in the screening as needed. The procedure of smear collection was carried out using a Rovers® Endcervex-Brush® (Rovers Medical Devices, B.V., Netherlands). The smear specimens were made in a BD SurePath™ liquid-based Pap test (Becton, Dickinson and Company. USA). Two

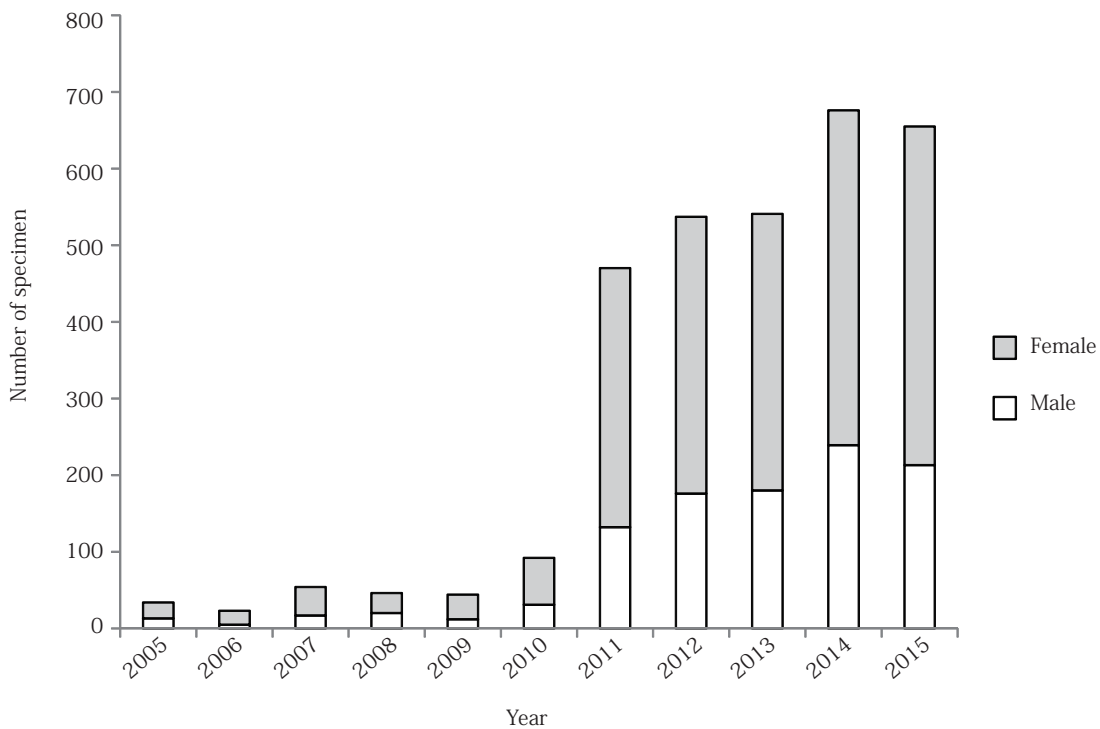


Fig. 1 Trend of the number of specimens from 2005 to 2015

table 1 Results of exfoliative cytology for the past 11 years

	Age	Total	Negative	Pseudo-positive	Positive	Inadequate
Male	20 ~ 29	2	2	0	0	0
	30 ~ 39	5	5	0	0	0
	40 ~ 49	116	115	1	0	0
	50 ~ 59	114	112	1	0	1
	60 ~ 69	357	349	6	2	0
	70 ~ 79	377	371	6	0	0
	80 ~	67	66	1	0	0
	Unknown	0	0	0	0	0
	Total number of case		1038	1020	15	2
Average age		63.6	63.5	68.5	63	51
Female	20 ~ 29	2	2	0	0	0
	30 ~ 39	22	22	0	0	0
	40 ~ 49	269	268	1	0	0
	50 ~ 59	349	344	5	0	0
	60 ~ 69	787	779	7	0	1
	70 ~ 79	592	582	7	1	2
	80 ~	109	106	3	0	0
	Unknown	4	4	0	0	0
	Total number of case		2134	2107	23	1
Average age		63.6	63.5	67.3	70	73
All	20 ~ 29	4	4	0	0	0
	30 ~ 39	27	27	0	0	0
	40 ~ 49	385	383	2	0	0
	50 ~ 59	463	456	6	0	1
	60 ~ 69	1144	1128	13	2	1
	70 ~ 79	969	953	13	1	2
	80 ~	176	172	4	0	0
	Unknown	4	4	0	0	0
	Total number of case		3172	3127	38	3
Average age		63.6	63.5	67.8	65.3	67.5
Rate		100%	98.58%	1.20%	0.09%	0.13%

(2005 - 2015)

experts in cytology (i.e. a specialized dentist or oral pathologist, a cytoscreener and/or a cytology charge dentist) then diagnosed each smear specimen in the Department of Clinical Laboratory at the Tokyo Dental College Chiba Hospital. Each specimen was classified with a diagnosis of negative, pseudo-positive or positive. The results of the cytodiagnosis were then summarized according to age each year between 2005 and 2015. The pseudo-positive and positive cases were considered to require a detailed examination. We investigated the smear collection site and clinical diagnosis at the time of the screening in cases where a detailed examination was required. Furthermore, we assessed later pathological diagnoses and re-cytology in cases where a follow-up survey was possible.

Results

The total number of exfoliative cytology cases in the past 11 years was 3,172 (Fig. 1), of which 32.7%

(1,038/3,172) were male and 67.3% (2,134/3,172) were female. The ages of males ranged from 96 to 29 years old, and the average age was 63.6 years old. The ages of females ranged from 92 to 23 years old and also averaged 63.6 years old. The average age of all cases was 63.6 years old. Most of the patients were in their 60s according to age and those in their 70s were the next most common age group (Table 1). The number of negative, pseudo-positive and positive cases was 98.58% (3,127/3,172), 1.20% (38/3,172) and 0.09% (3/3,172), respectively. In addition, the number of specimens diagnosed as inadequate material was 0.13% (4/3,172). The rate of cases of detailed examination required for each year was 4.3% (2/46) in 2008, 1.1% (1/91) in 2010, 0.4% (2/470) in 2011, 2.4% (13/537) in 2012, 1.8% (10/541) in 2013, 1.8% (12/675) in 2014 and 0.2% (1/355) in 2015. Cases of detailed examination required are summarized in Table 2 and in Figure 2. The positive cases include 2 males

and 1 female. The pseudo-positive cases include 15 males and 23 females. The average ages of positive and pseudo-positive cases were 65.3 and 67.8 years old, respectively. The smear collection sites of positive cases were 2 cases in the tongue and 1 case in the oral floor. Moreover, the pseudo-positive cases included 19 cases in the tongue, 8 cases in the gingiva, 4 cases in the paratal mucosa and 4 cases in the alveolar mucosa. Thus, the smear collection sites can include multiple areas. Stomatitis was the most common clinical diagnosis with 4 cases while Leukoplakia and Decubital ulcer were 3 cases each. In addition, No particular diagnosis was listed in 4 cases. The number of cases where a follow-up survey was possible was 10, and 2 of those cases had a diagnosis of squamous cell carcinoma by biopsy.

#### Discussion

The five year survival rate of patients with early stages of oral cancer is approximately 90%<sup>3)</sup> and compared with other organ cancers, that is a good result. However, in recent years, the prevalence of oral cancer and the death rate from that has increased in Japan<sup>1, 2)</sup>. It is supposed that in many cases the stage of a disease progresses when a patient consults a specialty hospital. According to

Ashizawa et al.<sup>4)</sup>, the ratio of progression of oral cancer (stage III+IV) patients at the time of a first medical examination at a specialty hospital is 46.7% and Suzuki et al.<sup>5)</sup> reported it as 54%. From this, it is clear that diagnosing oral cancer at an early stage is critically important to decrease the death rate from that disease. Most oral cancers develop in areas that can be seen and/or palpated and early detection should be possible. Furthermore, the dental associations of various areas of Japan or area base hospitals play a key role in the increased rate of early detection by the widespread oral cancer screening<sup>6-9)</sup>. The rate of detection of oral cancer in the population subjected to oral cancer screening in Japan has been reported as 0.09-0.4%. In this study, the rate of detection of oral cancer was 0.06% (2/3,172) because we had been able to follow-up only 10 of 41 cases where detailed examination was required. This included 1 of the 3 positive cases. However, 2 cases of epithelial dysplasia were detected that were malignant border lesions, and the rate of detection of oral cancer and malignant border lesions was 0.13% (4/3,172). Some studies have reported screening for head and neck cancers or oral cancers in other countries. According to a study done by Garrote et al.<sup>10)</sup>, the detection rate of abnormal lesions in the

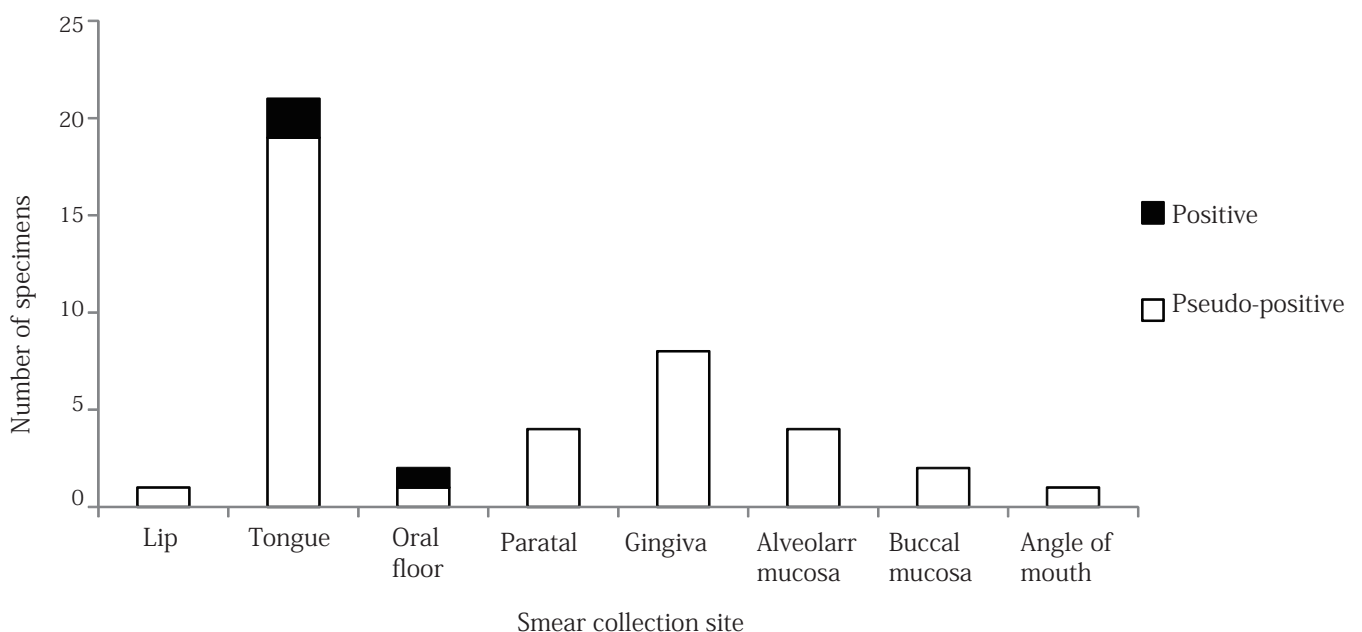


Fig. 2 Smear collection sites of detailed examination required cases (multiple areas)

table 2 Results of cases of detailed examination required and follow-up survey

Year	Cytodiagnosis	Sex	Age	Clinical diagnosis	Follow-up survey	
2015	Positive	Female	70	-	Moderately differentiated Squamous Cell Carcinoma	
2014	Pseudo-positive	Male	78	No particular		
	Pseudo-positive	Male	60	Stomatitis		
	Pseudo-positive	Male	62	Stomatitis		
	Pseudo-positive	Male	73	Decubital ulcer		
	Pseudo-positive	Male	72	Mucous cyst, suspected	Epithelial dysplasia	
	Pseudo-positive	Female	56	Stomatitis		
	Pseudo-positive	Female	55	-		
	Pseudo-positive	Female	71	-		
	Pseudo-positive	Female	65	Stomatitis		
	Pseudo-positive	Female	73	Herpes simplex, suspected		
	Pseudo-positive	Female	67	Excoritation		
	Pseudo-positive	Female	73	Decubital ulcer		
	2013	Pseudo-positive	Male	75	No particular	
		Pseudo-positive	Female	41	Decubital ulcer	
Pseudo-positive		Female	73	Geographic tongue		
Pseudo-positive		Female	72	-		
Pseudo-positive		Female	58	No particular	Negative	
Pseudo-positive		Female	64	No particular		
Pseudo-positive		Female	80	Glossitis		
Pseudo-positive		Male	69	Extraction socket healing failure	Negative	
Pseudo-positive		Female	69	Leukoplakia	Negative	
Positive		Male	64	Oral floor tumor		
2012	Pseudo-positive	Male	96	Denture stomatitis, suspected		
	Pseudo-positive	Male	74	Leukoplakia	Negative → Negative → Pseudo-positive	
	Pseudo-positive	Male	58	Leukoplakia	Epithelial dysplasia	
	Pseudo-positive	Male	64	Lichen planus, suspected		
	Pseudo-positive	Male	62	Lichen planus		
	Pseudo-positive	Male	49	Oral cancer, suspected		
	Pseudo-positive	Male	63	-		
	Pseudo-positive	Female	79	Erythoplakia		
	Pseudo-positive	Female	90	Abnormality mucosa		
	Pseudo-positive	Female	82	-	Fibrous polyp	
	Pseudo-positive	Female	56	No particular		
	Pseudo-positive	Female	61	-		
	Pseudo-positive	Female	62	No particular		
	2011	Pseudo-positive	Male	73	Erythoplakia	Negative → Negative → Pseudo-positive
Pseudo-positive		Female	72	Excoritation		
2010	Pseudo-positive	Female	66	Post tumor excision	Moderately differentiated Squamous Cell Carcinoma	
2008	Pseudo-positive	Female	59	Redness		
	Positive	Male	62	-		

screening for oral cancers was 0.23% in Cuba, and Santana<sup>11)</sup> reported that the detection rate was 0.03% in Europe. A study of a cluster randomized controlled trial was carried out on a large-scale population for oral cancer screening in India as reported by Sankaranarayanan et al.<sup>12)</sup>. That study reported that after three courses of screening for 87,655 people, the detection rate of abnormal lesions was 0.03%, 0.01% and 0.01% in each course. If the results of our study are compared with the cancer rate detection in the population-based cancer screening for other organs, such as for lung cancer or cervical cancer, carried out in Japan, the results are approximately

equal<sup>13)</sup>. This supports the usefulness of oral cancer screening using exfoliative cytology.

We used the BD SurePath™ liquid-based Pap test, Liquid Based Cytology (LBC) for the exfoliative cytology. According to Fukatsu et al.<sup>14)</sup>, LBC is more useful than conventional direct smear cytology from the viewpoints of easy cell observation, increased information about the cell judgment due to the plural special stains and the ability to observe cell counts, all of which improves the proper diagnosis rate. Navone et al.<sup>15)</sup> reported a study that compared LBC with conventional cytology. According to that report, the inadequate material rate was 12.4%, the

sensitivity was 85.7% and the specificity was 95.9% by conventional cytology. However, those numbers improved to 8.8%, 95.1% and 99.0%, respectively, with LBC. Thus we conclude that LBC is highly useful for the proper diagnosis rate of cytology in the oral cavity. This is because the results are good compared with the uterine cervix cytology, which has characteristics similar to the oral cavity cytology. In addition, the handling of specimens after the smear collection is easier than with a direct smear, and LBC has a low risk of drying the specimen. Thus, LBC is a method more suitable for oral cancer screening than conventional cytology, because dentists with little experience in smear collection may carry out the oral cancer screening in the dental clinic.

The problem seems to be that men in the prime of life who should receive oral cancer screening are the least likely to do that due to the consultation hours of dental clinics. Moreover, the follow-up rate after the oral cancer screening is low because our department is in charge of only the diagnosis of the exfoliative cytology. The accumulation of further data is necessary to improve the diagnostic accuracy by strengthening the cooperation with dental associations and attempting to follow-up the oral cancer screening.

## Conclusions

We reported the results of exfoliative cytology of Oral Cancer Individual Screening carried out in Chiba city for 11 years between 2005 and 2015, with a review of the literature. The total number of exfoliative cytology cases was 3,172. The number of pseudo-positive, positive and inadequate material cases was 1.20% (38/3,172), 0.09% (3/3,172) and 0.13% (4/3,172), respectively. In the pseudo-positive and positive cases, we were able to follow-up 10 cases. Moreover, 2 cases were diagnosed as squamous cell carcinoma and the cancer detection rate was 0.06%. Two cases were diagnosed as epithelial dysplasia case and the abnormal detection rate was 0.13% when those cases were added.

## Acknowledgements

The authors would like to thank members of the Chiba Oral Cancer Study Group and the Chiba Dental Association who performed the Chiba city Oral Cancer Individual Screening, and relevant persons for their cooperation and involvement.

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