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Original Article

Screening frequency and histologic type influence the efficacy of cervical cancer screening: A nationwide cohort study

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ABSTRACT

Objective: To evaluate the influence of age, screening interval, and histologic type on the effect of Pap smears in cervical cancer screening.

Materials and methods: Data were retrieved from the Taiwan National Cancer Registry and Cervical Cancer Screening Registration System for the period from 2002 to 2010. Age, Pap smear interval, FIGO stage, and histology were further analyzed.

Results: A total of 12,294 women with cervical cancer were enrolled, including 10,040 with squamous cell carcinoma (SCC), 1720 with adenocarcinoma (ADC), 401 with adenosquamous carcinoma (ASC), and 133 with small cell neuroendocrine carcinoma (SMC). Women who had a Pap smear at an interval of <3 years had a significantly higher proportion of stage I disease than women who had never undergone cervical cancer screening ($p < 0.0001$). Greater than 40% of women with SCCs in each age group had never had a Pap smear; however, women with ADCs were predominantly in the younger age and greater than 40% of women with ADCs had Pap smear at intervals < 3 years.

Conclusions: Pap smear is more effective in screening for cervical SCCs compared to cervical ADCs. Improving adherence to screening recommendations is important for the prevention of cervical SCC, especially in elderly women.

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Introduction

Cervical cancer is a major cause of mortality and morbidity among women worldwide, including Taiwan. The incidence of cervical cancer has decreased significantly with the introduction of Pap smear screening programs in many countries; however, it remains a major issue among women living in less developed countries. Human papillomavirus (HPV) is regarded to be the cause of cervical cancer [1]. A combination of HPV testing and Pap smear is currently considered the optimal method for detecting cervical lesions [2]. Indeed, Pap smear remains the most simple and important screening tool for cervical cancer in most parts of the world, especially in regions with limited resources [3]. The factors required to successfully implement Pap screening include a comprehensive screening program, adequate training of providers, and adherence to the screening program [4–10]. Pap smear can decrease the incidence of cervical cancer (mainly squamous cell carcinoma) in many parts of the world [3,6,11–16]; however, the incidence of cervical adenocarcinoma has not shown the same decreasing trend. An increase in the incidence of adenocarcinoma

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has been reported in the US [12], Canada [13], and the Asia-Pacific region [6].

In the present study, data on Pap smear from women with invasive cervical cancer were retrieved from the Taiwan National Cancer Registry and Taiwan Cervical Cancer Screening Registration System. The aim of this study was to analyze the relationships between age, Pap smear history, and Pap smear results in women with primary invasive cervical cancer.

Materials and methods

The National Taiwan Cancer Registry was implemented in 1979 [17]. The information in the system is processed according to the standard guidelines of the International Agency for Research on Cancer (IARC). The disease codes are based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), and the histologic types are classified according to the World Health Organization Classification of Tumors [18]. A total of 214 hospitals with >50 beds are mandated to report cancer cases to the Taiwan Cancer Registry. The quality of the Taiwan Cancer Registry database has been excellent after enactment of the Cancer Control Act in 2003 [19]. The morphologic verification (MV% [the proportion of incident cases with histologic and/or cytologic verification of a cancer diagnosis]) increased from 87.4% in 2002 to 91.3% in 2011. The rate of death certificates only (DCO% [the proportion of incident cases with information based on death certificates only]) decreased from 2.9% in 2002 to 0.8% in 2011. The MV% and DCO% for cervical cancer were 99.6% and 0.3%, respectively, in 2011. Because the MV% and DCO% are complete and of high quality, the database is regarded as an important resource for academic research and establishment of cancer control policy in Taiwan [19].

An annual cervical screening program using the Pap smear was launched in Taiwan for women ≥30 years in 1995. Registered data include age, date of diagnosis, histologic diagnosis, and treatment. Cervical Pap smears were performed by gynecologists, family physicians, and trained public health nurses. Approximately 100 cytologic laboratories with cytologists or cytotechnicians performed the cytologic examinations of the Pap smears, and the results were further confirmed by certified cytopathologists. All Pap smears were revised according to the 2001 Bethesda system [20].

The research protocol was approved by the Ethics Committee of the National Taiwan University Hospital. Women diagnosed with a primary cancer of the cervix (ICD-O-3 C53) were eligible for this study. The data of women diagnosed with invasive cervical cancer from 1 January 2002 to 31 December 2010 were retrieved from the Taiwan National Cancer Registry, and individual Pap smear results were retrieved from the Taiwan Cervical Cancer Screening Registration System from 1 January 1995 to 31 December 2010. Staging of cervical cancer was based on the criteria of the International Federation of Gynecology and Obstetrics (FIGO staging) [21]. Four major histologic types, including squamous cell carcinoma (histologic codes 8050, 8051, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8077, 8082, 8094, and 8130), adenocarcinoma (histologic codes 8140, 8143, 8144, 8255, 8260, 8262, 8263, 8323, 8380, 8384, 8441, 8461, 8470, 8480, 8482, 8500, and 8570), adenosquamous carcinoma (histologic code 8560), and small cell neuroendocrine carcinoma (histologic codes: 8041, 8042, 8043, 8044, and 8045) were recruited. Mixed type tumors, sarcomas, melanomas, undefined tumor types, and other rare histologic types were excluded in the current study. Although an annual Pap screening program has existed in Taiwan for years, women undergo Pap screening voluntarily. Thus, the Pap smear interval was defined as the average time between Pap smears from the earliest Pap smear to the diagnosis of cervical cancer.

Statistical analysis

All data were analyzed using SAS software (version 9.1; SAS, Inc., Cary, NC). Comparisons between unpaired groups were made using a chi-square test for categorical variables. Age-standardized rates were calculated using the direct method with the world standard population in 2000, as defined by the World Health Organization, and expressed as cases per 100,000 population. Trends in the age-standardized rates were analyzed using the annual percent change by joinpoint regression analysis (Joinpoint Regression Program, version 3.5 [April 2011]; National Cancer Institute, Bethesda, MD) [22]. The best fitting trend lines where the rate changed significantly were chosen by Monte Carlo permutation tests. To quantify the trend in incidence, the average annual percentage change (AAPC) was estimated for four histologic types of invasive cervical cancer for women ≥ 30 years of age between 2002 and 2010. All statistical tests were two-tailed, and a p value < 0.05 was considered statistically significant.

Results

There were 554 women excluded from the study for undefined or rare histological types. A total of 12,294 women with invasive cervical carcinoma were finally enrolled in this study (Table 1), including 10,040 women with squamous cell carcinoma (SCC), 1720 women with adenocarcinoma (ADC), 401 women with adenosquamous carcinoma (ASC), and 133 women with small cell neuroendocrine carcinoma (SMC). With respect to age, 1177 women were 30–39 years of age, 3135 women were 40–49 years of age, 3190 women were 50–59 years of age, 2196 women were 60–69 years of age, and 2596 women were ≥70 years of age. Overall, 6666 women had FIGO stage I disease, 3439 women had FIGO stage II disease, 1332 women had FIGO stage III disease, and 857 women had FIGO stage IV disease. With respect to Pap smear interval, 3106 women had a Pap smear interval <3 years, 1333 women had a Pap smear interval between 3 and 5 years, 2070 women had a Pap smear interval >5 years, and 5785 women had never had a Pap smear.

The incidence of cervical cancer decreased especially for squamous cell carcinoma

As shown in Fig. 1A, the standardized incidence rate of cervical cancer decreased from 2002 (SCC: 27.83, ADC: 4.32, ASC: 0.95, SMC:

Table 1
Characteristics of 12,294 women with cervical cancer.

	SCC[a]	%	ADC[a]		ASC[a]	%	SMC[a]	%	Total
	N		N	%	N		N		N
Age									
30–39	859	8.6	249	14.5	46	11.5	23	17.3	1177
40–49	2335	23.3	612	35.6	142	35.4	46	34.6	3135
50–59	2571	25.6	464	27.0	128	31.9	27	20.3	3190
60–69	1925	19.2	215	12.5	40	10.0	16	12.0	2196
70–	2350	23.4	180	10.5	45	11.2	21	15.8	2596
FIGO stage									
I	5166	51.5	1161	67.5	276	68.8	63	47.4	6666
II	2997	29.9	333	19.4	77	19.2	32	24.1	3439
III	1188	11.8	100	5.8	24	6.0	20	15.0	1332
IV	689	6.9	126	7.3	24	6.0	18	13.5	857
Pap screening interval									
<3 years	2174	21.7	759	44.1	133	33.2	40	30.1	3106
3–5 years	1040	10.4	228	13.3	49	12.2	16	12.0	1333
>5 years	1724	17.2	275	16.0	54	13.5	17	12.8	2070
Never	5102	50.8	458	26.6	165	41.1	60	45.1	5785
Total	10,040		1720		401		133		12,294

[a] SCC: squamous cell carcinoma, ADC: adenocarcinoma, ASC: adenosquamous carcinoma, SMC: small cell neuroendocrine carcinoma, FIGO: International Federation of Gynecology and Obstetrics.

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