RESEARCH ARTICLE

Effectiveness of Cervical Cancer Screening Based on a Mathematical Screening Model using data from the Hiroshima Prefecture Cancer Registry

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Abstract

Here we assessed the effectiveness of cervical cancer screening using data from the Hiroshima Prefecture Cancer Registry regarding patient age at the start of screening and differences in screening intervals. A screening model was created to calculate the health status in relation to prognosis following cervical cancer screening and its influence on life expectancy. Epidemiological data on the mortality rate of cervical cancer by age groups and mortality rates from the Hiroshima Prefecture Cancer Registry were used for the model projections. Our results showed that life expectancy when screening rate was 100% compared with 0% was extended by approximately 1 month. Furthermore, when the incidence of cervical cancer was 0% compared with the screening rate was 100%, life expectancy was extended by a maximum of 3 months. Moreover, among individuals affected by cervical cancer, a difference of 13 years in life expectancy was calculated between screened and unscreened groups.

Keywords: Cancer registry - cervical cancer - mathematical screening model

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Introduction

In 2008, there were an estimated 530,000 new cervical cancer cases worldwide and about 270,000 deaths from the disease (The GLOBOCAN 2008 database, http://www-dep.iarc.fr). According to the Japanese cancer information service (http://ganjoho.jp/public/cancer/data/cervix_uteri.html), as of 2006, roughly 9000 women per year developed cervical cancer in Japan, of which approximately 2700 died from the disease. In recent years, there has been an increasing trend in both the incidence and mortality rate of cervical cancer in younger women in their 20s and peaking in those in their 30s. Furthermore, it was reported that invasive cervical cancer in the 20-29 year age group had increased 4-fold from 1984 to 1996 (Urushigawa et al., 2001) and, 20 years from now, the number of cases is expected to increase by >1.5-fold. (http://ganjoho.jp/data/public/statistics/backnumber/odjrh3000000o8is-att/FIG21.PDF). It is believed that the increased incidence in cervical cancer is due to women having their first sexual experience at a younger age.

The effectiveness of cervical cancer screening is widely recognized and while it is important to determine the rate of advanced cervical cancer cases, screening is also important for early detection of the disease. However, the low rate of cervical cancer screening remains a crucial issue (Basic Plan to Promote Cancer Control). Although cervical cancer screening had been recommended annually, in 2004, the age to undergo an initial exam was lowered from 30 to 20 years and the interval between screenings was increased to 2 years. According to an international comparison of cancer mortality and screening rates, the rate of cervical cancer screening in Japan is extremely low compared with those in Europe and the USA (21% vs. 85%, respectively; International Comparisons of Cancer Mortality and Cancer Screening Rates), which is believed to be a significant factor contributing to the delay in early detection. According to reports on cervical cancer screening, the most common reason why women do not undergo the procedure is that they do not have the time or it is too much of a trouble (48.3%) (http://www.cczeropro.jp/kenshin/img/result/result.pdf#search = "report on cervical cancer screening"). Although patients are exposed to virtually no risks or physical pain incurred by the scraping of cells from the cervix in itself, the psychological stress is considered significant (Guidelines for Cervical Cancer Screening Based on Effective Evaluation, 2009). Moreover, the disadvantages of cervical screening due to over-diagnosis and false-negative results should be considered (Guidelines for Cervical Cancer Screening Based on Effective Evaluation, 2009).

The Hiroshima Prefecture Cancer Registry was established in 2002 to collect data on residents of Hiroshima Prefecture who develop cancer from the time of

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diagnosis to recovery or until death and perform analyses according to cancers of different organs. The data is collected through a notification system, in which medical institutions within Hiroshima Prefecture submit data on every cancer patient at the time of diagnosis according to primary site, all cases of malignant tumors, including carcinomas in situ, and those with central nervous system tumors, regardless if they are benign or malignant.

In 2007, there were 221 new cases of cervical cancer reported in Hiroshima Prefecture, while the number of deaths was 46 (Hiroshima Prefecture Cancer Registry, 2007), making it the 12th most common disease among women and the 15th leading cause of death. However, neither the incidence nor the mortality rates included carcinoma in situ cases. If we consider the age-adjusted incidence rate of cervical cancer in 2007, it tended to decrease in women aged >40 years, but increased in those 20-39 years old, thereby demonstrating the importance of early detection. Thus, if the rate of cervical screening is increased, it would allow for improved detection and treatment of early stage cervical cancer and uterus preservation by local excision. In other words, early detection is crucial to preserve fertility in young women and reduce the mortality rate of cervical cancer and subsequent medical care expenses. Therefore, we created a cancer screening model based on data from the Hiroshima Prefecture Cancer Registry and quantitatively evaluated the extent of mean life expectancy according to rate of cervical cancer screening.

Materials and Methods

Here we evaluated invasive cervical cancer cases diagnosed between 2005 and 2007 and entered into the Hiroshima Prefecture Cancer Registry (Hiroshima Prefectural Medical Association, 2005; 2006; 2007). Local cancer registry data includes the condition of cancer cases when first diagnosed and the extent of the lesion. Two groups were classified from these items, the screened group (n=80) and the non-screened group (n=410). In the screened group, diagnosis was made by cancer screening, whereas in the non-screened group, cancer was diagnosed via "health/medical check-up," "during observation for a different illness," and "other or unknown".

Creation of a screening model

In the present study, we created a screening model to estimate changes in life expectancy using Mathematica 8.0 computational software (http://www.wolfram.com/mathematica/new-in-8/), which included the incidence of cervical cancer (excluding carcinoma *in situ*) according to different age groups, death rate according to different age groups, death rate in 2009, age at initial examination or follow-up, cervical cancer screening rate within Hiroshima Prefecture, excess mortality rate of cervical cancer, age at first screening, and final age calculated from Hiroshima Prefecture Cancer Registry data. To evaluate changes in life expectancy according to changes in cervical cancer screening, the incidence and mortality rates of cervical cancer in Japan were estimated with the model and compared with epidemiological data from the Hiroshima Prefecture Cancer Registry and the validity of the estimation model was verified. Furthermore, changes in risk factors due to human papillomavirus (HPV) infection prevention were not included because there was insufficient evidence to determine whether HPV testing lowered the cervical cancer mortality rate.

The screening model was designed to reflect changes in health status over time. At the time of the start of the simulation, all 100,000 virtual cohort members were healthy and over time (1 year) their health status was modified according to probable disease-specific changes, such as "cervical cancer localization" and "invasion of adjacent organs by cervical cancer." Moreover, all virtual cohort members ended up "dying from cervical cancer" or "dying from other causes" using a simulation including a maximum life span of 100 years.

Values used in the screening model

For clinical cervical cancer staging, we used the Union for International Cancer Control Tumor-Lymph node-Metastasis classification system and other cancer staging manuals developed by various academic societies and research institutions, while the local cancer registry was used to determine the extent of lesions modified into four stages: *i*) localized; *ii*) regional lymph node metastasis; *iii*) invasion of adjacent organs; and *iv*) distal metastasis. In the model, "extent of lesion" was designated as a stage and the parameter value was estimated so that the likelihood was maximized from observed data using the maximum likelihood method. Cervical cancer screening reduces the incidence of invasive cancer by early detection and treatment of precancerous lesions and carcinomas in situ, and is expected to reduce the cervical cancer mortality rate. However, when suitable treatment is administered, even in cases with precancerous lesions or carcinoma in situ, the tumor control rate of carcinoma in situ (stage 0) is reportedly almost 100% (Quinn et al., 2006). In other words, there was not much difference between healthy individuals and the death rate. Moreover, it is rare to progress to advanced stage cancer; thus, we excluded carcinoma in situ from the screening model.

Other parameters

Numerical values of the incidence and mortality rates of cervical cancer according to different age groups were obtained from the Hiroshima Prefecture Cancer

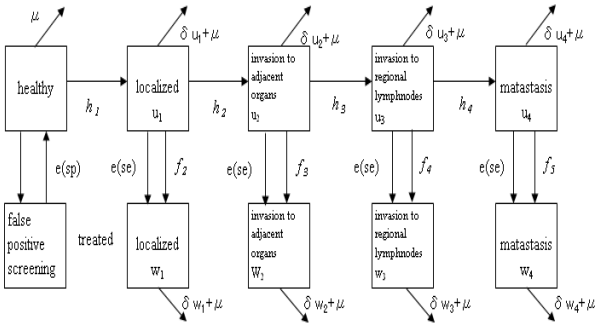

Figure 1. Transition Probability. μ: Mortality rate, δw: Mortality rate among those with cancer screening, δu: Mortality rate among those without cancer screening, se: Sensitivity, sp: Specificity, e: Cervical cancer screening rate

Table 1. Transition Probability and Additional Parameters used in the Screening Model

Transition probability	h_2	Localized to invasion to adjacent organs	0.25
	h_3	Invasion to adjacent organs to invasion to regional lymphnodes	0.47
	h_4	Invasion to regional lymphnodes to matastasis	0.24
	f_2	Localized (u_1) to localized (w_1)	0.12
	f_3	Invasion to adjacent organs (u_2) to invasion to adjacent organs (w_2)	0.24
	f_4	Invasion to regional lymphnodes (u_3) to invasion to regional lymphnodes (w_3)	0.09
	f_5	Matastasis (u_4) to matastasis (w_4)	0.44
Additional parameters used in the screening model			
Incidence rate			age-adjusted incidence rate 2005-2007
Mortality rate			age-adjusted death rate 2005-2007
All-cause mortality			all-cause mortality 2009
Screening rate			0%,100%
Screening interval			1,2,3,4,5years
Excess mortality rate for cervical cancer untreated group:		Localized	0.027
		Invasion to adjacent organs	0.168
		Invasion to regional lymphnodes	0.162
		Matastasis	0.485
Excess mortality rate for cervical cancer treated group:		Localized	0.0184
		Invasion to adjacent organs	0.112
		Invasion to regional lymphnodes	0.108
		Matastasis	0.323
		Sensitivity	0.95
		Specificity	0.9

Registry (2005-2007). For the overall mortality rate, we included the mortality rates of other diseases as analytical parameters obtained from the Abridged Life Table of National Health Trends (2010-2011). Screening age was assumed as 20-65 years, 30-65 years, and 40-65 years. Intervals between screenings were defined from 1 to 5 years. According to data obtained from reports on community health services and promotion, the cervical cancer screening rate was 20%. Regression analysis was performed to determine a coefficient for the excess mortality rate of cervical cancer from the survival curve of the 5-year survival rate. The age at start of follow-up was set at 20 years to study the effect of screening.

Evaluation of mean life expectancy

The mean life expectancy under each screening condition was evaluated based on the maximum theoretical value of the effects of cervical cancer screening (life expectancy from the mortality rate of all causes of death when the incidence rate of cervical cancer is 0% minus the life expectancy when the cervical cancer screening rate is 0%).

Mean life expectancy of cervical cancer patients

We calculated the difference in life expectancy between the screened group and the non-screened group among cervical cancer patients.

Results

Model validity

Model validity was verified by comparing estimated values calculated by the screening model against the epidemiological data calculated from the Hiroshima Prefecture Cancer Registry (incidence and mortality rates of cervical cancer). According to our model, the expected incidence rate of cervical cancer was 15.3 cases/100,000 women, whereas the Hiroshima Prefecture database reported an incidence rate of 17.18 cases/100,000 women, thereby confirming the validity of the model (Figure 2A).

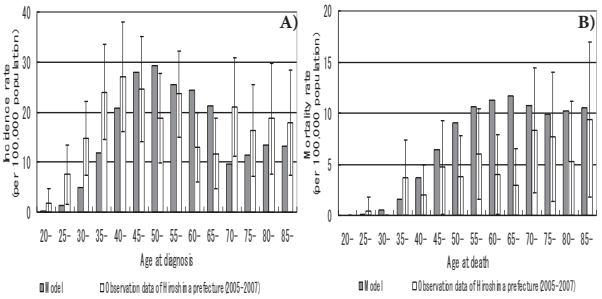

Figure 2. Validity of A) Incidence B) Mortality Rate According to Different Age Groups

Furthermore, we confirmed the estimated mortality rate calculated using the model as 6.9 deaths/100,000 women (Figure 2B).

Estimated mea life expectancy of cervical cancer patients

Based on the results of a simulation with a virtual static population of 100,000 cases with a cervical cancer incidence rate of 0%, the mean life expectancy of women was 87.523 years, but when the cervical cancer screening rate was 100%, the maximum life expectancy was 87.382 years. Furthermore, the mean life expectancy of women with a history of cervical cancer, but with a screening rate of 0%, was calculated to be 87.309 years. The theoretical maximum value of cervical cancer screening was 78 days (0.21 years; range, 87.523-87.309 years). Moreover, the mean life expectancy with a screening rate of 100%, compared with a screening rate of 0%, was increased by 26 days (0.07 years; range, 87.382-87.309 years).

Age at first screening

The age at the start of cervical cancer screening and the interval between screenings of the 100,000 virtual

Table 2. Mean Life Expectancy According to Condition and Effects of Screening

Age at stating screening	Interval (years)	Life expectancy	Screening efficacy (%)	Life expectancy by screening (days)	Incidence rate *1	*2	*3	*4	Deaths	False negative
Incidence rate		87.523	-	78	0	0	0	0	0	
20	1	87.382	33.82	26	1210	276	69	41	732	449,864
30		87.378	32.13	25	1180	282	74	43	739	350,247
40		87.361	24.19	19	1025	297	92	59	781	251,103
20	2	87.364	25.69	20	1005	316	102	57	792	224,759
30		87.361	24.24	19	980	318	105	59	798	174,959
40		87.348	17.94	14	858	320	113	73	833	125,404
20	3	87.353	20.36	16	873	326	113	70	833	146,634
30		87.351	19.38	15	856	327	114	72	838	116,754
40		87.342	15.23	12	777	324	118	80	860	86,999
20	4	87.346	17.05	13	795	330	119	78	857	117,190
30		87.343	15.83	12	774	329	120	80	863	87,311
40		87.336	12.47	10	711	325	121	87	881	67,486
20	5	87.339	13.97	11	713	323	116	86	885	88,244
30		87.338	13.40	10	703	323	117	87	888	68,314
40		87.331	10.32	8	646	318	117	94	904	48,471
Screening rate 0%		87.309	0	-	397	274	80	120	991	0

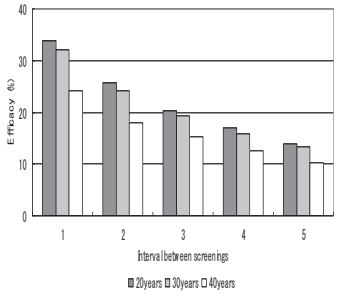

Figure 3. Relative Efficacy with a Screening Rate of 100%. The age at the start of cervical cancer screening and the interval between screenings of the 100,000 virtual cohort members were adjusted to compare the efficacy of screening (screening rate, 100%). The difference in life expectancy between the screened group and the non-screened group among cervical cancer patients

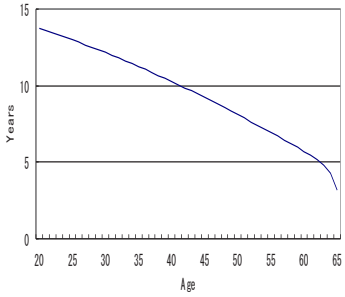

Figure 4. Mean Life Expectancy of Cervical Cancer Patients. The difference in life expectancy between the screened group and the non-screened group among cervical cancer patients

cohort members were adjusted to compare the efficacy of screening (screening rate, 100%). When the age at the start of screening (screening interval, 1 year; screening rate, 100%) was 20 years, the screening efficacy was approximately 34%, at 30 years, it was 32%, and at 40 years, approximately 24% (Figure 3, Table 2).

Mean life expectancy of cervical patients

As mentioned above, the theoretical maximum value of mass screening was 0.21 years; therefore, we calculated

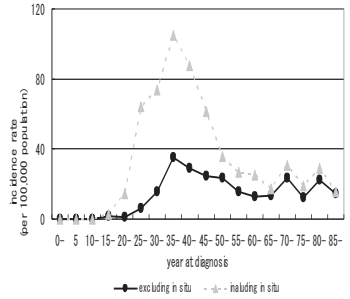

Figure 5. Cervical Cancer 2007

the difference in life expectancy between the screened group and the non-screened group among cervical cancer patients. For instance, if an individual developed cervical cancer by age of 20, then there was a difference in mean life expectancy of approximately 13 years between the screened and non-screened groups (Figure 4).

Discussion

We examined the extent of changes in mean life expectancy according to changes in the rate of cervical cancer screening using a mathematical screening model. As a general rule, in Japan, women aged ≥30 years underwent annual screenings from 1983 to 2002. According to earlier studies and systems implemented in other nations (Sawaya et al., 2003; Sasieni et al., 2003), as of 2003, women aged ≥20 years underwent screenings at 2-year intervals. While the age at the first screening was relatively young (20 years), a final age has not yet been established. Although a 2-year interval between screenings is short compared with other nations, the screening rate was very low. The current low rate of cervical cancer screenings may be attributed to the limited knowledge regarding preventive medicine and the correlation between HPV infection and cervical cancer in Japanese women, thus demonstrating that there is low interest in cancer screening (Vaccination Against Cervical Cancer,2008). Furthermore, cervical cancer is most common among women aged 20-40 years; thus, if we consider the fact

that the employment rate in this age bracket is 65-80%, then drastic reforms are warranted, such as offering health examinations in the workplace or educating primary and junior high school students (Guidelines for Cervical Cancer Screening Based on Effective Evaluation, 2009).

In the present screening model, when the cervical cancer screening rate was 100% (staring at 20 years of age at 1-year intervals) the mean life expectancy was calculated at 87.382 years and when the screening rate was 0%, the mean life expectancy decreased from 87.523 to 87.309 years, a difference of 0.21 years. Thus, if cervical cancer screening starts at 20 years of age, is performed at 2-year intervals, and the virtual cohort screening rate is 100%, we can expect a cervical cancer-free state close to approximately 30%, thereby indicating the extent to which cancer screening contributes to disease prevention.

The screening model also indicated that there was virtually no difference in the incidence of cervical cancer among women who began screening at 20 or 30 years of age, although there were more cervical cancer-free women among those who started screening at 20 years of age.

Although the present screening model did not factor in carcinoma in situ, the incidence rate according to age group, including carcinoma in situ cases (diagnoses in 2007, Figure 5), was 2.9% in young women aged 15-19 years, 14.7% of 20-24-year-olds, then suddenly increased to 63.9% in 25-29-year-olds, indicating the benefit of screening at 20 years of age. If precancerous lesions and early stage cancers are detected and treated early, then the uterus can be preserved. Thus, to preserve fertility in young women, screening from 20 years of age is preferable. Although other nations recommend cervical cancer screening from 20 to 30 years of age, women aged ≥30 years in almost all countries are typically screened. In the United Kingdom, cervical cancer screening typically begins at the age of 25 years; however, in recent years, efforts have been made to begin screening at 20 years, but this recommendation remains controversial (National Health Service Cervical Screening Programme,2008).

A comparison of the virtual cohort population at a 100% annual screening rate beginning at 30 years of age compared with 40 years revealed that the effects of screening decreased from 18-13%. The incidence rate of cervical cancer in Hiroshima (2007) was 15.5% in 30-34-year-olds, 34.9% in 35-39-year-olds, and 28.8% in 40-44-year-olds. These results indicate the importance of cervical cancer screening before 30 years of age before the incidence rate peaks.

Usually, cervical cancer screening is performed annually; however, in 2003, it was recommended for alternate years. In our screening model, a shorter interval between screenings increased the mean life expectancy. However, biennial screenings may be problematic because women who consider screening may be unsure of the relevant year and thus may not undergo screening. Results of a case-control study conducted in Japan revealed that between individuals screened annually and biennially, there was a significant decrease in the rate of early detection in those who underwent biennial screenings (Morimura and Ito, 2005). Moreover, a 2-year prevention may be anticipated from a negative biennial cytodiagnostic result; thus, annual screenings are likely much more effective (Makino et al., 1995; Sato et al., 1997). Therefore, an investigation into restoring annual screening is warranted.

Recent analyses on cervical cancer have revealed the natural history of invasive cancer resulting from high-risk HPV infection of the cervical mucous membrane and the development of cervical carcinoma in situ or precancerous lesions (Cervical Cancer Screening Guidelines Based on Effective Evaluation,2009). In brief, there are approximately 150 types of HPV strains, of which 16 are high-risk (Miura et al., 2006), and >90% of HPV infections are eliminated naturally, although persistent infections can lead to cancer. After the discovery of high-risk HPV infection, an HPV vaccine was developed to prevent the onset of cervical cancer and today it is administered extensively throughout the world. A cost-effectiveness analysis on the introduction of the HPV vaccine indicated that it may contribute to a decrease in cervical cancer mortality among young women, but was not effective in women aged ≥40 years; therefore, screenings should be continued (Coupé et al., 2009). Moreover, there is concern regarding the effect of HPV vaccination on cervical cancer screening. Although the HPV vaccine has been directly linked to cervical cancer prevention in young women, those already infected by the HPV virus realize no benefits from the vaccination. Furthermore, although the HPV vaccine prevents cervical cancer in 70% of cases (Muñoz et al., 2004; A National Clinical Guideline.2008), the remaining 30% of cervical cancer cases are not prevented. Therefore, as in the past, cervical cancer screening should be provided for women aged ≥30 years.

The introduction of the HPV vaccine may greatly change the way cervical cancer screenings are performed in the future; however, since adolescents are the primary target for vaccine administration and there is no data regarding the duration HPV vaccine effectiveness, it is expected that preventive measures by cancer screening and vaccination will continue to coexist into the near future. HPV vaccine was not taken into account in this study, but screening procedures and preventive vaccines do exist for cervical cancer. Current cervical cancer treatments are designed to protect life and preserve the uterus, which is quite different compared with treatments for other solid cancers. Thus, in the future, cervical cancer therapy should also include preventative measures.

The disadvantages of cervical cancer screening include false-negative and -positive results as well as emotional stress and unnecessary medical costs incurred when detailed examinations are performed based on positive cases that are unwarranted (Cervical Cancer Screening Guidelines Based on Effective Evaluation,2009). In the virtual cohort population of 100,000 members, we calculated that when the screening rate was 20% and the screening interval was 1 year, there were a total of 4,499,868 screenings, of which 449,864 (10%) resulted in false-positive diagnoses. Thus, the anxiety and psychological stress caused by false-positive cervical cancer results should be considered a disadvantage of screening; thus, a follow-up system needs to be included in the examinations.

Nonetheless, early detection of cervical cancer allows for the preservation of the uterus and fertility. Moreover, the survival rate after treatment differs according to the tumor size and degree of invasion of cervical cancer when detected early. Therefore, early detection is crucial. As the rate of cervical screening increases, the incidence of cervical cancer will approach 0%. The cervical screening rate in Hiroshima Prefecture is below the national average and should, therefore, be increased.

Epidemiological data used in this study was collected from the Hiroshima Prefecture Cancer Registry, a notification-based clinical registry, and, at present, the data can be expected to be highly accurate even at an international level, as epidemiological studies using this data have been shown to yield highly reliable results. Although cancer registration is not mandatory in Japan, the nation is moving to make it so by the end of 2013. Thus, if cancer registration becomes mandatory, we can expect highly accurate cancer registries to be established throughout Japan, which will allow us to ascertain trends that could not be estimated from regional data, clarify particularities of rare cancers, and analyze regional differences and survival rates. In the future, more data will be added to the registry thereby allowing further analyses.

In conclusion, We developed a cervical cancer screening model based on data from the Hiroshima Prefecture Cancer Registry. Here we examined the effect of mass cervical cancer screening on mean life expectancy, which, at most, increased by 1 month.

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