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

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/odjr03000000008is-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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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 Hiroshima Prefecture Cancer Registry and compared with epidemiological 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 Registry and compared with epidemiological data from the Hiroshima Prefecture Cancer Registry. The values were used in the screening model and included the following:

- Mortality rate among those with cancer screening, \( \mu \): Mortality rate among those with cancer screening.
- Mortality rate among those without cancer screening, \( \delta_w \): Mortality rate among those without cancer screening.
- Sensitivity, \( se \): Sensitivity.
- Specificity, \( sp \): Specificity.

\[
\begin{align*}
\mu & \quad \text{Mortality rate} \\
\delta_w & \quad \text{Mortality rate} \\
se & \quad \text{Sensitivity} \\
sp & \quad \text{Specificity}
\end{align*}
\]
Observation data of Hiroshima prefecture (2005-2007) incidence rate of cervical cancer was 15.3 cases/100,000 women. According to our model, the expected incidence rate in the Hiroshima Prefecture Cancer Registry (incidence and mortality rates values calculated by the screening model against the static population of 100,000 cases) was 20.3 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).

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

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).

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

Estimated mean 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 patients was set at 20 years to study the effect of screening.
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 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% (starting 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 20 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.

References


