Cost-Effectiveness Analysis of Mass Screening for Cervical Cancer in Japan

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Cost-effectiveness analysis for cervical cancer screening in Japan was performed to estimate the cost per life-year saved by the screening; cost-effectiveness ratio (CER). The analysis was made using a simulation model to estimate long-term cost and effectiveness of the screening programs. CER of cervical cancer screening was estimated to be US\$ 40,604 which was 2.4 times more expensive than that for gastric cancer screening but was about the same as that for colorectal cancer screening. It was within the range of cost-effectiveness of other cancer screening programs financed under the Health and Medical Services Law for the Aged in Japan. We performed sensitivity analysis on the following seven estimates, the screening charge, the sensitivity and the specificity of the screening test, the frequency of carcinoma in situ (CIS) among cases detected in the screening program, the initial cost and the terminal cost for patients with invasive cancer, and the incidence rate of cervical cancer. The sensitivity analysis demonstrated that the screening charge was the most influential factor on CER. CER was fairly stable under various assumptions on the accuracy of the screening test, the frequency of carcinoma in situ (CIS), the treatment cost for patient, and the incidence of cervical cancer. CER was less sensitive to the changes in incidence, even to as low as a 50% decrease of the current figure. Then if the incidence rate becomes 85% of the current figure in 2015, CER would be US\$ 48,176 and it was suggested that the cervical cancer screening would remain reasonably cost-effective until the year 2015. *J Epidemiol*, 1997; 7: 135-141.

cervical cancer, mass screening, cost-effectiveness analysis, simulation study

Uterine cancer, the eighth leading cause of cancer deaths among females in Japan, had a mortality rate of 7.4 per 100,000 population and an age-adjusted (world population) incidence rate of 16.2 in 1991. Cervical cancer screening using the Papanicolaou (Pap) smear was first established in Miyagi Prefecture in 1961, and has spread throughout Japan. In 1982, cervical cancer screening was introduced in Japan as a government financed program under the Health and Medical Services Law for the Aged. Its coverage rate, 15.4% in 1992, has been increasing annually.

Evidence on the effectiveness of cervical cancer screening in Japan has been provided by ecological and case-control studies. Kuroishi, based on observations between mortality and coverage rate during 1969 to 1977, reported that mortalities

were more greatly reduced in areas with higher coverage rates¹. Gao et al. reported a similar trend for the period from 1979 to 1983². In case-control studies Sobue et al. described that the odds ratio of uterine cancer death among those receiving the Pap smear was 0.22³, and Makino reported that the odds ratio of invasive cervical cancer for women screened was 0.16⁴, compared with those without screening. These studies strongly suggest the effectiveness of mass screening for cervical cancer.

Evaluation of cervical cancer screening from the economic aspect is, however, scarce^{5,6}. Most previous studies have estimated only the cost for detecting cervical cancer, but not life-years saved by the screening. This study was initiated to estimate the cost per life-year saved (cost-effectiveness ratio;

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CER) for cervical cancer and to compare this figure with those of other nationally-funded cancer screening programs such as those for gastric and colorectal cancers.

Another purpose of the present study was to evaluate the influence of the decreased incidence upon the cost per life-year saved. According to Tsukuma et al., the crude incidence rate of uterine cancer including carcinoma in situ (CIS) in the year 2015 would become 20.7, that is, 85% of the figure for 1985². Since a decline in the incidence generally makes cancer screening less efficient, cervical cancer screening is expected to become less cost-effective. Accordingly, how long would the current screening system be economically justified? To answer this question, we performed a cost-effectiveness analysis (CEA) based on a simulation study.

MATERIALS AND METHODS

Structure of the cost-effectiveness analysis

In this simulation study, a hypothetical cohort of 200,000 asymptomatic women at the age of 30 years was followed for 40 years. Half of the subjects were allocated to the Pap smear screening program, and the other half to a "no screening" program. Those with positive Pap smear result were sent for workup examinations consisting of colposcopy and punch biopsy for a diagnosis of cervical cancer. Among those negative at screenings, there still might be cases with cancer (false negative cases). We assumed that one-third of these overlooked CIS cases would progress to the invasive cancer state, and all of them would be detected in the next screening test. Based on the incidence rate of cervical cancer, sensitivities and specificities of the screening and the workup examinations, we calculated the number of subjects who would take workup examinations and the number of cancer cases. We also estimated the life-year which the patients could survive, based on the five-year survival rate and the life expectancy. We calculated the number of cervical cancer death patients annually, based on the five-year survival rate, and their life-year of survival assuming that they survived half year when they died. If the patients would survive for five years, we calculated their life-year survived for their life expectancy. This life-year of survival was adopted as the parameter of effectiveness.

This model defined the costs from the payers' view⁸ to compared with other studies^{6,9,10}. The payers consisted of the following three groups; the government subsidizing the screening program, the national health insurance covering a part of the medical charge, and the patients paying for their own screening and medical services. The costs included expenses for screening test, workup and diagnostic tests, initial care for cervical cancer, and its terminal care.

The cancer cases in the "no screening" program would visit a hospital only after developing symptoms. We analyzed the effectiveness and the cost of the "no screening" program in the

same way as for the screening program.

CER, defined as the cost required for a life-year saved, was calculated as the differences in the costs between the screening and the "no screening" programs (marginal cost) divided by the differences in the total life-year of survival between the two programs (marginal effectiveness).

Data resource

- Incidence rate of cervical cancer (including CIS); We estimated the incidence rate in Japan by adjusting the incidence rate in Miyagi Prefecture, which was based on the regional cancer registry (Miyagi Prefectural Cancer Registry) in 1989. Then by using the five-year age-specific incidence of cervical cancer in Miyagi Prefecture, a standardized mortality ratio (SMR) of cervical cancer in Miyagi Prefecture was compared with the total mortality in Japan. Since the ratio was 0.81, we estimated the incidence in Japan, by dividing the incidence in Miyagi at each age-group by 0.81.
- Mortality rates of uterine cancer and other causes; We cited the 1989 Vital Statistics in Japan.
- Stage distribution among cancers detected in the "no screening" program; Based on the data of Miyagi Prefectural Cancer Registry, we estimated that 30% of cases to be CIS and 70% to be invasive cancer.
- Stage distribution among cancers detected in the screening program; We assumed that 94% of cases to be CIS and 6% to be invasive cancer. This assumption was based on a case-control study of cervical cancer screening⁴, which demonstrated that the odds ratio of invasive cervical cancer for women who were screened annually was 0.086 (95% confidence interval: 0.045-0.165), as compared with women who were never screened.
- Five-year survival rate of cases with cervical cancer; Estimated to be 100% for patients with CIS and 67% for those with invasive cancer¹¹.
- Efficacy of Pap smear; Sensitivity of Pap smear was estimated to be 90% and the specificity 98%¹². This study was the only one to calculate sensitivity and specificity of Pap smear using the data of local cancer registry.
- Life expectancy; The Life Tables in Japan in 1990¹³.
- Cost for screening and diagnosis; Cost was expressed dollarwise, in which one US dollar was assumed to be equal to 100 Japanese yen. A screening charge of US\$ 29 / person was the average cost in Japan in 1989¹⁴ to compared with other studies^{6,9,10}. The charge for colposcopy combined with punch biopsy together is set at US\$ 100 according to the National Health Insurance Policy. We assumed that the diagnostic procedure at hospitals in the "no screening" program would include Pap smear, colposcopy and punch biopsy. This charge was estimated to be US\$ 150 / person, summing the examination and other fees including the doctor's diagnosis charge.

i) Cost for medical treatment; The mean medical charges at the Department of Obstetrics and Gynecology, Tohoku University School of Medicine from 1989 to 1994 for cervical cancer were about US\$ 4,000 (the mean was US\$ 4,092.5) for patients with CIS and about US\$ 10,000 (the mean was US\$ 11,515.5) for those with invasive cancer. The terminal cost for cervical cancer patient was assumed to be about US\$ 15,000 (the mean was US\$ 14,757.8).

Discount

This analysis deals with occurrences for 50 years. In order to adjust the future cost value and effectiveness into the present value¹⁸, we assigned a discount rate of 5% per year to both cost and life-years.

Sensitivity analysis

To examine the stability of the present analysis and to identify the most influential factor on CER, we performed sensitivity analysis on the following seven estimates.

- Charge of screening tests (US\$ 10-60); this range reflected the fact that the lowest price for the screening was US\$ 10 and the highest was US\$ 60.
- Sensitivity of screening test (80-100%); according to the report from the Office of Technology Assessment (OTA) in the United States in 1990, the sensitivity of Pap smear in western countries was over 80%¹⁹.
- Specificity of screening test (80-100%); according to the OTA report, the specificity of Pap smear was over 95%¹⁹.
- Frequency of CIS in the screening program (88-100%); 95% confidence interval (95% CI) of the odds ratio of invasive cervical cancer for women who were screened annually was ranged from 0.045 to 0.165, as compared with women who were never screened⁴. Based on this 95% CI of the odds ratio, we assumed that the percent of CIS would range from 88 to 97%.

- Initial cost for patients with invasive cancer (10,000-100,000 US\$)
- Terminal cost for patients with invasive cancer (10,000-100,000 US\$)
- Incidence rate of cervical cancer (0.1-2.0 times)

RESULTS

Table 1 presents the estimated cost and effectiveness for the "no screening" and screening programs, respectively. The life-year of survival in the "no screening" program was 6,346 years, while that in the screening program was 7,689 years. Accordingly, the screening program prolonged survival by 1,343 years. The total cost of the screening program, US\$ 59,977,000, was about 11 times higher than that of the "no screening" program. Although the treatment costs were saved by the screening program, the cost for the screening test was very high occupying about 95% of total cost for the screening program. The marginal cost between the screening and the "no screening" programs was US\$ 54,555,000. Accordingly, the cost per life-year saved of cervical cancer (CER) was US\$ 40,604.

Figure 1 illustrated the effect of the screening charge upon the CER. Due to the fact that screening cost accounts for about 95% of total cost for screening program, CER was very sensitive to the change of the screening charge i.e., if the screening charge is twice, the cost per life-year saved would cost about twice as much. The most influential factor on CER was the screening charge itself.

Figure 2 illustrated the effects of the sensitivity and the specificity of the screening test on CER, respectively. According to the report from the Office of Technology Assessment (OTA) in the United States in 1990, the sensitivity of Pap smear in western countries was over 80%, and the specificity was over 95%¹⁹. In our model, CER was estimated

Table 1. Cost and effectiveness for "no screening" and screening program.

	No screening	Screening
Life-year of survival (year)	6,346	7,689
Screening cost (US\$)	-	57,703,000
Diagnosis cost (US\$)	70,000	-
Cost for initial treatment (US\$)	3,866,000	2,103,000
Cost for terminal treatment (US\$)	1,485,000	171,000
Total cost (US\$)	5,422,000	59,977,000
Cost per life-year saved (US\$)	-	40,604

Figure 1. The relationship between the screening charge and the cost-effectiveness ratio (CER).

Figure 2. The relationship between the accuracy of the screening test and cost-effectiveness (CER).
SE: the sensitivity of the screening test. SP: the specificity of the screening test.

to be US\$ 43,712 assuming that the sensitivity of screening test was 80%, and was estimated to be US\$ 37,899 when the sensitivity was 100%. Thus, the difference of CER was estimated to be about US\$ 6,000. Based on a specificity of 95%, CER

was estimated to be US\$ 44,755, and at 100%, CER was calculated to be US\$ 37,836. The difference of CER was estimated to be about US\$ 7,000.

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Figure 3. The relationship between the frequency of carcinoma in situ (CIS) among case detected in the screening program and the cost-effectiveness ratio (CER).

CIS in the screening program and CER. According to a case-control study ⁴, the odds ratio of invasive cervical cancer for women who had been screened was 0.089 (95% CI: 0.045-0.165), compared with women who had never been screened. For this 95% CI of the odds ratio, the percent of CIS for women who were screened was estimated to range from 88% to 97%. Assuming the percent of CIS to be 88%, CER was estimated to be US\$ 44,850, and at 97%, the estimate was US\$ 38,756. Accordingly, CER does not change greatly within the range of CIS frequencies detected in the screening program.

Figure 4 demonstrated the relationship between the medical charges for patients with invasive cancer and CER. The change of CER was less than US\$ 20,000 if these cost ranged from US\$ 10,000 to US\$ 100,000.

All these sensitivity analyses showed that the present estimate of CER was less sensitive to the changes estimating the accuracy of the screening test, the stage distribution, and the treatment cost. The analyses also demonstrated that the screening charge was the most influential factor on CER. These results suggest the validity of the present estimate of CER for cervical cancer in Japan.

We estimated the relationship between the incidence and CER (Figure 5). Changes in the incidence were analyzed within the range from one-tenth to twice of that in 1989 (crude incidence: 18.1 per 100,000). CER was inversely related with the incidence. The cost was relatively less sensitive to the changes in the incidence up to about 50% of the current figure and CER was less than US\$ 100,000. According to Tsukuma

et al., the crude incidence rate of uterine cancer, including CIS, in the year 2015 would be decreased by 15% of the rate in 1985 ⁷. Assuming the incidence rate at 85% of the current figure, CER was estimated to be US\$ 48,176.

DISCUSSION

Since screening for cervical cancer has been widely performed in Japan, it is impossible to evaluate its economic effect by randomized control trial (RCT). Its economic evaluation should be based on simulation studies using the best available data of cost and effectiveness.

The present analysis on cervical cancer screening using a simulation study indicated that the CER was approximately US\$ 40,000. This value was fairly stable over the range of various assumptions on the accuracy of screening test, frequency of CIS, treatment cost for patients, and incidence of cervical cancer. CER for cervical cancer screening was compared with those of the four other nationally-funded cancer screening programs in Japan; stomach, colorectal, breast, and lung cancers.

CER for cervical cancer screening was 2.4 times more expensive than that for gastric cancer screening ⁸ but was about the same as that for colorectal cancer screening¹⁰. Iinuma estimated CER for lung cancer screening was over ten times more expensive than that for gastric cancer screening and was most expensive ⁹. CER for breast cancer screening was estimated to be about 1.5 times more expensive than that for gastric cancer screening. Accordingly, the cervical cancer

Figure 4. The relationship between the medical charges for patients with invasive cancer and the cost-effectiveness ratio (CER).

Figure 5. The relationship between the incidence rate and the cost-effectiveness ratio (CER).

screening was within the range of cost-effectiveness among the cancer screening programs in Japan.

OTA reported the costs and effectiveness for cervical cancer screening for elderly women in the United States in 1990 ¹⁰. In this report, the cost-effectiveness ratio in annual screening

program as compared with the "no screening" program was approximately US\$ 40,000. This value was in agreement with that in a report by Eddy, based on the data from several of the largest screening programs in the world conducted by the International Agency for Research on Cancer (IARC) ¹⁰. These

estimates of CER for cervical cancer screening in the United States were quite similar to ours in Japan.

According to the sensitivity analysis, the most influential factor on CER was the screening charge, because the screening cost accounted for about 95% of the total cost. Then, if the screening charge is twice, CER would be about twice. According to a report by the Japan Cancer Association, the screening charge among the prefectures in Japan in 1989 varied greatly ranging from US\$ 10 to US\$ 58¹⁰. Such variations in the charge imply that regional differences in CER of cervical cancer screening varied more than five times among the prefectures, given that the other factors were constant.

The incidence rate of uterine cancer has been decreasing over the past decades. We demonstrated that CER for cervical cancer screening would increase if the incidence rate decreases. However, CER would not be over US\$ 100,000 even if the incidence rate decreased by about 50% of the current incidence. In a prediction of cancer incidence in Japan up to the year 2015⁷, Tsukuma et al. estimated the crude incidence rate of uterine cancer, including CIS, in the year 2015 would be 20.7, that is, a decrease of 15% from that in 1985. If the incidence rate becomes 85% of the current figure, CER would be US\$ 48,176. Therefore, it was suggested that the cervical cancer screening would remain reasonably cost-effective until the year 2015.

We described that CER for cervical cancer was within the range of cost-effectiveness of other cancer screening programs financed under the Health and Medical Services Law for the Aged in Japan. This study has some bias because it is simulation study. But it is impossible to evaluate its economic effect by randomized control trial (RCT) since screening for cervical cancer has been widely performed in Japan. It is necessary to examine its economic effect and other programs by several studies, not only annual screening but also every other year screening and so on.

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