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Effectiveness of Cervical Cancer Screening Over Cervical Cancer Mortality Among Japanese Women

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Background: Various studies have revealed that cervical cancer (CC) screening significantly reduces both CC incidence and mortality in developed countries. Although Japan introduced a nationwide government funded annual CC screening for the women aged 30+ in 1982, the effectiveness of CC screening on CC mortality has not yet been evaluated by any prospective cohort study. Therefore, the present study evaluated the association of CC mortality with self-reported CC screening and some other factors by a nationwide cohort study.
Methods: Baseline survey of the Japan Collaborative Cohort Study for the enrollment of subjects was completed during 1988–90 and followed until 2003. This study only analyzed 63 541 women, aged 30–79 years, who were free from any cancer history at enrollment.
Results: During the follow-up period, 38 CC deaths were identified. The mean age at mortality was 67.0 years, with a mortality rate of 4.2 per 100 000 person-years. Participation rate in CC screening was 46.9%. Age-adjusted Cox model indicated significantly lower CC mortality [hazard ratio (HR) = 0.30, 95% confidence interval (CI) = 0.12–0.74] due to CC screening. Protectiveness remained almost the same (HR = 0.30, 95% CI = 0.12–0.76) when adjusted for age, body mass index and number of deliveries. The results also revealed that CC screening could reduce at least 50% of CC deaths even after excluding the effect of possible self-selection bias.
Conclusions: CC screening in Japan may reduce CC mortality significantly for women aged 30–79 years. However, further studies with more CC deaths and increased statistical power are needed to validate the findings.

Key words: cervical cancer mortality – Pap smear test – cohort study – Japan

INTRODUCTION

Cervical cancer (CC) is the seventh in incidence for both sexes, but the second most common cancer among women worldwide, with an estimated 493 000 new cases and 274 000 deaths in the year 2002 (1). It occurs mostly (∼80%) in developing countries (1–3). This disproportionate burden of CC in the developing societies may be due to the absence or inadequacy of well-organized Pap smear screening programs (2,4). In developed countries, on the other hand, incidence rates of CC are generally low and accounts for only 3.6% of new cancers. This pattern is relatively recent and can be attributed to the screening programs (1,5,6), which have been introduced over 50 years (7–9). Cytological Papanicolaou (Pap) smear screening remains the best method readily available in reducing the incidence and mortality of CC (10). Various studies (mainly time series and case–control) revealed that widespread use of cervical screening in developed societies has been associated with the substantial reduction in the incidence rate of and mortality from CC (1,3,5,7,11–19), including Japan (14,18).

CC screening in Japan using the Pap smear was first established in Miyagi Prefecture in the early 1960s (20,21), after which the rate of screening has been increasing gradually. For instance, the screening rate has increased from 5.4% in 1965 to ∼30% in 1993 in Miyagi Prefecture (14). In 1982, Japan has introduced, under the Health and Medical Services Law for the Aged, a nationwide CC screening through this test as a

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government funded program for women older than 30 years (20–22). The Japanese Ministry of Health, Labor and Welfare recommends these women to receive the Pap smear test once in a year (22).

Like other industrialized countries (11,23), both the CC incidence and mortality have been decreasing steadily in Japan for the women aged 30+ years. For example, invasive CC incidence rate has decreased by approximately half from 13.4 to 7.2 per 100 000 women during 1975–98 (24). Similarly, mortality rate from CC has decreased ~66.6%, from 12.1 to 4.0 per 100 000 women during 1962–94 (20). The increasing survival or the reducing mortality from CC must at least partly be due to the nationwide CC program (20,22). In addition to the protective effect of CC screening, the incidence and mortality of CC may have been reduced in developed countries owing to the increased consumption of certain foods and nutrients such as dark green or yellow vegetables, fruit juices, vitamin C, folate and β-carotene (25–28). Higher socioeconomic status and care for better genital hygiene in developed countries may also be the reasons for reducing the CC mortality (29,30).

Other risk factors for CC may include infection with human papillomavirus (HPV), early age at first intercourse, early age at first pregnancy, higher parity, earlier age at menopause, sex with multiple partners, husband's extramarital sex, history of sexually transmitted diseases and smoking cigarettes (8,29–36).

Although CC screening in Japan started in 1982, and a few case–control studies (14,18) have been reported, to our knowledge no cohort study has been conducted until today which addressed the association of CC mortality with CC screening, with references to some other potential factors. The present study has been prompted on this background and focused on the effectiveness of screening over CC mortality in Japan for the first time.

METHODS

Study Subjects

Details of the study methods that adopted in the baseline and follow-up surveys are explained elsewhere (37). Briefly, the Japan Collaborative Cohort Study (JACC) Study for Evaluation of Cancer Risk (sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan) is a large and nationwide multicenter prospective cohort study which enrolled 127 477 healthy inhabitants (men = 54 032, women = 73 445) from 45 municipal areas (6 cities, 34 towns and 5 villages) located in 7 districts (out of 8) of Japan who responded the baseline questionnaire between 1988 and 1990. Number of participants were 525 under age 30 and 3760 over age 79. Most subjects were recruited from the general population or when undergoing routine health checks in the municipalities (38). Informed consent for participation was obtained, either by asking to sign the cover page of the questionnaire (at the individual level which covered majority of the participants) or by explaining the aim of the study and confidentiality of the data (at the group level) to the community leader. For analytical purpose, this study only included the women aged between 30 and 79 years at baseline survey. This provided a total of 70 955 women, of which 798 women were again excluded because of past medical history of cancer. Thus, we had a total of 70 157 women for analysis.

CC Screening and Other Selected Variables

At the time of enrollment, the subjects completed a self-administered questionnaire that included demographic characteristics such as age, sex, education; anthropometric measures such as height and weight; lifestyles related factors such as smoking, drinking, sport activity and dietary habits; past medical history such as diabetes mellitus and cancer; reproductive factors such as number of pregnancies and deliveries; and screening for CC and breast cancer which they received during the previous 1 year of baseline survey. However, the present study utilized only some selected variables which are shown in Table 1 with their categories. For the variables of number of pregnancies and number of deliveries, we used two categories $\leqslant 2$ and $\geqslant 3$, because no death was found for the women with zero pregnancy and delivery.

Follow-up Period and Determination of CC Death

Follow-up survey was conducted annually until the end of 2003 and 1999 in 42 and 3 areas, respectively, to determine the vital status of the women using resident registration records available in the respective municipalities. In the most recent data, cause of death was recorded by following International Classification of Disease version 10 (ICD-10). In the present analysis, code C53 of ICD-10 was taken as CC death. All other deaths (except CC) and subjects who were alive until the follow-up period or who moved out of the study areas or lost to follow-up were considered as censored cases during analysis.

Statistical Analysis

Present study analyzed the data by Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, NC). We used Cox proportional hazard model (PHREG procedure) to estimate the age-adjusted hazard ratio (HR) of CC mortality including 95% confidence interval (CI) for all the selected variables. Multivariate [age, body mass index (BMI) and number of deliveries] adjusted Cox model was also used to estimate the HR of CC by CC screening. Although the main outcome variable of interest was the CC mortality, we also calculated the HR for both total cancer and total mortality excluding CC deaths for estimating the benefit of CC screening over CC mortality after excluding the possible self-selection bias, following the formula [Benefit = $\{(HR^{\ddagger} - HR^{\dagger})/HR^{\ddagger} \times 100$, where $HR^{\ddagger}$ = HR for total mortality or total cancer mortality except CC

Table 1. Distribution of subjects, person-years, number of deaths, age-adjusted hazard ratio of cervical cancer mortality including 95% confidence interval due to some selected variables, Japan Collaborative Cohort Study, 1988–2003

Variables	Category	N^1	Person-years	Number of deaths	HR	95% CI	*P*
Age (in years)^2	30–39	6616	98 781	3	1.00		
	40–49	15 391	217 332	7	1.04	0.27–4.04	0.95
	50–59	19 720	272 028	10	1.19	0.33–4.33	0.79
	60–69	19 391	250 328	8	1.03	0.27–3.90	0.96
	70–79	9039	103 825	10	3.13	0.86–11.40	0.084
							P for trend = 0.065
Highest age at education	⩽15 years	19 423	248 227	11	1.00		
	⩾16 years	31 202	409 646	13	0.83	0.36–1.90	0.65
Sport activity	Seldom	41 843	552 533	24	1.00		
	⩾1–2 h/week	13 284	174 196	3	0.37	0.11–1.24	0.11
Body mass index (kg/m^2)	<18.5	4261	54 804	5	2.30	0.86–6.10	0.096
	18.5–25.0	47 381	641 908	23	1.00		
	⩾25.0	14 242	191 107	8	1.16	0.52–2.61	0.71
Number of pregnancies	⩽2	20 675	282 338	7	1.00		
	⩾3	42 164	560 873	28	1.89	0.82–4.37	0.14
Number of deliveries	⩽2	30 956	420 894	10	1.00		
	⩾3	30 945	408 670	25	2.38	1.11–5.11	0.026
Screening of cervical cancer during past year	No	28 586	376 647	24	1.00		
	Yes	24 417	331 216	6	0.30	0.12–0.74	0.009
Screening of breast cancer during past year	No	36 174	478 546	25	1.00		
	Yes	14 762	202 100	2	0.20	0.05–0.85	0.030
Smoking	Non-smoker	56 396	761 484	31	1.00		
	Ever-smoker^3	4788	63 859	4	1.55	0.54–4.39	0.41
Drinking	Non-drinker	46 408	619 550	25	1.00		
	Ever-drinker^3	17 447	239 134	8	0.89	0.40–2.00	0.78

HR, hazard ratio; CI, confidence interval.
[1]Total subjects vary for missing observations.
[2]Unadjusted HR was shown for age.
[3]Ever-smokers (drinkers) = current + ex-smokers (drinkers).

deaths among screened group and HR† = HR for CC mortality only among screened group used by Mizoue et al. (39).

RESULTS

In total, 38 deaths from CC (4.2 deaths/100 000 person-years) were identified during the follow-up period. The age at deaths from CC was 65.6 years (standard deviation = 12.9 years). Table 1 summarizes the information (number of subjects, person-years, deaths, HR and 95% CI) for some of the potential variables that may influence the CC mortality. Unadjusted HR and 95% CI of CC mortality for age indicated that highest age category differed largely from the lowest age category (P = 0.084). P for trend was also found to be nearly significant. Age-adjusted results of Cox model indicated higher risk of CC mortality for higher number (⩾3) of deliveries (HR = 2.4, 95% CI = 1.11–5.11). In contrast, screening for CC (HR = 0.30, 95% CI = 0.12–0.74), screening for breast cancer (HR = 0.20, 95% CI = 0.05–0.85) decreased the risk of CC mortality significantly. Lower BMI increased the risk of CC mortality although insignificant (P = 0.096). All other factors were insignificantly associated with CC mortality.

Table 2 presents the rate of CC screening by some selected variables. Rate of CC screening was significantly associated with age, which was found to be highest for the women aged 40–59 years (>50%), and lowest for them aged 70–79 years (18.5%). The screening rate was significantly lower for women with lower age at education (P < 0.0001), seldom sports activity (P < 0.0001), lower BMI (P < 0.0001), lower number of pregnancies (P < 0.001), higher number of deliveries (P < 0.001), for ever smoker (P < 0.0001) and ever-drinker (P < 0.05). Breast cancer screening was found to be positively and significantly (P < 0.0001) associated with CC screening. The rate of CC screening was 90.1% for those women who

Table 2. Use of cervical cancer screening percentage during the past year before baseline survey by some selected variables, Japan Collaborative Cohort Study, 1988–2003

Variables	Category	N[1]	No. of women screened for CC	Percentage of women screening for CC	P[2]
Age (in years)	30–39	4558	6731	36.7	<0.0001
	40–49	12 449	8571	54.1	
	50–59	15 483	6321	55.4	
	60–69	14 457	1121	43.7	
	70–79	6056		18.5	
Highest age at education	⩽15 years	15 692	6989	44.5	<0.0001
	⩾16 years	27 110	13 422	49.5	
Sport activity	Seldom	35 414	16 625	46.9	<0.0001
	⩾1–2 hours/w	10 819	5369	49.6	
Body mass index (kg/m^2)	<18.5	3103	1182	38.1	<0.0001
	18.5–25.0	36 099	17 072	47.3	
	⩾25.0	11 203	5246	46.8	
Number of pregnancies	⩽2	16 221	7332	45.2	<0.001
	⩾3	33 601	16 069	47.8	
Number of deliveries	⩽2	24 943	11 948	47.9	0.0002
	⩾3	24 258	11 212	46.2	
Screening of breast cancer during past year	No	35 938	9124	25.4	<0.0001
	Yes	14 299	12 884	90.1	
Smoking	Non-smoker	43 587	20 607	47.3	<0.0001
	Ever-smoker[3]	3617	1183	32.7	
Drinking	Non-drinker	35 542	16 573	46.6	0.0020
	Ever-drinker[3]	13 725	6187	45.1	

CC, cervical cancer.
[1]Total subjects vary for missing observations.
[2]Based on χ^2-test.
[3]Ever-smokers (drinkers) = current + ex-smokers (drinkers).

Table 3. Multivariate analysis for estimating hazard ratio for cervical cancer mortality, total cancer deaths excluding cervical cancer deaths, and total deaths excluding cervical cancer deaths by cervical cancer screening by some selected variables, Japan Collaborative Cohort Study, 1988–2003

Deaths	HR (95% CI)[1]	HR (95% CI)[2] (Final model)
Cervical cancer death		
Unscreened	1.00	1.00
Screened†	0.30 (0.12–0.74)	0.30 (0.12–0.76)
	P = 0.0094	P = 0.0113
Total cancer deaths excluding CC deaths		
Unscreened	1.00	1.00
Screened	0.80 (0.72–0.89)	0.79 (0.70–0.88)
	P < 0.0001	P < 0.0001
Total deaths excluding CC deaths		
Unscreened	1.00	1.00
Screened‡	0.73 (0.68–0.78)	0.73 (0.68–0.78)
	P < 0.0001	P < 0.0001
Benefit of CC screening (CC death versus total death except CC death)[3]	58.9%	58.9%

HR, hazard ratio; CI, confidence interval; CC, cervical cancer.
[1]Adjusted for age.
[2]Adjusted for age, body mass index and number of deliveries.
[3]Benefit = $\{(HR^{\ddagger} - HR^{\dagger})/HR^{\ddagger}\} \times 100$.

received breast cancer screening by health services providers as compared to those who did not receive (25.4%).

Table 3 revealed the modified strength of association (HR and 95% CI) between CC mortality and CC screening after adjusting three important factors, namely age, BMI and number of deliveries (final model). We did not include breast cancer screening (another age-adjusted significant variable) in order to avoid the multicollinearity problem with CC screening. Protectiveness of CC screening over CC mortality remained the same in the final model (HR = 0.30, 95% CI = 0.12–0.76). Although age and BMI revealed as highly insignificant variables for CC mortality in the final model, higher number of deliveries was found as a risk factor (HR = 2.70, 95% CI = 1.15–6.35) for CC mortality (not shown in Table 3). CC screening participation was also associated with a significantly reduced risk of mortality from other causes of deaths (total cancer—as well as total deaths—except CC deaths) when adjusted for same variables. However, the rate of reduction was much greater for CC mortality as compared to other deaths (except CC deaths). Results also indicated that 58.9% (for both age-adjusted and multivariate-adjusted/final model) CC deaths could be reduced by CC screening (i.e. benefit) even after excluding the effect of possible self-selection bias (Table 3).

DISCUSSION

Present cohort study, for the first time to our knowledge, demonstrated that CC screening through Pap smear test could significantly reduce the CC mortality (>65% reduction in risk of death) among Japanese women. However, the extent of risk reduction was much greater for CC deaths than all other deaths excluding CC deaths (Table 3). The effectiveness of CC screening in reducing CC mortality and incidence has also been reported by many other studies in developed countries (1,3,5,7,11–19,31,32) including Japan (14,18). According to the Japanese case–control study of Makino et al. (14), odds ratio (OR) for CC incidence was 0.14 (95% CI = 0.09–0.23) for those women who were screened as compared to those women who were not screened. Although insignificant, the effectiveness of CC screening in Japan in reducing the mortality (OR = 0.22) and incidence (OR = 0.41) of invasive CC has been suggested by Sobue et al. (18).

The present study, focusing on the effectiveness of screening over CC mortality, may suffer from self-selection bias (39). Self-selection bias, which may arise from the factors that influence the study participation, may affect the efficacy of the screening test. It comes about when the association between exposure (e.g. screening test) and disease (e.g. CC) differs for those who participate and those who do not (40). Very likely, people who volunteer for cancer screening are generally more health conscious than those who do not, and people who are more health conscious may have better lifestyle and genital hygiene, which in turn reduce the mortality (29,40–42). Magnus et al. (43) reported that women who do not attend the CC screening may constitute a high risk group. Another important problem is that women who repeatedly undergo screening account for a large percentage (20), indicating their health consciousness. The statements above regarding self-selection bias may also be supported by our findings in Table 2. For instance, women with less education, lower physical activity, lower BMI, ever smoking status and not undergoing the breast cancer check up, showed significantly lower rate of CC screening than their counterparts.

Like the study of Mizoue et al. (39), we also assessed the magnitude of potential self-selection bias by comparing the risk of death for CC with that of deaths from causes other than CC. This approach may be useful in examining the effects of a bias that cannot be controlled using available information on known confounding factors. Screened women showed a 22–28% reduced risk of death from causes other than CC. The risk of death from CC was lower than that from other causes of deaths of by more than 55 percentage points (Table 3), which raises the possibility that screening may have protective effects on CC mortality.

The effectiveness of widespread cervical cytologic screening in reducing the incidence of and mortality from invasive CC has been varied in many countries. The effect of screening may depend on several factors as follows: (i) the proportion of women screened in each age group; (ii) the age-specific prevalence of preinvasive lesions; (iii) the sensitivity of a smear test, which mainly reflects age, sampling techniques and diagnostic accuracy; and (iv) the effectiveness of diagnostic and therapeutic follow-up in eliminating precursors (5,8). Saslow et al. (44) reported that largest gain in reducing CC incidence and mortality could be attained by increasing screening rates among women who are currently unscreened or screened only infrequently. Higher coverage showed higher reduction in mortality by other studies (3,19). Sato et al. (20) also showed inverse association between CC mortality and screening rate.

Baseline data of the present study indicated that the rate of CC screening among the women aged 30 and over was only 47%. According to Sato et al. (20), the first problem is the lack of further increase in screening rate, because a negligible increase has been observed after 1990. Generally, the percentage of previously unscreened women is very low in the repeated screening (20). According to Kitazawa (45), some important reasons for low screening rate among the Japanese population are as follows: people are too busy to get screened for cancer; people feel fine, and therefore do not see the need to get screened for cancer; and people feel that screening tests are a hassle. Therefore, further efforts should be made to increase the participation rate. One Japanese study reported that well-organized data management systems and involvement of community organizations could play important roles to disseminate necessary information regarding the importance of prevention and early cancer detection and to encourage participation in screening. Fee exemption for the low income population can also contribute to increased participation rate (46). Another Japanese study recommended that every woman should be encouraged to undergo CC screening whenever they come to a clinic or hospital for a physical checkup or pregnancy test (47). Encouraging a greater number of women to attend the screening program by invitation (48), provision of effective nationwide outreach interventions (22), allocation of resources and widespread educational programs (8) especially for those who missed screening, may all improve the situation and reduce the death rate from SCC of the cervix.

Although many risk factors are reported to be associated with CC mortality (8,31–36), our study found only the number of deliveries as significant. Dietary items (32 items were analyzed) were also found to be insignificantly associated with CC mortality (results not shown), which were inconsistent with the findings of some other studies (25–28).

Limitations of the present study, in addition to possibility of self-selection bias, are discussed below. First, small number of deaths limited the statistical power of the study. Second, we did not further classify the CC mortality into either from SCC or from adenocarcinoma of the cervix. In Japan, the cumulative rates of adenocarcinoma of the cervix exhibits an increasing trend particularly for the women aged 25–49 years old (49). Generally speaking, screening by Pap smear test is more effective for SCC as compared to adenocarcinoma (14,49). False negative rates for adenocarcinoma are higher than those for SCC (14), because adenocarcinoma of the cervix arises from the endocervical epithelium (frequently within the endocervical canal) and tends to produce fewer early symptoms, consequently the precancerous lesions may be missed by Pap smear screening and more likely to be diagnosed at a later stage than SCC (15). However, as most of the CCs ($\sim$85%) are histologically SCC in Japan (14,50) which is also supported by Hoffman and Cavanagh (8), the results of the present study may be reliable.

Third, healthy screenee bias, which is distinct from self-selection bias, could also influence the effectiveness of screening (51,52). It may occur when the frequency of screening depends on the health status of the subject and failure to correct such bias may result in an inflated estimate of the benefit of multiple examinations (52). Raffle (53) mentioned that the OR in a case–control study will be distorted if there is a relationship between an individual's risk of an adverse outcome, and their likelihood of participating in screening. This healthy screenee effect bedevils all studies that incorporate comparisons between those who self-report to participate and those who self-report not to. Fourth, we could not report whether Pap smear test was conducted under the Health and Medical Service Law for the Aged (organized screening) or whether the screening was done as part of a health checkup.

Fifth, although reporting the validity of self-reported CC screening is important, which is found to be inconsistent by many studies (54–58), unfortunately we do not report this due to lack of information. A Danish study indicated that 13% of the women aged 20–29 years could not state correctly that they had been screened for CC (57). Self-reported screening rate was found to be 13–29% higher in Australia as compared to the rate of Health Insurance Commission data (56). Bowman et al. (58) and Rossi et al. (54) mentioned that self-reported Pap smear histories consistently result in overreporting of screening. A Canadian cohort study by Bancej et al. (55) reported that among women who reported having a mammogram at baseline, 5.9% reported at follow-up that they had never had mammogram. Recall bias may play an important role in this regard. However, recall bias may not be an important factor in the present study, as this study only used 1 year interval at the time of baseline survey while asking question about CC screening. Sixth, we adjusted only three factors, namely age, BMI and number of deliveries in the final Cox model to estimate the effectiveness of screening over CC mortality. Lack of HPV data did not allow us to adjust the impact of HPV, which is the main cause of CC (8,33). Finally, the estimated HR for CC screening may suffer from the changing status of self-reported screening, because screening status of unscreened women may change anytime during the long follow-up period as it is recommended annually in Japan. However, according to Mizoue et al. (39), recent participation in screening is a reasonable predictor of future participation.

In conclusion, CC screening has been found to be significantly effective in reducing the CC mortality for the Japanese women aged 30–79 years, although the reduction in the risk of CC mortality may be altered largely by general self-selection bias. Further attempts will be needed to increase the participation rate for screening in Japan in order to reduce the burden of this disease. Finally, further studies with increased statistical power are recommended to validate the present findings, especially by including more cases of death from CC.

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