Jpn. J. Cancer Res. (Gann), 79, 1269–1275 ; December, 1988

A Case-Control Study of the Effectiveness of Cervical Cancer Screening in Osaka, Japan

Tomotaka SOBUE,[*1, *4] Takaichiro SUZUKI,[*1] Sumiyo HASHIMOTO,[*2] Nobuko YOKOI[*3] and Isaburo FUJIMOTO[*1]

[*1]*Department of Field Research, The Center for Adult Diseases, Osaka, Higashinari-ku, Osaka 537,* [*2]*Nose Town Office, Shukuno Nose-cho, Osaka 563-03 and* [*3]*Nose Branch, Ikeda Health Center, Imanishi Nose-cho, Osaka 563-03*

In the small town of Nose in Osaka, Japan, a population-based screening program for cervical cancer by Papanicolaou smear has been conducted since 1965. In order to evaluate the effectiveness of screening in terms of the reduction of the mortality and the incidence of invasive cervical cancer, two types of case-control studies were carried out. In the first study, the case series consisted of all women who died of cervical cancer under 80 years of age at the time of diagnosis in 1965–1987 (N=15). For each case, 10 controls were chosen from living residents, matched by year of birth. It showed that the odds ratio (OR) of dying of cervical cancer for screened versus non-screened women was 0.22 (95%CI=0.03–1.95). In the second study, the case series consisted of all women who were diagnosed as having invasive cancer under 80 years of age at the time of diagnosis in the same period (N=28). For each case, 10 controls were chosen from living residents without invasive cancer, matched by year of birth and according to whether or not they were screened at the year of the diagnosis of the matched case. It showed that the OR of getting invasive cancer for screened versus non-screened women was 0.41 (95%CI=0.13–1.29). From these results, it was estimated that 78% of cervical cancer mortality and 59% of invasive cervical cancer incidence among non-screened women could be prevented by cervical cancer screening.

Key words: Cervical cancer — Screening — Effectiveness — Case-control study

Cervical cancer screening by Papanicolaou smear is one of the most widespread cancer screening programs in Japan.[1] So far, evidence accumulated in western countries suggesting the effectiveness of the screening in reducing the mortality and the incidence of invasive cervical cancer is convincing, although a randomized controlled trial has never been performed. Most of the studies were based on comparisons of incidence and mortality rates of invasive cervical cancer between populations with different screening intensity,[2–8] or case-control studies.[9–13]

A case-control study was proposed as an alternative method to evaluate the effectiveness of screening, which has already become widespread in the general population and is impossible to evaluate by means of a randomized controlled trial.[14] In this method, individual screening histories are compared between cases and controls, instead of comparing overall mortality rates or incidence rates in particular groups. This approach enables us to estimate what proportion of the mortality and incidence of invasive cervical cancer can be reduced by the screening in terms of a quantitative value, namely the odds ratio (OR).[*5]

In Japan, there have been some studies dealing with the effectiveness of cervical cancer screening. Most of them are the studies about screening histories only for cervical cancer patients,[15–17] or the mortality trend in particular areas where cervical screening had been conducted intensively with no control areas,[18, 19] or correlation studies between the mortality trends and intensity of screening activity.[20] None of these studies could estimate the effectiveness of cervical cancer screening for the reduction of the mortality or incidence of invasive cervical cancer in a quantitative manner. In Japan, a case-control

[*4] To whom communications should be addressed.
[*5] Abbreviations: OR, odds ratio; CI, confidence interval; CIS, carcinoma *in situ*.

study for evaluating a cancer screening program has so far been used only for stomach cancer.[21] This is the first study designed to evaluate the effectiveness of cervical cancer screening in Japan by means of a case-control study.

Materials and Methods

In Nose Town, which is located in the northern rural area of Osaka Prefecture, with a highly stable population of about 10,000, cervical cancer screening has been conducted since 1965. As a screening policy, all women aged 30 or above have been invited to the Health Center. After 1984, a mobile unit program was also started.

The first study was designed to evaluate the effectiveness of the screening of cervical cancer in terms of the mortality of the disease. The case series consisted of all women who died of cervical cancer, under 80 years of age at the time of diagnosis, in Nose Town in the period of 1965–1987. These data and medical information concerning the patients were collected through the Osaka Cancer Registry and the Nose Health Center, and a total of 15 cervical cancer deaths were identified. For each case, 10 controls were chosen from women of the same year of birth, who were alive at the time of diagnosis of the case. These controls were selected from the computer file of all residents, created in 1965.

Information on screening histories for cases and controls was obtained from the records of screenees kept at the Nose Health Center and the Nose Town Office. For each set of case and controls, the screening histories of both case and controls were compared within 10 years up to the year of diagnosis of the matched case. The screening test which led to the diagnosis of cervical cancer was included in the screening history, if the case was detected by screening. For controls, screening tests were counted in the same calendar time as the matched case. Residential histories of cases in Nose Town were also investigated, and if the case had moved to Nose Town after 1964, the comparison was limited to after the year of her move, so that chances to participate in the screening program should be equal between case and controls.

The second study was designed to evaluate the effectiveness of the screening in terms of the incidence of invasive cervical cancer. The case series consisted of all women who were diagnosed as having invasive cancer under 80 years of age at the time of diagnosis in the period of 1965–1987. These were collected through the Osaka Cancer Registry and the results of the screening, and a total of 28 cases were identified. Cervical cancers which were not reported as carcinoma *in situ* (CIS) were counted as invasive. For each case, 10 controls were chosen from women of the same year of birth, who were alive at the time of diagnosis of the matched case. Besides, if the cases had been detected by screening, controls were chosen from women who were screened at the year of the detection of the matched case. Also, if the cases had been detected on the basis of symptoms, controls were chosen from women who were not screened at the year of detection of the matched case. For 1 screen-detected case, only 2 controls were available, but otherwise 10 controls for each case could be chosen successfully.

Screening histories were obtained from the same source mentioned above. For each set of case and controls, the screening histories of both case and controls were compared within 10 years of the same calendar time before and excluding the year of diagnosis of the case. The screening test which led to the diagnosis of cervical cancer was not included in the screening history. Only screening tests whose results were negative were counted. Residential histories of cases were treated in the same way mentioned above. Screening histories were also categorized by the number of screenings within 10 years before diagnosis and in the years since the last negative test.

In order to calculate ORs and 95% confidence intervals (95%CI), a logistic regression analysis with conditional likelihood functions was used. The analysis was done with the PROC MCSTRAT in the computer program SAS.[22]

Results

Table I shows the person-years of women aged 30 or more, the person-years of screenees and screening rate in Nose Town by 5- or 4-year period. Screening rates were less than 10% until 1983, and increased to 13% in the period of 1984–1987.

Table II shows the age distribution of all cervical cancer cases and those who died of the disease. There was no death in CIS cases up to February 1, 1988. Clearly, invasive cancer cases were older than CIS cases. For invasive cancer, 25% of the cases were detected by screening, while for CIS, 88% of the cases were detected by screening. For both groups, only 1 case was detected by screening in women aged 60 or more.

Table III shows the first case-control comparison, which is the distribution of matched sets of dead cases and their controls according to screening history. There was only one dead case who had been screened within 10 years

Table I. Results of Cervical Cancer Screening in Nose Town, 1965–1987

Period	Person-years of women over 30 years of age	Person-years of screenees	Screening rate (%)
1965–1969	13,460	689	5.1
1970–1974	14,639	1,336	9.1
1975–1979	15,188	1,170	7.7
1980–1983	13,099	1,060	8.1
1984–1987	13,933	1,859	13.3

Table II. Age Distribution of Cervical Cancer Cases

Age[a]	Incidence		Mortality[b]
	Invasive	CIS	
30–39	3(1)[c]	3(3)	0
40–49	8(5)	2(2)	1
50–59	7(0)	3(2)	4
60–69	5(0)	0(0)	5
70–79	5(1)	0(0)	5(1)
Total	28(7)	8(7)	15(1)

a) Age at the time of diagnosis.
b) Observed up to February 1, 1988.
c) Screen-detected cases in parentheses.

up to the year of diagnosis of the case. For this case-control set, none of the 10 controls had been screened within the 10-year period. The remaining 14 cases had never been screened. For these case-control sets, none of the 10 controls had been screened in 6 sets, 1 of 10 controls had been screened in 2 sets, 2 of 10 controls had been screened in 1 set, and so on. The OR of dying of cervical cancer for screened versus non-screened women was 0.22 (95%CI=0.03–1.95).

Table IV shows the second case-control comparison, which is the distribution of matched sets of invasive cancer cases and their controls according to screening history, by sets of screen-detected and symptom-detected cases. For sets of screen-detected cases, the OR of getting invasive cancer for screened versus non-screened women was 0.43 (95%CI=0.05–3.71). For sets of symptom-detected cases, the OR of getting invasive cancer was 0.41 (95%CI=0.11–1.56), which is almost the same as that for sets of screen-detected cases. The OR for both sets of screen-detected and symptom-detected cases combined was 0.41 (95%CI=0.13–1.29).

Table V shows the ORs of getting invasive cancer according to the number of tests within 10 years. Compared to those who had never been screened, the OR for being screened once was 0.54, and twice or more was 0.11. Although the confidence intervals of these ORs were not statistically different from 1.0, the trend for the linearity was statistically significant.

Table VI shows the ORs of getting invasive cancer according to the number of years since the last screening test. Compared to those who had never been screened, the OR for

Table III. Distribution of Matched Sets of Dead Cases and Their Controls According to Screening History

1:10 Match Case	Number of matched controls screened											Total
	0	1	2	3	4	5	6	7	8	9	10	
Screened	1	0	0	0	0	0	0	0	0	0	0	1
Not screened	6	2	1	1	1	0	2	1	0	0	0	14

OR=0.22 (95%CI=0.03–1.95).

Table IV. Distribution of Matched Sets of Invasive Cancer Cases and Their Controls According to Screening History, by Sets of Screen-detected and Symptom-detected Cases

(Sets of screen-detected cases)

1:2 Match Case	Number of matched controls screened			Total
	0	1	2	
Screened	0	0	0	0
Not screened	1	0	0	1

1:10 Match Case	Number of matched controls screened											Total
	0	1	2	3	4	5	6	7	8	9	10	
Screened	0	0	0	0	0	0	0	0	0	3	1	4
Not screened	0	0	0	1	0	0	0	1	0	0	0	2

OR=0.43 (95%CI=0.05–3.71)

(Sets of symptom-detected cases)

1:10 Match Case	Number of matched controls screened											Total
	0	1	2	3	4	5	6	7	8	9	10	
Screened	0	0	2	0	0	1	0	0	0	0	0	3
Not screened	6	3	2	0	2	1	2	2	0	0	0	18

OR=0.41 (95%CI=0.11–1.56).
OR for both groups combined=0.41 (95%CI=0.13–1.29).

Table V. ORs of Getting Invasive Cancer According to the Number of Screening Tests within 10 Years

Number of tests within 10 years	OR	(95%CI)
None	1.00	
Once	0.54	(0.18–1.65)
Twice or more	0.11	(0.01–1.06)

χ^2 for linearity=4.06 ($P<0.05$).

Table VI. ORs of Getting Invasive Cancer According to the Number of Years since the Last Screening Test

Years since last test	OR	(95%CI)
None	1.00	
1–2	0.27	(0.06–1.23)
3–4	0.23	(0.02–2.24)
5 or more	0.55	(0.13–2.29)

χ^2 for linearity=3.36 ($P<0.10$).

Table VII. Previously Reported ORs of Getting Invasive Cancer for Screened versus Non-screened Women

Author	Study area	Age of women	OR(95%CI)[a]
Clarke *et al.*[9]	Toronto, Canada	20–69 yr.	0.37(0.37–0.50)
Aristizabal *et al.*[10]	Cali, Colombia	all	0.10
Graaf *et al.*[8]	Nijmegen, Netherlands	33–55 yr.	0.32(0.12–0.80)
Sobue *et al.* (this work)	Osaka, Japan	30–79 yr.	0.41(0.13–1.29)

a) Unadjusted for other risk factors of cervical cancer.

being screened 1–2 years before, 3–4 years before and 5 years or more before were 0.27, 0.23 and 0.55, respectively. Again, although the confidence intervals of these ORs were not statistically different from 1.0, the trend for the linearity showed marginal significance ($P=0.06$).

Discussion

The result of the study suggested the effectiveness of cervical cancer screening in Japan in reducing the mortality and incidence of invasive cervical cancer. The estimated ORs can be interpreted to mean that 78% of cervical cancer death and 59% of invasive cervical cancer under 80 years of age can be prevented by the screening. Also, dose-response relationships between incidence of invasive cervical cancer and intensities of screening histories were observed, which could be additional evidence that the relationships were real.

One of the weaknesses of this study is the fact that all the levels of significance were over 5%. This is not because the effect is small, but because the number of the cases is small. The reason why we finished the observation and analyzed the data with such a small number of cases is that it is thought unlikely that the number of cases in this small town will increase much in the future, because of the recent decreasing trends of mortality and incidence of cervical cancer. Since our main purpose in this study was to estimate the effectiveness of cervical cancer in terms of a quantitative value, a more serious point we have to consider is whether the estimated value of the OR itself is biased or not.

In this study, cases were defined as all patients with cervical cancer (dead or diagnosed as invasive) under 80 years of age in this town, and controls were chosen from the list which covers all women in this town at the time of the beginning of the screening program, namely in 1965. This means both cases and controls were chosen from the same population, so that no bias could exist in this selection process. The only possible bias is that the control series were chosen from among the women who lived in this town in 1965, while the cases could include women who moved to Nose Town after 1965. Actually, however, only one invasive cancer case had moved to Nose Town after 1965. Also, a survey conducted by the Town Office recently showed no difference in the screening rates between those who were born in this town and those who moved there afterwards.

Screening histories were obtained not from interviews with the study subjects but from the medical records of the screening. Therefore, no recall bias could influence the results. However, information on Pap smears performed in other facilities than the screening program could not be reviewed. A recent survey conducted in this town in 1988 revealed that at least 9% of the women who had never participated had been screened at other facilities once in their life. It is thought, however, that this could have occurred only within a recent period, and in the 1960s and 1970s the chances to have Pap smears other than by screening were small in this town.

In the first study (dead cases and controls), the screening histories were counted before and including the year of the diagnosis of the case, and in the second study (invasive cancer cases and controls) before and excluding the year of the diagnosis of the case. In both studies, the calendar time in which the screening histories were compared was exactly the same between case and controls within the matched set, so that comparability between case and control was completely maintained. This type of comparison was exactly the same as the one proposed as appropriate for evaluating the effectiveness of screening without biases.[14] Furthermore, in the second study, the ORs for the sets of screen-detected cases and symptom-detected cases were calculated separately first, and then combined, after confirming that the ORs for both sets were almost equal to each other. These two ORs are considered as prevalence OR and incidence OR, respectively.[14] The fact that the two ORs were almost equal can be interpreted to mean that the invasive component of the detectable preclinical phase of cervical cancer is about equal to a unit of time, which is a year in this case.

Marital, sexual and reproductive history, smoking history or contraceptive use are known risk factors for cervical cancer,[23–25] which tend to be inversely related to participation in the screening program,[26] and can be confounding factors. These factors were not

included as covariates in the analysis. This would not invalidate the results of the study, however, because in this particular area, women are thought to be quite homogeneous in terms of these factors. Most women are married non-smokers and do not use contraceptives. Actually, all cases and 98% of controls were married at least once in this study. The overall smoking rate for women in this town was only 8.4% in the survey conducted in 1983. Oral contraceptives are only available in physicians' offices, and are rarely used, particularly in rural areas. One survey conducted in a rural area in Aichi Prefecture showed that participants in cervical cancer screening tend to be married and non-smoking women compared to non-participants.[27] In this survey, however, over 95% of participants and non-participants were married and non-smoking. Therefore, as far as these factors are concerned, the expected incidence rates of cervical cancer should be almost equal for both groups, which means there would be no need to consider these factors as confounders.

Since a population-based case-control study like this does not evaluate the survival of the patients but only the mortality and incidence of invasive cervical cancer, the results of the study are not susceptible to lead time bias and length bias. In order for this to be so, however, the study period has to be sufficiently longer than the duration of the preclinical detectable phase and the survival of the disease. In this study, we accumulated data for 23 years, and 19 out of 28 invasive cases were followed for more than 10 years from the time of diagnosis.

The value of ORs obtained in this study were almost the same as those obtained in western countries. Table VII shows the ORs obtained in three other case-control studies.[9, 10, 12] All studies showed a protective effect of cervical cancer screening in reducing the incidence of invasive cervical cancer. The tendency that our OR was slightly closer to 1.0 than others could be explained by the fact that our study included older women than others. In Japan, there have been no data of this type available for cervical cancer screening. The ORs for stomach cancer screening of reducing the mortality were 0.595 for men and 0.382 for women,[21] which means that cervical cancer screening is more effective in terms of reducing the mortality.

The appropriate frequency of screening is a more advanced question to be considered. In 1980, the American Cancer Society recommended that all symptomatic women aged 20 and over, and those under 20 who are sexually active, should have a Pap test annually for two negative examinations and then at least every three years until the age of 65.[28] Refuting this, the International Academy of Cytology claimed that cytoscreening has to be done once a year until control over the precision of cytology has been established.[29] In this study, the OR for the women screened 3–4 years before was almost the same as that for those screened 1–2 years before, and both were lower than that for those screened 5 years or more before. These are in accordance with the results of previous case-control studies,[11–13] suggesting that a 3–4 year interval could be as effective as a 1–2 year interval. A large-scale case-control study is needed to determine the optimum schedule for screening in Japan, which may be dependent on various factors and could be different from the recommended schedule in western countries.

Acknowledgments

We thank the staff of the Nose Health Center, and of the Nose town Office for participating in this study, and the Osaka Cancer Registry and the Osaka Medical Association for supplying data. We also thank Mrs. Y. Murai for data processing.

(Received Aug. 15, 1988/Accepted Oct. 19, 1988)

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