

RESEARCH COMMUNICATION

Factors Relating to Poor Survival Rates of Aged Cervical Cancer Patients: a Population-based Study with the Relative Survival Model in Osaka, Japan

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Abstract

Poor survival of older cervical cancer patients has been reported; however, related factors, such as the extent of disease and the competitive risk by aging have not been well evaluated. We applied the relative survival model developed by Dickman et al to resolve this issue. Study subjects were cervical cancer patients retrieved from the Osaka Cancer Registry. They were limited to the 10,048 reported cases diagnosed from 1975 to 1999, based on the quality of data collection on vital status. Age at diagnosis was categorized into <30, 30-54, 55-64, and 65+ years. The impact of prognostic factors on 5-year survival was evaluated with the relative survival model, incorporating patients' expected survival in multivariate analysis. The age-specific relative excess risk (RER) of death was significantly higher for older groups as compared with women aged 30-54 years (RER, 1.58 at 55-64 and 2.51 at 65+ years). The RER was decreased by 64.8% among the 55-64 year olds as an effect of cancer stage at diagnosis, and by 43.4% among those 65 years old and over. After adding adjustment for treatment modalities, the RER was no longer significantly higher among 55-64 year olds; however, it was still higher among 65 year olds and over. Advanced stage at diagnosis was the main determinant of poor survival among the aged cervical cancer patients, although other factors such as limitations on the combination of treatment were also suggested to have an influence in those aged 65 years and over.

Key Words: Cervical cancer - age - cancer stage - relative excess risk

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Introduction

Cervical cancer is one of the leading cancers in women worldwide; in Japan approximately 7,500 women are estimated to have been affected each year in the last decade. The relative 5-year survival for uterine cancer has improved on the whole, but it remains poor among the older age group (Kinoshita et al., 1998; Osaka Prefectural Department of Environment and Public Health et al., 1998; Ajiki et al., 2004; Ioka et al., 2005). Our previous study showed the relation between lower survival and higher age to be mainly due to a more advanced stage at diagnosis; however, the impact of prognostic factors in respect with the expected survival in the general population has never been well evaluated. Dickman et al (2004) have developed the relative survival model applicable to this issue.

According to the clinical staging, patients with cervical cancer are usually treated by the combination of surgery (i.e., simple/radical hysterectomy and/or bilateral pelvic lymphadenectomy), radiotherapy and chemotherapy (Benedet et al., 2000; Green et al., 2001; Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration, 2004). Prior studies showed that concomitant chemotherapy with radiotherapy is superior

to radiotherapy alone for bulky, locally advanced disease. Therefore, we used the relative survival model to improve the interpretation of differences in cervical cancer survival among various age groups, estimating statistical significance of variation in excess risk of death about cancer stage and treatment modalities etc.

Materials and Methods

Data Sources

A total of 10,048 reported cases of cervical cancer (ICD Tenth Revision, C53) newly diagnosed in 1975-1999 were retrieved from the Osaka Cancer Registry's database. Osaka Cancer Registry (OCR) has been operating since December 1962, covering Osaka Prefecture with its population of 8.8 million (2005 census). Cancer incidence data in Osaka have been reported in 'Cancer Incidence in Five Continents', from volume III in 1976 to IX in 2007 (Curado et al., 2007). Therefore it can be assumed that the quality of this data meets the standards set by the International Association of Cancer Registries during the last four decades. In 1998-2002, the proportion of death certificate only (DCO) cases was 6.4%, and the mortality to incidence ratio (M/I) was 0.42 for cancer of cervix uteri.

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Based on the quality of data collection on the vital status of registered cases (Ioka et al., 2005), survival analysis was restricted to cases who lived in Osaka Prefecture (except for Osaka City) in 1975-1999 or resided in Osaka City in 1993-1999 when they were diagnosed as cervical cancer, since they had active follow-up information. In addition they met the following criteria:

1) In the case of multiple tumors, only the first was included; 2) Cases diagnosed as carcinoma in situ were excluded.

In total, 445 cases (4.4%) were lost to follow-up which meant unknown through reference to basic resident register and treated as censored cases at the latest date when they were confirmed as alive.

In line with our previous study, the age at first diagnosis was classified into four categories: less than 30 years, from 30 to 54 years, from 55 to 64 years and 65 years and over. In the detection by screening categorized as yes or no, no included unknown which means no information available (the proportion of unknown was 4.7% in <30 years, 5.3% in 30-54, 6.3% in 55-64, and 6.5% in 65+). The cancer stage at diagnosis was classified into the following four groups in OCR: localized (cancer is confined to the original organ), regional (cancer spreads to regional lymph nodes and/or spreads to immediately adjacent organs/tissues), distant (cancer metastasizes to distant organs/tissues), and unknown. In consideration of combination of surgery/radiotherapy/chemotherapy categorized as done or not done, treatment was assorted into eight categories, and also unknown was treated as not done (the proportion of unknown in surgery/radiotherapy/chemotherapy was 0.5/1.6/1.1% in <30 years, 0.6/1.7/2.3% in 30-54, 0.8/1.5/2.6% in 55-64, and 1.5/1.4/3.0% in 65+):

surgery(+)-radiotherapy(+)-chemotherapy(+);
surgery(+)-radiotherapy(+)-chemotherapy(-);
surgery(+)-radiotherapy(-)-chemotherapy(+);
surgery(+)-radiotherapy(-)-chemotherapy(-);
surgery(-)-radiotherapy(+)-chemotherapy(+);
surgery(-)-radiotherapy(+)-chemotherapy(-);
surgery(-)-radiotherapy(-)-chemotherapy(+);

and others. The year of diagnosis was categorized into five groups: 1975-1979, 1980-1984, 1985-1989, 1990-1994 and 1995-1999.

Statistical Analyses

The distribution of patients' characteristics was assessed with chi-squared tests for categorical variables. Survival time was computed from the date of first diagnosis to the end-point, defined as death from any cause. Closing date was defined as the date 5 years after the first diagnosis. Relative 5-year survival was calculated with adjustment for differences in the probability of death from causes other than cervical cancer among subjects. Relative survival was calculated as the ratio of observed survival to expected survival; the latter was estimated using the probability of survival in the general population of Japan for similar subjects with respect to sex, age, and calendar year at diagnosis.

Differences in 5-year relative survival among age groups were modeled with multiple regression approach based on generalized linear models and adopting the

Poisson assumption for the observed number of deaths (Dickman et al., 2004). The relative excess risks (RERs) derived from these models quantify the extent to which the hazard of death in a given category (i.e., 55-64 years/65+ group) differs from the hazard in the reference category (i.e., 30-54 years group), after taking into account the background risk of death in the general population of each age group. To adjust for prognostic factors, we started from a simple model to complicated model.

Model 1 (null): age

Model 2: age + diagnosed year

Model 3: age + diagnosed year + detection by screening

Model 4: age + diagnosed year + detection by screening + cancer stage

We used localized stage as the reference group for stage. Moreover, we also tried to add adjustment for treatment as below,

Model 5: age + diagnosed year + detection by screening + cancer stage + treatment

In treatment, surgery, radiotherapy and chemotherapy were classified as yes or no including unknown, regardless of the type of surgery, type and dose of radiotherapy, or regimens of chemotherapy (reference group: women who underwent surgery, radiotherapy and chemotherapy). Differences were considered as statistically significant if *p* values were less than 0.05 by two-sided test. Data management and statistical analyses were conducted with STATA (StataCorp, 2006).

Results

Table 1 presents the characteristics and relative 5-year survival data for cervical cancer cases. For all cases, the average age was 54.3 years (standard error (SE) 0.1) and the proportion of cases detected by screening was only 3.1% during 1975-1999 (2.1% in <30 years/4.3% in 30-54/3.1% in 55-64/0.9% in 65+, *p*<0.01). The 5-year survival decreased gradually with higher age (88.3%/77.6%/66.6%/52.8%), as did the proportion of the localized stage (83.2%/66.6%/50.6%/42.5%, *p*<0.01). Among cases with localized disease/those who underwent only surgery, the survival decreased at higher ages: the survival among the 30-54 year old was obviously higher than those 55-64 years old/65 years old and over (91.8%/85.6%/74.6% in localized stage and 97.0%/90.1%/85.3% in only surgery, *p*<0.01).

The age-specific RER of death for cervical cancer was significantly higher for both groups of women aged 55-64 years and those aged 65 years and over compared with those aged 30-54 years (RER, 1.58 and 2.51; 95% confidence interval [CI], 1.43-1.74 and 2.30-2.73) (Table 2, Model 1). The RER decreased slightly after adjusting for diagnosed year (Model 2), and also after adjusting for diagnosed year and detection by screening (Model 3). Adding adjustment for cancer stage at diagnosis, the RER among the 55-64 year old decreased to 1.16 (95% CI 1.05-1.28), and also in the 65 year old and over to 1.63 (95% CI 1.49-1.79) (Model 4). The stage-specific RER increased from 5.60 to 19.51 for a more advanced stage at diagnosis; therefore, cancer stage at diagnosis was found

Table 1. Characteristics and Relative 5-year Survival for All Cervical Cancer Cases

	<30 years old		30-54 years old		55-64 years old			65+ years old		
	Number	Survival	Number	Survival	Number	Survival	P-value***	Number	Survival	P-value
Total	190	88.3 (2.0)**	5,111	77.6 (0.6)	2,161	66.6 (1.1)	<0.01	2,586	52.8 (1.1)	<0.01
Diagnosed year										
1975-1979	19 (10.0)	--	1,143 (22.4)	74.0 (1.3)	482 (22.3)	59.0 (2.4)	<0.01	429 (16.6)	48.3 (2.8)	<0.01
1980-1984	29 (15.3)	--	1,276 (25.0)	80.3 (1.1)	496 (23.0)	68.7 (2.1)	<0.01	514 (19.9)	52.8 (2.5)	<0.01
1985-1989	28 (14.7)	--	981 (19.2)	79.8 (1.3)	418 (19.3)	72.6 (2.2)	<0.01	542 (21.0)	52.3 (2.4)	<0.01
1990-1994	56 (29.5)	91.1 (2.7)	848 (16.6)	80.9 (1.3)	345 (16.0)	69.4 (2.4)	<0.01	485 (18.8)	56.4 (2.5)	<0.01
1995-1999	58 (30.5)	85.6 (3.6)	863 (16.9)	71.8 (1.5)	420 (19.4)	63.6 (2.3)	<0.01	616 (23.8)	53.3 (2.2)	<0.01
Detection by screening										
Yes	4 (2.1)*	--	220 (4.3)	93.5 (1.5)	67 (3.1)	88.5 (3.4)	0.18	24 (0.90)	--	-
No	186 (97.9)	88.0 (3.0)	4,891 (95.7)	76.9 (0.7)	2,094 (97)	65.9 (1.1)	<0.01	2,562 (99.1)	52.3 (1.1)	<0.01
Cancer stage										
Localized	158 (83.2)	94.0 (1.5)	3,406 (66.6)	91.8 (0.5)	1,094 (50.6)	85.6 (1.1)	<0.01	1,098 (42.5)	74.6 (1.6)	<0.01
Regional	23 (12.1)	--	1,161 (22.7)	47.4 (1.5)	776 (35.9)	49.2 (1.8)	0.43	1,074 (41.5)	40.1 (1.7)	<0.01
Distant	1 (0.5)	--	162 (3.2)	8.2 (2.5)	97 (4.5)	9.6 (3.6)	0.76	164 (6.3)	6.6 (2.6)	0.65
Unknown	8 (4.2)	--	382 (7.5)	74.4 (2.2)	194 (9.0)	58.7 (3.7)	<0.01	250 (9.7)	42.6 (3.6)	<0.01
Treatment										
S + R + C	11 (5.8)	--	662 (13.0)	55.2 (2.0)	346 (16.0)	64.0 (2.8)	<0.05	211 (8.2)	55.9 (3.8)	0.87
S + R	19 (10.0)	--	981 (19.2)	73.6 (1.5)	452 (20.9)	70.9 (2.4)	0.35	281 (10.9)	70.4 (3.4)	0.39
S + C	28 (14.7)	--	415 (8.1)	79.1 (2.2)	160 (7.4)	80.9 (3.8)	0.68	96 (3.7)	67.8 (5.9)	0.07
Surgery	88 (46.3)	96.5 (3.7)	2,170 (42.5)	97.0 (0.5)	455 (21.1)	90.1 (1.9)	<0.01	306 (11.8)	85.3 (2.9)	<0.01
R + C	4 (2.1)	--	266 (5.2)	30.9 (2.8)	253 (11.7)	41.0 (3.2)	<0.05	443 (17.1)	40.3 (2.7)	<0.05
Radiotherapy	2 (1.1)	--	337 (6.6)	47.4 (2.8)	356 (16.5)	54.3 (2.8)	0.08	920 (35.6)	52.8 (1.9)	0.11
Chemotherapy	0 (0.0)	--	29 (0.6)	--	25 (1.2)	--	-	104 (4.0)	8.5 (2.4)	-
No therapy	38 (20.0)	--	251 (4.9)	81.5 (2.9)	114 (5.3)	54.8 (5.2)	<0.01	225 (8.7)	20.7 (2.8)	<0.01

* Figures in parentheses are proportions of total number of patients; ** Standard errors; *** Relative 5-year survival was evaluated as compared with cases between 30 and 54 years old; S, Surgery; R, Radiotherapy; C, Chemotherapy

Table 2. The Estimated Relative Excess Risk (RER) for Cervical Cancer Cases

	Model 1		Model 2		Model 3		Model 4		Model 5	
	RER	95% CI *	RER	95% CI	RER	95% CI	RER	95% CI	RER	95% CI
Age										
30-54 years old	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
55-64 years old	1.58	1.43-1.74	1.57	1.42-1.73	1.56	1.41-1.72	1.16	1.05-1.28	0.98	0.89-1.08
65+ years old	2.51	2.30-2.73	2.49	2.28-2.72	2.43	2.22-2.66	1.63	1.49-1.79	1.22	1.11-1.34
Diagnosed year										
1975-1979			1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
1980-1984			0.77	0.69-0.87	0.78	0.69-0.87	0.98	0.87-1.11	0.93	0.83-1.05
1985-1989			0.76	0.67-0.85	0.75	0.67-0.85	0.83	0.74-0.95	0.81	0.71-0.91
1990-1994			0.74	0.66-0.84	0.74	0.65-0.84	0.80	0.71-0.92	0.79	0.69-0.90
1995-1999			0.94	0.84-1.06	0.95	0.85-1.06	0.92	0.82-1.03	0.88	0.78-0.99
Detection by screening										
Yes					1.00	(ref)	1.00	(ref)	1.00	(ref)
No					4.18	2.66-6.56	2.70	1.76-4.15	2.19	1.43-3.35
Cancer stage										
Localized							1.00	(ref)	1.00	(ref)
Regional							5.60	5.04-6.22	3.53	3.17-3.93
Distant							19.5	17.0-22.4	10.3	8.91-11.9
Unknown							3.53	3.02-4.14	2.20	1.87-2.58
(1/df) Deviance **										
	4.06		1.88		1.22		1.29		1.21	

* Confidence interval; ** The deviance (1/df) is a measure of the model's goodness of fit

to be strongly and significantly associated with the prognosis. For women with cervical cancer of unknown stage, the risk was 3.53-fold as compared with a localized stage. After adding adjustment for treatment in model 5, the RER among women aged 55-64 years was no longer significantly higher than those aged 30-54 years (RER, 0.98; 95% CI, 0.89-1.08), whereas it was still obviously higher among women aged 65 years and over (RER, 1.22; 95% CI, 1.11-1.34).

Figure 1 indicates reducing age-specific differences after adjusting for prognostic factors, namely impact of prognostic factor effect. Among the 55-64 year old, the age-specific RER in model 1 has decreased only by 1.4% (1-ln1.57/ln1.58) in model 2 which shows the effect of diagnosed year, and also by 2.8% (1-ln1.56/ln1.58) in model 3 which shows the effect of diagnosed year and detection by screening. The RER has decreased by 67.6% (1-ln1.16/ln1.58) in model 4 which shows the effect of

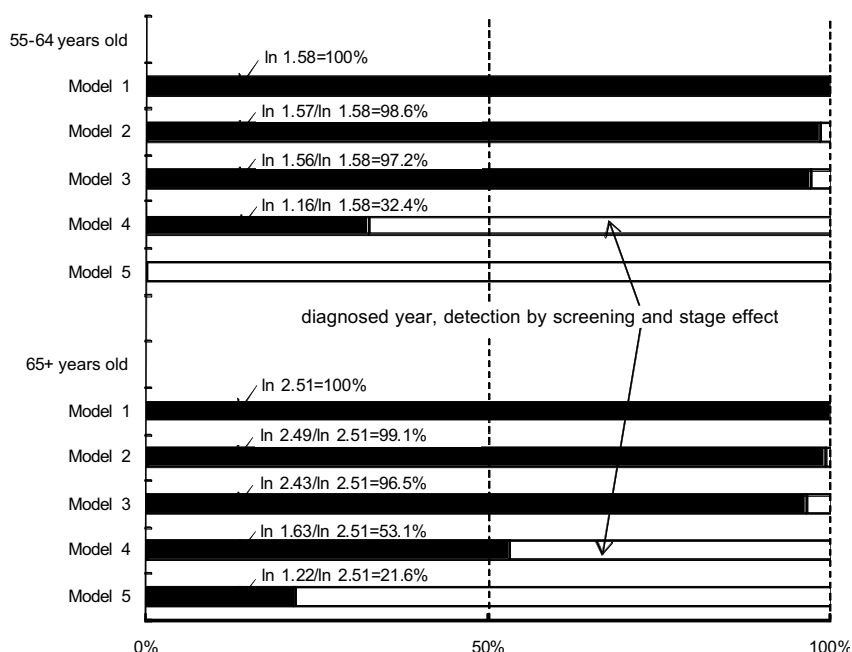


Figure 1. Reducing Age-specific Differences by Adjustment for Prognostic Factors

diagnosed year, detection by screening and cancer stage, and was almost equivalent to the reference in model 5 which shows the effect of diagnosed year, detection by screening, cancer stage and treatment. Also among the 65 year old and over, the RER in model 1 has decreased only by 0.9% ($1 - \ln 2.49 / \ln 2.51$) in model 2, by 3.5% ($1 - \ln 2.43 / \ln 2.51$) in model 3, by 46.9% ($1 - \ln 1.63 / \ln 2.51$) in model 4 and by 78.4% ($1 - \ln 1.22 / \ln 2.51$) in model 5.

Discussion

Decreased relative 5-year survival among the aged patients was attributable mainly to their advanced stage at diagnosis: The age-specific RER has decreased by 64.8% among the 55-64 year old as the effect of cancer stage at diagnosis, and by 43.4% among the 65 year old and over.

The difference of estimates of RER which has decreased with adjustment for cancer stage showed that cervical cancer patients aged 65 years and over still might have some other risk of death for cervical cancer as compared with patients aged 55-64 years, for example, more difficulty in applying complete therapy protocols because of complications associated with higher age. Elderly patients with malignancies in general are less likely to receive aggressive primary therapy than their younger counterparts. This trend has been observed for surgery, radiation and chemotherapy (Wright et al., 2005; Neugut et al., 2002; Mandelblatt et al., 2000; de Perrot et al., 1999). Therefore, decreased relative 5-year survival among the geriatric patients might be attributable mainly to not only their advanced stage at diagnosis but also limitation on the combination of treatment.

Our population-based study suggests that there are increasing demands for diagnosis at an earlier cancer stage especially in those aged 55 to 64 years. Screening programs have been offered by the municipal governments for citizens, and by employers for some workers.

According to recommendation of the Japanese Ministry of Health, Labor and Welfare, women over age 30 have been screened for cervical cancer every year since 1982, and then women over age 20 have been screened every two years since 2004. However, many women are not using these services in Japan including Osaka: the coverage of this nationwide screening program was only 20.8% among women aged 20 years and over in 2004 (Comprehensive Survey of the Living Conditions of People on Health and Welfare, http://www.dbtk.mhlw.go.jp/toukei/cgi/sse_kensaku). Widespread use of cervical screening has been associated with a substantial reduction in the incidence rate of and mortality from cervical cancer (Quinn et al., 1999; Macgregor et al., 1994). We, therefore, need to improve the nationwide cervical cancer screening program in order to increase coverage and the number of earlier diagnosis. For example, a tailored outreach intervention (Marcus et al., 1998; Dietrich et al., 2007; Wagner et al., 2007; Agurto et al., 2006) may be useful for women who do not follow the screening recommendations, as they tend to be diagnosed at a more advanced stage and be symptomatic at the time of diagnosis (Sung et al., 2000; Leyden et al., 2005).

As reported in our prior study, a limitation of this study is that the reporting of cancer diagnoses to the cancer registry by medical institutions was incomplete, because the proportion of DCO cases for cervix uteri in OCR was higher than that in North American or northern/western European registries. Furthermore, there is some difference in the degree of its completeness by age. The DCO % was higher with increasing age; therefore, the survival for cervical cancer might have been underestimated in our study. We need to reanalyze the association between cervical cancer survival and age when notifications reach a satisfactory level of completeness. The proportion of detection by screening also might be underestimated as, in Japan, there is no system to catch the information

whether patients diagnosed as cancer were detected by screening or not. Other limitation is in the generalization of these study findings, since this study was based on the OCR database only. It is necessary to ascertain from nationwide cancer registry data whether or not similar problems exist in other areas in Japan.

Despite some limitations inherent in our study, decreased relative 5-year survival was caused mostly by their advanced stage at diagnosis among the aged patients. The authors consider that cervical cancer screening in Japan should be performed as an organized screening with effective outreach interventions to increase the detection of earlier stage disease at the time of diagnosis and to improve the survival for cervical cancer patients.

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