Population and Prevention Science

Cancer Research

Epidemiologic and Clinical Analysis of Cervical Cancer Using Data from the Population-Based Osaka Cancer Registry

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Abstract

Cervical cancer screening rate is extremely low and the governmental recommendation of HPV vaccine has been suspended for 5 years in Japan. Here, we utilized data from the Osaka Cancer Registry, collected between 1976 and 2012, to evaluate cervical cancer trends in Japan. Age-adjusted incidence, relative survival, and conditional survival rates were calculated using multiple imputation methods and period analyses in 25,826 cervical cancer cases. Association of survival rates and clinical factors, including patients' age, clinical stage, and treatment procedures, were also analyzed. A trend for significantly decreasing age-adjusted incidence of cervical cancer (per 100,000) began in 1976 but reversed after 2000, increasing significantly to date (annual percent change = 3.8, 95% confidence interval, 2.7–4.8; age-adjusted rate: 28.0 in 1976, 9.1 in 2000, 14.1 in 2012). The 10-year relative survival rate improved significantly after 2002, especially in cases of "localized" and "adjacent organs" disease; this was likely due to the introduction of concurrent chemotherapy and radiation. The conditional 5-year relative survival rate improved significantly yearly until the fourth survival year. In the surgery-based group, we observed no age-dependent differences in outcomes. Unexpectedly, however, prognosis for younger age groups was poorer in the radiation-based treatment group. These results indicate that although relative survival rates have recently increased, treatment for more advanced cases with distant metastasis requires further improvement. In addition, this study is the first to suggest that age might be an important predictor of radiotherapy resistance in cervical cancer.

Significance: A large-cohort analysis of cervical cancer cases reveals that age-adjusted incidence in Japan has increased since 2000 and that age may negatively correlate with resistance to radiotherapy.

Introduction

Because the etiology and onset mechanisms of cervical cancer are now relatively well known, it is clear that the vast majority of cervical cancer cases can be prevented by a combination of timely HPV vaccination and cervical cancer screening. As illustrated by some reports (U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2014 Incidence and Mortality Web-based Report. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and NCI, 2017. https://wonder.cdc.gov/cancer.html, Cancer Research UK. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk. Accessed August 18, 2018), the rates of diagnoses and deaths from cervical cancer continue to decline in the United States and United Kingdom, where cervical cancer screening rates are relatively high. The prevention effectiveness of the HPV vaccine has also been reported (1).

In Japan, cervical cancer screening rate is extremely low, around 40% (Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan. https://ganjoho.jp/en/index.html. Accessed August 18, 2018.), and Japan's HPV vaccination program is currently at a standstill, clearly due to a suspension in 2013 of the Ministry of Health, Labor and Welfare (MHLW) recommendation for HPV vaccination following repeated media reports of so-called adverse events. Understanding of the emerging epidemiologic trends of cervical cancer in Japan under these current dismal clinical conditions and conducting an evaluation of the clinical attitudes regarding the disease are critical to our efforts to effectively decrease future morbidity and mortality from cervical cancer.

The Osaka Prefecture of Japan has a population of 9,000,000, constituting nearly one-tenth of all of Japan, with its population being nearly equal to that of all of Sweden. The Osaka Cancer Registry database has been registering patients with cancer since 1962, with an accurate record of patient survival beginning in 1975.

Main treatment strategy for cervical cancer consisted of surgery and radiation, however, concurrent chemotherapy and

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radiation [concurrent chemoradiotherapy (CCRT)] has been introduced recently to improve survival outcome of cervical cancer cases.

In this survey, we collected data of the Osaka Cancer Registry for cervical cancer cases registered from 1976 to 2012, which should give us the breadth and depth to better understand our current and future status for cervical cancer prevention and treatment here in Japan.

Trends in age-adjusted incidence and relative survival in association with various treatments were analyzed in this study. The conditional 5-year survival rate, which is the 5-year survival of the patients who are alive 1–4 years after diagnosis, was also analyzed. It can be useful information for patients because the conditional 5-year survival rate can present subsequent 5-year survival rates to patients who survived for more than 1 year.

Materials and Methods

Data sources

In this survey, first, we collected data of the Osaka Cancer Registry, consisting of 50,365 cases registered as C53 (cervical cancer), C54 (corpus cancer) and C55 (uterus/NOS), from 1976 to 2012. The cases of C55 (uterus/NOS) actually developed from uterine cervix or corpus. Subsequently, the 3,804 cases of C55 (uterus/NOS) were sorted to C53 (cervical cancer) or C54 (corpus cancer) depending on stage, age class, diagnosis period, and histologic type by "multiple imputation", a method of estimating missing values by an imputation model and analyzing by substituted plural datasets. This model has recently been applied to clinical research and epidemiologic research (2–4). In case of the rate of missing value being over around several percent, estimation of missing values by an imputation model may be applied.

The age-adjusted incidence rate was calculated using cases diagnosed from 1976 to 2012. The 5-year and 10-year survival rates were calculated for the cases diagnosed from 1976 to 2010. Among these, for the recent cases diagnosed from 2003 to 2010, we calculated more up-to-date long-term 10-year survival by period analysis (5, 6).

Variables

Stages of disease were classified as "localized" (T1N0M0), "regional lymph nodes" (N1), "adjacent organs" (T2, 3, 4), and "distant" metastasis (M1). Primary treatments were classified into two groups, as follows: surgery-based group (which included three subsets: surgery, surgery + radiation, surgery + radiation + chemotherapy); radiation-based group (which included radiation, radiation + chemotherapy). We excluded from our analysis of association of treatment procedures and other variables any patients whose treatment procedures were unknown.

Statistical analysis

We used STATA MP 13 (Stata Corp) for the statistical analysis. Age-standardized incidence rate was calculated per 100,000 population. We made adjustments regarding age distribution using the population pyramid for 1985 as the standard population (model population). We applied the piece-wise log linear regression model and showed trends for age-adjusted incidence rates by using the Joinpoint 4.2.0.2 package (National Cancer Institute. Joinpoint Regresssion Program Ver. 4.2.0.2 2015. http://surveillance.cancer.gov/joinpoint/. Accessed June 1, 2015; ref. 7). Relative survival was calculated as the ratio of the observed survival (overall survival) and the survival that would have been expected if the patient with cancer had only experienced the normal (background) mortality of the general population in which they lived (8). Relative survival by histology, stage, age, and treatment was analyzed. Relationship between the number of cases by disease spread, age, and treatment procedure was also analyzed.

Furthermore, we estimated conditional 5-year relative survival, which is the 5-year relative survival rate corresponding to the elapsed years after diagnosis. For the statistical analysis based on the relative survival setting, we applied the excess hazard model (9).

Results

Characteristics of cervical cancer cases registered in Osaka during 1976–2012

The study subjects we analyzed are characterized in Table 1. The number of cervical cancer cases per population per year changed over time, initially decreasing year to year, then changing around 2000 to a trend of increase (Age-adjusted rate: 28.0 in 1976, 9.1 in 2000, 14.1 in 2012). The cases that were registered as disease in "adjacent organs" or "distant" showed more of an increasing trend compared with "localized" or as "regional lymph nodes" cases. In addition, the proportion of tumors that were adenocarcinoma was increasing over this period.

Conversion to a trend for significant increase in age-adjusted incidence rate

To evaluate actual cervical cancer trends, the age-adjusted incidence rate was analyzed using the model population group of 1985 Japan. The results of our Joinpoint regression analysis of the data are shown in Fig. 1. The age-adjusted incidence-rate per

Table 1. Annual changes in number of cervical cancer cases by tumor stage (1976–2012)

	Number of cases							
	Localized	Regional lymph nodes	Adjacent organs	Distant	SCC	Adeno	Others	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*N*
1976–1980	2,662 (56)	651 (14)	1,098 (23)	321 (7)	3,190 (67)	192 (4)	1,350 (29)	4,732
1981–1985	2,660 (61)	578 (13)	840 (19)	275 (6)	3,414 (78)	227 (5)	712 (17)	4,353
1986–1990	2,013 (58)	390 (11)	802 (23)	296 (8)	2,654 (76)	229 (7)	618 (17)	3,501
1991–1995	1,471 (51)	249 (9)	856 (30)	324 (12)	2,032 (70)	258 (9)	610 (21)	2,900
1996–2000	1,212 (46)	239 (9)	865 (33)	294 (11)	1,727 (66)	293 (11)	590 (23)	2,610
2001–2005	1,350 (47)	187 (7)	972 (34)	364 (13)	1,776 (62)	462 (16)	635 (22)	2,873
2006–2010	1,489 (45)	157 (5)	1,207 (37)	433 (14)	2,245 (68)	578 (18)	463 (14)	3,286
2011–2012	754 (48)	73 (5)	535 (34)	209 (13)	1,119 (71)	271 (17)	181 (12)	1,571
Total	13,611 (53)	2,524 (10)	7,175 (7)	2,516 (10)	18,157 (70)	2,510 (10)	5,159 (20)	25,826

NOTE: The number of cervical cancer cases per population per year changed over time, from decrease to increase. The proportion of tumors that were adenocarcinoma was increasing over this period.

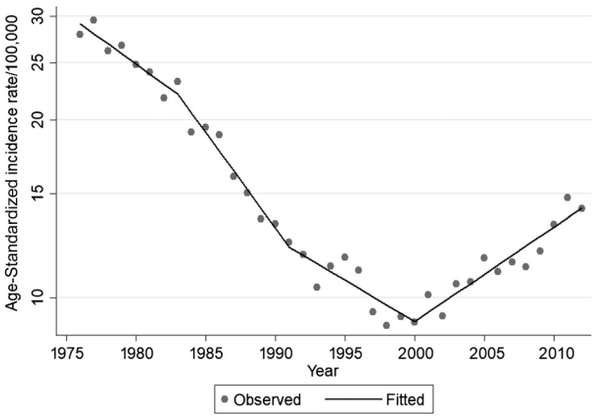

Figure 1.

Age-adjusted incidence rate (1976–2012, invasive cervical cancer). Age-adjusted incidence rate of cervical cancer was analyzed using the Japanese model population for 1985. APC = −3.9* [−5.6 to −2.1] (1976–1983), −7.2* [−9.0 to −5.2] (1983–1991), −3.2* [−5.1 to −13] (1991–2000), 3.8* [2.7 to 4.8] (2000–2012). *, significant increase/decrease.

100,000 significantly decreased over the first three study periods, from 1976 to 1983 [annual percent change (APC) = −3.9, 95% confidence interval (CI), −5.6 to −2.1], 1983 to 1991 (APC = −7.2, 95% CI, −9.0 to −5.2), and 1991 to 2000 (APC = −3.2, 95% CI, −5.1 to −1.3), but it converted to a trend for significant increases in incidence after 2000 (APC = 3.8, 95% CI, 2.7–4.8).

Improved relative survival by period

The 5-year and 10-year relative survival rates were calculated by period (Table 2; Supplementary Fig. S1). Compared with the earliest period studied, 1976 to 1986, the 10-year relative survival rates for the next two time periods, 1987–1994 and 1995–2002, were relatively unchanged. However, period analysis, using the most recent data for 2003 to 2010, showed that the 5-year relative survival rate was 64.3% (95% CI, 62.7%–65.8%) and the 10-year relative survival rate was 59.6% (95% CI, 57.9%–61.3%), indicating a modern-day significant improvement in the prognosis of patients with cervical cancer, compared with the three periods examined prior to 2002.

The 5-year and 10-year relative survival rates for each clinical stage of tumor are also shown in (Table 2; Supplementary Fig. S1). The 10-year relative survival rates of cases registered from 2003 to 2010 as "localized" or "adjacent organs" were those most significantly improved compared with similar cases before 2002 (87.1% (95% CI, 84.8%–89.1%), 42.6% (95% CI, 39.3%–45.8%).

To clarify the relationship between these improvements of prognosis of "localized" cases and the change of adjuvant therapy after surgery as primary treatments, we analyzed the number of cases that received "surgery + radiation" or "surgery + radiation + chemotherapy," including CCRT. In the "localized" cases, the proportion of cases using chemotherapy as an adjuvant treatment to surgery and radiation increased from 33% (669/2,047) in the years 1976–2002 to 64% (185/288) in the most recent period studied (2003–2010; $P < 0.001$; Supplementary Table S1). Cases where the tumor had invaded into adjacent organs exhibited a similar tendency for increased use of chemotherapy in the primary

Table 2. Ten-year relative survival rate by periods (1976–2010, invasive cervical cancer)

	Total			Localized			Regional lymph nodes			Adjacent organs			Distant		
		Relative survival rate			Relative survival rate			Relative survival rate			Relative survival rate			Relative survival rate	
Period	*n*	5-year	10-year	*n*	5-year	10-year	*n*	5-year	10-year	*n*	5-year	10-year	*n*	5-year	10-year
1976–1986	9,909	56.8 (55.6–58.1)	52.3 (51.0–53.6)	5,835	79.9 (78.3–81.4)	76.1 (74.3–77.8)	1323	40.8 (37.3–44.4)	33.4 (29.9–37.0)	2,090	27.1 (24.8–29.4)	21.2 (18.9–23.6)	661	4.1 (2.5–6.3)	1.9 (0.8–3.8)
1987–1994	4,966	58.6 (56.9–60.3)	54.0 (52.2–55.7)	2,705	83.4 (81.1–85.5)	79.8 (77.3–82.1)	494	45.5 (40.1–50.8)	35.9 (30.6–41.3)	1,283	35.8 (32.5–39.2)	28.9 (25.6–32.3)	484	5.1 (3.0–8.0)	3.2 (1.5–6.0)
1995–2002	4,297	56.8 (55.1–58.5)	52.7 (50.9–54.4)	1,980	84.5 (82.1–86.7)	81.5 (78.8–83.9)	357	47.8 (41.4–53.8)	40.8 (34.5–47.0)	1,442	39.1 (36.0–42.3)	33.3 (30.2–36.4)	500	3.5 (2.0–5.8)	1.7 (0.6–3.7)
2003–2010	5,204	64.3 (62.7–65.8)	59.6 (57.9–61.3)	2,389	90.4 (88.5–92.1)	87.1 (84.8–89.1)	291	59.6 (52.3–66.2)	52.1 (44.5–59.1)	1,856	50.3 (47.3–53.2)	42.6 (39.3–45.8)	677	6.9 (4.6–9.7)	2.9 (1.3–5.7)

NOTE: The 10-year relative survival rates of cases registered from 2003 to 2010 as "localized" or "adjacent organs" were those most significantly improved compared with similar cases before 2002 [87.1% (CI, 84.8–89.1%); 42.6% (CI, 39.3–45.8%)]. 95% CI values are in parentheses.

treatment. The proportion of cases using chemotherapy as the primary treatment in addition to radiation has also increased from 37% (713/1,919) in the years 1976–2002 to 52% (390/744) in the most recent period studied (2003–2010; $P < 0.001$). Following primary surgical treatment, rather than radiation alone, CCRT has been used increasingly in recent years as an adjuvant therapy following primary surgery for cases of localized disease and as a primary treatment for cases where the tumor had invaded only into adjacent organs. Unfortunately, the relative survival of cases of "distant" metastasis, which were not expected to be cured by CCRT or surgery, has not significantly improved over the study period (1976–1986: 1.9% (95% CI, 0.8%–3.8%); 2003–2010: 2.9% (95% CI, 1.3%–5.7%).

Improved conditional 5-year relative survival until the fourth year

The conditional 5-year relative survival rates for patients with all tumor stages were calculated (Fig. 2). In 1976–2002, the longer the time after diagnosis, the higher got the conditional 5-year relative survival after diagnosis. In our period analysis, using the most recent data (from 2003 to 2010), the conditional 5-year relative survival rate improved significantly each year, up until the fourth year [Initial: 64.3% (95% CI, 62.7%–65.8%); first year: 74.9% (95% CI, 73.3%–76.5%); second year: 82.7% (95% CI, 81.1%–84.2%); third year: 87.2% (95% CI, 85.6%–88.7%); fourth year: 90.6% (95% CI, 89.0%–92.0%)].

Age-adjusted incidence rate by histology and age group

The age-adjusted incidence rates for cases that were diagnosed as squamous cell carcinoma (SCC) or adenocarcinoma were calculated for age groups of "39 or younger," "40–59," and "60 or over" (Fig. 3). For SCC cases of the age groups "39 or younger" and "40–59," although the age-adjusted incidence rates per 100,000 decreased significantly from 1976 up until 2000, starting in 2000 the trend reversed direction, leading to significant increases from 2000–2010 (APC = 5.9, 95% CI, 5.9–8.1; APC = 6.5, 95% CI, 4.8–8.2). In the age group of "60 or older" the age-adjusted incidence rate started to increase after 2002 (APC = 2.0, 95% CI, −0.3–4.2).

For adenocarcinoma cases in the age group of "39 or younger," the age-adjusted incidence rate has consistently and significantly increased over the 26-year study period (APC = 5.0, 95% CI, 3.9–6.0). The age-adjusted incidence rate in the adenocarcinoma cases aged "40–59" was flat until 1998, but it increased significantly thereafter (APC = 6.6, 95% CI, 4.3–9.0). Within the age group of "60 or over," there was a decreasing trend until 1993, but this turned to a significant increase after 1993 (APC = 4.3, 95% CI, 2.0–6.7).

Worse relative survival in the older age group in both SCC and adenocarcinoma

The results of comparing the 5-year relative survival rates by histologic type and age group are shown in Table 3 and Supplementary Fig. S2. In the SCC cases, the prognosis was significantly better in the younger age group [0–39: 86.4% (95% CI, 84.8%–87.8%); 40–59: 71.3% (95% CI, 70.1%–72.4%); 60+: 60.8% (95% CI, 59.3%–62.2%)]. In the adenocarcinoma cases, the prognoses for the age group of "39 or younger" and "40–59" were significantly better than that for the group of "60 or older" [0–39: 68.0% (95% CI, 62.6%–72.8%); 40–59: 63.5% (95% CI, 60.5%–66.4%); 60+: 44.6% (95% CI, 40.3%–48.7%)].

For cases of SCC, the proportion of advanced cases, compared with localized case, has increased from 21% (613/2,930) in the "39 or younger" cases through 38% (3,108/8,146) in the "40 –59" group to 56% (3,939/7,081) in the "60 or older" cases significantly ($P < 0.001$, respectively). For adenocarcinoma cases, it has increased from 35% (147/416) in the "39 or younger" cases through 42% (550/1,314) in the "40–59" group ($P = 0.054$) to 60% (467/780) in the "60 or older" cases significantly ($P < 0.001$; Supplementary Table S2). Our finding that both SCC and adenocarcinoma cases showed a trend for poorer prognosis with older age (Table 3) parallels the proportion of advanced cases that increased significantly with age.

Better relative survival in the younger age group in both localized and advanced stages

We analyzed the relative survival rates for each age group, after dividing the SCC and adenocarcinoma cases into localized and advanced groups (Table 3; Supplementary Fig. S2). The number of cases with data for 10-year relative survival in each group was too small for a detailed analysis; so instead, we calculated 5-year relative survival rates, including the latest data for cases registered

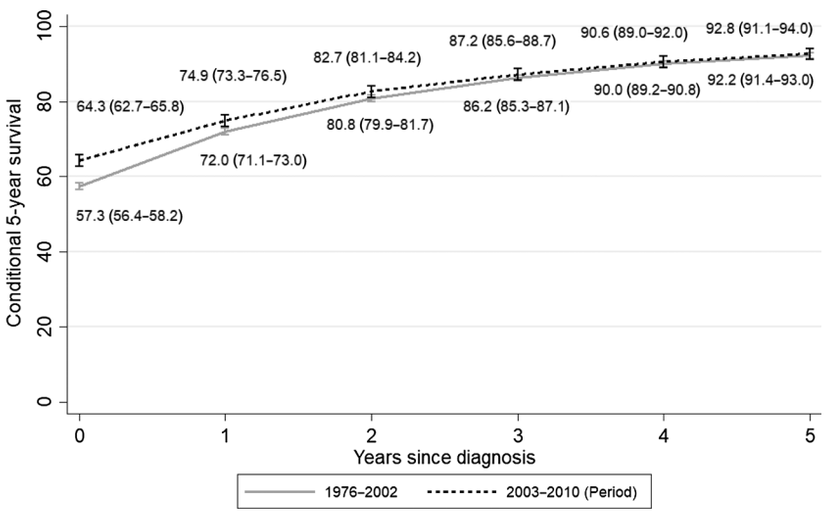

Figure 2.
Conditional 5-year survival rate (1976–2010, invasive cervical cancer).

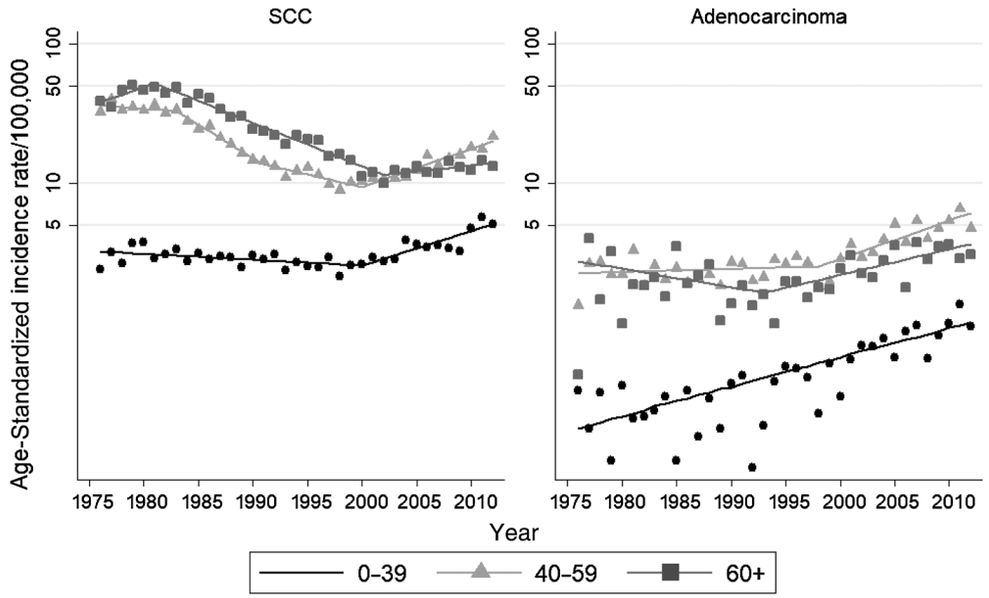

Figure 3.

Age-adjusted incidence rate of SCC and adenocarcinoma of the cervix by age group. SCC: Age 0–39: APC = −1.0* [−1.0 to −1.8] (1976–2000), 5.9* [5.9–8.1] (2000–2012); age 40–59: APC = −1.4* [−3.8 to −1.1] (1976–1983), −10.5* [−13.0 to −7.9] (1983–1991), −4.0* [−7.0 to −1.0] (1991–2000), 6.5* [4.8–8.2] (2000–2012); age 60+: APC = 6.3* [0.5 – 12.6] (1976–1981), −7.0* [−7.6 to −6.3] (1981–2002), 2.0 [−0.3–4.2] (2002–2012). Adenocarcinoma: Age 0–39: APC = 5.0* [3.9–6.0] (1976–2012); age 40–59: APC = 0.5 [−0.9–1.9] (1976–1998), 6.6* [4.3–9.0] (1998–2012); age 60+: APC = −3.0 [−6.9–1.0] (1976–1993), 4.3* [2.0 – 6.7] (1993–2012). *, significant increase/decrease.

up to 2010. In localized cases of SCC, the younger the age group, the significantly better was the prognosis [0–39: 95.3% (95% CI, 94.0%–96.3%); 40–59, 89.4% (95% CI, 88.3%–90.5%); 60+: 83.1% (90% CI, 81.0%–85.0%)]. In more advanced cases of SCC, the prognosis of "39 or younger" cases was also significantly better than that of the "40–59" and "60 or older" groups [0–39: 53.1% (95% CI, 48.3%–57.7%); 40–59: 44.8% (95% CI, 42.8%–46.8%); 60+: 43.2% (90% CI, 41.2%–45.1%]. In localized cases of adenocarcinoma, the 5-year relative survival rate of the "60 or older" was significantly lower than that of the "40–59" [40–59: 87.6% (95% CI, 84.1%–90.3%); 60+: 77.5%, 95% CI, 69.4%–83.7%). For advanced cases of adenocarcinoma there was no significant difference in the poor 5-year relative survival rate between any of the age groups [0–39: 37.0% (95% CI, 28.3%–45.8%); 40–59: 33.0% (95% CI, 28.5%–37.5%); 60+: 23.7% (90% CI, 19.2%–28.5%)].

We divided the cases of localized disease into two groups based on primary treatment: surgery-based or radiation-based, and analyzed for patterns of usage and change in outcomes. In the SCC cases, the proportion of surgery-based cases compared with radiation-based cases has decreased from 98% (1,668/1,700) in the "39 or younger" cases through 90% (3,518/3,920) in the "40–59" group to 54% (1,310/2,430) in the "60 or older" cases significantly ($P < 0.001$, respectively). For adenocarcinoma cases, it was 97% (155/159) in the "39 or younger" cases and 95% (441/465) in the "40–59" group ($P = 0.54$), however, it decreased to 77% (144/186) in the "60 or older" cases significantly ($P < 0.001$; Supplementary Table S3). The finding that, overall, the prognosis tended to be better for younger cases of cervical cancer (Table 3; Supplementary Table S1) was in parallel with the fact that the proportion of cases where the primary treatment was surgery-based was increasingly higher with younger age.

Worse survival after radiation-based treatment in the younger age group

We focused on the cases of localized disease and calculated 5-year relative survival rates by age group and treatment (Fig. 4). We found that the prognosis of the surgery-based group was better than that of the radiation-based group at any age, and that, in the surgery-based group, there was no age-dependent difference in outcome. Interestingly, however, in the radiation-based group, the prognosis for the younger age groups tended to be poorer. The 5-year relative survival rate for the "40–59" group was significantly lower than for the "60 or older" group [60.6% (95% CI, 55.2–65.5) versus 69.1% (95% CI, 65.5–72.4)].

Table 3. Five-year relative survival rate by stage and age group (1976–2010, SCC and adenocarcinoma of the cervix)

	SCC (total)		Adeno (total)		SCC (by stage)				Adeno (by stage)			
					Localized		Others		Localized		Others	
Age group	*n*	5-year relative survival rate	*n*	5-year relative survival rate	*n*	5-year relative survival rate	*n*	5-year relative survival rate	*n*	5-year relative survival rate	*n*	5-year relative survival rate
0–39	2,677	86.4 (84.8–87.8)	359	68.0 (62.6–72.8)	2,132	95.3 (94.0–96.3)	545	53.1 (48.3–57.7)	198	86.4 (80.1–90.9)	130	37.0 (28.3–45.8)
40–59	7,706	71.3 (70.1–72.4)	1,188	63.5 (60.5–66.4)	4,803	89.4 (88.3–90.5)	2,903	44.8 (42.8–46.8)	690	87.6 (84.1–90.3)	498	33.0 (28.5–37.5)
60+	6,655	60.8 (59.3–62.2)	692	44.6 (40.3–48.7)	3,020	83.1 (81.0–85.0)	3,635	43.2 (41.2–45.1)	185	77.5 (69.4–83.7)	420	23.7 (19.2–28.5)

NOTE: Both SCC and adenocarcinoma cases showed a trend for poorer prognosis with older age. 95% CI values are in parentheses.

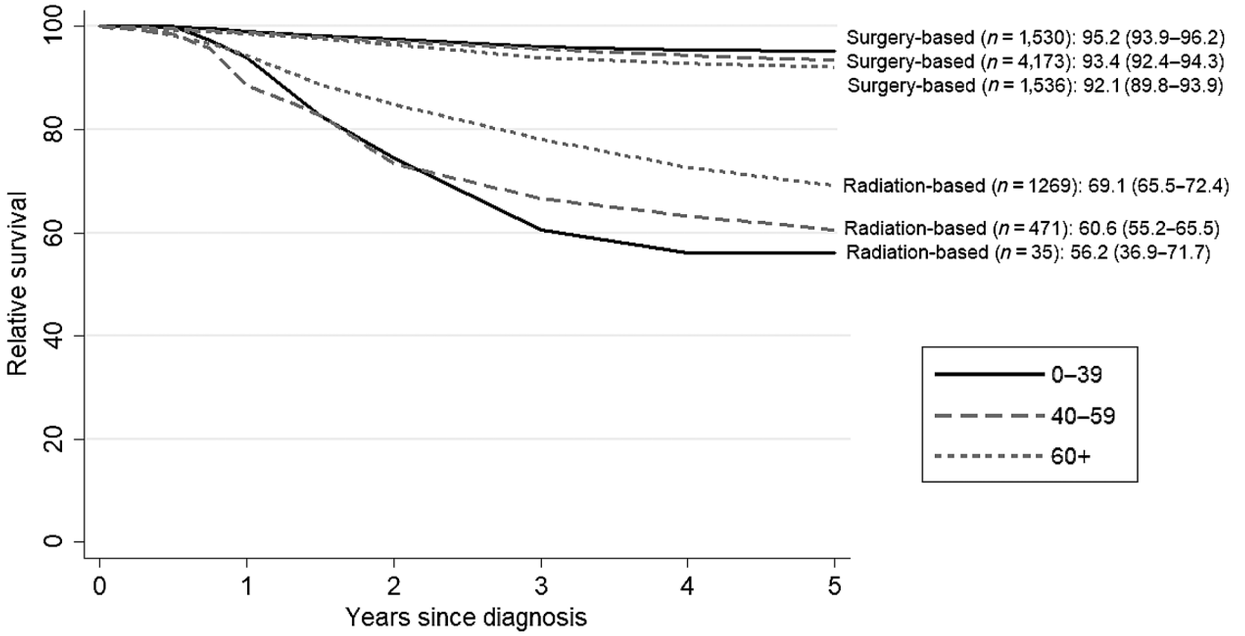

Figure 4.

Five-year relative survival rate by age group and treatment (1976–2010, localized cervical cancer). Surgery-based: surgery, surgery + radiation, surgery + radiation + chemotherapy; radiation: radiation, radiation + chemotherapy.

Discussion

We found that the age-adjusted incidence rate of cervical cancer has increased significantly since the year 2000 in Japan, and that the prognosis of cases where radiation was performed was worse than for cases where surgery was performed, especially significant for younger versus older cases.

In Japan, beginning in 2000, the age-adjusted incidence rate for cervical cancer has been increasing steadily over time (Fig. 1). This new trend has not been seen in any other advanced country. Changes in sexual lifestyle, the spread of HPV infection in ever younger women, and the consistently low rate of cervical cancer screening are all reflected in this deadly trend. HPV vaccination does not affect age-adjusted incidence rate of cervical cancer because HPV vaccine was introduced just in 2009. However, there has been little data of trend of high-risk HPV infection rate, slight difference of age-adjusted incidence rate between SCC and adenocarcinoma might be resulted from change of distribution of HPV types. Recent increase of SCC and consistent increase of adenocarcinoma in younger generation might reflect recent spread of HPV-16 and 18 infection in the young

The authors of the WHOIARC Monograph concluded that, after adjustment of confounders, there is sufficient evidence for establishing a causal relationship between smoking and SCC cervical cancer (WHOIARC Monograph on the Evaluation of Carcinogenic Risks to Humans. Vol 100E. Tobacco Smoke and Involuntary Smoking. 2012. http://monographs.iarc.fr/ENG/Monographs/vol100E/index.php. Accessed August 18, 2018). Similar conclusions were obtained by numerous researchers in Japan (10–13). According to a MHLW database of current state of nutrition in Japan, the rate of habitual smoking in twenties and thirties had been increasing from around 1995 and 2000, respectively, and turned downward recently. Increasing trend of cervical cancer incidence might be expected to decrease in near future (JAPAN HEALTH PROMOTION & FITNESS FOUNDATION. http://www.health-net.or.jp/tobacco/product/pd100000.html. Accessed August 18, 2018).

In recent years, the survival rate for cervical cancer has been improving significantly, especially for tumors that are localized or have only invaded into adjacent organs. In Japan, up until around 2000, the standard treatment for International Federation of Gynecology and Obstetrics (FIGO) stage IB-IIB cervical cancer was a radical hysterectomy followed by adjuvant radiotherapy. However, starting in 1999, it was shown that CCRT led to a significantly better prognosis than radiation alone (14–19). Subsequently in Japan, the guidelines for treatment of uterine cervical cancer were revised, and in the 2000 edition of those guidelines, CCRT was recommended as the primary treatment for FIGO stage IB2 to IIB cases and as the postoperative therapy for stage IB1 (20). It should be noted that the degree of tumor progression in the cancer registry used in this study was slightly different from the current FIGO classification system. Although a simple direct comparison of them is now next to impossible, the improvement of survival rate in Japan seen after 2003 (Table 2; Supplementary Fig. S1) is likely due in large part to the introduction of CCRT (Supplementary Table S1).

In cervical cancer, the conditional 5-year survival rate increases significantly over time (Fig. 2). Presenting this positive data to the patient can lead to better motivation for participating in post-treatment examinations and reduction of posttreatment anxiety.

In both SCC and adenocarcinoma disease, the proportion of advanced cases at diagnosis increased with age (Supplementary Table S2) and survival rate was poorer with increasing age (Table 3; Supplementary Table S1). These results were consistent with a previous report (21). Analyzing by stage, the 10-year relative

survival rate was clearly better for the younger generation, even in the localized or more advanced cases. Particularly in the localized cases, surgery-based treatment tended to be selected as the primary treatment in younger patients and radiation-based treatment tended to be selected as primary treatment in older patients (Supplementary Table S3). In contrast, Landoni and colleagues reported in 1997 that, in their large randomized study in Italy, the prognosis after surgery was equal to the prognosis for radiotherapy. They also reported that their surgery group had a higher rate of severe morbidity compared with the radiotherapy group of patients (28% vs. 12%; $P = 0.0004$; ref. 22). They acknowledged that the combination of surgery and adjuvant radiotherapy had the worst morbidity, especially urological complications.

To examine in detail the association between the choice of therapy and the prognosis by age, we limited our analysis to the data for localized cases and compared the 5-year relative survival rate by age group and primary treatment (Fig. 4). In the surgery-based cases, the 5-year relative survival rate was extremely high and there were no age-dependent differences in that rate. On the other hand, in our study, the radiation-based therapy cases showed a poorer prognosis than the surgery-based cases for all age groups. More interestingly, the radiation-based cases tended to have a better prognosis with higher age, especially the 5-year relative survival rate of the age group of "60 or older" was significantly better than "40–59". It seems very interesting that the prognosis of the radiation-based cases differed depending on age. A previous study also showed that the prognosis after radiotherapy for women younger than 50 tended to be worse than that of those older than 50 (23); although their result, unlike ours, was not statistically significant due to the small sample size in their study. Our current study is the first to demonstrate that age is an important predictor of sensitivity/resistance to radiotherapy other than tumor size and histologic type (20).

Estrogen and other hormones, and specific receptor subset levels, may be involved in the reduced radiation sensitivity of tumors in younger women, along with associated elevated DNA-damage repair responses. In this regard, it is interesting that phytoestrogens are being used for combined therapy to decrease the radiation dose delivered to patients and subsequent side effects and improve radiosensitivity, regardless of estrogen receptor status in breast cancer (24).

However, the current analysis was retrospective, and not randomized, so there is always the possibility that there was a bias for surgery in the younger patients to be selected for smaller tumors, and radiation was performed for larger tumors, even in "localized" cases and that radiation-based treatment was performed for both smaller and larger tumors of "localized" cases in the older patients. A prospective randomized study or at least a propensity score matching study will be required to resolve this question.

There are other limitations to this study. The time relationship of treatments was not always clear. It is unknown whether the cases in which radiation and chemotherapy were performed as the primary treatment received CCRT. Furthermore, although we speculated that publication of guidelines and the change of trend of therapy might be a reason for prognosis improvement, this was not shown directly.

In conclusion, in our current analysis we found that the age-adjusted incidence rate of cervical cancer has increased significantly since the year 2000 in Japan, which has been offset by an improvement in the relative survival rate, possibly due to the recommendation for CCRT. As far as localized cases, in our cohort, the prognosis of cases where radiation was performed was worse than for cases where surgery was performed, especially significant for younger versus older cases. Although further studies will be needed to confirm them, these findings should influence future treatment strategy choices here in Japan.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Ethics Statement

This study was approved by the Osaka University Medical Hospital and Osaka International Cancer Institute.

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