

Original Article



Conditional relative survival of cervical cancer: a Korean National Cancer Registry Study

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ABSTRACT

Objective: Conditional relative survival (CRS) considers changes in prognosis over time and may offer more useful estimates for survivors. We aimed to investigate CRS among patients with cervical cancer stratified by various factors that influence survival probability.

Methods: This nationwide retrospective study used data from the Korean Central Cancer Registry. We included 78,606 patients diagnosed with cervical cancer as their first cancer between January 1, 1996 and December 31, 2015, and who were followed until December 31, 2016. CRS and the conditional probabilities of death for the following 1 year were stratified by age at diagnosis, histology, cancer stage, treatment, year of diagnosis, and social deprivation index.

Results: The 5-year relative survival rate at the time of diagnosis was 80.6% for all cases. The probability of surviving an additional 5 years conditioned on having already survived 1, 2, 3, 4, and 5 years after diagnosis was 85.7%, 90.6%, 93.5%, 95.3%, and 94.3%, respectively. Patients with poorer initial survival estimates (older, advanced stage, non-squamous cell histology) generally showed the largest increases in CRS over time. Patients aged ≥ 70 years had the highest probability of death in the first year after diagnosis (24.5%), but the conditional probability of death in the 2nd, 3rd, 4th, and 5th years declined abruptly to 13.1%, 7.5%, 5.4%, and 3.9%, respectively.

Conclusions: The CRS rates for patients with cervical cancer improved over time, particularly among patients with poorer initial prognoses. Our estimates enable patients to make better informed decisions regarding follow-up care and their personal life.

Keywords: Cervical Cancer; Relative Survival; Conditional Survival; Korea

INTRODUCTION

Despite the decreasing incidence and mortality of cervical cancer, it remains a major public health issue worldwide, including in Korea. Cervical cancer is the 4th most common female cancer for both incidence and mortality, with age-standardized rates of 8.4 and 1.8 per 100,000 person-years, respectively [1]. In Korea, cervical cancer is the 6th most common female cancer, with age-standardized incidence and mortality rates of 8.7 and 1.7, respectively [2].

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: S.D.W., B.J., J.K.W.; Data curation: H.J., J.K.W.; Formal analysis: J.K.W., H.J.; Funding acquisition: J.K.W.; Investigation: H.J., J.K.W.; Methodology: S.D.W., B.J., J.K.W.; Project administration: S.D.W., J.K.W.; Software: H.J.; Supervision: B.J.; Writing - original draft: S.D.W., B.J.; Writing - review & editing: S.D.W., B.J., J.K.W.

Survival statistics are important to both patients and clinicians. In real-world practice, survival probabilities change significantly according to time elapsed after diagnosis. However, survival estimates are traditionally reported as survival from time of diagnosis to a certain time point, such as the 5-year relative survival (5YRS) rate. Although these relative survival estimates provide important information at the time of diagnosis, they might not be relevant to patients who have already survived a period of time after treatment.

Conditional relative survival (CRS) is a statistical method that reflects the dynamic nature of prognosis after cancer diagnosis. It describes the probability of a patient surviving a given time into the future (often 5 years) at various points during the cancer experience relative to the expected survival of the general population of the same age and sex. CRS considers changes in prognosis over time and may offer more useful estimates for survivors and clinicians [3].

Most previous studies on CRS in cervical cancer patients investigated a heterogeneous group of cancers arising at different subsites [3-6] and mainly reported CRS rates for the overall cervical cancer population without comprehensive stratification by patient characteristics, such as age, stage, histology, and year of diagnosis, which might affect survival probability. Several reports include stratification by age group [5,7] or disease stage [6,7], but to our knowledge, there are no comprehensive CRS analyses of cervical cancer that based on patient age, disease stage, histological characteristics, treatment, and year of diagnosis. Furthermore, studies are mostly from the US, Europe, or Japan, and no relevant data have been obtained in Korea.

Therefore, this study aimed to investigate the CRS among patients with cervical cancer based on Korea Central Cancer Registry (KCCR) data, with comprehensive stratification by various factors that influence survival probability.

MATERIALS AND METHODS

1. Data source and study population

The KCCR is a national cancer registry run by the Korean Ministry of Health and Welfare. The completeness and validity of KCCR data are evidenced by publication from volumes IX (1999–2002) to XI (2008–2012) of the “Cancer Incidence in Five Continents” [8]. The KCCR collects data on primary tumor site, histology, date of diagnosis, stage at diagnosis, treatment received during the 4 months after diagnosis, as well as patient age and sex.

From the KCCR, we included 78,606 patients who were diagnosed with cervical cancer as their first cancer between January 1, 1996 and December 31, 2015, and who were followed up until December 31, 2016.

2. Variables

Age at diagnosis was categorized as <40 years, 40–49 years, 50–59 years, 60–69 years, and ≥70 years. Year of diagnosis was classified into 1996–2000, 2001–2005, 2006–2010, and 2011–2015. Histology was categorized as squamous cell carcinoma (SCC) (International Classification of Disease (ICD) code: ICD-O-3: 8050–8130), adenocarcinoma (ICD-O-3: 8140–8147, 8160–8162, 8180–8221, 8250–8506, 8520–8550, 8570–8573, and 8940–8941), unspecified (ICD-O-3: 8000–8004), and others. Stage at diagnosis, which was available after

January 1, 2005, was classified as localized, regional, distant, or unknown using Surveillance, Epidemiology, and End Results (SEER) staging criteria. Treatment information was available as receipt of surgery, chemotherapy, or radiotherapy during the first 4 months after diagnosis, but the intent of each treatment type could not be identified. Those who received surgery and either chemotherapy or radiation therapy were likely receiving adjuvant therapy. Those who received chemotherapy and radiation would be those who received chemoradiation as the primary treatment. Those who received either chemotherapy or radiotherapy only or who did not receive any treatment are most likely those on palliative treatment.

Relative area deprivation based on Carstairs method [9] was used to presenting area-level social disparity. Areal deprivation was categorized into quintiles, with the 1st the wealthiest area among the five subgroups and the 5th being the poorest area.

3. Statistical analysis

Relative survival was defined as the ratio of observed survival among the studied cancer cases to the expected survival of a general population with the same sex, age, and year of death. Relative survival was estimated using an excess rate model, in which the observed mortality rate was assumed to be the sum of the expected mortality rate and the excess mortality rate, i.e., mortality from cancer. The information for expected mortality rate in the general population was obtained from Statistics Korea.

The CRS is defined as the probability of surviving an additional y years given that a patient had already survived x years. Thus, the CRS for another y years can be expressed as

$$CRS(y|x) = \frac{S(x+y)}{S(x)}$$

where $S(x)$ is the relative survival at time x . For example, the 5-year CRS for a patient who has already survived 3 years is computed as the ratio of the relative survival at 8 years divided by the relative survival at 3 years. In our study, the 5-year CRS was conditioned on 1 through 5 years survived after diagnosis.

The 5YRS and 5-year CRS were computed within strata defined by age group (<40, 40–49, 50–59, 60–69, and ≥ 70 years), disease stage (localized, regional, distant, and unknown), histology (SCC, adenocarcinoma, adenosquamous, and others), and year of diagnosis (1996–2000, 2001–2005, 2006–2010, and 2011–2015). Relative survival was modeled using the life table method [10], and we calculated the conditional probabilities of death for the following 1 year according to age group and survival time since diagnosis.

To examine the relative impact of each baseline characteristic on survival based on time period already survived, we estimated the relative excess risk (RER) and its 95% confidence interval (CI) of baseline characteristics with all patients at baseline, patients surviving 2 years ($n=64,976$), and patients surviving 5 years ($n=50,773$). All significance tests were two-sided, and p -values <0.05 were considered statistically significant. All analyses were conducted using Stata version 15.0 (StataCorp LP, College Station, TX, USA).

RESULTS

1. Baseline characteristics

A total of 78,606 patients with cervical cancer was evaluated. Their baseline characteristics are presented in **Table 1**. The most frequent age range at diagnosis was 40s, followed by 50s, and <40 years. SCC accounted for 79.5% of diagnosis, and the incidence of cervical cancer was declining during the study period. Information on SEER stage was available in 39,649 patients, for whom it was localized in 22,014 (55.5%) patients, regional in 10,411 (26.2%) patients, and distant in 2,836 (7.2%) patients. Overall, 36.7% and 30.4% of patients were from the wealthiest and second wealthiest quintile area group, respectively.

2. Relative survival and CRS

The 5 and 10YRS rates as well as the 5-year CRS at 1 to 5 years after diagnoses are presented in **Table 2**. The 5-year CRS rates according to age group, stage, histological type, treatment received, year of diagnosis, and level of social deprivation are depicted in **Fig. 1**.

Table 1. Baseline characteristics of Korean cervical cancer patients, 1996–2015

Variables	No. of patients (%)	Patients available for CRS after year	
		2	5
Total	78,606 (100.0)	64,976	50,773
Age (yr)			
<40	16,155 (20.6)	14,396	11,939
40–49	21,767 (27.7)	19,243	15,647
50–59	16,839 (21.4)	14,193	11,027
60–69	13,106 (16.7)	10,817	8,380
≥70	10,739 (13.7)	6,327	3,780
Histology (ICD-O-3)			
SCC	62,460 (79.5)	52,567	41,650
Adenocarcinoma	9,159 (11.7)	7,430	5,301
Adenosquamous	1,840 (2.3)	1,557	1,177
Others	3,445 (4.4)	2,243	1,792
Unknown	1,702 (2.2)	1,179	863
Stage at diagnosis (since 2005, n=39,649)			
Localized	22,014 (55.5)	19,032	12,830
Regional	10,411 (26.2)	7,770	4,496
Distant	2,836 (7.2)	1,126	443
Unknown	4,388 (11.1)	3,341	2,534
Treatment received			
Surgery	33,380 (42.5)	31,039	25,888
Surgery + (chemo or radiation)	13,511 (17.2)	11,334	8,086
Chemo + radiation	8,438 (10.7)	6,211	3,974
Others (chemo only, radiation only, no treatment)	23,220 (29.6)	16,335	12,778
Year of diagnosis			
1996–2000	22,068 (28.1)	19,022	17,143
2001–2005	20,680 (26.3)	17,949	16,261
2006–2010	18,656 (23.7)	16,118	14,544
2011–2015	17,202 (21.9)	11,887	2,825
Deprivation index			
1 (Wealthiest)	28,839 (36.7)	24,254	19,060
2	23,853 (30.4)	19,741	15,433
3	11,720 (14.9)	9,477	7,369
4	7,913 (10.1)	6,387	4,899
5 (Poorest)	6,224 (7.9)	5,060	3,965

CRS, conditional relative survival; ICD, International Classification of Disease; SCC, squamous cell carcinoma.

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Table 2. Relative and conditional survival (%), 1996–2015

Characteristics	Relative survival (95% CI)		Conditional 5-year relative survival (95% CI)				
	5-year	10-year	1-year	2-year	3-year	4-year	5-year
Total	80.6 (80.3–80.9)	77.4 (77.1–77.8)	85.7 (85.4–86.0)	90.6 (94.1–94.9)	93.5 (93.2–93.7)	95.3 (95.1–95.6)	94.3 (91.8–96.3)
Age (yr)							
<40	88.9 (88.4–89.4)	87.3 (86.8–87.9)	90.8 (90.3–91.3)	94.5 (94.1–94.9)	96.3 (96.0–96.7)	97.5 (97.1–97.8)	95.8 (87.8–98.8)
40–49	86.7 (86.2–87.2)	84.3 (83.8–84.9)	89.1 (88.7–89.6)	92.7 (92.3–93.1)	94.9 (94.5–95.3)	96.4 (96.0–96.7)	95.6 (90.5–98.3)
50–59	81.8 (81.2–82.4)	78.3 (77.6–79.0)	85.3 (84.6–85.9)	90.0 (89.5–90.6)	92.8 (92.3–93.3)	94.8 (94.3–95.3)	96.1 (95.6–96.6)
60–69	78.1 (77.3–78.9)	72.8 (71.8–73.7)	83.0 (82.2–83.8)	88.0 (87.2–88.8)	91.1 (90.3–91.9)	92.9 (92.0–93.6)	90.8 (83.1–96.3)
≥70	55.0 (53.8–56.2)	49.3 (47.7–50.9)	69.4 (67.9–70.8)	79.1 (77.4–80.7)	85.5 (83.7–87.3)	90.0 (87.9–92.0)	86.1 (71.1–98.5)
Year of diagnosis							
1996–2000	80.4 (79.8–80.9)	77.2 (76.6–77.9)	85.4 (84.8–85.9)	90.6 (90.1–91.1)	93.6 (93.1–94.0)	95.5 (95.1–95.9)	95.0 (91.0–97.8)
2001–2005	81.4 (80.8–82.0)	78.3 (77.7–79.0)	86.6 (86.0–87.1)	91.2 (90.7–91.7)	94.1 (93.6–94.5)	95.7 (95.3–96.2)	93.3 (87.3–97.3)
2006–2010	80.6 (79.9–81.2)	77.1 (76.3–77.8)	85.8 (85.2–86.4)	90.3 (89.7–90.8)	92.9 (92.3–93.4)	94.6 (94.0–95.1)	94.3 (89.5–97.5)
2011–2015	79.9 (79.1–80.7)	-	75.2 (70.3–80.1)	84.2 (78.0–90.4)	87.9 (81.3–94.4)	89.8 (83.4–96.2)	90.9 (84.8–97.0)
Histology							
Squamous cell	82.6 (82.2–82.9)	79.6 (79.2–80.0)	86.9 (86.6–87.2)	91.5 (91.2–91.8)	94.1 (93.8–94.4)	95.9 (95.6–96.1)	94.9 (92.2–97.0)
Adenocarcinoma	78.5 (77.5–79.4)	74.2 (73.2–75.3)	82.7 (81.8–83.6)	87.5 (86.6–88.4)	90.8 (89.9–91.6)	93.0 (92.2–93.8)	94.9 (94.1–95.7)
Adenosquamous	79.2 (77.1–81.1)	74.8 (72.4–77.0)	82.1 (80.0–84.0)	86.2 (84.1–88.0)	90.4 (88.4–92.1)	92.7 (90.8–94.4)	73.2 (22.6–95.2)
Others	60.0 (58.2–61.7)	56.0 (54.1–57.9)	77.3 (75.3–79.1)	86.2 (84.4–87.9)	90.1 (88.3–91.7)	92.4 (90.7–94.0)	94.3 (92.6–95.8)
Unknown	63.7 (61.2–66.1)	60.6 (57.9–63.1)	74.4 (71.8–76.8)	84.9 (82.5–87.2)	90.7 (88.4–92.7)	94.0 (91.7–95.8)	95.5 (93.3–97.3)
Stage at diagnosis							
Localized	91.9 (91.5–92.3)	89.9 (89.3–90.6)	93.6 (93.2–94.0)	95.4 (94.9–95.8)	96.7 (96.2–97.1)	97.8 (97.3–98.2)	96.0 (90.0–99.5)
Regional	72.3 (71.3–73.3)	66.2 (64.8–67.5)	76.4 (75.4–77.5)	83.2 (82.1–84.2)	87.1 (85.9–88.2)	89.7 (88.5–90.9)	92.2 (90.8–93.5)
Distant	27.0 (25.2–28.8)	21.5 (19.4–23.6)	37.4 (34.8–40.0)	52.0 (48.4–55.5)	63.0 (58.6–67.2)	71.7 (66.6–76.2)	79.9 (74.0–84.9)
Unknown	73.9 (72.4–75.3)	69.9 (68.2–71.6)	83.3 (81.9–84.7)	88.3 (86.9–89.7)	91.8 (90.4–93.1)	93.0 (91.5–94.3)	95.3 (93.9–96.6)
Treatment received							
Surgery only	96.8 (96.5–97.0)	96.0 (95.6–96.3)	97.7 (97.4–97.9)	98.4 (98.1–98.6)	98.9 (98.7–99.2)	99.2 (98.9–99.4)	97.2 (93.0–99.7)
Surgery + (chemo or radiation)	78.6 (77.8–79.4)	73.5 (72.6–74.4)	80.3 (79.5–81.0)	85.4 (84.6–86.1)	88.7 (88.0–89.5)	91.5 (90.7–92.2)	90.4 (81.8–95.7)
Chemo + radiation	65.5 (64.3–66.6)	58.9 (57.6–60.2)	69.6 (68.4–70.8)	78.7 (77.4–79.9)	84.3 (83.0–85.5)	88.6 (87.3–89.8)	90.7 (89.3–91.9)
Others (chemo only, radiation only, no treatment)	63.8 (63.1–64.5)	59.5 (58.7–60.2)	75.0 (74.3–75.7)	84.0 (83.3–84.6)	89.1 (88.4–89.7)	92.3 (91.6–92.9)	92.0 (87.1–95.8)
Deprivation Index							
1 (Wealthiest)	82.8 (82.3–83.2)	79.9 (79.3–80.5)	87.1 (86.6–87.6)	91.7 (91.2–92.1)	94.1 (93.7–94.5)	96.0 (95.6–96.4)	94.0 (88.9–97.5)
2	80.8 (80.2–81.3)	77.6 (76.9–78.2)	85.8 (85.3–86.3)	90.6 (90.0–91.0)	93.5 (93.0–94.0)	95.4 (94.9–95.8)	94.7 (90.2–97.7)
3	78.5 (77.6–79.3)	75.1 (74.1–76.1)	84.4 (83.5–85.2)	90.1 (89.3–90.8)	93.0 (92.3–93.7)	95.0 (94.3–95.7)	96.4 (95.6–97.0)
4	77.1 (76.1–78.1)	73.4 (72.2–74.6)	83.4 (82.4–84.4)	88.8 (87.8–89.8)	92.2 (91.2–93.1)	93.9 (92.9–94.8)	95.9 (94.9–96.8)
5 (Poorest)	78.2 (77.1–79.3)	74.4 (73.1–75.7)	84.0 (82.9–85.1)	89.2 (88.1–90.2)	92.5 (91.4–93.5)	94.3 (93.3–95.3)	88.7 (69.4–98.0)

CI, confidence interval.

The 5YRS rate at the time of diagnosis was 80.6% for all cervical cancer cases. The probability of surviving an additional 5 years conditioned on having already survived 1, 2, 3, 4, and 5 years after diagnosis was 85.7%, 90.6%, 93.5%, 95.3%, and 94.3%, respectively.

Patients had higher 5YRS when they were diagnosed younger: the 5YRS rate for patients aged <40 years at diagnosis was 88.9%, while it was 55.0% for patients aged over 70 years. CRS continued to be higher for younger patients, but the difference decreased over time. The CRS after 5 years of survival was not significantly different among patients aged under 60 years (around 96%), although it remained significantly lower in patients aged over 60 years (90.8% for patients aged 60–69 and 86.1% for patients aged ≥70 years).

Patients who were diagnosed with local disease had a relatively small change of survival probability, which increased only slightly from a 5YRS rate of 91.9% to CRS rates of 95.4% and 96.0% after 2 and 5 years of survival, respectively. Patients with regional stage showed substantial increase of survival probability: 72.3% at diagnosis, 83.2% after 2 years, and

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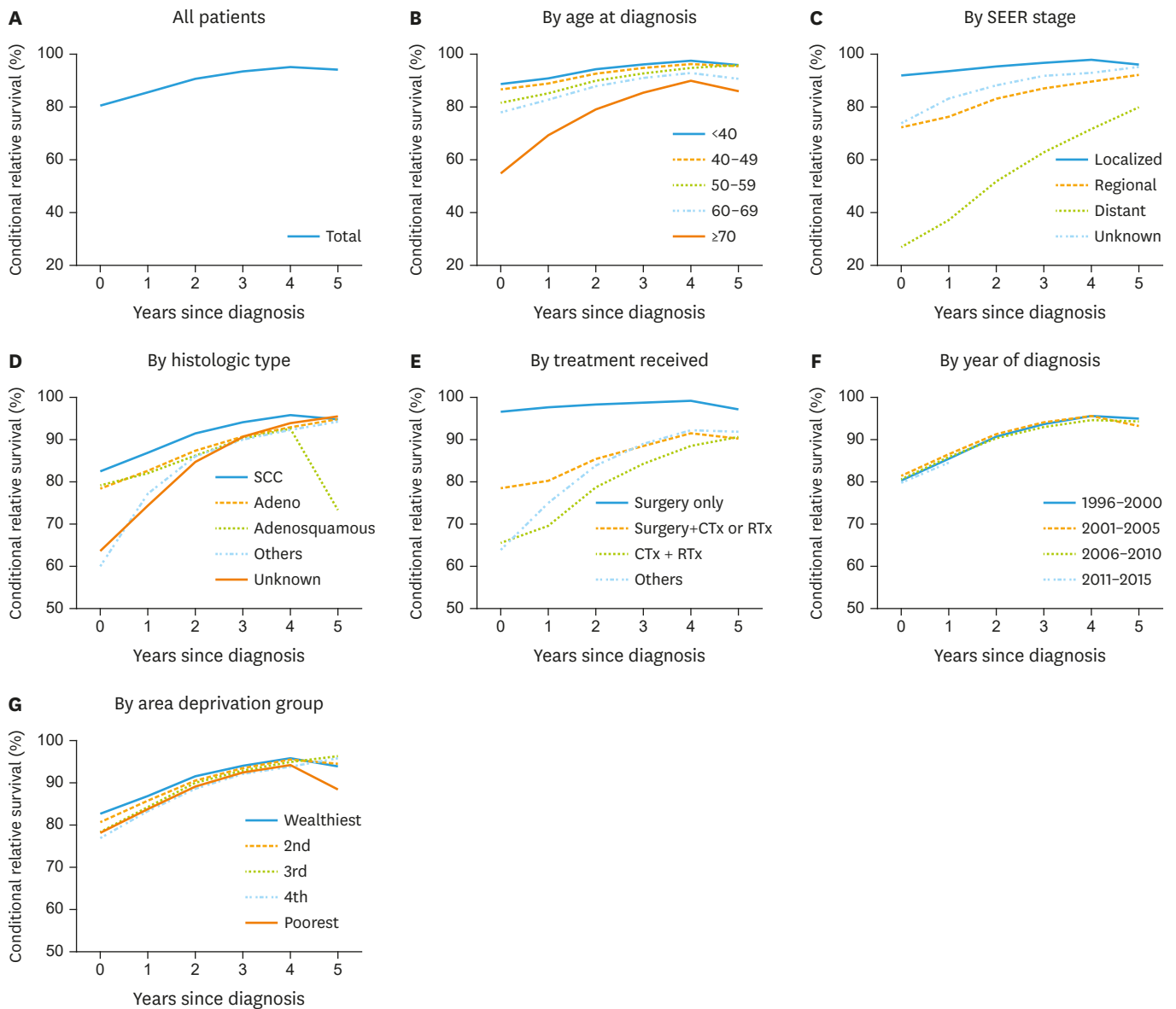


Fig. 1. Five-year conditional survival rates of cervical cancer patients according to patient characteristics. (A) All patients; (B) by age at diagnosis; (C) by SEER stage; (D) by histologic type; (E) by treatment received; (F) by year of diagnosis; and (G) by area deprivation group. SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results.

92.2% after 5 years. Patients with distant stage showed marked increase in CRS; 27.0% at diagnosis, 52.0% after 2 years, and 71.7% after 5 years. As a result, the disparity by disease stage decreased over time.

At diagnosis, the 5YRS among patients with SCC (82.6%) was better than the rate for all other histological types (adenocarcinoma, 78.5%; adenosquamous, 79.2%; and others, 60.0%). However, the disparity decreased over time, and the CRS at 5 years after diagnosis was around 95% across histology types, except for the adenosquamous type at 73.2%, which might be due to the small number of patients with this histology in this analysis (n=829 who survived 10 years).

Patients who received surgery only showed high survival from time of diagnosis (5YRS 96.8%), which reached nearly 100% after 4 years. Those who had undergone chemotherapy or radiation therapy in addition to surgery showed 78.6% survival at diagnosis, which increased to >90% after 4 years. Other patients showed low survival under 70% at diagnosis, but this reached >90% if they survived for 5 years.

There was no substantial difference in survival probability by years of diagnosis: the 5YRS remained around 80%, and the CRS after 2 and 5 years remained around 90.3%–91.2% and 93.3%–95.0%, respectively. Patients living in deprived areas showed slightly lower survival rate (82.8 in wealthiest area vs. 78.2% in poorest area), and this gap decreased with longer survival.

3. Conditional probability of death

Table 3 and **Fig. 2** show the conditional probabilities of death according to years since diagnosis and age group. Older patients were at higher risk of death at the time of diagnosis, but their probability of death rapidly declined with time: patients aged ≥ 70 years had the highest probability of death in the first year after diagnosis (24.5%), though the conditional probability of death in the 2nd, 3rd, 4th, and 5th years after diagnosis declined abruptly to 13.1%, 7.5%, 5.4%, and 3.9%, respectively. In comparison, younger patients were at lower risk of death at the time of diagnosis, but their mortality risk increased at the 2nd year and then slowly declined with time: patients aged <40 years had only 2.6% of probability of death

Table 3. Conditional probabilities of death by age group

Year since diagnosis	Total	Age group (yr)				
		<40	40–49	50–59	60–69	≥ 70
0	7.3	2.6	3.5	5.3	7.6	24.5
1	6.4	4.3	4.4	6.1	6.9	13.1
2	3.8	2.2	2.8	3.6	4.8	7.5
3	2.6	1.3	1.9	2.7	3.2	5.4
4	1.9	1.0	1.3	1.9	2.8	3.9
5	1.5	0.6	0.8	1.2	2.1	3.8
6	1.2	0.5	0.6	1.0	1.8	3.0
7	1.1	0.5	0.7	1.0	2.0	2.5
8	1.0	0.3	0.5	0.9	1.9	2.6
9	0.9	0.2	0.4	0.9	1.9	2.3
10	1.0	0.3	0.4	0.9	2.2	2.7

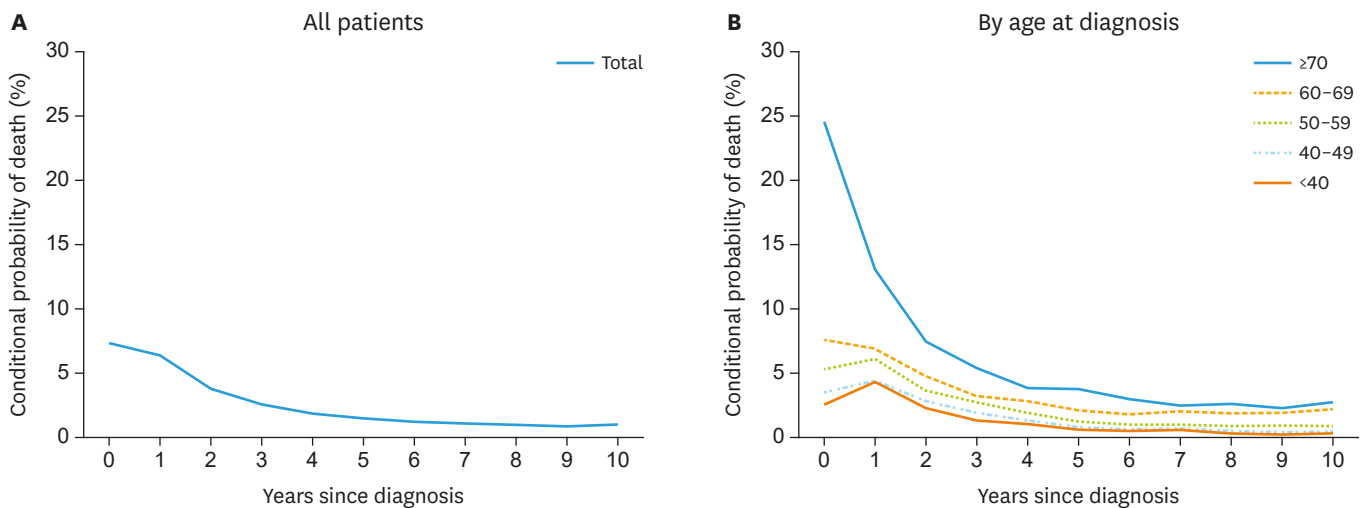


Fig. 2. Conditional probability of death according to years since diagnosis. (A) All patients and (B) by age at diagnosis.

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Table 4. Factors associated with survival according to survival time since diagnosis

Variables	All patients			Patients from 2005–2016		
	At diagnosis	2 years after diagnosis	5 years after diagnosis	At diagnosis	2 years after diagnosis	5 years after diagnosis
	RER (95% CI)	RER (95% CI)	RER (95% CI)	RER (95% CI)	RER (95% CI)	RER (95% CI)
Age (yr)						
<40	1	1	1	1	1	1
40–49	1.35 (1.09–1.52)	1.15 (1.06–1.24)	1.21 (1.14–1.29)	1.36 (1.12–1.64)	1.01 (0.09–1.14)	1.02 (0.93–1.12)
50–59	1.99 (1.76–2.24)	1.65 (1.53–1.78)	1.72 (1.61–1.83)	1.43 (1.19–1.73)	1.11 (0.99–1.25)	1.14 (1.04–1.25)
60–69	2.74 (2.43–3.09)	2.04 (1.88–2.20)	2.13 (2.00–2.27)	1.77 (1.46–2.15)	1.24 (1.09–1.40)	1.25 (1.28–1.38)
≥70	8.72 (7.82–9.70)	5.68 (5.29–6.10)	5.42 (5.10–5.75)	5.56 (4.69–6.60)	3.27 (2.93–3.64)	3.10 (2.84–3.39)
Year of diagnosis						
1996–2000	1	1	1	-	-	-
2001–2005	0.90 (0.83–0.97)	0.87 (0.82–0.92)	0.88 (0.84–0.92)	-	-	-
2006–2010	0.88 (0.82–0.96)	0.87 (0.82–0.92)	0.88 (0.83–0.92)	1	1	1
2011–2015	0.87 (0.80–0.94)	0.89 (0.84–0.95)	0.90 (0.85–0.95)	0.94 (0.86–1.02)	0.97 (0.91–1.04)	0.98 (0.92–1.03)
Histology						
SCC	1	1	1	1	1	1
Adenocarcinoma	1.44 (1.31–1.58)	1.38 (1.29–1.47)	1.17 (1.39–1.55)	1.27 (1.12–1.45)	1.35 (1.24–1.48)	1.46 (1.36–1.57)
Adenosquamous	1.07 (0.85–1.35)	1.19 (1.03–1.38)	1.43 (1.28–1.59)	1.34 (0.99–1.83)	1.38 (1.12–1.70)	1.52 (1.29–1.79)
Others	3.24 (2.98–3.51)	2.65 (2.48–2.84)	2.31 (2.17–2.46)	2.21 (1.92–2.54)	2.04 (1.81–2.30)	1.85 (1.65–2.07)
Unknown	3.17 (2.79–3.60)	2.86 (2.59–3.16)	2.63 (2.42–2.87)	2.41 (2.02–2.87)	2.32 (2.02–2.66)	2.35 (2.09–2.65)
Stage at diagnosis						
Localized	-	-	-	1	1	1
Regional	-	-	-	3.67 (3.17–4.26)	4.04 (3.66–4.45)	3.87 (3.58–4.17)
Distant	-	-	-	16.41 (14.20–18.96)	16.11 (15.48–17.80)	14.92 (13.75–16.17)
Unknown	-	-	-	4.84 (4.10–5.71)	3.93 (3.49–4.43)	3.32 (3.01–3.67)

CI, confidence interval; RER, relative excess risk; SCC, squamous cell carcinoma.

within the first year but increased 4.3% in second year, after which it declined to 2.2%, 1.3%, and 1.0% in the 3rd, 4th, and 5th years, respectively.

4. Impact of baseline characteristics on mortality according to survived time since diagnosis

The impact of age on survival declined with time since diagnosis: for example, RER (95% CI) for mortality in patients aged ≥70 years was 8.72 (7.82–9.70) at diagnosis and decreased to 5.68 (5.29–6.10) and 5.42 (4.69–6.60) after 2 and 5 years since diagnosis, respectively. Analysis of patients by SEER stage produced similar results. There was no significant difference by stage at diagnosis, histology, or year of diagnosis according to survival time since diagnosis (Table 4).

DISCUSSION

To our knowledge, this is the first comprehensive study to investigate the CRS of cervical cancer patients stratified by age, disease stage, histologic subtype, and year of diagnosis. We found that patients with cervical cancer had a higher probability of surviving an additional 5 years for each additional year that they survive after diagnosis, and patients with poorer initial survival estimates generally showed the largest increases in CRS over time. This increase in CRS was most noticeable for patients who were older and had advanced stage disease, non-SCC histology, and residence in deprived areas, indicating that the prognostic importance of these factors decreases as survival time increases.

As expected, the 5-year CRS rates improved with time from diagnosis. At 3 years since diagnosis, the CRS was approximately 95%, and patients have only a 5% higher mortality risk

compared to the general population. Such risk of excessive mortality is not higher than that in other chronic diseases, such as diabetes [11]. However, in the real clinical setting, some cancer survivors are excessively anxious about cancer recurrence and show negative coping behaviors. Previous studies suggest that fear of cancer recurrence tends not to decrease over time, even in long-term survivors (i.e., those who survive >5 years after diagnosis) [12]. A high perceived risk of recurrence and illness perception have consistently been associated with higher fear of cancer recurrence [12]. The probability of survival is not static; however, current patients are only informed of the 5YRS rates. Lack of updated information about the disease can contribute to the feeling of uncertainty and results in a higher level of fear of cancer recurrence [13]. Providing updated CRS rates, which are more relevant prognostic information than 5YRS rates, could help to reduce patient fear and enable more reasonable decisions.

In the present study, older patients with cervical cancer (≥ 60) tended to have consistently lower CRS rates than younger women, consistent with previous studies [5,7]. The age-related difference in CRS rates diminished with time, indicating that elderly cancer patients had a higher excess risk for early mortality than younger patients during the post-treatment period. This might be due to undertreatment due to old age [14], higher susceptibility to toxic effects of cancer treatment [15], and higher risks of death from other competing causes, such as cardiovascular disease or second primary cancer [16,17]. This underlines the need for best tolerable treatment at an individual approach without ageist discrimination [18,19], attentive surveillance for recurrence, better management of comorbidities, and thorough screening for other cancers in the elderly patient population [20].

In the older population, the conditional probability of death declined rapidly with time since diagnosis. However, in younger patients, the conditional probability of death, which was highest at the 2nd year, declined slowly. As non-cancer mortality is markedly lower in younger cervical cancer patients, the observed pattern seems to reflect the higher mortality after treatment for metastatic cancer. For example, younger women are less likely to receive cervical cancer screening [21], so some are diagnosed at an advanced stage. In such cases, patients can only tolerate palliative treatment and are likely to die at the 2nd year because there is currently no effective treatment option after failure of first-line platinum-based chemotherapy [22]. Indeed, the mean survival of stage IV cervical cancer patients is around 2 years in Korea [23].

The 5YRS for localized stage cervical cancer at the time of diagnosis was 91.9% and improved continuously to 96%–98% after 3 years, reflecting the relatively good prognosis for patients diagnosed at this stage. Patients with localized stage cervical cancer generally have lower chance of recurrence, but they also showed similar rate of fear of cancer recurrence, which is also associated with poor quality of life and anxiety [24]. Based on our data, clinicians can reassure these patients that they can anticipate near-normal life expectancy without excessive surveillance.

Meanwhile, the CRS rates for regional and distant stage diseases continuously increased with years of survival but did not reach that of local stage even after 5 years. Moreover, the prognostic impact (i.e., RER) of initial SEER cancer stage remained similar after 2 or 5 years since diagnosis. This suggests that delayed mortality after anti-cancer treatment, risk of late recurrence, and toxic late effect from radiation and/or chemotherapy contribute to excessive death in this population even after long-term survival [17]. This shows that clinicians should continuously monitor such risk. However, survivors should be counselled against excessive fear of recurrence after a certain survival period, as the CRS rates for both regional and distant stage are 92% and 80%, respectively.

With respect to histologic type, the 5YRS for adenosquamous carcinoma (79.2%), adenocarcinoma (78.5%), others (60.0%), and unknown (63.7%) types was lower than that of SCC (82.6%) at the time of diagnosis. However, the CRS reached a similar level after 5 years of survival (94%–95%), except for that of adenosquamous carcinoma, although this seems to be because of the small number of adenosquamous carcinoma patients included in the study. This finding shows that the risk of mortality in cervical cancer types, other than SCC, diminishes with time.

Patterns of CRS by treatment largely reflect stage information. For example, those who received surgery only would be those with early stage disease (e.g. International Federation of Gynaecology and Obstetrics [FIGO] stage IA, IB1, IB2, or IIA1), which required only surgical treatment. Those who are considered to have received adjuvant therapies or primary chemoradiation had lower survival (e.g., FIGO stage IIB or III), but their 5-year CRS reached >90%, which is generally considered as ‘cured,’ with no significant excess mortality compared to the general population [5].

Survival rates slightly improved from 1996–2000 to 2001–2005 but showed a decreasing trend thereafter, although the difference was not significant. While the introduction of a cervical cancer screening program decreased the incidence and mortality of cervical cancer in Korea, a higher positive impact on incidence and mortality was obtained from early detection and resection of precancerous lesions (i.e., carcinoma in situ) [25]. For invasive cervical cancer, there has been no major advancements in treatment since year 2000. During the study period, the use of laparoscopic radical hysterectomy to reduce operative complications markedly increased [26], but a recent randomized trial involving minimally invasive surgery vs. traditional abdominal hysterectomy was terminated early due to higher recurrence and mortality in the first group [27], and a real-world study confirmed this finding [28]. Our result is consistent with such findings and warns against unneeded use of minimally invasive surgery.

Living in a socially deprived area was associated with slightly poorer 5YRS, but the difference in CRS between differently deprived areas decreased over time. People with lower educational level or household income showed lesser participation in a cervical cancer screening program. However, rural residence itself was not associated with cervical screening participation [29]. A small deprivation gap would reflect such disparity in cervical cancer screening practice.

This study has several limitations. First, the KCCR does not include information on disease recurrence, and we were not able to analyze conditional disease-free survival, which is important in revealing what the cancer itself contributes to prognosis after years from initial treatment. Second, information on disease stage was available only starting in 2005. Third, there was no information on factors that could affect survival probability, such as income status, educational status, smoking, and body mass index, so their effect could not be examined. Fourth, no information on recurrence or cause of death was available in the KCCR, and we could not calculate recurrence-free survival or cause-specific survival. Finally, the generalizability of our data is limited as Korea has a universal health insurance system and a free national cervical cancer screening program. The 5YRS in Korea (80.6%) is higher than those reported in Australia (73.2%) [7], Japan (around 70%) [4], and the United States (67%) [30].

In conclusion, the CRS rates for patients with cervical cancer improved over time, particularly among patients with poorer initial prognoses. The largest improvements in CRS were

observed for older women and those diagnosed with distant stage disease. The CRS estimates provided in our study enable more evidence-driven approaches for appropriate patient management and surveillance based on a patient's evolving risk profile. Our estimates also enable patients to make better informed decisions regarding follow-up care and their personal life.

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