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Improved long-term survival of corpus cancer in Japan: A 40-year population-based analysis

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Abstract

The incidence of uterine corpus cancer has been increasing globally due to increase in obesity. However, a detailed analysis of long-term epidemiological trends of corpus cancer in Japan, where obesity is relatively minimal, has not been conducted. In this retrospective, population-based study using the Osaka Cancer Registry, we analyzed 15 255 cases of corpus neoplasia registered between 1977 and 2016. We determined the age-standardized incidence, mortality, relative survival and conditional survival rates, and the treatment trends for corpus cancer over the last 40 years in Japan. The age-standardized incidence rate of corpus neoplasia increased sharply in 2000-2011 (APC = 9.9, 95% CI: 8.4-11.3), whereas the mortality rate trended to a much more modest increase (APC = 3.3, 95% CI: 2.7-3.8). Compared to 1977-2000, 10-year survival rates for post-2000 cases of localized and regional corpus cancers significantly improved (from 87.7% [95% CI: 85.8-89.4] to 94.2% [95% CI: 92.7-95.7] and from 47.5% [95% CI: 43.3-51.6] to 64.4% [95% CI: 61.0-67.6], respectively). This was largely associated with the significant increase in the percentage of localized and regional patients who received chemotherapy instead of radiation as an adjuvant therapy combined to surgery ($P < .001$ for both). We found that each histological type (endometrioid carcinoma, serous carcinoma, clear cell carcinoma and carcinosarcoma) has different characteristics of trend of age-standardized incidence rate, relative survival and distribution of extent of disease. In endometrioid carcinoma, the age-standardized incidence rate increased consistently after 1990, but the rate of increase was decreasing after 1997.

Abbreviations: %DCO, Proportion Death Certificate Only Cases; AP, adriamycin and cisplatin; APC, annual percent change; CAP, cyclophosphamide, adriamycin, and cisplatin; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; TC, paclitaxel and carboplatin.

KEYWORDS

adjuvant treatment, cancer registry, incidence, relative survival, uterine corpus cancer

What's new?

For the past 40 years, age-standardized incidence of corpus cancer in Japan, similar to other countries worldwide, has been increasing. However, whereas global increases in corpus cancer are linked to increasing obesity, obesity rates in Japan remain uniquely low. This population-based study, drawing on data from the Osaka Cancer Registry, reveals a sharp increase in age-standardized incidence of corpus neoplasia from 2000-2011 in Japan. Each histological cancer type differed in incidence trend, relative survival, and distribution of extent of disease. Additional analyses indicate that recent changes in adjuvant therapy, particularly increased use of chemotherapy over radiation, have improved prognosis.

1 | INTRODUCTION

The worldwide age-standardized incidence rate of corpus cancer was 8.7 per 100 000, making it globally the seventh most common cancer in women.[1] The incidence trend in many countries was upward, and the highest average annual percent change in incidence rate was in South Africa.[2] In Japan, a previous study reported that corpus cancer also had a consistent increase in age-standardized incidence between 1985 and 2015[3]; however, a detailed analysis of age-standardized incidence by extent of disease or histological type of uterine cancer was not performed. The main histological types of uterine corpus cancers are endometrioid, serous, clear cell and carcinosarcoma. Because clinical behavior varies by histological types,[4] epidemiological analysis for each histological type has been required.

Previous studies using cancer registry in the United States and Europe reported that the 5-year relative survival rate was around 80%.[5-7] The 5-year relative survival rate in Japan during roughly the same period, from 2001 to 2006, was 80.2%.[8] These analyses provided only short-term survival rates ranging from 1 to 5 years, and there were no detailed analyses of 10-year survival rates that would indicate a complete cure. Many patients with a variety of cancers can live more than 5 years and thus need more information about their long-term prognosis.[9-12] Moreover, the reasons for the recent change of the survival rate were not investigated. No population-based analysis has yet been reported for the improvement survival rate by the introduction of chemotherapy[13-16] in a place of radiation[17,18] as adjuvant therapy.

The objective of our study was to demonstrate the basic epidemiological features of corpus cancers, such as the age-standardized incidence and mortality rates, in Japanese women. In addition, we have analyzed the trend of long-term (10-year) relative survival rate over time since the 1970s, and have evaluated whether the reason for the change was due to a change in treatment procedures. We also analyzed the conditional survival rates to clarify useful information that could be presented by doctors to patients after their diagnosis of uterine cancer.

2 | MATERIALS AND METHODS

2.1 | Data sources

The Osaka Cancer Registry is a full-longitudinal survey that collects information on the diagnosis and treatment of all cancers occurring in Osaka Prefecture, Japan. The Osaka Prefecture has a population of approximately 9 million people, which is about one-thirteenth of the total population of Japan and is roughly equivalent to the population of Sweden, making it comparable to a national database.

In our study, we analyzed 15 255 cases of uterine corpus neoplasia (International Classification of Disease, 10th revision [ICD-10] Code: C54—Malignant neoplasm of the corpus uteri) registered in the Osaka Cancer Registry from 1977 to 2016. The cases of C55 (uterus/NOS) actually developed from uterine cervix or corpus. Because there were only 3838 cases registered as C55 during 40 years of the study period from 1977 to 2016, which consisted of only 6.1% of all the neoplasia of the uterus (C53, C54 and C55), these cases were excluded from the present analysis (Figure S1).

Age-standardized incidence and mortality were calculated using cases registered in the recent 40 years between 1977 and 2016. The 10-year relative survival rate was calculated using only cases enrolled between 1977 and 2007, thus having a full 10-year followed-up period after diagnosis, and the 5-year relative survival rate was calculated adding cases enrolled between 2008 and 2012, with a 5-year followed-up period after diagnosis.

2.2 | Variables

Extent of disease was categorized as either "Localized", "Regional" or "Distant metastases" disease groups. The correspondence between the degree of extent of disease and its FIGO classification is as described here: Localized—Stage I; Regional—Stage II, III, IVA and Distant metastasis—Stage IVB. The degree of extent of disease was

unknown or missing in 11.7% of cases. These were excluded from the analysis by degree of extent of disease.

The histological type was determined using the morphology code of the International Classification of Diseases for Oncology, 3rd Edition (ICD-O3M). Endometrioid carcinoma, serous carcinoma, clear cell carcinoma and all the other carcinomas such as squamous cell carcinoma, neuroendocrine carcinoma and adenocarcinoma not otherwise specified (NOS) were analyzed together as the carcinoma group, excluding mesenchymal tumors.

Because carcinosarcoma is listed as a subset of corpus cancer rather than of uterine sarcoma in the FIGO staging system and clinically treated in the same way as endometrial carcinoma, the cases of carcinosarcoma were combined into the carcinoma group in the present study. Histological grades of endometrioid carcinomas were not included in the data.

2.3 | Statistical analysis

STATA MP 16 software (Stata Corp, College Station, Texas) was used for the analyses.[19] The age-standardized incidence and mortality rates were calculated per 100 000 population. For the standard population, we used the Japanese Model Population of 1985.

We applied the piece-wise log-linear regression model and used the Joinpoint 4.8.0.1 package by which the number and location of the age-standardized incidence rate and mortality rate

TABLE 1 Basic characteristics of the study targets: the case number of the neoplasia of the uterine corpus by histological type, age and extent of disease (1977 to 2016)

	Number of cases								
	1977 to 1981	1982 to 1986	1987 to 1991	1992 to 1996	1997 to 2001	2002 to 2006	2007 to 2011	2012 to 2016	Total
Uterine corpus neoplasia	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Histological type									
Carcinoma									
Adenocarcinoma									
Endometrioid carcinoma	4 (0.8)	11 (1.6)	6 (0.6)	63 (5.6)	612 (42.3)	1081 (49.6)	2404 (69.4)	3580 (74.1)	7761 (51.0)
Serous carcinoma	17 (3.3)	43 (6.1)	28 (2.9)	33 (2.9)	36 (2.5)	57 (2.6)	135 (3.9)	252 (5.2)	601 (4.0)
Clear cell carcinoma	0 (0.0)	0 (0.0)	7 (0.7)	9 (0.8)	24 (1.7)	43 (2.0)	55 (1.6)	91 (1.9)	229 (1.5)
Other carcinomas	338 (64.9)	517 (73.0)	719 (75.1)	786 (70.2)	541 (37.4)	695 (31.9)	421 (12.2)	373 (7.7)	4390 (28.8)
Carcinosarcoma	1 (0.2)	2 (0.3)	13 (1.4)	21 (1.9)	28 (1.9)	74 (3.4)	129 (3.7)	184 (3.8)	452 (3.0)
Mesenchymal	35 (6.7)	64 (9.0)	82 (8.6)	68 (6.1)	54 (3.7)	85 (3.9)	183 (5.3)	226 (4.7)	797 (5.2)
Others	126 (24.2)	71 (10.0)	102 (10.7)	139 (12.4)	152 (10.5)	143 (6.6)	138 (4.0)	124 (2.6)	995 (6.5)
Age									
<29	6 (1.2)	9 (1.3)	10 (1.0)	10 (0.9)	13 (0.9)	13 (0.6)	22 (0.6)	27 (0.6)	110 (0.7)
30-39	27 (5.2)	31 (4.4)	32 (3.3)	44 (3.9)	45 (3.1)	105 (4.8)	148 (4.3)	204 (4.2)	636 (4.2)
40-49	100 (19.2)	140 (19.8)	183 (19.1)	172 (15.4)	201 (13.9)	266 (12.2)	437 (12.6)	793 (16.4)	2292 (15.0)
50-59	212 (40.7)	274 (38.7)	382 (39.9)	425 (38.0)	583 (40.3)	791 (36.3)	1098 (31.7)	1272 (26.3)	5037 (33.1)
60-69	109 (20.9)	146 (20.6)	222 (23.2)	284 (25.4)	338 (23.4)	527 (24.2)	964 (27.8)	1333 (27.6)	3923 (25.8)
70<	67 (12.9)	108 (15.3)	128 (13.4)	184 (16.4)	267 (18.5)	476 (21.9)	796 (23.0)	1201 (24.9)	3227 (21.2)
Extent of disease									
Localized	266 (51,1)	427 (60.3)	533 (55.7)	625 (55.9)	793 (54.8)	1237 (56.8)	1947 (56.2)	3296 (68.2)	9124 (59.9)
Regional	68 (13.1)	109 (15,4)	163 (17.0)	200 (17.9)	274 (18.9)	483 (22.2)	890 (25.7)	888 (18.4)	3075 (20.2)
Distant	31 (6.0)	60 (8.5)	76 (7.9)	70 (6.3)	103 (7.1)	161 (7.4)	312 (9.0)	423 (8.8)	1236 (8.1)
Missing	156 (29.9)	112 (15.8)	185 (19.3)	224 (20.0)	277 (19.1)	297 (13.6)	316 (9.1)	223 (4.6)	1790 (11.8)
Total	521 (100.0)	708 (100.0)	957 (100.0)	1119 (100.0)	1447 (100.0)	2178 (100.0)	3465 (100.0)	4830 (100.0)	15 225 (100.0)

Note: Among those 59 years of age or younger, the number of cases increased 6.7-fold, from 345 during 1977-1981 to 2296 during 2012-2016, and among those 60 or older, it increased 14.4-fold, from 176 during 1977-1981 to 2534 during 2012-2016.

inflection points (Joinpoints) were determined,[20] and the Annual Percent Change (APC) between Joinpoints was calculated. The maximum number of Joinpoints was set at three. We also used Joinpoints to assess whether the changes in trends for the age-standardized incidence and mortality rates were statistically significant.

The incidence rate by age group and by histological type was examined in cases diagnosed in the most the recent year of 2016. The distribution of degree of extent of disease by histological type was also analyzed.

The relative survival rate was obtained by dividing the survival rate by the expected survival rate, calculated from the expected survival probability of the general population with the same characteristics (sex, age, calendar year and region), as the subject for whom the survival rate was calculated.[21] The expected survival rate for the general Japanese population with the same characteristics as the subject was calculated by using the cohort survival rate table published by the National Cancer Center.[22] For statistical analysis, the excess hazard model was applied.[23]

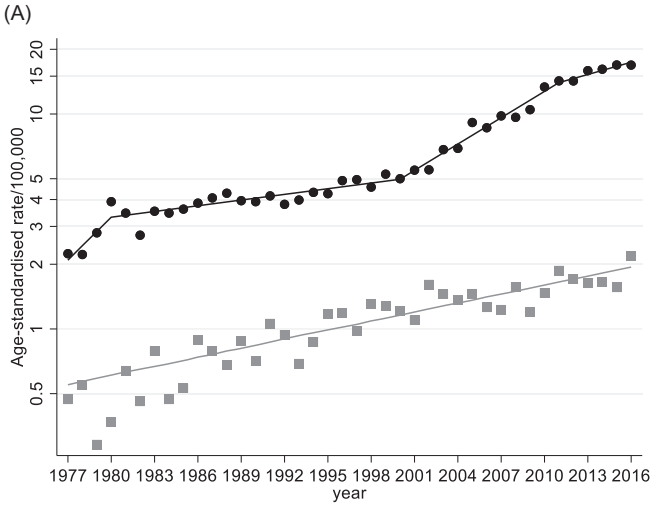
We estimated the subsequent 5-year relative survival rate by degree of extent of disease as the conditional 5-year survival rate according to the number of years survived after diagnosis to obtain data that can help provide useful information to those who are still undergoing treatment or follow-up after diagnosis.[24]

3 | RESULTS

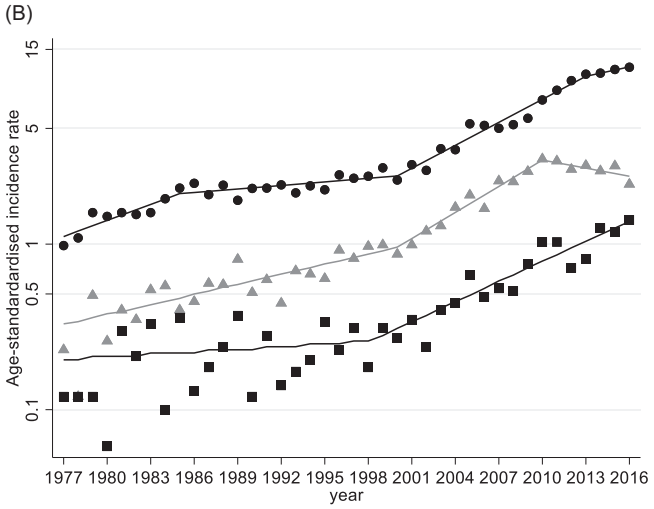
3.1 | Age-standardized incidence rate and mortality rate of uterine corpus neoplasia (1977-2016)

Total 15 225 cases were analyzed (Table 1). There was a consistent increase in the number of uterine corpus neoplasia over the 40-year study period. The age-standardized incidence rate per 100 000 people increased significantly since 1980 (Figure 1A). The age-adjusted incidence rate for sarcomas including leiomyosarcoma, endometrial stromal sarcoma and other sarcomas was increasing overall (data not shown).

The age-standardized mortality rate per 100 000 people increased consistently from 1977 to 2016. The APC of age-standardized mortality for the years 2000 to 2011 was significantly lower than the age-standardized incidence for the same period.



	Period	Age-standardized incidence rate	APC	95% CI
Incidence	1977-1980	2.2/3.9	16.6	-3.8 to +41.3
	1980-2000	3.9/5.0	2.1*	+1.3 to +2.8
	2000-2011	5.0/14.3	9.9*	+8.4 to +11.3
	2011-2016	14.3/16.9	4.5*	+1.6 to +7.4
Mortality	1977-2016	0.5/2.2	3.3*	+2.7 to +3.8



	Period	Age-standardized incidence rate	APC	95% CI
Localized	1977-1985	1.0/2.2	7.7*	+1.8 to +13.9
	1985-2000	2.2/2.4	1.7*	+0.1 to +3.3
	2000-2013	2.4/10.6	11.3*	+9.8 to +12.7
	2013-2016	10.6/11.7	4.5	-3.2 to +12.8
Regional	1977-2000	0.2/0.9	4.8*	+3.3 to +6.3
	2000-2010	0.9/3.3	12.9*	+9.7 to +16.2
	2010-2016	3.3/2.3	-3.7	-7.6 to +0.4
Distant	1977-1998	0.1/0.2	1.2	-1.9 to +4.4
	1998-2016	0.2/1.4	9.7*	+7.6 to +11.9

FIGURE 1 (A) Age-standardized incidence rate and mortality rate of uterine corpus neoplasia (1977-2016). Age-standardized incidence and mortality rates of neoplasia of uterine corpus were analyzed using the Japanese model-population of 1985. (B) Age-standardized incidence rate by degree of extent of disease in the carcinoma group (1977-2016). Age-standardized incidence rates by degree of extent of disease in the carcinoma group were analyzed using the Japanese model-population of 1985. APC, annual percent change. * Significant increase/decrease

3.2 | Age-standardized incidence rate by degree of extent of disease in the carcinoma group (1977-2016)

The localized and regional groups have shown a flat trend from around 2010 (Figure 1B). On the other hand, the distant metastasis group has continued to increase significantly since 1998.

3.3 | Five-year and ten-year relative survival rate by age group (carcinoma group)

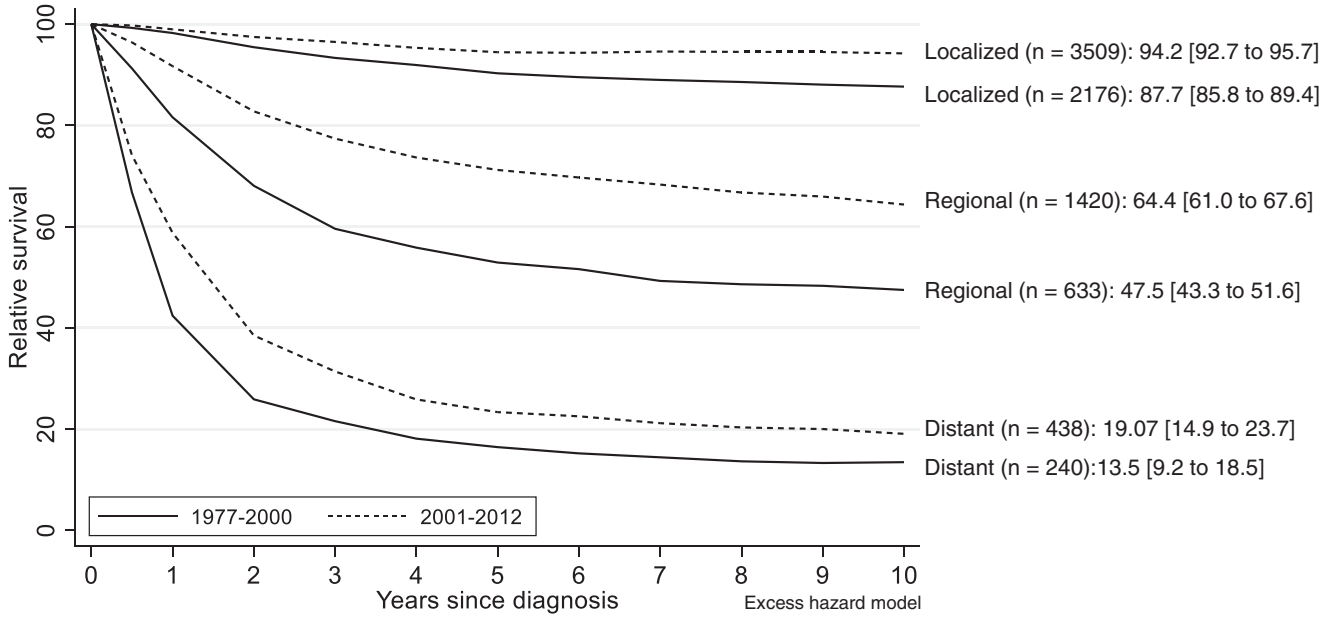
The 5-year and 10-year relative survival rates relative to extent of disease for patients younger than 60 years versus those 60 or older were compared (Table S1). The prognosis of patients younger than 60 years was better than that of patients 60 or older in all extent of disease. Age was shown to be a significant prognostic factor, irrespective of extent of disease.

3.4 | Ten-year relative survival rate by period and degree of extent of disease (carcinoma group)

When the study period was divided into three equal 12-year parts and analyzed, the 10-year relative survival rate for 1977 to 1988 and that for 1989 to 2000 were almost identical 71.2% and 71.2%, respectively (data not shown). We merged the two groups to perform a sufficient analysis with a larger number of cases.

Compared to 1977 to 2000, the prognosis of the cases of the localized was significantly improved from 87.7% (95% CI: 85.8-89.4) to 94.2% (95% CI: 92.7-95.7) (Figure 2A). The rate of regional group

(A)



(B)

		Surgery only	Combination therapy		
			Surgery + radiation (± Chemotherapy)	Surgery + chemotherapy	*P* value (Fisher's exact test)
Localized	1977-2000	225	40 (20.4%)	156 (79.6%)	<.001
	2001-2012	1859	63 (8.2%)	702 (91.8%)	
Regional	1977-2000	13	32 (22.7%)	109 (77.3%)	<.001
	2001-2012	206	59 (7.1%)	778 (92.9%)	

FIGURE 2 (A) Ten-year relative survival rate by period and degree of extent of disease (carcinoma group). Because the cases between 1977 to 1988 and 1989 to 2000 had almost identical survival rates (71.2% and 71.2%), we merged the two groups to perform a sufficient analysis with a larger number of cases. As for the relative survival rate of the period of 2001 to 2012, 0 to 5 year and 6 to 10 relative survival rates were calculated from the cases diagnosed in 2001 to 2012 and 2001 to 2007, respectively. (B) Changes by period in adjuvant therapy usage for localized and regional carcinomas. The proportions of cases in the radiation and chemotherapy groups were compared for 1977 to 2000 and 2001 to 2012 in the localized and regional groups of the carcinoma group; the results were evaluated by Fisher's exact test. First-line treatments were classified into surgery, radiation, chemotherapy and others; adjuvant therapy combined to surgery was classified as radiation-based (surgery + radiation, or surgery + radiation + chemotherapy) and chemotherapy-based (surgery + chemotherapy)

was also significantly improved from 47.5% (95% CI: 43.3-51.6) to 64.4% (95% CI: 61.0-67.6). In the distant metastasis group, the prognosis tended to improve over the years; however, the 10-year relative survival rate in both age groups overlapped and so was not significantly different.

3.5 | Changes by period in adjuvant therapy usage for localized and regional carcinomas

To clarify the reasons for the improvement in prognosis after 2001 for localized and regional carcinomas, we compared the proportion of cases where radiation-based versus chemotherapy-based adjuvant therapy was conducted between 2001 to 2012 and 1977 to 2000 (Figure 2B). In the localized cases, the proportionate number of patients who received adjuvant chemotherapy for their initial treatment increased significantly in the more recent period ($P < .001$). In the regional group, there was also a significant increase ($P < .001$).

3.6 | Conditional 5-year relative survival rate by degree of extent of disease (carcinoma group)

In the localized group, the subsequent 5-year survival rate for 5-year survivors was significantly higher (98.0% [95% CI: 96.9-98.7]) than the subsequent 5-year survival rate for 0 to 2 year survivors (ranging from 93.5% [95% CI: 92.6-94.4] to 95.5% [95% CI: 94.5-96.3]) (Figure 3). In the regional and distant metastasis groups, there was a significant improvement with each year of survival to the subsequent

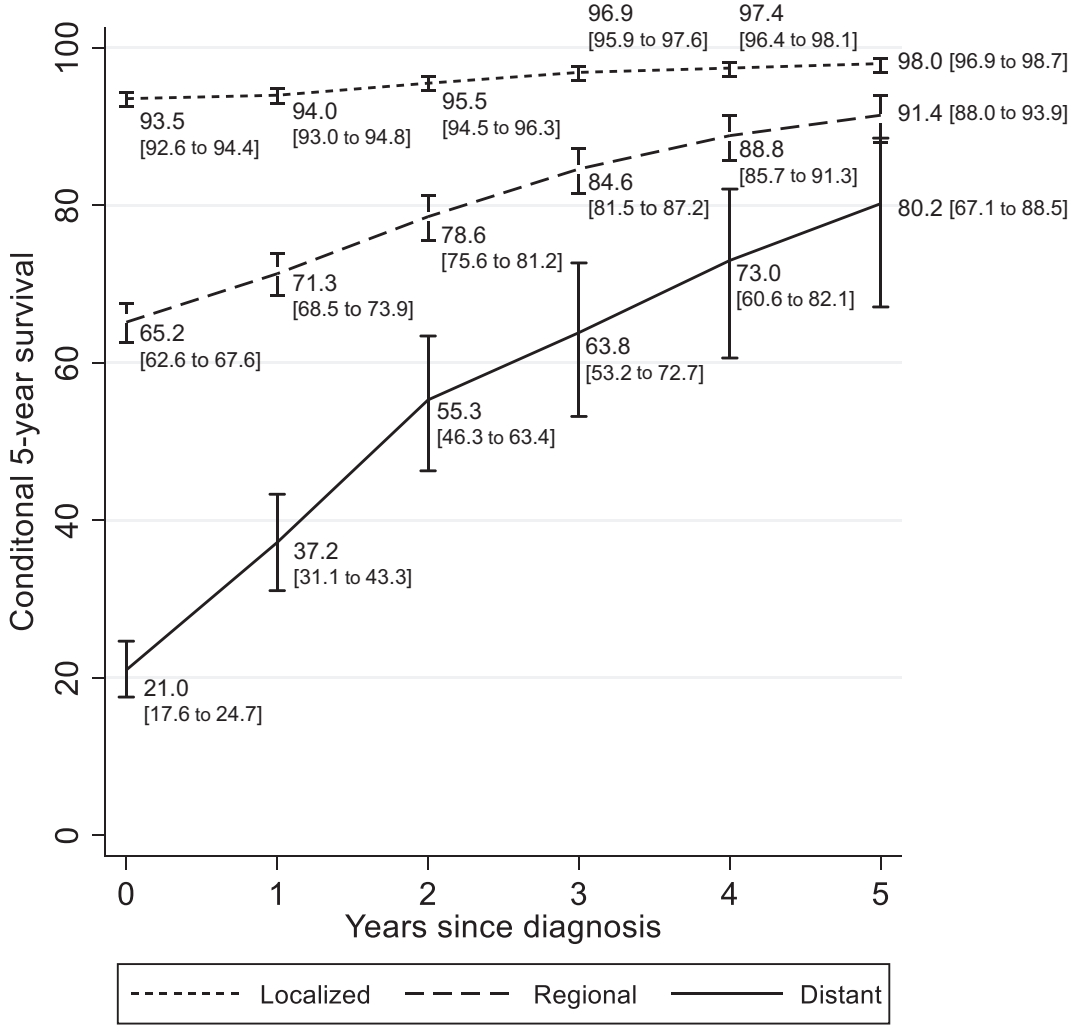


FIGURE 3 Conditional 5-year relative survival rate by degree of extent of disease (carcinoma group). In the localized group, the subsequent 5-year survival rate for 5-year survivors was significantly higher (98.0% [95% CI: 96.9-98.7]) than the subsequent 5-year survival rate for 0 to 2 year survivors (ranging from 93.5% [95% CI: 92.6-94.4] to 95.5% [95% CI: 94.5-96.3]). In the regional group, there was a significant improvement with each year of survival to the subsequent 5-year survival rate for 3-year survivors (ranging from 65.2% [95% CI: 62.6-67.6] to 84.6% [95% CI: 81.5-87.2]). The conditional 5-year relative survival rates for the cases of distant metastasis were significantly improved with each year of survival to the subsequent 5-year survival rate for 2-year survivors (ranging from 21.0% [95% CI: 17.6-24.7] to 55.3% [95% CI: 46.3-63.4])

5-year survival rate for 3-year survivors and 2-year survivors, respectively. Interestingly, the distant metastasis group, the subsequent 5-year survival rate for 3-year survivors (63.8%, 95% CI: 53.2-72.7) was similar to the subsequent 5-year survival rate for 0-year survivors of the regional group (65.2%, 95% CI: 62.6-67.6).

3.7 | Differences in age distribution at the onset by histological type in cases diagnosed in 2016

The age group-specific incidence of endometrioid carcinoma in 2016 peaked within the 50 to 54 years old age group (Figure S2). Serous

(A)

		Number of cases		
		1977-1988	1989-2000	2001-2012
Endometrioid carcinoma	Localized	9 (64.3%)	319 (70.7%)	2,579 (70.2%)
	Nonlocalized	5 (35.7%)	132 (29.2%)	1,097 (29.8%)
Serous carcinoma	Localized	38* (62.3%)	29 (46.0%)	72** (36.9%)
	Nonlocalized	23** (37.7%)	34 (54.0%)	123* (63.1%)
Clear cell carcinoma	Localized	0 (0.0%)	16 (61.5%)	47 (43.1%)
	Nonlocalized	1 (100.0%)	10 (38.5%)	62 (56.9%)
Carcinosarcoma	Localized	4 (57.1%)	17 (44.7%)	89 (44.5%)
	Nonlocalized	3 (42.9%)	21 (55.3%)	111 (55.5%)

*Significantly more, **Significantly less, $P<.05$ (chi-square test with residual analysis)

(B)

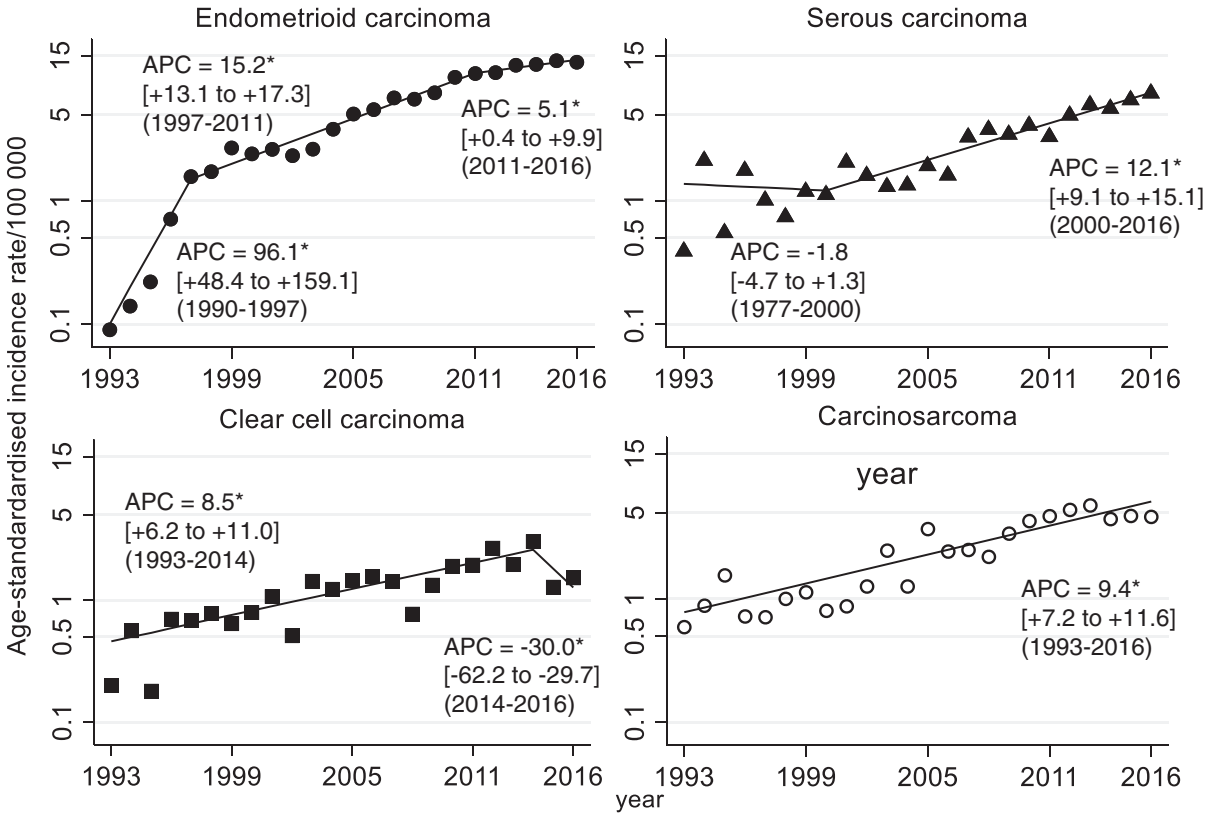


FIGURE 4 (A) Changes in the distribution of degree of extent of disease by histological type. Changes in the distribution of histology and degree of extent of disease were analyzed by the Chi-square test with residual analysis. In serous carcinoma, the proportion of localized cases was significantly more in 1977 to 1988, and that of non-localized cases was significantly more in 2001 to 2012. *Significantly more, **Significantly less, $P < .05$ (Chi-square test with residual analysis). (B) Age-standardized incidence rate by histological type. Age-standardized incidence rates by histological type were calculated during the period when the number of cases was at least 1. For clear cell carcinoma and carcinosarcoma, age-standardized incidence curve could be drawn only since 1993 because the incidence in 1992 was zero. Therefore, in this figure, only the portion of the age-standardized incidence curve after 1993 is shown for endometrioid and serous carcinoma

carcinoma incidence was highest in the 65 to 69 years old age group, clear cell carcinoma in the 75 to 79 years old age group and carcinosarcoma in the 75 to 79 years old age group. The age of onset differed by histological type.

3.8 | Changes in the distribution of degree of extent of disease by histological type

Compared to localized cases, the proportion of nonlocalized cases had increased significantly in serous carcinoma over the period (Figure 4A). In other histological types, there was no significant change in the proportion of localized and nonlocalized cases.

3.9 | Age-standardized incidence rate by histological type

In endometrioid carcinoma, the age-standardized incidence rate increased consistently after 1990, but the rate of increase was decreasing (Figure 4B). The age-standardized incidence of serous carcinoma remained unchanged from 1977 to 2000, then began increasing significantly from 2000 onward. In contrast, clear cell carcinoma had a significant upward trend from 1993 to 2014, but then leveled off from 2014 onward. Carcinosarcoma has been consistently increasing the entire time in 1993 to 2016. The change patterns in age-standardized incidence rates over time thus differed by histological type.

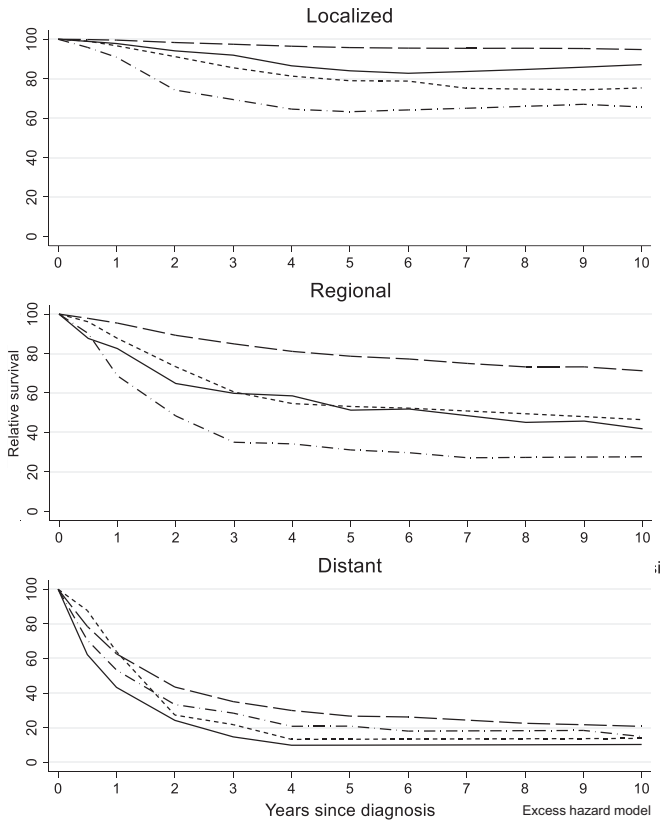
3.10 | The relative survival rate for each degree of extent of disease by histological type

In the localized cases, the prognosis of endometrioid carcinoma was better than the survival rate of the carcinosarcoma cases: 94.8% (95% CI: 93.1-96.3) versus 65.7% (95% CI: 53.8-76.1), respectively (Figure 5). There was no significant difference in prognosis between the clear cell and endometrioid carcinoma cases.

In the regional tumor group, the prognosis for endometrioid carcinoma was significantly better than for carcinosarcoma: 71.3% (95% CI: 67.4-74.9) versus 27.7% (95% CI: 18.0-38.4), respectively. The cases of serous carcinoma and clear cell carcinoma had a similar prognosis. There was little difference by histology in the dismal relative survivals in those cases with distant metastases.

3.11 | Changes in first-line treatments by period in regional and distant metastasis cases in the elderly (carcinoma group)

In patients aged 75 and older, the proportion of patients treated with surgery or radiation therapy alone at the time of initial treatment was



		n	10-year relative survival rate	n
Localized	Endometrioid carcinoma	2974	94.8	93.1 to 96.3
	Serous carcinoma	142	75.3	65.4 to 83.5
	Clear cell carcinoma	65	87.1	73.0 to 96.7
	Carcinosarcoma	110	65.7	53.8 to 76.1
Regional	Endometrioid carcinoma	1053	71.3	67.4 to 74.9
	Serous carcinoma	114	46.5	34.9 to 57.6
	Clear cell carcinoma	55	41.8	25.1 to 58.6
	Carcinosarcoma	97	27.7	18.0 to 38.4
Distant	Endometrioid carcinoma	212	20.7	14.6 to 27.7
	Serous carcinoma	71	13.7	6.8 to 23.4
	Clear cell carcinoma	21	10.3	1.8 to 28.2
	Carcinosarcoma	40	14.8	5.4 to 29.0

FIGURE 5 The relative survival rate for each degree of extent of disease by histological type

significantly higher at any degree of extent of disease than the proportion of patients treated with combined therapies of either surgery-radiation or surgery-chemotherapy ($P < .001$, $P < .001$, respectively) (Table S2). In other words, our data shows that the proportion of elderly patients who received only palliative local therapy, rather than systemic therapy, was higher than for salvageable younger patients.

4 | DISCUSSION

The present study revealed that overall age-standardized incidence and mortality rates for neoplasia of the uterine corpus have both been increasing, but the increase in mortality has been less than the increase in the incidence. Population-based data suggested that the recent changes in adjuvant therapy, from radiation to chemotherapy, have significantly improved the overall prognosis for uterine corpus cancer.

Increasing trends in the incidence of the uterine corpus cancer occurring between 1977 and 2016 in Japan's Osaka Prefecture was consistent with a previous study using three population-based cancer registries (Yamagata, Fukui and Nagasaki). One of the reasons for the increase in incidence might be that detection of the disease has becoming easier by screening, but we consider this to be negative because screening for the corpus cancer has not been established and there was a significant increase in metastasis cases as well as localized cases in the present analysis (Figure 1B). Occurrence of corpus cancer itself was thought to have been increasing.

Although the dramatic increase in obesity has been suggested to be the main cause of the increase in uterine corpus cancer in many countries, BMI values have remained low here in Japan.[25] The percentage of Japanese aged 20 years and older with a BMI of 25 or higher increased from 17.8% to 29.1% for men between 1980 and 2012, while the percentage of women changed from 20.7% to 19.4%, showing no increase at all with only an exception of a slight increase in those aged 70 or older.[26] Another possible reason for the increase in uterine corpus cancer in Japan has been suggested to be its extremely low birth rate.[2] The number of births in Japan in 2020 was 840 832, and it is estimated that the number of births reached a record low.[23] The total fertility rate in 2020 was 1.34 as the lowest level internationally.[27,28] According to a previous study, a reduction of endometrial cancer risk was observed in women with late menarche, early menopause, high parity and a shorter time since last full-term pregnancy, especially for endometrioid type.[29] After mutual adjustment, cumulative duration of full-term pregnancies was demonstrated to be the strongest factor associated with decreased risk of endometrial cancer (22% per year). The increases in both serous carcinoma and carcinosarcoma that we found, which occur in a nonestrogen-dependent manner, augments this increasing trend of corpus cancers in part.

Our study does confirm that the increasing trend of uterine corpus cancer in Japan is now slowing down. In terms of age-standardized incidence rates by histological type, the trend of increase in endometrioid carcinoma, which accounts for the majority of uterine corpus cancers, is slowing down the most, suggesting that the age-standardized incidence rate of uterine corpus cancer as a whole may level off or even decrease in the future; however, there is no change in the increasing trend of serous carcinoma and carcinosarcoma, so it is unlikely that any overall decline will be rapid.

Our analysis strongly suggests that the introduction of adjuvant chemotherapy significantly improves the prognosis for localized and regional cases of uterine corpus cancer. Our study showed that the 10-year relative survival rate, a long-term relative survival rate suggestive of a complete cure, has improved since 2001. The first choice of treatment for uterine corpus cancer is surgical treatment, after which either chemotherapy or radiation therapy is used as adjuvant therapy—based on an assessment of the risk factors for recurrence. Previous clinical trials showed that adjuvant chemotherapy was superior to radiation therapy for improving prognosis.[15,16] In the present study, we report for the first time that the population-based data shows that the change of adjuvant therapy from radiation to chemotherapy led to a significant improvement in patient survival.

Age-standardized incidence rate by histological type was also presented for the first time. Molecular features of well to moderately differentiated endometrioid carcinoma include abnormalities in DNA mismatch repair genes, PTEN and CTNNB1 accumulation, K-ras mutations and microsatellite instability, which can be observed during the endometrial hyperplasia progression. In contrast, serous and clear cell carcinomas are characterized by de novo mutations in the tumor suppressor p53 and other genes. These tumor types are more common in elderly women and are more prone to dissemination and metastasis, with a poor prognosis.[30] The poorly differentiated endometrioid carcinoma and the carcinosarcoma have similar clinicopathological features to the serous and clear cell types of corpus cancers and are often treated clinically in the same manner.[31] We found that these four histological types had different characteristics of trend of age-standardized incidence rate, relative survival and distribution of extent of disease, suggesting that these histological types are different entities based on different molecular characteristics.[32-36]

We found that the conditional 5-year relative survival rate increases with increasing years of survival, depending on degree of extent of disease. It is expected that presenting such positive information to the patient, that their subsequent 5-year relative-survival rate improves significantly, based on the number of years that have passed since their diagnosis, would encourage them during the depression that often occurs during the follow-up period after their initial treatments.

The strength of our study lied in our analysis of long-term cancer registry data. Since the establishment of the Osaka Cancer Registry, various efforts have been made to improve the system, and the Proportion Death Certificate Only Cases (%DCO) has decreased from the initial 17% to 7% (data not shown).

One of the limitations of our study is that the number of cases registered as "other carcinomas" during the study period was 4390 (28.8%). Especially in 1977 to 1991, it accounted for about 70% of the cases. It might be possible that cases of endometrial cancer were registered as adenocarcinoma NOS and classified as "other carcinomas." Further detailed analysis is unfortunately impossible in the present data. Even if many of the cases of "other carcinomas" were

endometrioid carcinomas, the number of such cases is very small compared to the number of recent cases of endometrioid carcinoma, and the trend in the incidence of endometrioid carcinoma will not change significantly. However, a direct comparison of the incidence of endometrioid carcinoma with that of serous carcinoma or clear cell carcinoma may not be appropriate.

Another limitation of our study is that details of the treatments, including types of surgical procedures and chemotherapy regimens, and an indication of adjuvant therapy in each case was not included in the data we analyzed. For example, in Japan, AP and CAP chemotherapies were replaced by TC chemotherapy, more recently.[37] The impact of this change was not analyzed in our analysis. However, we thought that the changes in specific types of chemotherapy regimens given had less of an impact on the recent improvements in prognosis than did the drastic change of adjuvant therapy from radiation to chemotherapy. Moreover, the order of treatments, which we could not ascertain in the present study. However, surgery is the main treatment for corpus cancer and impact of combination of radiation therapy or chemotherapy to surgery, at least, was demonstrated in the present study. Further studies will be required to fully clarify the epidemiological and clinical features of corpus cancer using another database.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of the study will be available from corresponding authors, after permission of Osaka Prefecture (https://oici.jp/ocr/index.html).

ETHICS STATEMENT

Our study was approved by the Osaka University Medical Hospital. Informed consents from the patients were not required for this analysis using cancer registry data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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