

ORIGINAL ARTICLE

Hospital volume and postoperative 5-year survival for five different cancer sites: A population-based study in Japan

Sumiyo Okawa¹  | Takahiro Tabuchi¹ | Toshitaka Morishima¹  | Shihoko Koyama¹ | Yukari Taniyama² | Isao Miyashiro¹

¹Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan

²Department of Mathematical Health Science, Graduate School of Medicine, Osaka University, Osaka, Japan

Correspondence

Sumiyo Okawa, Cancer Control Center, Osaka International Cancer Institute, 3-1-69, Otemae, Chuo-ku, Osaka 541-8567, Japan. Email: ookawa-su@mc.pref.osaka.jp

Funding information

Japan Society for the Promotion of Science, Grant/Award Number: JP19K19452; Osaka Cancer Society, Japan; Ministry of Health, Labour and Welfare, Japan, Grant/Award Number: H29-Gantaisaku-ippan-016 and H30-Gantaisaku-ippan-009

Abstract

The relationship between hospital volume and patient outcome is globally known; thus, hospital volume is widely used as a quality indicator. In Japan, however, recent studies on this topic are scarce. The present study examined whether hospital surgery volume is associated with postoperative 5-year survival among cancer patients. Using the Osaka Cancer Registry, we identified a sample of 86 145 patients who were diagnosed with cancer at any of five different sites (stomach, colorectum, lung, breast and uterus) and underwent surgeries between 2007 and 2011 in Osaka. We ranked hospitals by annual surgical volume, sorted patients in descending order by hospital volume, and assigned them into quartiles (high, medium, low and very low volume). We analyzed the association between hospital volume and 5-year survival among 80 959 patients aged between 15 and 84 years using Cox proportional hazard models. Adjustments were made for characteristics of patients, type of surgery and adjuvant treatment received. The mortality hazard of patients treated at very low-volume hospitals was 1.36-1.82-fold higher than that of patients treated at high-volume hospitals. Absolute differences in adjusted survival rates between high-volume and very low-volume hospitals varied with the cancer site: 14.9 in stomach, 11.5 in colorectal, 10.8 in lung, 2.4 in breast and 3.3 in uterine cancers. Hospitals with lower surgery volumes showed higher mortality risks after cancer surgery than those with higher volumes. Monitoring site-specific surgery volumes and referring patients from low-volume to high-volume hospitals may be beneficial for improving the long-term survival of cancer patients.

KEYWORDS

high-volume, hospitals, Japan, surgery, survival

1 | INTRODUCTION

Cancer is the second leading cause of death worldwide, with an estimated 9.6 million lives lost in 2018.¹ Following the diagnosis of cancer, receiving treatment at a “good” hospital would be a critical

issue for patients because cancer is a life-threatening disease. Since the effect of surgery volumes on mortality was reported in the United States in 1979,² several studies have accumulated evidence on the volume-outcome relationship; patients undergoing treatment at high-volume hospitals have better outcomes compared to

Abbreviations: CI, confidence interval; ICD-10, International Classification of Diseases 10th edition; OCR, Osaka Cancer Registry.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *Cancer Science* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association.

those treated at low-volume hospitals.^{3,4} A potential mechanism of the volume-outcome relationship is that hospitals with greater case volumes are likely to be equipped with skilled resources and advanced medical infrastructure, thereby providing optimal treatment and care; consequently, their patients obtain better treatment outcomes.⁵

Hospital volumes have been measured according to various definitions, including the number of patients who were diagnosed, received treatment⁵⁻⁸ or underwent surgeries.⁴ Surgical procedure volume is a commonly used measurement to assess the volume-outcome relationship.⁴ To date, there is no gold standard for the thresholds of hospital volume. As an alternative, studies have categorized hospital volume by percentiles,⁹⁻¹² clinically relevant cutoffs,^{13,14} or convenient cutoffs.¹⁵⁻¹⁷ This heterogeneity of surgical volume measurements may affect the external validity of study results.⁴ Patient outcomes used in previous studies have also varied; these include 5-year survival,^{7,18} postoperative mortality,^{19,20} procedure-related complications^{11,21} and recurrence of cancer.^{16,22} Although a number of studies have demonstrated that patients treated at high-volume hospitals have better outcomes, patient characteristics are critical confounders to the choice of hospital and patient outcomes.^{23,24} In addition, the variation of volume-outcome relationships may be affected by the clinical rarity and technical complexity of the surgical procedure. For instance, rare, complex cancer operations have stronger associations with mortality than common and simple operations.²⁵

Although the strength of the association between hospital volume and mortality varies according to the type of surgery,²⁵ some countries have applied the evidence of volume-outcome relationships to quality and safety control programs. For instance, state authorities or professional societies in European and North American countries assess whether hospitals meet minimum volume standards for pancreatic, esophageal, lung, hepatic or biliary tract resections, and levy penalties or offer interventions to non-compliant hospitals.²⁶ In the United States, the National Cancer Policy Board recommends surgery volume as a quality indicator,^{3,27} and a non-profit organization conducts hospital surveys and presents the achievement status of minimal surgical volume to individual hospitals.²⁸

In Japan, a minimum hospital volume standard is used as an eligibility criterion for designated cancer care hospitals, and as an indicator to monitor their performance.²⁹ The majority of studies on the volume-outcome relationship previously conducted in Japan focused on a single cancer site.^{21,30-35} One study reported the volume-survival relationship for multiple sites of cancer diagnosed in 1994-1998; hospital volume was defined by the number of patients treated.⁷ Since then, Osaka has changed in terms of its population structure, medical technology and cancer control policy, and has improved its cancer registry system. Moreover, patients undergo surgeries or non-surgical treatments in real-world settings. Surgical indications are influenced by the preoperative functional ability and are predictive of prognosis. Therefore, focusing on surgical cases is likely to illustrate the volume-outcome association more clearly than

cases undergoing treatment by all modalities. Updated evidence in a sample of patients undergoing surgeries is therefore needed. This study examined the association between surgery-based hospital procedure volumes and survival of cancer patients between 2007 and 2011.

2 | MATERIALS AND METHODS

2.1 | Study design, setting and data source retrieved

This retrospective cohort study used individual data of cancer patients from the Osaka Cancer Registry (OCR). The OCR is a population-based longitudinal database that registers all cancer cases and follows up their vital status in Osaka Prefecture, Japan. An estimated population of 8.9 million resided in Osaka according to the 2010 census.³⁶ Since the registry system was introduced in 1962, the OCR has been collecting data on new cancer cases from medical facilities and the prefectural administration. The database includes individual information on sex, age, date of diagnosis and death, cancer sites defined by the International Classification of Diseases 10th edition (ICD-10), cancer stage, treatment type (ie, surgery, adjuvant therapy and radiation therapy), medical facilities utilized at the first contact, diagnosis and primary treatment. The database does not have information on socioeconomic characteristics of individuals, their comorbidity status, functional ability or details of treatment (eg the period of treatment or any treatment undergone for cancer or other diseases after the primary treatment). Although the database does not have information on the social health insurance status of individuals, nearly the entire population in Japan is insured, and the contents and the fees for medical and health services covered by the insurance scheme are fixed across medical facilities.³⁷ The OCR updates the vital status of all registered cases at 3, 5 and 10 years from diagnosis. The proportion of incident cases in the database notified only by death certificates in 2011 was 8.7%, and the incidence/mortality ratio was 2.24.³⁸

2.2 | Study sample

Cancer cases of the following five sites were analyzed: stomach (C16 in ICD-10), colorectum (C18, C19, and C20), lung (C33 and C34), breast (C50) and uterus (C53, C54 and C55). We selected these cancer sites as they accounted for 55.5% of the overall cancer incidence during the study period. The study sample met the following criteria: diagnosed with cancer between 2007 and 2011, lived in Osaka at the time of diagnosis, aged 15-99 years at diagnosis, and had undergone surgery at hospitals in Osaka. We excluded those who underwent surgery at clinics or those whose deaths were exclusively notified by death certificates. The remainder were included in the study sample for generating variables for hospital volume. For survival analysis, we excluded those aged

85-99 years as older age is a critical confounder to the choice of hospital^{23,24} and survival probability. Male breast cancer cases and cases where there was a lack of information regarding the survival status at 5 years from diagnosis or the survival period between the diagnosis and the last observation were excluded from the analysis (Figure 1).

2.3 | Potential confounders

The following variables were used as potential confounders: year of diagnosis (2007, 2008, 2009, 2010 and 2011), sex (men and women), age group (15-54, 55-64, 65-74 and 75-84), stage of cancer (localized [cancer remained in the initial organ], regional [cancer spread to regional lymph nodes or adjacent tissues],

distant [cancer spread to distant organs] and unknown), extent of resection of primary tumor (all, partial and unknown), receipt of adjuvant therapy (received, not received and unknown), receipt of radiation therapy (received, not received and unknown) and residential area (eight divisions according to the prefectural medical administration system).

2.4 | Study outcome

The primary outcome of this study was the 5-year survival from the time of cancer diagnosis. We terminated observations on the date of death that might have occurred any time within 5 years from diagnosis or were censored at 5 years from diagnosis, if participants survived.

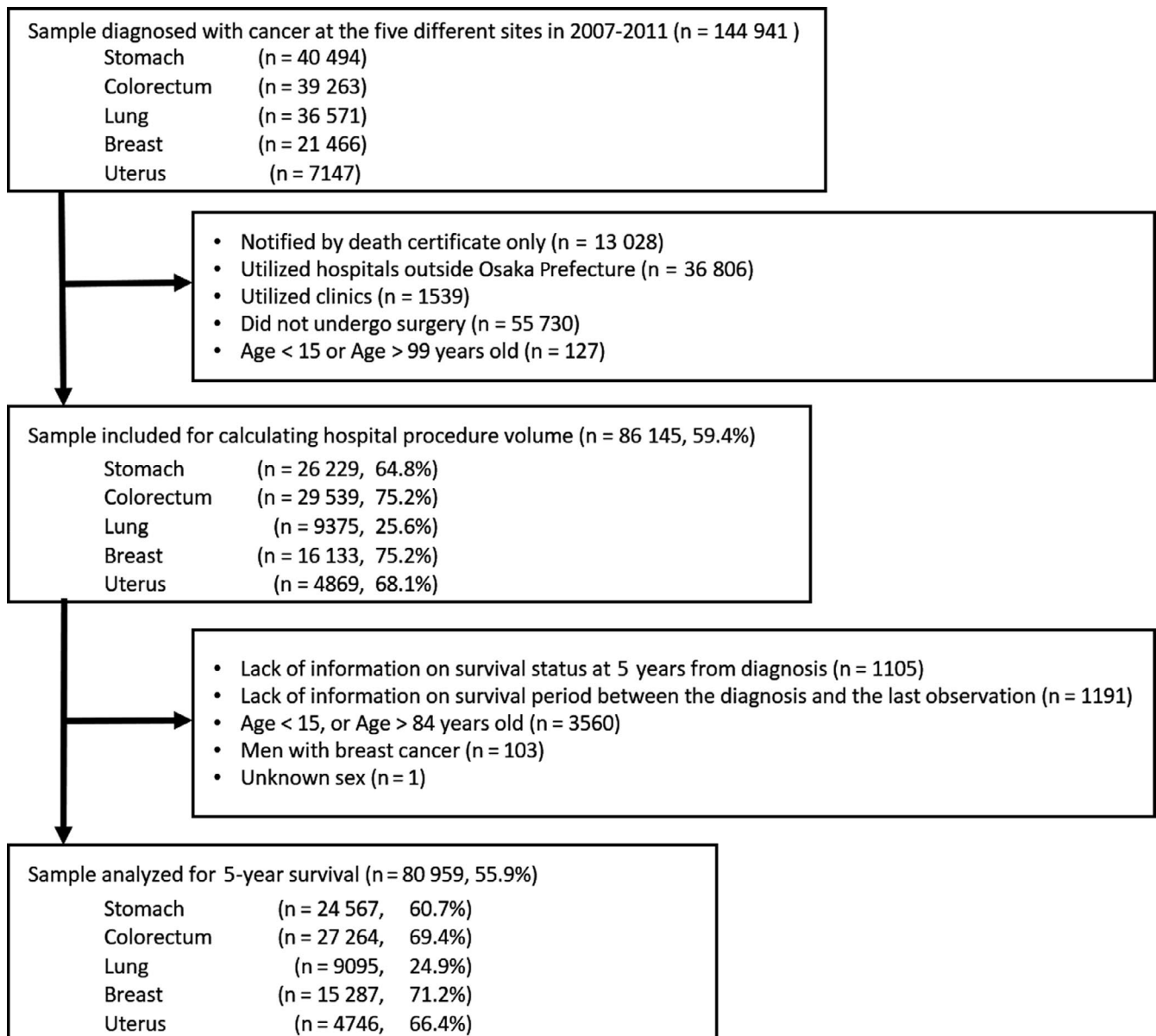


FIGURE 1 Flowchart of the study sample selection

2.5 | Categorization of hospital volume

We defined hospital volume as the annual average volume of surgeries undertaken by a hospital for each site of cancer. The surgical procedures referred to were open, endoscopic or laparoscopic resections performed on patients aged 15-99 years. For categorization of hospital volumes, we calculated average annual surgery volumes during 2007-2011, and ranked hospitals by their annual surgery volume. We then sorted patients in descending order of surgery volumes and assigned them into four equally sized groups (high-volume, medium-volume, low-volume and very low-volume hospitals).

2.6 | Statistical analysis

First, we calculated the number of hospitals, mean and the range of annual surgery volume, and the number of patients for each hospital volume category. We compared the distribution of the basic characteristics of the study sample among the five selected cancer sites. We then estimated the mortality hazard ratios of hospital volumes using the Cox proportional hazard regression model. In the model, we controlled potential confounders, including the year of diagnosis, sex, age group, cancer stage, extent of resection of primary tumor, receipt of adjuvant therapy, receipt of radiation therapy and residential area. We adjusted the confidence intervals of the hazard ratio using robust estimators of variance as the study sample within the same hospital would have cluster correlations. Finally, we estimated adjusted survival rates based on multivariable Cox proportional hazard regression. To provide further supporting information, we examined factors associated with surgery at very low-volume hospitals (1 = very low-volume

hospitals, 0 = high-volume, medium-volume and low-volume hospitals) using multivariable logistic regression. We defined statistical significance as a *P*-value of <0.05. The Stata 14.2 statistical software package was used for all analyses (Stata).

2.7 | Ethical considerations

We obtained ethical approval from the Institutional Review Board of Osaka International Cancer Institute (approval number: 18-0018) before initiating the study. The data had been anonymized before use.

3 | RESULTS

We identified 144 941 cases diagnosed with cancer at any of the five selected sites between 2007 and 2011, selected 86 145 cases for generating categorical variables for hospital volume, and identified 80 959 cases for survival analysis (Figure 1). After excluding ineligible samples, the number of study samples included in the analysis was: 24 567 for stomach cancer, 27 264 for colorectal cancer, 9095 for lung cancer, 15 287 for breast cancer and 4746 for uterine cancer. In comparison to the initial sample diagnosed with cancer at the selected sites, the sample who received surgery and met the criteria for analysis fell to 60.7% for stomach cancer, 69.4% for colorectal cancer, 24.9% for lung cancer, 71.2% for breast cancer and 66.4% for uterine cancer.

Table 1 shows the hospital characteristics per hospital volume category. After assigning study samples to the hospital volume quartiles, the number of hospitals included in the analysis was 170 for stomach cancer, 183 for colorectal cancer, 105 for lung cancer, 120

TABLE 1 Distribution of hospitals and annual hospital volume by hospital volume category

	Stomach	Colorectum	Lung	Breast	Uterus
Hospital: N (%)	170 (100.0)	183 (100.0)	105 (100.0)	120 (100.0)	69 (100.0)
High	6 (3.5)	8 (4.4)	3 (2.9)	5 (4.2)	3 (4.3)
Medium	11 (6.5)	13 (7.1)	6 (5.7)	8 (6.7)	5 (7.2)
Low	18 (10.6)	20 (10.9)	11 (10.5)	13 (10.8)	8 (11.6)
Very low	135 (79.4)	142 (77.6)	85 (81.0)	94 (78.3)	53 (76.8)
Hospital volume: mean (range)					
High	197.1 (167.4-228.8)	169.6 (141.2-205.0)	140.0 (111.2-164.2)	154.8 (112.6-197.8)	71.9 (64.8-84.6)
Medium	128.7 (98.6-151.2)	119.5 (100.0-139.0)	83.0 (68.0-109.0)	95.8 (86.0-108.0)	53.5 (45.4-59.0)
Low	73.3 (57.8-93.8)	73.8 (53.6-94.6)	44.2 (31.2-65.4)	66.4 (44.8-80.6)	29.8 (19.4-45.0)
Very low	9.8 (0.2-50.6)	10.7 (0.2-53.4)	5.5 (0.2-26.0)	8.8 (0.2-43.6)	4.8 (0.2-17.4)
Patients: N (%)	24 567 (100.0)	27 264 (100.0)	9095 (100.0)	15 287 (100.0)	4746 (100.0)
High	5661 (23.0)	6400 (23.5)	2048 (22.5)	3760 (24.6)	1062 (22.4)
Medium	6167 (25.1)	6813 (25.0)	2422 (26.6)	3700 (24.2)	1309 (27.6)
Low	6582 (26.8)	7228 (26.5)	2205 (24.2)	3873 (25.3)	1154 (24.3)
Very low	6157 (25.1)	6823 (25.0)	2420 (26.6)	3954 (25.9)	1221 (25.7)

Note: Annual hospital volume was calculated based on the average annual number of surgeries undergone by patients per hospital during 2007-2011.

for breast cancer and 69 for uterine cancer. Among them, the number of very low-volume hospitals accounted for nearly 76.8%-81.0% of all hospitals. The mean annual volume in the high-volume hospitals was 197.1 for stomach, 169.6 for colorectal, 140.0 for lung, 154.8 for breast and 71.9 for uterine cancer, whereas in the very low-volume hospitals the mean annual volume was 9.8 for stomach, 10.7 for colorectal, 5.5 for lung, 8.8 for breast and 4.8 for uterine cancer.

Table 2 shows the distribution of the study sample characteristics for each cancer site. Men accounted for a higher proportion than women, particularly in the case of stomach cancer (70.7%). Among the four age groups, the group aged 65-74 years accounted for the highest proportion in stomach, colorectal and lung cancers, whereas the group aged 15-54 years accounted for the highest proportion in breast and uterine cancers. Approximately 62%-66% of the study sample was diagnosed with localized stage cancer, except for colorectal cancers (47%). Approximately 76%-86% had undergone complete tumor resection. The distribution of the study sample characteristics per hospital volume category is presented in Tables S1-S5.

Table 3 shows the mortality hazards per hospital volume category per cancer site. For each cancer site, the very low-volume hospitals showed significantly higher mortality hazards than the high-volume hospitals, after controlling for the potential confounders: 1.82 (95% CI: 1.54-2.17) in stomach cancers, 1.57 (95% CI: 1.36-1.81) in colorectal cancers, 1.49 (95% CI: 1.09-2.04) in lung cancers, 1.39 (95% CI: 1.17-1.64) in breast cancers, and 1.36 (95% CI: 1.13-1.64) in uterine cancers. The low-volume hospitals also presented higher mortality hazards than the high-volume hospitals at two sites: 1.30 (95% CI: 1.10-1.53) for stomach cancers and 1.16 (95% CI: 1.02-1.31) for colorectal cancers. The hazard ratios of the other variables are presented in Table S6. Patients who were male, of older age and had regional/distant stages of cancer at diagnosis (except colorectal and uterine cancers) were more likely to undergo surgery at very low-volume hospitals (Table S7).

Figure 2 shows plots of the adjusted 5-year survival rates per hospital volume category. The adjusted 5-year survival rates in high-volume hospitals were 77.1% for stomach cancers, 74.5% for colorectal cancers, 71.8% for lung cancers, 93.4% for breast cancers and 90.0% for uterine cancers. The adjusted 5-year survival rates in very low-volume hospitals were 62.2% in stomach cancers, 63.0% in colorectal cancers, 61.0% in lung cancers, 91.0% in breast cancers and 86.7% in uterine cancers. Thus, the absolute difference (percentage points) in the adjusted 5-year survival rates between high-volume and very low-volume hospitals was 14.9 in stomach cancers, 11.5 in colorectal cancers, 10.8 in lung cancers, 2.4 in breast cancers and 3.3 in uterine cancers. The Kaplan-Meier survival curve and the adjusted survival curve of the Cox proportional hazards model are presented in Figures S1-S5.

4 | DISCUSSION

Patients treated at very low-volume hospitals showed a significantly higher mortality hazard than those treated at high-volume hospitals

across the five selected sites of cancer. However, the strength of the volume-survival relationship varied with the cancer site. The differences in survival probability between very low-volume and low-volume hospitals were greater than those among low-volume, medium-volume and high-volume hospitals. Overall, the results were consistent with those of a previous study conducted at the same study site.⁷ Factors associated with undergoing surgery at very low-volume hospitals were male gender, older age and regional/distant stage at cancer diagnosis.

The absolute differences in survival rates between high-volume and very low-volume hospitals were relatively large in stomach, colorectal and lung cancers (10-15 percentage point difference) compared to breast and uterine cancers (2-3 percentage point difference). This highlights that the strength of the volume-survival relationship varied with the cancer site. Such variations with cancer sites suggest that the surgery volume standard should be defined by the cancer site or surgery type, and the application of a minimum volume standard would be beneficial for improving patient survival, particularly in surgeries for cancer with a strong volume-survival relationship. Based on this idea, many countries have adopted minimum surgery volumes per cancer site; however, their thresholds vary. For instance, the minimum surgery volume for lung cancer is 50 cases in Canada and 20 in the Netherlands.²⁶ This suggests that volume standards should be formulated based on country-specific characteristics, such as the burden of cancer and healthcare systems.

Moreover, the plots of adjusted survival rates per hospital volume category showed a wider interval between very low-volume and low-volume hospitals, whereas narrower intervals were observed among low-volume, medium-volume and high-volume hospitals. The findings have two implications. First, a hospital with a lack of surgical experience may negatively affect patient survival. This supports the idea that applying a minimum hospital volume standard, is advantageous. Second, patient survival may not be affected by the hospital volume if hospitals perform a greater number of surgical procedures than the minimum volume threshold. Because the site of the study was an urban area with the third largest population in the country, the hospitals with low-volume or medium-volume may have had frequent opportunities to perform surgeries^{32,33} compared to rural areas. Thus, hospitals with very low surgery volumes should proactively refer their patients to higher volume hospitals. The performance of hospitals with very low surgery volumes should be carefully monitored to raise the standard of surgeries across hospitals in the study area.

The volume-survival relationship observed in this study was generally consistent with that of a previous study conducted in Osaka in 1994-1998⁷; the lower volume hospitals showed higher mortality hazards. However, the hazard ratios of medium-volume and low-volume hospitals relative to high-volume hospitals were not necessarily comparable. Definitions of hospital volume may have been responsible for the difference; we used surgery volume as the definition, whereas the previous study used treatment volumes, including surgery, radiotherapy, chemotherapy and others;

TABLE 2 Basic characteristics of study sample

Characteristics	Stomach	Colorectum	Lung	Breast	Uterus
	N (%)	N (%)	N (%)	N (%)	N (%)
Years of diagnosis					
2007	4619 (18.8)	5198 (19.1)	1672 (18.4)	2963 (19.4)	866 (18.2)
2008	4549 (18.5)	4927 (18.1)	1611 (17.7)	2843 (18.6)	790 (16.6)
2009	4845 (19.7)	5301 (19.4)	1711 (18.8)	2840 (18.6)	867 (18.3)
2010	5100 (20.8)	5717 (21.0)	1940 (21.3)	3295 (21.6)	1073 (22.6)
2011	5454 (22.2)	6121 (22.5)	2161 (23.8)	3346 (21.9)	1150 (24.2)
Sex					
Men	17 369 (70.7)	16 341 (59.9)	5829 (64.1)	–	–
Women	7198 (29.3)	10 923 (40.1)	3266 (35.9)	15 287 (100.0)	4746 (100.0)
Age group					
15-54	2022 (8.2)	2597 (9.5)	671 (7.4)	5700 (37.3)	2132 (44.9)
55-64	5758 (23.4)	6737 (24.7)	2289 (25.2)	4228 (27.7)	1464 (30.8)
65-74	9621 (39.2)	10 358 (38.0)	3833 (42.1)	3492 (22.8)	838 (17.7)
75-84	7166 (29.2)	7572 (27.8)	2302 (25.3)	1867 (12.2)	312 (6.6)
Cancer stage					
Localized	15 347 (62.5)	12 892 (47.3)	5702 (62.7)	10 074 (65.9)	3071 (64.7)
Regional	6320 (25.7)	9256 (33.9)	2660 (29.2)	4665 (30.5)	1325 (27.9)
Distant	2501 (10.2)	4569 (16.8)	566 (6.2)	275 (1.8)	230 (4.8)
Unknown	399 (1.6)	547 (2.0)	167 (1.8)	273 (1.8)	120 (2.5)
Extent of resection of primary tumor					
All	19 486 (79.3)	21 288 (78.1)	6910 (76.0)	13 117 (85.8)	3817 (80.4)
Partial	3320 (13.5)	4125 (15.1)	1459 (16.0)	1280 (8.4)	533 (11.2)
Unknown	1761 (7.2)	1851 (6.8)	726 (8.0)	890 (5.8)	396 (8.3)
Adjuvant therapy					
Yes	5733 (23.3)	9511 (34.9)	2589 (28.5)	10 796 (70.6)	1977 (41.7)
No	18 325 (74.6)	17 145 (62.9)	6316 (69.4)	4145 (27.1)	2695 (56.8)
Unknown	509 (2.1)	608 (2.2)	190 (2.1)	346 (2.3)	74 (1.6)
Radiation therapy					
Yes	73 (0.3)	484 (1.8)	516 (5.7)	5499 (36.0)	597 (12.6)
No	24 016 (97.8)	26 234 (96.2)	8405 (92.4)	9618 (62.9)	4055 (85.4)
Unknown	478 (1.9)	546 (2.0)	174 (1.9)	170 (1.1)	94 (2.0)
Residential area					
Area A	7380 (30.0)	8796 (32.3)	2736 (30.1)	4474 (29.3)	1375 (29.0)
Area B	2710 (11.0)	3163 (11.6)	869 (9.6)	1865 (12.2)	543 (11.4)
Area C	2168 (8.8)	2286 (8.4)	942 (10.4)	1281 (8.4)	380 (8.0)
Area D	2765 (11.3)	2574 (9.4)	983 (10.8)	1594 (10.4)	578 (12.2)
Area E	2365 (9.6)	2854 (10.5)	882 (9.7)	1504 (9.8)	475 (10.0)
Area F	1934 (7.9)	1996 (7.3)	778 (8.6)	1170 (7.7)	418 (8.8)
Area G	2462 (10.0)	2886 (10.6)	1031 (11.3)	1672 (10.9)	515 (10.9)
Area H	2783 (11.3)	2709 (9.9)	874 (9.6)	1727 (11.3)	462 (9.7)

those who did not undergo surgery were also included. We used surgery-based hospital volumes as having undergone surgery implies that the patient had sufficient prior functional ability needed to tolerate surgical damage; this could be a confounder to patient

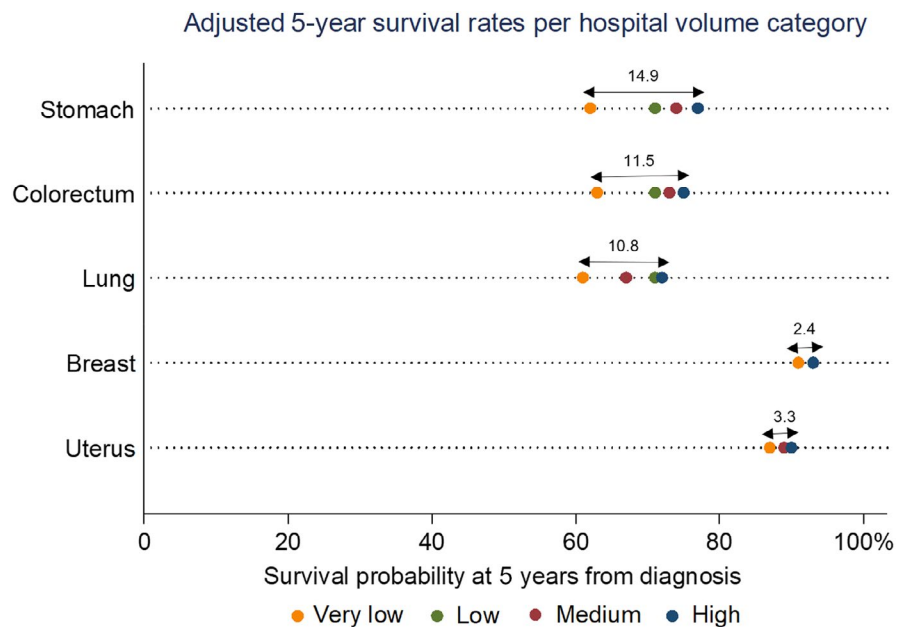
survival. Despite such differences, our study updated the evidence on the volume-survival relationship at the study site. A future analysis with a restricted sample not receiving surgery may be worthwhile.

TABLE 3 Mortality hazards by multivariable Cox proportional hazard regression

	Stomach		Colorectum		Lung		Breast		Uterus	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Crude HR										
High	1.00		1.00		1.00		1.00		1.00	
Medium	1.17	0.93-1.47	1.08	0.93-1.25	1.17	0.83-1.65	1.18	0.98-1.42	0.97	0.82-1.15
Low	1.39	1.11-1.73	1.20	1.04-1.39	1.11	0.81-1.52	1.29	1.06-1.56	1.15	1.05-1.24
Very low	2.29	1.81-2.91	1.76	1.49-2.07	1.70	1.23-2.36	1.75	1.43-2.12	1.19	1.00-1.41
Adjusted HR										
High	1.00		1.00		1.00		1.00		1.00	
Medium	1.14	0.95-1.36	1.08	0.94-1.24	1.20	0.87-1.67	1.09	0.91-1.30	1.10	0.89-1.35
Low	1.30	1.10-1.53	1.16	1.02-1.31	1.03	0.75-1.42	1.10	0.92-1.31	1.15	1.00-1.32
Very low	1.82	1.54-2.17	1.57	1.36-1.81	1.49	1.09-2.04	1.39	1.17-1.64	1.36	1.13-1.64

Note: Adjusted hazard ratios were controlled for year of diagnosis, sex, age group, cancer stage, extent of resection of primary tumor, adjuvant therapy received, radiation therapy received and residential area (The full result is reported in Table S6).

Abbreviations: CI, confidence interval; High, high-volume hospitals; HR, hazard ratio; Low, low-volume hospitals; Medium, medium-volume hospitals; Very low, very low-volume hospitals.

FIGURE 2 Adjusted 5-y survival rates per hospital volume category based on post-estimations of multivariable Cox proportional hazard regression. High, high-volume hospitals; Low, low-volume hospitals; Medium, medium-volume hospitals; Very low, very low-volume hospitals

This study has several limitations. First, the relationship between hospital volumes and patient survival does not explain causality. Second, the lack of individual information, such as socioeconomic characteristics, comorbidity and functional status may have affected the relevance of the study results. Lack of information on hospital characteristics was another limitation as patient volume per surgeon, patient-surgery ratio or the availability of expert surgeons could affect patient outcomes. Furthermore, we could not control time-varying factors, such as the introduction of a new drug or technology, transfer of patients to other hospitals after the primary treatment or experience with other diseases that may affect patient survival.

In conclusion, patients treated at low-volume hospitals were at higher risk of mortality from five cancers. Monitoring hospital

volumes and promoting referral of patients from very low-volume hospitals to specialized hospitals would be beneficial for improving the survival of cancer patients. Furthermore, minimum surgery volume standards per cancer site are worth exploring in future research, and the application of the standards would potentially improve long-term survival among cancer patients in Japan.

ACKNOWLEDGMENTS

This study was supported by Health Labour and Welfare Sciences Research Grants (H29-Gantaisaku-ippan-016 and H30-Gantaisaku-ippan-009) from the Ministry of Health, Labour and Welfare, Japan, a KAKENHI Grant (JP19K19452) from Japan Society for the Promotion of Science, and Osaka Cancer Society, Japan. The funding sources had

no role in the design of the study, in the analysis and interpretation of the data, or in the preparation, review or approval of the manuscript.

DISCLOSURE

The authors have no conflicts of interest to declare.

ORCID

Sumiyo Okawa  <https://orcid.org/0000-0002-2197-7078>

Toshitaka Morishima  <https://orcid.org/0000-0002-0747-3287>

REFERENCES

1. WHO. Cancer key facts. Geneva: WHO; 2018. <https://www.who.int/news-room/fact-sheets/detail/cancer>. Accessed September 4, 2019.
2. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med*. 1979;301:1364-1369.
3. National Research Council. *Interpreting the Volume-Outcome Relationship in the Context of Cancer Care*. Washington, DC: The National Academies Press; 2001.
4. Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. *CA Cancer J Clin*. 2009;59:192-211.
5. Haj Mohammad N, Bernards N, van Putten M, Lemmens V, van Oijen MGH, van Laarhoven HWM. Volume-outcome relation in palliative systemic treatment of metastatic oesophagogastric cancer. *Eur J Cancer*. 2017;78:28-36.
6. Wright JD, Huang Y, Ananth CV, et al. Influence of treatment center and hospital volume on survival for locally advanced cervical cancer. *Gynecol Oncol*. 2015;139:506-512.
7. Ioka A, Tsukuma H, Ajiki W, Oshima A. Hospital procedure volume and survival of cancer patients in Osaka, Japan: a population-based study with latest cases. *Jpn J Clin Oncol*. 2007;37:544-553.
8. Mokdad AA, Zhu H, Marrero JA, Mansour JC, Singal AG, Yopp AC. Hospital volume and survival after hepatocellular carcinoma diagnosis. *Am J Gastroenterol*. 2016;111:967-975.
9. Fischer C, Lingsma H, Klazinga N, et al. Volume-outcome revisited: the effect of hospital and surgeon volumes on multiple outcome measures in oesophago-gastric cancer surgery. *PLoS ONE*. 2017;12:e0183955.
10. Derogar M, Sadr-Azodi O, Johar A, Lagergren P, Lagergren J. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. *J Clin Oncol*. 2013;31:551-557.
11. Billingsley KG, Morris AM, Dominitz JA, et al. Surgeon and hospital characteristics as predictors of major adverse outcomes following colon cancer surgery: understanding the volume-outcome relationship. *Arch Surg*. 2007;142:23-31; discussion 32.
12. Chen CS, Liu TC, Lin HC, Lien YC. Does high surgeon and hospital surgical volume raise the five-year survival rate for breast cancer? A population-based study. *Breast Cancer Res Treat*. 2008;110:349-356.
13. Dikken JL, Dassen AE, Lemmens VE, et al. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009. *Eur J Cancer*. 2012;48:1004-1013.
14. Gooiker GA, Lemmens VE, Besselink MG, et al. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg*. 2014;101:1000-1005.
15. David EA, Cooke DT, Chen Y, Perry A, Canter RJ, Cress R. Surgery in high-volume hospitals not commission on cancer accreditation leads to increased cancer-specific survival for early-stage lung cancer. *Am J Surg*. 2015;210:643-647.
16. Peltoniemi P, Peltola M, Hakulinen T, Hakkinen U, Pylkkanen L, Holli K. The effect of hospital volume on the outcome of breast cancer surgery. *Ann Surg Oncol*. 2011;18:1684-1690.
17. Siesling S, Tjan-Heijnen VC, de Roos M, et al. Impact of hospital volume on breast cancer outcome: a population-based study in the Netherlands. *Breast Cancer Res Treat*. 2014;147:177-184.
18. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. *Ann Surg*. 2007;245:777-783.
19. Haneuse S, Dominici F, Normand SL, Schrag D. Assessment of between-hospital variation in readmission and mortality after cancer surgical procedures. *JAMA Netw Open*. 2018;1:e183038.
20. Aquina CT, Probst CP, Becerra AZ, et al. High volume improves outcomes: the argument for centralization of rectal cancer surgery. *Surgery*. 2016;159:736-748.
21. Murata A, Muramatsu K, Ichimiya Y, Kubo T, Fujino Y, Matsuda S. Influence of hospital volume on outcomes of laparoscopic gastrectomy for gastric cancer in patients with comorbidity in Japan. *Asian J Surg*. 2015;38:33-39.
22. Enzinger PC, Benedetti JK, Meyerhardt JA, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. *Ann Surg*. 2007;245:426-434.
23. Liu JB, Bilimoria KY, Mallin K, Winchester DP. Patient characteristics associated with undergoing cancer operations at low-volume hospitals. *Surgery*. 2017;161:433-443.
24. Tsukada Y, Nakamura F, Iwamoto M, et al. Are hospitals in Japan with larger patient volume treating younger and earlier-stage cancer patients? An analysis of hospital-based cancer registry data in Japan. *Jpn J Clin Oncol*. 2015;45:719-726.
25. Dimick JB, Birkmeyer JD, Upchurch GR Jr. Measuring surgical quality: what's the role of provider volume? *World J Surg*. 2005;29:1217-1221.
26. Morche J, Renner D, Pietsch B, et al. International comparison of minimum volume standards for hospitals. *Health Policy*. 2018;122:1165-1176.
27. Agency for Healthcare Research and Quality. Toolkit for using the AHRQ quality indicators. Rockville, MD; 2017. <https://www.ahrq.gov/patient-safety/settings/hospital/resource/qitool/index.html>. Accessed October 7, 2019.
28. The Leapfrog Group. About our rating: inpatient surgery surgical volume. Washington, DC; 2018. <http://www.leapfroggroup.org/ratings-reports/surgical-volume>. Accessed October 7, 2019.
29. Ministry of Health Labour and Welfare. Maintenance of eligibility criteria for designated cancer care hospitals. Tokyo: Ministry of Health Labour and Welfare; 2018. <https://www.mhlw.go.jp/content/000347080.pdf>. Accessed October 7, 2019.
30. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of hospital procedure volume on ovarian cancer survival in Japan, a country with low incidence of ovarian cancer. *Cancer Sci*. 2004;95:233-237.
31. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of hospital procedure volume on uterine cancer survival in Osaka, Japan. *Cancer Sci*. 2005;96:689-694.
32. Nomura E, Tsukuma H, Ajiki W, Oshima A. Population-based study of relationship between hospital surgical volume and 5-year survival of stomach cancer patients in Osaka, Japan. *Cancer Sci*. 2003;94:998-1002.
33. Nomura E, Tsukuma H, Ajiki W, Ishikawa O, Oshima A. Population-based study of the relationship between hospital surgical volume and 10-year survival of breast cancer patients in Osaka, Japan. *Cancer Sci*. 2006;97:618-622.
34. Odagiri H, Yasunaga H, Matsui H, Matsui S, Fushimi K, Kaise M. Hospital volume and adverse events following esophageal endoscopic submucosal dissection in Japan. *Endoscopy*. 2017;49:321-326.

35. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886.
36. Osaka Prefectural Government. Census 2010. Osaka: Osaka Prefectural Government; 2011. <http://www.pref.osaka.lg.jp/attach/1891/00039840/h22kokuchou1jikihon.pdf>. Accessed October 7, 2019.
37. Ikegami N, Yoo BK, Hashimoto H, et al. Japanese universal health coverage: evolution, achievements, and challenges. *Lancet*. 2011;378:1106-1115.
38. Osaka Prefectural Department of Public Health and Welfare (OPDPHW), Osaka Medical Association, Osaka Medical Center for Cancer and Cardiovascular Diseases. Annual report of Osaka Cancer Registry No.80 - cancer incidence and medical care in Osaka in 2012/2011 and the survival in 2009. Osaka: OPDPHW; 2016.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Okawa S, Tabuchi T, Morishima T, Koyama S, Taniyama Y, Miyashiro I. Hospital volume and postoperative 5-year survival for five different cancer sites: A population-based study in Japan. *Cancer Sci*. 2020;111:985-993. <https://doi.org/10.1111/cas.14309>