How asymptomatic are early cancer patients of five organs based on registry data in Japan

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Abstract

Background

One reason for the low cancer screening rate in Japan is that people are not concerned about cancer if they do not have symptoms.

Methods

The authors retrospectively analyzed 18,405 cancer patients using hospital-based cancer registry data collected between 2007 and 2013 at the 13 hospitals of Shimane Prefecture, Japan. The symptomatic rates of five cancers (stomach, colorectal, lung, breast, and cervix) at each stage and the time of early diagnosis were investigated. The early detection rates of symptomatic and asymptomatic individuals were investigated.

Results

The percentages of symptomatic cases tended to increase with progressive stages. The odds ratio (OR) of stage IV compared with that of stage I was 12.23 for stomach, 7.21 for colorectal, 16.91 for lung, 10.30 for breast, and 51.62 for cervical cancer. The proportions of early symptomatic cases at the time of diagnosis were low. Compared with the percentage of early symptomatic cases of stomach cancer of 25.5%, the percentage of lung cancer was the lowest, at 8.2% (OR, 0.26), and the percentage of breast cancer was the highest, at 30.2% (OR, 1.26). The percentage of early symptomatic cases of colorectal and cervical cancer were 18.9% (OR, 0.68) and 19.9% (OR, 0.73), respectively. The early detection rates of the asymptomatic and symptomatic groups were 77.6 % and 36.1 %, respectively.

Conclusion

Cancer registry data indicate that early cancers are asymptomatic, and once symptoms appear, treatment may

not be effective. Policy makers should inform people of the necessity of cancer screening before they have symptoms.

(250 words)

Key words: symptomatic rate, hospital-based cancer registry, cancer screening, cancer stage

Text

Introduction:

There are primary and secondary cancer prevention policies to reduce cancer mortality. Primary prevention reduces the cancer incidence by improving lifestyle habits, such as smoking cessation[1)], and secondary prevention consists of cancer screening for early detection and early treatment[2-6)]. Data are indispensable for deciding how to proceed with cancer policy and to evaluate whether the cancer policy is effective. Cancer registration can provide data on cancer incidence and patient survival, telling us whether a high mortality rate is due to a high incidence rate, low survival rate, or a lack of screening. The evidence gained using cancer registration data is indispensable for effective cancer screening.

Cancer screening guidelines for breast, cervical, lung, and colorectal cancer have been published by the American Cancer Society[7)] and the US Preventative Services in the United States[8)]. The first screening test to be widely used for cancer was the Pap test, which became widely used in the early 1960s. Modern mammography methods were developed late in the 1960s and were recommended in 1976[7)]. Lung cancer screening was suspended in the 1970s because radiography showed no mortality benefit[9-10)]; however, screening was reintroduced in the 1990s because chest CT with radiography was superior to chest radiography alone for detecting lung cancer[11-12)].

In Japan, the Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, publishes cancer screening guidelines for the colorectum, lung, breast, cervix, and stomach[13-16)], which are common cancer sites in Japan. Stomach cancer screening began in Miyagi Prefecture circa 1960. The Health and Medical Service Law for the Aged was enacted in 1983, and cancer screening supported by law

began in many prefectures at that time. Screening for cancer in five organs has been defined by guidelines from the Japanese Ministry of Health, Labour and Welfare. The guidelines recommend photofluorography or endoscopy for the stomach, a fecal occult blood test for colorectal cancer, sputum cytology and X-rays for lung cancer, a mammogram for breast cancer, and a smear test for uterine cancer [17].

The screening rate is extremely low in Japan compared with other Organisation for Economic Co-operation and Development (OECD) countries. For example, for both breast and cervical cancer screening in 2013, the frequency of screening in Japan (41.0% and 42.1%, respectively) was much lower than in the U.S. (80.8% and 84.5%), the UK (75.9% and 78.1%) and France (52.1% and 73.6%)[18-19]. Many Japanese people were diagnosed with cancer after visiting a medical institution because they presented with subjective symptoms. Several studies have been performed on the association between subjective symptoms and cancer of a single organ[20-27]; however, little is known about the relationship between symptoms and the cancer stage for several organs.

The aim of this study was to analyze symptom severity according to the cancer stage for five organs. In addition, this study investigated the relationship between subjective symptoms and early detection. These data could be used to encourage people to receive cancer screening, contributing to the early detection and treatment of cancer.

Methods

Cancer registry data

The authors used hospital-based cancer registry data[28] collected between 2007 and 2013 by 13 hospitals in Shimane Prefecture, Japan. To improve cancer care, Shimane Prefecture has collected hospital-based cancer registry data at Shimane University, which is a designated prefecture cancer care hospital. Of the 13 hospitals, five are designated by the Ministry of Health, Labour and Welfare, and eight are designated by Shimane Prefecture. The hospital-based cancer registry data from the 13 hospitals include more than 90% of the regional-based cancer registrations in the area.

In the hospital-based cancer registry, information on all primary cancer patients diagnosed or treated at the hospitals is collected by cancer registrars belonging to each hospital. Each registry item used in this study was extracted from cancer registrars based on the medical records according to the standard registry definition[29], although the information extraction was insufficient when the medical records were incomplete. The authors used the registration items, the topology (site) and morphology (histology) code of the International Classification of Diseases for Oncology, third Edition (ICD-O-3)[30], the clinical and pathological stages of the Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) system[31-32], route to discovery, and subjective symptoms at diagnosis[28].

Subjective symptoms were registered in cases of direct symptoms due to the tumor from the description of the medical record. If symptoms were caused by other diseases, they were registered as ‘nothing’. Subjective symptoms were defined by their presence or absence, and the type was unknown. Subjective symptoms at diagnosis were not recorded in the nationwide collection[33], but these symptoms were recorded in Shimane Prefecture.

The final cancer stages were a combination of the clinical stages and pathological stages of the UICC TNM.

Cancer stages were classified according to the UICC TNM classification 6th edition[31] from 2007 to 2011, and the UICC TNM classification 7th edition[32] from 2012 to 2013. There were 104 cases (0.6%) of the 18,405 cases in which the UICC TNM classification in the 6th edition and the 7th edition became different stages. We converted all the classifications from the UICC 7th edition to those of the 6th edition.

Cervical cancer has different characteristics even in stage I, so the authors analyzed it by subdividing the classification into stage IA and IB. Stage 0 of cervical cancer is equivalent to cervical intraepithelial neoplasia grade 3 (CIN 3). CIN 3 that involves severe dysplasia and carcinoma in situ (CIS) is registered as stage 0 in the cancer registration.

Although different stages are regarded as early stages depending on the organ, early stage cancer was defined as stages 0 and I in this study.

Of the 41,202 cases registered between 2007 and 2013, 35,076 initial-treatment cases were included in our study to avoid duplication among patients who visited multiple medical institutions. Cases of diagnosis only and cases registered after the start of the initial treatment were excluded. Overall, 30,985 data points were used for the analysis, and items that indicated final stages and unknown symptoms were excluded because these aspects were the object of the analysis. Finally, a total of 18,405 data points were selected: 4,897 for stomach cancers, 6,614 for colorectal cancers, 3,481 for lung cancers, 2,514 for breast cancers, and 899 for cervical cancers (Figure 1).

To evaluate early detection, the stage distribution at the time of diagnosis was investigated. The percentage of symptomatic cases for each stage and the percentage of symptomatic cases at the time of early diagnosis were investigated. Then, the rates of early detection for the symptomatic and asymptomatic groups were investigated.

Statistical analysis

This study was approved by the institutional review board of Shimane University Hospital, and the authors obtained permission to use data from the Shimane Prefecture cancer registration review committee.

The percentages of symptomatic cases were compared using the chi-square test and Fisher's exact test. P-values < 0.05 were considered significant. A logistic regression model was used to calculate the odds ratio with a 95% confidence interval. The statistical analyses were conducted using JMP® 12 (SAS Institute Inc., Cary, NC, USA).

Results

Distribution of UICC TNM stages at diagnosis

To evaluate early detection by organ, the distribution of the UICC TNM stages at diagnosis for both the Shimane data and the nationwide collection[33] was examined (Figure 2). The percentage of early detection was defined as the number of cases diagnosed at stages 0 and I among all cases in this study. The percentages of early detection in the Shimane and the nationwide collections were 62.8 % and 66.4% in the stomach, 52.4% and 42.4% in the colorectum, 39.1% and 43.4% in the lungs, 53.4% and 55.1% in breast tissue, and 83.5% and 81.0% in the cervix.

The Shimane and the nationwide collections had similar stage distributions. Cervical cancer tended to be detected early, whereas the early detection of lung cancer was the least frequent among the five organs. However, the relative frequency of detection of stage IV lung cancer was 32.0%, which was higher than the relative frequency of detection of stage IV cancer in any of the other organs.

The frequency of symptoms at each UICC TNM stage

The percentages of the symptomatic cases for each cancer UICC TNM stage are shown in Table 1. The proportion of symptomatic cases tended to increase as the cancer stage progressed in the five organs. The frequencies of symptomatic cases for each cancer stage showed different trends depending on the organ. For the stomach and colorectum, the frequencies of symptomatic cases at stages 0 and I were less than 50%, whereas the proportion at stage II was greater than 50%. Lung cancer had a lower proportion of symptomatic cases than cancer of any other organ at any stage from stages 0 to IV. The percentage of symptomatic cases for the lungs in stage IV was 81.9%, and approximately 20% of patients did not present subjective symptoms at the time of diagnosis. Breast tissue had the most subjective

symptoms, and the symptomatic cases represented 44.7% even at stage 0. Cervical cancer has a symptomatic frequency exceeding 70% at the stage IB or higher, but a symptomatic frequency of only 20% to 30% in CIN3 to the stage IA.

The relative frequencies of symptomatic cases in early cancer stages

As Table 2 shows, the frequencies of symptomatic cases in early cancer stages were low in the five organs. The frequency of symptomatic cases at an early cancer stage was the highest for breast at 30.2% and the lowest for lung at 8.2%. Compared with stomach cancer, the odds ratio of the subjective symptoms at the early cancer stage for breast cancer was the highest, at 1.26, and that for lung cancer was the lowest, at 0.26.

Early detection in the symptomatic and asymptomatic groups

The early detection rates for the symptomatic and asymptomatic groups were calculated (Table 3). The early detection rates for the asymptomatic groups were higher than for the symptomatic groups for each organ. The percentage of early detection of stomach cancer among the asymptomatic group was 86.2%, whereas the percentage for the symptomatic group was 44.9%. Similar percentage of 74.9% and 34.2% were observed for colorectal cancer, 64.5% and 15.8% for lung cancer, 76.7% and 43.3% for breast cancer, and 98.8% and 55.9% for cervical cancer.

Discussion

This study found that the proportion of symptomatic cases increased with the progression of the cancer stage. The percentages of symptomatic cases in early cancer were low, with the highest being 30% for breast cancer and the lowest being 8% for lung cancer. Cancer must be detected at an early stage for a high probability of survival. However, the relative frequencies of symptomatic cases in early cancer stages were low, and cancer might already have become advanced by the time the subjective symptoms appeared.

The frequencies of symptomatic cases for each cancer stage showed different trends depending on the organ. Although the percentages of symptomatic cases in the early stomach and colorectum cancer stages were low (stomach 25.5% and colorectum 18.9%), the early detection percentages at diagnosis were high (stomach 62.8% and colorectum 52.4%). Some cases were diagnosed before symptoms appeared. Similar trends were observed for the stage distributions in the hospital-based cancer registration nationwide data[33)] and the regional cancer registration nationwide data[34-35)].

The percent (8.2%) of symptomatic cases in the early stages of lung cancer was the lowest, the symptoms appearing at the odds ratio of 0.26 compared with that of stomach cancer. The stage distribution of lung cancer seemd to have two peaks; the early stages was at 39.1% and the stage IV was at 32.0%. The same trend was observed for other cancer registration data[33-35)]. Because lung cancer was asymptomatic at the early stages, if it was not detected by cancer screening or by an examination during follow-up for another disease, then it might be found by an examination after it had progressed and symptoms appeared. This characteristic was presumed to be the cause of many advanced cases of lung cancer.

Breast cancer tended to be the most symptomatic among the five organs because the tumor could often be

detected by touch by the patient. The frequency of symptomatic cases in the early stages of breast cancer was approximately 1.3 times higher than for the stomach. Nevertheless, the percentage was only 30.2% for breast cancer, and breast cancer screening is necessary for efficient early detection.

The percentages of symptomatic cases in cervical cancer were 19.1% in CIN3, 30.4% in stage IA, and more than 72.7% in stage IB. Early cervical cancer has a good prognosis, but it tends to be asymptomatic, so it is important to detect it by screening. In addition, if patients wish to become pregnant and their cancer is in an early stage, fertility preservation therapy can be considered[36].

According to our survey, asymptomatic patients tended to be diagnosed earlier than symptomatic patients (Table 3). Therefore, it is important for Japanese people to be screened for cancer even when they are asymptomatic.

Various cancer policies are proposed to reduce cancer mortality, including primary and secondary prevention approaches. Early detection and early treatment can enhance the quality of life for patients through minimally invasive treatment[37-40]. Cancer screening in Japan began in 1983. The cancer screening rate in Japan has been much lower than the rates in other OECD countries. Although the different survey methods used in each country might have affected the OECD cancer screening rate data[18]. The basic plan for promoting cancer control in Japan proposed to increase the cancer screening rate to 50% in 2007[40], but this has not been achieved.

The Cabinet Office Government of Japan conducted a public opinion poll on the reasons for not receiving cancer screening in 2014. The main reasons were "No time to receive cancer screening", "Economic burden", "Afraid of detecting cancer", "Confident in health", and "Able to see a doctor at any time"[41]. Psychological problems and medical system problems were also mentioned as factors. Even if people do not receive a cancer screening, they can be examined

at a medical institution at any time because Japan has nationwide insurance with free access. If they are visiting a medical institution for other diseases, they can undergo a detailed examination such as image diagnosis and endoscopic examination. However, rising medical costs are a problem in Japan. It is becoming difficult to pay medical insurance for diseases unrelated to the main disease since the introduction of the Diagnosis Procedure Combination/Per-Diem Payment System[42] of 2003. If examinations unrelated to the main disease are reduced, cancers might not be discovered by chance during observation for another disease.

In the United States, medical insurance covers cancer screening, so the cancer screening rate is higher. For those who do not have medical insurance, the country provides cancer screening. Organized cancer screening is carried out by the local government in European countries. Organized cancer screening is a mechanism by which the local government prepares a list of people and thoroughly calls and recalls them to recommend screening based on scientific evidence[43-44].

In Japan, cancer screening is provided by local governments. When cancer screening began in 1983 based on the Health and Medical Service Law for the Aged, there was a specific financial resource that could be used for cancer screening. Since the financial resources for cancer screening were converted to general resources in 1998, expenses for cancer screening became the burden of local governments.

However, local governments are trying to improve the cancer screening rate by organized cancer screening as in European countries. Baron et al. reported that a reminder-recall system (in which a healthcare provider sends letters to target persons) is effective for improving cancer screening rates of patients in a systematic review[45].

Ishikawa et al. proposed a more effective reminder-recall system. They stratified people into three groups:

group 1, high screening intention; group 2, low screening intention and high cancer worry; and group 3, low screening intention and low cancer worry. They found that it was effective to give different messages to the different groups[46].

This study adds further information in the form of numerical values to the reminder-recall system message. The low screening intention/high cancer worry group could be informed that if they are diagnosed asymptomatically by cancer screening, the probability of detecting cancer at an early stage is 64.5-98.8%. The low screening intention/low cancer worry group could be informed that 8.2-30.2% of cancers are asymptomatic at an early stage, so it could be beneficial to receive cancer screening even without symptoms.

Policy makers and healthcare providers need to improve the cancer screening rate by implementing an effective reminder-recall system. Lung cancer rarely shows symptoms, so the reminder-recall system needs to emphasize that. In addition, women should not be rely on self-checks because only 30% of early breast cancer cases are symptomatic

Conclusions

To reduce the mortality rates, cancer must be detected and treated at an early stage. The results of this study show that the frequency of symptomatic cases tended to increase as the cancer stage progressed, and the frequency of symptomatic cases at the early stages of cancer were lower than those at advanced stages in the five organs. Therefore, the cancer may have already progressed when the patients received a consultation at a medical institution after the appearance of subjective symptoms. Lung cancer was the least symptomatic and the most advanced at diagnosis among the five organs, and breast cancer was the most frequently symptomatic at the early stages, but the frequency was only 30%. If patients are diagnosed asymptomatically, the probability of the cancer being at an early stage is 77.6%, but if

patients are diagnosed after symptoms appear, the probability of the cancer being at an early stage will drop to 36.1%. Thus, policy makers should inform people of the necessity of receiving cancer screening before they have symptoms.

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Conflicts of Interest

The authors declare that they have no conflicts of interest associated with this manuscript.

(2997words)

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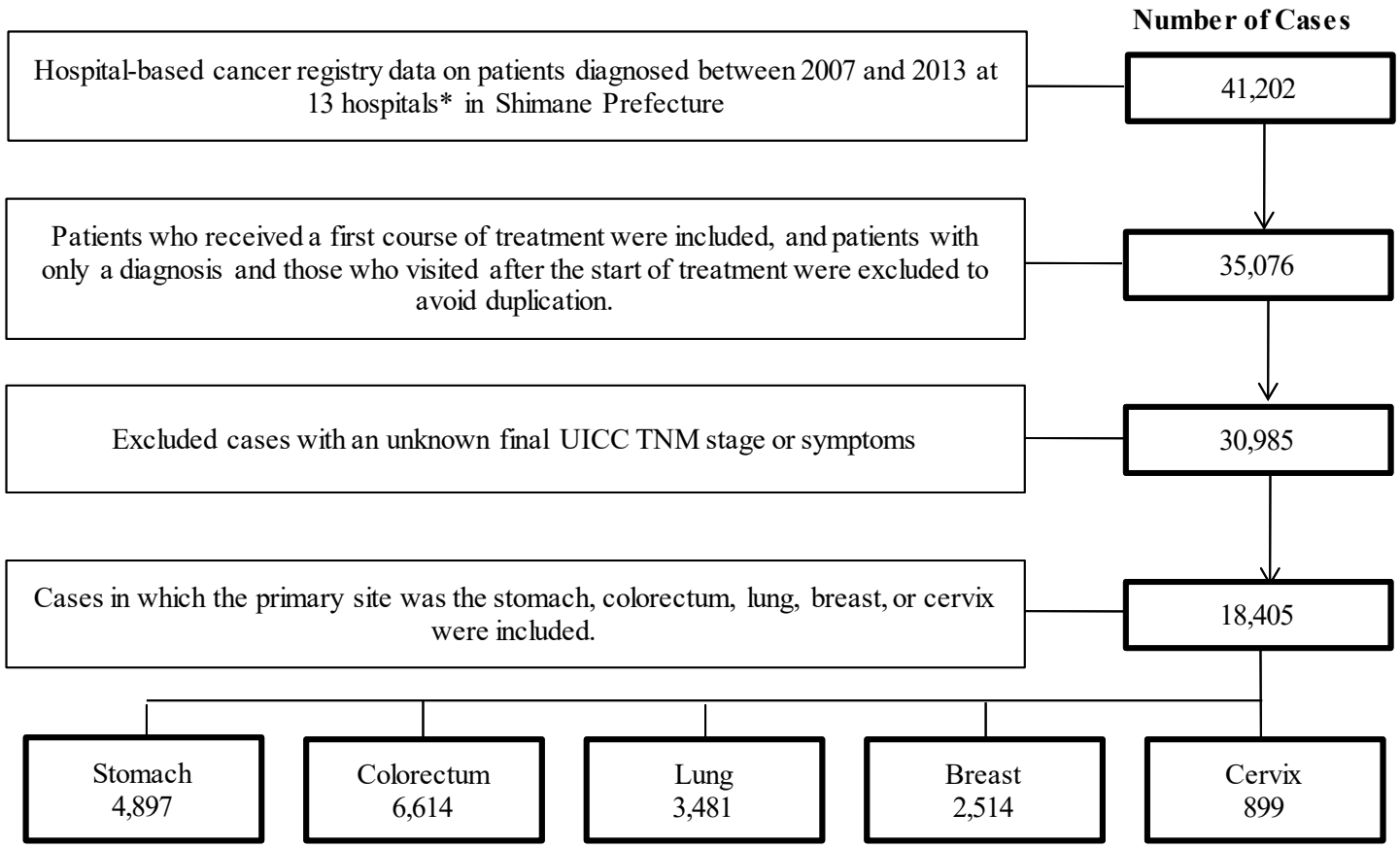

Figure 1. Schematic of data collection

*Five hospitals are government-designated cancer care hospitals, and 8 hospitals are cancer information promotion hospitals designated by Shimane Prefecture.

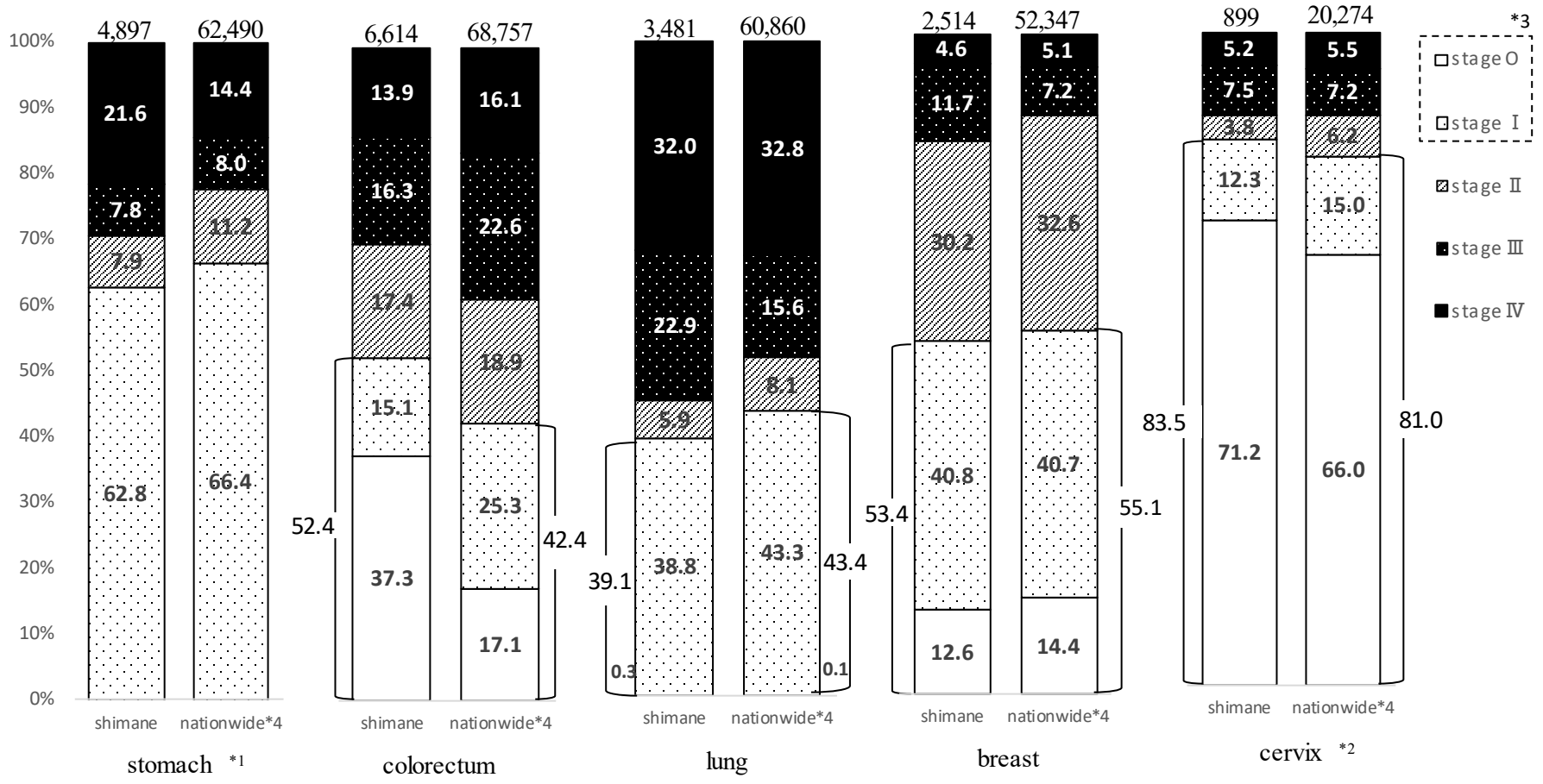

Figure 2.Distribution of UICC TNM stage at diagnosis of Shimane and Nationwide collection

*1 Stage 0 in the stomach is not defined according to the Japanese Hospital-based cancer registry .

*2 Stage 0 in the cervix is equivalent to CIN III (cervical intraepithelial neoplasia, grade III).

*3 Early-stage cancer was defined as stage 0 and I in this study.

*4 NCC, The 2015 National Cancer Statistics Report from hospital-based cancer registry

Table 1. Symptomatic cases in each cancer UICC TNM stage

Cancer types and stages	No. of total cases	Symptomatic cases		Asymptomatic cases		*p*-value[*1]	Odds ratio symptoms (+)/(-) [*3]	(95% CI)				*p*-value[*2]
Stomach						<.0001						
stage I	3,075	1,248	(40.6)	1,827	(59.4)		1.00					
stage II	385	284	(73.8)	101	(26.2)		4.12	(	3.26	-	5.24	) <.0001
stage III	380	302	(79.5)	78	(20.5)		5.67	(	4.40	-	7.39	) <.0001
stage IV	1,057	944	(89.3)	113	(10.7)		12.23	(	9.98	-	15.13	) <.0001
Colorectum						<.0001						
stage O	2465	805	(32.7)	1660	(67.3)		0.61	(	0.52	-	0.70	) <.0001
stage I	1,001	445	(44.5)	556	(55.5)		1.00					
stage II	1,150	829	(72.1)	321	(27.9)		3.23	(	2.70	-	3.86	) <.0001
stage III	1,077	792	(73.5)	285	(26.5)		3.47	(	2.89	-	4.18	) <.0001
stage IV	921	785	(85.2)	136	(14.8)		7.21	(	5.80	-	9.02	) <.0001
Lung						<.0001						
stage O	11	1	(9.1)	10	(90.9)		0.37	(	0.02	-	1.97	) 0.2854
stage I	1,351	285	(21.1)	1,066	(78.9)		1.00					
stage II	206	98	(47.6)	108	(52.4)		3.39	(	2.51	-	4.37	) <.0001
stage III	798	516	(64.7)	282	(35.3)		6.84	(	5.64	-	8.33	) <.0001
stage IV	1,115	913	(81.9)	202	(18.1)		16.91	(	13.86	-	20.71	) <.0001
Breast						<.0001						
stage O	318	142	(44.7)	176	(55.3)		0.53	(	0.41	-	0.69	) <.0001
stage I	1,025	617	(60.2)	408	(39.8)		1.00					
stage II	760	617	(81.2)	143	(18.8)		2.85	(	2.29	-	3.57	) <.0001
stage III	295	268	(90.8)	27	(9.2)		6.56	(	4.41	-	10.15	) <.0001
stage IV	116	109	(94.0)	7	(6.0)		10.30	(	5.10	-	24.59	) <.0001
Cervix						<.0001						
stage O(CIN3)	640	122	(19.1)	518	(80.9)		0.54	(	0.30	-	1.01	) 0.0535
stage I	111	57	(51.4)	54	(48.6)							
IA	56	17	(30.4)	39	(69.6)		1.00					
IB	55	40	(72.7)	15	(27.3)		6.12	(	2.74	-	14.31	) <.0001
stage II	34	33	(97.1)	1	(2.9)		75.71	(	14.45	-	1400.86	) <.0001
stage III	67	63	(94.0)	4	(6.0)		36.13	(	12.50	-	133.52	) <.0001
stage IV	47	45	(95.7)	2	(4.3)		51.62	(	13.79	-	339.41	) <.0001

[*1] Fisher's exact test [*2] Logistic regression model

[*3] "Odds ratio symptoms(+)/(-)" indicates ratio symptomatic cases to asymptomatic cases

The percentage of symptomatic cases tended to increase as the cancer stage progressed in the five organs.

Table 2. Symptomatic cases of early cancer stages

Cancer types	No. of total cases	No. of symptomatic cases at stage 0 & I		Others		*p*-value[*1]	Odds ratio symptoms (+)/(-) [*3]	(95% CI)	*p*-value[*2]
Stomach	4,897	1,248	(25.5)	3,649	(74.5)	<.0001	1.00		
Colorectum	6,614	1,250	(18.9)	5,364	(81.1)	<.0001	0.68	(0.62 - 0.74)	<.0001
Lung	3,481	286	(8.2)	3,195	(91.8)	<.0001	0.26	(0.23 - 0.30)	<.0001
Breast	2,514	759	(30.2)	1,755	(69.8)	<.0001	1.26	(1.14 - 1.41)	<.0001
Cervix	899	179	(19.9)	720	(80.1)	<.0001	0.73	(0.61 - 0.86)	0.0003

[*1] Fisher's exact test

[*2] Logistic regression model

[*3] "Odds ratio symptoms(+)/(-)" indicates ratio symptomatic cases to asymptomatic cases

The symptomatic cases of early cancer stages were low in the five organs.

Table 3. Early detection rates in the symptomatic and asymptomatic groups of cancer patients

Cancer types	No. of total cases	Symptomatic group			Asymptomatic group			*p*-value[*2]
		No.of patients	No.of patients at stage 0 and I	Early detection rates[*1]	No.of patients	No.of patients at stage 0 and I	Early detection rates[*1]	
Five organs	18,405	10,320	3,722	36.1	8,085	6,275	77.6	<.0001
Stomach	4,897	2,778	1,248	44.9	2,119	1,827	86.2	<.0001
Colorectum	6,614	3,656	1,250	34.2	2,958	2,216	74.9	<.0001
Lung	3,481	1,813	286	15.8	1,668	1,076	64.5	<.0001
Breast	2,514	1,753	759	43.3	761	584	76.7	<.0001
Cervix	899	320	179	55.9	579	572	98.8	<.0001

[*1] The early detection rates are the cases which are stages 0 and I at diagnosis among each group.

[*2] Fisher's exact test

The early detection rates of the asymptomatic cancer patients were higher than those of symptomatic patients for each organ .