JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(12)1219–1221
doi:10.1093/jjco/hys157
Advance Access Publication 5 October 2012

A Randomized Controlled Trial on the Efficacy of Thoracic CT Screening for Lung Cancer in Non-smokers and Smokers of <30 Pack-years Aged 50–64 Years (JECS Study): Research Design

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Received August 10, 2012; accepted September 7, 2012

In order to assess the efficacy of lung cancer screening using low-dose thoracic computed tomography, compared with chest roentgenography, in people aged 50–64 years with a smoking history of <30 pack-years, a randomized controlled trial is being conducted in Japan. The screening methods are randomly assigned individually. The duration of this trial is 10 years. In the intervention arm, low-dose thoracic computed tomography is performed for each participant in the first and the sixth years. In the control arm, chest roentgenography is performed for each participant in the first year. The participants in both arms are also encouraged to receive routine lung cancer screening using chest roentgenography annually. The interpretation of radiological findings and the follow-up of undiagnosed nodules are to be carried out according to the guidelines published in Japan. The required sample size is calculated to be 17 500 subjects for each arm.

Key words: lung cancer screening – computed tomography – efficacy – randomized controlled trial

INTRODUCTION

Lung cancer is the leading cause of cancer death in Japan as well as western countries. To decrease the lung cancer mortality, lung cancer screening using low-dose thoracic computed tomography (CT) may be a promising measure (1,2). Although there has been one report of a randomized controlled trial (RCT) in smokers (30 pack-years or over) demonstrating mortality reduction in the CT screening group (3), the efficacy of CT screening for lung cancer in non-smokers/smokers of <30 pack-years has not been reported so far. To demonstrate the efficacy in non-smoking subjects is very important, because non-smokers have recently been increasing in Western countries and lung cancer mortality even in non-smokers is considerably high.

In a recent Japanese cohort study, mortality reduction by thoracic CT screening was even suggested in non-smokers/smokers of <30 pack-years. Therefore, we are now conducting the JECS Study (The Japanese randomized trial for evaluating the Efficacy of low-dose thoracic CT Screening for lung cancer in non-smokers and smokers of <30 pack-years).

PROTOCOL DIGEST OF THE STUDY

Purpose

The aim of this study is to assess the efficacy of lung cancer screening tests using low-dose thoracic CT once every 5 years, compared with chest roentgenography (XP), in people aged 50–64 years with a smoking history of <30 pack-years.

Study Setting

This study is a multi-regional prospective RCT, with 6 participating centers and 11 municipalities in 5 prefectures in Japan as of 1 May 2012.

Endpoints

The primary endpoints of this trial are comparing the sensitivity and specificity of the screening modality for lung cancer between CT and XP performed in the first year of this study. The secondary endpoints are comparing the distribution of the stages of lung cancers, the diameter of lung cancers and the rate of advanced lung cancers, which are possible surrogate markers for mortality reduction. The potential risks of this screening, such as surgical resection, needle aspiration cytology or bronchoscopy for benign nodules, will also be identified and compared, by collecting further data on diagnostic procedures in all screening-positive cases. Although mortality reduction will be directly evaluated after a follow-up of 10 years, evaluating mortality reduction cannot be set as primary endpoint because of a short-term funding regulation.

Eligibility Criteria

The inclusion criteria are as follows:

(i) people aged 50–64 years when registered,
(ii) people whose smoking history is <30 pack-years,
(iii) people who received a lung cancer screening using chest XP in the previous year,
(iv) people who provide informed consent to participate in this study.

The exclusion criteria are as follows:

(i) people with a history of lung cancer,
(ii) people under investigation/follow-up due to a suspicion of lung cancer,
(iii) people with a history of a malignant disease other than lung cancer within 5 years,
(iv) people with a history of thoracic CT screening within 10 years,
(v) people in poor general condition, who are not expected to live for 5 years.

Screening Methods

After informed consent is obtained from each participant, the participants' eligibility will be confirmed. Then, the screening methods will be randomly assigned individually by the Assignment Center of the Japanese Study Group for Evaluating the Efficacy of Thoracic CT Screening (4,5).

The duration of this trial is 10 years. In the intervention arm, low-dose thoracic CT is performed for each participant in the first year and the sixth year. The participants in this arm are encouraged to receive annual routine lung cancer screening using chest XP in the other years.

In the control arm, chest XP is performed for each participant in the first year. The participants in this arm are encouraged to receive annual routine lung cancer screening using chest XP in the other years.

The interpretation of CT findings, especially determining whether some invasive diagnostic procedure should be adopted or not, and the follow-up of undiagnosed nodules are performed according to the 'Low-dose CT Lung Cancer Screening Guidelines for Pulmonary Nodules Management (6)' established by the Japanese Society of CT Screening. A positive rate of <5% is preferred. The interpretation of chest XP findings is performed according to 'The Manual of the Lung Cancer Screening (7)' section in the 'General rule for clinical and pathological record of lung cancer' published by the Japan Lung Cancer Society.

Statistical Considerations

The sample size was calculated on the hypothesis that thoracic CT is expected to improve the sensitivity to 95% in the CT group compared with 60% in the XP group. Assuming the detection rate of lung cancer by thoracic CT screening to be 320/100 000, 17 500 subjects in each arm are needed to achieve a 5% statistical significance with an 80% power. The same sample size is also required to detect a 60% mortality reduction after 10 years.

Acknowledgements

We are grateful to Dr Toshiya Sato for advising statistical analysis and to Ms Kazuko Yamamoto and Ms Kanoko Matsushima for their assistance. This protocol was approved by the Institutional Review Board of Kanazawa Medical University in 2009 and was registered on the University Hospital Medical Information Network Clinical Trial Registration (UMIN-CTR), Japan in 2011 (registration number: UMIN000005909). Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000006988&language=J. The members of the JECS Study Group are as follows: Headquarters: Dr Motoyasu Sagawa (Principle investigator), Dr Tomotaka Sobue, Dr Kenji Nishii, Dr Kenji Eguchi, Dr Tomio Nakayama, Dr Tomoshige Hayashi, Dr Takeshi Kobayashi, Dr Toshiya Sato, Dr Hiroshi Tanaka, Dr Masami Sato, Dr Katsuhiro Ichikawa, Dr Satomi Takahashi, Dr Chisato Hamashima, Dr Hiroshi Saito, Dr Takaichiro Suzuki, Dr Kyoko Sato, Dr Ryutaro Kakinuma, Mr Jun Misawa and Dr Makoto Tanaka. Regional Centers (From North to South): Miyagi Center: Dr Satomi Takahashi, Dr Chiaki Endo, Dr Akira Sakurada, Dr Takashi Kondo and Mr Tohru Kanno. Niigata Center: Dr Hiroshi Tanaka, Dr Maki Hosoi, Dr Tohru Hiura, Dr Akira Yokoyama and Dr Yuzo Kurita. Ishikawa Center: Dr Motoyasu Sagawa, Dr Takeshi Kobayashi, Dr Makoto Tanaka, Dr Tsutomu Sakuma, Dr Yoshinori Kibe, Mr Kozo Nishida, Mr. Satoru Mizukami, Mr. Kazuhiro Ikeda, Mr Tetsuo Matsunaga, Mr Kazuhiro

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Funding

This study was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare, and the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Conflict of interest statement

None declared.

References

1. Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998;351:1242–5.
2. International Early Lung Cancer Action Program Investigators Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, et al. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763–71.
3. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New Engl J Med* 2011;365:395–409.
4. Sagawa M, Tanaka M, Kobayashi T, Sobue T, Nishii K, Nakayama T, et al. The feasibility of performing a randomized controlled trial to evaluate the efficacy of lung cancer screening by thoracic CT in Japan. *J Thorac CT Screen* 2012;18:159–162.
5. Sagawa M, Tanaka M, Mizukami S, Nishida K, Nishii K, Usuda K, et al. Recruitment for 'A pilot study of randomized controlled trial to evaluate the efficacy of lung cancer screening by thoracic CT'. *J Kanazawa Med Univ* 2011;36:25–32 (in Japanese).
6. The Japanese Society of CT Screening. http://www.jscts.org/pdf/guideline/gls3rd_english120719.pdf.
7. The Japan Lung Cancer Society. The manual of the lung cancer screening. In: *General Rule for Clinical and Pathological Record of Lung Cancer*. Tokyo: Kanehara Shuppan 2010;179–213.

JJCO Japanese Journal of Clinical Oncology

Epidemiology Note

Jpn J Clin Oncol 2012;42(10)974–983
doi:10.1093/jjco/hys132
Advance Access Publication 5 September 2012

Trends in 'Cure' Fraction from Colorectal Cancer by Age and Tumour Stage Between 1975 and 2000, Using Population-based Data, Osaka, Japan

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Received June 12, 2012; accepted July 26, 2012

Since the 1960s, Japan has experienced a striking increase in the incidence of colorectal cancer, now the second most common cancer in the country. Meanwhile, the management of colorectal cancer has changed dramatically with the implementation of, for example, screening, endoscopy and adjuvant chemotherapy. It is therefore of interest to monitor the long-term trends in population 'cure' in Japan. We analysed 33 885 colorectal cancer cases diagnosed between 1975 and 2000 in Osaka. We applied the multivariable mixture cure model to estimate cure fraction and median survival time (MST) for 'uncured' patients, by sex, age, stage, period at diagnosis and subsite. For colon cancer, the cure fraction increased by about 25%, while MST for the uncured was prolonged from 8 to 12 months. The cure fraction was 5% higher in men than in women, while MST was similar in both. The cure fraction also increased for localized and regional tumours. For rectal cancer, the cure fraction increased by about 25–30%, but remained lower than for colon cancer. From the late 1970s, the cure fraction for colorectal cancer increased dramatically due to better management of detection and care for colorectal cancer. This improvement was obtained at the cost of shorter MST for uncured patients.

Key words: cure – cancer registry – cancer survival – colorectal cancer

BACKGROUND

As a result of a rapid increase in incidence for four decades since the mid-1960s, colorectal cancer has become one of the most common cancers in Japan (1,2). Colorectal cancer incidence in Japan is one of the highest worldwide (3) due to rapid diet transformations (4,5) and colorectal cancer is a predominant public health burden. In the past three decades, there have been important changes in the management of colorectal cancer in Japan: a programme of mass screening by the faecal occult blood test was initiated in 1992, while several major improvements in treatment have also been implemented.

Prognosis for colorectal cancer has improved significantly in Japan, with 5-year survival at about 30% in the early 1970s and 55% in early 2000 (6). However, this single indicator may be insufficient to completely and accurately reflect the numerous, important changes in managing colorectal cancer patients and to identify the remaining weaknesses. We aimed to assess the impact of these changes by monitoring the trends in population 'cure' of colorectal cancer in

Osaka, Japan. The effect of age and tumour stage at diagnosis on these trends was also examined.

METHODS

Data Sources

We analysed 21 032 colon (ICD-10 code: C18) and 12 757 rectal (C19–C20) cancer cases diagnosed and registered in the population-based cancer registry of Osaka Prefecture between 1975 and 2000. The Osaka cancer registry regularly receives death certificates for patients resident in the Osaka Prefecture at the time of their death. Furthermore, the vital status of the patients who are known as still alive 5 and 10 years after diagnosis was checked using the city-level residence registries. Those cases diagnosed from 1975 to 1995 were followed up for 10 years after their diagnosis, whereas follow-up was limited to 5 years for those diagnosed from 1996 to 2000. We did not include patients of Osaka city (36%) in our analysis, because the vital status of patients in Osaka city diagnosed before 1993 was not recorded. A small proportion of cases were lost to follow-up, 2.2% of the patients diagnosed in 1975–95 (10-year follow-up) and 1.2% of the patients diagnosed in 1996–2000 (5-year follow-up).

Statistical Analysis

Cure Parameters

Within the relative survival framework, population cure is a statistical concept corresponding to the absence of excess mortality among cancer patients in comparison to a similar general population (7). The mortality of this general population, the background mortality, is provided by life tables. Cure models assume that the cancer patients can be split into two groups: the 'cured' group and on top of that, the 'uncured' group for which relative survival function is estimated. Using separate calculations for men and women, and for colon and rectum, we estimated the cure fraction and median survival time (MST) for uncured cases, by the period of diagnosis (1975–80, 1981–85, 1986–90, 1991–95 and 1996–2000), age at diagnosis (15–49, 50–59, 60–69, 70–79 and 80–99), tumour stage at diagnosis (localized, regional and distant metastasis) and, for colon, subsite (left and right colon). We applied a multivariate mixture cure fraction model with a logit link and a Weibull distribution for the survival of the uncured patients. Both Weibull parameters (i.e. shape and scale parameters) were allowed to vary by period, age and stage at diagnosis since proportional excess hazards were unlikely for these variables (8). Background mortality was provided by national life tables for Japan, defined by sex, single year of age and single calendar year.

Missing Data

Tumour stage data were missing for 10% of the colorectal cancer patients and subsite for about 25% of the colon cancer patients (Table 1). Multiple imputation by chained equation (9) was applied to deal with this missing information. The imputation model consisted of multinomial logistic models containing, in addition to tumour stage and subsite (for colon), follow-up time, vital status, period and age at diagnosis, tumour morphology as well as interactions between follow-up time and age and stage. Ten 'completed' data sets were generated with imputed values for the cases with missing information for stage and subsite. Cure parameters were then estimated on the 10 completed data sets using Rubin's rules (10).

Patients with missing stage data were more likely to be older and diagnosed in the earlier calendar periods, while there was very little variation with time among the proportion with missing subsite data (11). The imputed stage was mostly regional metastasis in the early period and then shifted to the localized stage. The imputed subsite was a little more left-side colon. For older patients, survival time for patients missing stage or subsite data was shorter than patients with known stage or subsite.

All data management and analyses were carried out using Stata MP version 11.1 (12).

RESULTS

During the study period, age at diagnosis of colorectal cancer increased. The proportion of patients with localized tumours increased until the mid-1990s while the proportion of both the regional and distant tumours decreased. The pattern of change seems to have reached a plateau in the late 1990s (Table 1).

Although their levels differed in some ways, trends in both cure parameters were very similar for men and women, and for colon and rectum cancers (Tables 2 and 3; Supplementary Figs S1 and S2). Overall, both the cure fraction and the MST for uncured increased during the study period, with a dramatic improvement for the cure fraction. However, the MST for uncured shortened in the early (colon) or late (rectum) 1990s, while the cure fraction did not improve in the late 1990s. Among the patients diagnosed with colon cancer from 1996 to 2000, 62% of men and 58% of women were predicted to be cured of their cancer, with an MST for uncured of just below 1 year. For rectal cancer and both sexes, the cure fraction was about 57% with an MST of slightly less than 18 months.

The overall temporal trends by age group were very similar, with a dramatic increase in cure fraction across all age groups for both cancer sites and sexes. Overall, the cure fraction varied little with age until the age of 80 and over (Tables 2 and 3; Supplementary Figs S3 and S4). For the period 1996–2000, if the MST for uncured reached 12 months or more (colon) and 18 months (rectum) for patients under 70 years old, it remained particularly short for the elderly, lower than 6 months (colon) or around 8 months (rectum).

Table 1. Characteristics of colorectal cancer patients in Osaka (Japan), 1975–2000

	Period of diagnosis											
	1975–80		1981–85		1986–90		1991–95		1996–2000		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Colon												
Men												
Total	879	100.0	1361	100.0	2171	100.0	3496	100.0	3677	100.0	11 584	100.0
Age												
<50	216	24.6	237	17.4	310	14.3	387	11.1	275	7.5	1425	12.3
50–59	189	21.5	339	24.9	599	27.6	928	26.5	771	21.0	2826	24.4
60–69	227	25.8	328	24.1	613	28.2	1173	33.6	1340	36.4	3681	31.8
70–79	208	23.7	348	25.6	487	22.4	723	20.7	905	24.6	2671	23.1
80+	39	4.4	109	8.0	162	7.5	285	8.2	386	10.5	981	8.5
Stage (before imputation)												
Localized	209	28.2	382	31.6	843	43.5	1639	52.9	1647	48.1	4720	45.3
Regional	343	46.2	490	40.6	654	33.7	863	27.8	998	29.1	3348	32.1
Distant	190	25.6	336	27.8	442	22.8	599	19.3	782	22.8	2349	22.5
Missing	137	(15.6)	153	(11.2)	232	(10.7)	395	(11.3)	250	(6.8)	1167	(10.1)
Stage (after imputation)												
Localized	254	28.9	422	31.0	934	43.0	1841	52.7	1757	47.8	5208	45.0
Regional	402	45.8	551	40.5	731	33.7	974	27.9	1069	29.1	3727	32.2
Distant	223	25.3	388	28.5	506	23.3	681	19.5	851	23.1	2649	22.9
Subsite (before imputation)												
Right	301	45.6	421	40.4	604	35.9	911	36.4	1113	39.5	3350	38.5
Left	359	54.4	621	59.6	1077	64.1	1592	63.6	1705	60.5	5354	61.5
Missing	219	(24.9)	319	(23.4)	490	(22.6)	993	(28.4)	859	(23.4)	2880	(24.9)
Subsite (after imputation)												
Right	404	45.9	549	40.4	791	36.4	1278	36.5	1461	39.7	4483	38.7
Left	476	54.1	812	59.6	1380	63.6	2219	63.5	2216	60.3	7101	61.3
Women												
Total	764	100.0	1191	100.0	1815	100.0	2671	100.0	3007	100.0	9448	100.0
Age												
<50	139	18.2	210	17.6	251	13.8	317	11.9	236	7.8	1153	12.2
50–59	143	18.7	244	20.5	414	22.8	589	22.1	598	19.9	1988	21.0
60–69	234	30.6	297	24.9	480	26.4	777	29.1	853	28.4	2641	28.0
70–79	184	24.1	330	27.7	466	25.7	623	23.3	806	26.8	2409	25.5
80+	64	8.4	110	9.2	204	11.2	365	13.7	514	17.1	1257	13.3
Stage (before imputation)												
Localized	156	24.8	322	30.1	587	35.7	1008	42.7	1183	43.0	3256	38.5
Regional	315	51.8	459	52.8	632	51.5	819	49.2	959	52.6	3184	51.4
Distant	159	54.3	287	70.0	426	71.5	532	63.0	610	70.5	2014	67.0
Missing	134	(17.5)	123	(10.3)	170	(9.4)	312	(11.7)	255	(8.5)	994	(10.5)

Continued

Table 1. *Continued*

	Period of diagnosis											
	1975–80		1981–85		1986–90		1991–95		1996–2000		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Stage (after imputation)												
Localized	188	24.6	349	29.3	645	35.5	1132	42.4	1269	42.2	3582	37.9
Regional	384	50.2	516	43.3	701	38.6	926	34.7	1050	34.9	3576	37.9
Distant	193	25.2	326	27.4	470	25.9	613	23.0	689	22.9	2290	24.2
Subsite (before imputation)												
Right	263	47.7	366	40.8	605	42.9	839	43.5	1084	47.8	3157	44.7
Left	288	52.3	531	59.2	804	57.1	1090	56.5	1186	52.2	3899	55.3
Missing	213	(27.9)	294	(24.7)	406	(22.4)	742	(27.8)	737	(24.5)	2392	(25.3)
Subsite (after imputation)												
Right	371	48.6	503	42.3	782	43.1	1163	43.5	1429	47.5	4248	45.0
Left	393	51.4	688	57.7	1033	56.9	1509	56.5	1578	52.5	5200	55.0
Rectum												
Men												
Total	847	100.0	1151	100.0	1588	100.0	2005	100.0	2371	100.0	7962	100.0
Age												
<50	210	24.8	234	20.3	283	17.8	263	13.1	239	10.1	1229	15.4
50–59	189	22.3	278	24.2	466	29.3	590	29.4	643	27.1	2166	27.2
60–69	204	24.1	284	24.7	436	27.5	693	34.6	893	37.7	2510	31.5
70–79	209	24.7	282	24.5	300	18.9	319	15.9	437	18.4	1547	19.4
80+	35	4.1	73	6.3	103	6.5	140	7.0	159	6.7	510	6.4
Stage (before imputation)												
Localized	184	28.0	381	36.7	620	43.6	903	48.1	1016	46.0	3104	43.1
Regional	330	50.2	440	42.4	537	37.7	663	35.3	792	35.9	2762	38.3
Distant	143	21.8	216	20.8	266	18.7	313	16.7	400	18.1	1338	18.6
Missing	190	(22.4)	114	(9.9)	165	(10.4)	126	(6.3)	163	(6.9)	758	(9.5)
Stage (after imputation)												
Localized	241	28.5	420	36.5	688	43.3	950	47.4	1089	45.9	3389	42.6
Regional	422	49.8	488	42.4	602	37.9	708	35.3	847	35.7	3067	38.5
Distant	184	21.7	243	21.1	298	18.8	347	17.3	435	18.3	1506	18.9
Women												
Total	588	100.0	750	100.0	976	100.0	1198	100.0	1283	100.0	4795	100.0
Age												
<50	155	26.4	171	22.8	226	23.2	208	17.4	164	12.8	924	19.3
50–59	108	18.4	155	20.7	241	24.7	290	24.2	301	23.5	1095	22.8
60–69	147	25.0	193	25.7	222	22.7	334	27.9	381	29.7	1277	26.6
70–79	136	23.1	167	22.3	212	21.7	261	21.8	282	22.0	1058	22.1
80+	42	7.1	64	8.5	75	7.7	105	8.8	155	12.1	441	9.2

Continued

Table 1. *Continued*

	Period of diagnosis											
	1975–80		1981–85		1986–90		1991–95		1996–2000		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Stage (before imputation)												
Localized	154	33.5	268	40.3	362	41.8	519	46.5	521	43.9	1824	42.5
Regional	221	48.0	279	42.0	356	41.1	443	39.7	443	37.3	1742	40.6
Distant	85	18.5	118	17.7	148	17.1	154	13.8	224	18.9	729	17.0
Missing	128	(21.8)	85	(11.3)	110	(11.3)	82	(6.8)	95	(7.4)	500	(10.4)
Stage (after imputation)												
Localized	191	32.5	294	39.2	406	41.6	556	46.4	559	43.6	2007	41.9
Regional	286	48.6	313	41.7	397	40.7	471	39.3	477	37.2	1944	40.5
Distant	111	18.9	143	19.1	173	17.7	171	14.3	246	19.2	845	17.6

Frequencies of stage before imputation are shown for the cases without missing stage information; on top of that is shown between parentheses the proportion of the missing stage.

For both colon and rectum cancer, the proportion of men and women cured from a local tumour rose steadily until the mid-1990s and reached a plateau over 85% (Tables 2 and 3; Supplementary Figs S5 and S6). The improvement over the study period was also impressive among the patients diagnosed with a regional tumour since the cure fraction more or less doubled and between 46 (men, rectum) and 57% (men, colon) of these patients were cured. Although the cure fraction also increased among the patients with a metastatic tumour, less than 7% of these patients were cured from 1996 to 2000. Apart from the last period of diagnosis, the MST for uncured lengthened considerably for all tumour stages, including the distant. This pattern was however somewhat attenuated for women with colon cancer.

The temporal patterns of the cure fraction and the MST for uncured patients were similar for the left and right colon. However, cure parameters were higher for the left colon (Table 2).

DISCUSSION

We observed a dramatic increase in cure fraction until the mid-1990s and a less noticeable lengthening of the MST for the uncured cases. All age groups and stage groups (with the exception of metastasis patients group) also showed a dramatic increase in cure fraction until the mid-1990s and then levelled-off. The overall increase in cure fraction might be due to both the shifting to a more favourable stage and the increase in age- and stage-specific cure fraction. Improvement in the management of colorectal cancer may also have played a role.

Distribution of age at diagnosis shifted considerably in the older groups from 1975 to 80 and 1996 to 2000: the under-50 age group, 22% of the patients in the first period represented less than 8% in the last period. However, trends in cure and MST for uncured were similar across all age groups. This explains why, after adjusting for other factors, age did not play a notable role in the observed improvements in cure parameters. At the same time, tumour stage at diagnosis shifted widely, mostly from regional to local stages and particularly until the mid-1990s. This shift is very likely to be related to the wider use of endoscopy to detect tumours at an earlier stage. While diagnostic endoscopy was used in less than 30% of colon cancer patients and less than 60% of rectal cancer patients in the late 1970s, the figures were around 80% in the late 1990s (13), an upper limit hard to exceed (Fig. 1). The more tumours were detected at earlier stage, the more curative resections were possible, as shown by the parallel trends in the proportion of curative resections (Fig. 1).

We have observed lower cure fraction in women, both overall and by age group, while stage-specific cure fractions were similar in both sexes. Women were diagnosed with more advanced stage than men (Table 1). We observed similar pattern for stomach cancer (14). Regular health monitoring is offered by large companies and for full-time workers, which means that women, more often part-time employees in small companies, may have fewer opportunities for earlier diagnosis than men.

These observations are good news and reflect a general improvement in the diagnosis and the treatment of these two cancers according to the interpretation of Verdecchia et al. (15). However, the figures showed some divergences from that general pattern. From the 1990, both cure fraction and MST for uncured levelled off or slightly decreased. This pattern was mostly seen among the patients at the localized tumour stage. It might reflect a change in patients' characteristics, in particular in the localized tumour group because of the wider use of early detection method, smaller tumours

Table 2. Trends in cure fraction (%) and median survival time for uncured patients (months), colon cancer, Osaka (Japan), 1975–2000

	Men		Women	
	Cure fraction (95% CI)	Median survival time (95% CI)	Cure fraction (95% CI)	Median survival time (95% CI)
All				
1975–1980	37.2 (33.2–41.3)	8.3 (7.1–9.7)	31.9 (28.0–36.0)	8.2 (7.0–9.5)
1981–1985	42.0 (38.8–45.2)	9.5 (8.5–10.7)	43.2 (40.1–46.4)	8.6 (7.7–9.5)
1986–1990	54.7 (52.1–57.3)	12.2 (11.0–13.7)	49.2 (46.6–51.8)	11.7 (10.7–12.7)
1991–1995	67.0 (65.0–69.0)	10.8 (9.8–12.0)	57.6 (55.4–59.7)	10.6 (9.7–11.6)
1996–2000	62.0 (60.1–64.0)	11.7 (10.7–12.7)	57.5 (55.5–59.5)	10.6 (9.8–11.5)
By age				
<50				
1975–1980	41.4 (36.7–46.2)	10.4 (8.6–12.6)	34.6 (29.9–39.6)	10.6 (8.9–12.6)
1981–1985	47.0 (42.9–51.2)	12.5 (10.7–14.6)	47.0 (42.9–51.2)	10.6 (9.4–12.1)
1986–1990	58.9 (55.1–62.5)	16.0 (13.8–18.7)	52.9 (49.1–56.7)	14.6 (13.0–16.4)
1991–1995	70.9 (67.8–73.8)	13.7 (11.7–15.9)	61.5 (58.0–64.8)	13.9 (12.3–15.7)
1996–2000	66.9 (63.6–70.1)	15.0 (13.0–17.2)	62.4 (58.9–65.8)	13.9 (12.4–15.6)
50–59				
1975–1980	39.6 (35.1–44.2)	10.7 (9.0–12.8)	34.4 (29.9–39.2)	10.9 (9.3–12.9)
1981–1985	45.2 (41.5–48.9)	12.7 (11.1–14.4)	46.9 (43.1–50.7)	11.0 (9.7–12.3)
1986–1990	57.0 (53.9–60.1)	16.0 (14.1–18.2)	52.8 (49.4–56.1)	15.1 (13.6–16.7)
1991–1995	69.3 (66.8–71.7)	13.8 (12.3–15.4)	61.3 (58.4–64.2)	14.4 (12.9–16.1)
1996–2000	65.2 (62.6–67.8)	15.0 (13.5–16.6)	62.3 (59.4–65.1)	14.4 (13.0–15.9)
60–69				
1975–1980	38.0 (33.6–42.6)	8.7 (7.3–10.5)	35.1 (30.7–39.8)	8.8 (7.4–10.3)
1981–1985	43.5 (39.8–47.3)	10.6 (9.2–12.2)	47.6 (43.9–51.4)	9.1 (8.0–10.3)
1986–1990	55.4 (52.1–58.6)	13.7 (12.0–15.6)	53.5 (50.3–56.8)	12.8 (11.4–14.3)
1991–1995	67.9 (65.3–70.4)	11.7 (10.3–13.3)	62.1 (59.3–64.7)	12.0 (10.7–13.4)
1996–2000	63.7 (61.2–66.1)	12.9 (11.7–14.3)	63.0 (60.4–65.6)	12.2 (11.1–13.5)
70–79				
1975–1980	35.1 (30.7–39.8)	5.1 (4.2–6.2)	28.5 (24.5–32.9)	6.6 (5.5–7.9)
1981–1985	40.5 (36.6–44.5)	6.5 (5.5–7.6)	40.1 (36.5–43.9)	7.1 (6.3–8.1)
1986–1990	52.3 (48.6–55.9)	8.5 (7.3–9.8)	45.9 (42.6–49.3)	10.2 (9.1–11.5)
1991–1995	65.1 (62.0–68.1)	7.3 (6.4–8.5)	54.6 (51.5–57.8)	9.4 (8.3–10.6)
1996–2000	60.8 (57.7–63.7)	8.3 (7.4–9.4)	55.6 (52.7–58.6)	9.8 (8.8–10.8)
80+				
1975–1980	29.2 (23.8–35.1)	2.2 (1.7–2.9)	18.6 (15.2–22.6)	3.2 (2.6–4.0)
1981–1985	34.1 (28.8–39.9)	3.0 (2.4–3.8)	27.7 (23.9–31.9)	3.9 (3.3–4.6)
1986–1990	45.5 (39.8–51.2)	4.0 (3.1–5.0)	32.7 (28.8–36.9)	5.6 (4.9–6.5)
1991–1995	58.7 (53.3–63.9)	3.5 (2.8–4.4)	40.8 (36.7–45.1)	4.9 (4.3–5.7)
1996–2000	54.1 (48.7–59.4)	4.2 (3.4–5.2)	41.8 (37.9–45.9)	5.4 (4.8–6.2)

Continued

Table 2. *Continued*

	Men		Women	
	Cure fraction (95% CI)	Median survival time (95% CI)	Cure fraction (95% CI)	Median survival time (95% CI)
By stage				
Localized				
1975–1980	71.2 (65.0–81.6)	25.2 (6.8–93.3)	71.8 (65.2–77.6)	22.0 (16.1–30.0)
1981–1985	80.2 (72.4–86.2)	35.2 (16.9–73.4)	84.1 (80.6–87.0)	19.3 (15.3–24.3)
1986–1990	85.1 (78.9–89.8)	45.0 (21.2–95.7)	86.5 (83.8–88.8)	24.0 (19.6–29.4)
1991–1995	89.1 (84.2–92.7)	47.9 (21.9–104.7)	89.1 (87.0–90.9)	25.4 (20.2–32.1)
1996–2000	89.7 (85.1–93.0)	43.1 (21.1–88.0)	89.8 (87.8–91.6)	24.0 (19.3–29.9)
Regional				
1975–1980	30.2 (25.2–35.8)	11.3 (9.6–13.4)	25.0 (20.1–30.6)	11.4 (9.5–13.6)
1981–1985	37.9 (33.6–42.5)	13.6 (12.0–15.4)	40.8 (36.6–45.2)	11.3 (10.1–12.6)
1986–1990	46.3 (42.1–50.6)	16.7 (14.9–18.7)	45.6 (41.7–49.5)	14.7 (13.4–16.2)
1991–1995	55.3 (51.4–59.2)	17.5 (15.6–19.6)	51.7 (48.2–55.3)	14.7 (13.2–16.2)
1996–2000	56.9 (53.2–60.4)	16.9 (15.3–18.7)	53.7 (50.3–57.0)	14.3 (13.1–15.7)
Distant				
1975–1980	2.4 (1.7–3.3)	5.2 (4.5–6.1)	1.4 (0.9–2.0)	5.2 (4.5–6.2)
1981–1985	3.3 (2.6–4.3)	6.5 (5.8–7.3)	2.8 (2.1–3.7)	6.0 (5.4–6.7)
1986–1990	4.7 (3.6–5.9)	8.1 (7.3–8.9)	3.4 (2.5–4.4)	8.1 (7.5–8.9)
1991–1995	6.5 (5.3–8.1)	8.4 (7.7–9.2)	4.3 (3.3–5.5)	7.5 (6.9–8.2)
1996–2000	6.9 (5.6–8.5)	8.6 (7.9–9.3)	4.6 (3.6–5.9)	7.7 (7.1–8.3)
By subsite				
Right				
1975–1980	33.1 (29.2–37.3)	7.4 (6.3–8.8)	27.8 (24.0–31.8)	7.5 (6.4–8.8)
1981–1985	37.1 (33.7–40.7)	8.6 (7.5–9.9)	38.0 (34.7–41.4)	7.9 (7.1–8.9)
1986–1990	49.3 (46.0–52.6)	11.1 (9.8–12.6)	43.9 (41.0–46.9)	10.8 (9.8–11.9)
1991–1995	61.9 (59.1–64.6)	10.0 (8.9–11.2)	52.3 (49.7–54.9)	9.9 (8.9–10.9)
1996–2000	57.1 (54.4–59.8)	10.8 (9.7–11.9)	52.8 (50.4–55.3)	9.9 (9.0–10.8)
Left				
1975–1980	41.0 (36.7–45.5)	8.9 (7.5–10.6)	35.6 (31.3–40.1)	8.9 (7.6–10.5)
1981–1985	45.3 (41.9–48.9)	10.2 (9.0–11.6)	46.8 (43.5–50.2)	9.2 (8.2–10.3)
1986–1990	57.7 (54.8–60.5)	13.1 (11.6–14.8)	53.0 (50.1–55.8)	12.5 (11.3–13.9)
1991–1995	69.5 (67.3–71.7)	11.8 (10.5–13.2)	61.2 (58.8–63.5)	11.6 (10.4–12.9)
1996–2000	65.2 (62.9–67.4)	12.5 (11.4–13.8)	61.7 (59.3–64.0)	11.4 (10.4–12.6)

CI, confidence interval.

were found and were curatively resected. However, more *in situ* tumours were diagnosed and removed from the localized tumour group, leaving the 'more advanced' cases within the localized tumour group. Although only 20% of the target population in Osaka is covered by the mass-screening programme (16), such a stage-shifting phenomenon is quite similar to what has been observed in cervical cancer in countries with high screening coverage, in which survival plateaued or even declined (17). It may reflect the high use of opportunistic screening.

The cure fraction of colorectal cancer in Osaka was generally higher than in other countries. For example, in the EUROCARE study, the cure fraction ranged between 24.8 and 48.0% for patients diagnosed from 1988 to 99 (18). This could be largely attributable to the differences in stage distribution. In Osaka, the advanced stage (distant metastasis) constituted 23% of colon cancer and 18.6% of rectal cancer from 1996 to 2000, whereas in Europe, the proportion of advanced stage for colorectal cancer ranged between 25% (France) and 37% (Poland) between 1996 and 1998 (19).

Table 3. Trends in cure fraction (%) and median survival time for uncured patients (months), rectal cancer, Osaka (Japan), 1975–2000

	Men		Women	
	Cure fraction (95% CI)	Median survival time (months) (95% CI)	Cure fraction (95% CI)	Median survival time (months) (95% CI)
All				
1975–1980	31.3 (27.4–35.6)	14.5 (12.7–16.5)	24.9 (20.3–30.2)	15.0 (12.6–17.8)
1981–1985	40.9 (37.4–44.5)	15.8 (14.0–17.7)	41.9 (37.9–46.1)	15.6 (13.7–17.7)
1986–1990	51.1 (48.1–54.1)	18.4 (16.8–20.2)	48.0 (44.3–51.8)	19.4 (17.2–22.0)
1991–1995	54.9 (52.0–57.8)	20.5 (18.4–22.8)	58.3 (55.0–61.6)	19.7 (17.6–22.2)
1996–2000	57.0 (54.5–59.4)	17.5 (16.2–18.9)	56.5 (53.3–59.7)	16.5 (14.8–18.3)
By age				
<50				
1975–1980	31.3 (26.8–36.2)	18.6 (16.0–21.5)	25.4 (20.4–31.1)	19.8 (16.6–23.6)
1981–1985	41.7 (37.5–46.0)	19.4 (17.1–21.9)	42.6 (37.6–47.7)	19.4 (16.9–22.2)
1986–1990	50.9 (46.9–54.9)	21.7 (19.5–24.2)	48.0 (43.4–52.7)	24.1 (21.1–27.5)
1991–1995	54.7 (50.7–58.7)	24.5 (21.6–27.7)	58.0 (53.5–62.4)	23.9 (21.2–26.9)
1996–2000	56.8 (52.9–60.7)	20.9 (18.9–23.2)	56.8 (52.1–61.4)	20.7 (18.4–23.2)
50–59				
1975–1980	34.9 (30.2–40.0)	18.5 (15.7–21.6)	28.2 (22.7–34.3)	17.4 (14.1–21.3)
1981–1985	45.7 (41.5–49.9)	19.3 (16.9–22.1)	46.0 (41.0–51.2)	17.5 (15.1–20.3)
1986–1990	55.0 (51.3–58.5)	21.9 (19.7–24.3)	51.6 (46.9–56.2)	22.1 (19.0–25.7)
1991–1995	58.7 (55.2–62.1)	24.8 (21.8–28.1)	61.4 (57.2–65.5)	22.1 (19.3–25.4)
1996–2000	60.8 (57.5–63.9)	21.1 (19.1–23.2)	60.2 (56.0–64.3)	19.1 (17.0–21.5)
60–69				
1975–1980	32.3 (27.9–37.2)	13.6 (11.7–15.9)	28.5 (23.2–34.6)	16.2 (13.3–19.6)
1981–1985	42.8 (38.7–47.1)	14.6 (12.7–16.7)	46.5 (41.5–51.6)	16.5 (14.2–19.2)
1986–1990	52.1 (48.4–55.8)	17.2 (15.4–19.2)	52.0 (47.2–56.8)	20.8 (17.9–24.3)
1991–1995	55.9 (52.4–59.3)	18.9 (16.8–21.3)	61.9 (57.6–65.9)	21.0 (18.3–24.0)
1996–2000	58.0 (54.9–61.0)	16.7 (15.3–18.3)	60.7 (56.6–64.6)	18.2 (16.2–20.4)
70–79				
1975–1980	28.8 (24.1–33.9)	11.0 (9.1–13.3)	23.2 (18.3–29.0)	10.5 (8.2–13.4)
1981–1985	38.8 (34.1–43.6)	12.1 (10.1–14.3)	39.7 (34.3–45.5)	11.8 (9.6–14.4)
1986–1990	47.9 (43.3–52.5)	15.0 (12.9–17.4)	45.1 (39.7–50.6)	15.3 (12.6–18.7)
1991–1995	51.7 (47.0–56.4)	16.3 (13.7–19.3)	55.2 (50.0–60.2)	16.0 (13.3–19.3)
1996–2000	53.8 (49.5–58.1)	14.6 (12.8–16.7)	53.9 (48.9–58.8)	13.9 (11.8–16.3)
80+				
1975–1980	21.2 (15.7–27.8)	4.9 (3.5–6.7)	15.8 (11.1–21.8)	4.7 (3.3–6.7)
1981–1985	29.6 (23.1–37.0)	5.7 (4.3–7.6)	28.9 (22.2–36.7)	6.1 (4.5–8.2)
1986–1990	37.9 (30.6–45.9)	7.9 (6.2–10.2)	33.7 (26.4–41.8)	7.9 (5.8–10.7)
1991–1995	41.6 (34.1–49.5)	8.0 (6.0–10.5)	43.2 (35.3–51.4)	8.8 (6.6–11.6)
1996–2000	43.7 (36.1–51.5)	8.0 (6.3–10.1)	41.9 (34.4–49.9)	7.9 (6.2–10.0)

Continued

Table 3. *Continued*

	Men		Women	
	Cure fraction (95% CI)	Median survival time (months) (95% CI)	Cure fraction (95% CI)	Median survival time (months) (95% CI)
By stage				
Localized				
1975–1980	65.4 (61.0–73.7)	26.8 (10.8–66.6)	53.2 (42.7–63.5)	34.9 (24.2–50.3)
1981–1985	75.6 (70.6–80.0)	32.0 (25.9–39.5)	72.2 (64.4–78.9)	38.2 (26.6–54.8)
1986–1990	81.8 (78.3–84.9)	33.3 (27.7–40.0)	78.3 (72.0–83.5)	43.2 (30.6–61.1)
1991–1995	83.1 (79.8–86.0)	39.1 (31.6–48.4)	84.4 (79.5–88.3)	42.6 (30.1–60.3)
1996–2000	85.9 (83.1–88.3)	31.8 (26.5–38.0)	85.5 (80.5–89.3)	38.4 (27.5–53.6)
Regional				
1975–1980	23.0 (18.7–27.9)	18.7 (16.6–21.2)	15.3 (11.2–20.6)	16.7 (14.5–19.4)
1981–1985	30.6 (26.5–35.0)	20.3 (18.3–22.5)	29.2 (24.5–34.4)	19.8 (17.6–22.2)
1986–1990	39.0 (35.0–43.1)	22.4 (20.6–24.4)	36.4 (31.7–41.3)	22.4 (20.1–25.0)
1991–1995	41.2 (37.2–45.3)	25.0 (22.8–27.5)	46.2 (41.6–50.8)	22.7 (20.5–25.2)
1996–2000	46.4 (42.8–50.1)	21.8 (20.3–23.5)	48.3 (43.5–53.0)	21.3 (19.3–23.4)
Distant				
1975–1980	2.4 (1.7–3.4)	7.3 (6.2–8.6)	1.0 (0.6–1.7)	6.0 (4.9–7.4)
1981–1985	3.5 (2.5–4.7)	8.5 (7.4–9.8)	2.3 (1.5–3.6)	8.5 (7.3–10.0)
1986–1990	5.0 (3.7–6.7)	11.0 (9.9–12.2)	3.2 (2.1–4.9)	10.1 (8.7–11.7)
1991–1995	5.4 (4.1–7.2)	11.3 (10.0–12.7)	4.7 (3.1–7.0)	10.8 (9.3–12.4)
1996–2000	6.6 (5.1–8.6)	11.1 (10.1–12.1)	5.1 (3.4–7.6)	10.4 (9.3–11.8)

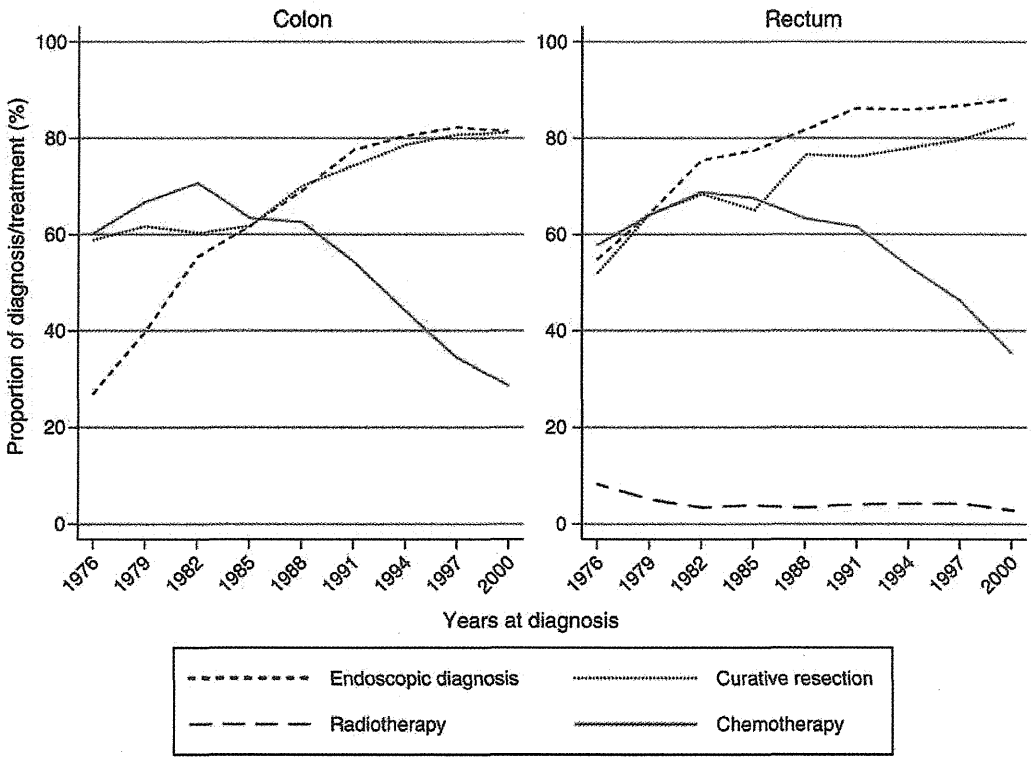

Figure 1. Trends in the diagnostic method and treatment for colorectal cancer in Osaka, Japan, in 1975–2001.

This may be related to the difference in the use of endoscopic diagnosis in clinical settings between countries. Increasing in cure fraction and MST for uncured patients was also observed in Finland for colorectal cancer. While in the early 1970s, both cure parameters were comparable for all age groups in Finland and Osaka, the bigger increase in cure fraction observed in Osaka in the late 1990s was obtained to the cost of shorter MST for uncured patients, in comparison with Finland, regardless the age group (20). It is striking that this shortening in MST occurred while the use of in particular chemotherapy dramatically decreased (Fig. 1).

Compared with analysis on data after imputation, the complete-case analysis showed slightly higher cure fractions and longer MST for uncured cases, especially among localized stage patients. Such over-estimations hardly modify the interpretation of our findings.

This study was implemented using population-based cancer registry data in Osaka. Compared with hospital series and hospital-based cancer registry data, the information available in our study was limited, which prevented us from evaluating the influence of type of treatment and detection method on the trends in cure parameters. However, in contrast to the clinical database, our study included all cancer cases within defined geographical areas, regardless of their age, co-morbidities or prognosis. Furthermore, our population-based results, among the highest cure fraction worldwide, show that since virtually all colorectal cancer patients are diagnosed by endoscopy and received surgical treatment with curative intent, any further progress in survival and cure is likely to require new, innovative strategies of colorectal cancer management.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Funding

Y.I. was supported by a Grant-in-Aid for Research Activity Start-up (10020027) from the Ministry of Education, Culture, Sports and Science Technology. B.R. was supported by Cancer Research UK (Collaborator Bursary C1336/A12446) during his stay at the Osaka Medical Centre for Cancer and Cardiovascular Diseases, Japan.

Conflict of interest statement

None declared.

References

1. Ministry of Health Labour and Walfare. *Vital Statistics of Japan.* [cited 2012 June 10]. http://ganjoho.ncc.go.jp/professional/statistics/odjrh3000000hwsa-att/cancer_mortality(1958-2006).xls.
2. Matsuda T, Marugame T, Kamo K, et al. Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2011;41:139–47.
3. Curado MP, Edwards B, Shin HR, et al. *Cancer Incidence in Five Continents*, Vol. IX. IARC Scientific Publications No. 160. Lyon: IARC 2007.
4. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2009;18:1688–94.
5. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009;59:366–78.
6. Osaka Prefectural Department of Public Health and Welfare, Osaka Medical Association, Osaka Medical Center for Cancer and Cardiovascular Disease. Annual Report of Osaka Cancer Registry No. 71—Cancer Incidence and Medical Care in Osaka in 2004 and the Survival in 2000. OPDPHW 2008.
7. Berkson J, Gage RP. Calculation of survival rates for cancer. *Proc Staff Meet Mayo Clin* 1950;25:270–86.
8. Lambert PC. Modeling of the cure fraction in survival studies. *Stata J* 2007;7:351–75.
9. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999;18:681–94.
10. Rubin DB. *Multiple Imputation for Nonresponse in Surveys.* New York: John Wiley & Sons 1987.
11. Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP. Modelling relative survival in the presence of incomplete data: a tutorial. *Int J Epidemiol* 2010;39:118–28.
12. StataCorp. *Stata Statistical Software: Release 11.* College Station, TX: StataCorp LP 2009.
13. Osaka Prefectural Department of Public Health and Welfare, Osaka Medical Association, Osaka Medical Center for Cancer and Cardiovascular Disease. Series of Annual Report of Osaka Cancer Registry—Cancer Incidence, Survival, and Medical Care in Osaka. OPDPHW, 1975–2008.
14. Sato N, Ito Y, Ioka A, Tanaka M, Tsukuma H. Gender differences in stomach cancer survival in Osaka, Japan: analyses using relative survival model. *Jpn J Clin Oncol* 2009;39:690–4.
15. Verdecchia A, De Angelis R, Capocaccia R, et al. The cure for colon cancer: results from the EUROCARE study. *Int J Cancer* 1998;77:322–9.
16. Ministry of Health Labour and Walfare. *The National Health and Nutrition Survey in Japan.* [cited 2012 Jun 10]. http://www.nih.go.jp/eiken/chosa/kokumin_eiyou/index.html.
17. de Vries E, Karim-Kos HE, Janssen-Heijnen ML, Soerjomataram I, Kiemeney LA, Coebergh JW. Explanations for worsening cancer survival. *Nat Rev Clin Oncol* 2010;7:60–3.
18. Francisci S, Capocaccia R, Grande E, et al. The cure of cancer: a European perspective. *Eur J Cancer* 2009;45:1067–79.
19. Gatta G, Zigon G, Aareleid T, et al. Patterns of care for European colorectal cancer patients diagnosed 1996–1998: a EUROCARE high resolution study. *Acta Oncol* 2010;49:776–83.
20. Lambert PC, Dickman PW, Osterlund P, Andersson T, Sankila R, Glimelius B. Temporal trends in the proportion cured for cancer of the colon and rectum: a population-based study using data from the Finnish Cancer Registry. *Int J Cancer* 2007;121:2052–9.

Cancer Epidemiology 36 (2012) 128–132

Contents lists available at SciVerse ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Role of age and tumour stage in the temporal pattern of 'cure' from stomach cancer: A population-based study in Osaka, Japan

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ARTICLE INFO

Article history:
Received 22 July 2011
Received in revised form 21 December 2011
Accepted 26 December 2011
Available online 31 January 2012

Keywords:
Stomach cancer
Cancer survival
Cure model
Population-based cancer registries

ABSTRACT

Objectives: To evaluate progress in stomach cancer care in Japan since 1975. *Design*: Population-based study of data extracted from the Osaka Cancer Registry. *Setting*: Population-based cancer registry in the area of Osaka Prefecture. *Participants*: All 66,032 cases diagnosed with a stomach cancer in Osaka Prefecture, Japan between 1975 and 2000 and registered in the Osaka Cancer Registry. *Main outcome measures*: 'Cure' fraction and median survival time for 'uncured' patients were estimated with multivariable mixture 'cure' model. The role played by age and stage at diagnosis on the changes in 'cure' parameters between 1975 and 2000 was evaluated. Missing stage was handled by multiple imputation approach. *Results*: More than 50% of the patients diagnosed with a stomach cancer in 1996–2000 were estimated 'cured' from their cancer, corresponding to a 20% increase since 1975–1980. Median survival time for 'uncured' patients however remained unchanged at about 8 months. 'Cure' fraction was over 85% for localised tumours and 30% for regional tumours, but stayed as low as 2.5% for distant metastatic cancers. Improvement was underestimated by about 10% because of ageing of cancer patients. Changes in stage distribution explained up to 40% of the increase in 'cure' fraction among men and up to 13% in women. Overdiagnosis was unlikely to play any role in these patterns. *Conclusions*: 'Cure' fraction from stomach cancer dramatically increased in Osaka, Japan since 1975, partly because of earlier stage at diagnosis, but mostly due to improvement in treatment of stomach cancer patients. This study, based on a leading country in term of stomach cancer management, provides insightful results for other countries in which 'cure' fraction is usually much lower.

1. Introduction

Stomach cancer has been the leading incident site in Japan for the last half century [1]. Stomach cancer screening started in Japan in the early 1960s, followed later by successive improvements in surgical treatment. As a result, five-year relative survival from stomach cancer has dramatically increased in Japan, doubling in Osaka since the 1970s [2].

'Cure' fraction models [3–7] enable us to estimate proportion of patients 'cured', defined as the proportion of cancer patients which life expectancy goes back to that of general population. Population 'cure' is a statistical concept defined at population level rather than an individual, clinical concept. Five-year survival, traditionally used as an indicator of recovering from cancer, is however affected by lead-time bias, which occurs typically with earlier diagnosis not associated with improved prognosis. By contrast, 'cure' fraction is not influenced by lead-time bias and represents then a useful indicator for evaluating long-term trends in cancer care using population-based data. 'Cure' models can also estimate the median survival of 'uncured', or 'fatal', patients.

'Cure' fraction has been estimated for stomach cancer in low-incidence areas such as Europe and the US [8,9], but none, to our knowledge, in an area with high incidence of stomach cancer such as Japan.

We aim to monitor trends in 'cure' fraction and median survival time for 'uncured' patients for stomach cancer in Osaka, Japan, in order to evaluate cancer care in long-term period. 'Cure' fraction model was applied on population-based Osaka cancer registry data. Missing information for tumour stage was handled by multiple imputation [10].

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doi:10.1016/j.canep.2011.12.008

2. Patients and methods

2.1. Data sources

We analysed 66,032 patients diagnosed with a first, primary malignant tumour of the stomach (ICD-10 code, C16) in Osaka between 1975 and 2000. The vital status of the patients is not centralised and automatic, and is therefore assessed only at five and ten years after diagnosis. The minimum potential follow-up was ten years patients, except for those diagnosed in 1996–2000 with a follow-up limited at five years. The Osaka Cancer Registry (OCR), one of the largest population-based cancer registries in the world, was established in 1962, allowing evaluation of long-term trends in cancer survival. Tumour stage was defined according to UICC TNM classification: localised tumour as T1–T2/N0/M0, regional metastases as T1–T2/N1–N2–N3/M0 or T3–T4/N0/M0, and distant metastasis as M1, regardless T and N.

2.2. Statistical methods

Statistical 'cure' is defined when the cancer patients group has the same mortality as general population with similar general characteristics (sex, age, etc.). In other words, the cancer population does not express any excess mortality when compared to the general population or the relative survival curve reaches a plateau [4,7].

Mixture parametric 'cure' fraction model [7,8,11,12] was employed with *strsmix* command for the statistical package Stata [6]. Such mixture models model the survival function of the group of the 'uncured' patients ($S_u(t)$) on top of the fraction of 'cured' patients. In the mixture cure fraction model, the all-cause survival can be written as the product of the expected survival, $S^*(t)$ and the disease-related survival functions

$$S(t) = S^*(t)(\pi + (1-\pi)S_u(t))$$

where π is the 'cure' fraction. The expected (or background) mortality was provided by complete (i.e. by single year of age), smoothed national life tables by sex and calendar year [13].

'Cure' fraction was estimated from the logit link and the survival function of the 'uncured' patients ($S_u(t)$), by a Weibull distribution. The survival function can therefore be written as:

$$S(t) = S^*(t)\exp(-\lambda t^{\gamma})$$

or equivalently on the hazard scale:

$$h(t) = h^*(t) + \lambda\gamma t^{\gamma-1}$$

with the Weibull parameters of scale (λ) and shape (γ). The 'cure' fraction is estimated using:

$$\pi = \text{invlogit}(\alpha + \beta' X)$$

when we used logistic link function with modelling covariates X. 'Cure' models were applied separately by sex, and included as covariables calendar period of diagnosis (1975–80, 1981–85, 1986–90, 1991–95, 1996–2000), age at diagnosis (15–39, 40–59, 60–74, 75–99) and tumour stage at diagnosis (localised, regional, distant). The 'cure' fraction and both Weibull parameters were allowed to vary by calendar period, age and stage.

Such multivariable models enabled us to predict 'cure' parameters for patients diagnosed in 1996–2000, whose maximum potential follow-up was five years. We examined the characteristics of patients with missing stage before multiple imputation, then we assumed the mechanism of missingness as Missing At Random. The 'cure' models were applied on the ten completed data sets containing the imputed values of stage for cases with missing information (11.4%). The imputation model was a multinomial logistic regression including follow-up time, vital status, period of diagnosis, age at diagnosis, and interactions between follow-up time and the other factors. Rubin's rules were applied to estimate the 'cure' fraction, median survival time for 'uncured' and their respective standard errors from the ten completed data sets [10].

The effects of age and stage at diagnosis on the time trends in 'cure' fraction and median survival time of 'uncured' patients were determined by the percentage change in the model parameters for period, age and stage at diagnosis estimated by successive multivariable 'cure' models. Given the full model including period, age and stage, the effect of, say, stage on the temporal trends is the

Table 1
Characteristics of stomach cancer patients in Osaka (Japan), 1975–2000.

	Period of diagnosis										Total	
	1975–80		1981–85		1986–90		1991–95		1996–2000			
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Total	11,811	100.0	12,387	100.0	13,595	100.0	14,035	100.0	14,204	100.0	66,032	100.0
Sex												
Men	7300	61.8	7915	63.9	8850	65.1	9368	66.7	9737	68.6	43,170	65.4
Women	4511	38.2	4472	36.1	4745	34.9	4667	33.3	4467	31.4	22,862	34.6
Age												
15–39	1066	9.0	878	7.1	682	5.0	397	2.8	309	2.2	3332	5.0
40–59	4012	34.0	4428	35.7	5122	37.7	4899	34.9	4268	30.0	22,729	34.4
60–74	5003	42.4	4943	39.9	5284	38.9	5855	41.7	6484	45.6	27,569	41.8
75–99	1730	14.6	2138	17.3	2507	18.4	2884	20.5	3143	22.1	12,402	18.8
Stage (before imputation)												
Localised	2552	27.2	3691	33.7	5169	41.5	5688	45.4	6219	47.4	23,319	39.9
Regional	4823	51.4	4932	45.0	4715	37.9	4444	35.4	4305	32.8	23,219	39.7
Distant	2014	21.5	2341	21.4	2573	20.7	2410	19.2	2601	19.8	11,939	20.4
Missing[a]	2422	(20.5)	1423	(11.5)	1138	(8.4)	1493	(10.6)	1079	(7.6)	7555	(11.4)
Stage (after imputation)												
Localised	3206	27.1	4056	32.7	5520	40.6	6279	44.7	6631	46.7	25,692	38.9
Regional	6055	51.3	5580	45.0	5168	38.0	4985	35.5	4687	33.0	26,474	40.1
Distant	2551	21.6	2751	22.2	2908	21.4	2771	19.7	2887	20.3	13,867	21.0

[a] Frequencies of stage before imputation are shown for the cases without missing stage information; on top of that is shown between brackets the proportion of missing stage.

percentage change between the period-specific parameters estimated by the full model and the model excluding stage. The approach was applied for the 'cure' Weibull parameters. All statistical analyses were performed using the standard statistical package Stata [14].

3. Results

Table 1 shows the main characteristics of the study subjects. Proportion of men slightly increased since 1975, to represent more than two third of the patients in 1996–2000. The patients also were diagnosed at older ages in the most recent periods while the distribution of stage at diagnosis shifted dramatically to earlier stage.

'Cure' fraction increased in absolute term by more than 20% since 1975 for all age groups, overall from 34% to 56% in men, from 27% to 50% in women (Table 2), with a constant, clear advantage for men. By contrast, no such improvement was observed for the median survival time for 'uncured', stabilised around 8 months for 25 years. In 1996–2000, around 65% of less than 60 year-old men

Table 2
Trends in 'cure' fraction (%) and median survival time for 'uncured' patients (month), stomach cancer, Osaka (Japan), 1975–2000.

	Men						Women					
	'Cure' fraction (%)			Median survival time for 'uncured' patients (month)			'Cure' fraction (%)			Median survival time for 'uncured' patients (month)		
	95% CI			95% CI			95% CI			95% CI		
Total												
Period of diagnosis												
1975–1980	34.0	32.7	35.3	7.5	7.2	7.8	27.2	25.8	28.7	7.5	7.2	7.9
1981–1985	43.0	41.8	44.3	8.3	7.9	8.7	38.5	36.9	40.1	8.5	8.1	9.0
1986–1990	49.1	47.9	50.3	8.9	8.5	9.2	45.2	43.6	46.8	10.0	9.5	10.6
1991–1995	52.6	51.4	53.9	8.4	8.1	8.8	48.4	46.8	50.0	7.9	7.4	8.3
1996–2000	55.9	54.7	57.0	8.4	8.1	8.8	49.7	48.0	51.3	7.6	7.2	8.0
By age												
15–39 years old												
Period of diagnosis												
1975–1980	40.4	37.7	43.2	9.2	8.3	10.2	27.3	25.0	29.7	9.2	8.4	10.0
1981–1985	50.1	47.3	53.0	10.3	9.3	11.4	39.2	36.5	42.0	10.6	9.7	11.6
1986–1990	56.2	53.4	59.1	11.1	10.0	12.3	46.5	43.6	49.4	12.6	11.6	13.8
1991–1995	60.5	57.7	63.3	10.9	9.8	12.1	50.2	47.2	53.2	10.4	9.5	11.4
1996–2000	64.5	61.8	67.2	10.6	9.6	11.7	52.6	49.5	55.6	10.0	9.1	11.0
40–59 years old												
Period of diagnosis												
1975–1980	40.2	38.7	41.8	9.0	8.6	9.5	31.8	30.0	33.6	9.0	8.5	9.6
1981–1985	49.9	48.4	51.4	10.1	9.6	10.6	44.4	42.5	46.3	10.4	9.8	11.0
1986–1990	56.0	54.6	57.4	10.8	10.3	11.4	51.9	50.0	53.7	12.3	11.6	13.1
1991–1995	60.3	58.9	61.6	10.6	10.1	11.2	55.6	53.7	57.4	10.2	9.5	10.9
1996–2000	64.3	63.0	65.6	10.4	9.9	10.9	57.9	56.0	59.8	9.8	9.2	10.5
60–74 years old												
Period of diagnosis												
1975–1980	31.5	30.2	32.9	7.4	7.0	7.7	27.6	25.9	29.3	7.5	7.1	8.0
1981–1985	40.6	39.1	42.0	8.3	7.9	8.7	39.5	37.7	41.4	8.7	8.2	9.2
1986–1990	46.6	45.2	48.0	8.9	8.5	9.3	46.8	44.9	48.7	10.3	9.7	11.0
1991–1995	51.0	49.6	52.4	8.7	8.3	9.1	50.6	48.7	52.5	8.5	8.0	9.1
1996–2000	55.3	54.0	56.6	8.6	8.2	9.0	52.9	51.0	54.8	8.3	7.8	8.8
75–99 years old												
Period of diagnosis												
1975–1980	20.7	19.3	22.2	4.7	4.4	5.0	16.5	15.1	18.0	4.4	4.2	4.8
1981–1985	27.9	26.3	29.6	5.4	5.0	5.7	25.3	23.5	27.2	5.1	4.8	5.5
1986–1990	33.1	31.3	34.9	5.8	5.5	6.2	31.3	29.3	33.4	6.2	5.8	6.6
1991–1995	37.1	35.3	39.0	5.6	5.2	5.9	34.6	32.6	36.7	5.1	4.8	5.5
1996–2000	41.2	39.3	43.1	5.8	5.4	6.1	36.8	34.7	39.0	5.0	4.7	5.4
By stage												
Localised												
Period of diagnosis												
1975–1980	80.6	78.7	82.3	14.8	12.6	17.3	74.1	71.4	76.6	12.6	10.8	14.6
1981–1985	86.0	84.5	87.3	16.6	14.2	19.4	85.0	83.3	86.6	14.8	12.8	17.2
1986–1990	87.4	86.1	88.6	17.1	14.7	19.9	86.5	85.0	87.9	17.1	14.8	19.8
1991–1995	87.4	86.2	88.6	16.6	14.2	19.5	86.2	84.7	87.6	13.4	11.5	15.5
1996–2000	89.5	88.5	90.4	16.7	14.4	19.3	87.5	86.0	88.8	13.0	11.3	15.1
Regional												
Period of diagnosis												
1975–1980	20.4	19.0	21.9	10.1	9.7	10.6	15.9	14.5	17.5	10.1	9.6	10.7
1981–1985	27.5	26.0	29.1	11.3	10.8	11.8	27.4	25.5	29.4	11.7	11.1	12.3
1986–1990	30.0	28.4	31.7	11.7	11.3	12.2	29.9	27.8	32.0	13.2	12.6	13.9
1991–1995	30.1	28.4	31.8	11.3	10.9	11.8	29.3	27.3	31.5	10.7	10.2	11.3
1996–2000	34.5	32.8	36.2	11.6	11.1	12.0	31.6	29.4	33.9	10.6	10.0	11.2
Distant												
Period of diagnosis												
1975–1980	1.4	1.1	1.7	4.5	4.3	4.7	1.0	0.8	1.3	4.6	4.3	4.8
1981–1985	2.0	1.7	2.4	5.2	4.9	5.4	1.9	1.5	2.5	5.3	5.0	5.6
1986–1990	2.3	1.9	2.7	5.5	5.3	5.8	2.2	1.7	2.8	6.2	5.8	6.5
1991–1995	2.3	1.9	2.7	5.2	5.0	5.5	2.1	1.7	2.7	5.0	4.7	5.3
1996–2000	2.8	2.3	3.3	5.6	5.4	5.8	2.4	1.8	3.0	5.0	4.7	5.3

Table 3
Effect of age and stage at diagnosis on trends in 'cure' fraction since 1975–80, stomach cancer, Osaka (Japan).

Period of diagnosis		Age	Stage
Men	1975–1980	–	–
	1981–1985	−3%	−3%
	1986–1990	−4%	19%
	1991–1995	−12%	39%
	1996–2000	−13%	19%
Women	1975–1980	–	–
	1981–1985	−1%	−22%
	1986–1990	−5%	−2%
	1991–1995	−10%	13%
	1996–2000	−13%	5%

and 55% less than 74 year-old women patients, respectively, were predicted to be 'cured'. 'Cure fraction' then decreased for older groups of patients. Almost 90% and 35% of the patients diagnosed in 1996–2000 with a localised or regional tumour, respectively, were predicted to be 'cured'. Most of the improvement in 'cure' fraction for localised tumours was observed in the early eighties while, for regional tumours, 'cure' fraction rose steadily over the entire period. Mean survival time for 'uncured' patients hardly changed for both tumour stage categories (shorter than 18 or 12 months, respectively). For distant tumours, 'cure' fraction remained lower than 3% while the median survival time for the vast majority of 'uncured' patients was still shorter than six months.

The proportions of increase in 'cure' fraction explained respectively by changes in age and tumour stage distributions were estimated by a multivariable modelling approach (Table 3). Results for median survival time for 'uncured' patients are not presented since it barely moved, age had little impact for both sexes, but, as stomach cancer population aged, improvement in 'cure' fraction was under-estimated by up to 13%. Stage adjustment explained up to about 40% of the increased 'cure' fraction in men, but little in women.

4. Discussion

To our knowledge, this is the first report of long-term trends in 'cure' from stomach cancer using population-based cancer registry data in Japan. Furthermore, the use of multiple imputation approach for handling missing data enabled us to investigate the role of tumour stage on the 'cure' parameters trends. About 56% of men and 50% of women diagnosed with stomach cancer in 1996–2000 were estimated 'cured' in Osaka Prefecture, Japan, corresponding to a 22% overall absolute increase in 'cure' fraction in two decades. On the other hand, the median survival time for 'uncured' patients hardly changed at around 8 months. This dramatic increase in 'cure' fraction is quite remarkable considering the ageing stomach cancer patients, their mean age at diagnosis going from 60 years in 1975–80 to 65 years in 1996–2000, and the lower survival among the elderly. After adjusting for age and accounting for differences in background mortality by age, up to 13% of the increase in 'cure' fraction was hidden by this ageing. Such improvement could however be the sole result of stage shifting. Both widespread screening and dedicated early detection increased the proportion of localised tumours from 27% to 47%, with a similar inverse shift in the proportion of regional tumours and an unchanged proportion of distant tumours (Table 1). As a consequence, increasing proportion of so-called over-diagnosed cases (i.e. cases whose cancer is unlikely to be clinically symptomatic and lethal during their lifetime), as reported for prostate and breast cancers [15,16], could explain the rise on 'cure' fraction. However, the participation rate to stomach cancer screening has remained around 20% of the eligible population in Japan or in Osaka during the study period [17,18]. Furthermore, the (non age-adjusted) 'cure' fraction moderately increased for localised tumours. Intensification of any over-diagnosis phenomenon seems therefore unlikely.

Although role of early diagnosis is unquestionable, stage distribution shifting however never explained more than 40% in men and 13% in women of the overall increase in 'cure' fraction, i.e. most of this increase remains unexplained. Improvement in the management of the patients, with more accurate staging and then more adequate treatment, may have played an important role. Proportion of curative resection among patients rose from 60% in the late 1970s to up to 80% in the late 1990s. Diagnostic procedures also changed dramatically, use of endoscope increasing from 56% to 90% through the study period. Most of the 'cure' fraction improvement occurred during the eighties, in particular among the women. Although D2 dissection has been operated as a standard surgery for the advanced stomach cancer cases in Japan, its role on increase in 'cure' fraction could not be evaluated because of lack of detailed individual clinical data. The none-improvement in median survival time for 'uncured' patients is reasonable given the absence of randomised study which has demonstrated any survival benefit of chemotherapy or radiotherapy during study period. Similarly, the constantly poor prognosis of metastatic stage patients can be explained by the lack of new effective treatment.

In the late nineties, proportions of the patients 'cured' from stomach cancer were below 30% both in European countries [8] and in the US [9], compared to 50% or more in both sexes in Osaka. In Osaka, around 40% of the stomach cancer patients were diagnosed with localised tumours and around 20% with distant metastatic tumours since the mid eighties (see Table 1). The comparable figures were 20% in Slovenia and the USA for localised tumours [19] and between 20 and 24% in Netherlands (Stage I) [20] and 13 and 20% in some European countries (T1/T3, N0, M0) [21]. That advantage found in Japan over Western countries could be due to higher proportions in young patients and in non-cardia tumours, both factors of good prognosis [22]. However, Japan has also witnessed the worldwide decrease in stomach cancer incidence observed for decades, a decrease which involves mostly the non-cardia tumours [23]. Such trends could not be examined directly on our data because of non-specific sub-site for more than 60% of the records. However, according to the results from cancer registry in Hiroshima city, which systematically collect subsite data, incidence in non-cardia tumours (C16.0: upper stomach cancer) started to decrease during the 80s in Japan [24].

It has also been suggested differences in pathological definition of stomach tumours with some tumours not considered as invasive by European pathologists [25]. Interpretation of these results was controversial [26,27] and discrepancies could result from under-diagnosed tumours in Europe rather than over-diagnosed in Japan [28]. There is also evidence that early gastric tumours progressed to advanced cancers and to death from gastric cancer in a long natural history [29].

The advantage of men in proportion 'cured' was consistent with a previous study about sex difference in five-year relative survival [30], but contrasted with pattern found in Europe [31]. In Japan, men are likely to be diagnosed earlier, because of more opportunistic screening than women within their workplace. The effect of age and stage on the trends in 'cure' fractions were similar with previously estimated trends in five-year relative survival in Osaka, Japan [2].

Patients with missing information on tumour stage were more likely old and diagnosed in the late seventies, and they had slightly lower survival than the comparable subjects. On average, the distribution of imputed stage was skewed to more advanced stages (Table 1). Analysis based on complete cases tended to provide 0.1–3.9% higher 'cure' fractions and 0.1–1.0% larger increase in 'cure' over time than when based on completed cases. However, both the

overall picture of the results and their interpretation remain unchanged. Further investigations were limited by the paucity of clinical information of good quality available in the population-based cancer registry data over the whole study period. Using multivariable 'cure' model enabled us to estimate the respective role of age and stage at diagnosis on trends in 'cure' parameters. In addition, by contrast to five-year survival, the estimation of 'cure' fraction is not affected by lead-time bias.

In conclusion, despite ageing of the patients and decreasing incidence in non-cardia tumours, 'cure' fraction dramatically rose since 1975–80 and reached 56% and 50% among men and women, respectively, in 1996–2000. Improved management of the stomach cancer patients is likely to explain most of this enhancement, with earlier diagnosis due to screening organised and provided by local government and workplace, more accurate staging and appropriate treatment, more radical surgical procedures, and at least part of the persisting survival advantage seen in Japan over Western countries. Such results, from a leading country for the management of stomach cancer, could help improving stomach cancer control policy first in the regions with high or intermediate levels of stomach cancer incidence, but also in those with low incidence. Nevertheless, almost half of the patients remained 'uncured', most of them dying within less than a year after diagnosis, a parameter unchanged for 25 years. Collecting more detailed population-based clinical data on diagnosis and treatment should be prioritised, using linkage with clinical database.

Conflict of interest statement

None declared.

Acknowledgements

This study was supported by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour and Welfare (20-2) and Grant-in-Aid for Research Activity Start-up (10020027). BR was supported by Cancer Research UK (Collaborator Bursary C1336/A12446) during his stay at the Osaka Medical Centre for Cancer and Cardiovascular Diseases, Japan.

References

[1] Matsuda T, Marugame T, Kamo KI, Katanoda K, Ajiki W, Sobue T, et al. Cancer incidence and incidence rates in Japan in 2003: based on data from 13 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol 2009;39(12):850–8.
[2] Ito Y, Ohno Y, Rachet B, Coleman MP, Tsukuma H, Oshima A. Cancer survival trends in Osaka, Japan: the influence of age and stage at diagnosis. Jpn J Clin Oncol 2007;37(6):452–8.
[3] Boag J. Maximum likelihood estimates of the proportion of patients cured by cancer therapy. J Royal Stat Soc Ser B Methodological 1949;11(1):15–53.
[4] De Angelis R, Capocaccia R, Hakulinen T, Soderman B, Verdecchia A. Mixture models for cancer survival analysis: application to population-based data with covariates. Stat Med 1999;18(4):441–54.
[5] Verdecchia A, De Angelis R, Capocaccia R, Sant M, Micheli A, Gatta G, et al. The cure for colon cancer: results from the EUROCARE study. Int J Cancer 1998;77(3):322–9.
[6] Lambert PC. Modeling of the cure fraction in survival studies. Stata J 2007;7(3):351–75.
[7] Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics 2007;8(3):576–94.
[8] Francisci S, Capocaccia R, Grande E, Santaquilani M, Simonetti A, Allemani C, et al. The cure of cancer: a European perspective. Eur J Cancer 2009;45(6):1067–79.
[9] Tai P, Yu E, Cserni G, Vlastos G, Royce M, Kunkler I, et al. Minimum follow-up time required for the estimation of statistical cure of cancer patients: verification using data from 42 cancer sites in the SEER database. BMC Cancer 2005;5:48.
[10] Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons, 1987.
[11] Lambert PC, Dickman PW, Osterlund P, Andersson T, Sankila R, Glimelius B. Temporal trends in the proportion cured for cancer of the colon and rectum: a population-based study using data from the Finnish Cancer Registry. Int J Cancer 2007;121(9):2052–9.
[12] Woods LM, Rachet B, Lambert PC, Coleman MP. 'Cure' from breast cancer among two populations of women followed for 23 years after diagnosis. Ann Oncol 2009;20(8):1331–6.
[13] National Cancer Centre. Abridged life tables in Japan for 1962–2008; 2009.
[14] StataCorp. Stata statistical software: release 11. College Station, TX: StataCorp LP, 2009.
[15] Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. JAMA 2009;302(15):1685–92.
[16] Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986–2005. J Natl Cancer Inst 2009;djp278.
[17] Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol 2008;38(4):259–67.
[18] Ministry of Health, Labour and Welfare. Comprehensive survey of living conditions of the people on health and welfare (H.16); 2004.
[19] Lambert R, Guilloux A, Oshima A, Pompe-Kirn V, Bray F, Parkin M, et al. Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. Int J Cancer 2002;97(6):811–8.
[20] Dassen AE, Lemmens VE, van de Poll-Franse LV, Creemers GJ, Brenninkmeijer SJ, Lips DJ, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. Eur J Cancer 2010;46(6):1101–10.
[21] Bouvier AM, Sant M, Verdecchia A, Forman D, Damhuis R, Willem Coebergh J, et al. What reasons lie behind long-term survival differences for gastric cancer within Europe? Eur J Cancer 2010;46(6):1086–92.
[22] Verdecchia A, Mariotto A, Gatta G, Bustamante-Teixeira MT, Ajiki W. Comparison of stomach cancer incidence and survival in four continents. Eur J Cancer 2003;39(11):1603–9.
[23] Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, Negri E, et al. Recent patterns in gastric cancer: a global overview. Int J Cancer 2009;125(3):666–73.
[24] Sugiyama H, Nishi N, Sakata R, Kodama K. Trends in incidence of stomach cancer by subsite in Hiroshima city, Japan. Proc Annu Meet Japanese Soc Publ Health 2006;Supplement:611 [In Japanese].
[25] Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, et al. Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. Lancet 1997;349(9067):1725–9.
[26] Rugge M, Cassaro M, Farinati F, Di Mario F. Diagnosis of gastric carcinoma in Japan and western countries. Lancet 1997;350(9075):448.
[27] Stolte M. Diagnosis of gastric carcinoma in Japan and western countries. Lancet 1997;350(9075):448.
[28] Sakamoto J, Yasue M. Do Japanese statistics on gastric carcinoma need to be revised? Lancet 1997;349(9067):1711–2.
[29] Tsukuma H, Oshima A, Narahara H, Morii T. Natural history of early gastric cancer: a non-concurrent, long term, follow up study. Gut 2000;47(5):618–21.
[30] Sato N, Ito Y, Ioka A, Tanaka M, Tsukuma H. Gender differences in stomach cancer survival in Osaka, Japan: analyses using relative survival model. Jpn J Clin Oncol 2009;39(10):690–4.
[31] Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer 2009;45(6):1017–27.

IJC
International Journal of Cancer

Does removal of out-of-pocket costs for cervical and breast cancer screening work? A quasi-experimental study to evaluate the impact on attendance, attendance inequality and average cost per uptake of a Japanese government intervention

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Reducing out-of-pocket costs is known to improve mammography attendance, but an evidence gap remains concerning Pap smear testing. The Japanese government implemented a politically determined intervention to remove out-of-pocket costs for Pap smear tests and mammography attendance, costing US$148 million, in 2009. It targeted women when they reached the first year of a 5-year age group (*i.e.*, 20, 25, 30 years) with the aim of reducing attendance inequality. Our objective is to evaluate the intervention in terms of uptake and average cost per uptake for cancer screening attendance and to assess socioeconomic inequalities in cancer screening attendance pre- and postintervention. A quasi-experimental study utilizing national repeated cross sections, observed pre- and postintervention, which compared intervention and comparison groups by the Difference-in-Differences method, was conducted. Outcome measures were uptake of cancer screening attendance resulting from the intervention with average cost per uptake and broad inequality indicators for cancer screening attendance according to socioeconomic inequality. In total, 34,043 age-eligible, noninstitutionalized women were analyzed. Uptake among the overall population was 13.9% point in the age- and income-adjusted model for Pap smear and 9.8% point for mammography, with an average cost of US$139 per uptake. The intervention increased inequality indicators in Pap smear attendance (more than +100%) but decreased inequality in mammography attendance (ranging from −12.9 to −74.1%) within the intervention group. In conclusion, removing out-of-pocket costs improves female cancer screening uptake in Japan but may not be cost-saving. Although cost removal reduces inequalities in attendance for mammography, it appears to increase inequalities in Pap smear attendance.

Breast cancer is the most commonly diagnosed female cancer worldwide. Cervical cancer is the third most commonly diagnosed but is a smaller problem in Japan.[1] Every 2 years women are invited for screening in accordance with recommendations by the Japanese Advisory Committee on Cancer Screening. Women of 20 years or more (no upper age limit) are invited for cervical cancer screening (CCS) (Pap smear), and women of 40 years or more (no upper age limit) are invited for breast cancer screening (BCS) (mammography), through local municipal governments or workplace-based medical insurances.[2] Despite national cancer screening recommendations and evidence for prevention and early detection of cancer, female cancer screening (FCS) attendance rates remain low. A possible reason for this is the absence of a population-based FCS system.[3] The current system is composed of various different structures implemented by local municipalities or workplaces, each with different approaches to individual elements of the system (*e.g.*, out-of-pocket costs setting, letters of invitation, no guideline for workplace-based cancer screening).[4] FCS is performed either as part of a health checkup for residents offered by a local municipal government or a workplace-based health checkup. If housewives and unemployed women are covered by workplace-based medical insurances for entire families, they may not attend the local government residential checkups. This makes it difficult for municipal staff to select a target population for FCS and improve FCS attendance rates. In 2007, only 24.5% of women aged 20–69 years reported having CCS and 23.8% of

Key words: Pap smear, mammography, removing out-of-pocket costs, socioeconomic inequalities in cancer screening attendance, Japan
Additional Supporting Information is available in the Web site of Int. J. Cancer. (http://onlinelibrary.wiley.com/journal/)
Conflict of interest: The authors have declared no conflicts of interest.
Grant sponsor: Japanese Ministry of Health, Labour and Welfare; **Grant number:** H23-ganrinsho-011; **Grant sponsor:** Osaka Prevention Center for Cancer and Cardiovascular Diseases; **Grant number:** H23-03
DOI: 10.1002/ijc.28095
History: Received 7 Sep 2012; Accepted 28 Jan 2013; Online 7 Feb 2013
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What's new?

Out-of-pocket costs may be a barrier to cancer screening, though their removal in some countries has met with mixed results. Here, analysis of uptake, government expenditure, and socioeconomic inequalities associated with a cost-free breast and cervical cancer screening program introduced in Japan in 2009 indicates that while attendance increased for both types of screening, overall spending for the program was considerable. Furthermore, while inequalities in attendance decreased for breast cancer screening, they increased for cervical cancer screening.

women aged 50–69 years reported having BCS, within the past year.[5] These figures are considerably lower than those for other developed countries such as the USA, Canada, Germany, the Netherlands, Korea and Australia.[5]

In 2009, the Japanese government introduced a new, politically determined policy that provided cost-free CCS and BCS attendance. Although financial barriers to screening are generally reduced in most European countries where free tests are available,[6] out-of-pocket costs have been a barrier to access in the USA and Japan.[7] To increase access to BCS, interventions to reduce or eliminate out-of-pocket costs have been recommended, especially for the lower socioeconomic population, aimed at reducing socioeconomic inequality in cancer screening attendance.[7–9] However, to date, there is insufficient evidence to determine whether reducing out-of-pocket costs is effective in increasing CCS attendance, and thus, an evidence gap was identified.[7,9] Data on cost from interventions for cancer screening attendance are also limited.[7,10] This quasi-experimental study aims to fill the evidence gap that has arisen in the absence of a governmental strategy to evaluate the intervention in Japan.

Socioeconomic inequalities in mortality, morbidity and health-related behaviors, including cancer screening attendance, have been demonstrated worldwide.[11,12] Attendance levels at FCS for Japanese women in the lowest quintile of household income were approximately half those of women in the highest quintile.[13] Inequalities in cancer screening are responsible for the higher mortality rate among people of lower socioeconomic position because of the associated decrease in the chance of early detection of cancer.[14,15] Broad policy frameworks, such as the World Health Organization Commission on the Social Determinants of Health report and the Japanese health promotion plan "Healthy Japan 21 (2nd)," present moral arguments for reducing health inequalities.[16,17] In addition to improving overall attendance, addressing inequalities in uptake must remain a priority for screening programs.[18,19]

We utilized repeated cross sections as a quasi-experimental study, which includes two consecutive population-based studies of Japanese people, observed pre- and postintervention. Our objective is to evaluate uptake and average cost per uptake of the intervention on CCS and BCS attendances and to assess socioeconomic inequalities in FCS attendance pre- and postintervention.

Material and Methods

Data

We used data from pre- and postintervention cross-sectional studies: the 2007 and 2010 Comprehensive Survey of Living Conditions of People on Health and Welfare (CSLCPHW), conducted by the Japanese Ministry of Health, Labour and Welfare (MHLW).[20] The CSLCPHW collects information on health-related factors, such as cancer screening and smoking behavior, every 3 years. Out of 940,000 inhabited census tracts (sampling unit for national census in 2005), 5,440 were randomly sampled across Japan in 2007 (5,510 in 2010) for the collection of data from all household members within each census tract. Of 11,000 units (around 5,500 census tracts were further divided into 11,000 units for appropriate alignment of territory management), 2,000 units were randomly selected across Japan for the income survey. Income data were available for 23,513 (response rate: 64.8%) households in 2007 and 26,115 (72.6%) in 2010. Data were used with permission from MHLW.

Intervention and FCS attendance

The intervention was implemented from September 2009 to March 2010 across Japan and was intended to increase uptake of attendance for Pap smear or mammography. It comprised two elements. First, vouchers were distributed (usually by mail but occasionally by hand)[4] to remove out-of-pocket costs to clients, and second, the vouchers were accompanied by small media (information leaflets). All women reaching the first year in a 5-year age group were invited to attend, that is, aged 20, 25, 30, 35 and 40 years on 31 March 2009 (identified from municipal resident registries) for Pap smear and aged 40, 45, 50, 55 and 60 years for mammography.[2] The invitees themselves made appointments for the tests (although these were rarely necessary for Pap smear tests, they were often required for mammography) at any local providers. Upon presentation of the voucher, they received the FCS without out-of-pocket costs. We assembled groups of women aged ±1 and ±2 years of the intervention group as a comparison group.

Attendance for FCS was surveyed preintervention (2007) and postintervention (2010) as follows. "Have you participated in cervical (breast) cancer screening in the past 12 months? (CCS means Pap smear test; BCS means mammography or breast echography.) (yes/no)." Because only cancer