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Conditional survival for longer-term survivors from 2000–2004 using population-based cancer registry data in Osaka, Japan

Yuri Ito*, Tomio Nakayama, Isao Miyashiro, Akiko Ioka and Hideaki Tsukuma

Abstract

Background: We usually report five-year survival from population-based cancer registries in Japan; however these survival estimates may be pessimistic for cancer survivors, because many patients with unfavourable prognosis die shortly after diagnosis. Conditional survival can provide relevant information for cancer survivors, their family and oncologists.

Methods: We used the period approach to estimate the latest 10-year survival of 38,439 patients with stomach, colorectal, lung, breast and prostate cancer diagnosed between 1990 and 2004 and followed-up from 2000–04 in Osaka, Japan. Conditional survival is an estimate, with the pre-condition of having already survived a certain length of time. Conditional five-year relative survival of one to five years after diagnosis was calculated by site, age and stage for survivors under the age of 70.

Results: Five-year relative survival for stomach cancer was 60%. Conditional five-year relative survival was 77% one year after diagnosis and 97% five years after diagnosis. This means that 97% of patients who survive five years after diagnosis can survive a further five years. Conditional five-year relative survival improved successively with each additional year that patients lived after diagnosis for stomach, colorectal and lung cancer. These figures for breast and prostate cancer were stable at high survival. Liver cancer did not show an increase in conditional five-year survival.

Conclusion: Conditional five-year survival is a relevant figure for long-term cancer survivors in Japan. It is important for population-based cancer registries to provide figures which cancer patients and oncologists really need.

Keywords: Conditional survival, Cancer registries, Relative survival, Japan

Background

In recent years cancer patients have been able to survive for longer than those diagnosed a few decades ago. We usually report five-year relative survival rates after diagnosis in the annual reports of regional cancer registries in Japan. However, these survival estimates may be pessimistic for cancer survivors, because many patients with unfavourable prognosis die shortly after diagnosis.

Conditional survival analysis is a method to estimate survival rates, with the pre-condition of having already survived a certain length of time. The figures have been reported in the US and other countries, and can provide cancer survivors, their families and oncologists with more relevant information [1-11].

In 2007, the Basic Plan to Promote Cancer Control Programs of Japan was approved, following the establishment of the Cancer Control ACT of Japan in 2006. Improvement of cancer care support and information services is one of the specific goals of this program [12]. Longstanding population-based cancer registry data can provide this type of useful information to cancer survivors. We used cancer patient data from the Osaka Cancer Registry, which has a long history and covers the largest population in Japan, to report conditional survival in patients with six major cancers by age group and stage at diagnosis.

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Methods

Data sources

We analysed 38,439 cases diagnosed with first, primary, invasive malignant tumour of the following cancers: stomach (International Classification of Diseases, 10th revision code [13]: C16), colorectal (C18-C20), lung (C33, C34), breast (C50, female only) and prostate (C61) from 1990–2004. They were followed up between 2000 and 2004 in Osaka, Japan, from the Osaka Cancer Registry database. We limited the data to patients who were diagnosed at age 15 to 69 years. Patients over 70 years of age at diagnosis were excluded from the analyses as long-term survival estimates are unstable for older age groups. In the Osaka Cancer Registry, we followed patients up using the death certificate database for residents in Osaka prefecture. However, if patients had moved outside the Osaka Prefecture after diagnosis the death certificate database would be unable to capture their details. In these cases resident registries were used to follow the patients up. Residents in Osaka-city (30% of total population of Osaka prefecture) were not followed-up using residence registries before 1993, so patients who lived in Osaka-city were excluded from the analysis. Cases diagnosed from 1990 to 1999 were followed up for 10 years after diagnosis, whereas follow-up was limited to 5 years for those diagnosed from 2000 to 2004 (Figure 1).

Statistical analysis

First, we estimated ten-year relative survival using the Osaka Cancer Registry data by sex, age group (15–49, 50–59 and 60–69 years old) and stage at diagnosis (localised, regional and distant metastasis). Relative survival is a ratio of the observed survival (overall survival) and the survival that would have been expected if the cancer patient had only experienced the normal (background) mortality of the general population in which they live [14]. In this study we estimated relative survival using the maximum likelihood method developed by Esteve et al. [15] and the publicly available Stata programme *strel* [16]. We derived the expected survival from complete (single-year-of-age) national population life tables by sex [17]. We used conventional 10-year relative survival estimating based on data from patients who were diagnosed from1995-1999 and were followed-up over 10 years (dashed line in Figure 1). However, calculation of long-term survival using the conventional method is outdated. We therefore used period analysis to derive more up-to-date long-term survival using data from recently followed-up cancer patients [18]. In this study, we used data from cancer patients who were diagnosed from 1990–2004 and followed-up between 2000 and 2004 (solid black line, in Figure 1).

Second, we calculated conditional five-year survival for patients who survived for 0 to 5 years after diagnosis using ten-year cumulative relative survival. To estimate the five-year conditional survival of patients who survived x years, the (x + 5)-year cumulative survival rates is divided by the x-year cumulative survival. In the other words, conditional five-year survival is five-year survival of the patients who are alive several years after diagnosis [2,10].

Third, for missing stage cases, we used the multiple imputation approach [19]. We examined the characteristics of patients with missing stage before multiple imputation, then we assumed the mechanism of missingness as Missing At Random. The relative survival of the ten completed data sets contained the imputed value of stage for cases with missing information (6.4-17.1%). 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 other factors. Rubin's rules were applied to estimate relative survival and standard errors combining the ten completed data sets. All statistical analyses were performed using the standard statistical package Stata Ver. 12.1 [20].

Results

The characteristics of patients we analysed are shown in Table 1. Conditional five-year survival for all stage

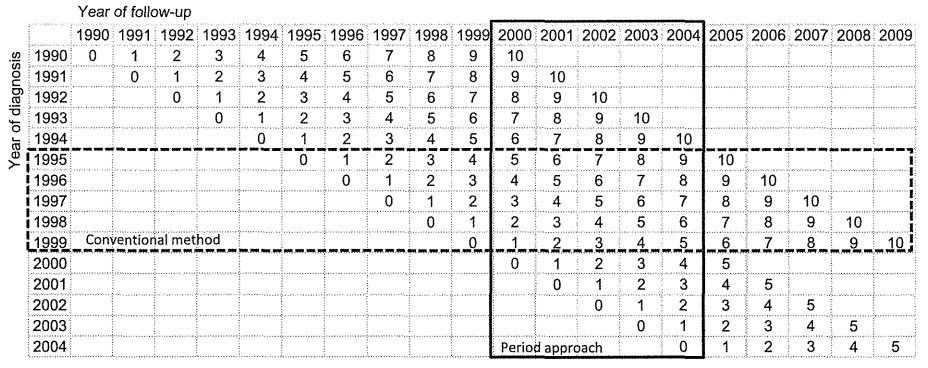

Figure 1 Illustration of period approach to estimate up-to-date long-term survival.

Table 1 Characteristic of cancer patients for selected sites of cancer in Osaka, Japan in 1990–2004

	Stomach		Colon/rectum		Liver		Lung		Breast		Prostate	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Total	10278	100.0	8411	100.0	4800	100.0	6397	100.0	7229	100.0	1324	100.0
Age												
15-49	1266	12.3	897	10.7	296	6.2	549	8.6	2591	35.8	6	0.5
50-59	3442	33.5	2830	33.6	1344	28.0	2024	31.6	2752	38.1	214	16.2
60-69	5570	54.2	4684	55.7	3160	65.8	3824	59.8	1886	26.1	1104	83.4
Stage (before imputation)												
Localised	4863	50.7	3568	45.3	2897	72.8	1426	23.8	3747	57.3	785	65.4
Regional	2758	28.8	2577	32.7	663	16.7	2167	36.2	2439	37.3	175	14.6
Distant	1972	20.6	1728	21.9	421	10.6	2397	40.0	350	5.4	241	20.1
Missing	685	(6.7)	538	(6.4)	819	(17.1)	407	(6.4)	693	(9.6)	123	(9.3)
Stage (after imputation)												
Localised	5202	50.6	3817	45.4	3436	71.6	1511	23.6	4139	57.3	865	65.3
Regional	2960	28.8	2757	32.8	818	17.0	2304	36.0	2701	37.4	196	14.8
Distant	2116	20.6	1837	21.8	546	11.4	2582	40.4	389	5.4	263	19.9

patients under the age of 70 by site of cancer is shown in Figure 2. For stomach cancer, the five-year relative survival for all cases is 60% at diagnosis. 77% of patients who survived one year (one-year survivor) can survive an additional five years. Conditional five-year survival at two years after diagnosis was 87%. Conditional five-year survival at five years after diagnosis was 97%. This means 97% of the stomach cancer patients who survived for more than five years can survive another five years. Colorectal and lung cancer showed similar results to stomach cancer patients. However, conditional five-year survival for liver cancer did not increase after any period post diagnosis. Conditional survival for breast and prostate cancer patients was stable at around 85-90%.

By age group

Results by age group are shown in Figure 3. Most cancer sites showed similar results among the different age

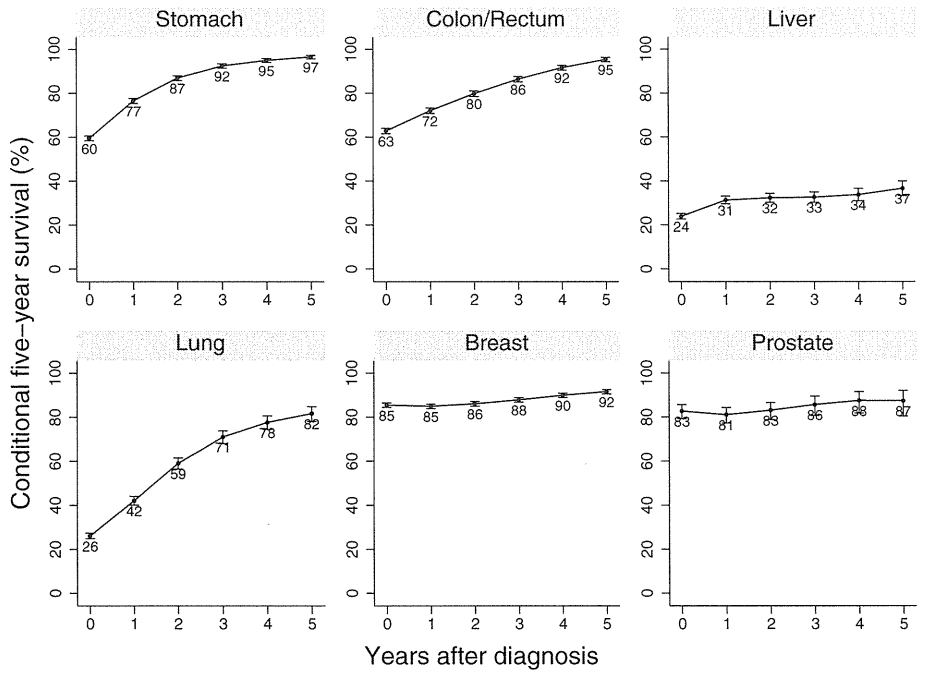

Figure 2 Conditional five-year survival for all patients diagnosed in 1990–2004 and followed-up in 2000–2004 in Osaka, Japan.

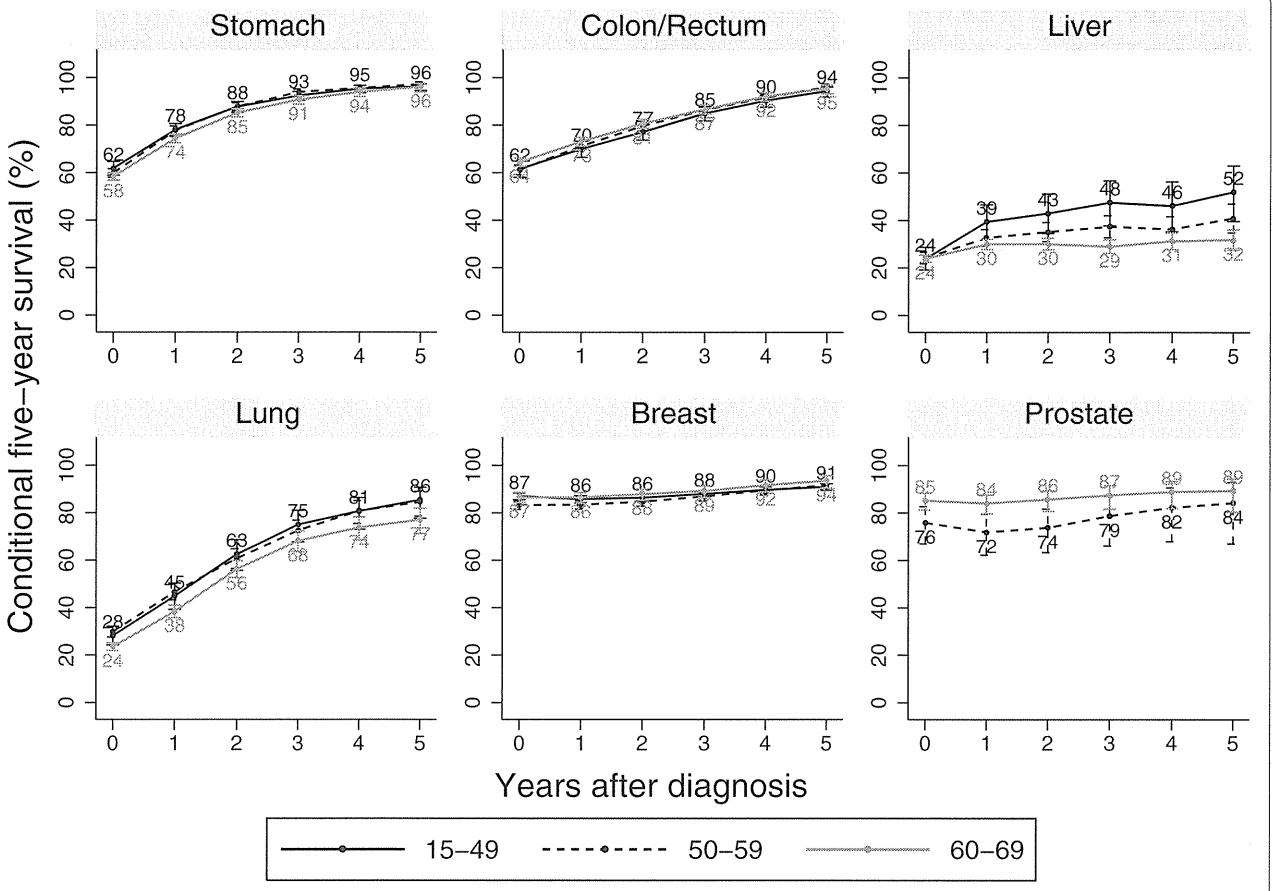

Figure 3 Conditional five-year survival of the patients diagnosed in 1990–2004 and followed-up in 2000–2004 in Osaka, Japan: by age group.

groups. In liver cancer patients, conditional survival increased in the young group (under the age of 50). In prostate cancer patients, the older age group (60–69 years old) showed better conditional survival than the younger age group (50–59 years old).

By stage

Figures for conditional survival by stage at diagnosis were different for different cancers (Figure 4). In all except liver cancer patients, the figures for conditional survival for localised patients were high at around 90%. In stomach, colorectal and lung cancer patients, even the regional and distant metastasis cases showed high five-year survival for five-year survivors. In liver cancer patients, even localised cases showed low conditional five-year survival. In breast and prostate cancer patients, conditional five-year survival for each stage was stable.

Discussion

Conditional five-year relative survival improved successively with each additional year that patients lived following diagnosis for stomach, colorectal and lung cancer. This pattern was also similar to the regional or distant metastasis cases. Breast and prostate cancer showed different trends; conditional five-year survival was stable at a higher level. Liver cancer did not show any increase in conditional five-year survival.

Stomach and colorectal cancer

For stomach and colorectal cancer patients who survived more than five years after diagnosis, conditional five-year survival was close to 100%. This means that those who survived five years would have the same survival probability as the general population, i.e. they can be considered as 'cured' of cancer. Although it is difficult to define clinical 'cure' at the individual level, we can define the concept of 'cure' at population level [21,22]. Conditional five-year survival for localised cases was stable at more than 90%. Those for regional or distant metastasis increased according to the number of years since diagnosis. Even late stage patients who survive a few years have a chance of living another five years.

Lung cancer

Conditional survival in lung cancer patients increased according to the additional years after diagnosis.

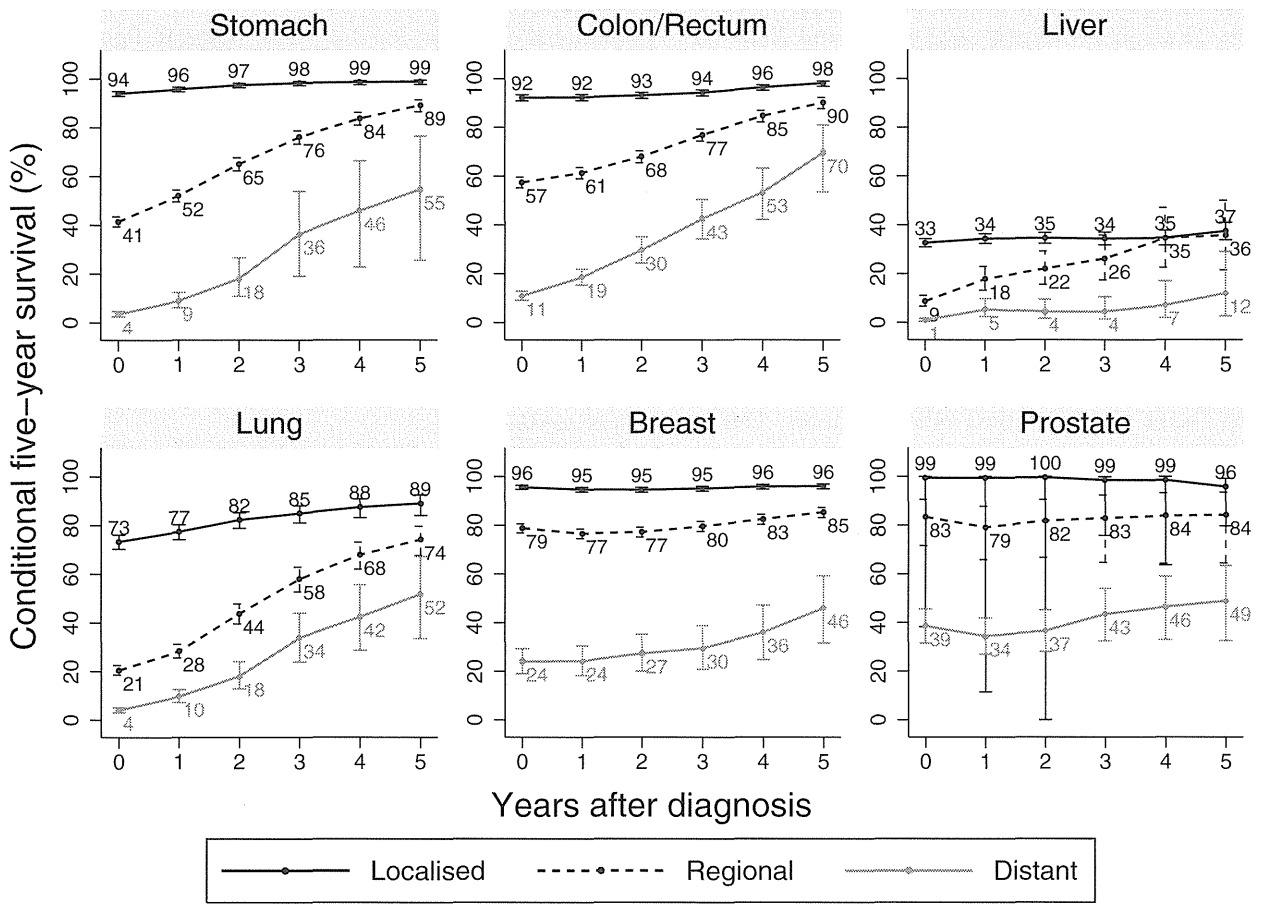

Figure 4 Conditional five-year survival of the patients diagnosed in 1990–2004 and followed-up in 2000–2004 in Osaka, Japan: by stage at diagnosis.

However, the figures were lower than those for stomach and colorectal cancer. This was because lung cancer patients have a higher risk of death due to complications related to cancer or cancer risk (smoking), such as ischemic heart disease.

Breast and prostate cancer

Conditional five-year survival rates for all cases of both breast and prostate cancer were around 80-90%, due to the higher proportion of localised patients in all cases. Conditional five-year survival for localised prostate cancer patients slightly decreased five years after diagnosis. This could be partly explained by the recurrence or progression of tumours during long-term follow-up. For these cancers, we need to follow-up patients for a longer period.

Liver cancer

Conditional survival for liver cancer was much lower than for other cancers at any stage or age after several years. Even in localised patients, conditional five-year survival was less than 40% after five years. This is probably because many liver cancer patients experienced a recurrence of cancer, or died from liver cirrhosis or liver failure related to the hepatitis B or C virus.

Effect of age and stage at diagnosis

Trends in conditional survival by age group were quite similar except for liver and prostate cancer. For most cancers, age did not significantly affect conditional survival. In the case of liver cancer, conditional survival for young patients (15–49 years old) was higher than for old patients (60–69 years old) after several years. This could be explained by the fact that the old patients had been exposed to hepatitis viruses for long time; as a result, they tended to develop liver cirrhosis and liver failure more than young patients. Conditional survival of young prostate cancer patients (50–59 years old) was lower than old patients (60–69 years old). This is probably because young patients are diagnosed at a more advanced

stage than old patients (the proportion of distant metastasis was 35.2% in 50-59-year-old patients and 28.3% in 60-69-year-old patients).

The conditional survival curve was different by stage; stage at diagnosis was an important prognostic factor. Conditional survival for localised patients was stable at 85-95%, while for regional and distant metastasis patients it increased after several years of diagnosis.

Trends in conditional survival for breast and colorectal cancer patients in Osaka were similar to other countries (shown in Additional file 1: Figures S1-S4 from Australia [2,6], US [8], Canada [5,11] and European countries [3,9]). Conditional survival for prostate cancer at all stages in Osaka was lower than other countries. This is due to the low proportion of localised patients in Japan compared to other countries. Conditional survival of stomach cancer for all stage and localised in Osaka was higher than in Australia [2]. Stomach cancer patients in Osaka were diagnosed at an earlier stage than in Australia (e.g. 51% patients diagnosed at localised stage in Osaka, 28% in Australia). In addition, approximately half of the stomach cancer patients in Japan were diagnosed at T1 (UICC TNM classification) [23]. Therefore we can estimate a higher proportion of T1 in localised patients in Osaka than in Australia. Higher conditional survival for localised patients can be partly explained by differences in tumour. This may be due to stomach cancer screening programmes [24] and wide use of endoscopy in clinical settings in Japan. Conditional survival of localised lung cancer in Osaka was higher than in other countries. This could be explained by differences in tumour size and histology [25,26]. Conditional survival for liver cancer patients in Canada increased some years after diagnosis [11], while in Osaka it was stable at low survival. This can be explained by the differences in etiological factor among these countries. In the US and Canada, prevalence of hepatitis B or C viruses in liver cancer cases was lower than in Japan [27]. Liver cancer patients in Japan might have greater likelihood of liver failure or hepatitis-related cirrhosis than those in the US and Canada.

Conditional five-year survival for stomach and colorectal cancer patients who were alive five years after diagnosis was about 100%; this means those patients have similar survival probability to the general population. Therefore those patients can be considered as 'cured'. For other sites of cancer, further long-term follow-up time may be needed to estimate 'cured' time.

Conditional survival is an important statistic for planning long-term life after diagnosis, not only for cancer patients and their families, but also patients with other diseases. However, a population-based disease registry system, such as the population-based cancer registry, is essential to estimate this type of statistic.

Conclusion

Conditional five-year survival is a relevant figure for long-term cancer survivors in Japan. It is important for population-based cancer registries to provide figures which cancer patients and oncologists really need.

Additional file

Additional file 1: Figure S1-S4. Comparison of conditional survival between countries, by site and stage.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YI, TN and HT developed the study concept. YI and IA were responsible for data management and statistical analysis. TN, IM and HT reviewed the clinical background of the results. YI wrote the draft of the report. All authors critically reviewed and revised the manuscript.

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References

1. National Research Council: 2 Cancer Survivors. In *From Cancer Patient to Cancer Survivor: Lost in Transition*. Edited by Hewitt M, Greenfield S, Stovall E. Washington D.C.: The National Academies Press; 2005:23–65.
2. Yu XQ, Baade PD, O'Connell DL: Conditional survival of cancer patients: an Australian perspective. *BMC Cancer* 2012, 12:460.
3. Allemani C, Minicozzi P, Berrino F, Bastiaannet E, Gavin A, Galceran J, Ameijide A, Siesling S, Mangone L, Ardanaz E, *et al*: Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000–2002. *Int J Cancer* 2013, 132(10):2404–2412.
4. Abbott AM, Habermann EB, Parsons HM, Tuttle T, Al-Refaie W: Prognosis for primary retroperitoneal sarcoma survivors: a conditional survival analysis. *Cancer* 2012, 118(13):3321–3329.
5. Ellison LF, Bryant H, Lockwood G, Shack L: Conditional survival analyses across cancer sites. *Health Rep* 2011, 22(2):21–25.
6. Baade PD, Youlden DR, Chambers SK: When do I know I am cured? Using conditional estimates to provide better information about cancer survival prospects. *Med J Aust* 2011, 194(2):73–77.
7. Xing Y, Chang GJ, Hu CY, Askew RL, Ross MI, Gershenwald JE, Lee JE, Mansfield PF, Lucci A, Cormier JN: Conditional survival estimates improve over time for patients with advanced melanoma: results from a population-based analysis. *Cancer* 2010, 116(9):2234–2241.
8. Merrill RM, Hunter BD: Conditional survival among cancer patients in the United States. *Oncologist* 2010, 15(8):873–882.
9. Janssen-Heijnen ML, Houterman S, Lemmens VE, Brenner H, Steyerberg EW, Coebergh JW: Prognosis for long-term survivors of cancer. *Ann Oncol* 2007, 18(8):1408–1413.
10. Skuladottir H, Olsen JH: Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. *J Clin Oncol* 2003, 21(16):3035–3040.
11. Bryant H, Lockwood G, Rahal R, Ellison L: Conditional survival in Canada: adjusting patient prognosis over time. *Current oncol (Toronto Ont)* 2012, 19(4):222–224.

12. *The Basic Plan to Promote Cancer Control Programmes in Japan.* http://www.mhlw.go.jp/shingi/2007/06/dl/s0615-1a.pdf [in Japanese].
13. World Health Organization: *International Classification of Diseases, 10th revision.*.
14. Berkson J, Gage R: **Calculation of survival rates for cancer.** *Proceed Staff Meeting Mayo Clinic* 1950, **25**:270–286.
15. Esteve J, Benhamou E, Croasdale M, Raymond L: **Relative survival and the estimation of net survival: elements for further discussion.** *Stat Med* 1990, **9**(5):529–538.
16. Cancer Research UK Cancer Survival Group, London School of Hygiene and Tropical Medicine: *strel computer program version 1.2.7 for cancer survival analysis*; 2009.
17. *Abridged life tables in Japan for 1962–2011.* http://ganjoho.jp/professional/statistics/cohort01.html [in Japanese].
18. Brenner H, Gefeller O: **Deriving more up-to-date estimates of long-term patient survival.** *J Clin Epidemiol* 1997, **50**(2):211–216.
19. Rubin DB: *Multiple Imputation for Nonresponse in Surveys.* New York: John Wiley & Sons; 1987.
20. StataCorp: *Stata Statistical Software: Release 12. College Station.* TX: StataCorp LP; 2011.
21. Verdecchia A, De Angelis R, Capocaccia R, Sant M, Micheli A, Gatta G, Berrino F: **The cure for colon cancer: results from the EUROCARE study.** *Int J Cancer* 1998, **77**(3):322–329.
22. Lambert PC, Thompson JR, Weston CL, Dickman PW: **Estimating and modeling the cure fraction in population-based cancer survival analysis.** *Biostatistics* 2007, **8**(3):576–594.
23. Isobe Y, Nashimoto A, Akazawa K, Oda I, Hayashi K, Miyashiro I, Katai H, Tsujitani S, Kodera Y, Seto Y, *et al*: **Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry.** *Gastric cancer official j Int Gastric Cancer Association Japanese Gastric Cancer Association* 2011, **14**(4):301–316.
24. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, Sobue T: **The Japanese guidelines for gastric cancer screening.** *Jpn J Clin Oncol* 2008, **38**(4):259–267.
25. Toyoda Y, Nakayama T, Ioka A, Tsukuma H: **Trends in lung cancer incidence by histological type in Osaka.** *Japan Jpn J Clin Oncol* 2008, **38**(8):534–539.
26. Devesa SS, Bray F, Vizcaino AP, Parkin DM: **International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising.** *Int J Cancer* 2005, **117**(2):294–299.
27. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M: **Global burden of cancers attributable to infections in 2008: a review and synthetic analysis.** *Lancet Oncol* 2012, **13**(6):607–615.

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Epidemiology Note

Descriptive Epidemiology of Bile Duct Carcinoma in Osaka

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Objective: An outbreak of bile duct carcinoma has been reported among workers in a certain printing company in Osaka, Japan, where there was no descriptive epidemiological study. We conducted descriptive studies of bile duct carcinoma in Osaka.
Methods: Based on the data from the Osaka Cancer Registry, the incidence and survival rate of intrahepatic and extrahepatic bile duct carcinomas, gallbladder carcinomas and hepatocellular carcinomas were analyzed. The study period was between 1975 and 2007, and total 108 407 incidents were retrieved from the Osaka Cancer Registry. Age- and sex-specific incidence rates and age-standardized incidence rates were calculated. Standardized incidence ratios were evaluated for each municipality in Osaka prefecture. Relative 5-year survival rates were also calculated for the cases diagnosed between 1993 and 2005.
Results: Age-standardized incidence rates of bile duct carcinomas increased distinctly from the middle of the 1970s to the early 1980s in males and the 1990s in females. However, no distinct increase in the incidence rates was observed in 2000. Standardized incidence ratios of those did not exceed the unity significantly in males between 1992 and 2007. In females, standardized incidence ratios exceeded the unity significantly in a few regions without any relation to the location of the printing company where the outbreak was reported. The relative 5-year survival rate is generally poor; however, patients who were diagnosed with localized disease at the age of 25–49 years showed a better survival.
Conclusion: Neither change in trend nor regional accumulation of bile duct carcinoma was confirmed in Osaka, corresponding to the outbreak reported in the printing company.

Key words: bile duct carcinoma – incidence – relative survival rate – cancer registry

INTRODUCTION

An outbreak of bile duct carcinoma has been reported among workers in a certain printing company in Osaka (1). There have been neither descriptive epidemiological studies nor reports of relative survival of patients with intrahepatic and/or extrahepatic bile duct carcinomas in Osaka, Japan. This study describes characteristics of bile duct carcinoma in Osaka, Japan, and examined whether any change in the time trend and disproportional geographical distribution was recognized in relation to the outbreak.

PATIENTS AND METHODS

The analysis was made using the data from the Osaka Cancer Registry between 1975 and 2007. Totally, 108 407 incidence data were retrieved; coded ICD-10 C22.1 (Intrahepatic bile duct carcinoma), C23 (malignant neoplasm of gallbladder), C24.0 (extrahepatic bile duct carcinoma) and C22.0 (hepatocellular carcinoma). Among those 108 407 cases, newly reported cases were 78 762. C22.9 (Malignant neoplasm of liver, unspecified) were 1.1% of C22 (malignant neoplasm of liver and intrahepatic bile ducts), while C24.1 (malignant

Table 1. Outlines of the newly reported cases with hepatocellular, intrahepatic, gallbladder and extrahepatic bile duct carcinomas, Osaka 1975–2007

		Hepatocellular n = 61315				Intrahepatic bile duct n = 3095				Gallbladder n= 7836				Extrahepatic bile duct n = 6516			
		Male		Female		Male		Female		Male		Female		Male		Female	
		n = 45898		n = 15417		n = 1797		n = 1298		n = 2801		n = 5035		n = 3638		n = 2878	
Age	Mean ± SE	63.7 ± 0.05		68.9 ± 0.08		66.5 ± 0.21		68.0 ± 0.34		69.2 ± 0.21		70.9 ± 0.16		68.9 ± 0.19		72.0 ± 0.22	
			%		%		%		%		%		%		%		%
	0–24	38	0.1	23	0.1	0	0.0	2	0.2	1	0.04	1	0.02	1	0.03	7	0.2
	25–29	38	0.1	14	0.1	1	0.1	3	0.2	5	0.2	4	0.1	4	0.1	1	0.0
	30–34	102	0.2	25	0.2	5	0.3	7	0.5	6	0.2	6	0.1	8	0.2	5	0.2
	35–39	315	0.7	53	0.3	16	0.9	10	0.8	20	0.7	23	0.5	19	0.5	9	0.3
	40–44	826	1.8	149	1.0	37	2.1	24	1.8	40	1.4	53	1.1	44	1.2	33	1.1
	45–49	2148	4.7	296	1.9	78	4.3	47	3.6	77	2.7	137	2.7	98	2.7	71	2.5
	50–54	4591	10.0	618	4.0	155	8.6	91	7.0	140	5.0	244	4.8	200	5.5	128	4.4
	55–59	7277	15.9	1314	8.5	225	12.5	125	9.6	246	8.8	354	7.0	342	9.4	193	6.7
	60–64	8630	18.8	2210	14.3	259	14.4	156	12.0	329	11.7	535	10.6	512	14.1	253	8.8
	65–69	8772	19.1	3082	20.0	339	18.9	203	15.6	466	16.6	745	14.8	588	16.2	406	14.1
	70–74	6789	14.8	3114	20.2	309	17.2	217	16.7	519	18.5	855	17.0	615	16.9	441	15.3
	75–79	3905	8.5	2359	15.3	222	12.4	190	14.6	459	16.4	873	17.3	537	14.8	496	17.2
	80–84	1736	3.8	1338	8.7	99	5.5	122	9.4	295	10.5	663	13.2	419	11.5	430	14.9
	85 +	1462	3.2	822	5.3	52	2.9	101	7.8	198	7.1	542	10.8	251	6.9	405	14.1
Year of diagnosis	1975–1991	18548	40.4	5116	33.2	443	24.7	352	27.1	1048	37.4	2073	41.2	1164	32.0	933	32.4
	1992–2007	27350	59.6	10301	66.8	1354	75.3	946	72.9	1753	62.6	2962	58.8	2474	68.0	1945	67.6
Age 25–45	Total	1565	3.4	285	1.8	74	4.1	49	3.8	78	2.8	103	2.0	94	2.6	53	1.8
Year of diagnosis	1975–1991	979	(5.3)	169	(3.3)	39	(8.8)	23	(6.5)	47	(4.5)	60	(2.9)	55	(4.7)	28	(3.0)
	1992–2007	586	(2.1)	116	(1.1)	35	(2.6)	26	(2.7)	31	(1.8)	43	(2.1)	39	(1.6)	25	(1.3)
Extent of disease																	
Stage	Localized	21578	47.0	7655	49.7	441	24.5	312	24.0	403	14.4	691	13.7	699	19.2	490	17.0
	Regional	6420	14.0	1938	12.6	602	33.5	434	33.4	1220	43.6	2183	43.4	1487	40.9	1175	40.8
	Distant	5779	12.6	1635	10.6	448	24.9	326	25.1	801	28.6	1531	30.4	595	16.4	528	18.3
	Unknown	12121	26.4	4189	27.2	306	17.0	226	17.4	377	13.5	630	12.5	857	23.6	685	23.8
Surgery	Yes	7522	16.4	1953	12.7	624	34.7	439	33.8	1158	41.3	2077	41.3	1477	40.6	954	33.1
	No	35494	77.3	12405	80.5	1099	61.2	805	62.0	1525	54.4	2776	55.1	2004	55.1	1804	62.7
	Unknown	2882	6.3	1059	6.9	74	4.1	54	4.2	118	4.2	182	3.6	157	4.3	120	4.2

neoplasm of ampulla of Vater), C24.8 (malignant neoplasm of overlapping lesion of biliary tract) and C24.9 (malignant neoplasm of biliary tract, unspecified) were 16.8, 0.1 and 5.8% of C24 (malignant neoplasm of other and unspecified parts of biliary tract), respectively.

The age of diagnosis was grouped by 5-year range for those who were between 25 and 84 and those data were obtained every 3-year interval. The age-standardized incidence rates (ASRs) were calculated by using Japanese 1985 model population as a standard. Standardized incidence rates (SIRs) of each municipality in Osaka were calculated using the age-specific incidence rates of Osaka as unity, and tested whether statistically significant differences existed with a 0.05 significance level, on Poisson's distribution.

Relative 5-year survival time and median survival time (MST) were calculated for each group (25–49, 50–74 and 75–99), and the extent of disease (localized, regional and distant) (2) for the cases was diagnosed between 1993 and 2005, who were followed up for at least 5 years after the diagnosis.

RESULTS

Outlines of the Study Subjects

Outlines of the newly reported cases are shown in Table 1. The proportion of the cases between 25 and 45 years, the same age range at which workers in the printing company in Osaka were diagnosed with bile duct carcinomas, was 3.0% for hepatocellular carcinoma (males 3.4%, females 1.8%), 4.0% for intrahepatic bile duct carcinoma (males 4.1%, females 3.8%), 2.3% for gallbladder carcinoma (males 2.8%, females 2.0%) and 2.3% for extrahepatic bile duct carcinoma (males 2.6% females 1.8%). The female-to-male ratios were 0.34, 0.72, 1.80 and 0.79, respectively.

Trends of ASRs and Age-specific Incidence Rates

ASRs of the intrahepatic bile duct carcinoma in both males and females rapidly increased from the year 1975 to the 1990s, and turned to decrease in the beginning of 2000 (Figure 1). ASRs of the extrahepatic bile duct carcinoma increased remarkably until the early 1980s, and then has become almost plateau from the beginning of 1990s in males. In females, the ASR increased until the early 1980s, and plateaued or decreased slightly thereafter (Figure 1). For the gallbladder carcinoma, ASRs had increased since 1975, plateaued in the 1980s and then decreased later. Age-specific incidence rates of both the intrahepatic and extrahepatic bile duct carcinomas have never increased since around 2000 (Figure 2). Incidence rates of intrahepatic and extrahepatic bile duct carcinomas were higher in males than in females (Figure 2).

SIR of Each Municipality in Osaka

SIRs of the bile duct carcinomas combined with intrahepatic and extrahepatic bile duct carcinomas did not exceed the unity significantly in males between 1992 and 2007 (Figure 3). SIRs

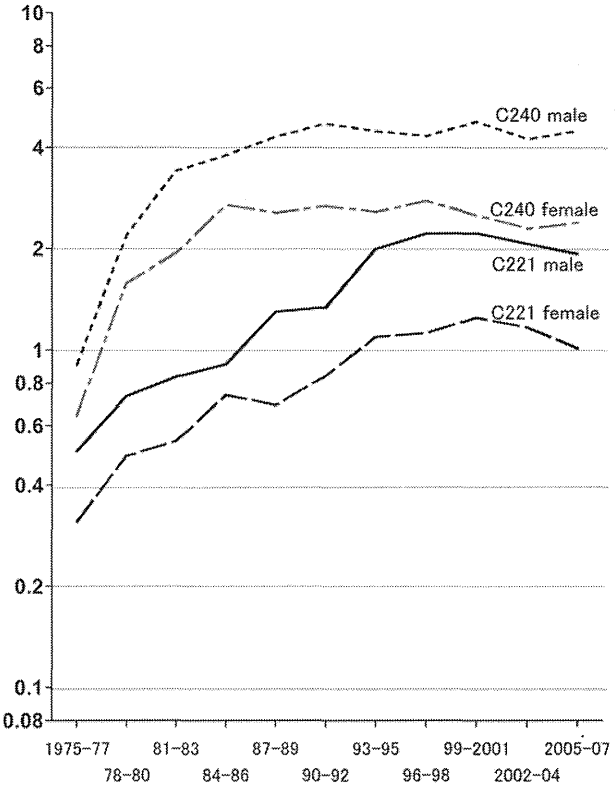

Figure 1. Age-standardized incidence rates (ASRs per 100 000 Japanese 1985 model population) of intrahepatic and extrahepatic bile duct carcinomas in Osaka, 1975–2007.

in females were significantly higher than the unity in Higashi-yodogawa-ku (ward) and Suminoe-ku. In Chuo-ku, where that printing company is located, SIRs of the bile duct carcinoma were 1.11 (95%CI 0.79–1.44) in males and 1.10 (95%CI 0.75–1.44) in females. Any SIR (not shown) never exceeded significantly than the unity.

Relative 5-year Survival and MST

Relative 5-year survival is generally poor among patients who are diagnosed with bile duct carcinoma in Osaka between 1993 and 2005. Some patients who were 25–49 years old with localized disease showed a better survival: 52.7% for the intrahepatic bile duct carcinoma and 76.4% for the gallbladder carcinoma, although they show a poor survival: 26.9% for the extrahepatic bile duct carcinoma. The difference in the relative survival of patients with localized disease between the age groups 25–49 and 50–74 was getting smaller, in the order of intrahepatic bile duct carcinoma, gallbladder carcinoma and extrahepatic bile duct carcinoma. There was no remarkable difference in relative survival among the age groups for regional and distant diseases, except regional cases of the extrahepatic bile duct carcinoma. In the age group of 25–49, the MST of the patients with intrahepatic bile duct carcinoma was 8.0 months for the regional and 6.0 months for the distant, while the MST of the patients with extrahepatic bile duct carcinoma was 16.4 months for the regional and 6.0 months for the distant (Figure 4).

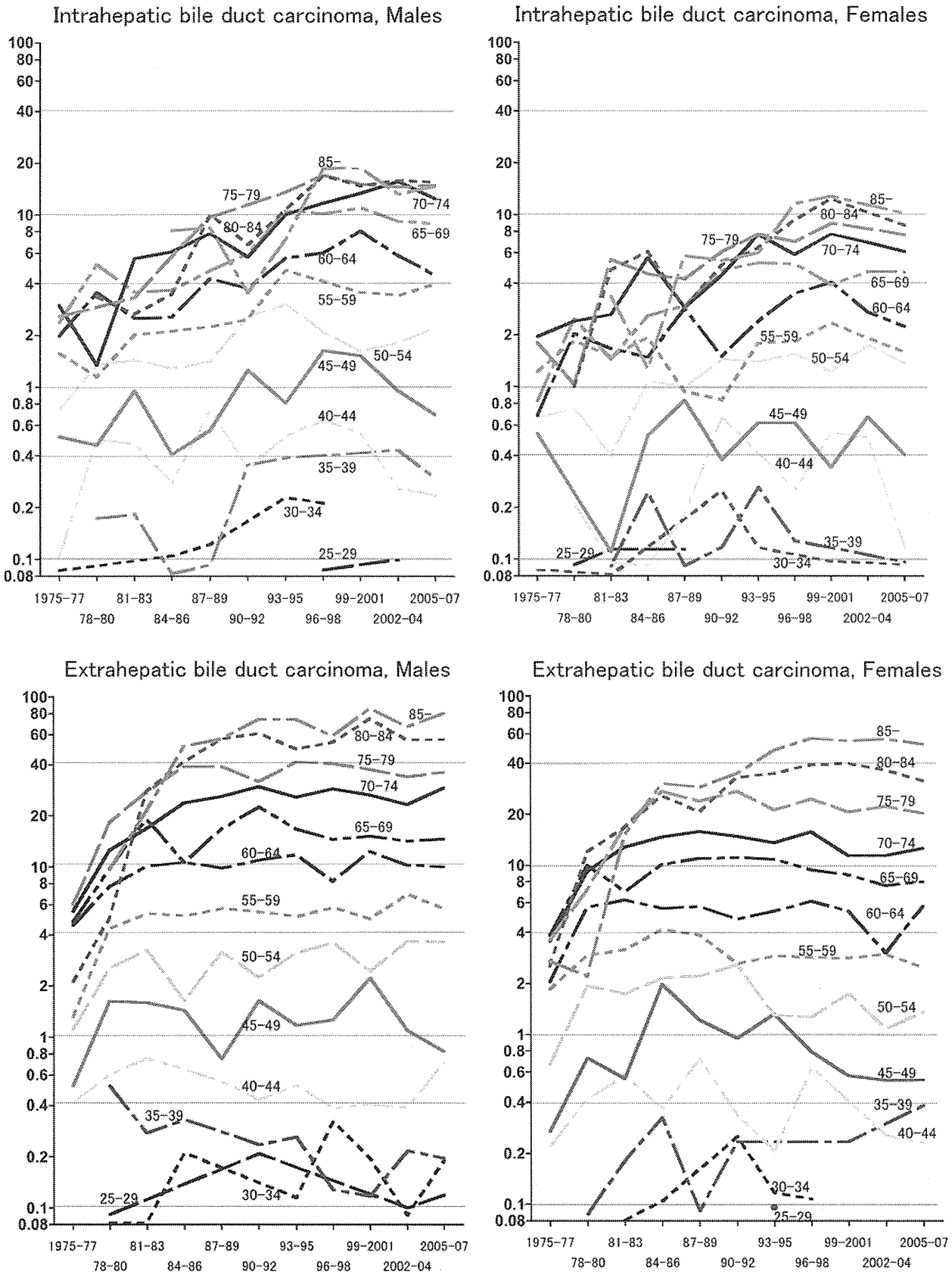

Figure 2. Age-specific incidence rates (per 100 000 population) of intrahepatic and extrahepatic bile duct carcinomas in Osaka, 1975–2007.

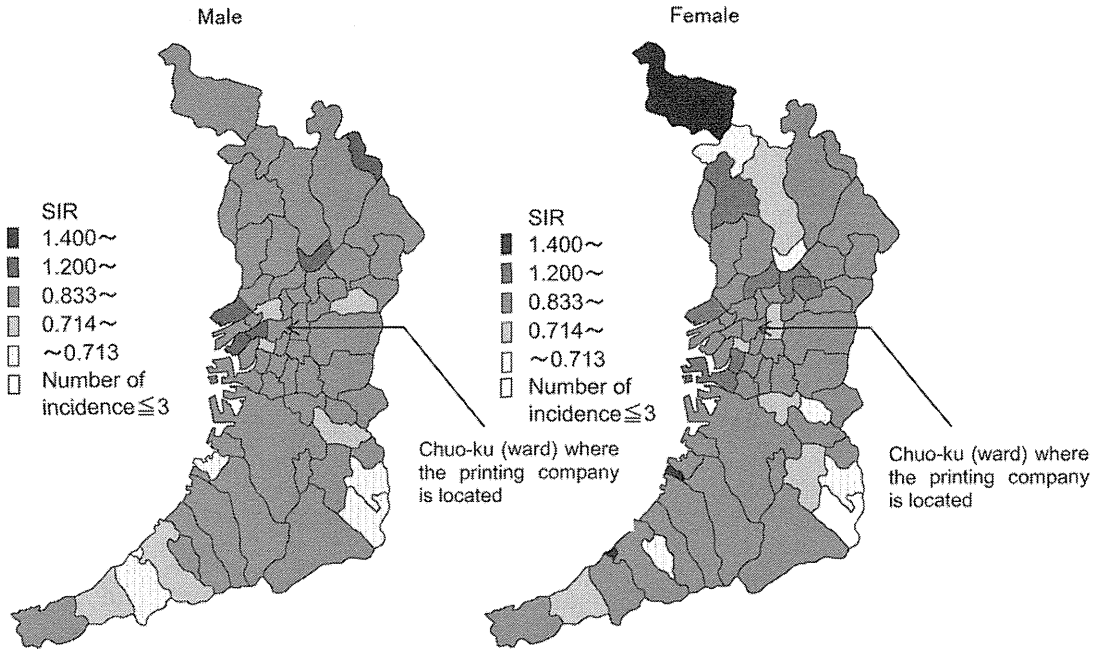

Figure 3. Standardized incidence ratios (SIRs) of bile duct carcinomas (C22.1 + C24.0) by municipality in Osaka, 1992–2007.

DISCUSSION

This study presented descriptive epidemiological profiles of bile duct carcinoma in Osaka, Japan, where the outbreak of bile duct carcinoma has been reported among workers in a printing company. Observed findings did not support any change in the time trend and disproportional geographical distribution related to the outbreak.

Advantages and Limitations of This Study

Osaka Cancer Registry has provided reliable and high-quality incidence data for a long period. This enabled us to examine incidence and survival of bile duct carcinoma in Osaka for over 30 years. Possible underreporting to the Osaka Cancer Registry may lead to lower estimation of cancer incidence and survival; however, cancers with poor survival are not caused by this bias. Therefore, we consider that our findings are reliable.

Our study did not support that any change in the time trend and disproportional geographical distribution was recognized in relation to the outbreak; however, this does not mean that such outbreak has never affected the environment. Exposure must be widely distributed and more people might have been exposed to some extent, according to the exert impact of the incidence rate. Although this study has some limitations to evaluate the effect of the outbreak, the geographical cluster analysis may be a suitable procedure to approach this problem.

Reason of the High Incidence of Bile Duct Carcinoma

ASRs of biliary tract cancer had increased since 1975, and reached peak or plateau in the 1980s to 1990s. These increases starting in 1975 were considered to be caused mainly by the improved diagnostic image techniques, such as endoscopic retrograde cholangiopancreatography (3), ultrasonography, computed tomography and magnetic resonance cholangiopancreatography (MRCP) (4,5). The detection rate for bile duct carcinoma by MRCP has been reported to be over 90% (6). In the USA, the increased incidence of the intrahepatic bile duct carcinoma between 1973 and 1997 was reported (7), and they have suggested that this might be related to increase in metabolic syndrome. However, this explanation is unlikely in Japan.

Survival of Bile Duct Carcinoma

Relative 5-year survival is generally poor among patients with bile duct carcinoma in Osaka. However, patients aged 25–49 years with localized disease showed a better survival: 52.7% for the intrahepatic bile duct carcinoma and 76.4% for the gallbladder carcinoma. The Biliary Tract Cancer Statistics Registry (8) in Japan reported that 5-year survival of extrahepatic biliary tract cancer patients with Stage I was >60% after surgical resection. These results suggest the importance of early detection and surgical resection for a better prognosis in the biliary tract cancer. To detect this cancer in the early stage, it will be necessary to build a screening system for high-risk workers by skilled clinical staffs.

Funding

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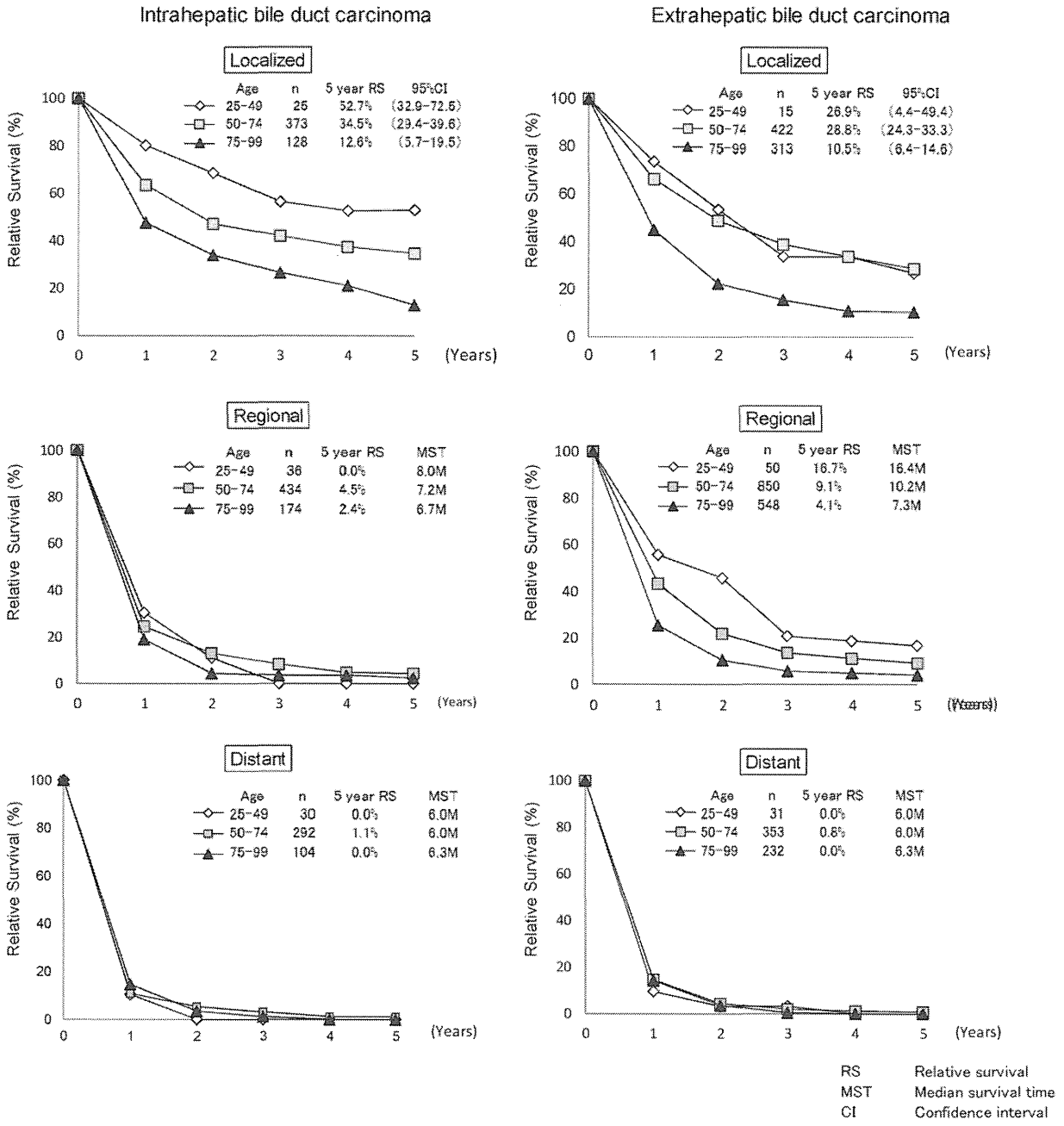

Figure 4. Relative survival of intrahepatic and extrahepatic bile duct carcinomas in Osaka, cases, 1993–2005.

Conflict of interest statement

None declared.

References

1. Kumagai S, Kurumatani N, Arimoto A, et al. Cholangiocarcinoma among offset color proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. OEM Online First, published on 14 March 2013 as 10.1136/oemed-2012–101246 (in press).
2. Sobue T, Tsukuma H, Okamoto N, et al. *Handbook on population-based caner registration in Japan fifth revision (cited 2013)* http://ganjoho.jp/data/hospital/cancer_registration/files/toroku08.pdf.
3. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of Vater a preliminary report. *Ann Surg* 1968;167:752–6.
4. Wallner B, Schumacher K, Weidenmaier W, et al. Dilated biliary tract: evaluation with MR cholangiography with a T2-weighted contrast-enhanced fast sequence. *Radiology* 1991;181:805–8.
5. Morimoto K, Shimoi M, Shirakawa T, et al. Biliary obstruction: evaluation with three-dimensional MR cholangiography. *Radiology* 1992;183:578–80.
6. Joseph R, Marc B, Elham R, et al. Magnetic Resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. *Ann Intern Med* 2003;139:547–57.
7. Welzel TM, Graubard BI, Zeuzem S, et al. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology* 2011;54:463–71.
8. Miyakawa S, Ishihara S, Horiguchi A, et al. Biliary tract cancer treatment: 5584 results from the biliary tract cancer statistics registry from 1998 to 2004 in Japan. *J Hepatobiliary Pancreat Surg* 2009;16:1–7.

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最新肺癌学

—基礎と臨床の最新研究動向—

IX　肺癌の検査・診断

検　　診

肺がん検診の現状と成績

中山富雄

IX 肺癌の検査・診断

検　診

肺がん検診の現状と成績

The present situation and the results of lung cancer screening in Japan

中山富雄

Key words：肺がん検診，screening

1 国内での肺がん検診の歴史

胸部単純X線写真を用いた検診として，かつては結核予防法に基づく結核検診が広く行われてきた．結核検診の大規模な施行は昭和26年の結核予防法改定に基づくものであり，撮影や読影などの技術的なことに関しては何も縛りのないものであった．しかし結核の死亡率の減少と相反して肺がんが増加するにつれ，昭和62年に老人保健法第2期計画として肺がん検診が開始されるに至った．肺がん検診として開始される前年度の秋に，肺がんの初期像を検出しうる撮影や読影の方法をとりまとめた'肺がん検診の手引き'が日本肺癌学会の集団検診委員会により作成され，それを運用上の指針という形で開始されるようになった[1]．しかし，結核予防法が18歳以上の全国民を対象とした幅広いものであり，検診の提供元が自治体に加えて勤め先も含まれるのに比べて，肺がん検診が自治体のみであったことから，国内では撮影・読影方法の縛りのない結核検診と，縛りのある肺がん検診が混在するという状況がみられている．雇用者を対象に行われている胸部X線検診は現在では労働安全衛生法に基づくものであり，その撮影方法や読影方法の縛りはなく結核検診に該当するため，どの程度肺がんが発見されているのか，といった統計は収集されていない．一方，市町村を実施主体とし40歳以上の住民を対象とした肺がん検診は毎年の受診者数，発見肺がん数などの詳細な統計が公開されている．その成績について概説する．

2 肺がん検診の現状

肺がん検診として市町村で行われている検診は，現在は健康増進法をその根拠とし，健康増進事業報告として毎年都道府県を通じて集計され，政府統計の総合窓口e-Statに公開されている．

検診の対象者数・受診者数・要精検者数までは1年遅れで掲載されており，例えば平成23年度成績は25年度の5月頃に掲載されている．一方精密検査以降の成績は，年度末の受診者の診断および治療内容の把握に時間がかかることから，更に1年後(平成23年度では26年度初め)に掲載されている．

対象者は'住民から職場で健康診断を受診する機会のないもの'として定義されているが，これを自治体が正確に把握することは困難であり，市町村によって定義や計算方法がまちまちである．現在国立がん研究センターのがん情報サービスにおいて，全市町村を同じ定義で計算

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表1 肺がん検診対象者の性・年齢分布(平成22年度)

	40-49歳	50-59歳	60-69歳	70歳以上	計
男性	2,745,141	2,794,522	4,488,425	5,595,237	15,623,325
女性	3,921,416	4,355,873	6,050,323	8,627,773	22,955,385
男女計	6,666,557	7,150,395	10,538,748	14,223,010	38,578,710

表2 肺がん検診の男女別・年齢階級別受診者数・受診率(平成22年度)

	40-49歳	50-59歳	60-69歳	70歳以上	計
男性	195,455(7.1)	271,220(9.7)	898,493(20.0)	1,283,374(22.9)	2,648,542(17.0)
女性	411,790(10.5)	606,433(13.9)	1,476,227(24.4)	1,651,314(19.1)	4,145,774(18.1)
男女計	607,245(9.1)	877,653(12.3)	2,374,720(22.5)	2,934,688(20.6)	6,794,316(17.6)

( )内は受診率(%).

表3 男女別・年齢階級別にみた医療機関個別検診受診者割合(%)(平成22年度)

	40-49歳	50-59歳	60-69歳	70歳以上	計
男性	0.53	0.41	0.49	0.62	0.55
女性	0.49	0.41	0.49	0.69	0.55
男女計	0.5	0.41	0.49	0.68	0.56

医療機関個別検診受診者数/(医療機関個別検診受診者数+集団検診受診者数)で求めた.

した推定対象者数が公開されている[2]. 全国の比較をするときはそれを用いるべきである.

現在直近の成績である平成22年度の成績を示す(表1)[3].

対象者数は38,578,710人(男性15,623,325人, 女性22,955,385人)で, これは40歳以上人口(平成22年度)の53.3%にあたる. この対象者数を基準とした年齢階級別受診率を表2に示す. 40歳以上(100歳以上も含まれる)の受診率は17.6%であった. 年齢階級別にみると60歳以上の年齢階級では20%強の受診率であったが, 60歳未満では10%前後の受診率であった.

60歳未満の年齢では職場で受診機会がなくても仕事を休んで受診する余裕がないことが住民検診の受診率が低い理由と考えられる.

検診の方式別にみると医療機関個別方式と集団方式との比はほぼ0.5前後であったが, 70歳以上では男性0.64, 女性0.71と医療機関個別方式の割合が急増した(表3). この年齢は合併症を多く有することから医療機関への親和性が高いと考えられる.

肺がん検診は年1回の経年検診でないと効果が出ないといわれており, 受診者集団の8割以上の経年受診率が望ましいとされている. 医療機関個別方式は集団方式よりも経年受診が高いこと, 年齢階級が若くなるほど経年受診率が低いことが明らかである(表4). 60歳未満の年齢階級では受診がイレギュラーで効果が期待できない.

表5に要精検以降の成績を示す. 要精検率は2.8%, 精検受診率は78.9%であった. ここでいう精検受診は要精検者から精検未受診者(精密検査を受診していないことが確認されている者)と精検結果未把握者(精密検査を受診したことは確認されているものの, その結果が把握されていないもの)を除したものと定義されている. 精検受診率は高ければ高いほどよいはずだが, それを低下せしめている理由の多くは精検未把握が多いことである.

がん発見数は4,296人で, これは肺がんの年

表4　男女別・年齢階級別・検診方式別にみた非初回割合(%)

		40-49歳	50-59歳	60-69歳	70歳以上	計
男性	集団方式	53.4	65.7	68.2	79.2	71.9
	個別方式	39.8	53.5	60.8	72.4	64.9
女性	集団方式	53.9	68.1	73.2	79.2	72.7
	個別方式	40.6	57.1	66.7	73.1	66.1
男女計	集団方式	54.4	67.3	71.3	79.2	72.4
	個別方式	40.8	56.0	64.5	72.8	65.6

肺がん検診の場合，非初回は前年度受診者を指すため，非初回割合は経年受診割合と同義語である．肺がん取扱い規約によれば80％以上が望ましいとされている．

表5　肺がん検診の要精検以降のプロセス指標

	数	率
要精検者数	198,962	2.8(%)
精検受診	154,551	78.9(%)
精検未受診	17,760	8.9(%)
精検結果未把握	26,651	13.4(%)
がん発見数	4,296	60.9(10万人比)
原発性肺がん	2,651	61.7(%)
I期の肺がん	875	33.3(%)

間罹患数が約9万人程度と推定される[4]ことから全罹患数の5％程度であり，妥当な成績であろう．一方原発性肺がん数はがん発見数のわずか61.7％となっている．残り38.3％が他臓器癌の肺転移とは考えられず，市町村が把握した情報に原発性肺がんの有無がはっきり書かれていないために，過小評価した数字であろう．原発性肺がんと判明したもののうちI期のがんの割合は33.3％にすぎない．これも病期不明が多いためと考えられる．

3　現状のまとめ

我が国の肺がん検診は普及しかつ義務化された結核検診と共存するような形で運営されてきた．結核検診の標的疾患ではない肺がんも含めた疾患がどの程度発見されているのか，といった情報は主に結核検診として行われている職場健診では収集されておらず，その精度は確認のしようがない．一方，市町村が実施主体である健康増進法に基づく肺がん検診は，曲がりなりにでも結果を収集する仕組みが存在する．今回分析に用いた平成22年度集計と前年度の21年度集計との間で集計フォーマットに大きな変化があった．'発見されたがん'，'発見された原発性の肺がん'，'原発性肺がんのうちI期のがん'という3つの区分が加わったものの，今回の分析結果からは，情報の漏れが非常に多かったと考えられる．発見がんが原発性か転移性か，ということは診断・治療を行う専門病院の医師レベルでは明らかであるものの，集計を取りまとめる市町村の保健師や結果報告用紙を記入するかかりつけ医には判断ができなかったのではないかと考えられる．肺がんの場合治療にあたっては組織型やTNM分類などの詳細情報が必要であるが，検診で発見されたがんの統計としては，原発か転移か，I期かII期以上かという情報だけで十分であり，読者が専門医療機関の勤務医の立場であれば，最低その情報がわかるように市町村に返事をしていただきたい．また患者が複数の医療機関を受診して治療する場合，このような調査は漏れが生じやすくなる．転院で紹介状を発行する際は，検診の結果報告用紙も同時に手渡して次の医療機関につなげることが望ましい．

肺がん検診の受診率が低いとはいえ，40歳以上の住民というあいまいな定義では明らかに非効率的である．一回受診さえすれば効果のある検診ではなく継続的な受診行動を担保でき，かつ有効な治療法が行いうる年齢階級であるべきだ．実際の成績をみると，60歳未満の受診は非初回割合が低く，受診パターンが不規則であ

り効果は期待できない．60歳代以降に多い肺がんという疾患の特徴を考えると，肺がん検診の対象者を60-70歳代に限定することが効率的であろう．

高齢者の特に女性は集団方式よりも医療機関個別方式を多く受診していた．検診日程の縛りがなく，ほぼ毎日受診が可能な個別方式の方が受診者には便利であろう．ただし検診を専門とした集団方式に比べると個別方式での専門性は低いため質の担保が必要である．個別方式に従事する医師は肺がん検診と結核検診の違い，検診と診療の違いなどをよくよく理解したうえで臨むことが必要である．

日本の検診制度は複雑であり理解は困難である．その中で住民を対象とした肺がん検診についてはそれなりの成績が得られている．ただし対象者などの定義があいまいなために効率的な運営が図られているとはいいがたい．今後は枠組みの抜本的な整理が望まれる．

文　献

1) 厚生省老人保健福祉局老人保健課(監)：老人保健法による健康診査マニュアル．日本医事新報社，1994.
2) 独立行政法人国立がん研究センターがん対策情報センター：がん情報サービス．がん検診受診率データ(市区町村による地域保健・健康増進事業報告データ)．[http://ganjoho.jp/professional/statistics/statistics.html#07]
3) 厚生労働省大臣官房統計情報部：平成22年度地域保健・健康増進事業報告(健康増進編)．厚生労働統計協会，2012.
4) Matsuda A, et al: Cancer incidence and incidence rates in Japan in 2007: a study of 21 population-based cancer registries for the Monitoring of Cancer Incidence in Japan(MCIJ) project. Jpn J Clin Oncol 43(3): 328-336, 2013.

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Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study

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Background: Smoking is a well-known risk factor for cancer; however, there is little evidence as to whether the smoking status of cancer survivors has any risk for subsequent primary cancer (SPC) incidence, regardless of the first cancer sites.

Patients and methods: In total, 29 795 eligible patients with a first cancer between 1985 and 2004 were examined for SPC until the end of 2006, using a record linkage between hospital-based and population-based cancer registries. The association between smoking at the time of the first cancer diagnosis and three SPC groups (i.e. specific SPC, smoking-related SPCs, and all SPCs) was calculated by Poisson regression.

Results: Ever smokers had 59% and 102% higher risk for all SPCs and smoking-related SPCs, respectively, than never smokers. Cancer survivors who had recently stopped smoking had 18% and 26% less risk, respectively, for these SPCs than those who smoked at the diagnosis. We also found that, compared with those who had never smoked, cancer survivors who had ever smoked had a significantly elevated risk of oral/pharyngeal, esophageal, stomach, lung, and hematological SPCs, regardless of the first cancer sites.

Conclusions: These findings indicate that smoking increases not only the first cancer but also a second or SPC. Moreover, the results from recent quitters versus current smokers suggest that smoking cessation may decrease the risk for SPC, especially for smoking-related SPCs in cancer survivors. Preventive measures are necessary to reduce not only SPC incidence but also tobacco use.

Key words: tobacco smoking, subsequent primary cancer, cancer survivors, Japan

introduction

Tobacco smoking is the most attributable risk factor for cancer incidence and adult mortality in Japan and worldwide [1, 2]. Approximately 50% of males and 40% of females in Japan will develop a cancer during their lifetime [3]. Owing to prolonged survival times for cancer patients and population aging, it is estimated that 5–15% of cancer patients develop a subsequent primary cancer (SPC) [4, 5]. Although risk of SPC among cancer survivors may be strongly associated with smoking behaviors [6], insufficient direct investigation of the relationship between smoking behavior and SPC incidence has been conducted owing to the lack of information in population-based cancer registries. Furthermore, to date, most studies that examined the association between smoking (and/or smoking cessation) and SPC incidence were conducted according to each first cancer, not a comprehensive list of cancers [7–14]. This study comprised a retrospective cohort study which estimated the risk for SPC incidence according to smoking behaviors at the first cancer diagnosis among a comprehensive group of cancer survivors. We used record linkage between a hospital-based cancer registry and the Osaka Cancer Registry (OCR), one of the largest population-based cancer registries [15]. We aimed to provide not only information for advancing tobacco control, but also insights into preventive measures for clinical oncologists and other health professionals [16].

methods

data

Study subjects were all eligible patients initially diagnosed with a first cancer, excluding *in situ* carcinomas and benign intracranial tumors, from 1985–2004 at the Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC), and who had survived for at least 3 months. Subjects were restricted to those living in Osaka and aged 20–79 years at the time of diagnosis. Those with a history of cancer or who developed synchronous SPC within 3 months were excluded. Subjects were identified from the hospital-based cancer registry, which has collected information on cancer

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diagnosis, clinical stage, first course of treatment, and lifestyle factors including smoking behavior, since 1963. They were followed up using medical records or resident offices, for up to 10 years, and the follow-up was 99% complete. Their files were collated with the OCR files to obtain other information on SPC incidence, by means of a semi-automated record linkage using patients' surname, given name, birth-year and birth-month. The study was approved by the OMCC institutional review board.

smoking behaviors

Information on smoking behaviors was collected through an integrated common questionnaire across all departments at the time of the first cancer diagnosis. The following definitions were used: ever smokers were persons who had smoked tobacco regularly either before or at diagnosis, including current smokers, recent quitters, and former smokers. Never smokers were those who had never smoked regularly. Current smokers were those who smoked cigarettes regularly at diagnosis. Recent quitters were those who had stopped smoking up to 3 years before diagnosis. Former smokers were those who stopped smoking ≥3 years before diagnosis.

The smoking behavior variable was used in two ways. First, never smoker was used as a reference category to examine whether cancer survivors who had ever smoked or who currently smoked were more likely to develop SPCs than never smoked. Secondly, current smoker was used as a reference category to examine whether cancer survivors who had recently stopped smoking have lower risk for SPC than those who currently smoked. The latter was based on a clinical perspective, suggesting a reversible effect of smoking in cancer survivors [17], although this was an observational study and intervention is necessary to test this hypothesis [14, 18].

outcomes: SPC definitions

Metachronous SPC was defined as that diagnosed between 3 months and 10 years after the first cancer diagnosis. The incidence of three SPC groups (i.e. specific SPC, smoking-related SPCs, and all SPCs) was examined up to the end of 2006 for a maximum of 10 years after the first cancer diagnosis. Each cancer was categorized into 16 selected major groups and the others according to ICD-10, corresponding to the specific SPC sites. Smoking-related cancer sites comprised the mouth/pharynx, esophagus, stomach, colorectum, liver, gall-bladder, pancreas, larynx, lung, and kidney/urinary tract/bladder [19]. A cancer survivor can contribute to several outcomes (SPCs), provided these SPCs fit the eligibility criteria. In other words, these events have been assumed to be independent of one another. For more details on outcomes and SPC definitions, please see supplementary data, available at *Annals of Oncology* online.

statistical analyses

To estimate the risk for SPC, person-years at risk were calculated as the time from 3 months after the first cancer diagnosis until: 31 December 2006; date of SPC diagnosis; date of death; or 10 years after the first cancer diagnosis, whichever came first [5]. The expected number was calculated according to stratified person-years with all, smoking-related and site-specific cancer incidence rates among Osaka residents (from OCR) stratified for sex, age group (5 years), and calendar period (5 years). The observed number of SPCs was compared with the expected number, according to smoking behaviors, sex, age group, calendar period, clinical stage, smoking-related first cancer site, and follow-up interval. A standardized incidence ratio (SIR) was then obtained by dividing the observed number of SPCs by the expected number. Another indicator is the excess absolute risk (EAR), which is the absolute number of excess cancer cases, obtained by subtracting the expected number from the observed number of SPC. The EAR may be of interest for clinical and public health purposes. The SIR and EAR are used to estimate the risk of a cancer patient developing SPC compared with the incidence of cancer among the general population. The statistical significance and 95% confidence intervals (CIs) for the SIRs were tested by Poisson distribution analysis. For more details on statistical analysis, see supplementary data, available at *Annals of Oncology* online.

We used Poisson regression analysis to estimate the incidence rate ratio (IRR) and 95% CIs for SPC in cancer survivors according to their smoking behaviors. These ratios were adjusted for potential confounding factors: sex and age at the first cancer diagnosis. They were additionally adjusted for stage, calendar period, follow-up interval, and smoking-related first cancer site, using the expected number of cancer incidence in the general population as an offset [20, 21].

Probability values for statistical tests were two-tailed, and $P < 0.05$ was regarded as statistically significant. All statistical analyses were carried out using the SAS statistical package version 9.2 (SAS Institute, Inc., Cary, NC, USA) with macros [22].

results

There were 29 795 study subjects after excluding those with a missing value for smoking behaviors ($n = 4$). When recent quitters were used, subjects with missing cessation age were excluded ($n = 649$). Distribution of cancer sites in Osaka, Japan, and this study (OMCC) is shown in supplementary Table S1, available at *Annals of Oncology* online. During the follow-up (median follow-up duration: 4.5 years, mean: 5.2 years), SPCs were found in 1721 subjects (5.8%) as the second cancer, 122 (0.4%) as the third cancer, 18 (0.1%) as the fourth cancer, and 1 (0.003%) as the fifth cancer. Smoking-related SPCs were found in 1161 (3.9%) as the second, third, or fourth primary cancer.

Most patient characteristics were associated with the risk of SPC (supplementary Tables S2 and S3, available at *Annals of Oncology* online). Table 1 shows IRRs for SPC according to smoking behaviors from Poisson regression analyses. In the fully adjusted model, ever or current smokers had 59% and 76% higher risk for all SPCs, respectively, than never smokers. Cancer survivors who recently stopped smoking had 18% less risk for developing all SPCs than current smokers. For smoking-related SPCs, ever and current smokers had 102% and 136% higher risk, respectively, than never smokers. Recent quitters had 26% less risk than current smokers.

Table 2 shows SIRs and EARs for specific SPCs according to dichotomized smoking behaviors (ever versus never smokers). Although never smoker cancer survivors had significantly high SIRs of 2.92 and 3.04 for prostate and thyroid SPC, respectively, never smokers had a significantly lower SIR of 0.67 for lung SPC. Ever smoker cancer survivors had significantly high SIRs for oral/pharyngeal, esophageal, stomach, laryngeal, lung, prostate, kidney/urinary tract/bladder, and thyroid SPCs. EARs in SPCs of the esophagus, stomach, and lung were >50. In the fully adjusted Poisson regression model, ever smoker cancer survivors had significantly elevated risk for oral/pharyngeal, esophageal, stomach, lung, and hematological SPCs, compared with never smokers. A tendency toward an IRR of >1.0 was observed in other smoking-related SPCs. Although fully adjusted IRR for laryngeal SPC among ever smokers was non-significant (8.08) with a wide 95% CI, it was significant among current smokers (see supplementary Table S4, available at *Annals of Oncology* online). Supplementary Table S5, available at *Annals of Oncology* online, shows SIRs, EARs, and