registry. Thus, we assumed that the tests were performed before the start of the therapy and we therefore overestimated the quality scores.

Despite these limitations, we have demonstrated that the Liver Cancer Registry Database can be a tool for quality measurement. To date, cancer registries have primarily focused on clinical and epidemiological research, and the examination of the quality of care is a new area of research. Professional societies, however, have the responsibility to promote improved quality of patient care. Because the ultimate goal is to improve patient outcome, the role of these societies should not be limited to the discovery of new knowledge but should also include the monitoring of the extent to which the new knowledge is applied to patient care nationwide. This study serves as an initial step for the future growth of such activities.

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REFERENCES

1 International Agency for Research on Cancer. *GLOBOCAN*. [Cited 10 Jan 2011.] Available from URL: http://globocan.iarc.fr/factsheets/cancers/liver.asp
2 Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; **27**: 1485–91.
3 Bosch FX, Ribes J, Diaz M *et al.* Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004; **127**: S5–16.
4 National Cancer Center of Japan. *Cancer Infromation (Ganjoho) Services (Japanese)*. [Cited 10 Jan 2011.] Available from URL: http://ganjoho.ncc.go.jp/public/statistics/pub/statistics01.html
5 Foundation for Promotion of Cancer Research. Cancer Statistics in Japan 2009. [Cited 10 Jan, 2011] Available from URL: http://ganjoho.ncc.go.jp/data/public/statistics/backnumber/1isaao000000068m-att/date06.pdf
6 Kokudo N, Makuuchi M. Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: the J-HCC guidelines. *J Gastroenterol* 2009; **44** (Suppl 19): 119–21.
7 Makuuchi M, Kokudo N, Arii S *et al.* Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. *Hepatol Res* 2008; **38**: 37–51.
8 Kokudo N, Sasaki Y, Nakayama T *et al.* Dissemination of evidence-based clinical practice guidelines for hepatocellular carcinoma among Japanese hepatologists, liver surgeons and primary care physicians. *Gut* 2007; **56**: 1020–1.
9 Donabedian A. *The Definition of Quality and Approaches to Its Assessment*. Ann Arbor, MI: Health Administration Press, 1980.
10 Higashi T. Lessons learned in the development of process quality indicators for cancer care in Japan. *Biopsychosoc Med* 2010; **4**: 14.
11 Research Group on the Development of Quality Indicators and the Measurement System for Cancer Care. *Quality Indicator (Japanese)*. [Cited 28 Jun 2011.] Available from URL: http://qi.ncc.go.jp
12 Fitch K, Bernstein SJ, Aguilar MD *et al.* The RAND/UCLA appropriateness method user's manual: RAND. 2001.
13 Shekelle PG, MacLean CH, Morton SC *et al.* Acove quality indicators. *Ann Intern Med* 2001; **135**: 653–67.
14 Ikai I, Arii S, Okazaki M *et al.* Report of the 17th nationwide follow-up survey of primary liver cancer in Japan. *Hepatol Res* 2007; **37**: 676–91.
15 Higashi T, Sobue T, Nishimoto H. Current status of site-specific cancer registries in Japan (in Japanese). *Geka-Chiryo* 2011; **2**: 169–76.
16 Liver Cancer Study Group of Japan. *General Rules for the Clinical and Pathological Study of Primary Liver Cancer*, 2nd English edn. Tokyo: Kanehara & Co, 2003.
17 Omagari K, Ohba K, Kadokawa Y *et al.* Comparison of the grade evaluated by "Liver damage" of liver cancer study group of Japan and Child–Pugh classification in patients with hepatocellular carcinoma. *Hepatol Res* 2006; **34**: 266–72.
18 Bilimoria KY, Stewart AK, Winchester DP *et al.* The national cancer data base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol* 2008; **15**: 683–90.

APPENDIX

The list of the quality indicators (QIs) approved by the expert panel

	Denominator (target patients)	Numerator (standard care processes)
Pre-treatment work-up		
1	Patients who were diagnosed with hepatocellular carcinoma (HCC)	AFP and PIVKA-2 levels were measured before treatment
2	HCC patients who underwent surgical resection, percutaneous local ablation therapy and transarterial chemoembolization (TACE) therapy	Dynamic CT/MRI study was performed before treatment
3	Patients who were diagnosed with HCC and received treatment	The medical records documented the clinical stage (TNM or TNM factors) and liver function level (the Child–Pugh class or the liver damage class)
4	Patients who underwent surgical resection of HCC for the first time	15-min ICG retention rate was measured before treatment
Treatment choice of local therapy		
5	HCC patients with liver damage class A, having three or less tumors of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT, or RFA) was performed.
6	HCC patients with liver damage class A having a solitary tumor of 3–5 cm in diameter	Surgical resection was performed.
7	HCC patients with liver damage class A or B and three or fewer tumors smaller than 3 cm who had surgical resection or percutaneous local ablation therapy	The advantages and disadvantages of each therapy were explained and documented in the medical records
8	HCC patients with liver damage class C who underwent surgical resection, percutaneous local ablation therapy or TACE	The risks and benefits of the treatments received were explained and documented in the medical records
9	HCC patients receiving percutaneous ethanol injection (PEI) as the initial treatment	Medical records documented the reasons why RFA was not performed
10	HCC patients with Stage IVa or earlier, Vp 0–2 and Child–Pugh class A or B, in whom surgery and percutaneous local ablation therapy were not possible (patients who did not receive surgery or percutaneous local ablation therapy within 3 months after diagnosis)	TACE was performed.
11	Recurrent HCC patients with liver damage class A and a solitary tumor of 3–5 cm in diameter	Surgical resection was performed, or the medical record documented the reasons for not performing surgery
12	Recurrent HCC patients with liver damage class A and solitary tumor of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT or RFA) is performed or the medical record documents the reasons for not performing these therapy
13	Recurrent HCC patients with liver damage class A and two or three tumors of 3 cm or smaller in diameter	Surgical resection, percutaneous local ablation therapy (PEI, MCT or RFA), or TACE was performed, or the medical record documented the reason for not performing these therapies.
14	HCC patients who received TACE	Lipiodol was used in the procedure
15	HCC patients with liver damage class C who satisfied Milan criteria	The option of liver transplantation was explained and documented
Documentation and explanation		
16	HCC patients who underwent surgical resection	Medical record (including pathological report) documented the degrees of vascular invasion and tumor differentiation was postoperatively determined.
17	HCC patients who underwent surgical resection	The medical record documented the physician's judgment on the postoperative risk of recurrence
18	HCC patients who underwent surgical resection	The pathological findings after surgery were explained to patients and were documented in the medical record

	Denominator (target patients)	Numerator (standard care processes)
Systemic therapy		
19	HCC patients who received systemic chemotherapy	Medical records documented the explanation to patients that surgical resection, percutaneous local ablation therapy or TACE could not be performed and that evidence for the efficacy of chemotherapy was lacking.
20	Patients who received treatment for HCC	Hormone therapy was avoided
Follow-up monitoring		
21	HCC patients who underwent surgical resection or percutaneous local ablation therapy	AFP and PIVKA-2 were monitored for at least 4-month intervals for 2 years after the curative treatment
22	HCC patients who received TACE	CT/MRI and tumor marker tests were performed within 2 months after TACE
23	HCC patients who received TACE	Image studies (contrast-enhanced CT/MRI, if not contraindicated) were performed at least every 3 months
24	HCC patients who received TACE	Tumor marker tests (AFP, PIVKA-2) were monitored at least every 3 months
25	HCC patients who received TACE and who showed elevated tumor marker levels, increases in the tumor size from diagnostic imaging or the appearance of new tumors with rich blood flow	TACE was repeated, or the medical record indicates the TACE was considered

AFP, Alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; ICG, indocyanine green; MCT, microwave coagulation therapy; MRI, magnetic resonance imaging; PEI, percutaneous ethanol injection; PIVKA-2, protein induced by vitamin K absence-2; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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Cancer Statistics Digest

Time Trends in Breast Cancer Screening Rates in the OECD Countries

Cancer screening rates were reported by the Organization for Economic Co-operation and Development (OECD) in Health Data 2010, which presents the existing set of quality of care indicators considered suitable for international comparison. We used mammography screening rates of breast cancer from 12 OECD countries. The screening rates were reported during the period 2000–09. The selected OECD countries, which had sufficient information, were Japan and the Republic of Korea (Asia); the United States of America (USA) and Canada (America); Australia and New Zealand (Oceania); Finland, Norway, the United Kingdom (UK), the Czech Republic, Belgium and Netherlands (Europe).

The mammography screening rates reported by OECD were based on 'programme data' or 'survey data' for women aged 50–69 years. The 'programme data', which has national coverage, were used for the all European and Oceanian countries studied; the 'survey data' based on a national representative sample, were used for the Asian countries and the USA and Canada. The screening rates were based on women aged 50–69 years who have completed the survey on mammography (survey data) or were eligible for organized screening programme (programme data) and reported having received a bilateral mammography according to the specific screening frequency recommended in each country.

Women were recommended to receive mammography screening every 2 years in their screening programme, with the exception of Canada and the USA which recommended screening every 1 or 2 years.

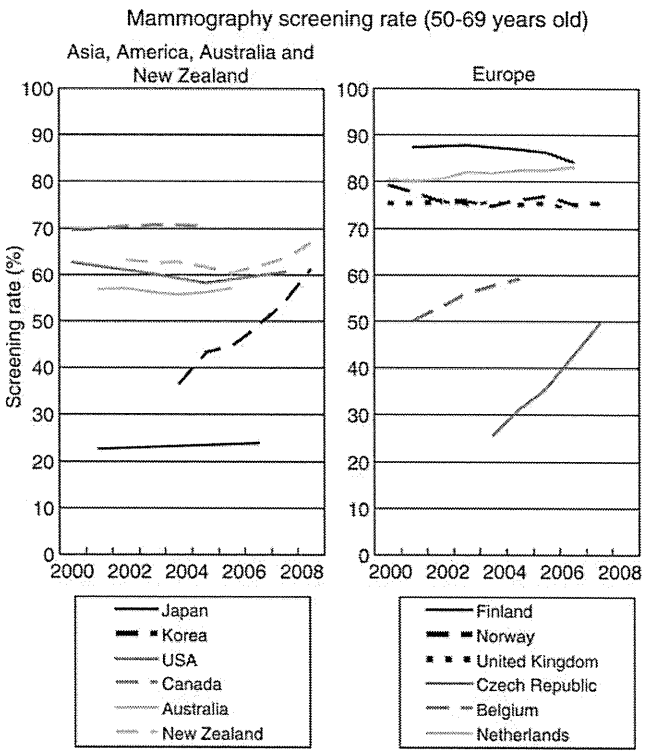

Figure 1. Trends in mammography screening rates (age 50–69 years) during 2000–09 in 12 OECD countries.

Note: Mammography screening rates, abstracted from the OECD Health Data 2010, were available from a CD-ROM provided by the Organization for Economic Co-operation and Development (OECD) (www.oecd.org/health). Data were tabulated by the authors of this article. Responsibility for this presentation and interpretation lies with the authors of this article.

Mammography screening rates among women aged 50–69 years in the 12 selected countries between 2000 and 2009 are shown in Fig. 1. Mammography screening rates were highest in Finland, Norway, the UK and Netherlands, which have been consistently >70% during this period. In Canada, the USA, Australia and New Zealand, the screening rates were stable ranging from 50 to 70%. The screening rates in Korea and the Czech Republic rapidly increased reaching 60 and 50%, respectively. The screening rate in Japan was the lowest among these countries with rates below 25% and stable over the observation period.

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Population-based Survival of Cancer Patients Diagnosed Between 1993 and 1999 in Japan: A Chronological and International Comparative Study

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Objective: The purpose of the present study was to collect data from population-based cancer registries and to calculate relative 5-year survival of cancer patients in Japan. We also sought to determine time trends and to compare the results with international studies.
Methods: We asked 11 population-based cancer registries to submit individual data for patients diagnosed from 1993 to 1999, together with data on outcome after 5 years. Although all these registries submitted data (491 772 cases), only six met the required standards for the quality of registration data and follow-up investigation. The relative 5-year survival calculated by pooling data from 151 061 cases from six registries was taken as the survival for cancer patients in Japan.
Results: Relative 5-year survival (1997–99) was 54.3% for all cancers (males: 50.0%, females: 59.8%). Survival figures for all sites changed slightly over the 7-year period, from 53.2% for the first 4 years of the study (1993–96) to 54.3% for the last 3 years (1997–99), however, a major improvement was observed in several primary sites. Some overall survival was lower in Japan than in the USA, but similar to that in European countries. Specifically, survival for uterine cancer, prostate cancer, testis cancer, lymphoma and leukemia was much lower in Japan than in other countries. However, survival was better in Japan mainly for cancers of the esophagus, stomach, colon, liver and gallbladder.
Conclusion: The study suggests an improvement in cancer survival in several primary sites in Japan, which is consistent with the development of treatments and early detection.

Key words: epidemiology/public health – prognostic factors – epidemiol-prevention

INTRODUCTION

Cancer survival, as assessed based on population-based cancer registries, is a valuable medical indicator to evaluate the progress of cancer control in a country or region. Precise population-based cancer survival is a comprehensive, practical and timely index for cancer control in a country. Use of relative 5-year survival statistics is useful to evaluate therapeutic effect in cancer incidence/mortality trends in real time. Cancer survival has also been shown to be powerful when comparing survival between sex, age groups and socioeconomic groups or between geographic areas where incidence or death due to other causes may differ.

However, this information is not often available because of legislative, financial and technical difficulties in following-up patients, even in population-based cancer registries in developed nations.

Clinical research groups frequently publish hospital-based survival rates for cancer patients at specific medical facilities (1–3); however, these data do not provide useful information to political planners because of inevitable recruitment bias. Population-based survival is a thus prerequisite for designing

public health projects and evaluating the efficacy of cancer prevention, screening and treatment.

In 1998, we proposed standard methods which required checking of vital status of patients by inquiring to the resident registration 5 years after diagnosis (4). We reported relative 5-year survival based on these methods for stomach, lung and breast cancer diagnosed from 1985 to 1989, using data from cancer registries of Yamagata, Fukui and Osaka Prefectures (5), which had collected data satisfying the methodological criteria. In 2001, we collected, from 12 registries belonging to the study group, individual data from all cancer patients (for all sites) diagnosed in 1993 for whom outcome information after 5 years was available. From this data we attempted to produce a nationwide relative 5-year survival according to standard methods (6). This nationwide survival, however, could not be completed because there were differences in the quality of registration and assessment methods of outcome among the 12 registries. A population-based survival was therefore not published in Japan until 2006 (7). This first population-based study reported that relative 5-year survival calculated by pooling 279 000 data from 7 registries was 49.2% for males and 59.4% for females.

The aims of the study were first to calculate the most recent relative 5-year survival of cancer patients in Japan, and second to observe changes in survival by comparing the data between two observation periods, 1993–96 and 1997–99, and by comparison with the results of international studies.

PATIENTS AND METHODS

Eleven among 15 registries (Miyagi, Yamagata, Niigata, Chiba, Kanagawa, Fukui, Aichi, Shiga, Osaka, Tottori, Okayama, Saga, Nagasaki, Kumamoto and Okinawa) submitted individual data (a total of 491 772 cases) to the survival study. These 15 registries were selected because they had relatively high-quality data tracing the 5-year outcome of patients diagnosed from 1993 to 1999. They had also participated in the Monitoring of Cancer Incidence in Japan (MCIJ) project for 2002 incident cases (8). We requested 11 population-based cancer registries to submit patient data for cancers at all sites, diagnosed from 1993 to 1999, including information on outcome after 5 years. We pooled cancer registry data that met standards of data quality in terms of both registration and outcome assessment.

Quality Criteria for Area Selection

The quality criteria were based on the standards adopted in the above-mentioned MCIJ project: DCO% (death certificate only: proportion of patients for whom the death certificate provides the only notification to the registry) <25% or DCN% (death certificate notification: proportion of patients for whom the death certificate provides the first notification to the registry) <30%, and IM ratio (incidence to mortality ratio) less than 1.5 (8). Among the 11 registries, six (Miyagi, Yamagata, Niigata, Fukui, Osaka and Nagasaki) met the required standards for the quality of registration and outcome assessment. According to the data provided by these registries, we calculated survival rates and considered them to be a nationwide index.

As far as the quality of outcome assessment was concerned, we set two criteria relating to follow-up methods. For registries checking survival of patients by referring to resident registries (active follow-up; Yamagata, Fukui and Osaka), we specified that the proportion of outcome-unknown cases 5 years after diagnosis should be <5%. For registries having no confirmation of survival 5 years after diagnosis (passive follow-up; Miyagi, Niigata and Nagasaki), we specified that information on personal identification including names would be computerized in order to collate the registered patients with death information with high accuracy. Registries that met these criteria were therefore guaranteed to have sufficiently accurate information about death.

Survival Calculation

Referring to other studies, since 1996 the research group has set standardized methods of calculating survival in Japan through the collaborative study of population-based cancer registries. The method of calculating survival is mainly based on the EUROCARE study (9). In concrete terms, we excluded DCO cases, cancers *in situ* and mucosal cancers of the large bowel from the analysis. In the case of multiple cancers, only the first-diagnosed tumor was analyzed.

This study calculated the survival for cancers including followed-back cases from DCN (Subjects 1) and excluding these cases (Subjects 2). The former method was that used in the EUROCARE study, and is suitable for international comparison of survival based on population-based cancer registries. The latter should instead be utilized for domestic comparison of survival in Japan where some registries do not conduct follow-back inquiries to medical institutions for DCN cases, according to death certificate information.

Survival for Subjects 2 is generally better than that for Subjects 1 because the latter include cases regarded as incident according to death information. Given the high proportion of incident cases not reported by medical facilities but registered on the basis of death certificates, the survival calculated for Subjects 1 may be underestimated. In contrast, it is also possible for survival to be overestimated in Subjects 2. In Japan, each population-based registry decides whether to apply active follow-up; consequently, the survival of Subjects 2 would be better than that of Subjects 1. In this study, we will regard the survival calculated for Subjects 2 as that of cancer patients in Japan.

Cumulative 5-year survivals were calculated starting from the date of diagnosis. Expected survivals were calculated using the cohort survival table based on life tables of the Japanese population and then using the survival probability in the general population similar to the patients in sex, birth

year and age. The former were divided by the latter to obtain relative 5-year survivals.

If vital status was unknown at 5 years after diagnosis, cases were dealt with as alive at the last contact date (5). However, for the three registries that had not checked the survival of patients by referring to the resident registry, we regarded all cases whose death was not confirmed as being alive until 5 years, and survival was calculated on this basis.

RESULTS

Survival Data Quality

Table 1 shows the number of incident cases, validity indices of registration, and the number of study subjects for survival analysis, for each registry in the two studies. In 1997–99 there were 221 080 incident cases, and the following cases were excluded from the survival analysis: DCO (36 939 cases, 16.7% of the total), subsequent primary tumors (17 814 cases, 8.1% of the total), non-malignant tumors (565 cases, 0.3% of the total), and *in situ* cancers (3 264 cases, 1.5% of the total). In addition, after excluding patients with unknown age at diagnosis and those over 100 years old, we considered the rest (164 738 cases, 74.5% of the total) as Subjects 1. Moreover, for DCN cases, additional cancer reports were requested in Yamagata, Fukui and Osaka Prefectures, and the registry records of cases originating from death information were distinguished in Miyagi Prefecture. The number of cases in which we traced the death information to incidence was 13 677, 8.3% of the total. The number of final analysis subjects (Subjects 2) excluding these cases was 151 061, corresponding to 68.3% of the total.

Table 2 shows the vital status at 5 years from diagnosis. In the Miyagi, Yamagata and Niigata Cancer Registries, in which the vital status of patients was checked after 5 years by referring to resident registries, the proportion of cases with unknown vital status was 2.0% among these three registries. Survival rate varied from 38.0 to 45.8%.

Survival by Age and Sex

Table 3 shows 5-year relative survival rate and standard error according to the primary site and sex, excluding the follow-back cases (i.e. in Subjects 2). The 5-year relative survival was 53.2% for all cancers diagnosed in 1993–96 (M: 48.9%, F: 59.0%), while that for 1997–99 was 54.3% (M: 50.0%, F: 59.8%).

When all sites were considered together, females had a higher survival than males (M: 50.0%, F: 59.8%). This tendency was evident for lip, oral cavity and pharynx (M:

Table 1. Number of incident cases, validity indices of registration and number of study subjects for survival calculations, according to registry—cases diagnosed in 1993–96 (the previous study) and in 1997–99

Observation period	Registry	*n*	DCO		Subsequent primary		Non-malignant tumors		CIS		Subjects 1		Follow-back cases		Subjects 2	
			n	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[b]	*n*	%[a]
1993–96	Miyagi	37 194	5709	15.3	4359	11.7	127	0.3	919	2.5	26 832	72.1	183	0.7	26 649	71.6
	Yamagata	24 416	2546	10.4	1211	5.0	0	0.0	285	1.2	20 406	83.6	2531	12.4	17 875	73.2
	Niigata	44 818	10 843	24.2	1621	3.6	5	0.0	495	1.1	31 867	71.1	–	–	31 867	71.1
	Fukui	13 886	575	4.1	797	5.7	3	0.0	153	1.1	12 395	89.3	1586	12.8	10 809	77.8
	Osaka	120 040	23 386	19.5	7488	6.2	360	0.3	1507	1.3	88 551	73.8	13 411	15.1	75 140	62.6
	Nagasaki	30 338	2790	9.2	2663	8.8	0	0.0	601	2.0	24 576	81.0	–	–	24 576	81.0
	Total	270 692	45 849	16.9	18 139	6.7	495	0.2	3960	1.5	204 627	75.6	17 711	8.7	186 916	69.1
1997–99	Miyagi	32 439	4232	13.0	4015	12.4	181	0.6	767	2.4	23 741	73.2	844	3.6	22 897	70.6
	Yamagata	19 248	1949	10.1	1202	6.2	1	0.0	195	1.0	15 953	82.9	1709	10.7	14 244	74.0
	Niigata	35 908	8737	24.3	1958	5.5	18	0.1	387	1.1	24 824	69.1	–	–	24 824	69.1
	Fukui	11 559	562	4.9	922	8.0	14	0.1	132	1.1	9974	86.3	1016	10.2	8958	77.5
	Osaka	97 641	19 268	19.7	7050	7.2	351	0.4	1223	1.3	71 093	72.8	10 108	14.2	60 985	62.5
	Nagasaki	24 285	2191	9.0	2667	11.0	0	0.0	560	2.3	19 153	78.9	–	–	19 153	78.9
	Total	221 080	36 939	16.7	17 814	8.1	565	0.3	3264	1.5	164 738	74.5	13 677	8.3	151 061	68.3
Total		491 772	82 788	16.8	35 953	7.3	1060	0.2	7224	1.5	369 365	75.1	31 388	8.5	337 977	68.7

DCO, Death certificate only cases; Follow-back cases: cases notified by death certificates require follow-back to obtain their clinical information.
Subjects 1: including followed-back cases from DCN; Subject 2: excluding followed-back cases.
[a]Proportion of total cases.
[b]Proportion of Subject 1 cases.

Table 2. Vital status at 5 years from diagnosis

Registry	Subjects 1	Dead		Alive		Unknown		Survival proportion (excl. unknown cases), %
		n	%[a]	*n*	%[a]	*n*	%[a]	
1993–96								
Active follow-up								
Yamagata	20 406	11 041	54.1	9219	45.2	146	0.7	45.5
Fukui	12 395	6905	55.7	5111	41.2	379	3.1	42.5
Osaka	88 551	54 229	61.2	32 447	36.6	1875	2.1	37.4
Total	121 352	72 175	59.5	46 777	38.5	2400	2.0	43.9
Passive follow-up								
Niigata	31 867	15 183	47.6	16 684	52.4	–	–	–
Miyagi	26 832	12 811	47.7	14 021	52.3	–	–	–
Nagasaki	24 576	13 180	53.6	11 396	46.4	–	–	–
Total	204 627	113 349	55.4	88 878	43.4	–	–	–
1997–99								
Active follow-up								
Yamagata	15 953	8563	53.7	7231	45.3	159	1.0	45.8
Fukui	9974	5377	53.9	4238	42.5	359	3.6	44.1
Osaka	71 093	43 135	60.7	26 399	37.1	1559	2.2	38.0
Total	97 020	57 075	58.8	37 868	39.0	2077	2.1	44.8
Passive follow-up								
Niigata	24 824	11 541	46.5	13 283	53.5	–	–	–
Miyagi	23 741	11 256	47.4	12 485	52.6	–	–	–
Nagasaki	19 153	9885	51.6	9268	48.4	–	–	–
Total	164 738	89 757	54.5	72 904	44.3	–	–	–
Total	369 365	203 106	55.0	161 782	43.8	–	–	–

[a]Proportion of total cases.

48.3% vs. F: 63.0%) and lung cancer (M: 22.4% vs. F: 33.5%). In contrast, females had a lower survival than males in for cancers of the larynx (M: 77.0% vs. F: 64.4%) and bladder (M: 78.6% vs. F: 69.8%).

The relative 5-year survivals for all sites decreased markedly in the elderly. In males, this difference was pronounced for cancers of the lip, oral cavity and pharynx, bladder and thyroid, as well as in malignant lymphoma and all leukemias. For women, there was a marked age-related decrease in survival for cancers of the lip, oral cavity and pharynx and uterus (cervix and corpus), as well as malignant lymphoma, multiple myeloma and all leukemias (Fig. 1).

Survival and Time Trends for Survival by Primary Site

Survival probabilities for cancers of the cervix, prostate, larynx, bladder, corpus uteri, female breast, testis and thyroid ranged from 71.5 to 92.4%; those for ovary, mouth, oral cavity and pharynx, stomach, rectum and anus, and colon ranged from 52.0 to 68.9%; those for pancreas, gallbladder, liver, lung, multiple myeloma, esophagus, all leukemias and malignant lymphoma ranged from 6.7 to 49.9% (Table 3).

Survival figures for all sites improved significantly over the 7-year period, increasing from 53.2% for the first observation period (1993–96) to 54.3% in the second (1997–99) (Table 3). Proportion of localized tumor at diagnosis increased; 43.0–52.0% for prostate, 5.4–10.1% for multiple myeloma, 25.0–28.6% for lung, 26.7–29.3 for malignant lymphoma, 43.3–45.5% for lip, oral cavity and pharynx, 31.6–33.5% for esophagus, 34.5–36.4% for ovary, 70.1–71.7% for liver and 55.6–57.2% for female breast. Accordingly survival also improved significantly for cancers of the prostate (by 8.7 points), esophagus (by 4.7 points), lung (by 3.1 points) and liver (by 1.9 points).

Survival and Time Trends for Survival by Extent of Disease

Table 4 shows observed and relative 5-year survival by extent of disease at diagnosis. Relative survival for all sites

Table 3. Relative 5-year survival by sex for selected sites of cancer diagnosed in 1993–96 and in 1997–99 (Subjects 2)

Primary sites	Male			Female			Total		
	n	Relative survival rate		*n*	Relative survival rate		*n*	Relative survival rate	
		%	SE		%	SE		%	SE
1993–96									
All sites (C00–C96)	106 022	48.9	0.2	77 473	59.0	0.2	183 495	53.2	0.1
Lip, oral cavity and pharynx (C00–C14)	2535	48.6	1.1	1022	64.7	1.7	3557	53.2	0.9
Esophagus (C15)	4401	25.7	0.7	843	33.1	1.7	5244	26.9	0.7
Stomach (C16)	29 318	62.1	0.3	14 817	60.4	0.5	44 135	61.6	0.3
Colon (C18)	10 542	71.3	0.6	8609	66.1	0.6	19 151	68.9	0.4
Rectum and anus (C19–C21)	7089	65.0	0.7	4316	63.9	0.8	11 405	64.6	0.5
Liver (C22)	9958	21.0	0.4	3619	21.8	0.7	13 577	21.2	0.4
Gallbladder etc. (C23–C24)	2475	19.0	0.9	2962	20.1	0.8	5437	19.6	0.6
Pancreas (C25)	2855	7.0	0.5	2205	5.9	0.5	5060	6.5	0.4
Larynx (C32)	1570	78.2	1.4	90	75.9	6.3	1660	78.1	1.4
Trachea, bronchus and lung (C33–C34)	15 124	20.8	0.4	5618	27.1	0.6	20 742	22.5	0.3
Female breast (C50)				14 094	84.4	0.4	14 094	84.4	0.4
Uterus (C53–C55)				5332	74.4	0.7	5332	74.4	0.7
Cervix uteri (C53)				3472	73.4	0.8	3472	73.4	0.8
Corpus uteri (C54)				1688	79.5	1.1	1688	79.5	1.1
Ovary (C56)				2116	49.4	1.1	2116	49.4	1.1
Prostate (C61)	4220	66.8	1.0				4220	66.8	1.0
Testis (C63)	505	89.6	1.6				505	89.6	1.6
Bladder (C67)	3481	80.0	1.0	1049	70.6	1.8	4530	77.8	0.9
Thyroid (C73)	541	86.3	2.1	2483	93.2	0.7	3024	92.0	0.7
Malignant lymphoma (C81–85, C96)	2349	46.3	1.1	1800	51.4	1.3	4149	48.5	0.9
Multiple myeloma (C88, C90)	508	29.3	2.2	446	30.9	2.3	954	30.0	1.6
All leukemias (C91–C95)	1686	31.7	1.2	1234	33.2	1.4	2920	32.3	0.9
1997–99									
All sites (C00–C96)	84 851	50.0	0.2↑**	62 860	59.8	0.2↑**	147 711	54.3	0.1↑**
Lip, oral cavity and pharynx (C00–C14)	1853	48.3	1.3	854	63.0	1.9	2707	52.9	1.1
Esophagus (C15)	3834	30.7	0.8↑**	643	37.3	2.0	4477	31.6	0.8↑**
Stomach (C16)	2190	62.6	0.4	10 485	61.2	0.5	32 375	62.1	0.3
Colon (C18)	8370	71.0	0.6	7106	66.4	0.7	15 476	68.9	0.5
Rectum and anus (C19–C21)	5797	65.7	0.8	3475	64.5	0.9	9272	65.2	0.6
Liver (C22)	7689	23.7	0.5↑**	3118	21.8	0.8	10 807	23.1	0.4↑**
Gallbladder etc. (C23–C24)	1884	21.8	1.1↑*	2430	18.9	0.8	4314	20.2	0.7
Pancreas (C25)	2386	6.2	0.5	1900	7.3	0.6	4286	6.7	0.4
Larynx (C32)	1130	77.0	1.7	78	64.4	6.6	1208	76.1	1.6
Trachea, bronchus and lung (C33–C34)	12 737	22.4	0.4↑**	4963	33.5	0.7↑**	17 700	25.6	0.4↑**
Female breast (C50)				12 334	85.5	0.4	12 334	85.5	0.4
Uterus (C53–C55)				3995	72.5	0.8	3995	72.5	0.8
Cervix uteri (C53)				2244	71.5	1.1	2244	71.5	1.1

Continued

Table 3. *Continued*

Primary sites	Male			Female			Total		
	n	Relative survival rate		*n*	Relative survival rate		*n*	Relative survival rate	
		%	SE		%	SE		%	SE
Corpus uteri (C54)				1571	76.8	1.2	1571	76.8	1.2
Ovary (C56)				1800	52.0	1.2	1800	52.0	1.2
Prostate (C61)	4508	75.5	1.0↑**				4508	75.5	1.0↑**
Testis (C63)	369	92.0	1.9				369	92.0	1.9
Bladder (C67)	2824	78.6	1.1	870	69.8	2.0	3694	76.5	1.0
Thyroid (C73)	437	87.6	2.3	1986	93.5	0.8	2423	92.4	0.7
Malignant lymphoma (C81–85, C96)	1949	46.6	1.3	1473	54.2	1.4	3422	49.9	0.9
Multiple myeloma (C88, C90)	422	31.5	2.5	403	28.1	2.4	825	29.8	1.7
All leukemias (C91–C95)	1242	32.2	1.4	986	33.8	1.6	2228	32.9	1.0

↑Improved significantly between the two observation periods $^{**}P < 0.01$, $^{*}P < 0.05$.

(C00–C96) was 85.2% for localized tumors, 43.7% for those with regional lymph node or direct invasion to the adjacent tissue/organ and 10.1% for those with distant metastasis. When all sites were considered together, improvement in survival was found only for localized tumors; survival rate increased from 84.6 to 85.2% ($P < 0.05$).

Among localized tumors, survival improvement between the two periods was observed for the esophagus, liver, lung and female breast; among tumors with regional lymph node or direct invasion to the adjacent tissue/organ, improvement was seen for the pancreas, lung, prostate and testis. No improvement was observed in distant metastatic tumor cases.

In contrast, survival deteriorated significantly between the two observation periods for localized bladder cancer, laryngeal cancer with regional lymph node or adjacent organ metastasis, and gallbladder cancer with distant metastasis.

Comparison with International Data

Table 5 shows relative 5-year survivals in the current study, SEER study (10) and EUROCARE4 study (11). Compared with the American data (SEER study), overall all-age survival was lower in Japan (64.9–54.3%); however, age-standardized survival in Japan was similar to that in European countries (53.3–51.9%). In particular, the survivals for Japanese patients with uterine cancer, prostate cancer, testicular cancer, lymphoma and leukemia were much lower than for their American counterparts. Survival in Japan was better than in Europe or the USA mainly for cancers of the digestive and hepatobiliary organs, such as the esophagus, stomach, colon, liver and gallbladder.

DISCUSSION

Survival in Japan

On the basis of the data from six population-based cancer registries in Japan that met standards for data quality in terms of both registration and outcome assessment, we calculated the latest relative 5-year survival for major cancers.

Age differences were observed in survival when all sites were considered together and in some specific primary sites. Ioka et al. (12) found that advanced cervical cancers leading to poor survival are common in older people. Otherwise, this may be explained by histological differences or simply physical decline in older patients. Farley et al. (13) reported a similar decreasing survival with age in their study of uterine cancer. Studies of leukemia (14) and bladder cancer (15) also show similar effects of age.

Sex differences in survival for cancers at two primary sites, the larynx and lung, might be caused by biological differences between the two sexes and diagnostic circumstances. These differences could relate to smoking behavior in the two sexes, even for cancers of the same histology. Nordquist et al. (16) found differences in survival according to the smoking status of patients with adenocarcinoma of the lung. Another study showed that the survival of bladder cancer patients varies according to current smoking, age and gender, in addition to a latent promoter hypermethylation (17). Bladder cancer is often at a more advanced tumor stage at diagnosis in women than in men.

Comparison Between the Two Periods and with the Results of International Studies

Overall chronological improvement of survival in several primary sites was observed, confirming the findings of a

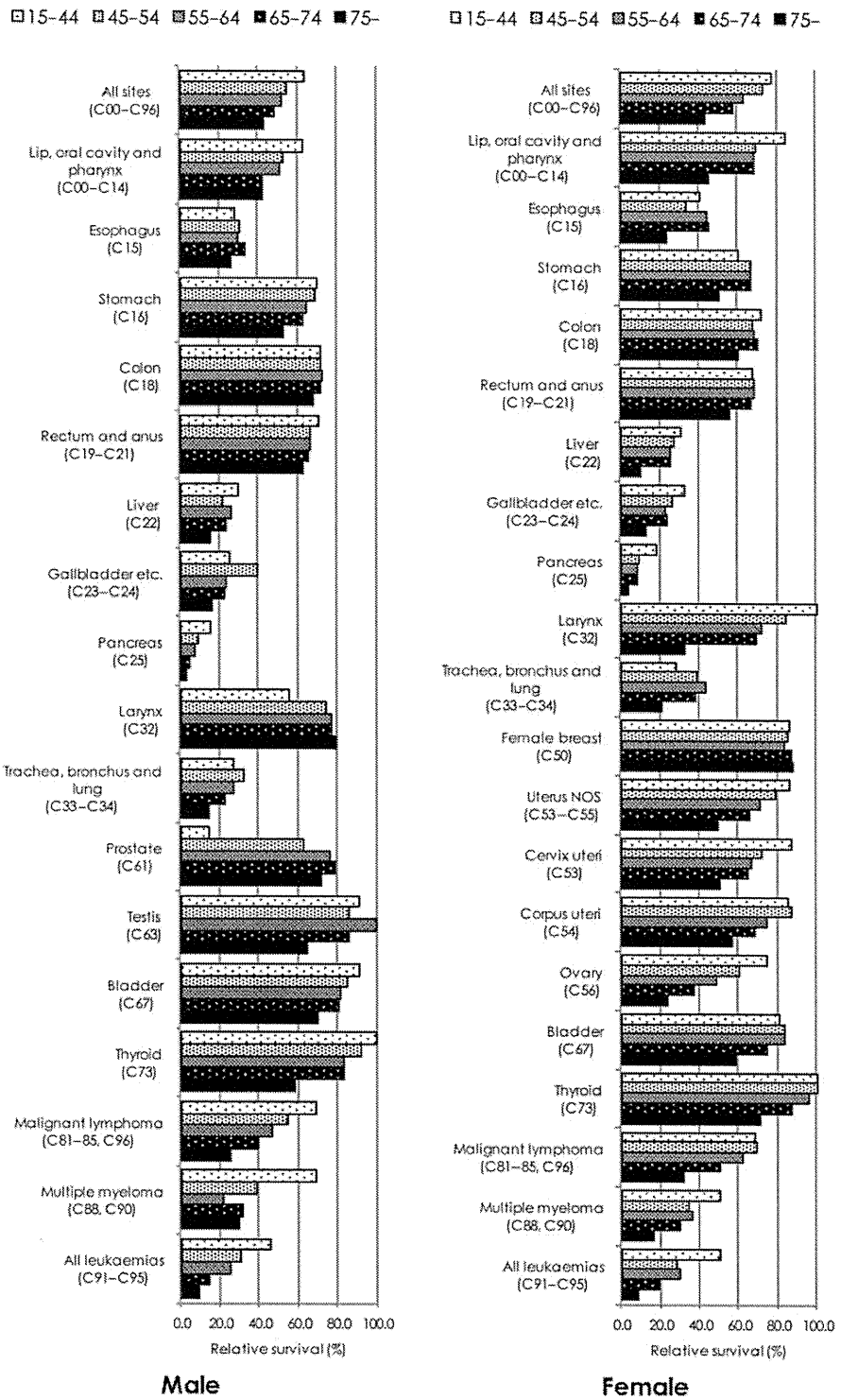

Figure 1. Relative 5-year survival for major sites of cancer by sex and age at diagnosis (1997–99, Subject 2).

regional study (18). Unfortunately, no change was seen in survival of cancers with distant metastases.

There were particularly marked improvements in survival for cancers of the esophagus, liver and female breast, which might be mainly due to diffusion of organized screening programs in the society or development of early detection systems in cases of opportunistic screening (19–22). Treatment has also evolved during these two observational periods. Yamanaka et al. (23) reported, for example, that the establishment of indication criteria for hepatectomy and the

Table 4. Relative 5-year survival for major sites of cancer by extent of tumor at diagnosis (Subjects 2)

Primary sites	Localized		Regional lymph node metastases, adjacent organ metastases		Distant metastasis	
	%	SE	%	SE	%	SE
1993–96						
All sites (C00–C96)	84.6	0.2	43.2	0.2	10.3	0.2
Lip, oral cavity and pharynx (C00–C14)	75.0	1.5	39.4	1.4	16.5	2.8
Esophagus (C15)	55.2	1.6	19.1	0.9	3.7	0.6
Stomach (C16)	94.4	0.3	40.2	0.5	3.1	0.2
Colon (C18)	96.6	0.5	64.8	0.8	8.2	0.5
Rectum and anus (C19–C21)	93.0	0.6	55.3	0.9	8.1	0.7
Liver (C22)	30.3	0.6	8.6	0.8	4.0	0.5
Gallbladder etc. (C23–C24)	61.5	1.8	12.6	0.8	1.6	0.3
Pancreas (C25)	37.1	2.5	4.5	0.5	1.1	0.2
Larynx (C32)	89.3	1.6	51.8	3.2	14.2	5.4
Trachea, bronchus and lung (C33–C34)	65.8	0.9	16.0	0.5	2.5	0.2
Female breast (C50)	96.6	0.3	78.3	0.7	25.3	1.7
Uterus (C53–C55)	93.1	0.6	54.1	1.4	15.2	2.0
Cervix uteri (C53)	93.6	0.8	52.8	1.6	9.8	2.1
Corpus uteri (C54)	92.9	1.0	63.4	3.1	22.7	3.7
Ovary (C56)	89.6	1.6	40.5	2.0	15.4	1.6
Prostate (C61)	96.5	1.7	71.0	2.9	35.2	1.7
Testis (C63)	99.5	1.1	86.3	6.3	60.9	6.1
Bladder (C67)	91.4	1.0	35.1	2.7	7.6	1.9
Thyroid (C73)	98.6	0.8	94.0	0.9	40.7	4.3
Malignant lymphoma (C81–85, C96)	75.3	2.0	55.4	2.4	36.2	1.4
Multiple myeloma (C88, C90)	56.4	11.5	55.0	15.6	25.3	2.2
All leukemias (C91–C95)	–	–	–	–	–	–
1997–99						
All sites (C00–C96)	85.2	0.2↑*	43.7	0.3	10.1	0.2
Lip, oral cavity and pharynx (C00–C14)	76.1	1.7	39.2	1.6	12.7	2.9
Esophagus (C15)	64.9	1.6↑**	21.0	1.0	4.8	0.8
Stomach (C16)	95.2	0.3	39.8	0.6	2.9	0.3
Colon (C18)	95.7	0.5	65.0	0.9	9.3	0.6
Rectum and anus (C19–C21)	94.0	0.7	56.4	1.0	9.7	0.8
Liver (C22)	33.2	0.7↑**	10.4	0.9	3.2	0.5
Gallbladder etc. (C23–C24)	57.4	2.0	14.0	0.9	0.8	0.2↓*
Pancreas (C25)	34.7	2.7	6.1	0.6↑*	1.0	0.2
Larynx (C32)	90.0	1.9	37.5	3.5↓**	5.7	2.7
Trachea, bronchus and lung (C33–C34)	68.7	0.9↑*	18.6	0.6↑**	2.8	0.2
Female breast (C50)	97.7	0.3↑**	78.4	0.7	27.6	1.8
Uterus (C53–C55)	92.2	0.7	52.4	1.6	12.8	2.0
Cervix uteri (C53)	92.3	1.1	53.1	2.0	10.2	2.4
Corpus uteri (C54)	92.4	1.1	53.7	3.1↓*	17.2	3.2

Continued

Table 4. *Continued*

Primary sites	Localized		Regional lymph node metastases, adjacent organ metastases		Distant metastasis	
	%	SE	%	SE	%	SE
Ovary (C56)	86.0	1.8	43.6	2.1	20.3	2.1
Prostate (C61)	97.6	1.3	79.2	2.9↑*	39.6	1.8
Testis (C63)	97.8	1.8	100.0	0.0↑*	70.7	6.3
Bladder (C67)	88.1	1.1↓*	34.3	2.8	8.8	2.4
Thyroid (C73)	99.6	0.8	93.6	1.1	41.7	4.9
Malignant lymphoma (C81–85, C96)	79.8	2.1	58.4	2.7	34.1	1.6
Multiple myeloma (C88, C90)	51.2	10.2	52.7	15.7	24.4	2.8
All leukemias (C91–C95)	–	–	–	–	–	–

↑ improved significantly between the two observation periods $^{**}P < 0.01$, $^{*}P < 0.05$.
↓ deteriorated significantly between the two observation periods $^{**}P < 0.01$, $^{*}P < 0.05$.

introduction of multimodal treatment for recurrence were contributory factors. Lung cancer patients, particularly those with early stage disease, also benefit from improvements in surgical technique (24). The increase in breast cancer survival likely results from development of new treatments. The breast conserving treatment with or without axillary dissection has been developed and replaced Halsted radical mastectomy in early 1990s in Japan. At the same time, endocrine therapy has progressed remarkably with acceptance of tamoxifen use in 1981. Since then LHRH agonist and aromatase inhibitors were approved one after another in the mid-1990s, and effective chemotherapy regimens in premenopausal women have also been developed: the majority of the university hospitals and clinics employed these new treatment strategies. We have to be cautious when considering prostate cancer survival because the early detection of micro tumors by PSA screening has been evident for more than a decade. However, considering that survival was particularly improved for cases with metastasis to regional lymph nodes or adjacent organs, the introduction of more effective radiation therapy might have contributed to the survival of older patients with prostate cancer (25).

We found that the overall survival of cancer patients in Japan is comparable with that in Europe (51.9%), although survival for some cancer types, particularly prostate cancer, lymphoma and leukemia, is much lower than in these Western countries. In contrast, the overall survival in the USA was much higher than Japan. This is probably due to the large difference of weights on breast and prostate cancer in cancer incidence. Survival for digestive organ and hepatobiliary cancers was better in Japan than in Western countries. For specific types of cancer, greater survival in a particular country tends to be correlated with higher incidence in that country (8). A high survival rate might result from greater surgical volume for these primary sites (26). In other words, compared with their Western counterparts, Japanese oncologists are usually more aware of digestive organ and hepatobiliary cancers and have greater experience in treatment of these cancers. Conversely, tumors that are sensitive to chemotherapy seem to be treated less effectively by Japanese oncologists. This slow progress in chemo-sensitive malignancies may demonstrate weaknesses of the system of oncology in Japan; serious shortage of oncologists specialized in chemotherapy and less centralized primary cancer treatment.

Changes over time in Japan were similar to those in the international studies examined. For example, considering changes in lung cancer and breast cancer, the time trends identified in Japan were very similar to those seen when comparing EUROCARE 3 and EUROCARE 4 (27).

Limitations

To perform survival analyses in Japan, it is a priority to improve the quality of cancer registry data, because the high proportion of patients not registered will diminish the accuracy of survival estimates according to international criteria (28). In this study, we required each registry to meet the necessary standards for participating in nationwide estimates of incidence (8). It would be reasonable to assume, therefore, that the current study has been conducted on the basis of fairly accurate data from population-based cancer registries.

In the three prefectures where the vital status of patients was checked after 5 years from diagnosis, the proportion of unknown cases for vital status was only 2%, which implies that the assessment of outcome was highly accurate. The other three prefectures did not have the resources to check the vital status of patients in the resident registry. Table 2 shows that the survival proportion from these three registries was higher than that from the other three referring resident registries. The best way to collect more accurate survival

Table 5. Comparison of the survival between the SEER (96-03), the EUROCARE 4 and the present study

Primary sites	Present study (Subjects 2) 1997–99		SEER 1996–2003	EUROCARE4 1995–99
	All ages	Age standardized rate	All ages	Age standardized rate
All sites (C00–C96)	54.3	53.3	64.9	51.9
Lip, oral cavity and pharynx (C00–C14)	52.9	51.6	59.1	–
Esophagus (C15)	31.6	30.6	15.6	12.3
Stomach (C16)	62.1	61.4	24.3	24.1
Colon (C18)	68.9	68.7	63.5	53.9
Rectum and anus (C19–C21)	65.2	64.7	65.0	53.5
Liver (C22)	23.1	22.0	10.8	8.6
Gallbladder etc. (C23–C24)	20.2	22.1	15.1[a]; 18.6[b]	14.1
Pancreas (C25)	6.7	7.2	5.0	5.5
Larynx (C32)	76.1	75.2	62.9	63.1
Trachea, bronchus and lung (C33–C34)	25.6	25.8	15.0	12.6
Female breast (C50)	85.5	86.1	88.6	81.1
Cervix uteri (C53)	71.5	70.6	71.6	66.5
Corpus uteri (C54)	76.8	69.9	83.9	78.3
Ovary (C56)	52.0	41.3	44.9	41.6
Prostate (C61)	75.5	69.7	98.1	77.0
Testis (C63)	92.0	88.4	98.4	93.8
Bladder (C67)	76.5	77.5	79.5	65.8
Thyroid (C73)	92.4	91.2	93.9	86.5
Malignant lymphoma (C81–85, C96)	49.9	45.6	66.8	–
Hodgkin's lymphoma	68.3	71.8	84.9	83.0
Non-Hodgkin's lymphoma	49.1	45.5	63.4	54.6
Multiple myeloma (C88, C90)	29.8	30.7	33.7	34.4
All leukemias (C91–C95)	32.9	20.6	49.6	–
Acute lymphocytic leukemia	50.0	25.3	64.0	30.0
Acute myelogenous leukemia	26.6	17.1	21.2	19.0
Chronic myelogenous leukemia	44.0	32.5	47.5	39.5

[a]Gallbladder.
[b]Intrahepatic bile duct.

data are to assess patient outcome by referring to resident registries. However, the fact that these registries do not check the survival of patients appears to have a modest effect on the overestimation of survival, because death information is very precise in Japan, and collation could be done with high accuracy in these three prefectures. Further, the frequency of patients moving to different prefectures is considered to be relatively low.

Mucosal cancers of the large bowel should have been excluded from the survival analysis, since they are regarded as *in situ* cancers according to the agreement of the International Union Against Cancer (UICC) (29). However, some population-based cancer registries in Japan still do not distinguish them. In this study, it seems that the proportions of mucosal cancer of the large bowel and of multiple primary cancers (except the first-diagnosed tumor) were negligible; it is therefore reasonable to think that they did not greatly affect survival results.

Future of Survival Analysis in Japan

The EUROCARE study is one of the most important collaborative studies of the European Union (9), currently involving 67 population-based cancer registries operating in 22 European countries (11). Furthermore, the CONCORD study extends the EUROCARE study to include North America

(the USA and Canada), Australia and Asian countries, involving 101 population-based cancer registries in 31 countries (30). The International Agency for Research on Cancer has published an article on cancer survival in Africa, Asia and Central America recently including nine Asian countries (31), in addition, a similar international project on survival is ongoing in the Asia region; an Asian cancer registry network is being formed (32).

We confirmed the importance of calculating a comparable population-based survival as a measure of cancer control programs through the present study. Comparing the data chronologically and internationally, we figured out current situation, progress and international position of cancer screening and treatments in Japan. Drawing up a project or evaluating outcomes based on such a useful index is undoubtedly the basic principle of cancer control. Currently, it is highly recommended to analyze incidence, mortality and survival together in order to more fully understand the characteristics of cancer in a country (27,33). The Japanese research group is also conducting the MCIJ to monitor incidence, mortality and survival as the index of the progress of the cancer control routinely in Japan (34), and we hope to show the results to the world in the near future.

Conclusion

The study suggests an improvement in cancer survival in Japan in several primary sites during a relatively short period, which is consistent with the development of treatments and early detection. We confirmed that the overall survival of cancer patients in Japan is comparable with that in Europe. In contrast, the overall survival in the USA was much higher than Japan, but this is probably due to the difference of cancer incidence proportion.

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Conflict of interest statement

None declared.

References

1. Sakamoto K, Machi J, Prygrocki M, Watanabe T, Hosoda S, Sugano M, et al. Comparison of characteristics and survival of colorectal cancer between Japanese–Americans in Hawaii and native Japanese in Japan. *Dis Colon Rectum* 2006;49:50–7.
2. Ichinose Y, Kato H, Koike T, Tsuchiya R, Fujisawa T, Shimizu N, et al. Overall survival and local recurrence of 406 completely resected stage IIIa-N2 non-small cell lung cancer patients: questionnaire survey of the Japan Clinical Oncology Group to plan for clinical trials. *Lung Cancer* 2001;34:29–36.
3. Bunt AM, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 1995;13:19–25.
4. Ajiki W, Matsuda T, Sato Y, Fujita M, Yamazaki S, Murakami R, et al. A standard method of calculating survival rates in population-based cancer registries. *Jpn J Cancer Clin* 1998;44:981–93.
5. Ajiki W, Matsuda T, Sato Y, Fujita M, Yamazaki S, Murakami R, et al. Standard method of calculating relative survival rates in population-based cancer registries—an investigation using stomach cancer patients. *Jpn J Cancer Clin* 1997;43:1005–14.
6. Oshima A, Ajiki W, Tsukuma H. Estimation of survival of cancer patients in Japan (preliminary report). In: Tajima K, Kuroishi T, Oshima A, editors. *Cancer Mortality and Morbidity Statistics: Japan and the World.* Tokyo: Japan Scientific Societies Press 2004;131–5.
7. Tsukuma H, Ajiki W, Ioka A, Oshima A, Research Group of Population-Based Cancer Registries of Japan. Survival of cancer patients diagnosed between 1993 and 1996: a collaborative study of population-based cancer registries in Japan. *Jpn J Clin Oncol* 2006;36:602–7.
8. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and incidence rates in Japan in 2002: based on data from 11 population-based cancer registries. *Jpn J Clin Oncol* 2008;38:641–8.
9. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Esteve J. *Survival of Cancer Patients in Europe: The EUROCARE Study.* Lyon: International Agency for Research on Cancer 1995
10. Gloeckler Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. *Oncologist* 2003;8:541–52.
11. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. *Eur J Cancer* 2009;45:931–91.
12. Ioka A, Ito Y, Tsukuma H. Factors relating to poor survival rates of aged cervical cancer patients: a population-based study with the relative survival model in Osaka, Japan. *Asian Pac J Cancer Prev* 2009;10:457–62.
13. Farley JH, Nycum LR, Birrer MJ, Park RC, Taylor RR. Age-specific survival of women with endometrioid adenocarcinoma of the uterus. *Gynecol Oncol* 2000;79:86–9.
14. Sorensen JT, Gerald K, Bodensteiner D, Holmes FF. Effect of age on survival in acute leukemia. 1950–1990. *Cancer* 1993;72:1602–6.
15. Nielsen ME, Shariat SF, Karakiewicz PI, Lotan Y, Rogers CG, Amiel GE, et al. Advanced age is associated with poorer bladder cancer-specific survival in patients treated with radical cystectomy. *Eur Urol* 2007;51:699–706. discussion-8.
16. Nordquist LT, Simon GR, Cantor A, Alberts WM, Bepler G. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. *Chest* 2004;126:347–51.
17. Marsit CJ, Houseman EA, Schned AR, Karagas MR, Kelsey KT. Promoter hypermethylation is associated with current smoking, age, gender and survival in bladder cancer. *Carcinogenesis* 2007;28:1745–51.
18. 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;37:452–8.
19. Sasaki A, Iwashita Y, Shibata K, Matsumoto T, Ohta M, Kitano S. Improved long-term survival after liver resection for hepatocellular carcinoma in the modern era: retrospective study from HCV-endemic areas. *World J Surg* 2006;30:1567–78.

20. Kawano T, Nakajima Y, Suzuki T, Haruki S, Ogiya K, Kawada K, et al. [Esophageal carcinoma - from the viewpoint of surgery]. *Gan To Kagaku Ryoho* 2007;34:824–30.
21. Kudo M. Early detection and curative treatment of early-stage hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2005;3(10 Suppl 2):S144–8.
22. Kawai M, Kuriyama S, Suzuki A, Nishino Y, Ishida T, Ohnuki K, et al. Effect of screening mammography on breast cancer survival in comparison to other detection methods: a retrospective cohort study. *Cancer Sci* 2009;100:1479–84.
23. Yamanaka N, Takata M, Tanaka T, Yamanaka J, Yasui C, Ando T, et al. Evolution of and obstacles in surgical treatment for hepatocellular carcinoma over the last 25 years: differences over four treatment eras. *J Gastroenterol* 2000;35:613–21.
24. Koike T, Yamato Y, Asamura H, Tsuchiya R, Sohara Y, Eguchi K, et al. Improvements in surgical results for lung cancer from 1989 to 1999 in Japan. *J Thorac Oncol* 2009;4:1364–9.
25. Sandhu A, Mundt AJ. Radiation therapy for urologic malignancies in the elderly. *Urol Oncol* 2009;27:643–52.
26. Nomura E, Tsukuma H, Ajiki W, Oshima A. Population-based study of relationship between hospital surgical volume and 5-year survival of stomach cancer patients in Osaka, Japan. *Cancer Sci* 2003;94: 998–1002.
27. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008;44:1345–89.
28. Parkin D, Whelan S, Ferlay J, Teppo L, Thomas D. *Cancer Incidence in Five Continents*, Vol. VIII. Lyon: International Agency for Research on Cancer 2002.
29. Sobin L, Wittekind C. *TNM Classification of Malignant Tumours*. 6th edn. New Jersey: John Wiley & Sons 2002.
30. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9:730–56.
31. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2009;11:165–73.
32. Moore MA, Shin HR, Curado MP, Sobue T. Establishment of an Asian Cancer Registry Network—problems and perspectives. *Asian Pac J Cancer Prev* 2008;9:815–32.
33. Sant M, Francisci S, Capocaccia R, Verdecchia A, Allemani C, Berrino F. Should we use incidence, survival or mortality to assess breast cancer trends in European women? *Nat Clin Pract Oncol.* 2006;3:228–9.
34. Matsuda T, Marugame T, Kamo KI, Katanoda K, Ajiki W, Sobue T. 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;39:850–8.

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Nonfilter and filter cigarette consumption and the incidence of lung cancer by histological type in Japan and the United States: analysis of 30-year data from population-based cancer registries

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Shifts in the histologic type of lung cancer accompanying changes in lung cancer incidence have been observed in Japan and the United States. We examined the association between the shift in tobacco design from nonfilter to filter cigarettes with changes in the incidence of adenocarcinoma (AD) and squamous cell carcinoma (SQ) of the lung. We compiled population-based incidence data from the Surveillance, Epidemiology and End Results in the United States (1973–2005) and from selected Japanese cancer registries (1975–2003). Trends in age-standardized rates of lung cancer incidence by histologic type were characterized using joinpoint analyses. A multiple regression framework was used to examine the relationship between tobacco use and incidence by histologic type. We observed that AD has replaced SQ as the most frequent histologic type in males and females in both Japan and the United States. Filter cigarette consumption was positively associated with the incidence of AD, with time lags of 25 and 15 years in Japan and the United States, respectively ($\hat{\beta}_2^{AD}$: 1.946×10^{-3}, $p < 0.001$ and 3.142×10^{-3}, $p < 0.001$). In contrast, nonfilter cigarette consumption was positively associated with the incidence of SQ, with time lags of 30 and 20 years in Japan and the United States, respectively ($\hat{\beta}_2^{SQ}$: 0.464×10^{-3}, $p = 0.006$ and 0.364×10^{-3}, $p = 0.008$). In conclusion, the shift from nonfilter to filter cigarettes appears to have merely altered the most frequent type of lung cancer, from SQ to AD.

Epidemiology

The association between cigarette smoking and lung cancer was firmly established in the 1950s.[1] The rapid increase in incidence rates in the 20th century has led to an epidemic of lung cancer, particularly among men in industrialized countries.[2,3] In the United States, where serious smoking control efforts were instituted almost 50 years ago, the incidence of lung cancer among men peaked in 1982 and began to decline thereafter,[4] but it continues to rise in countries where smoking control efforts have been less aggressive. In Japan, despite a continuous decline in smoking rates over the last 50 years, lung cancer incidence continues to rise.[4,5]

Lung cancer incidence patterns and trends vary by histological type[6] and have been shown to be related to smoking patterns and exposures to other lung risk factors.[3] Shifts in histologic type have been reported to accompany changes in lung cancer incidence. Relative and absolute increases in adenocarcinoma (AD) of the lung were first recognized in the 1970s[7] and continued to be observed in the United States[8,9] and European countries.[10] Although this trend has now peaked in the United States,[11,12] incidence appears to be still increasing in certain areas of Japan.[13–15]

Trends in the incidence of lung cancer by histologic type are of interest in the evaluation of the impact of changes in cigarette manufacture. In particular, although low-tar, low-nicotine, filtered cigarettes appear to have contributed to the overall decline in lung cancer, and most notably in squamous

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cell carcinoma (SQ),[16] they may have simultaneously increased the risk of certain peripheral tumors, such as AD,[17–20] and it has been hypothesized that the upward trend in the incidence of AD is mainly due to the dissemination of low-tar filtered cigarettes.[18–20] Smoke from low-yield filter-tipped cigarettes is inhaled more deeply than that from earlier unfiltered cigarettes.[21,22] Inhalation transports tobacco-specific carcinogens more distally toward the bronchioalveolar junction, where ADs often arise. The change in cigarette consumption from nonfiltered to filtered cigarettes also reduces the yield of carcinogenic polycyclic aromatic hydrocarbons, which are inducers of SQs, while simultaneously increasing that of carcinogenic tobacco-specific N-nitrosamines, which are inducers of ADs.[19]

Here, we investigated differences in the effects of nonfilter and filter cigarette consumption on changes in the incidence of SQ and AD in Japan and the United States.

Material and Methods

Lung cancer incidence data in Japan were obtained from nine of the 36 regional registries used to estimate nationwide incidence, namely Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga, Nagasaki and Hiroshima City, which together account for about 18% of the Japanese population. For the United States, lung cancer incidence data were obtained from the Surveillance and End Results (SEER) program of the US National Cancer Institute, which makes aggregate data available to the public. The data cover about 10% of the US population in nine geographical regions, namely the states of Connecticut, Hawaii, Iowa, New Mexico and Utah, as well as the metropolitan areas of Atlanta (GA), Detroit (MI), San Francisco-Oakland (CA) and Seattle-Puget Sound (WA). We selected cases diagnosed with lung or bronchus cancer from 1973 through 2005 for the US data and from 1975 through 2003 for the Japanese data. Morphology codes indicating lung cancer cell type were grouped into eight major categories according to the WHO scheme[23]: (*i*) SQ (International Classification of Disease for Oncology version 3 (ICD-O-3) codes 8050–8078, 8083–8084); (*ii*) AD (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, 8576); (*iii*) small cell carcinoma (8041–8045, 8246); (*iv*) large cell carcinoma (including giant cell, clear cell and large cell undifferentiated carcinoma 8010–8012, 8014–8031, 8035, 8310); (*v*) other specified carcinoma; (*vi*) sarcoma (8800–8811, 8830, 8840–8921, 8990–8991, 9040–9044, 9120–9133, 9150, 9540–9581); (*vii*) other specified malignant neoplasm and (*viii*) unspecified malignant neoplasm (8000–8005). The percentages of cases with unspecified morphology in the United States and Japan differed by an order of magnitude: only 3.9% of the US cases had morphology codes of 8000–8005, indicating "unspecified malignant neoplasm," whereas 33.6% of case reports in Japan were coded 8000–8005. In accordance with Devesa *et al.*,[10] we proportionally allocated the cases with unspecified morphology 8 to the other seven categories on a registry-, year at diagnosis-, sex- and age-specific basis.

US age-standardized incidence rates (ASR) were calculated for the years 1973–2005 and Japanese ASR for the years 1975–2003, by major morphological type, namely SQ, AD and small cell carcinoma. Age standardization incorporated the Segi world standard.[24] All incidence rates were expressed as newly diagnosed cases of malignant neoplasm per 100,000 person-years.

The trends in ASR were also characterized by the widely used joinpoint regression analysis, as described in detail elsewhere.[25] Briefly, joinpoint regression is a statistical technique that describes changing trends over successive segments of time and the magnitude of an increase or decrease within each segment after identifying the best fitting model. Essentially, within each time segment, the log of the ASR is modeled as a linear function of time (calendar year), thereby yielding annual exponential rates of change in ASR. The technique identifies the timepoint(s), also referred to as joinpoint(s), at which there is a statistically significant change in the incidence trend. A maximum of three joinpoints in the model was allowed in the model fitting. The resulting trend segments, as delimited in time by joinpoints, were described by the annual percentage change (APC), that is, the slope of the line segment.[25] The calculation assumes that rates increase or decrease at a constant rate over time, although the validity of this assumption has not been tested. APC is calculated based on the following regression model:

$$\log(R_y) = b_0 + b_1 y$$

where $\log(R_y)$ is the natural log of the rate in year y

The APC from year y to $y+1$

$$= \left(\frac{R_{y+1} - R_y}{R_y}\right) \times 100$$

$$= \left(\frac{e^{b_0+b_1(y+1)} - e^{b_0+b_1(y)}}{e^{b_0+b_1(y)}}\right) \times 100$$

$$= \left(e^{b_1} - 1\right) \times 100$$

In describing the trends, the terms "increase" or "decrease" were used when the slope (APC) of the trend was statistically significant ($p < 0.05$); otherwise, the terms "stable" or "level" were used.

Data on cigarette consumption were based on the market share of nonfilter and filter cigarettes sale in each year. These data were obtained from the US Federal Trade Commission,[26] the Ministry of Health, Labour and Welfare, Japan,[27] the Ministry of Finance, Policy Research Institute, Japan,[28] Japan Tobacco and Salt Co. and the Tobacco Institute of Japan.

To assess whether the incidence rates of SQ and AD of the lung were correlated to annual nonfilter and filter cigarette consumption per capita, we used a multiple regression framework.[29] For a specific subpopulation (*i.e.*, Japanese), we let $Y^{AD}(t)$ represent the ASR (per 100,000 person-years) of AD at time t, and $Y^{AD}(t^+)$ represent the ASR of AD at one time point ahead of time t. For example:

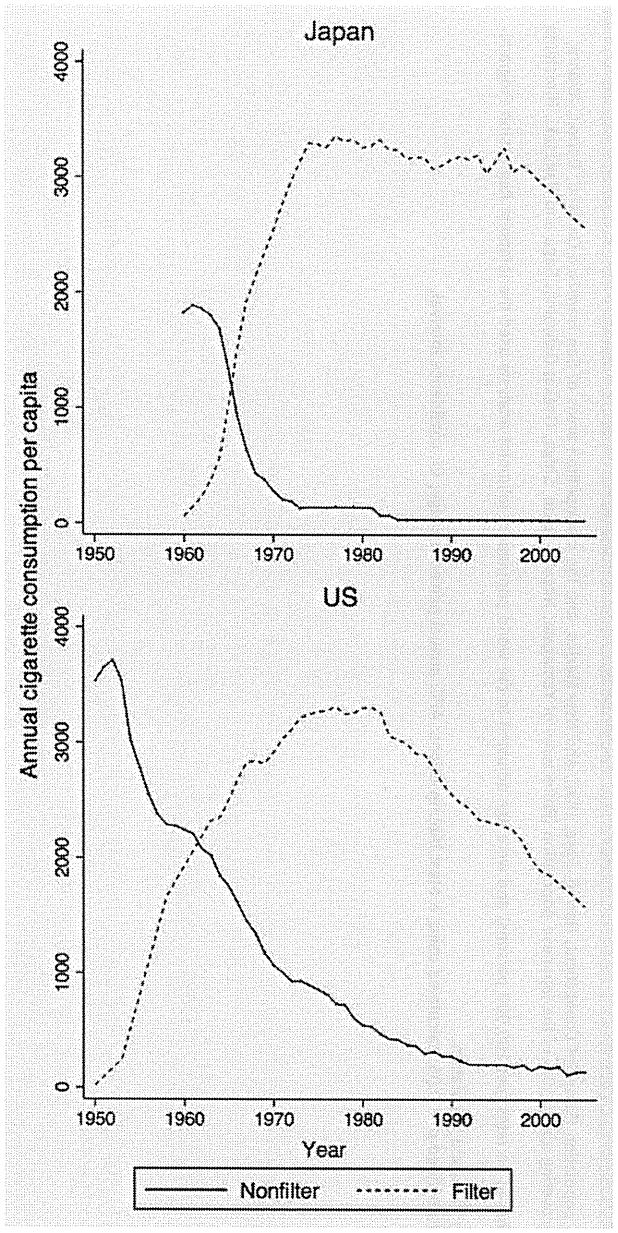

Figure 1. Japan and US nonfilter and filter cigarette consumption. Data for annual consumptions of nonfilter (solid line) and filter (dashed line) cigarettes per capita are presented. The shift from nonfilter to filter cigarettes occurred in the 1960s and the 1950s in Japan and the United States, respectively.

$$Y^{AD}(t) = [Y^{AD}(1), Y^{AD}(2), \ldots, Y^{AD}(T-1)]$$
$$Y^{AD}(t^+) = [Y^{AD}(2), Y^{AD}(3), \ldots, Y^{AD}(T)]$$

Likewise, we let $Y^{SQ}(t)$ represent the ASR (per 100,000 person-years) of SQ at time t and $Y^{SQ}(t^+)$ represent the ASR of SQ at one time point ahead of time t. Additionally, we let

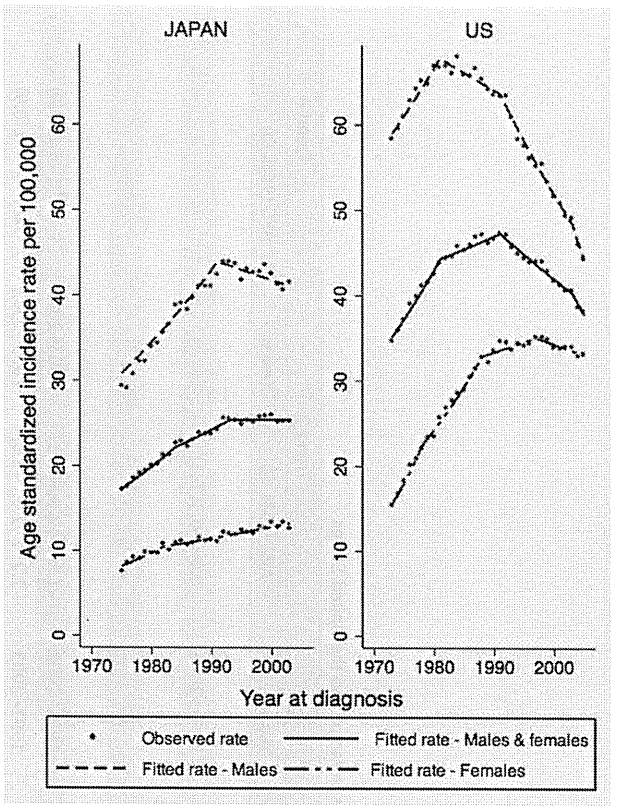

Figure 2. Joinpoint analysis of the overall age-standardized incidence rates (ASR) of lung cancer among individuals in Japan and the United States.

$X(t^+ - \tau)$ represent the nonfilter or filter cigarette consumption at time $t^+ - \tau$, where τ is the appropriate time lag. Thus, for each subpopulation, we have the following models:

$$Y^{SQ}(t^+) = \beta_0^{SQ} + \beta_1^{SQ} Y^{SQ}(t) + \beta_2^{SQ} X(t^+ - \tau) + \varepsilon^{SQ} \quad (1)$$
$$Y^{AD}(t^+) = \beta_0^{AD} + \beta_1^{AD} Y^{AD}(t) + \beta_2^{AD} X(t^+ - \tau) + \varepsilon^{AD} \quad (2)$$

We set τ from 5 to 30 years according to the epidemiological evidence: in this regard, because the incidence of lung cancer does not appear to be lower among ex-smokers who quit smoking within 5 years than current smokers,[30,31] the sum of the induction period and latent period of lung cancer caused by tobacco smoking is likely longer than 5 years.

We then examined the adjusted R^2 in the model with different time lags τ among subpopulations and cigarette designs to find the best fitting models (1) and (2) for nonfilter and filter cigarettes among Japanese and Americans. R^2 value was interpreted to mean that for every unit increase in annual nonfilter or filter consumption per capita, we expect a β_2 point increase in the ASR of AD or SQ, holding all other variables constant.