Table 1. Incidence, completeness of reporting and accuracy of diagnosis in Japan according to sex and primary site, 2003

Primary sites	ICD-10th	Number of incidence	Crude rate[a]	Age-standardized rate[a]		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Male								
All sites (incl. CIS)	C00–C96, D00–D09	372 374	597.7	288.0	409.8	16.5	1.99	74.8
All sites	C00–C96	364 072	584.3	281.4	400.5	16.8	1.95	74.4
Lip, oral cavity and pharynx	C00–C14	7835	12.6	6.7	9.1	11.7	1.94	81.0
Esophagus	C15	13 658	21.9	10.8	15.1	15.5	1.45	78.3
Stomach	C16	73 798	118.4	57.1	81.1	13.8	2.30	82.4
Colon	C18	35 262	56.6	27.0	38.5	11.9	2.74	82.6
Rectum and anus	C19, C20	21 892	35.1	18.0	24.8	11.1	2.68	84.2
Liver	C22	29 126	46.7	22.7	31.9	25.2	1.25	38.4
Gallbladder etc.	C23, C24	8755	14.1	6.1	9.2	27.2	1.20	46.0
Pancreas	C25	12 511	20.1	9.5	13.7	28.7	1.11	37.0
Larynx	C32	3921	6.3	3.1	4.3	7.3	4.24	88.5
Trachea, bronchus and lung	C33, C34	55 928	89.8	39.6	59.5	24.2	1.34	69.8
Skin	C43, C44	3325	5.3	2.6	3.6	7.1	6.08	90.6
Prostate	C61	40 062	64.3	27.3	41.4	9.5	4.76	85.7
Bladder	C67	12 646	20.3	9.3	13.6	11.1	3.40	84.7
Kidney, renal pelvis, ureter etc.	C64–C66, C68	8217	13.2	6.7	9.3	16.0	2.27	74.3
Brain and nervous system	C70–C72	2571	4.1	3.1	3.5	27.5	2.95	65.3
Thyroid	C73	2023	3.2	2.0	2.6	5.9	4.53	90.2
Malignant lymphoma	C81–C85, C96	12 881	20.7	11.6	15.5	17.0	2.65	79.9
Multiple myeloma	C88–C90	2251	3.6	1.6	2.4	30.6	1.20	65.8
All leukaemias	C91–C95	5606	9.0	5.8	7.0	25.3	1.37	82.9
Female								
All sites (incl. CIS)	C00–C96, D00–D09	269 220	412.2	193.9	260.8	17.1	2.20	73.6
All site	C00–C96	255 939	391.9	179.3	242.5	17.9	2.09	72.4

Continued

Table 1. *Continued*

Primary sites	ICD-10th	Number of incidence	Crude rate[a]	Age-standardized rate[a]		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Lip, oral cavity and pharynx	C00–C14	3180	4.9	2.2	2.9	15.0	2.01	76.6
Esophagus	C15	2742	4.2	1.7	2.3	20.0	1.66	69.3
Stomach	C16	36 525	55.9	22.1	31.2	17.9	2.10	78.3
Colon	C18	29 859	45.7	17.4	24.7	15.8	2.30	77.1
Rectum and anus	C19, C20	11 902	18.2	7.9	10.9	13.1	2.43	81.5
Liver	C22	13 535	20.7	7.0	10.4	29.3	1.26	32.8
Gallbladder etc.	C23, C24	10 200	15.6	4.7	7.1	32.3	1.18	40.5
Pancreas	C25	10 371	15.9	5.5	7.9	34.0	1.05	30.1
Larynx	C32	448	0.7	0.3	0.4	3.8	7.34	91.4
Trachea, bronchus and lung	C33, C34	22 817	34.9	12.8	18.4	25.1	1.51	66.5
Skin	C43, C44	4497	6.9	2.5	3.4	9.6	8.52	89.2
Breast (incl. CIS)	C50, D05	45 716	70.0	43.4	56.1	5.6	4.66	90.5
Uterus (incl. CIS)	C53–C55, D06	24 240	37.1	25.5	32.3	7.4	4.57	88.9
Uterus (only invasive)	C53–C55	17 285	26.5	16.1	20.8	10.0	3.26	85.7
Cervix uteri	C53	8674	13.3	8.8	11.3	7.1	3.65	89.4
Corpus uteri	C54	7430	11.4	6.5	8.5	5.6	5.41	89.6
Ovary	C56	7946	12.2	7.2	9.2	17.2	1.88	77.0
Bladder	C67	3713	5.7	1.8	2.7	18.8	2.19	74.5
Kidney, renal pelvis, ureter etc.	C64–C66, C68	4689	7.2	3.0	4.1	18.3	2.38	71.7
Brain and nervous system	C70–C72	2034	3.1	1.8	2.1	24.6	3.10	60.2
Thyroid	C73	6046	9.3	5.6	7.2	7.6	6.17	87.4
Malignant lymphoma	C81–C85, C96	8592	13.2	6.1	8.2	16.8	2.36	80.8
Multiple myeloma	C88–C90	2234	3.4	1.2	1.7	34.4	1.23	62.3
All leukaemias	C91–C95	3951	6.0	3.8	4.3	25.2	1.35	81.0

ICD-10th, International Classification of Disease, 10th Revision; DCO/I, proportion of cases with the death certificate only to incident cases; I/M, number of incidence/number of deaths; MV/I, proportion of microscopically verified cases to incident cases; CIS, carcinoma *in situ*.
[a]Per 100 000 population.

Table 2. Age-specific incidence in Japan according to sex and primary site, 2003

Primary sites	ICD-10th	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96, D00–D09	372 374	401	290	190	416	656	1021	1510	2353	4422	7922	18 940	29 913	44 332	57 691	72 125	63 779	36 791	29 622
All sites	C00–C96	364 072	401	290	190	405	650	1020	1497	2310	4213	7732	18 421	29 054	43 110	56 281	70 601	62 386	36 217	29 294
Lip, oral cavity and pharynx	C00–C14	7835	2	0	2	8	34	39	99	127	117	316	626	924	1180	1342	1220	910	543	346
Esophagus	C15	13 658	0	0	0	0	0	0	0	14	93	317	850	1629	2351	2281	2621	1945	981	576
Stomach	C16	73 798	0	0	0	17	47	70	154	281	878	1741	4439	6714	9286	12 022	14 013	12 042	6472	5622
Colon	C18	35 262	0	3	0	8	18	54	120	204	339	713	1698	2905	4591	5634	7014	5589	3432	2940
Rectum and anus	C19, C20	21 892	0	0	1	8	5	15	83	158	420	709	1582	2564	3380	3828	3652	2925	1445	1117
Liver	C22	29 126	11	2	3	0	19	12	33	82	266	573	1792	2714	4018	5290	6146	4455	2127	1583
Gallbladder etc.	C23, C24	8755	0	0	0	0	0	1	4	23	57	79	294	410	820	1137	1483	1697	1438	1312
Pancreas	C25	12 511	0	0	0	0	14	4	1	41	157	194	727	1081	1666	1880	2247	2119	1365	1015
Larynx	C32	3921	0	0	0	0	19	0	0	6	31	72	229	434	604	713	746	616	304	147
Trachea, bronchus and lung	C33, C34	55 928	0	0	0	1	5	3	68	175	296	820	1944	3549	5091	7296	11 701	11 923	7446	5610
Skin	C43, C44	3325	0	0	3	0	13	42	68	50	46	77	107	148	349	358	572	590	364	538
Prostate	C61	40 062	0	0	0	0	0	0	0	0	9	58	430	1251	3704	6719	9914	9291	4852	3834
Bladder	C67	12 646	7	0	0	10	4	23	32	101	92	229	645	862	1196	1544	2623	2287	1520	1471
Kidney, renal pelvis, ureter etc.	C64–C66, C68	8217	14	5	0	0	26	50	35	70	164	280	648	834	932	1226	1487	1223	760	463
Brain and nervous system	C70–C72	2571	67	111	18	45	85	72	88	84	139	146	230	149	319	313	290	202	105	108
Thyroid	C73	2023	0	3	0	1	34	49	44	126	88	137	245	215	224	188	270	193	117	89
Malignant lymphoma	C81–C85, C96	12 881	12	38	76	96	113	123	175	307	528	680	791	1184	1415	2002	1705	1680	1107	849
Multiple myeloma	C88–C90	2251	0	0	0	0	0	0	4	8	10	33	88	184	240	344	349	450	304	237
All leukaemias	C91–C95	5606	138	94	50	77	73	162	142	81	200	211	319	459	518	795	844	699	390	354
Female																				
All sites (incl. CIS)	C00–C96, D00–D09	269 220	397	219	202	332	821	1909	4996	6722	9210	13 421	19 959	22 867	25 392	28 998	34 319	34 339	29 314	35 803
All site	C00–C96	255 939	397	219	202	315	612	1301	3433	5118	7788	12 156	18 900	21 931	24 287	28 108	33 190	33 601	28 888	35 493

Continued

Table 2. *Continued*

Primary sites	ICD-10th	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Lip, oral cavity and pharynx	C00–C14	3180	0	0	2	18	42	23	33	56	74	100	219	248	332	370	363	468	385	447
Esophagus	C15	2742	0	0	0	0	0	0	1	14	13	123	140	243	250	378	392	335	323	530
Stomach	C16	36 525	0	0	0	2	17	70	234	418	783	1101	1851	2752	3010	4149	5208	5706	4850	6374
Colon	C18	29 859	0	0	0	2	11	36	121	214	346	634	1480	2021	2853	3709	4420	4681	4120	5211
Rectum and anus	C19, C20	11 902	0	0	0	0	0	12	62	120	239	414	852	1162	1444	1511	1695	1602	1264	1525
Liver	C22	13 535	1	0	11	0	0	12	13	10	36	68	246	575	946	1989	2754	2677	2228	1969
Gallbladder etc.	C23–C24	10 200	0	0	0	4	0	0	6	4	44	108	229	337	609	894	1274	1758	2086	2847
Pancreas	C25	10 371	0	0	0	0	0	6	6	33	69	197	394	551	860	1080	1583	1619	1637	2336
Larynx	C32	448	0	0	2	0	0	0	7	2	0	38	2	37	59	83	47	92	39	40
Trachea, bronchus and lung	C33, C34	22 817	5	0	0	5	0	36	35	126	190	417	955	1525	2005	2774	3558	3831	3272	4083
Skin	C43, C44	4497	10	0	10	7	15	13	24	98	56	90	137	168	250	512	441	561	734	1371
Breast (incl. CIS)	C50, D05	45 716	0	0	0	0	29	222	934	1986	3547	5722	6882	5832	5657	4570	3724	3098	2009	1504
Uterus (incl. CIS)	C53–C55, D06	24 240	0	0	0	8	268	835	2479	2529	2299	2167	2432	2876	2030	1557	1609	1360	899	892
Uterus (only invasive)	C53–C55	17 285	0	0	0	2	77	259	988	1114	1146	1408	1978	2557	1791	1377	1531	1291	879	887
Cervix uteri	C53	8674	0	0	0	2	74	223	791	889	870	832	753	879	701	613	600	552	443	452
Corpus uteri	C54	7430	0	0	0	0	3	29	193	203	245	520	1148	1577	997	661	817	606	248	183
Ovary	C56	7946	0	0	20	40	47	150	182	258	412	683	1183	1183	801	695	761	536	488	507
Bladder	C67	3713	0	0	0	0	0	0	2	14	10	42	78	136	197	403	608	659	684	880
Kidney, renal pelvis, ureter etc.	C64–C66, C68	4689	17	8	8	4	2	3	26	25	111	95	348	345	441	559	693	737	593	674
Brain and nervous system	C70–C72	2034	53	27	27	21	9	28	106	43	46	54	79	156	233	223	217	208	225	279
Thyroid	C73	6046	0	0	11	21	89	133	233	325	339	448	715	716	723	591	704	443	225	330
Malignant lymphoma	C81–C85, C96	8592	19	33	13	45	81	86	117	113	217	282	592	637	808	918	1471	1248	969	943
Multiple myeloma	C88–C90	2234	0	0	0	0	0	0	9	11	33	20	81	84	200	215	375	378	368	460
All leukaemias	C91–C95	3951	114	98	32	68	81	44	108	96	97	147	289	321	319	411	483	476	378	389

Table 3. Age-specific incidence rate per 100 000 population in Japan according to sex and primary site, 2003

Primary sites	ICD-10th	All ages	Age group (years)																
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96, D00–D09	597.7	13.5	9.5	6.1	11.6	16.3	22.1	30.8	55.2	111.9	199.2	379.7	661.4	1100.6	1643.2	2488.8	3093.1	3541.0	3954.9
All sites	C00–C96	584.3	13.5	9.5	6.1	11.3	16.2	22.0	30.6	54.2	106.6	194.5	369.3	642.4	1070.3	1603.0	2436.2	3025.5	3485.8	3911.1
Lip, oral cavity and pharynx	C00–C14	12.6	0.1	0.0	0.1	0.2	0.8	0.8	2.0	3.0	3.0	7.9	12.6	20.4	29.3	38.2	42.1	44.1	52.3	46.2
Esophagus	C15	21.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	2.4	8.0	17.0	36.0	58.4	65.0	90.4	94.3	94.4	76.9
Stomach	C16	118.4	0.0	0.0	0.0	0.5	1.2	1.5	3.1	6.6	22.2	43.8	89.0	148.4	230.5	342.4	483.5	584.0	622.9	750.6
Colon	C18	56.6	0.0	0.1	0.0	0.2	0.4	1.2	2.5	4.8	8.6	17.9	34.0	64.2	114.0	160.5	242.0	271.0	330.3	392.5
Rectum and anus	C19, C20	35.1	0.0	0.0	0.0	0.2	0.1	0.3	1.7	3.7	10.6	17.8	31.7	56.7	83.9	109.0	126.0	141.9	139.1	149.1
Liver	C22	46.7	0.4	0.1	0.1	0.0	0.5	0.3	0.7	1.9	6.7	14.4	35.9	60.0	99.8	150.7	212.1	216.1	204.7	211.3
Gallbladder etc.	C23, C24	14.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.5	1.4	2.0	5.9	9.1	20.4	32.4	51.2	82.3	138.4	175.2
Pancreas	C25	20.1	0.0	0.0	0.0	0.0	0.3	0.1	0.0	1.0	4.0	4.9	14.6	23.9	41.4	53.5	77.5	102.8	131.4	135.5
Larynx	C32	6.3	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.1	0.8	1.8	4.6	9.6	15.0	20.3	25.7	29.9	29.3	19.6
Trachea, bronchus and lung	C33, C34	89.8	0.0	0.0	0.0	0.0	0.1	0.1	1.4	4.1	7.5	20.6	39.0	78.5	126.4	207.8	403.8	578.2	716.7	749.0
Skin	C43, C44	5.3	0.0	0.0	0.1	0.0	0.3	0.9	1.4	1.2	1.2	1.9	2.1	3.3	8.7	10.2	19.7	28.6	35.0	71.8
Prostate	C61	64.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	1.5	8.6	27.7	92.0	191.4	342.1	450.6	467.0	511.9
Bladder	C67	20.3	0.2	0.0	0.0	0.3	0.1	0.5	0.7	2.4	2.3	5.8	12.9	19.1	29.7	44.0	90.5	110.9	146.3	196.4
Kidney, renal pelvis, ureter etc.	C64–C66, C68	13.2	0.5	0.2	0.0	0.0	0.6	1.1	0.7	1.6	4.1	7.0	13.0	18.4	23.1	34.9	51.3	59.3	73.1	61.8
Brain and nervous system	C70–C72	4.1	2.3	3.6	0.6	1.3	2.1	1.6	1.8	2.0	3.5	3.7	4.6	3.3	7.9	8.9	10.0	9.8	10.1	14.4
Thyroid	C73	3.2	0.0	0.1	0.0	0.0	0.8	1.1	0.9	3.0	2.2	3.4	4.9	4.8	5.6	5.4	9.3	9.4	11.3	11.9
Malignant lymphoma	C81–C85, C96	20.7	0.4	1.2	2.4	2.7	2.8	2.7	3.6	7.2	13.4	17.1	15.9	26.2	35.1	57.0	58.8	81.5	106.5	113.4
Multiple myeloma	C88–C90	3.6	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.8	1.8	4.1	6.0	9.8	12.0	21.8	29.3	31.6
All leukaemias	C91–C95	9.0	4.6	3.1	1.6	2.1	1.8	3.5	2.9	1.9	5.1	5.3	6.4	10.1	12.9	22.6	29.1	33.9	37.5	47.3
Female																				
All sites (incl. CIS)	C00–C96, D00–D09	412.2	14.1	7.5	6.8	9.7	21.4	42.6	104.0	159.9	235.7	339.5	397.2	492.1	594.0	744.7	991.9	1211.3	1479.0	1904.4
All site	C00–C96	391.9	14.1	7.5	6.8	9.2	16.0	29.1	71.5	121.8	199.3	307.5	376.1	471.9	568.1	721.8	959.2	1185.2	1457.5	1887.9

Continued

Table 3. *Continued*

Primary sites	ICD-10th	All ages	Age group (years)																
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Lip, oral cavity and pharynx	C00–C14	4.9	0.0	0.0	0.1	0.5	1.1	0.5	0.7	1.3	1.9	2.5	4.4	5.3	7.8	9.5	10.5	16.5	19.4	23.8
Esophagus	C15	4.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.3	3.1	2.8	5.2	5.8	9.7	11.3	11.8	16.3	28.2
Stomach	C16	55.9	0.0	0.0	0.0	0.1	0.4	1.6	4.9	9.9	20.0	27.9	36.8	59.2	70.4	106.5	150.5	201.3	244.7	339.0
Colon	C18	45.7	0.0	0.0	0.0	0.1	0.3	0.8	2.5	5.1	8.9	16.0	29.5	43.5	66.7	95.2	127.7	165.1	207.9	277.2
Rectum and anus	C19, C20	18.2	0.0	0.0	0.0	0.0	0.0	0.3	1.3	2.9	6.1	10.5	17.0	25.0	33.8	38.8	49.0	56.5	63.8	81.1
Liver	C22	20.7	0.0	0.0	0.4	0.0	0.0	0.3	0.3	0.2	0.9	1.7	4.9	12.4	22.1	51.1	79.6	94.4	112.4	104.7
Gallbladder etc.	C23, C24	15.6	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.1	1.1	2.7	4.6	7.3	14.2	23.0	36.8	62.0	105.2	151.4
Pancreas	C25	15.9	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.8	1.8	5.0	7.8	11.9	20.1	27.7	45.8	57.1	82.6	124.3
Larynx	C32	0.7	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	1.0	0.0	0.8	1.4	2.1	1.4	3.2	2.0	2.1
Trachea, bronchus and lung	C33, C34	34.9	0.2	0.0	0.0	0.1	0.0	0.8	0.7	3.0	4.9	10.5	19.0	32.8	46.9	71.2	102.8	135.1	165.1	217.2
Skin	C43, C44	6.9	0.4	0.0	0.3	0.2	0.4	0.3	0.5	2.3	1.4	2.3	2.7	3.6	5.8	13.1	12.7	19.8	37.0	72.9
Breast (incl. CIS)	C50, D05	70.0	0.0	0.0	0.0	0.0	0.8	5.0	19.4	47.3	90.8	144.8	137.0	125.5	132.3	117.4	107.6	109.3	101.4	80.0
Uterus (incl. CIS)	C53–C55, D06	37.1	0.0	0.0	0.0	0.2	7.0	18.7	51.6	60.2	58.8	54.8	48.4	61.9	47.5	40.0	46.5	48.0	45.4	47.4
Uterus (only invasive)	C53–C55	26.5	0.0	0.0	0.0	0.1	2.0	5.8	20.6	26.5	29.3	35.6	39.4	55.0	41.9	35.4	44.2	45.5	44.3	47.2
Cervix uteri	C53	13.3	0.0	0.0	0.0	0.1	1.9	5.0	16.5	21.2	22.3	21.0	15.0	18.9	16.4	15.7	17.3	19.5	22.4	24.0
Corpus uteri	C54	11.4	0.0	0.0	0.0	0.0	0.1	0.6	4.0	4.8	6.3	13.2	22.8	33.9	23.3	17.0	23.6	21.4	12.5	9.7
Ovary	C56	12.2	0.0	0.0	0.7	1.2	1.2	3.4	3.8	6.1	10.5	17.3	23.5	25.5	18.7	17.8	22.0	18.9	24.6	27.0
Bladder	C67	5.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.3	1.1	1.6	2.9	4.6	10.3	17.6	23.2	34.5	46.8
Kidney, renal pelvis, ureter etc.	C64–C66, C68	7.2	0.6	0.3	0.3	0.1	0.1	0.1	0.5	0.6	2.8	2.4	6.9	7.4	10.3	14.4	20.0	26.0	29.9	35.9
Brain and nervous system	C70–C72	3.1	1.9	0.9	0.9	0.6	0.2	0.6	2.2	1.0	1.2	1.4	1.6	3.4	5.5	5.7	6.3	7.3	11.4	14.8
Thyroid	C73	9.3	0.0	0.0	0.4	0.6	2.3	3.0	4.9	7.7	8.7	11.3	14.2	15.4	16.9	15.2	20.3	15.6	11.4	17.6
Malignant lymphoma	C81–C85, C96	13.2	0.7	1.1	0.4	1.3	2.1	1.9	2.4	2.7	5.6	7.1	11.8	13.7	18.9	23.6	42.5	44.0	48.9	50.2
Multiple myeloma	C88–C90	3.4	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.8	0.5	1.6	1.8	4.7	5.5	10.8	13.3	18.6	24.5
All leukaemias	C91–C95	6.0	4.0	3.4	1.1	2.0	2.1	1.0	2.2	2.3	2.5	3.7	5.8	6.9	7.5	10.6	14.0	16.8	19.1	20.7

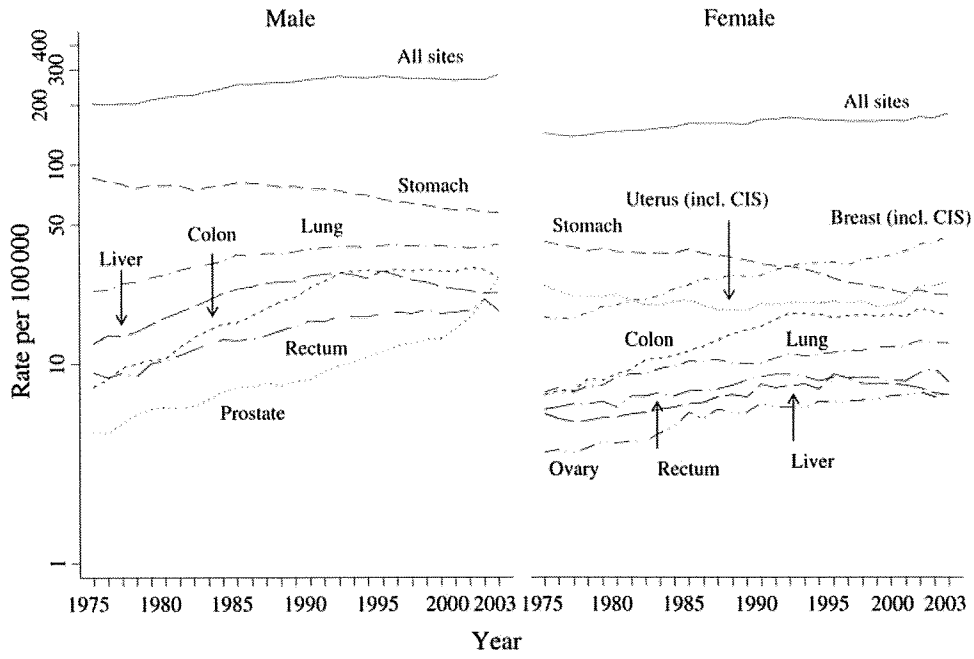

Figure 1. Trends of age-standardized cancer incidence rates for five major sites and specific sites for each sex (standard population: the world population). CIS, carcinoma *in situ*.

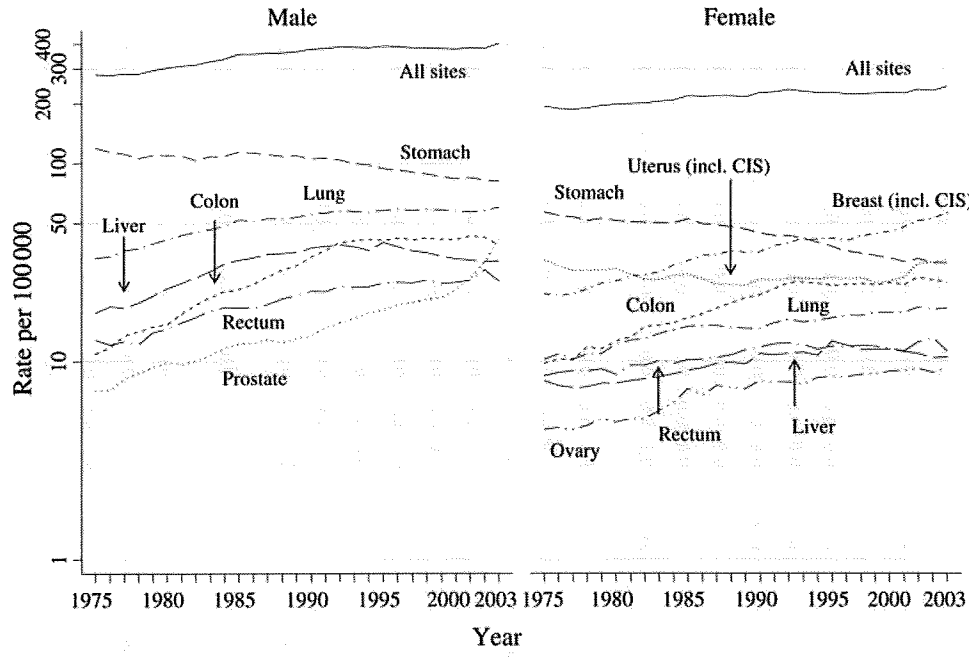

Figure 2. Trends of age-standardized cancer incidence rates for five major sites and specific sites for each sex (standard population: 1985 Japanese model population)

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Conflict of interest statement

None declared.

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Statistical Data

Secular Trends in Neuroblastoma Mortality Before and After the Cessation of National Mass Screening in Japan

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ABSTRACT

Background: In 2003, the Japanese government halted the national mass screening program for neuroblastoma (NB), which had been running since the mid-1980s. It is not known whether the NB mortality rate subsequently increased or decreased.

Methods: Utilizing vital statistics data from 1980 through 2006, we analyzed the secular trends in NB mortality by using cancer of the adrenal gland as a surrogate. We examined the validity of this substitution by comparing the results with data from death certificates. Using a joinpoint regression model, we examined the trends in age-specific mortality rates by calendar year and cumulative mortality rates by birth year. The cumulative mortality rate was analyzed for age under 1 or 2 years for infants born after the cessation of the mass screening program.

Results: The number of deaths from cancer of the adrenal gland was closely correlated with the number of deaths from NB. Significant decreases in the mortality rate were observed from 1980 through 2006 by calendar year for those aged under 1 year, 1 to 4 years, and 5 to 9 years. The cumulative mortality rates by birth year also significantly decreased from the 1980 birth cohort. Although the cumulative mortality rates under the age of 2 appear to have increased after the 2003 birth cohort, the change was not statistically significant.

Conclusions: No significant increase in the NB mortality rate was detected after the cessation of the mass screening program in Japan. However, continuous monitoring is still needed to fully evaluate this health policy decision.

Key words: mass screening; mortality; neuroblastoma

INTRODUCTION

Studies conducted in Germany and in the province of Quebec, Canada showed that screening infants for neuroblastoma (NB) did not result in lower NB mortality.[1,2] Although a large number of epidemiological studies have been conducted in Japan, the findings regarding the effectiveness of NB screening have been inconsistent.[3-8] Clinical studies have reported that a considerable fraction of NB patients whose disease was detected by mass screening had favorable outcomes, which suggests the possibility of over-diagnosis.[9-14] In 2003, the Japanese government halted the national mass screening program—which had been in place since the mid-1980s for infants aged 6 months—because of the potential for over-diagnosis and the lack of evidence for its effectiveness in reducing NB mortality.[15] Most local municipalities in Japan stopped the program during the following year. It is not known whether the NB mortality rate increased or decreased after this national change. Therefore, we analyzed secular trends in NB mortality in Japan before and after the cessation of the national mass screening program.

METHODS

As is the case in most countries, the Japanese government collects vital statistics data, in which the causes of death are classified according to the International Classification of Diseases (ICD). NB mortality cannot be directly identified in this classification because deaths attributable to NB are coded based on the organ affected, and are grouped together with deaths due to other cancers affecting the same organ.[16] Two different methods have been adopted to address this issue. The first approach (hereafter referred to as method-1) is to extract the data on deaths due to cancer of the candidate sites, inspect the relevant individual death certificates, and identify NB

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deaths based on the description of the cause of death or the histological type.[16] The second approach (hereafter referred to as method-2) is to use deaths from cancer of the adrenal gland as a surrogate index.[17]

Method-2 is less accurate than method-1 because NB can occur at sites other than the adrenal gland, and because other histological types of cancer can occur in this organ. Method-1 requires official permission for the use of unpublished vital statistics data, whereas method-2 uses only published vital statistics data, at least for the years after the ICD version 10 was applied.

The present study used method-1 to analyze data from the year 2006. We obtained individual mortality data from the vital statistics, with official permission, according to the following criteria: year of death = 2006; age at death = 0 to 14 years; cause of death (ICD) = malignant neoplasms of mediastinum (ICD-9 164.2, 164.3, 164.9; ICD-10 C38.1, C38.2, C38.8), connective and soft tissue (ICD-9 171.0, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9), peripheral nerves and autonomic nervous system (ICD-10 C47.0, C47.1, C47.2, C47.3, C47.4, C47.5, C47.6, C47.8, C47.9), retroperitoneum and peritoneum (ICD-9 158.0, 158.8, 158.9; ICD-10 C48.0, C48.1, C48.2, C48.8), adrenal gland (ICD-9 194.0; ICD-10 C74.0, C74.1, C74.9), or other/ill-defined sites (ICD-9 195.0, 195.1, 195.2, 195.3, 195.4, 195.5, 195.8; ICD-10 C76.0, C76.1, C76.2, C76.3, C76.4, C76.5, C76.7, C76.8). Then, we inspected individual death certificates for the extracted data, and identified NB deaths based on the recorded causes of death or histological types. This process was performed by one of the authors (K. K.) and was confirmed by another author (K. Y., a pediatrician). For the data from 1980 through 2001, we obtained data on NB deaths from previous reports[16,18] that had used a method identical to the present method-1 for extracting and identifying NB deaths. Thus, in the present study, data on the number of NB deaths based on method-1 were available for the years from 1980 through 2001, and for the year 2006. We could not apply method-1 to the time period from 2002 through 2005 because a previous application to use death certificates for research had been rejected,[19] and the document storage period had expired by the time of our application.

For method-2, we calculated the age-specific number of deaths from adrenal gland cancer, based on officially obtained individual mortality data from the vital statistics. The criteria for data collection were as follows: year of death = 1980 to 2006; age at death = 0 to 14 years; cause of death (ICD) = malignant neoplasms of the adrenal gland (ICD-9 194.0; ICD-10 C74.0, C74.1, C74.9).

To validate method-2, we calculated the Pearson correlation coefficient between the number of NB deaths and the number of adrenal gland cancer deaths, using data from 1980 through 2001, and from 2006.

We obtained population data from the published vital statistics and calculated the age-specific mortality rate by calendar year for cancer of the adrenal gland. For the age-specific mortality rate, age was stratified into the following 4 groups: 0 years, 1 to 4 years, 5 to 9 years, and 10 to 14 years. We also calculated the cumulative mortality rate by birth year, by summing the 1-year age-specific mortality rate according to each birth year.[20] The number of deaths according to each age and each birth year was used as the numerator for the 1-year age-specific mortality rate. The denominator was the number of births (for age younger than 1 year) or the population for each age (for 1 year or older). The most recent birth year that we analyzed was 2005 for the cumulative mortality rate under 1 year of age, 2004 for 2 years of age, 2003 for 3 years of age, and 2002 for 4 years of age.

For the statistical analysis, we used a joinpoint regression model,[21] implemented in the Joinpoint Regression Program (version 3.3.1) developed by the US National Cancer Institute. This method describes changes in data trends by connecting several different line segments on a log scale at joinpoints. The analysis starts with the minimum number of joinpoints (that is, 0, representing a straight line) and tests for the model fit with a maximum number of joinpoints. A Monte Carlo permutation method is used for tests of significance. In addition, the annual percent change (APC) for each line segment and the corresponding 95% confidence interval (CI) were estimated. In the statistical analysis, the number of deaths was assumed to follow a Poisson distribution. The maximum number of joinpoints was set at 3, the minimum number of observations from a joinpoint to either end of the data was set at 2 (including the end and joinpoint), and the minimum number of observations between 2 joinpoints was set at 4 (including the joinpoints).

RESULTS

Table 1 shows the secular trends in the age-specific number of deaths, according to the 2 methods. Although method-1 tended to yield slightly larger numbers than method-2, the secular trends were similar. The Pearson correlation coefficients between the annual numbers of deaths according to the 2 methods were close to 1 (1.00 for 0–14 years, 0.96 for <1 year, 0.98 for 1–4 years, 0.96 for 5–9 years, and 0.73 for 10–14 years; all 5 correlation coefficients were significantly different from 0 [number of data points = 23, $P < 0.001$]). In 2006, 45 deaths from cancer of the adrenal gland were observed, one of which was non-NB (malignant pheochromocytoma). In comparison, 45 NB deaths were identified by the inspection of death certificates from 2006, of which 1 case occurred at a site other than the adrenal gland (retroperitoneum).

Table 2 shows the results of the joinpoint analysis. Significant decreases in the age-specific mortality rate were observed from 1980 through 2006 by calendar year for those aged less than 1 year, 1 to 4 years, and 5 to 9 years. The cumulative mortality rates by birth year also significantly

Table 1. Numbers of deaths due to neuroblastoma (NB) and adrenal gland cancer from 1980 to 2006

Calendar year[a]	1) Number of deaths from NB identified by individual death certificates[b]					Calendar year[a]	2) Number of deaths from cancer of the adrenal gland[c]				
	0–14 years	<1 year	1–4 years	5–9 years	10–14 years		0–14 years	<1 year	1–4 years	5–9 years	10–14 years
1980–1982	381	28	209	119	25	1980–1982	338	22	194	103	19
1983–1985	329	31	174	102	22	1983–1985	294	28	150	94	22
1986–1988	280	15	132	101	32	1986–1988	249	15	119	88	27
1989–1991	221	10	109	81	21	1989–1991	207	8	106	74	19
1992–1994	178	11	72	77	18	1992–1994	171	8	68	76	19
1995–1997	185	16	67	78	24	1995–1997	181	14	65	79	23
1998–2000	147	9	55	59	24	1998–2000	139	8	53	56	22
2001–2003	(N.A.)	(N.A.)	(N.A.)	(N.A.)	(N.A.)	2001–2003	118	6	49	42	21
2004–2006	(N.A.)	(N.A.)	(N.A.)	(N.A.)	(N.A.)	2004–2006	123	7	55	45	16
2001, 2006	86	4	38	29	15	2001, 2006	84	4	38	27	15

[a]Consecutive 3-year periods from 1980 to 2006 were pooled. Two years (2001 and 2006) were also pooled.
[b]The numbers of NB deaths between 1980 and 2001 were obtained from previous reports (Hanawa et al, 1990 and Hayashi et al, 2004), and the numbers of NB deaths in 2006 were counted by one of the authors (K. K.).
[c]Deaths due to cancer of the adrenal gland were defined by codes in the ICD: 194.0 for 1980–1994, C74.0, C74.1, and C74.9 for 1995–2006.
N.A.: Not available

Table 2. Results of joinpoint regression analysis for the secular trends in adrenal gland cancer mortality

A) Age-specific mortality rate, by calendar year

	Number of joinpoints	Line segment		Annual % change	95% confidence interval	
		Start	End		Lower	Upper
0 year old	0	1980	2006	−3.6[a]	−5.8	−1.4
1–4 years old	0	1980	2006	−4.1[a]	−5.0	−3.3
5–9 years old	0	1980	2006	−1.1[a]	−2.0	−0.1
10–14 years old	0	1980	2006	1.4	−0.4	3.2

B) Cumulative mortality rate, by birth year[b]

	Number of joinpoints	Line segment		Annual % change	95% confidence interval	
		Start	End		Lower	Upper
<1 year old	0	1980	2005	−3.0[a]	−5.4	−0.5
<2 years old	0	1980	2004	−3.4[a]	−5.3	−1.4
<3 years old	0	1980	2003	−4.3[a]	−5.7	−2.8
<4 years old	0	1980	2002	−4.1[a]	−5.2	−2.9

[a]Annual % change is statistically significant from zero.
[b]The analyzed most recent birth year was 2005 for age <1 year, 2004 for <2 years, 2003 for age <3 years, and 2002 for age <4 years.

decreased from the 1980 birth cohort. Figure 1 shows the trends in the age-specific mortality rate. The mortality rates for 1 to 4 years of age in 2004 and 2006 were high, but no significant increase or joinpoint was detected around this time. Figure 2 shows the trends in the cumulative mortality rate. The cumulative mortality rate under the age of 2 for the 2004 birth cohort was considerably higher than the cumulative mortality rate for the past several birth cohorts. However, this change was not detected as a significant joinpoint.

DISCUSSION

We examined the secular trends in the mortality rate for NB, using mortality for cancer of the adrenal gland as a surrogate index, and found no significant increase before or after the cessation of the Japanese national mass screening program. We confirmed the validity of this surrogate method by examining the correlation between the numbers of deaths from the 2 cancers. Nationwide mass screening had previously been performed for infants aged 6 months, and the participation level was high (ranging from 84% to 90% in the period from 1990 through 2001). Because the most recent year of death that we analyzed was 2006, any increase in the age-specific mortality rate associated with the cessation of mass screening in 2003 would have been expected to occur among children aged 1 to 4 years. However, we did not observe any significant increase or joinpoint in the mortality rate among this age group around this time. It is possible that the time elapsed since the cessation of mass screening was still too short to detect any increase in mortality for this age group, which

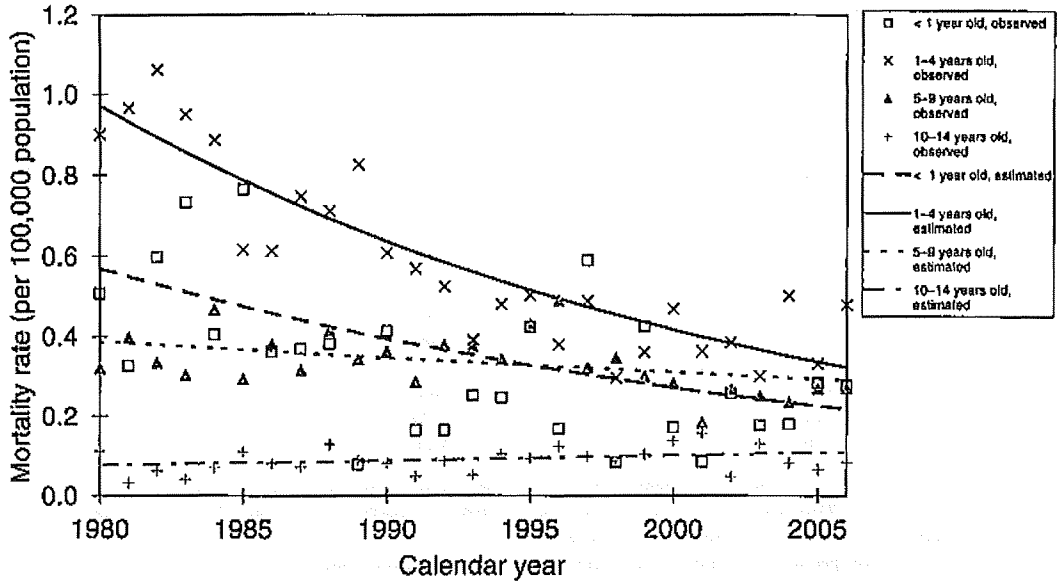

Figure 1. Annual trends in age-specific mortality rate for cancer of the adrenal gland, by calendar year

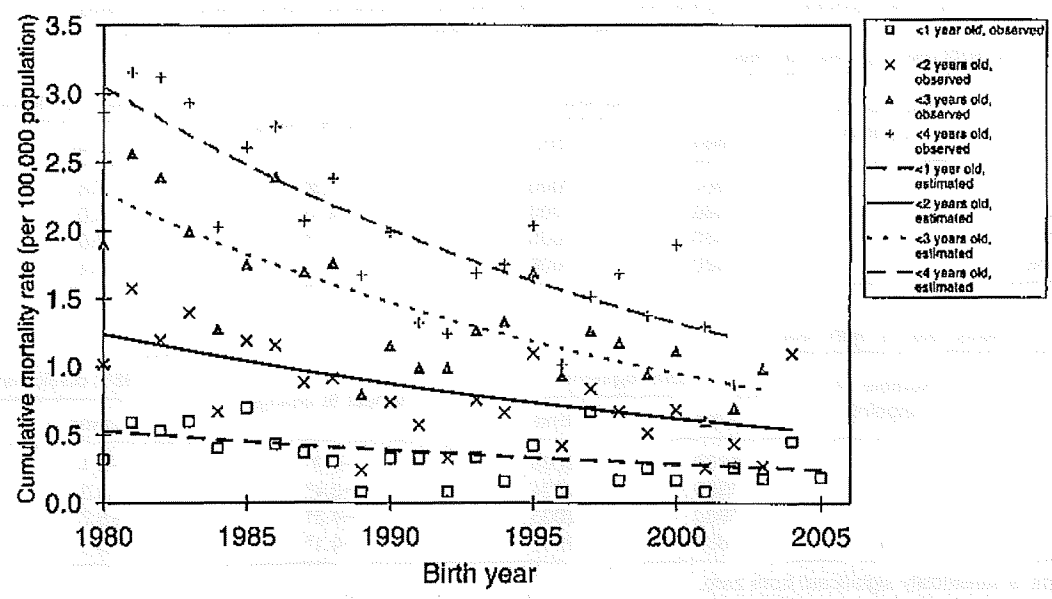

Figure 2. Annual trends in cumulative mortality rate for cancer of the adrenal gland, by birth year. Note: The most recent analyzed birth year was 2005 for age <1 year, 2004 for age <2 years, 2003 for age <3 years, and 2002 for age <4 years

included both screened and unscreened individuals, even at the end of our observation period.

The cumulative mortality rate according to birth year was a more direct index to examine the effect of the cessation of the mass screening program. It decreased significantly throughout the observed birth years, and the birth year 2003 was not detected as a significant joinpoint. However, these results should be interpreted with caution because the analyzed range of birth years and ages was limited after the cessation of the mass screening program. In consideration of the time from diagnosis to death, we should assume that any increase in the mortality rate for infants born after the cessation could occur later than the end of our observation period.

There are several Japanese municipalities that continued mass screening for NB after 2003. However, the number of such municipalities is very small, and our results did not change when we excluded the prefectures to which these municipalities belong (ie, Hokkaido, Kanagawa, Niigata, Shizuoka, Kyoto, Osaka, and Kumamoto).

We found a high correlation between the number of deaths from NB and the number of deaths from adrenal gland cancer, with the former slightly and consistently higher than the latter (Table 1). This tendency was in agreement with a previous report, in which approximately 90% of NB deaths were attributable to cancer of the adrenal gland, and almost all of the cancers that occurred at this site were NB.[16] One death due

to non-NB cancer in the adrenal gland was included among the data for 2006, but this was considered to be an unusual case.

The effect of the cessation of the mass screening program for NB should be verified by monitoring the trend in incidence.[22] Studies have reported the trends in NB incidence and mortality before and after the start of a national mass screening program, based on data from a population-based cancer registry.[3,5] Additional similar studies need to be conducted, and should include a sufficient observation period after the cessation of the program.

In conclusion, no significant increase in the NB mortality rate was detected after the cessation of the national mass screening program in Japan. However, continuous monitoring is still needed to evaluate further this health policy decision.

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総　説

がん対策としてのがん検診と有効性評価

Cancer screening for cancer control and efficacy evaluation

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National Cancer Center

Abstract

One of the primary goals in the basic plan to promote cancer control program in June 2007 is 20 % reduction in cancer mortality by 2015. Cancer screening is one of the important methods to achieve this goal. Cancer screening in this context is considered as "population-based" or "policy-based" screening and should be separated from "individual-based" or "opportunistic" screening which is used for reducing cancer mortality risk at individual level. In population-based screening, screening method should be strictly limited to those which have sufficient scientific evidences in terms of mortality reduction and those which can be judged that the level of benefits exceeds the level of harms for majority of the target people.

Cancer screening guidelines, which provide the information for the screening efficacy, should be developed by the standardized procedure with objective judgment criteria. In order to do this, it is also important to provide high-quality evidences for the screening efficacy, hopefully using randomized controlled trial, which is global standard method for screening evaluation study. On the other hand, observational studies may be appropriate in some situations, such as when the screening method has been already widespread.

Keywords: cancer screening, cancer control, guideline

がん対策推進基本計画

「がん対策推進基本計画」では、全体目標として「がんによる死亡者の減少」と「すべてのがん患者及びその家族の苦痛の軽減並びに療養生活の質の維持向上」の2点が取り上げられた。「がんによる死亡者の減少」ついては、さらに具体的に、「がんの年齢調整死亡率（75歳未満）を今後10年で20％減少」させることが明記された。この根拠としては、1995～2005年のがんの年齢調整死亡率が年間1％減少し続けており、今後10年間この傾向が続くとすると10％の減少が期待できることに加え、がん対策を進めることで、さらに10％の減少を上乗せできるとの国立がんセンターによる試算結果がある。このがん対策の具体的内容としては、たばこ対策、がん検診、がん診療の均てん化の3つを想定しており、がん検診については、今後2005年から2015年までの10年間で受診率を50％に増加させることができれば、2015年におけるがん死亡率を3.9％減少させることができると推定されている。がん検診は、がん死亡を減少させるための有効な手段の1つとして認識されている。

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がん検診アセスメントとがん検診実施マネジメント

がん検診を実施することで、当該がんの死亡率を減少させるためには、「有効な検診を、正しく行う」必要がある。「有効な検診」とは、死亡率減少効果を示す科学的証拠があると判断させる検診のことであり、こうした判断をする過程を「がん検診アセスメント」と呼ぶ。具体的には、検診有効性評価ガイドラインを作成し、更新する作業に相当する。一方、「正しく行う」とは、質の高い検診を多くの対象者に受診していただくことであり、この過程を「がん検診実施マネジメント」と呼ぶ。具体的には、精度管理と受診率向上施策を実施することである。

がん検診アセスメント

わが国におけるがん検診アセスメントは、1998年の「がん検診の有効性評価に関する研究班」報告書（主任研究者　久道茂）に引き続いて、2001年「新たながん検診手法の有効性評価」報告書において実施されてきた。これを引き継いで、厚生労働省がん研究助成金「がん検診の適切な方法とその評価法の確立に関する研究」班（主任研究者　平成19年より濱島ちさと、平成15～18年は祖父江友孝）において、標準的な作成手順を定めたうえで、主要ながん検診に適用してガイドラインの更新が行われている。これは、上記久道班報告書の中で、「がん検診に関する研究は、国際的に急速な勢いで発展しており、新たな知見が次々と報告される現状にある。……最新の研究知見を踏まえて定期的・継続的に実施することのできる常設的な機関をわが国に設置することも今後の検討課題の1つと考えられる」との指摘に基づいている。

ガイドライン作成手順の概要

US Preventive Services Task Force（USPSTF）などの諸外国のガイドライン作成・更新の方法論を参考として、「有効性評価に基づくがん検診ガイドライン作成手順」を濱島／祖父江班にて定式化した[1]。ガイドライン作成手順は、

① 対象となるがん検診の選定
② Analytic Framework の作成
③ 文献検索
④ 抄録チェック
⑤ 個別研究の評価（質の評価のためのチェックリスト・構造化要約の作成）
⑥ 証拠のまとめ（採用文献リストの確定、個別研究評価の総括、「証拠のレベル」の決定）
⑦ 推奨への翻訳（推奨レベルの決定）
⑧ ガイドライン・ドラフトの作成
⑨ 外部評価、公開フォーラム開催
⑩ ガイドラインの再評価
⑪ ガイドライン更新

からなる。Analytic Framework とは、スクリーニングから当該がん死亡減少に至るまでの causal pathway を示したもので、文献検索の際にカバーすべき範囲を明らかにすることができ、死亡減少効果に関する直接証拠に加えて間接証拠として文献を採用する際に役立つ。個別の文献を評価したうえで、検診方法ごとに有効性についての「証拠のレベル」を決定する（表1）。主たる研究方法、研究の質、および、間接証拠の組み合わせに基づいて決定する。「証拠のレベル」によって定量化された有効性と定性的に記述された不利益に基づき、「推奨のレベル」を決定する（表2）。その際、CとIについては、対策型検診と任意型検診の違いを考慮して（表3）、対策型検診としては推奨できないこと、任意型検診として実施する場合には受診者に適切な説明が必要なこと、を明記している。

USPSTFでは、2007年に推奨レベルの判断基準を更新した[2]。大きな変更点としては推奨レベルC（利益と不利益が近接している場合）について、2001年の判断基準（表4）では、「勧めることも反対することもしない」としているのに対して、2007年の判断基準（表5）では、「日常的に提供しないことを推奨する」となり、濱島／祖父江班の対策型検診の判断と近づいた印象がある。

有効性ガイドライン作成更新に係わる課題

わが国においても、いくつかの組織においてがん検診に関わるガイドラインが作成されており、それにともなっていくつかの問題点が指摘されている。すなわち、新規課題設定の手順、作成委員会の公平性・透

明性の確保、複数のガイドラインの結果の相違に対する説明、ガイドラインと現実の施策の乖離の解消、ガイドラインの正しい理解の普及、常設機関による検討の必要性、などである。

USPSTFでは、ガイドライン作成に際して手順を文書化し、透明性（transparency）、説明責任（account-

表1　証拠のまとめの際に用いる証拠のレベル
研究デザインだけでなく、個別研究の質・結果の一致性を考慮した。
直接証拠だけでなく、間接証拠（AF組み合わせ）を取り入れた。

レベル	主たる研究方法	内容
1++	RCT／系統的総括	一致性を認める質の高いRCT・系統的総括
1+	RCT／系統的総括	一致性を認める中等度の質のRCT・系統的総括
	AF組み合わせ	AFの重要な段階においてRCTが行われており、2++以上の症例対照・コホート研究が行われ、死亡率減少効果が示唆される
1−	RCT／系統的総括	質の低いRCT・系統的総括
2++	症例対照／コホート	一致性を認める質が高い症例対照・コホート研究
2+	症例対照／コホート	一致性を認める中等度の質の症例対照・コホート研究
	地域相関・時系列 AF組み合わせ	一致性を認める質が高い地域相関研究・時系列研究 死亡率減少効果を指標とした直接的証拠はないが、AFの重要な段階においてRCTが行われており、一連の研究の組み合わせにより死亡率減少効果が示唆される
2−	症例対照／コホート	質が低い症例対照・コホート研究
	地域相関・時系列	中等度の質以下の地域相関研究・時系列研究
	AF組み合わせ	死亡率減少効果を指標とした直接的証拠はないが、AFを構成する複数の研究がある
3	その他の研究	横断的な研究、発見率の報告、症例報告など、散発的な報告のみでAFを構成する評価が不可能である
4	専門家の意見	専門家の意見

表2　推奨のレベルと表現
注　推奨Iと判定された検診の実施は、有効性評価を目的とした研究を行う場合に限定することが望ましい。

推奨	表現	対策型検診	任意型検診	証拠のレベル
A	死亡率減少効果を示す十分な証拠があるので、実施することを強く勧める。	推奨する	推奨する	1++／1+
B	死亡率減少効果を示す相応な証拠があるので、実施することを勧める。	推奨する	推奨する	2++／2+
C	死亡率減少効果を示す証拠があるが、無視できない不利益があるため、対策型検診として実施することは勧められない。 任意型検診として実施する場合には、安全性を確保し、不利益に関する説明を十分に行い、受診するかどうかを個人が判断できる場合に限り、実施することができる。	推奨しない	条件付きで実施できる	1++／1+／2++／2+
D	死亡率減少効果がないことを示す証拠があるため、実施すべきではない。	推奨しない	推奨しない	1++／1+／2++／2+
I	死亡率減少効果の有無を判断する証拠が不十分であるため、対策型検診として実施することは勧められない。 任意型検診として実施する場合には、効果が不明であることと不利益について十分説明する必要がある。その説明に基づく、個人の判断による受診は妨げない。	推奨しない	個人の判断に基づく受診は妨げない	1−／2−／3／4

ability)、一貫性(consistency)、独立性（independency）についての取り組みを明記している[3]。USPSTFは、Agency for Health Research and Quality（AHRQ）に事務局をおくが、committee memberはすべて外部委員であり、Evidence Practice Center（EPC）として大学等と契約してsystematic reviewを依頼することで、committee memberが作業を担当するのでなく、recommendationの判断に専念できる仕組みを実現している。また、Institute of Medicine（IOM）は、National Academy of Scienceから医療を担当する部署として独立した組織で、医療に関する政策提言をするためのレポートを科学的根拠に基づいて作成する機関であるが、ここでも作成に当たる委員会の委員長及び委員の人選には、一定期間ホームページ上に一般公開してコメントを求めるなど、透明性確保に細心の注意を払っている。一方、イギリスにおいては、National Institute of Health and Clinical Excellence（NICE）が診療ガイドライン作成を担当しているが（がん検診はNational Screening Committeeが担当している）、ガイドライン作成委員会とは別にTopic selection panelを設置して、検討課題についてカバーする範囲とゴールを予め設定する仕組みを機能させている。これらは、わが国におけるガイドライン作成の仕組みを考える際の基礎資料として重要である。

表3　対策型検診と任意型検診の対比

	対策型検診 Population-based screening (Organized screening)	任意型検診 Individual-based screening Opportunistic screening
目的	対象者全体の死亡率を下げる	個人の死亡リスクを下げる
費用負担	無料～安価（公費負担が主）	全額自己負担
検診方法	有効性の確立した検診方法に限る	有効性の確立していない新しい検診方法も含めて考える
利益と不利益のバランス	対象者のほとんどの人において、利益が不利益を上回ると判断できる場合に限る	個人において、利益と不利益のバランスを判断する
受診率	100％に近づける	目標設定なし
検診間隔	対象者全体が均等に受診できるように配慮	個人のリスクを考慮して決定（比較的頻回）
形態	市町村の行うがん集団検診	人間ドック

表4　米国予防サービス特別委員会（U.S.Preventive Services Task Force）において推奨に用いる標準的表現（2001）

推奨	表現
A	USPSTFは、臨床家が日常的に適格患者に対して当該サービスを提供することを**強く推奨する**。（USPSTFは、当該サービスが重要な健康指標を改善することを示す優良な証拠があると判断し、**利益が不利益を大きく上回る**と結論する。）
B	USPSTFは、臨床家が日常的に適格患者に対して当該サービスを提供することを**推奨する**。（USPSTFは、当該サービスが重要な健康指標を改善することを示す少なくとも相応の証拠があると判断し、**利益が不利益を上回る**と結論する。）
C	USPSTFは、当該サービスを日常的に提供することについて、**勧めることも反対することもしない**。（USPSTFは、当該サービスが重要な健康指標を改善することを示す少なくとも**相応の証拠があると判断するが、一般的な勧告を正当化するには利益と不利益のバランスが近接しすぎている**と結論する。）
D	USPSTFは、当該サービスを日常的に無症状の患者に対して提供することに**反対する**。（USPSTFは、当該サービスが**効果がない**、あるいは、**不利益が利益を上回るとする少なくとも相応の証拠があると判断する**。）
I	USPSTFは、当該サービスを日常的に提供することについて、勧めるまたは反対する勧告を出すための**証拠が不十分**であると結論する。（当該サービスに効果があるとする証拠がないか、質が悪いか、あるいは、一致した結果が得られていないため、利益と不利益のバランスを判断できない。）

今後、がん検診のみならず、科学的根拠に基づいた政策提言を進めていくためには、対策と研究を結ぶPolicy Researchの分野を強化していく必要がある（**図1**）。

表5　米国予防サービス特別委員会（U.S.Preventive Services Task Force）グレードの定義と診療への示唆（2007）

グレード	定義	診療への示唆
A	USPSTFは当該サービスを推奨する。正味の利益が大きいとする高い確実性がある。	当該サービスを提供すること。
B	USPSTFは当該サービスを推奨する。正味の利益が中等度であるとする高い確実性があるか、正味の利益が中等度から大きいとする中等度の確実性がある。	当該サービスを提供すること。
C	USPSTFは、当該サービスを日常的に提供しないことを推奨する。個別の患者への提供は考慮する余地がある。正味の利益が小さいとする少なくとも中等度の確実性がある。	個別の患者において、他の条件がそろった時にのみ、当該サービスを提供する。
D	USPSTFは、当該サービスを提供しないことを推奨する。正味の利益がないか、不利益が利益を上回るとする、中等度または高い確実性がある。	当該サービスの使用を控えさせる。
I ステートメント	USPSTFは、利益と不利益のバランスを評価するための現在の証拠は不十分であると判断する。証拠が存在しない、質が悪い、あるいは、一致しないために、利益と不利益のバランスが決定できない。	USPSTF推奨文の臨床的考察を読むこと。当該サービスが提供される場合には、利益と不利益のバランスの不確実性について、患者が理解していること。

文　献

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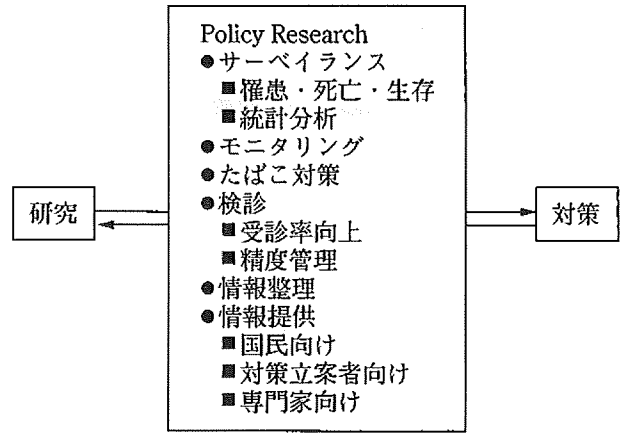

図1　科学的根拠に基づいた政策提言

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2007年6月に閣議決定された「がん対策推進基本計画」の全体目標の1つが75歳未満年齢調整がん死亡率の20％減少であり、がん検診はこれを達成するための主要な手段の一つである。対策の一環として行われるがん検診は、対象集団全体の死亡率を下げることを目的として行われる「対策型検診」と位置づけ、個人の死亡リスクを下げることを目的として行われる「任意型検診」とは区別して考えるべきである。対策型検診においては、有効性評価研究を系統的にレビューした結果、利益（死亡率減少効果）があると判断され、かつ、多くの人で利益が不利益を上回ると判断できる検診に限定して、受診率を可能な限り100％に近づけるべく徹底的に行うことが重要である。さらに、対象者を明確に定義し、対象者名簿に基づく系統的な受診勧奨の仕組みや、定期的な監査を含めた精度管理体制を有する組織化された検診（Organized screening）として行うべきである。

有効性評価に基づくガイドライン作成を透明性・説明責任・一貫性・独立性を確保したうえで実施するために、常設の公的機関において恒常的に機能する仕組みを構築することが重要である。一方で、死亡率減少を示すための有効性評価研究としては、ランダム化比較試験を行うことが国際標準であるにもかかわらず、わが国においては今までのところ実施報告例がない。がん検診のランダム化比較試験には、数万人を約10年フォローアップする必要があり、多くの場合、国家規模のプロジェクトとなる。新しい検診方法をより早く対策として導入するために、評価研究の系統的な実施とそのための基盤整備が緊急の課題である。ただし、評価研究を実施するタイミングを逸した検診については、症例対照研究などの観察研究を、迅速に実施することが適切な場合もある。

キーワード：がん検診、がん対策、ガイドライン

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Randomized Trial of High-Dose Interferon-α-2b Combined With Ribavirin in Patients With Chronic Hepatitis C: Correlation Between Amino Acid Substitutions in the Core/NS5A Region and Virological Response to Interferon Therapy

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The aim of this study was to compare the efficacy of high-dose interferon (IFN)-α-2b with standard dose of IFN-α-2b in combination with ribavirin (RBV) for patients with chronic hepatitis C virus (HCV) infection, and to investigate the predictive factors associated with virological response. Two hundred Japanese patients with high HCV viral load (>100 KIU/ml) were randomized to 6 or 10 mega units (MU) of 24-week IFN-α-2b with RBV. Predictive factors were investigated; including pretreatment amino acid (aa) sequences of the core region and the IFN-sensitive determining region (ISDR). The sustained virological response rate was not different in the two groups (24% vs. 30%) but the incidence of depression was significantly higher in the 10 MU group than 6 MU group (7% vs. 0%, $P=0.02$). Younger age (<60) and HCV genotype (2a/b) were significant predictors of sustained virological response. In patients infected with genotype 1b, substitutions of core aa 70 and/or 91 were predictive for non-virological response ($P<0.001$), and substitutions in the ISDR was observed frequently in virological responders. Early viral kinetics study showed that serum HCV core antigen decreased more slowly in both patients with aa 70 and/or 91 substitutions in the core and with absence of substitutions in the ISDR. In conclusion, the use of a higher dose of IFN-α-2b in combination with RBV did not improve virological response but resulted in higher incidence of depression. Amino acid substitutions in the core and ISDR are predictive of virological response to the therapy in patients with genotype 1b and high viral load. ***J. Med. Virol. 81:640–649, 2009.***

KEY WORDS: HCV; interferon; ribavirin; core region; ISDR

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is the leading cause of cirrhosis, liver failure, and hepatocellular carcinoma [Kiyosawa et al., 1990; Niederau et al., 1998]. Interferon (IFN) is an essential component of therapy for patients with chronic HCV infection. The most effective therapy available at present is the combination therapy of pegylated (PEG)-IFN and ribavirin (RBV) [Manns et al., 2001; Fried et al., 2002; Hoofnagle et al., 2003]. Among HCV genotypes, genotype 1b is the most resistant genotype to IFN therapy [Fried et al., 2002]. The limitation of use of the combination therapy for HCV infection with genotype 1b is due to the low response rate during therapy and high relapse rate after the therapy [McHutchison et al., 1998]. Several studies have evaluated the potential benefits of a larger dose of IFN with varying results [Lindsay et al., 1996; Fried et al., 2000; Ferenci et al., 2001; Hadziyannis et al., 2001; Di Marco et al., 2002; Brouwer et al., 2004]. Although treatment has been

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